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REVIEW

Diabetes mellitus and electrolyte disorders

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Abstract

Diabetic patients frequently develop a constellation of electrolyte disorders. These disturbances are particularly common in decompensated diabetics, especially in the context of diabetic ketoacidosis or nonketotic hyperglycemic hyperosmolar syndrome. These patients are markedly potassium-, magnesium- and phosphate-depleted. Diabetes mellitus (DM) is linked to both hypo- and hyper-natremia reflecting the coexistence of hyperglycemia-related mechanisms, which tend to change serum sodium to opposite directions. The most important causal factor of chronic hyperkalemia in diabetic individuals is the syndrome of hyporeninemic hypoaldosteronism. Impaired renal function, potassium-sparing drugs, hypertonicity and insulin deficiency are also involved in the development of hyperkalemia. This article provides an overview of the electrolyte disturbances occurring in DM and describes the underlying mechanisms. This insight should pave the way for pathophysiology-directed therapy, thus contributing to the avoidance of the several deleterious effects associated with electrolyte disorders and their treatment.

Key words: Glucose; Osmotic diuresis; Hyponatremia; Hyperkalemia; Hypomagnesemia

Core tip: Diabetic patients frequently develop a constellation of electrolyte disorders. These patients are often potassium-, magnesium- and phosphate-depleted, especially in the context of diabetic ketoacidosis or nonketotic hyperglycemic hyperosmolar syndrome. Diabetes is linked to both hypo- and hyper-natremia, as well as to chronic hyperkalemia which may be due to hyporeninemic hypoaldosteronism. This article provides an overview of the electrolyte disturbances occurring in diabetes and describes the underlying mechanisms. This insight should pave the way for pathophysiology-directed therapy, thus contributing to the avoidance of the several deleterious effects associated with electrolyte disorders and their treatment.

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INTRODUCTION

Electrolyte disorders are common in clinical practice. They are mainly encountered in hospital populations occurring in a broad spectrum of patients (from asymptomatic to critically ill) and being associated with increased morbidity and mortality[1-3]. The disturbances of electrolyte homeostasis are also frequently observed in community subjects. Community-acquired electrolyte disorders, even chronic and mild, are related to poor prognosis[3]. Electrolyte disorders are usually multifactorial in nature. Various pathophysiological factors, such as nutritional status, gastrointestinal absorption capacity, coexistent acid-base abnormalities, pharmacological agents, other comorbid diseases (mainly renal disease) or acute illness, alone or in combination, play a key role.

Diabetes mellitus (DM) is included among the diseases with increased frequency of electrolyte abnormali-

Table 1 Principal causes of electrolyte disorders in diabetic patients

Sodium disorders[1]
Hyponatremia
Pseudohyponatremia (marked hyperlipidemia)
Hyperglycemia (hypertonicity)-induced movement of water out of the cells (dilutional hyponatremia)
Osmotic diuresis-induced hypovolemic hyponatremia
Drug-induced hyponatremia: hypoglycemic agents (chlorpropamide, tolbutamide, insulin) or other medications (*e.g.*, diuretics, amitriptyline)
Pseudonormonatremia (marked hyperlipidemia, severe hypoproteinemia)
Hypernatremia
Pseudohypernatremia (severe hypoproteinemia)
Loss of water in excess of sodium and potassium (osmotic dieresis), if this water loss is replaced insufficiently
Potassium disorders
Hypokalemia
Shift hypokalemia: insulin administration
Gastrointestinal loss of K^+: malabsorption syndromes (diabetic-induced motility disorders, bacterial overgrowth, chronic diarrheal states)
Renal loss of K^+: osmotic diuresis, hypomagnesemia, diuretics (thiazides, thiazide-like agents, furosemide)
Hyperkalemia
Shift hyperkalemia: acidosis, insulin deficiency, hypertonicity, rhabdomyolysis, drugs (*e.g.*, beta blockers)
Reduced glomerular filtration of K^+: acute and chronic kidney disease
Reduced tubular secretion of K^+: hyporeninemic hypoaldosteronism, drugs (angiotensin-converting enzyme inhibitors, angiotensin Ⅱ receptor blockers, renin inhibitors, beta blockers, potassium-sparing diuretics)
Magnesium disorders
Hypomagnesemia
Pseudohypomagnesemia: hypoalbuminemia
Shift hypomagnesemia: insulin administration
Poor dietary Mg^{2+} intake
Gastrointestinal Mg^{2+} losses: diarrhea as a result of diabetic autonomic neuropathy
Increased renal Mg^{2+} losses due to osmotic diuresis, glomerular hyperfiltration, diuretic administration
Recurrent metabolic acidosis
Calcium disorders
Hypocalcemia
Pseudohypocalcemia: hypoalbuminemia[2]
Acute renal failure due to accompanying hyperphosphatemia
Advanced chronic renal insufficiency due to hyperphosphatemia and low levels of vitamin D
Nephrotic syndrome: loss of 25-hydroxyvitamin D3 and its binding protein in the urine
Hypomagnesemia
Vitamin D deficiency
Drug-mediated: loop diuretics
Hypercalcemia
Concurrent hyperparathyroidism
Thiazide therapy
Phosphorus disorders
Hypophosphatemia
Osmotic diuresis
Drugs: thiazides, loop diuretics, insulin
Malabsorption syndromes
Primary hyperthyroidism
Vitamin D deficiency

[1]Spurious sodium disorders occur when sodium is measured with indirect ion-selective electrodes; [2]The ionized serum calcium levels are normal.

ties given that the aforementioned factors (especially impaired renal function, malabsorption syndromes, acid-base disorders and multidrug regimens) are often present in diabetics[4].

This article provides an overview of the electrolyte disturbances occurring in DM and describes possible underlying mechanisms (Table 1). This insight should pave the way for pathophysiology-directed therapy, possibly contributing to the avoidance of several deleterious effects associated with electrolyte disorders and their treatment.

DYSNATREMIAS (HYPONATREMIA AND HYPERNATREMIA)

DM is a well-known cause of dysnatremias *via* several underlying mechanisms[3,5]. Glucose is an osmotically active substance. Hyperglycemia increases serum osmolality, resulting in movement of water out of the cells and subsequently in a reduction of serum sodium levels ($[Na^+]$) by dilution. Therefore, in hyperglycemic patients, the corrected $[Na^+]$ should be taken into account, which is calculated by adding to measured $[Na^+]$ 1.6 mmol/L for every 100 mg/dL (5.55 mmol/L) increment of serum glucose above normal; a correction factor by 2.4 mmol/L is used when serum glucose concentrations are higher than 400 mg/dL (22.2 mmol/L)[6,7]. It is worth mentioning that the corrected $[Na^+]$ after adjustment for the dilutional effect of hyperglycemia should be considered as a useful tool for the monitoring of treatment in hyperglycemic states[8]. Uncontrolled DM can also induce hypovolemic-hypo-

natremia due to osmotic diuresis. Moreover, in diabetic ketoacidosis ketone bodies (b-hydroxybutyrate and acetoacetate) obligate urinary electrolyte losses and aggravate the renal sodium wasting[7,9]. It should be emphasized, however, that hypotonic renal losses (loss of water in excess of sodium and potassium) due to osmotic diuresis can lead to hypernatremia if this water loss is replaced insufficiently. In a study in 113 hypernatremic patients hospitalized in an internal medicine clinic, poorly controlled DM was implicated in the development of hypernatremia in one third of cases (34.5%)[5]. Consequently, in patients with uncontrolled DM serum concentration of [Na^+] is variable, reflecting the balance between the hyperglycemia-induced water movement out of the cells that lowers [Na^+], and the glucosuria-induced osmotic diuresis, which tends to raise [Na^+].

Drug-induced hyponatremia due to hypoglycemic agents (chlorpropamide, tolbutamide, insulin) or other medications (*e.g.*, diuretics, amitriptyline for the treatment of diabetic neuropathy) should be considered in every diabetic patient with low [Na^+][10,11]. Chlorpropamide, which is now rarely used in the treatment of patients with DM, can induce hyponatremia in approximately 4% to 6% by potentiating the effect of antidiuretic hormone. Elderly patients concomitantly using diuretics have greater risk of developing hyponatremia[12,13]. Tolbutamide can lead to hyponatremia by decreasing renal free water clearance[13]. Noteworthy, despite fluid retention being a common adverse effect of thiazolidinediones (pioglitazone and rosiglitazone), hyponatremia related to these drugs was reported only once[14]. There is experimental evidence that glucagon-like peptide 1 receptor agonists influence water and electrolyte balance[15]. However, to the best of our knowledge, dysnatremias (or other electrolyte disorders) related to these drugs have not reported in humans. Moreover, the new class of oral antidiabetic agents known as sodium-glucose cotransporter type 2 (SGLT2) inhibitors does not appear to be associated with electrolyte abnormalities in early clinical studies[16,17].

It has been reported that DM *per se* (independently of drugs or hyperglycemia) is associated with hyponatremia[11]. Recently, in a study in 5179 community subjects aged 55 years or more DM was associated with hyponatremia (OR = 1.98; 95%CI: 1.47-2.68), with the serum glucose levels being too low to fully explain the degree of hyponatremia[3]. Altered vasopressin metabolism, interaction between insulin and vasopressin, both of which act in the renal collecting duct, and the reabsorption of more hypotonic fluid due to slower stomach emptying have been proposed as possible underlying mechanisms of this association[18-20]. Although rare, the inverse etiological relation between hyponatremia and DM also exists. In fact, brain edema in the setting of untreated symptomatic hyponatremia may induce cerebral herniation and infarction of pituitary and hypothalamus, leading to central DM and insipidus[21].

DM is also associated with an artificially decreased or elevated serum sodium value, that is different compared with the actual systemic level. In normal subjects, serum is composed of water (approximately 93%), with fats and proteins accounting for the remaining 7%. Sodium is located in the serum water phase only. A reduction in serum water fraction (< 80%) may occur in patients with marked hyperlipidemia as with lactescent serum in uncontrolled DM. In these settings, the serum sodium concentration, measured per liter of serum, not serum water, is artificially reduced (pseudohyponatremia). The presence of normal serum sodium levels in a patient with hyperlipidemia should also raise the suspicion that hypernatremia may be present (pseudonormonatremia). The opposite phenomenon of pseudohypernatremia and pseudonormonatremia may also occur as a result of severe hypoproteinemia, not infrequently observed in diabetics with nephrotic or malabsorption syndromes. In lipemic or hypoproteinemic samples the direct ion-selective electrodes (ISE) method for the measurement of serum sodium should be used, since the indirect ISE is prone to spurious dysnatremias[22].

It is known that rapid correction of serum sodium may be followed by development of central demyelinating lesions, particularly in the pons (a disorder called central pontinemyelinolysis orosmotic demyelination) with major disability or even fatal outcome[2]. Diabetics may have an increased risk for the osmotic demyelination syndrome (ODS) during correction of hyponatremia since risk factors for this disorder (thiazide diuretics, malnutrition, hypokalemia, and hypoxia)[23] are not infrequently present in such patients. Hypokalemia is also associated with a poor outcome in patients who develop the syndrome[24].

It should be emphasized that ODS is mainly observed during overly rapid correction of chronic hyponatremia. However, in diabetic patients hypernatremia and hypokalemia (in the absence of hyponatremia or hyperosmolality) are rarely associated with ODS. The mechanism by which these electrolyte disorders may cause ODS in the diabetic state is not yet known[25,26].

It has been suggested that in cases of nonketotic hyperglycemic hyperosmolar syndrome (HHS) altered mental status is predicted best by [Na^+]; serum glucose concentration alone is considered a poor indicator. In fact, there is evidence that hyperglycemic patients with hypertonicity are symptomatic only if hypernatremia is present[5,27]. On the contrary, neurological symptoms may be absent in the context of severe gradually developing hyperglycemia[27,28]. This could be attributed to the capacity of the brain tissue to restore intracellular water by accumulating electrolytes and the so-called idiogenic osmoles. Furthermore, the brain cells are relatively permeable to glucose even in the absence of insulin[28,29]. Therefore, hyperglycemia by itself does not create severe hypertonicity in central nervous system (CNS)[28]. On the other hand, hypernatremia induces severe cellular dehydration in CNS cells. This state is associated with a rather slow compensatory accumulation of brain osmolar content[28].

The development of hypernatremia is associated with endocrine dysfunction. There is some evidence in

animals and man that hypernatremia and hyperosmolarity are associated with impairment of both insulin-mediated glucose metabolism and glucagon-dependent glucose release[30-33]. Thus, hypernatremia and hyperosmolarity should be considered as contributing factors to the occurrence of hyperglycemia in critically ill patients[34]. Moreover, hypernatremia is implicated in the profound inhibition of gonadotrophin release in postmenopausal diabetic women with HHS. Although the underlying mechanisms remain unknown, it appears that hypernatremia induces a decrease in gonadotrophin-releasing hormone expression in GT1-7 neurons[35].

Rhabdomyolysis, though uncommon, has been described in the diabetic state[36]. It appears that high serum sodium and glucose levels represent the most important determinants for the occurrence of this complication[37].

HYPOKALEMIA

The causes of hypokalemia in diabetics include: (1) redistribution of potassium [K^+] from the extracellular to the intracellular fluid compartment (shift hypokalemia due to insulin administration); (2) gastrointestinal loss of K^+ due to malabsorption syndromes (diabetic-induced motility disorders, bacterial overgrowth, chronic diarrheal states); and (3) renal loss of K^+ (due to osmotic diuresis and/or coexistent hypomagnesemia). Hypomagnesemia can cause hypokalemia possibly because a low intracellular magnesium [Mg^{2+}] concentration activates the renal outer medullary K^+ channel to secrete more K^+[38].

Exogenous insulin can induce mild hypokalemia because it promotes the entry of K^+ into skeletal muscles and hepatic cells by increasing the activity of the Na^+-K^+-ATPase pump[39]. The increased secretion of epinephrine due to insulin-induced hypoglycemia may also play a contributory role[40]. The major setting in which insulin administration leads to hypokalemia is during the treatment of severe hyperglycemia. The majority of patients with diabetic ketoacidosis (DKA) and HHS are markedly K^+-depleted. The average K^+ deficit is 3-5 mEq/kg, but it can exceed 10 mEq/kg in some cases[41,42]. A number of factors contribute to the DKA- and HHS-associated potassium depletion, including vomiting, increased renal losses due to the osmotic diuresis and ketoacid anion excretion, and the loss of K^+ from the cells due to glycogenolysis and proteolysis[41,43]. On admission, however, the serum K^+ levels are usually normal, or, in about one-third of patients, increased despite the K^+ depletion[41,43]. It is thought that hyperosmolality and insulin deficiency are primarily responsible for the relative rise in the serum potassium concentration in this setting. As mentioned, hyperglycemia increases serum osmolality resulting in movement of water out of cells. The loss of intracellular water leads to an increased intracellular K^+ concentration, favoring a gradient for K^+ to move out of the cells. Simultaneously, the friction forces between solvent (water) and solute can result in K^+ being carried along with water through the water pores in the cell membrane[43]. In contrast, acidemia probably does not play a major role given that organic acids are much less likely to influence the internal K^+ distribution[44]. Insulin therapy lowers K^+ concentration driving K^+ into cells (both directly and indirectly by reversing hyperglycemia). Therefore, insulin therapy may cause severe hypokalemia, particularly in patients with a normal or low serum K^+ concentration at presentation. Insulin administration in patients with massive K^+ deficits who are hypokalemic prior to therapy should be delayed until the serum K^+ is above 3.3 mEq/L to avoid possible arrhythmias, cardiac arrest and respiratory muscle weakness[42,45,46]. It is obvious that the risk of hypokalemia-related complications is particularly higher in diabetic subjects who have hypertension, myocardial infarction/ischemia, or heart failure as comorbidities. In addition, since diabetics are frequently on diuretics, diuretic-associated hypokalemia (as well as hypomagnesemia and hypophosphatemia) should be taken into account in this setting.

Hypokalemia is associated with impaired insulin secretion and decreased peripheral glucose utilization resulting in carbohydrate intolerance and hyperglycemia[47]. This is particularly problematic in diabetic patients causing a vicious circle where low serum K^+ levels lead to poorly controlled DM and vice versa.

HYPERKALEMIA

The incidence of hyperkalemia is higher in diabetic patients than in the general population[48,49]. Redistribution of potassium from the intracellular to the extracellular compartment (shift hyperkalemia) can induce hyperkalemia with no net total body K^+ increase. Examples of shift hyperkalemia in DM include acidosis (for each 0.1 fall in pH, potassium increases by approximately 0.4 mmol/L), insulin deficiency, hypertonicity, cell lysis (rhabdomyolysis), and drugs (*e.g.*, beta blockers). Reduced glomerular filtration of K^+ (due to acute kidney injury and chronic kidney disease) and many drugs that interfere with K^+ excretion are associated with hyperkalemia. These include angiotensin-converting enzyme inhibitors, angiotensin Ⅱ receptor blockers, renin inhibitors, beta blockers and potassium-sparing diuretics. Of note, the typical healthy diabetic diet is often rich in K^+ and low in sodium contributing to the occurrence of hyperkalemia in susceptible individuals[48,49]. Nevertheless, the most common causal factor of chronic hyperkalemia in diabetics is the reduced tubular secretion of K^+ due to the syndrome of hyporeninemic hypoaldosteronism[50]. This syndrome is characterized by mild to moderate renal insufficiency and patients typically present with asymptomatic hyperkalemia. The development of overt hyperkalemia is most common in patients with other risk factors that further impair the efficiency of potassium excretion, such as renal insufficiency, volume depletion, or the use of medications that interfere with potassium handling (see above).

Of note, dapagliflozin (a SGLT2 inhibitor) may be protective from the development of hyperkalemia in

patients with moderate renal impairment due to osmotic diuresis[17]. However, the administration of SGLT2 inhibitors in hypovolemic patients may cause elevated serum creatinine levels and decreases in glomerular filtration rate due to deterioration of intravascular volume contraction. Indeed, worsening renal function and hyperkalemia may occur in patients on canagliflozin, particularly those predisposed to hyperkalemia due to impaired renal function, medications or other medical conditions[51]. Hyporeninemic hypoaldosteronism is more frequently observed in diabetic and elderly patients as well as in those with chronic renal impairment. Diabetic nephropathy accounts for 43%-63% of cases comprising the most common cause of hyporeninemic hypoaldosteronism[33,50,52]. Normal ageing, especially after the sixth decade, is associated with a decline in renin production. Moreover, elderly patients may have decreased renal function even without significant elevations in serum creatinine levels [< 1.2 mg/dL (106 μmol/L)]. Consequently, diabetics (especially the elderly) on medications known to interfere with K^+ homeostasis are at increased risk for hyperkalemia[33,53]. In such cases, close K^+ monitoring is fully warranted[54]. Clinicians must also be alert that hyperkalemia in patients with type 1 DM may be due to concurrent adrenal insufficiency in the setting of autoimmune polyglandular syndrome[55].

HYPOMAGNESEMIA

Hypomagnesemia is a frequent electrolyte disorder in diabetic patients[56]. Recently, DM was identified as an independent risk factor for hypomagnesemia in community subjects aged 55 years or more (OR = 3.32; 95%CI: 2.00-5.50)[3]. In a recent prospective study in hypomagnesemic patients (either on admission or during hospitalization in an internal medicine clinic) DM was evident in a considerable proportion (40%), mainly as a contributing factor. Osmotic diuresis accompanied by inappropriate magnesiuria was the prominent underlying mechanism of hypomagnesemia in these diabetic patients[57]. Except for glucosuria, several other possible explanations for hypomagnesemia in DM have been reported. These include poor dietary intake, glomerular hyperfiltration, altered insulin metabolism, diuretic administration and recurrent metabolic acidosis[56]. Increased gastrointestinal Mg^{2+} losses due to diarrhea as a result of diabetic autonomic neuropathy can also cause low serum Mg^{2+} levels. Of note, a case of symptomatic hypomagnesemia [serum Mg^{2+} concentration 0.66 mEq/L (0.33 mmol/L), reference range 1.42-1.84 mEq/L (0.71-0.94 mmol/L)] was attributed to metformin-induced diarrhea[58]. Furthermore, insulin promotes net shift of Mg^{2+} from extracellular to intracellular space and can contribute to hypomagnesemia[59,60]. The increased secretion of epinephrine due to insulin-induced hypoglycemia may also play a role. The risk of hypomagnesemia related to insulin therapy is increased in poorly controlled diabetic patients given that hyperglycemia induces increased renal Mg^{2+} loss *via* osmotic diuresis. Hypokalemia, hypophosphatemia as well as acidosis-related urinary Mg^{2+} losses contribute to the high incidence of hypomagnesemia in the setting of diabetic ketoacidosis[61,62]. It should be noted that hypoalbuminemia is associated with spurious hypomagnesemia. In hypoalbuminemic states (serum albumin < 4 g/dL) the corrected serum Mg^{2+} should be calculated using the formula: corrected Mg^{2+} (mEq/L) = measured Mg^{2+}(mEq/L) + 0.01 × (40 - albumin in g/L)[63].

Mg^{2+} is essential for life being involved in numerous enzymatic reactions, including ATP use, cell membrane, ion channels and mitochondrial function, as well as protein synthesis. The most clinically significant consequences of hypomagnesemia are ascribed to alterations in the function of excitable membranes in nerve, muscle, and the cardiac conducting system. Moreover, low serum Mg^{2+} levels can secondarily induce hypokalemia, hypocalcemia, and hypophosphatemia, potentially causing further derangements in neuromuscular and cardiovascular physiology. Hypomagnesemia has been implicated in various long-term complications of DM, such as hypertension, increased carotid wall thickness, coronary artery disease, dyslipidemia, diabetic retinopathy, neuropathy, ischemic stroke, and foot ulcerations[56]. Hypomagnesemia has also been linked to diabetic nephropathy (from microalbuminuria to advanced renal disease)[64-66]. It has been proposed that hypomagnesemia is a predictor of end-stage renal disease in patients with diabetic nephropathy[66]. In addition, magnesium deficit is associated with carbohydrate intolerance and insulin resistance, thus inducing or worsening existing DM[67,68]. On the contrary, increased dietary Mg^{2+} intake has been associated with a reduced risk of type 2 DM[69].

HYPOCALCEMIA

Patients with DM have an increased risk for development of acute renal failure due to volume depletion, sepsis, rhabdomyolysis and drugs (*e.g.*, radiographic contrast media). In this setting severe hyperphosphatemia may occur when phosphorus cannot be excreted by the malfunctioning kidney either with or without increased cell catabolism, thus resulting in hypocalcemia. Advanced chronic renal insufficiency may be associated with hypocalcemia due to accompanying hyperphosphatemia and low levels of vitamin D. Patients with nephrotic syndrome may exhibit hypocalcemia, even if the glomerular filtration rate is well preserved. This is attributed to the loss of 25-hydroxyvitamin D_3 and its binding protein in the urine. Hypomagnesemia is another potential cause of hypocalcemia in diabetics. Mg^{2+} depletion leads to hypocalcemia mainly because of impaired release of parathyroid hormone (PTH) or skeletal and renal tubule resistance to the action of PTH[1]. Vitamin D deficiency and furosemide administration may also play a role in the occurrence of hypocalcemia[70]. There is evidence that diabetic patients are relatively hypoparathyroid[71]. In fact, a mild shift downwards in the set-point for PTH secretion in patients

with insulin-dependent DM as well as a diminished parathyroid gland responsiveness to hypocalcemia in uremic diabetic patients have been reported[72,73].

Hypoalbuminemia is associated with pseudohypocalcemia defined as a reduction of total serum calcium concentration in the presence of normal ionized serum calcium levels. In hypoalbuminemic states, one of the commonly used formulas to correct total calcium levels is by adding 0.8 mg/dL (0.2 mmol/L) to measured calcium values for every 1 g/dL decrease in serum albumin from normal value (assumed to be 4 g/dL). Given that the accuracy of this method is poor (particularly among critically ill and geriatric patients), the biologically active ionized calcium concentration should be measured when possible[1,74].

HYPERCALCEMIA

The incidence of DM in primary hyperparathyroidism and that of primary hyperparathyroidism in DM is approximately 8% and 1%, respectively. Both values are about three-fold higher than that anticipated in the general population[75]. Hyperparathyroidism is related to long-term insulin resistance and relative insulin insufficiency, leading to overt DM or deterioration of glycemic control of established DM[75,76]. It is thought that an elevated intracellular free calcium concentration (by decreasing normal insulin-stimulated glucose transport) increases the requirement for insulin, resulting in hyperparathyroidism-mediated insulin resistance[75]. Diabetic patients should be evaluated for hypercalcemia given that untreated hyperparathyroidism is linked to hypertension[75,77]. The detection of high serum calcium levels in a patient with type 1 DM should raise the suspicion that autoimmune hyperparathyroidism associated with anti-calcium-sensing receptor autoantibodies may be present[78]. Recently, a case of severe hypercalcemia [15 mg/dL (3.75 mmol/L)] in DKA was reported[79]. Dehydration might represent the most important causative factor for the occurrence of hypercalcemia in this case. A decreased bone formation due to metabolic acidosis and an increased bone mineral dissolution and resorption due to severe insulin deficiency and metabolic acidosis may also play a role[80]. Hyperglycemia-mediated inhibition of bone mineralization, insulin growth factor-1 deficiency, hypophosphatemia and immobilization are also included among the potential contributory factors of hypercalcemia in DKA[79,81,82]. Also, diabetic patients on thiazide diuretics are more prone to exhibit hypercalcemia.

HYPOPHOSPHATEMIA

Diabetic patients have underlying conditions that predispose to the development of hypophosphatemia. These include primary hyperthyroidism, vitamin D deficiency, malabsorption, and the use of diuretics (thiazides and furosemide)[83]. It is known that increased insulin levels promote the transport of both glucose and phosphate into the skeletal muscle and liver cells. However, in normal subjects the administration of insulin leads only to a slight decrement of serum phosphate levels. The risk of severe hypophosphatemia is increased in cases of underlying phosphate depletion[62,84]. Decompensated DM with ketoacidosisis associated with excessive phosphate loss due to osmotic diuresis. Despite phosphate depletion, the serum phosphate concentration at presentation is usually normal or even high because both insulin deficiency and metabolic acidosis cause a shift of phosphate out of cells[85]. Administration of insulin and fluids, and correction of ketoacidosis may reveal phosphate deficiency and cause a sharp decrease in plasma phosphate concentration due to intracellular shift[83].

In a study of 69 patient with DKA, the incidence of hyperphosphatemia was 94.7% at presentation. The mean serum phosphate concentration fell from 9.2 mg/dL (3 mmol/L) to 2.8 mg/dL (0.9 mmol/L) 12 h after initiating treatment, while some patients exhibited values as low as 1.0 mg/dL (0.32 mmol/L)[85].

The routine administration of phosphate during treatment of DKA and HHS is not recommended since randomized trials failed to show any clinical benefit from phosphate administration[42,83,86,87]. What is more, correction of hypophosphatemia may have adverse effects, such as hypocalcemia and hypomagnesemia[42,83,88]. Careful phosphate replacement is required in patients with severe hypophosphatemia of less than 1.0 mg/dL (0.32 mmol/L) and in patients who develop cardiac dysfunction, hemolytic anemia, or respiratory depression[42,89,90].

CONCLUSION

Electrolyte abnormalities are common in diabetic patients and may be associated with increased morbidity and mortality. These disturbances are particularly common in decompensated DM, in the elderly as well as in the presence of renal impairment. Patients with DM may receive complex drug regimens some of which may be associated with electrolyte disorders. Discontinuation of these medications, when possible, as well as strict control of glycemia are of paramount importance to prevent electrolyte abnormalities in diabetic patients. The successful management of these disorders can best be accomplished by elucidating the underlying pathophysiologic mechanisms.

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REVIEW

Practical strategies for modulating foam cell formation and behavior

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Abstract

Although high density lipoprotein (HDL)-mediated reverse cholesterol transport is crucial to the prevention and reversal of atheroma, a recent meta-analysis makes evident that current pharmaceutical strategies for modulating HDL cholesterol levels lower cardiovascular risk only to the extent that they concurrently decrease low density lipoprotein (LDL) cholesterol. This corresponds well with findings of a recent Mendelian randomization analysis, in which genetic polymorphisms associated with HDL cholesterol but no other known cardiovascular risk factors failed to predict risk for myocardial infarction. Although it is still seems appropriate to search for therapies that could improve the efficiency with which HDL particles induce reverse cholesterol transport, targeting HDL cholesterol levels *per se* with current measures appears to be futile. It may therefore be more promising to promote reverse cholesterol transport with agents that directly target foam cells. Macrophage expression of the cholesterol transport proteins adenosine triphosphate binding cassette transporter A1, adenosine triphosphate binding cassette transporter G1, and scavenger receptor class B member 1 is transcriptionally up-regulated by activated liver X receptors (LXR), whereas nuclear factor (NF)-kappaB antagonizes their expression. Taurine, which inhibits atherogenesis in rodent studies, has just been discovered to act as a weak agonist for LXRalpha. Conversely, it may be possible to oppose NF-kappaB activation in macrophages with a range of measures. Induction of heme oxygenase-1, which can be attained with phase 2 inducer phytochemicals such as lipoic acid and green tea catechins, promotes reverse cholesterol transport in macrophages and inhibits atherogenesis in rodents, likely due to, in large part, NF-kappaB antagonism. Inhibition of macrophage nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity with the spirulina-derived bilirubin-mimetic phycocyanobilin may also oppose NF-kappaB activation, and salicylic acid similarly should be useful for this purpose. The 5' adenosine monophosphate-activated protein kinase activator berberine promotes macrophage reverse cholesterol transport in cell culture; metformin probably shares this property. Many of these measures could also be expected to promote plaque stability by suppressing foam cell production of inflammatory cytokines and matrix metalloproteinases, and to reduce intimal monocyte infiltration by anti-inflammatory effects on vascular endothelium. Direct targeting of foam cells with agents such as phase 2 inducers, spirulina, salicylate, taurine, and berberine or metformin, may hence have considerable potential for preventing and reversing atheroma, and for preventing the plaque rupture that triggers vascular thrombosis.

Key words: Atherosclerosis; Cholesterol; Inflammation;

Phytochemical; Nutraceutical; Atherogenesis; Plaque; Cytokine; Antioxidant

Core tip: Reverse cholesterol transport from foam cells is of key importance to prevention and control of atherosclerosis. This essay reviews the molecular biology of foam cell regulation, and proposes that certain agents may be capable of acting directly on foam cells to amplify reverse cholesterol transport while also promoting plaque stability by limiting foam cell production of inflammatory cytokines and matrix metalloproteinases. Phase 2 inducers such as lipoic acid and green tea catechins, spirulina, salicylate, taurine, and 5' adenosine monophosphate-activated protein kinase activators such as metformin or berberine, appear to have potential in this regard-while acting in additional ways to benefit vascular health.

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PHARMACEUTICAL HIGH DENSITY LIPOPROTEIN MODULATION HAS PROVED DISAPPOINTING

Although reverse cholesterol transport from foam cells mediated by high density lipoprotein (HDL) particles clearly plays a key role in the prevention and control of atherosclerosis (Figure 1) and its complications[1-3], a recent meta-analysis strongly suggests that current pharmaceutical measures for increasing HDL cholesterol (*e.g.*, niacin, fibrates, cholesterylester transfer protein inhibitors) do not enhance health outcomes in at-risk subjects-or rather, only do so to the extent that, like niacin, they favorably influence other determinants of atherogenesis such as low density lipoprotein (LDL) and apoB-bearing lipoproteins[4]. The failure of niacin in the AIM-HIGH trial-despite evidence of benefit in other studies[5,6]-might then be explained by the fact that patients in the control group received a higher dose of statin such that reductions of LDL cholesterol were equivalent in each group[7]. Analogously, a Mendelian randomization analysis has determined that genotypes associated with elevated HDL cholesterol (but no other known determinants of cardiovascular risk), are not associated with a decline in risk for myocardial infarction[8]. A similar analysis focusing on genetic determinants of LDL cholesterol provides striking confirmation of LDL's pathogenicity[9]. The well-established epidemiological association of low HDL cholesterol with increased cardiovascular risk might therefore reflect the fact that low HDL cholesterol levels can serve as a marker for metabolic states-such as the metabolic syndrome-that are truly pathogenic; a similar analysis applies to moderately elevated homocysteine. There still may be scope for developing new drugs or procedures that improve the capacity of HDL particles to achieve reverse transport[10-13]-but available pharmaceutical agents capable of elevating HDL cholesterol do not seem to have that property. As the authors of the recent meta-analysis note: "Raising high density lipoprotein cholesterol without considering effects on high density lipoprotein function seem to have little promise for the prevention of cardiovascular events"[4].

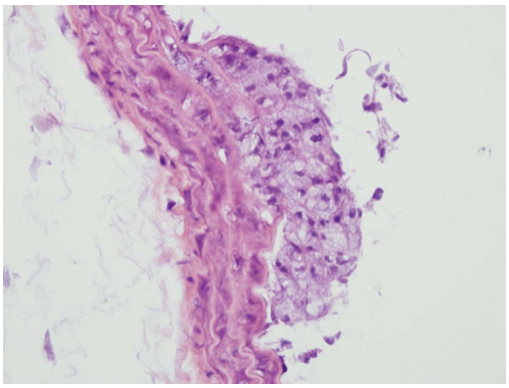

Figure 1 An atherosclerotic plaque at its early stage of development in the thoracic aorta of an apolipoprotein E-KO mouse is illustrated. The plaque is primarily composed of apparent foam cells. HE staining × 400.

It bears mentioning that the low HDL cholesterol levels seen in subjects carrying the Milano variant of apoA-1 are not associated with aggravated cardiovascular risk[14]; perhaps this reflects the efficiency with which Milano HDL delivers cholesterol to the liver for catabolism. Conversely, the elevation of HDL cholesterol associated with niacin therapy may reflect the fact that clinical concentrations of niacin impede the liver's ability to catabolize holo-HDL particles[15]; while this increases the circulating apoA-1 pool, the amount of cholesterol per HDL particle also rises. Whether the increase in HDL associated with moderate alcohol consumption-likely attributable to enhanced hepatic synthesis of apoA-1[16]-is partially responsible for the decrease in cardiovascular risk observed in by prudent drinkers, is not yet clear; activation of 5' adenosine monophosphate-activated protein kinase (AMPK) by ethanol-derived acetate may contribute to alcohol's vascular benefits[17].

TARGETING FOAM CELLS DIRECTLY TO MODULATE FOAM CELL FORMATION AND BEHAVIOUR

Despite the seeming inutility of current efforts to modulate HDL, it may still be feasible to promote reverse cholesterol transport with agents that act directly on foam cells to enhance their capacity to export cholesterol. Moreover, some of these agents could be expected to decrease foam cell uptake of modified LDL particles, and to work in other ways to promote plaque stabilization.

Egress of cholesterol from macrophages and foam

cells is mediated by several membrane transport proteins, namely adenosine triphosphate binding cassette transporter A1 (ABCA1), adenosine triphosphate binding cassette transporter G1 (ABCG1), and scavenger receptor class B member 1 (SRB-1); ABCA1 preferentially interacts with lipid-poor apoA-1, ABCG1 can transfer cholesterol to all HDL particles, and SRB-1 interacts with a wide range of lipoproteins[18]. The transcription of ABCA1 and ABCG1 is promoted by the liver X receptors (LXR) receptor, a transcription factor whose physiological activation is mediated by certain hydroxylated metabolites of cholesterol produced within macrophages which can function as ligands for LXR[19,20]. Increased intracellular cholesterol in macrophages also promotes increased expression of SRB-1, although this effect does not seem to be mediated *via* LXR[21]. In this way, increased cholesterol uptake by macrophages provokes a compensatory increase in cholesterol export induced by cholesterol metabolites. This LXR-mediated promotion of reverse cholesterol transport *via* HDL can be antagonized by a number of pro-inflammatory cytokines and agonists which have the common effect of activating nuclear factor (NF)-kappaB; concurrent suppression of NF-kappaB activity largely eliminates this inhibition of reverse cholesterol transport[22-27]. NF-kappaB activity somehow opposes the transcription of ABCA1, ABCG1, and SRB-1; how this occurs is still unclear. The balance between LXR and NF-kappaB activities is hence a key determinant of foam cell formation. NF-kappaB activation also is a mediator of inflammatory cytokine production by foam cells, and can promote plaque destabilization by inducing production of matrix metalloproteinases (MMP)[25,28]-whereas LXR suppresses production of MMP-9[29].

Heme oxygenase-1, phase 2 inducers, bilirubin, and spirulina

A number of studies reveal that induction of heme oxygenase-1 (HO-1) in foam cells promotes reverse cholesterol transport, induces increased expression of ABCA1, ABCG1, and SRB-1, and acts in other ways to suppress foam cell production of pro-inflammatory cytokines and plaque-destabilizing metalloproteinases[30-37]. Hence, HO-1 induction can aid prevention of plaque formation, promote plaque regression, and render plaque more stable. Suppression of NF-kappaB activation appears likely to underlie many of these protective effects, since HO-1 activity has been shown to impede NF-kappaB activation in a number of circumstances[38-47]. There appears to be no evidence that HO-1 could influence LXR function. Macrophage HO-1 induction can also oppose AP-1 activation, an effect which could be expected to reduce uptake of modified LDL by diminishing expression of the SR-A receptor[32,33]. The respective roles of HO-1 products carbon monoxide and biliverdin/bilirubin in favorable modulation of foam cell function have not yet been clarified. As HO-1 can be induced by phase 2-inductive phytochemicals *via* the Nrf2 transcription factor[48], such agents evidently have potential for promoting reverse cholesterol transport and aiding prevention, regression, and stabilization of plaque. Lipoic acid, a broad range of flavanoids (including notably green tea catechins), isothiocyanates from crucifera, and organosulfur compounds from garlic and onions, can serve as phase 2 inducers[49-57]-albeit what intakes of these might have a functionally significant impact on HO-1 in foam cells is unknown. Lipoic acid is of particular interest in this regard, inasmuch as well-defined dose schedules (600-1800 mg daily) exert protective effects in diabetic neuropathy, which seem likely to reflect phase 2 induction[58]. Not surprisingly, lipoic acid exerts anti-atherosclerotic activity in rodents[59-62].

The antioxidant effects of HO-1 are mediated largely by bilirubin, which functions physiologically to inhibit certain isoforms of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase[63-66]. The inverse correlation of serum bilirubin levels with cardiovascular risk observed in many epidemiological studies[67-69] may well reflect the antioxidant impact of free bilirubin on the vascular wall-endothelium, foam cells, and smooth muscle cells. A number of agonists which stimulate NF-kappaB activity in macrophages concurrently activate NADPH oxidase, which boosts NF-kappaB activation *via* oxidant mechanisms[70-79]. It is therefore reasonable to suspect that HO-1 induction promotes reverse cholesterol transport, in part, by suppressing the up-regulatory impact of NADPH oxidase on NF-kappaB activity. Consistent with this possibility, the ability of advanced glycation end-products to suppress expression of ABCA1 and ABCG1 expression in macrophages is blocked by inhibitors of NADPH oxidase[80,81]. Macrophage NADPH oxidase activity could also be expected to promote foam cell formation by promoting oxidative modification of LDL.

Recent studies indicate that bilirubin's antioxidant effect can be mimicked by phycocyanobilin (PhyCB), a prominent light-absorbing chromophore in cyanobacteria such as spirulina; PhyCB is a metabolite and close structural analog of biliverdin, the precursor of bilirubin[82,83]. Not surprisingly, the only study to date which has evaluated oral administration of spirulina or its PhyCB-bearing protein phycocyanin in a rodent model of atherogenesis (cholesterol-fed hamsters) observed a profound anti-atherosclerotic effect[84]. An anti-inflammatory impact on vascular endothelial cells, coupled with a suppressive impact on intimal foam cell formation, seems likely to account for this observation. The ability of bilirubin and of PhyCB to maintain reverse cholesterol transport in macrophages stimulated with various pro-inflammatory agonists that otherwise would inhibit it, should be assessed.

Salicylate suppresses NF-kappaB activity

Activation of NF-kappaB can often be suppressed more directly with salicylate, a direct inhibitor of inhibit the inhibitor of nuclear factor kappa-B kinase beta (IKK-beta), in clinical doses that do not entail important inhibition of cyclooxygenase, and hence are relatively safe[85-88]. In foam

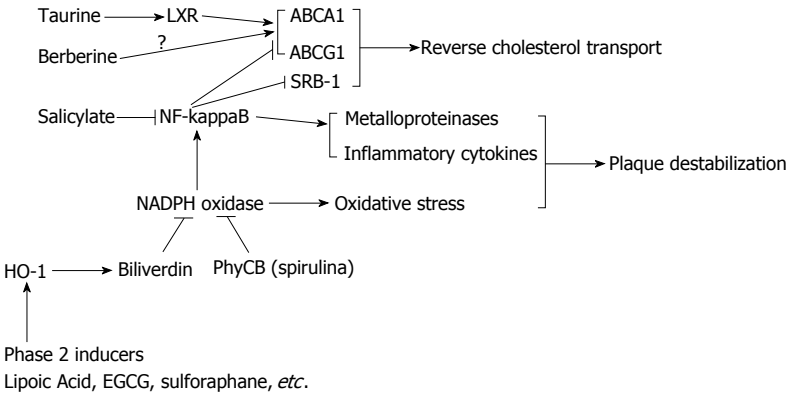

Figure 2 Nutraceutical/drug regulation of foam cell cholesterol transport and plaque stability. LXR: Liver X receptors; HO-1: Heme oxygenase-1; NF-kappaB: Nuclear factor-kappaB; ABCA1: Adenosine triphosphate binding cassette transporter A1; ABCG1: Adenosine triphosphate binding cassette transporter G1; SRB-1: Scavenger receptor class B member 1; NADPH oxidase:: Nicotinamide adenine dinucleotide phosphate oxidase:; EGCG: Epigallocatechin gallate; HO-1: Heme oxygenase-1; PhyCB: Phycocyanobilin.

cells *in vitro*, aspirin (which shares salicylate's capacity to inhibit IKK-beta) was found to suppress the transcriptional activity of NF-kappaB and-likely as a result - boost expression of ABCA1 and SRB-1 while suppressing that of matrix metalloproteinase-9 (a mediator of plaque instability)[25]. In doses of 3-4.5 g daily, salicylate (preferably as salsalate) has been shown to modestly aid glycemic control in diabetics, likely *via* its inhibition of IKK-beta[89-91]; it might be feasible to employ salicylate in comparable doses to promote reverse cholesterol transport and stabilize plaque in patients with atheroma.

Taurine as an LXR agonist

Pharmaceutical LXR agonists can promote reverse cholesterol transport in macrophages, and some of these are being evaluated as potential new drugs for control of atherosclerosis[92-94]. Unfortunately, most such agents also boost hepatic lipogenesis *via* LXR activity, an effect viewed as undesirable[94]. A particularly intriguing recent discovery is that the essential cofactor taurine can act as a weak agonist for LXRalpha; moreover, taurine can enhance the expression of ABCA1and ABCG1, and promote reverse cholesterol transport, in cultured macrophages[95]. Curiously, owing to a countervailing effect, taurine fails to promote hepatic lipogenesis, and is very well tolerated[95]. A number of studies have demonstrated that dietary taurine can impede atherogenesis in rodent models of this disorder[96-103]; this effect is stronger than could be predicted from the modest hypolipidemic effects of taurine in rodents, and it would be of interest to know whether a favorable impact on the function of intimal macrophages plays a role in taurine's anti-atherosclerotic activity. If so, taurine-which appears to have minimal impact on serum lipids in humans-might have clinical utility for preventing and controlling atherosclerosis[104,105]. Of related interest is the possibility that taurine's antioxidant activity may be helpful for preventing LDL modification mediated by hypochlorous acid, a myeloperoxidase product[106]. Moreover, rodent and limited clinical studies suggest that taurine supplementation has the potential to favorably influence platelet stability, blood pressure, and the failing heart[107]. The continuing neglect of this inexpensive and well tolerated nutrient by clinical researchers is mystifying.

AMPK activators

The anti-diabetic nutraceutical berberine, whose clinical efficacy resembles that of metformin in being contingent on activation of AMPK, has exerted anti-atherogenic effects in some but not all rodent models of this disorder[108-110]. The AMPK activator AICAR has been shown to promote reverse cholesterol transport in cultured macrophages by boosting expression of ABCG1[111]. Studies examining the impact of berberine on cultured macrophages report that it can exert a range of effects likely to antagonize foam cell formation and stabilize plaque-inhibiting activation of NADPH oxidase and NF-kappaB, inhibiting MMP-9 expression, and antagonizing cholesterol accumulation by inducing expression of ABCA1 or SRB-1, or suppressing expression of the LOX-1 LDL receptor for oxidized LDL[112-114]. On the other hand, one study found that berberine exposure increased macrophage uptake of modified LDL by increasing expression of the SRA-1 receptor[115]. The impact of metformin on foam cell function appears to have received little or no study. *In vivo*, berberine could also be expected to reduce foam cell formation by decreasing circulating LDL; it boosts hepatocyte expression of the LDL receptor by a mechanism that is complementary to that of statins[116].

CONCLUSION

It should not go unnoted that many of the agents discussed here-notably phase 2 inducers[117-122], PhyCB[123-125], salsalate[126-128], and berberine or metformin[129-134]-have the potential to impede foam cell formation by exerting anti-inflammatory effects on endothelial cells that would be expected to impede monocyte migration across the endothelial barrier into arterial intima. Each of these agents can work in various ways to inhibit endothelial NF-kap-

paB activity, which promotes the adhesion of monocytes to the endothelial surface and their subsequent transmigration (Figure 2)[135-137].

In summation-whereas current pharmaceutical strategies for increasing HDL cholesterol appear to have little clinical utility (aside from those which concurrently lower LDL levels), other clinically feasible measures which directly influence intimal macrophages have the potential to promote reverse cholesterol transport, and hence achieve the primary purpose intended for HDL elevation. These measures include administration of phase 2-inducing nutraceuticals (such as lipoic acid, green tea catechins, and cruciferous isothiocyanates), spirulina or PhyCB, salsalate, taurine, and berberine. These effects are mediated primarily by inhibition of NF-kappaB activation or by LXRalpha agonism. Moreover, most of these agents might be expected to impact foam cell function in other complementary ways that would be clinically useful-suppressing macrophage uptake of modified LDL, and inhibiting macrophage production of inflammatory cytokines and matrix metalloproteinases that could destabilize plaque. And most of them, *via* direct anti-inflammatory effects on vascular endothelium, should also impede foam cell formation by suppressing transendothelial migration of monocytes. These agents evidently merit further evaluation, both in animal models and ultimately clinical trials, as measures for preventing, reversing, and stabilizing arterial plaque. And the fact that most of these agents are nutraceuticals suggests that they might be especially feasible for use in primary prevention.

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REVIEW

Marjolin's ulcers in the post-burned lesions and scars

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Abstract

Marjolin's ulcer (MU) represents malignant degeneration that typically ensues over a period of time in the post-burned lesions and scars or any other chronic wound. This review highlights various facets of the presentation and management of MUs that originate from post-burned lesions. The incidence of MUs in such lesions is reported to be 0.77%-2%. This malignancy characteristically develops in the areas of full thickness skin burns that had been allowed for weeks to months to heal spontaneously by secondary intention, or burn wounds which never healed completely over years and the unstable post-burned scars. In the majority of cases, the MU is a squamous cell carcinoma (SCC). The MUs contribute to an overall 2% of all SCCs and 0.03% of all basal cell carcinomas of the skin. Clinically MUs present in two major morphologic forms. The commoner form is the flat, indurated, ulcerative variety while the less common form is the exophytic papillary variety. Lower limbs represent the most frequently affected body parts. Surgical resection of the primary tumor with 2-4 cm horizontal clearance margin, nodal clearance and radiotherapy constitute the cornerstones of effective oncologic management. Despite best efforts, the overall mortality is reported to be 21%.

Key words: Marjolin's ulcer; Malignant degeneration; Post-burned scars and wounds; Sentinel lymph node dissection; Squamous cell carcinoma; Full thickness skin burns; Healing by secondary intention

Core tip: This review on Marjolin's ulcer (MU) provides a comprehensive account of the key conceptual issues, historic background as well as recent updates on the management of MU developing in the post-burned lesions and scars. New concepts in the management in general and the evolving concepts in the prophylactic nodal treatment such as the sentinel lymph node mapping are highlighted. The epidemiologic and pathophysiologic factors that surround the development of MU in the post-burned lesions are described in vertical depth with subsequent emphasis on the preventive aspects, which certainly hold the key to eradication of this dreadful menace.

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INTRODUCTION

Malignant degeneration of post-burned lesions and scars is an inevitable eventuality, afflicting at least 0.77%-2% of the deep burns that had been allowed to heal by secondary intention, those which never healed completely and the unstable post-burned scars that frequently ulcerate on trivial traumatic insults of daily life activities[1-3]. Celsus AC deserves acknowledgment for his earliest recognition of this phenomenon in the first century AD[4]. Later on in 1828, the French physician Marjolin JN etiologically classified ulcers as those due to "local" causes

and those secondary to "internal" causes, however he couldn't specifically recognize the malignant potential of these lesions[5,6]. Dupuytren[7] in 1839 provided full description of a case of amputation for a cancer in a patient who had suffered a sulfuric acid burn injury. Da Costa[8] in 1903 was the first to coin the term Marjolin's ulcer (MU) to describe malignant degeneration of skin scars particularly the post-burned scars.

Not surprisingly, MUs can emanate from any chronic wound or unhealed scar, however the neglected burn wounds constitute their commonest seats of origin[9-11]. The following review focuses on the epidemiological and clinical details of MU emanating in the aftermath of burn injuries with a view to provide a comprehensive summary of the key conceptual issues as well as recent updates on management for those who happen to be the frontline care providers for the patients with MU.

EPIDEMIOLOGIC CONSIDERATIONS

Whereas 0.77%-2% of the post-burned wounds and scars are reported to undergo malignant degeneration[3], overall the post-burned wounds and scars contribute to 2% of all squamous cell carcinomas (SCCs) and 0.03% of all basal cell carcinomas (BCCs) of the skin[4].

MU is relatively commoner among males than females[12-15]. The exact explanation for this is not yet known, however more frequent initial burn trauma among males as well as their more prolonged exposure to sunlight are some of the possible contributors to this higher frequency of MU among males. No age is immune to MU with individuals from almost all age groups including children being afflicted worldwide[1-5]. MU has been reported among individuals of all races[16-20].

There is usually a prolonged latency period between sustaining initial burn insult and developing MU in the post-burned wounds and scars. There is considerable variation in this lag period reported in the published literature[1,2,13,14], ranging from as short as 6 wk[15] to as prolonged as 70 years[18]. The average latency period to malignant transformation is 35 years[1,21,22]. Based on the latency period, the MUs are subdivided into acute and chronic subtypes. The former type refers to the scar carcinoma that evolves within a year of sustaining burn injury, while the later type refers to those that develop from then on[22]. The acute MU usually develops in association with more superficial burn scars and is often a basal cell carcinoma on histology[23]. The latency period of MU inversely relates to the patient's age at the time of sustaining initial burn insult[24]. The younger the patient is at the time of initial burn insult, the longer the time it takes to undergo the malignant transformation. Contrary to this, the older the patient at the time of burn injury the shorter the lag period and more is the chance of acute MU. Understandably, a newly acquired burn injury in an adult of advancing age is more likely to evolve an acute MU, hence a biopsy of all such lesions (of a duration of > 6 wk) is imperative.

Although all underlying mechanisms of burn injury pose an equal risk for subsequent malignant transformation, MU has been reported more frequently among those who had sustained flame burns as compared to the other burn injury mechanisms such as scalds, electric burn injuries, chemical burns, and contact burns. Except for the BCC where contact is the most frequent underlying burn injury mechanism, the other histological types of MU occur with equal frequency amongst flame, scalds and contact burn injuries[2].

Given the global statistics, the burden of burn injuries is disproportionately shared across the globe with most of its brunt being taken by the developing nations such as India, Bangladesh and Pakistan[25]. These countries together with other south Asian countries like Sri Lanka, Bhutan, Nepal, Maldives, and Afghanistan collectively constitute 20% of the world's population, however they contributed only 1.1% of the total PubMed publications during the 25 years period from 1985-2009[26]. One can easily imagine the magnitude of MU that certainly exists in these burn injury endemic countries but is underreported. These developing nations have recognized limitations of their health care systems where the ideal treatment for acute burn injuries is often not instituted[27]. Also many of the patients in these developing countries present late, when the MU is not amenable to curative resection.

PATHOLOGIC CONSIDERATIONS

Etiopathogenesis of MU

MUs originating from post-burned scars possess certain peculiarities that make them distinct from other cutaneous malignancies. The exact mechanism of how the malignant transformation supervenes the post-burned scars continues to be explored. Many theories have been proposed to provide possible explanations of the mechanisms involved, however no single theory alone can provide a satisfactory answer to all questions that surround this complex process of malignant degeneration.

As per Ewing J's postulates[2,28], MU of post-burned scars would meet the criteria such as evidence of a burn scar, tumour within the boundaries of the scar, no previous tumour in that location, tumour histology being compatible with the cell types found in the skin/scar and presence of a lag period between the burn injury and the tumour development. The post-burned scars is certainly a mutogenic focus with continuous mitotic activity of regeneration and repair being in progress. The same represents the key mechanism that eventually triggers the malignant transformation[10,29,30]. A myriad of factors have been postulated as possible contributors toward the process of malignant transformation. Among these include chronic irritation, repeated trauma, impaired immunologic reactivity of the scar tissue to tumour cells, release of toxins from the unhealthy scar, relative avascularity of the scar tissue, lymphatic obstruction within the scar tissue making it an inaccessible site for the body's natural

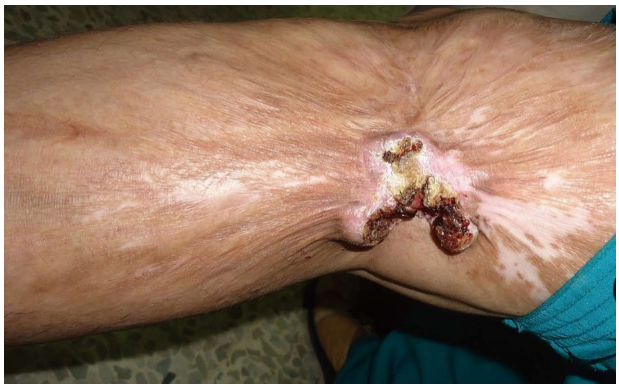

Figure 1 Marjolin's ulcer in the left popliteal fossa region in a 45 years old lady who had sustained flame burn injury at the age of 13. There is characteristic ulcer with everted edges and poorly granulating floor. The surrounding skin shows post-burned sequel. Histopathology confirmed it to be well differentiated squamous cell carcinom.

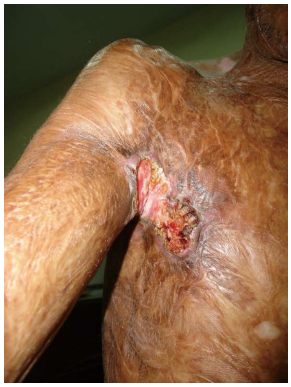

Figure 2 A 46 years male with 3 years history of ulceration and bleeding in right axilla. He had sustained scald burns at the age of 3. Biopsy confirmed it to be squamous cell carcinoma while computed tomography scan revealed metastasis in the axilla as well as chest.

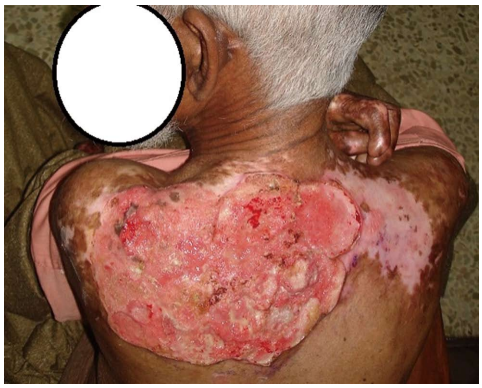

Figure 3 A 63 years old male presented with two years history of slowly progressive ulceration in the post burned white skin on his upper back. He had childhood scald burns at the age of 3 years, and had received burn injury treatment with months of dressings without skin grafting. Multiple biopsies revealed squamous cell carcinoma, while computed tomography scan revealed axillary nodal invasion without chest metastasis. Culture sensitivity revealed Methicillin resistant staphylococcus and pseudomonas aeruginsa.

immunosurveillance[2,10,31,32]. When the full thickness skin loss areas are allowed to heal by secondary intention, there is formation of unstable depigmented substitution tissue which lacks the qualities of normal skin. These unstable depigmented scars have reduced ability to withstand carcinogens[4,32]. Whether genetics or heredity have any contribution to the malignant degeneration of the post-burned scars is not exactly known, however abnormalities in the *p53* gene among these patients have been reported[33,34].

The major risk factors for the development of post-burn MU include healing of full thickness skin burns by secondary intention, non-healing burn wounds, and fragile scars that ulcerate and are easily traumatized[1,2]. The post-burned scars is typically less resistant to injuries, heals poorly especially in body areas such as the joints.

Histopathology of MU

In most cases, the MU is an SCC (71%), followed by BCC (12%), melanoma (6%), sarcoma (5%), squamobasal cell carcinoma (1%), SCC-melanoma (1%) and other rare neoplasms (4%)[2]. A variety of rare tumours may emerge in the post-burned wounds and scars and include fibrosarcoma, liposarcoma, dermatofibrosarcoma protuberans, and mesenchymal tumors[2,3,35,36]. The grade of the MU can be defined as follows: grade Ⅰ: more than 75% of the cells are differentiated; grade Ⅱ: 25%-75% of the cells are differentiated; grade Ⅲ: less than 25% of the cells are differentiated[10]. Grade of the tumour has bearing on the prognosis of MU. In general, the incidence of metastasis increases with increasing grade and so is the worsening of prognosis.

CLINICAL COSIDERATIONS

Clinical presentation

Clinically MU presents in two major morphologic forms[18,37]. The commoner form is the flat, indurated, infiltrative, ulcerative variant while the other less frequent form is the exophytic papillary variety which is generally less severe. The well-differentiated exophytic lesions have a better prognosis than the poorly differentiated, ulcerated and infiltrating forms. Typically the edge of the ulcerated lesion is everted and the floor has poor granulation tissue (Figures 1-9 are representative photographs of some patients with MUs secondary to burn injuries).

A history of a non healing post-burned wound of full thickness skin loss should alert the clinician of the possibility of an MU. It is usually painless. The easy bleeding fragile areas may at times present with unprovoked bleeding, offensive discharge or increasing pain. Superadded infection of the wound may at times be the first clinical presentation[18,38,39].

Anatomic sites affected by MUs

Lower limbs constitute the most frequent site of MUs. The other sites affected in order of reducing frequency include head and neck region (face, scalp, neck), upper limbs and other body parts[2,3,35]. MU has been reported in post burned scars at rare locations such as the nose[40].

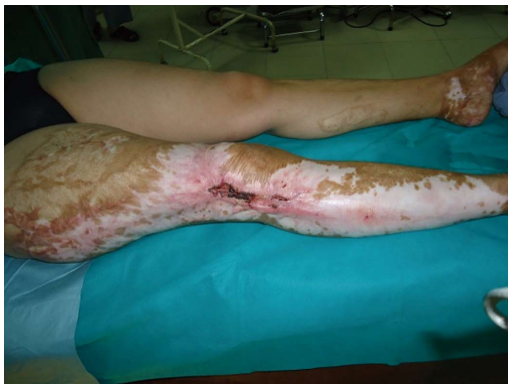

Figure 4 A lady aged 41, had sustained burn injury secondary to lightning 3 years ago. She had her burn injuries managed with months of dressing without skin grafting. Subsequently she had recurrent ulceration with bleeding from the unhealed wounds around the knee. Multiple biopsies of the lesions revealed well differentiated squamous cell carcinoma. The groin nodal basin was negative clinically as well as radiologically.

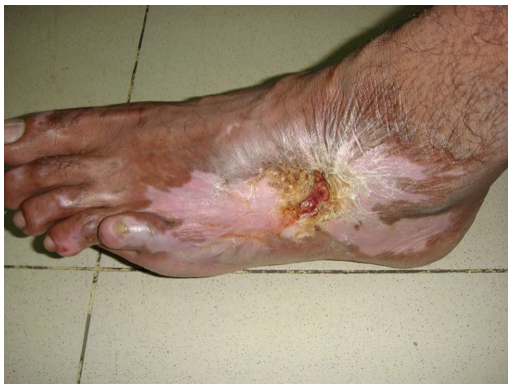

Figure 5 A 41 years male who had sustained flame burn injury to his left foot in childhood at the age of 4. The burn injury was managed with months of dressings and the wound never healed completely. There was history of recurrent bleeding and ulceration on the affected site. Multiple biopsies revealed moderately differentiated squamous cell carcinoma. The groin was clinically node positive.

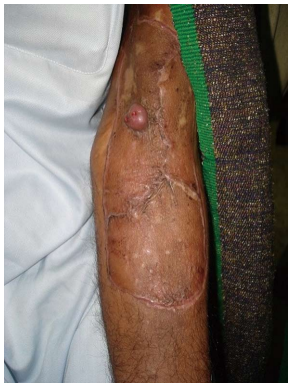

Figure 6 A 36 years male had sustained chemical burn injury to his left cubital fossa 7 years ago. The initial burn injury was managed with dressings and had never healed completely. The patient had undergone wide local excision and split thickness skin grafting for Marjolin's ulcer three months ago. Later he presented with a recurrent nodule which was confirmed as squamous cell carcinom on histopathology while the axilla was node negative clinically.

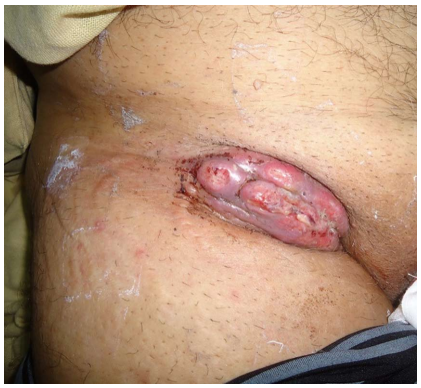

Figure 7 Right groin metastasis secondary to Marjolin's ulcer on the right side of ankle in 57 years male. Metastatic work up revealed ascites and lung metastasis. The patient had sustained flame burn injury to the right ankle at the age of 2 years and was managed with wound dressings without skin grafting.

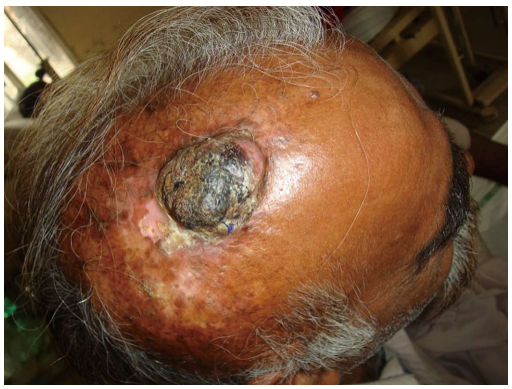

Figure 8 A 47 years male had sustained flame burn injury to his scalp at the age of 3. The initial burn injury was managed with months of dressings without skin grafting. Histopathology confirmed it as well differentiated squamous cell carcinoma. Computed tomography scan head and neck did not show deep structures invasion.

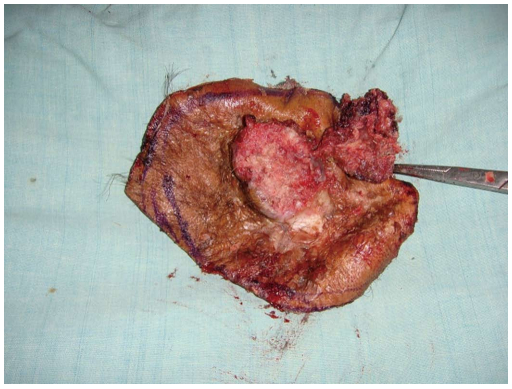

Figure 9 Same patient (as in Figure 8), the resected Marjolin's ulcer with wide local margins.

Lower limbs are the commonest sites of MU primarily owing to their more frequent involvement in burn injury insults involving full thickness skin loss. Additionally these patients often present with lesions around the knee

joints as the joints are frequently moved and recurrent ulcerations commonly ensue and persist without healing.

Diagnosis of MU

The diagnosis of MU is based on the suggestive findings in the patient's history, detailed examination of the ulcer and its draining nodal basin, and the histology of the lesion.

The classic triad of nodule formation, induration, and ulceration at the post-burned scars should prompt a biopsy to confirm the diagnosis[41]. Other clinical signs suggestive of MU include everted or rolled margins, exophytic granulation tissue formation, increasing size, bleeding and regional lymphadenopathy[1-10].

Once the biopsy confirms the diagnosis of MU, determination of the local extent of the lesion and staging comes to the fore. An magnetic resonance imaging (MRI) or computed tomography (CT scan) is performed to determine the local extent of the lesion and invasion of any underlying structures. MRI is certainly the ideal imaging tool for evaluation of the status of the soft-tissues, infiltration of any underlying bone and the involvement of adjacent neurovascular structures[42-44].

The draining lymphatic basin is staged clinically as well as radiologically with either high resolution ultrasonography, MRI or CT scan. Given the aggressive nature of MU, distant metastasis are ruled out with metastatic work up that includes chest CT scan, abdominal ultrasonography and CT scan brain (for lesions on the scalp and face)[1-10].

Metaststic spread of the MU and the stage of the MU disease

By and large, as long as the MU is confined to the scar it shows typically slow growth and is amenable to curative resection. However when the MU breaks free of the scar it metastasises rapidly *via* lymphatic spread[31]. Once broken free of the confines of the primary lesion, an SCC of the MU variety is known to possess greater metastatic potential than the SCC occurring de novo[18]. At presentation, regional lymph nodes are involved in 20%-36% of the patients[2,18,37,45]. Aydoğdu *et al*[18] have reported even higher percentage of patients (66.66%) with involved regional lymph nodes, dura or bone at initial presentation. Distant metastases are reported among 14% of the patients[2]. Although metastatic spread is primarily to the regional lymph nodes, metastasis to organs such as the liver, lung, brain, kidney may also occur[18].

Stage of the MU has implications for the management as well as the prognosis. As is the case with other malignancies, staging is performed by considering the size of the primary lesion (T), lymph node involvement (N), and distant metastasis (M). As yet there is no MU specific TNM classification of the Union for International cancer control, however the TNM classification for SCC is commonly applied to the MU.

TREATMENT OF MU

Role of surgery

Surgery constitutes the mainstay of treatment of the MU. The oncologic clearance entails excision of the primary lesion with a 2-4 cm horizontal clearance margins, and vertical clearance of the un-involved next barrier structure. All the wide local excisions are preferably performed initially with cautery dissection to prevent seeding of the tumor cells and their iatrogenic spread into the blood and lymphatic streams. Additionally a small margin of skin is then excised with a surgical scalpel to ensure good healing[14,20,35]. It is prudent to have the histopathologist onboard when performing such crucial resections to ensure resection of tumour free margins with the help of frozen section studies performed simultaneously with surgery. The defects resulting from MU extirpation are either skin grafted or flap covered. Anecdotally we are now preferring flap coverage of the resultant defects where ever possible and subsequently offer the patients radiotherapy for the tumor bed with the help of radiation oncologist.

As is the established norm of surgical oncology, the clinically or radiologically confirmed involved nodal basins are managed with therapeutic lymph node dissection.

Although there is lack of general consensus regarding management of the clinically negative nodal basins in MU, yet given the aggressive biologic behavior of MU, prophylactic nodal treatment with either elective lymph node dissection or regional nodal irradiation sounds rational[31,37,46-48]. Long term studies are certainly needed to confirm if this aggressive approach offers real benefits in terms of disease free survival or not, as the formal nodal clearance has its own morbidity (particularly lymphedema) attended to the procedure.

The sentinel lymph node dissection (SLND) has been primarily employed for staging the regional nodal basins in malignant melanoma of the limbs, however there is a recent growing recognition of its utility among patients with non-melanoma skin cancers also[49-54]. SLND technique holds the potential to be used more frequently in MU patients as it on one hand will save MU patients from the unnecessary morbidity of formal nodal clearance for negative nodes and on the other hand identify the MU patients who are clinically node negative but have subclinical nodal metastasis.

Role of radiotherapy

Given the aggressive biological behaviour of the MU and the frequent squamous cell histology, radiotherapy finds an important adjunctive role in managing these malignancies. The indications for radiotherapy include: (1) inoperable regional lymph node metastasis; (2) grade 3 lesions with positive lymph nodes after nodal dissection; (3) tumors with a diameter greater than 10 cm and with positive lymph nodes after regional lymph node dissection; (4) grade 3 lesions with a tumor diameter greater than 10 cm and negative lymph nodes after regional lymph dissection; and (5) lesions of the head and neck with positive lymph nodes after regional lymph node dissection[46].

Role of chemotherapy

The exact role of chemotherapy or indications thereof in managing MU are not yet established, however che-

motherapy constitutes part of the aggressive multimodal therapy which is often instituted among patients when surgical extirpation of the MU is not possible because of the unfit patient, presence of distant metastasis, recurrent disease, and patients not consenting for surgery.

The chemotherapy is usually based on 5-Fluorouracil with a combination of cisplatin, methotrexate and bleomycin. It may be in the form of adjuvant or neo adjuvant therapy[18].

PROGNOSIS

Generally speaking, the MU tends to be more aggressive and rapidly spreading as compared to other skin carcinomas of similar histotypes[1,55]. The overall mortality rate of MU is reported to be at least 21%[2]. The survival rates of MU are 52%, 34% and 23% at 5, 10 and 20 years[56].

Poor prognostic clinical features in MU include regional nodal spread, local extension of lesion, lower limb lesions (as these have a greater propensity for nodal involvement), infiltrative variety, primary lesions of $\geqslant$ 2 cm, latency period of $\geqslant$ 5 years, recurrent MU, and the presence of distant metastasis. The poor prognostic indicators on histology include poor differentiation, scarce or absent peritumour T cell infiltration, invasion of reticular dermis or deeper structures, and $\geqslant$ 4 mm vertical thickness of the neoplastic lesion[4,37,46,55-60].

PREVENTION

Although MU constitutes a formidable foe for reconstructive and burns surgeons around the globe, it is still surmountable to primary as well as secondary prevention. Early excision and grafting of deep burns adequately averts all the wound problems that otherwise predispose the post-burned scars to malignant transformation[61]. Moreover even if an initially neglected or mismanaged burn wound presents later with ulceration or frequent wounding, before any malignancy has set in, the choice of excision and grafting of these unstable scars should still be availed. So primary prevention is ensured by provision of adequate surgical care in the acute phase of burn injury management, while secondary prevention can be instituted where a patient had an initial mismanagement but seeks medical advice before MU has established.

CONCLUSION

MU is a largely preventable dreadful menace of considerable morbidity and mortality. Although over the years, significant progress has been made in managing MU, the key to successful eradication lies in prevention by ensuring adequate surgical care (with early excision and grafting) of the deep burns in their acute phase.

There is need for randomized controlled trials and high quality evidence on the not yet fully established aspects of the MU management such as the oncologically safe horizontal clearance margins of resection, prophylactic management of the negative nodal basins and MU specific TNM staging system. All these issues need be adequately addressed by future clinical studies.

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REVIEW

Gallbladder cancer: Clinical and pathological approach

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Abstract

Gallbladder cancer (GBC) shows a marked geographical variation in its incidence. Middle-aged and elderly women are more commonly affected. Risk factors for its development include the presence of gallstones, chronic infection and pancreaticobiliary maljunction. Controversy remains in regard to the theory of carcinogenesis from adenomyomatosis, porcelain gallbladder and adenoma of the gallbladder. The surgical strategy and prognosis after surgery for GBC differ strikingly according to T-stage. Discrimination of favorable cases, particularly T2 or T3 lesions, is useful for the selection of surgical strategies for individual patients. Although many candidate factors predicting disease progression, such as depth of subserosal invasion, horizontal tumor spread, tumor budding, dedifferentiation, Ki-67 labeling index, p53 nuclear expression, CD8+ tumor-infiltrating lymphocytes, mitotic counts, Laminin-5-gamma-2 chain, hypoxia-inducible factor-1a, cyclooxygenase-2 and the Hedgehog signaling pathway have been investigated, useful prognostic makers or factors have not been established. As GBC is often discovered incidentally after routine cholecystectomy and accurate preoperative diagnosis is difficult, close mutual cooperation between surgeons and pathologists is essential for developing a rational surgical strategy for GBC.

Key words: Gallbladder cancer; Surgical strategy; Pathology; Prognostic factors

Core tip: This review has documented the basic knowledge and surgical strategies for gallbladder cancer (GBC) based on the clinical and pathological data from previous studies. Discrimination of favorable cases, particularly T2 or T3 lesions, is useful for the selection of surgical strategies for individual patients. As GBC is often discovered incidentally after routine cholecystectomy and accurate preoperative diagnosis is difficult, close mutual cooperation between surgeons and pathologists is essential for developing a rational surgical strategy for GBC.

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EPIDEMIOLOGY

Gallbladder cancer (GBC) has a distinctly higher incidence in certain demographic groups and areas. Women are affected three times more often than men, and the vast majority of patients with GBC are older than 40 years of age. A high incidence has been reported in women in countries such as Chile, Poland, India, Israel, Pakistan, Ecuador, South Korea and Japan, whereas GBC is considered a rare neoplasm in most Western countries and the United States[1-4].

RISK FACTORS

Gallstones are a well-known risk factor for GBC[5,6]. It has been reported that a large stone size of more than 3

cm, a family history of GBC, and prolonged cholelithiasis are potential risk factors for GBC[7-9]. These factors could be used in the decision making when performing a cholecystectomy for asymptomatic gallstones. However, no definite evidence of a direct causal relationship between gallstones and gallbladder cancer has been presented and biases of other risk factors remain unsolved problems[10]. The composition and mutagenicity of gallstones have previously been studied with inconclusive results[11]. A prospective study of 123 consecutive patients with asymptomatic gallstones who were followed-up for 10 years or longer revealed no cases of GBC[12].

Historically, an association between calcified gallbladder (porcelain gallbladder) and GBC has been reported[13,14], although there has also been a report suggesting that porcelain gallbladder is not associated with GBC[15]. Therefore, the causal association of porcelain gallbladder and GBC remains controversial.

Pancreaticobiliary maljunction (PBM) is considered an established risk factor for biliary tract cancers involving GBC[16,17], especially in relatively young female patients without gallbladder stones[18,19]. It is generally accepted that pancreatic juice reflux into the biliary tract due to PBM plays a pathogenic role in biliary tract cancers. K-ras mutations are more common in biliary tract carcinomas associated with PBM[20].

Adenomyomatosis of the gallbladder has not been considered to have malignant potential; however, several reports have suggested that gallbladder cancer may originate from adenomyomatosis[21-24] or have insisted that segmental-type adenomyomatosis shows an increased risk of progression to gallbladder cancer[25]. Recently, a study showed that gross features of adenomyomatosis were found in approximately a quarter of gallbladders resected under the diagnosis of GBC[26]. Although the magnitude of risk for GBC in patients with adenomyomatosis remains unclear, studies suggesting a correlation between adenomyomatosis and GBC have been gradually accumulating.

In regard to the development of GBC, several theories have been proposed, including the adenoma-carcinoma sequence and dysplasia-carcinoma sequence theories[27-30]. However, recently reported articles have suggested that the vast majority of adenomas and/or polypoid lesions do not become GBC[31,32]. Therefore, the validity of the adenoma-carcinoma sequence theory remains controversial. Other risk factors recently receiving attention include bacterial infections. Although the supporting evidence for an association is weak, Salmonella[33,34] and Helicobacter species[35] would be prime candidates for a bacterial predisposition to GBC.

SURVIVAL AND GENERAL SURGICAL STRATEGIES ACCORDING TO T-STAGE

The surgical strategy for GBC depends on the extent of the disease, particularly the T-stage from the TNM classification[36]. The prognosis after surgery for GBC differs strikingly according to T-stage. Five-year survival rates after surgery for T1, T2, T3, and T4 stage tumors in 73 cases at our institution were 100%, 78.3%, 16.7%, and 25.0%, respectively[37]. The survival rates of our series were consistent with the results of other previous reports[38-41].

The survival of patients with T1a lesions (invasion restricted to the lamina propria) is particularly good, and lymph node metastasis is extremely rare in such cases. Simple cholecystectomy with or without lymphadenectomy is thus widely accepted as sufficient for T1a lesions[38,42,43]. Intraoperative perforation of the gallbladder and positive surgical margins around the cystic duct are important prognostic factors in surgery for T1a lesions[44].

Survival rates and strategies for T1b (invasion to the muscle layer) remain somewhat controversial. Several studies have reported LN metastasis in up to 20% of cases, with recurrence rates of 30%-60% following simple cholecystectomy[45-51]. In addition, distinguishing T1b lesions from T2 lesions pre- or intraoperatively is usually difficult. Therefore, it seems reasonable to perform cholecystectomy combined with lymphadenectomy with or without liver resection in patients with pre- or intraoperative presumption of T1b GBC. However, T1b GBC is often discovered after laparoscopic cholecystectomy for presumed benign disease. In our T1b series (n = 8), lymph vessel invasion was found only one case and no LN metastases or recurrences were observed, and thus additional operation of lymphadenectomy was not always needed in patients with T1b lesions diagnosed after routine cholecystectomy. However, caution is required in that the pathological work for resected specimens must be performed intensively with sections from the whole specimen, in order to minimize the possibility that a more invasive site or findings of residual lesion remain present in the resected specimen.

The prognosis for T2 (invasion to the subserosal layer) lesions varies widely, with the 5-year survival rates being approximately 20%-70% after simple cholecystectomy, compared to 60%-100% after radical surgery[37,43,52-55]. The surgical strategy for T2 lesions thus remains unclear. The conventional opinion is that patients with T2 lesions should be treated using radical cholecystectomy, including en bloc resection of the adjacent liver as well as regional lymphadenectomy with or without extrahepatic bile duct resection (BDR)[38,56]. Pathologists should pay close attention in order not to misdiagnose a T1a tumor with spreading into the Rokitansky-Aschoff sinuses (RAS) as a T2 tumor with invasion of the subserosal layer.

The prognosis is poor for most patients with T3 tumor, which shows perforation of the serosa and/or direct invasion of the liver and/or one other adjacent organ or structure. Surgery for T3 lesions is only appropriate if there is potential to achieve a curative resection. T3 lesions require hepatic resection with regional lymphadenectomy at a minimum. This can include major hepatectomy if there is extensive spreading into the liver or major vascular structures. In addition, if direct invasion

into an adjacent organ (duodenum, pancreas, stomach or colon) is suspected, *en bloc* resection would be required for curative resection[56]. Because of the high degree of surgical stress involved, the utility of aggressive surgery with extended resection for T3 lesions is often debated in clinical practice, and case-by-case selection is required with due consideration for the patient's performance status, complications, and age.

Chemotherapy or palliation is typically appropriate for T4 disease (tumor invading into the main portal vein or two or more extrahepatic organs or structures), except in rare cases where *en bloc* resection of multiple organs is possible. This is because of the unfortunate prognosis and difficulty of achieving curative resection. Unresectability discovered at the time of laparotomy may be treated with bypass surgery to relieve symptoms related to biliary obstruction. Cases identified preoperatively as unresectable may be considered for percutaneous biliary drainage or endoscopic stenting to address biliary obstruction[38].

CLINICAL CHALLENGES FOR T2 AND T3 TUMORS

As mentioned above, T2 and T3 tumors are indications for radical surgery. However, which type of radical surgery is most appropriate remains unclear. Although regional lymphadenectomy is widely accepted as necessary at a minimum, the efficacy of extended resection, such as hepatectomy, BDR or pancreatoduodenectomy (PD), remains controversial. BDR is usually necessary in cases with biliary infiltration associated with perineural invasion and complete lymphadenectomy and eradication of the connective tissue around the common bile duct[57-60]. In terms of hepatectomy for GBC, the resection may vary from a small wedge resection near the gallbladder fossa to an extended right hepatectomy. The appropriateness of segment 4a+5 (S4a+5) hepatectomy for advanced GBC is supported by the drainage of the cystic vein into anatomic Couinaud's segments IVa and V and the frequency of liver metastases in this anatomical area[61]. The results of our previous study support the use of S4a+5 hepatectomy combined with BDR and regional lymphadenectomy for the treatment of T2 or T3 GBC[37]. However, additional PD achieved no significant difference in survival in patients with T2 or T3 GBC. Indications for PD in these cases were obvious duodenal or pancreatic invasion, or infiltrating LN metastases at the retro-pancreatic head portion[37].

ATTEMPTS TO DISCRIMINATE FAVORABLE CASES IN T2 GBC

T2 GBC shows a wide variety of tumor spread. Some T2 tumors show none of the histological invasive factors of LN metastasis, lymphatic or venous invasion, but others show prominent LN metastases, along with venous, lymphatic, or perineural invasion, resulting in poor prognosis. This issue indicates that patients with T2 GBC can be allocated to a favorable prognosis group or a poor prognosis group. If discrimination of favorable cases is appropriately performed, patients with favorable prognosis could be spared excessive extended radical surgery. To identify cases with a favorable prognosis, subset analyses of patients with T2 tumor according to certain pathological criteria have been performed. Several studies, including one from our institution, reported the usefulness of discrimination of T2 GBC according to the depth of subserosal invasion and horizontal tumor spread in the subserosal layer with or without a scoring system[62-65]. Our study focused on the phenomena of dedifferentiation (DD) and tumor budding (BD) demonstrated a significant prognostic impact of both BD and DD in patients with T2 tumor[66].

INVESTIGATION OF USEFUL PROGNOSTIC MARKERS AND FACTORS

Although prognostic markers of GBC have been widely investigated, promising prognostic makers or factors have not yet been established. Ki-67 labeling index (LI), p53 nuclear expression, CD8+ tumor-infiltrating lymphocytes (TIL) and mitotic count (MC) have classically been considered as candidates for prognostic markers. However, several previous studies have reported no prognostic impact of p53 overexpression in GBC[67-71], although reports of poor prognosis in cases with p53 overexpression are also available in the literature[72,73]. A previous study showed that patients with GBC and high Ki-67 exhibited worse postoperative prognosis than those with low Ki-67[40], although here again, several previous studies also reported that Ki-67 LI of cancer cells was not correlated with patient survival[68,70,71]. Therefore, the prognostic impact of p53 overexpression and Ki-67 LI in GBC remains controversial. In regard to CD8+ TIL, there is little evidence that this is a prognostic indicator. Only one study has reported that CD8+ TIL was correlated with prolonged survival in a univariate analysis[74]. A study from our institution concerning Ki-67 LI, p53 nuclear expression, CD8+ TIL and MC status in a series of 101 GBC patients indicated that only MC reflected the prognosis of GBC. In that study, MC showed a particularly strong prognostic impact in patients with T3 tumor and was identified as an independent prognostic factor in multivariate analyses that included the N and M factors of the TNM system of classification[75]. It is difficult to distinguish the extension of carcinoma in situ (CIS) from invasive carcinoma along the RAS. Laminin-5-gamma-2 chain, which is expressed in various types of invasive carcinoma, can be detected in the invasive fronts of invasive GBC, but is not expressed in CIS with extension along the RAS[76]. The results indicate that laminin-5-gamma-2 chain is a useful marker of determining the T factor. Heparanase and its transcriptional factor, hypoxia-inducible factor-1a, contribute to the invasion and meta-

static potentials, and are correlated with poor survival in GBC[77]. Cyclooxygenase-2, a well-known oxidative stress factor expressed in invasive fronts, is also related with poor prognosis of GBC[78]. The Hedgehog signaling pathway is considered to be a potential therapeutic target for various cancers, and hedgehog signaling factor Gli1 may be involved in the invasive phenotype through the matrix metalloproteinases[79]. Other, more recently reported factors that may have a prognostic impact in GBC based on multivariate analyses include transmembrane protease/serine 4[80], loss of microRNA-335[81], aldehyde dehydrogenase-1A3 overexpression, and decreased glutathione peroxidase-3 expression[82].

PATHOLOGICAL EXAMINATION FOR OPTIMAL SURGERY

Preoperative diagnosis using an imaging study is very important for selecting the optimal surgery according to T-stage. However, preoperative diagnosis of the T-stage in T1 or T2 GBC is not easy, and it is especially difficult in GBC arising in the gallbladder concomitant with adenomyomatosis, despite advances in medical imaging[83]. As a result, stage T1 or T2 GBC is often discovered incidentally after routine cholecystectomy. In such cases, pathological evaluations of prognostic factors using entire tumor sections can be used to determine the need for additional extended radical surgery. Intraoperative histological examination is usually performed during surgery for lesions preoperatively diagnosed as "suspected GBC" or "possible T1 or T2 GBC". In such cases, the resected specimen from cholecystectomy with or without en bloc liver resection (S4a+5 or liver bed) is submitted for intraoperative histological examination. However, diagnosis of the depth of invasion from frozen sections of GBC is a difficult task, and care must be taken to avoid obstructing the pathological diagnosis of formalin-fixed specimens when the tumor lesion is small.

CONCLUSION

This review has documented the basic knowledge and surgical strategies for GBC based on clinical and pathological data from previous studies. Discrimination of favorable cases, particularly T2 or T3 lesions, is useful for the selection of surgical strategies for individual patients. To establish useful prognostic markers or factors, further accumulation of studies is needed. As GBC is often discovered incidentally after routine cholecystectomy and definite preoperative diagnosis is often difficult, close cooperation between surgeons and pathologists is essential for developing a rational surgical strategy for GBC.

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MINIREVIEWS

Endoscopic retrograde cholangiopancreatography-related perforation: Management and prevention

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Abstract

Endoscopic retrograde cholangiopancreatography (ERCP) is a procedure that can result in serious complications, and thus should be handled by a skilled endoscopist to minimize the risk of complications and to enhance the success rate. The incidence of ERCP-related complications is 5%-10%, most commonly involving post-ERCP pancreatitis and clinically significant post-endoscopic sphincterotomy bleeding. Although ERCP-related perforation has a relatively lower incidence of 0.14%-1.6%, this complication is associated with a high mortality rate of 4.2%-29.6%. A classification of perforation type based on the instrument that caused the perforation was recently described that we postulated could affect the implementation of perforation management. In the present article, an algorithm for management and prevention of ERCP-related perforations is proposed that is based on the perforation type and delay of diagnosis. Available evidence demonstrates that a delayed diagnosis and/or treatment of perforation results in a poorer prognosis, and thus should be at the forefront of procedural consideration. Furthermore, this review provides steps and recommendations from the pre-procedural stage through the post-procedural evaluation with consideration of contributing factors in order to minimize ERCP-related complication risk and improve patient outcome. To avoid perforation, endoscopists must evaluate the risks related to the individual patient and the procedure and perform the procedure gently. Once a perforation occurs, immediate diagnosis and early management are key factors to minimize mortality.

Key words: Endoscopic retrograde cholangiopancreatography; Endoscopic retrograde cholangiopancreatography; Perforation; Prevention; Management; Classification

Core tip: Endoscopic retrograde cholangiopancreatography (ERCP)-related perforation, is a rare complication with a high morbidity and mortality. An immediate diagnosis and early management of ERCP-related perforation are key factors to minimize mortality. In this review article, the authors shared their experiences and propose an algorithm to avoid perforation and for management once a perforation occurs.

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INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP)

Table 1 Previous classifications of endoscopic retrograde cholangiopancreatography-related perforations

	According to Stapfer *et al*[12]	According to Howard *et al*[13]
Type Ⅰ	Lateral or medial wall perforation	Duodenal perforation remote from the papilla
Type Ⅱ	Perivaterian injury	Periampullary retroperitoneal perforation
Type Ⅲ	Distal bile duct injury related to wire/basket instrumentation	Guidewire perforation
Type Ⅳ	Retroperitoneal air alone	None

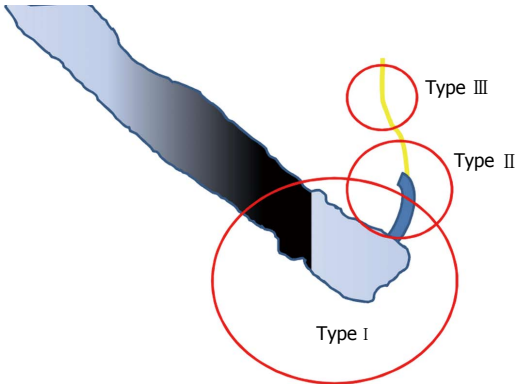

Figure 1 Classification of endoscopic retrograde cholangiopancreatography-related perforation (based on Kim *et al*[14]).

is a procedure that should be performed by a skilled endoscopist to maximize the success rate and minimize complications, which occur in 5%-10% of cases[1,2]. The most common complications are post-ERCP pancreatitis (1.0%-3.5% of cases)[3-5] and clinically significant post-endoscopic sphincterotomy bleeding (0.1%-2.0% incidence)[6-9]. ERCP-related perforations are relatively uncommon (incidence of 0.14%-1.6%), though associated with a high mortality rate of 4.2%-29.6%[10,11]. Whereas delayed recognition and treatment of this complication contribute to fatality, early detection and management confer a better prognosis. This review focuses on the classification, early diagnosis, management, and prevention of ERCP-related perforations.

CLASSIFICATIONS OF ERCP-RELATED PERFORATION

ERCP-related perforations were previously classified into 3-4 types, regardless of the site of perforation[12,13] (Table 1). In 2011, Kim *et al*[14] proposed a new classification based on the instrument that caused the perforation. A type I perforation results from the scope itself, which always causes a large perforation with heavy contamination (Figure 1). A type Ⅱ perforation can be caused by the needle-knife used during the sphincterotomy, from the ERCP cannula or the sphincterotome, which cause a moderate-sized hole with less contamination. Type Ⅲ refers to a perforation caused by the guidewire and is associated with the least risk of contamination. A review of cases presented by Kim *et al*[14] and an additional 62 cases from Kwon *et al*[15] that were reevaluated using the new classification, revealed that 80% of patients with type I perforations (20/25 cases) required surgery, compared to 19% (7/37) of those with type Ⅱ perforations. We therefore postulated that this classification could be used to direct the management of patients with perforations.

EARLY RECOGNITION OF PERFORATIONS

Most type I perforations are immediately recognized by the endoscopist during the procedure. Large perforations can be definitively indicated by visualization of intra-abdominal organs, whereas smaller perforations may show only yellowish tissue of intra/retroperitoneal fat or by bleeding from other sites such as a lateral wall of the duodenum (Figure 2). If the endoscopist who performed the procedure suspects a perforation, evaluation of the pneumoperitoneum by fluoroscopy can be very helpful (Figure 3A). Some experts also recommend changing the duodenoscope to an end-view type for better mucosal visualization.

Type Ⅱs are typically retroperitoneal perforations that occur during treatment interventions. In some cases, the endoscopist may recognize that an injury is "too deep" with increased bleeding, abnormal positioning of the guidewire, skin emphysema, and a clear kidney shadow. When this type of perforation is suspected, it should be confirmed by fluoroscopy, which can help identify unexplainable air in the retroperitoneum (Figure 3B), or by contrast injection, which will show contrast leakage into the retroperitoneal cavity (Figure 3C).

Type Ⅲ perforationscan be recognized by an unusual guidewire position. If recognized in a timely manner, this type of perforation can be adequately managed by simply pulling the guidewire back into a safe position. However, the perforation can become a type Ⅱ if the endoscopist does not recognize the perforation and continues pushing the instrument further. Up to 20%-30% of type Ⅱ and Ⅲ perforations are not immediately diagnosed, and patients may report abdominal pain and discomfort, which are followed by fever and leukocytosis. These perforations can be confirmed by a computed scan of the abdomen, which reveals retroperitoneal air (Figure 4) or fluid collection[16].

MANAGEMENT

General principles of management for ERCP-related perforation include a *nil per os* directive, *iv* fluid resuscitation, administration of antibiotics to decrease intra/retroperitoneal contamination or fluid collection, pneumoperitoneal decompression, and, if possible, endoscopic closure. In some cases, surgical consultation may also be needed to control sepsis and repair the perforation, depending on the site and degree of leakage, the patient's condition, and mechanism of injury. Radiologic interventions were

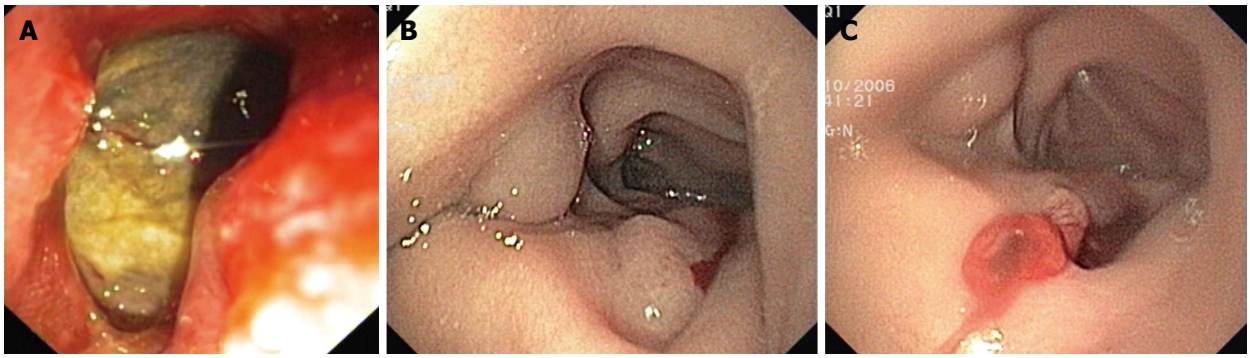

Figure 2 Endoscopic visualization of perforations. A: Image of yellowish tissue in the retroperitoneum; B and C: Bleeding from a lateral wall of the duodenum.

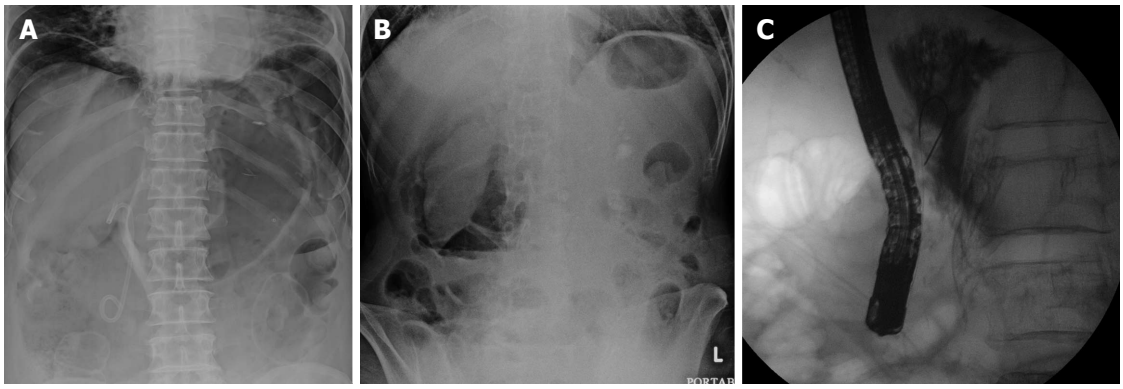

Figure 3 Fluoroscopy showing pneumoperitoneum (A), retroperitoneal air (B) and leakage of contrast media into the retroperitoneal cavity (C). The kidney outline (clear region on the right side of the image) showing retroperitoneal air.

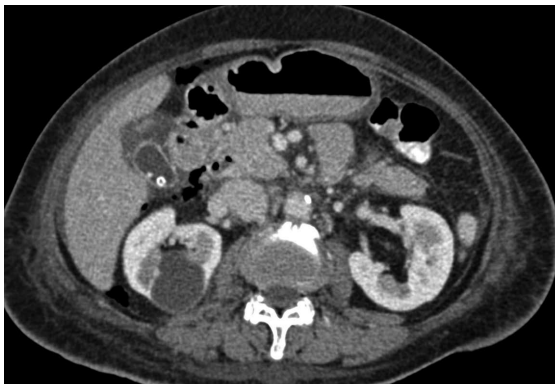

Figure 4 Computed tomography showing retroperitoneal air.

found to be useful in some particular cases, particularly those with localized retroperitoneal fluid collection and without clinical sign of peritonitis[17]. However, the management of ERCP perforation in that particular study was based upon whether the perforation was diagnosed immediately after it occurred, or delayed by at least 24 h after the procedure (recognized by abnormal vital or abdominal signs).

Immediate diagnosis

Type I perforations, which are typically 1.0-1.3 cm wide, have been successfully treated during ERCP with hemostatic clips either through the gastroscope(with or without cap assistance)[18,19] or with an endoloop[20], or with over-the-scope clips[21]. Contrast injections should be administered to rule out leakage, as 30%-60% of type I perforations fail endoscopic closure and require surgery. Patients who undergo immediate surgical correction typically remain in the hospital for 12-16 d. Prompt diagnosis is crucial, as evidenced by a study of Miller *et al*[11] that reported two deaths out of five cases involving type I perforations, resulting from delayed diagnosis in one case, and delayed operation in the other, and six deaths from delayed surgical repair of type Ⅱ perforations that were initially managed with a conservative treatment strategy[11]. Thus, some surgeons recommend immediate diagnosis and early surgery for ERCP-related perforations[22-24]. In our endoscopic center (within a tertiary care, university-based hospital), 4082 ERCP procedures were performed between January 2009 and June 2013, with a post-ERCP perforation rate of 0.29% (n = 10 type Ⅰ; n =2 type Ⅱ perforation cases). All of the patients (65-91 years old) were diagnosed during or immediately upon finishing the ERCP procedures. Eighty-three percent of these cases underwent surgical correction while only 17% received conservative treatment, with no deaths.

Mao *et al*[25] reported on nine cases of ERCP-related perforation (mostly type Ⅱ), six of which were managed conservatively with hospital stays ranging from 4 to 75 d. Subcutaneous emphysema was a significant clinical sign

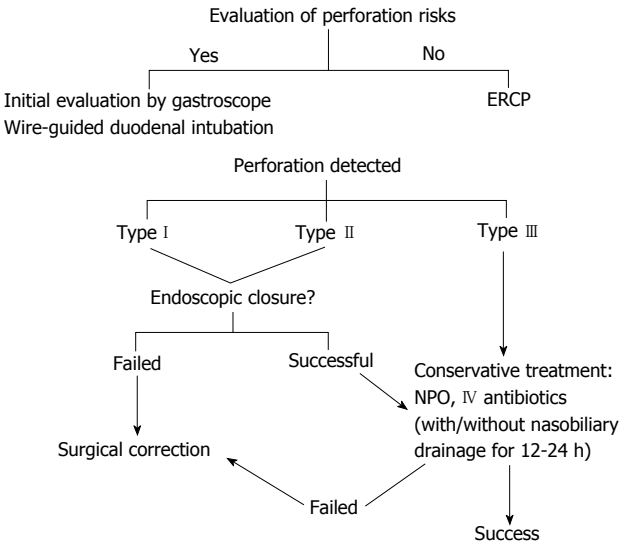

Figure 5 Algorithm for prevention and management of endoscopic retrograde cholangiopancreatography-related perforations.

found in seven of the nine patients. To aid in the success of conservative treatments, which included antibiotics, endoscopic treatment (when possible), intensive observation and follow-up imaging, nasobiliary and gastrointestinal drainage was recommended to reduce the leakage of digestive juices. However, very high success rates were also reported with conservative treatment (with or without nasobiliary drainage) by Park *et al*[26] and Vezakis *et al*[27], using fully covered self-expandable metal stents for closure of perforated sites at the ampullary region.

The majority of type Ⅲ perforations involve only mild contrast leakage or pneumoperitoneum without contrast leakage, and can be managed conservatively, requiring hospitalization for only 5-6 d[11,24]. Genzlinger *et al*[28] found that up to 29% of patients who underwent ERCP showed pneumoperitoneum on plain radiography without clinical significance. However, further investigation is recommended in patients who have pneumoperitoneum and clinical signs of infection.

The surgical indications in the studies mentioned here differed from recommendations stated by Stapfer *et al*[12], which include large extravasation of contrast, fluid collection in the peritoneal or retroperitoneal space on follow-up computed tomography scan, massive subcutaneous emphysema, or retained choledocholithiasis. Our recommendation is to perform salvage surgery in patients with: (1) failure of initial endoscopic closure, especially type Ⅰ or type Ⅱ perforations; (2) no improvement in clinical signs of sepsis, or follow-up abdominal signs worsening within 12-24 h after successful endoscopic closure (type Ⅰ) or conservative management (type Ⅱ); and (3) retained instruments or choledocholithiasis requiring surgical removal.

Delayed diagnosis

The prognosis is generally worse for any type of perforation with a delayed diagnosis, and most patients develop clinical signs of peritonitis and sepsis within 1-5 d after the procedure[26-28]. It is important to note that abdominal signs might be relatively benign within the first few hours, even for type Ⅰ perforations, however the presentation of peritoneal signs as a late finding is related to a poor clinical outcome[11]. Surgical drainage and correction is recommended in cases of delayed type Ⅱ diagnosis with clinical sepsis[11,21,26,27]. However, most patients (50%-90%) having type Ⅱ perforations with minimal leakage or type Ⅲ perforations will respond to conservative treatment.

Table 2 Factors associated with increased risk of post-endoscopic retrograde cholangiopancreatography perforation (from Enns *et al*[24])

Factors	Results of multivariate analysis [OR (95%CI)]
Dilated common bile duct	2.32 (1.02-5.03)
Sphincter of oddi dysfunction	3.20 (1.64-8.94)
Longer duration of procedure	1.02 (1.00-1.04)
Biliary stricture dilatation	7.29 (1.84-28.11)
Performance of sphincterotomy	6.94 (2.43-19.77)

PREVENTION OF ERCP-RELATED PERFORATION

There are several factors that have been associated with an increased risk for ERCP-related perforation (Table 2). Nonetheless, there are steps that can be taken to avoid causing ERCP-related perforations, beginning before the procedure, and continuing through the follow-up stage (Figure 5).

Pre-procedural evaluation

Some patients have a higher risk of perforation because of surgically altered anatomy. Such patients should undergo "endoscopic scanning" using an end-view gastroscope before starting ERCP. In cases of failure to pass the end-view scope owing to anastomotic stricture or too much resistance, continuation with the ERCP procedure should first be discussed with the patients and their families. If the endoscopist decides to follow through with the procedure, a duodenoscope should be inserted in an "over-the-guidewire" fashion to minimize duodenal wall injury. When narrowing of the anastomosis site is encountered, balloon dilatation over the guidewire can be helpful prior to duodenoscope insertion. However, this is not recommended for cases with malignant strictures, but rather duodenal stenting with a self-expandable metal stent followed by ERCP in the subsequent weeks is more appropriate.

During bile duct cannulation and intervention

There are several comments and recommendations concerning the procedure that should be kept in mind: (1) Patients with periampullary diverticula have a higher risk of perforation, especially from sphincterotomy. Therefore, the endoscopist must be very careful during this

process. A balloon sphincteroplasty is recommended in such cases, rather than endoscopic sphincterotomy; (2) Insertion of any ERCP instruments into the bile duct should be performed in an "over-the-guidewire" fashion to prevent a "false track." Furthermore, the endoscopist should perform ERCP as gently as possible to minimize tissue injury; (3) Endoscopic sphincterotomy should be carried out in the suggested direction of 11 to 12 o' clock for the common bile duct and 12 to 2 o'clock for pancreatic sphincterotomy. Over-bowing of the sphincterotome should be avoided to prevent a "zipper cut," and cutting should not go beyond the second fold above the papilla. Adequate knowledge and intensive observation of ampulla anatomy are essential for all endoscopists who perform ERCP; (4) Needle-knife sphincterotomy should be performed only by experienced endoscopists. Those who are less experienced should recognize their limitations and be responsible enough to request assistance; and (5) Dilatation of the ampulla increases the risk of perforation. Therefore, the endoscopist should consider the length of sphincterotomy or the size of balloon sphincteroplasty suitable for the objective of the maneuver, such as limited or no sphincterotomy for stenting, dilating the ampulla no more than the size of the common bile duct above, and an appropriately sized sphincterotomy depending on the size of the stone.

During fluoroscopy

The endoscopist should observe the patient's abdominal signs and perform fluoroscopy intermittently during the ERCP procedure. A diagnosis can be immediately made upon recognition of an abnormal guidewire position, extravasation of contrast, or pneumoperitoneum, which can allow for prompt treatment. Furthermore, a fluoroscopic abdominal scan should be performed after any difficult procedure to identify possible complications.

Post-procedural care

Patients should be encouraged to promptly report any abdominal symptoms and should be watched for abnormal clinical signs after the ERCP procedure. The ward staff should be notified to maintain special observation of patients with difficult cases for early detection of possible complications.

CONCLUSION

As ERCP-related perforations are a serious complication with a high mortality rate, endoscopists should perform the procedure with caution. To avoid perforation, endoscopists must evaluate the risks related to the patient and the procedure and perform the procedure with care. Once a perforation occurs, immediate diagnosis and early management are key factors to minimize mortality.

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MINIREVIEWS

Primary intestinal lymphangiectasia: Minireview

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Key words: Primary idiopathic intestinal lymphangiectasia; Mucosa-submucosa; Protein loosing enteropathy; Double balloon endoscopy; Biopsy

Core tip: Waldmann's disease is an unusual primary idiopathic intestinal lymphangiectasia, which results in protein loosing enteropathy. Recently, double balloon endoscopy and biopsy in combination is an effective diagnostic tool to hit the correct diagnosis to avoid untoward complications related to disease and treatment due to misdiagnosis. Thus, the clinician should keep in mind this rare condition as a differential diagnosis of oedema.

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Abstract

Primary idiopathic intestinal lymphangiectasia is an unusual disease featured by the presence of dilated lymphatic channels which are located in the mucosa, submucosa or subserosa leading to protein loosing enteropathy.Most often affected were children and generally diagnosed before third year of life but may be rarely seen in adults too. Bilateral pitting oedema of lower limb is the main clinical manifestation mimicking the systemic disease and posing a real diagnostic dilemma to the clinicians to differentiate it from other common systemic diseases like Congestive cardiac failure, Nephrotic Syndrome, Protein Energy Malnutrition, *etc.* Diagnosis can be made on capsule endoscopy which can localise the lesion but unable to take biopsy samples. Thus, recently double-balloon enteroscopy and biopsy in combination can be used as an effective diagnostic tool to hit the correct diagnosis. Patients respond dramatically to diet constituting low long chain triglycerides and high protein content with supplements of medium chain triglyceride. So early diagnosis is important to prevent untoward complications related to disease or treatment for the sake of accurate pathological diagnosis.

INTRODUCTION

Primary Intestinal lymphangiectasia (PIL) was originally described in 1961 by Waldmann *et al*[1]. It is an unusual cause of protein losing enteropathy either due to congenital malformation or obstruction of lymphatics of intestine[2]. Lymphangectasia is characterised by dilated and proliferating lymphatic channels located in mucosa, submucosa or subserosa leading to protein loosing enteropathy and loss of lymph into gut resulting in to hypoproteinemia, hypogammaglobulinemia, hypoalbuminemia and lymphopenia[3-5]. Peripheral oedema usually symmetrical (lower limb oedema) is the main clinical feature posing a real diagnostic dilemma to the clinicians to differentiate it from other common conditions like congestive cardiac failure, nephrotic syndrome, protein energy malnutrition, *etc*[3]. Other symptoms are ascites, pleural effusion, weight loss and abdominal pain, diarrhoea with increased faecal loss of protein and fat with increased serum levels of α1-antitrypsin[2,5]. Diagnosis is defined by endoscopic evaluation and confirmed on histopathologi-

cal evaluation of biopsy of small intestine[1].

Now a day double balloon endoscopy and biopsy is the mainstay to arrive at correct diagnosis.

EPIDEMOLOGY

The worldwide incidence and prevalence of PIL is not known[2,6]. After 1961, as per available literature less than 200 cases were reported[7,8]. Very few familial forms are reported[1,2,9]. There is no specific predilection for sex and race[6]. Most commonly, it has been seen in children and majority of the cases were diagnosed at or before 3 years of age but can be seen in adults also[5,6].

PATHOPHYSIOLOGY

Waldmann's disease is also called as exudative enteropathy. The pathogenesis is not clear. The proposed hypothetical theories for pathogenesis are.

Lymphatic obstruction theory

The basic cause for protein loss in PIL is poorly understood although lymphatic channel malformation/lymphatic hypoplasia leads to obstruction in lymph flow with resultant increase in intraluminal pressure in lymphatic channels[6,10,11]. This, increased intraluminal pressure will cause dilatation of the submucosal,subserosal lymphatic vessels in the intestine finally leading to the rupture of the cystically dilated channels and leading to discharge of the lymph into the bowel lumen[6,12]. Thus, net result is hypoalbuminemia, hypogammaglobinemia and lymphopenia.

Genetic theory: There are mutations in genes that regulate the process of lymphogenesis[5]. Multiple genes, *e.g.*, vascular endothelial growth factor receptor 3, prospero-related homeobox-transcriptional factor, forkhead transcriptional factor and *SOX18* play vital role in lymphogenesis[13]. Mutation of the *CCBE1* gene has been identified as a cause of intestinal lymphangiectasia in Hennekam syndrome.

CLINICAL PRESENATION

Age-PIL is mainly seen in paediatric age group (usually before 3 years of age) and young adults but may be diagnosed in adults too[2,14-16].

Oedema is the main clinical manifestation. The patient may present with ascites, pleural effusion and pericarditis. Other symptoms are lymphedema, abdominal pain, fatigue, moderate diarrhoea, weight loss and deficiency of fat soluble vitamins may also be present.

Oedema is of pitting type and usually symmetrical in distribution involving lower limb. Sometimes severe oedema involving face, scrotum or vagina[5].

Rarely lymphedema have been described which is elicited by "stemmer's sign" and it is difficult to differentiate from other systemic causes of oedema[2,5]. Sonographic evidence of fetal ascites had also been reported[2,5,17].

Non-specific clinical features such as fatigue, nausea, vomiting, abdominal pain, weight loss, failure to thrive, moderate diarrhoea with faecal loss of fat along with increased faecal loss of protein, leading to rise in alfa-1-antitrypsin levels and there is deficiency of fat soluble vitamins[5,18].

Hypocalcemia-patients can also develop hypocalcemia and tetany due to vitamin D deficiency[2,6,19]. A case of digital clubbing in PIL was reported[20]. Osteomalacia and osteoporosis associated with PIL was reported[21].

Rare Associations-An association of PIL with celiac sprue was described[5,22]. PIL has been reported as a rare cause of lower gastrointestinal bleeding. In addition iron deficiency may occur[5,18]. Recently proved association with angiodysplasia leading to occult blood loss in PIL[5,23,24].

A case of intestinal lymphangiectasia presenting as abdominal mass was reported[2,5,25]. Recurrent haemolytic uraemic syndrome has been described in association with intestinal lymphangiectasia[2,26]. Patients with PIL are prone to develop infections due to lymphopenia and hypogammaglobulinemia[18,27].

Only two cases of disseminated cryptococcal meningitis and osteomyelitis in-patient with lymphangectasia have been reported in the literature so far[28-30]. Recently another case of cryptococcal meningitis as primary manifestation in a patient with intestinal lymphangiectasia has been reported[30]. Lymphoma may complicate the long term outcome of PIL patients[5,31].

PIL may exist as a part of a genetic syndromes, *i.e.*, Noonan, Von Recklinghausen, Hennekam and Yellow nail syndrome[2,5,14]. Finally, an association with autoimmune poly glandular disease type 1 has been described[5,32,33]. Recently a case of intestinal lymphangiectasia in a patient with infantile systemic hyalinosis syndrome has been reported[34].

DIAGNOSTIC EVALUATION

Now days, diagnosis of Intestinal lymphangiectasia is based on characteristic findings during a double-balloon enteroscopy with further confirmation by histopathological examination of corresponding biopsy specimens[6,35]. To confirm the primary nature of waldmanns disease we must first exclude the secondary causes of intestinal lymphangiectasia[6].

Capsule endoscopy

Capsule endoscopy provides complete examination of small bowel mucosa thus can evaluate the extent of lymphangiectasia[36,37]. However, the drawback of capsular endoscopy is the inability to obtain biopsies. So recently double balloon enteroscopy is evolved.

Double balloon enteroscopy

In view of the drawback of capsular endoscopy, its inability to obtain biopsies, double balloon enteroscopy was

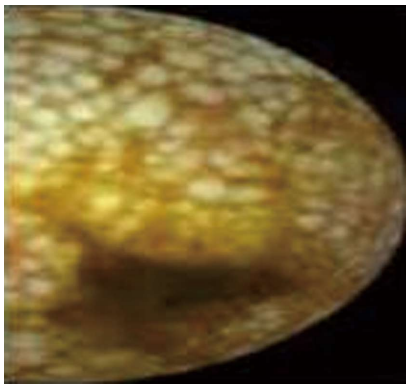

Figure 1 Snow flake appearance.

evolved which allowed obtaining biopsies from lesions detected by capsular endoscopy[35,36].

Endoscopy reveals scattered white spots, which have been described as a characteristic snowflake appearance, (Figure 1) overlying the small intestinal mucosa[4,38].

On endoscopy

Histopathological examination of biopsies shows dilated lymphatic vessels in mucosa, submucosa and serosa with polyclonal plasma cells confirming the intestinal lymphangiectasia (Figures 2).

Although various methods are available to investigate PIL, careful histopathological examination of biopsies is must to confirm the diagnosis. Various methods to investigate PIL are ^{99}Tc-HSA, 24 h stool alfa-1-antitrypsin clearance, lymphoscintigraphy, ultrasonography (USG), computed tomography (CT) scan, magnetic resonance imaging (MRI).

^{99}Technetium-labelled scintigraphy is useful to arrive at the diagnosis of PIL. Due to high cost and infectious risk, it has replaced with alfa-1-antitrypsin method[2,39].

Lymphoscintigraphy identifies abnormality in lymphatic tree but at present is not a routine method for PIL diagnosis[2,40,41].

On radiographic barium studies, thickened irregular mucosal fold with tiny nodules representing dilated lymphatic suggest the intestinal lymphangiectasia[42].

Non-invasive modalities

Imaging with USG/CT scan has shown diffuse thickening of small bowel wall because of engorgement of villi that contain the dilated lymphatic channels[5,43]. CT scan may show "halo sign". A halo sign that consist of thickened, low-attenuation inner ring representing dilated lymphatics and higher attenuation outer ring, which consist of muscularis propria and serosa[43-45]. Nonenhanced, fluid-sensitive MRI may show bright signal intensity, which corresponds to lymphangiectasia in the mucosa[42,44].

Other laboratory investigations

PIL is associated with many laboratory findings which include decreased albumin and total protein levels[2,5,45].

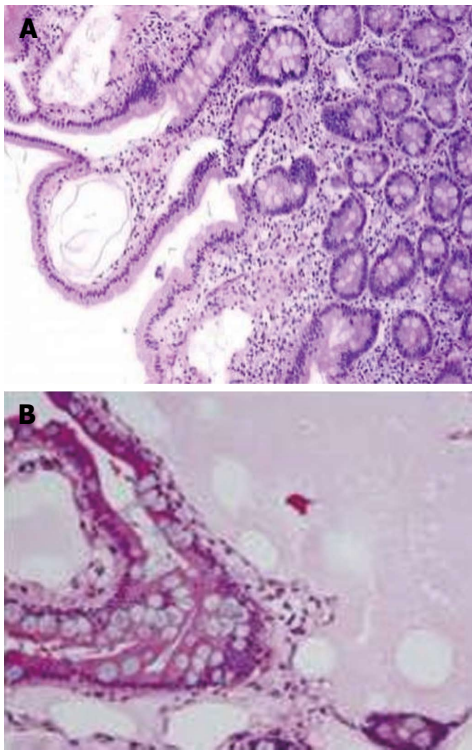

Figure 2 Histopathological examination of biopsies. A: Dilated lymphatics in mucosa and submucosa; B: 40 ×; showing dilated lymphatic channels filled with lymph.

In Addition diminished immunoglobulins IgG, IgA and IgM suggesting B cell depletion and reduced numbers of $CD4^+$ cells as naive $CD45RA^+$ lymphocytes and $CD45RO^+CD8^+$T cells reflecting T-cell depletion seen[2,5,46,47].

Finally, a recent report indicates there is failure of compensatory mechanism of production of T lymphocytes by the thymus to overcome the enteric loss of T lymphocytes leading to lymphopenia associated with lymphangiectasia[5,48].

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of PIL is large and involves many conditions producing protein-losinggastroenteropathy. Much closer differential are those, which involve protein loss associated with impaired intestinal lymphatic drainage. Such conditions include cardiac causes like congestive cardiac failure, constrictive pericarditis and cardiomyopathy[49-52]. Surgical repair of complex congenital heart disease (such as the Fontan procedure for a functional single ventricle), other conditions like lymphenteric fistula[10,53], Whipple's disease[54], Crohn's disease[55], sarcoidosis[56], human immunodeficiency virus-related enteropathy[57], intestinal tuberculosis[58], radiation and/or chemotherapy with retroperitoneal fibrosis[59] and portal hypertension or hepatic venous outflow obstruction after liver transplantation and in congenital hepatic fibrosis due to phosphomannose isomerase deficiency[60].

TREATMENT

The principal treatment for PIL is diet rich in protein, low in fat with supplementation of medium chain triglyceride. Medium chain triglyceride is directly absorbed in portal venous circulation by passing the intestinal lymphatics, thus provides the energy and lessens lacteal engorgement and lymph loss. A low fat diet reduces lymphatic flow and pressure preventing the lacteal dilation and lymph leakage resulting from their rupture. In some, reversal of clinical and biochemical changes has been seen with this dietary modification. In most patients, dietary treatment is permanently needed. This is found to be more effective in children than adults. In some cases, total parenteral nutrition is needed. Supportive therapy includes albumin infusion and paracentesis.

In patients, not responding to such therapy other options may be used after or in combination with dietary modification. These are octreotide, antiplasmin,tranexemic acid, vitamin D supplementation and surgical resection of segmental or localised intestinal lymphangiectasia[8,11,61].

To conclude PIL is an idiopathic protein loosing enteropathy either due to genetic defect or due to lymphatic obstruction. Careful endoscopic examination and meticulous histopathological evaluation is mandatory to arrive at correct pathological diagnosis to decide the proper treatment plan. One should keep in mind this rare condition as a differential diagnosis of oedema.

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CASE CONTROL STUDY

Comparison of semilunar coronally repositioned flap with gingival massaging using an Ayurvedic product (irimedadi taila) in the treatment of class- I gingival recession: A clinical study

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Abstract

AIM: To study the comparison in terms of root coverage the effect of gingival massaging using an ayurvedic product and semilunar coronally repositioned flap (SCRF) to assess the treatment outcomes in the management of Miller's class I gingival recessions over a-6 mo period.

METHODS: The present study comprised of total of 90 sites of Miller's class- I gingival recessions in the maxillary anteriors, the sites were divided into three groups each comprising 30 sites, Group I -were treated by massaging using a Placebo (Ghee) Group II-were treated by massaging using an ayurvedic product (irimedadi taila). Group III-were treated by SCRF. Clinical parameters assessed included recession height, recession width, probing pocket depth, width of attached gingiva, clinical attachment level and thickness of keratinized tissue. Clinical recordings were performed at baseline and 6 mo later. The results were analyzed to determine improvements in the clinical parameters. The comparison was done using Wilcoxon signed rank test. The overall differences in the clinical improvements between the three groups was done using Kruskal-Wallis test. The probability value (*P*-value) of less than 0.01 was considered as statistically significant.

RESULTS: Non-surgical periodontal therapy and gingival massaging improves facial gingival recessions and prevents further progression of mucogingival defects. Root coverage was achieved in both the experimental groups. The SCRF group proved to be superior in terms of all the clinical parameters.

CONCLUSION: Root coverage is significantly better with semilunar coronally repositioned flap compared with the gingival massaging technique in the treatment of shallow maxillary Miller class I gingival recession defects.

Key words: Gingival recession; Semilunar flaps; Gingi-

val massaging; Non-surgical

Core tip: Gingival recession is the migration of the gingival margin apical to the cemento-enamel junction. A variety of surgical procedures have been described for the correction and management of mucogngival deformities and defects, with a variable degree of success. However, it should be emphasized that shallow recessions are subject to progression, but there are no case reports or controlled clinical trials to compare the effects of gingival massaging in the treatment of gingival recessions. The aim of our study was to compare in terms of root coverage the effect of gingival massaging using an ayurvedic product and semilunar coronally repositioned flap to assess the treatment outcomes in the management of Miller's class I gingival recessions over a 6 mo period.

Mishra AK, Kumathalli K, Sridhar R, Maru R, Mangal B, Kedia S, Shrihatti R. Comparison of semilunar coronally repositioned flap with gingival massaging using an Ayurvedic product (irimedadi taila) in the treatment of class- I gingival recession: A clinical study. *World J Clin Cases* 2014; 2(10): 534-540 Available from: URL: http://www.wjgnet.com/2307-8960/full/v2/i10/534.htm DOI: http://dx.doi.org/10.12998/wjcc.v2.i10.534

INTRODUCTION

Gingival recession is defined as the migration of the marginal tissue apical to the cemento-enamel junction (CEJ). Its occurrence is common and its prevalence increases with age. The recession of the gingiva resultant of attachment loss and root exposure may be associated with one or more tooth surfaces and lead to clinical problems such as dentinal hypersensitivity, root caries, cervical root abrasions and diminished cosmetic appeal[1,2].

Miller[3] (1985) in his classification of recession has described class I recession as marginal tissue recession that does not extend up to the mucogingival junction and not accompanied by any loss of bone or soft tissue in the interdental area. Very often, it is the most coronal millimeter of recession which is visible when the patient smiles. Thus even a marginal gingival recession, can account for major aesthetic problems and persistent dentinal hypersensitivity[4]. In order to combat these clinical problems, various treatment modalities have been proposed that have in due course evolved based on the knowledge of healing of the gingiva and the attachment system.

Aimetti *et al*[5] (2005) proposed non-surgical therapy *viz* periodic scaling and polishing for the treatment of shallow gingival recession. It was hypothesized that reduction of root convexity and elimination of microbial toxins from the root surface by scaling and root planing promotes creeping attachment of gingival margin. Tarnow[6] (1986) introduced the semilunar coronally repositioned flap (SCRF) procedure as one of the surgical approaches to treat Class I gingival recessions. It entails coronal advancement of a semilunar flap without any tension or disturbance to the subjacent tissues. The flap is stabilized in the desirable position under gravity, hence a sutureless technique.

Gingival massaging an age old practice is said to increase capillary gingival microcirculation, thereby increasing oxygen sufficiency, gingival fibroblastic proliferation, keratinization of oral and sulcuar epithelium, and formation of dense bundles of collagenous connective tissue all of which are attributable to creeping attachment[5,7]. Gingival massaging is carried out using various agents that aid lubrication as well as medication of the tissues. IrimedadiTaila an ayurvedicproductis said to have been used for centuries by many communities in the Middle East and North Africa as a massaging agent[8]. It consists mainly of Acacia arabica a complex mixture of the calcium, magnesium and potassium salts of Arabic acid. Its antiplaque properties are said to create right conditions for gingiva to recapture its biologic dimensions[5,8].

However no much of information is available upon an electronic or manual search concerning the effects of gingival massaging in the treatment of gingival recessions. There is a dearth of information as to by what exact mechanisms the non-surgical approaches help root coverage and to what extent if at all. Given that many patients are skeptical about surgical treatment, scaling/root planing followed by gingival massaging with an agent could be a better option provided their benefits are proved. This study is one such attempt to evaluate the effect of gingival massaging using an ayurvedic product in comparison with SCRF to assess the treatment outcomes in the management of Miller's class I gingival recessions. Hence the aim of the present study was to assess the efficacy of SCRF and gingival massaging (by placebo and IrimedadiTaila) in terms of root coverage in Miller's Class I recession, with respect to clinical parameters [Recession height (RH), recession width (RW), probing depth (PD), clinical attachment level (CAL), thickness of keratinized tissue (TKT) and width of attached gingiva]. Further, intergroup which comparisons of treatment outcomes to assess advantages or disadvantages of one technique over the other was also assessed.

MATERIALS AND METHODS

A total of 90 sites of Miller's class- I gingival recessions on labial aspects of maxillary anteriors, were selected from the patients reporting to the out-patient department of Periodontics, Modern Dental College and Research Centre, Indore. Teeth associated with inadequate width of attached gingiva, caries/restorations were excluded. Pregnant females and individuals afflicted by systemic disease, tobacco/alcohol abuse, parafunctional habits were excluded from the study. Individuals who were already on the regimen of gingival massage or had undergone mucogingival surgery were dropped out of the study.

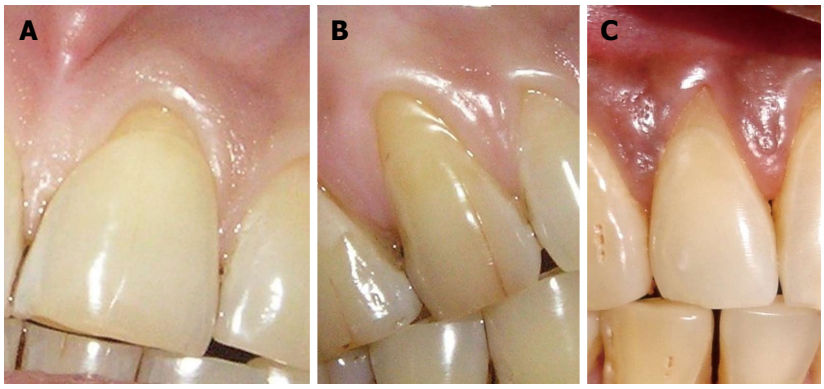

Figure 1 Miller's class- I gingival recession. A: Miller's class- I gingival recession with 11; B: Miller's class- I gingival recession with 13; C: Miller's class- I gingival recession with 12.

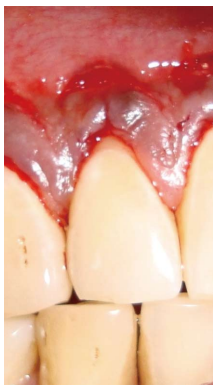

Figure 2 Coronally repositioned flap with 12.

The study protocol was approved by the ethical committee of Modern Dental College and Research Centre, Indore and study sites were randomly allocated to three different study groups after obtaining an informed consent. Group I (control group) comprised of 30 sites that were treated by massaging with placebo (clarified butter). Group Ⅱ (test group) included 30 sites that were treated by massaging with an ayurvdicoil (IrimedadiTaila). Group Ⅲ (test group) included 30 sites to be treated by SCRF[6].

Clinical evaluation

The sites were subjected to clinical assessments as follows: RH was measured as the distance from the CEJ to the gingival margin (GM), calculated in millimeters. RW was recorded as horizontal width of CEJ. Probing pocket depth was measured as the distance from the GM to the bottom of the gingival sulcus. CAL was calculated as recession height and probing depth (RH + PD). Width of attached gingiva was recorded as the distance between the free gingival groove and the MGJ. All the readings were recorded using a manual pressure-sensitive periodontal probe DB 764 R, (Aesculap, Tuttlingen, Germany) calibrated at a force of 0.2 N. Readings for TKT was obtained by penetrating the tissue with a 15 number endodontic spreader under lidocaine 15 gm spray and subsequently the penetration depth was measured with an electronic caliper of 0.01 mm resolution. The gingival thickness was assessed at midbuccal level in the attached gingiva, half way between the mucogingival junction and free gingival groove[9]. These readings were recorded preoperatively as well as 6 mo post-operatively and then subjected to statistical analysis.

Clinical procedures

After a detailed examination and diagnosis, scrupulous oral prophylaxis was accomplished to ensure that local etiological factors are eliminated; followed by oral care instructions and patient motivation towards compliance. Patients belonging to group I (Figure 1A) and group Ⅱ (Figure 1B) were trained to master the technique of gingival massaging with either of the agents as the case may be. The technique involved massaging their gums with finger three times daily for two minutes in the concerned area and then rinse away with water. Patients were instructed to comply with gingival massaging for the span of 6 mo, after which to report back for post-operative evaluation. Sites belonging to group Ⅲ (Figure 1C) were treated surgically by semilunar coronally repositioned flap (Figure 2) as recommended by Tarnow[6], followed by suitable postoperative surgical care and oral care instructions. The patients were recalled at 1, 3 and 6 mo post operatively. One and 3 mo postoperative recall visits were utilized for reinforcement of oral care regimen and massaging techniques, wherein, readings at 6 mo postoperative follow up only were utilized for statistical analysis.

Statistical analysis

Shapiro-Wilk test was applied to test for the Normalcy of the data. The parameters significantly differed from normal distribution, and therefore, all the comparisons were tabulated using Non-Parametric tests, *i.e.*, wilcoxon signed rank test, Kruskal Wallis and Mann Whitney *U* test. All comparisons were done using SPSS Statistical Software Package Version 10.0 and probability value (*P*-value) of less than 0.01 was considered as statistically significant.

RESULTS

Gingival massaging with placebo (Ghee) (Figure 3A)

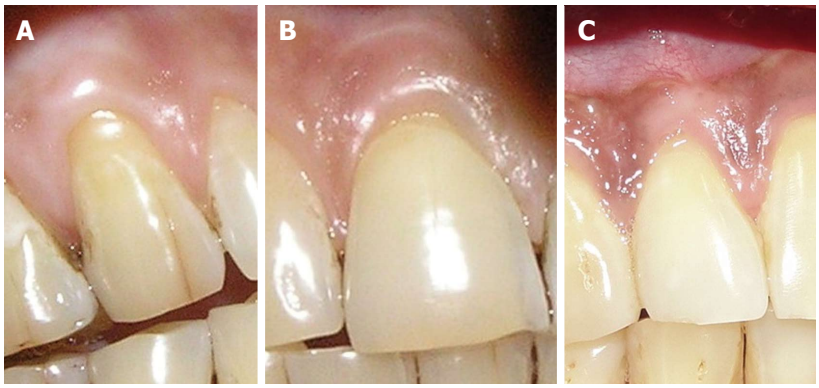

Figure 3 Six months post-operative view. A: Six months post-operative view of 12; B: Six months post-operative view of 11; C: Six months post-operative view of 13.

Table 1 Evaluation of clinical parameters from pre-operative to 6 mo post-operative period for group Ⅰ-gingival massaging using a placebo (Clarified butter) (n = 30)

Clinical parameters	Baseline (mean ± SD)	6 mo (mean ± SD)	*P*-value (significance)
Recession height	1.7 ± 0.65	1.5 ± 0.51	0.034
Recession width	3.8 ± 0.66	3.57 ± 0.63	0.100
Probing pocket depth	1.9 ± 0.40	1.5 ± 0.51	0.001[b] (S)
Clinical attachment level	3.5 ± 0.82	3 ± 0.87	0.002[b] (S)
Thickness of keratinized tissue	0.84 ± 0.18	0.97 ± 0.21	< 0.001[b] (S)
Width of attached gingiva	2.53 ± 0.57	2.8 ± 0.55	0.011

[b]P < 0.01, clinical parameters from pre-operative *vs* 6 mo post-operative period. S: Significant.

Table 2 Evaluation of clinical parameters from pre-operative to 6 mo post-operative period for group-Ⅱ gingival massaging using an ayurvedic oil (iremedadi taila) (n = 30)

Clinical parameters	Baseline (mean ± SD)	6 mo (mean ± SD)	*P*-value (significance)
Recession height	1.77 ± 0.63	1.27 ± 0.58	0.003[b] (S)
Recession width	3.3 ± 0.46	2.23 ± 0.43	< 0.001[b] (S)
Probing pocket depth	1.47 ± 0.50	1.63 ± 0.49	0.096 (NS)
Clinical attachment level	3.23 ± 0.82	2.9 ± 0.76	0.064 (NS)
Thickness of keratinized tissue	0.85 ± 0.17	1.07 ± 0.19	< 0.001[b] (S)
Width of attached gingiva	2.37 ± 0.56	2.9 ± 0.66	0.001[b] (S)

[b]P < 0.01, clinical parameters from pre-operative *vs* 6 mo post-operative period. S: Significant; NS: Non significant.

Table 3 Evaluation of clinical parameters from pre-operative to 6 mo post-operative period for Group-Ⅲ semilunar coronally repositioned flap (n = 30)

Clinical parameters	Baseline (mean ± SD)	6 mo (mean ± SD)	*P*-value (significance)
Recession height	2.33 ± 0.55	0.57 ± 0.50	< 0.001[b] (S)
Recession width	3.33 ± 0.76	1.1 ± 0.66	< 0.001[b] (S)
Probing pocket depth	1.57 ± 0.50	1.33 ± 0.48	0.071
Clinical attachment level	3.87 ± 0.73	1.9 ± 0.66	< 0.001[b] (S)
Thickness of keratinized tissue	0.97 ± 0.19	1.38 ± 0.23	< 0.001[b] (S)
Width of attached gingiva	2.63 ± 0.71	3.37 ± 0.56	0.001 (S)

[b]P < 0.01, clinical parameters from pre-operative *vs* 6 mo post-operative period. S: Significant.

resulted in a statistically significant reduction in probing pocket depth (P = 0.001), gain in clinical attachment level (P = 0.002) and increase in thickness of keratinized tissue (P < 0.001). The clinical improvements with respect to recession height, recession width and width of attached gingiva were statistically nonsignificant (Table 1). Gingival massaging using an ayurvedic product (IrimedadiTaila) (Figure 3B), on the contrary resulted in to statistically significant reductions in recession height and recession width (P < 0.003 and P < 0.001 respectively); also a significant gain in thickness of keratinized tissue and width of attached gingiva (P < 0.001) and (P = 0.001) respectively. But reductions in probing pocket depth and clinical attachment level were statistically nonsignificant (Table 2). Sites treated by semilunar coronally repositioned flap (Figure 3C) exhibited highly significant improvements with respect to all the clinical parameters except probing pocket depth (Table 3).

Intergroup comparisons (Table 4) *via* Kruskal Wallis test aided in the determination of advantages of one technique over the other. Sites treated by SCRF exhibited highly significant improvements with respect to recession height (P < 0.001), recession width (P < 0.001), CAL (P < 0.001), thickness of keratinized tissue (P < 0.004) as compared to those treated by gingival massaging with the ayurvedic substance. However no significant difference was observed in relation to probing pocket depth between the groups (Table 5). Sites treated by SCRF had similar advantages when compared with sites treated by gingival massaging using a placebo (Table 6).

When compared between gingival massaging with an ayurvedic substance and placebo, former showed remarkable improvements only with respect to recession width (P < 0.001), probing pocket depth (P < 0.001) and thickness of keratinized tissue (P < 0.001). However there was no significant difference with respect to CAL, recession height and width of keratinized gingiva (Table 7).

DISCUSSION

Gingival recession is a common condition whose extent and prevalence has been noted to increase with age. It

Table 4 Comparison of clinical parameters from pre-operative to 6 mo post-operative period between the three groups using Kruskal Wallis test[1]

Clinical parameter	Group Ⅰ	Group Ⅱ	Group Ⅲ	χ^2	*P*-value (significance)
Recession height	0.2 ± 0.48	0.5 ± 0.78	1.77 ± 0.73	47.56	< 0.001[b] (S)
Recession width	0.23 ± 0.77	1.07 ± 0.58	2.23 ± 0.82	51.28	< 0.001[b] (S)
Probing pocket depth	0.4 ± 0.49	-0.17 ± 0.53	0.23 ± 0.68	13.29	< 0.001[b] (S)
Clinical attachment level	0.5 ± 0.73	0.33 ± 0.96	1.97 ± 0.81	42.01	< 0.001[b] (S)
Thickness of keratinized tissue	-0.13 ± 0.12	-0.23 ± 0.15	-0.41 ± 0.27	22.86	< 0.001[b] (S)
Width of attached gingiva	-0.27 ± 0.52	- 0.53 ± 0.68	-0.73 ± 0.98	7.03	0.03 (NS)

[1]Degree of freedom: 2. [b]*P* < 0.01, clinical parameters from pre-operative *vs* 6 mo post-operative period. S: Significant; NS: Non significant.

Table 5 Comparison of clinical parameters between group 3 *vs* group 2 using Mann-Whitney *U* test

Clinical parameter	*Z* value	*P* value (significance)
Recession height	-5.064	< 0.001[b] (S)
Recession width	-4.996	< 0.001[b] (S)
Probing pocket depth	-2.455	0.014
Clinical attachment level	-5.390	< 0.001[b] (S)
Thickness of keratinized tissue	-2.841	0.004 (S)
Width of attached gingiva		

[b]*P* < 0.01, clinical parameters of group 3 *vs* group 2. S: Significant.

Table 6 Comparison of clinical parameters between group 3 *vs* group 1 using Mann-Whitney *U* test

Clinical parameter	*Z* value	*P* value (significance)
Recession height	-6.366	< 0.001[b] (S)
Recession width	-6.141	< 0.001[b] (S)
Probing pocket depth	-0.855	0.392
Clinical attachment level	-5.682	< 0.001[b] (S)
Thickness of keratinized tissue	-4.441	< 0.001[b] (S)
Width of attached gingiva		

[b]*P* < 0.01, clinical parameters of group 3 *vs* group 1. S: Significant.

Table 7 Comparison of clinical parameters between group 2 *vs* group 1 using Mann-Whitney *U* test

Clinical parameter	*Z* value	*P* value (significance)
Recession height	-1.772	0.076
Recession Width	-4.330	< 0.001[b] (S)
Probing pocket depth	-3.734	< 0.001[b] (S)
Clinical attachment level	-1.494	0.135
Thickness of keratinized tissue	-2.579	0.01[b] (S)
Width of attached gingiva		

[b]*P* < 0.01, clinical parameters of group 2 *vs* group 1. S: Significant.

has been estimated that 50% of the population has one or more sites with 1mm or more of such root exposure. This prevalence rate increases to 88% for individuals above 65 years of age[10].

Given the high prevalence rate of gingival recession defects among the general population, it is imperative that dental practitioners have an understanding of the etiology, complications and treatment options of the condition. Even in this era, when sophisticated techniques and materials are available, non-invasive approaches to treatment of recessions remain in practice with paramount importance. This study was carried out to assess the viability of surgical and non-surgical techniques for management of gingival recessions.

Numerous studies reported the efficacy and predictability of proposed surgical techniques. Several factors govern the selection of a surgical technique to treat recessed teeth such as the anatomy of the defect site, such as the size of the recession, width of keratinized tissue adjacent to the defect, dimensions of the interdental soft tissue, and the depth of the vestibule or the presence of frenula and evidence based predictability of various procedures[11-13]. The SCRF surgical procedure is easy to perform and highly reproducible in shallow recession defects (class I) when gingival augmentation is not needed. Case reports[2,14,15] have shown a high success rate for this procedure.

Gingival massaging, an age old traditional oral hygiene practice which has been used for centuries by many communities have two quite separate effects on gingival keratinization. One, the direct effect of frictional stimulation leading to an increased mitotic rate and greater thickness of both the malpighian region and the stratum corneum of the gingival epithelium and the other, an indirect effect of the more efficient removal of dental plaque which leads to a reduction in inflammation, allows the gingival epithelium to express more fully its keratinizing potential[16]. The other effects of gingival massaging is said to increase capillary gingival microcirculation[17,18] thereby increasing oxygen sufficiency[19], gingival fibroblastic proliferation[7], and formation of dense bundles of collagenous connective tissue[20]. However, only one case is available in the literature[21] showing successful root coverage at multiple sites resulting from gingival massage. To our knowledge, there have been no long term controlled studies to provide outcome assessment data with regard to predictability and percentage of recession coverage by gingival massaging using ayurvedicoil. Hence this study was undertaken to compare benefits of gingival massaging using ayurvedic oil with those of SCRF technique in the treatment of class I recession.

This study witnessed that, although SCRF technique proved to be far superior, the clinical outcomes of gingival massaging by an ayurvedic oil (IrimedadiTaila) were

almost close to it (Tables 1, 2 and 3). Both the procedures produced statistically significant improvement with relation to recession height, recession width, thickness of keratinized tissue and width of attached gingiva, implying that both the methods are equivalent in root coverage and increasing width and thickness of attached gingiva. The significant root coverage achieved with of SCRF technique in the present study is almost in accordance with numerous other studies with only slight differences[12,22-26]. Some of those studies with higher success in root coverage have notably used additional methods of flap fixation such as sutures/adhesives or microsurgical techniques that may have enhanced clinical outcomes. Thus the differences in surgical protocols and measurement methods adapted in the study could be held responsible for variations in the results. The significant increase in width of attached gingiva with SCRF technique could be attributed to the granulation tissue that fills the semilunar area. Other studies too have presented similar observation although with slight variations[24,25,27-29]. This variability could be attributed to the bias in the methods used to identify the mucogingival position, surgical approach and improper case selection. The significant increase in the thickness of keratinized tissue in our study goes well in accordance with Bittencourt *et al*[26]. Increase in the thickness of gingival tissue is desirable since it can resist gingival recession resulting from faulty tooth brushing and inflammatory reactions[29,30]. But some authors have questioned the ability of thick gingival tissue in the prevention of recession. Based on a 2 year prospective clinical study authors recommend the practice of correct brushing technique to prevent recession instead of relying on the ability of thickness of gingiva[31]. Only long term follow up studies can determine the sound basis for this association. SCRF technique also leads to significant gain in CAL in the study sample. Similar observations have been reported by other studies too[24,26,32]. The probing depth reductions were non-significant.

In this study, an attempt was made to elucidate the role of creeping attachment in root coverage following gingival massaging with ayurvedic oil. Gain in CAL was assumed to be reflecting creeping attachment but the gain in CAL following gingival massaging were negligible (0.4-0.89 mm) and statistically non-significant (Table 2). These results are weak to support the hypothesis that, gingival massaging brings root coverage *via* creeping attachment. The available literature also lacks exact details as to when and how the creeping attachment starts and progresses. Certain studies have observed that creeping attachment occurs between 1 mo to 1 year.

In contrast, there was increase in the probing depths although negligible. This leads us to speculate that, massaging action may have lead to flattening and adaptation of gingival margin, or even marginal hypertrophy that majorly attributes to reduction in width and height of visible recession. Though this speculation may not hold strong consideration, it cannot be denied.

Intergroup comparisons (Table 4) demonstrated clear advantages of SCRF over gingival massaging with ayurvedic oil, which inturn is advantageous over gingival massaging with placebo (clarified butter). This clearly states the superior nature of SCRF in the treatment of class I recessions, while, gingival massaging with ayurvedic oil maintains close proximity to SCRF in terms of its clinical outcomes. Unfortunately no such data is available in the literature against which our observations could be compared.

Nevertheless SCRF procedure is a gold standard approach in terms of all the clinical parameters except for probing pocket depth and width of attached gingiva compared to the gingival massaging group. Under the circumstances where SCRF procedure remains contraindicated, or in patients who are skeptical on having to undergo surgical therapy for recession coverage, gingival massaging with an ayurvedic substance (IrimedadiTaila) offers a best alternative with almost equivalent benefits. Even the simple gingival massaging using an inert lubricant (such as Ghee) can be opted for as an adjunct to Scaling and root planing in areas of recession during maintenance phase.

COMMENTS

Background

The Semilunar coronally repositioned flap (SCRF) is one of the procedure described in the *Journal of Clinical Periodontology* in 1986 for the treatment of shallow recession. So far, however, no controlled clinical study has evaluated the SCRF performed as originally described and compared it with gingival massaging using an Ayurvedic product.

Research frontiers

Root coverage was achieved in both the groups and was stable during the evaluation period of 6 mo.

Innovations and breakthroughs

This is the pioneer study, where authors have used Ayurvedic product for massaging and results were significant when compared with SCRF technique.

Applications

Daily home care by the patient and gingival massaging might play an important role in improving gingival recessions and prevents further progression of mucogingival defects.

Terminology

IrimedadiTaila: Name of Ayurvedic massaging oil, with ingrediants like Acacia Arabica, *etc.*, which is used for maintaining plaque free environment in the oral cavity.

Peer review

The authors have chosen a very interesting and inexhaustible theme for the article.

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CLINICAL TRIALS STUDY

HLA antigens in individuals with down syndrome and alopecia areata

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Abstract

AIM: To describe human leukocyte antigen (HLA) alleles in individuals with Down syndrome and alopecia areata.

METHODS: A cross-sectional study was conducted, which evaluated 109 individuals. Ten with down syndrome (DS) and alopecia areata (AA), ten with DS without AA and ten with AA without DS, and their families. The individuals were matched by gender and age. The following data were computed: gender, age, ethnic group, karyotype, clinical presentation and family history of alopecia areata. Descriptive analysis: measures of central tendency and frequency distribution. Inferential analysis: Fisher's exact test to compare categorical data between the three groups and Kruskal-Wallis *ANOVA* test for numerical data.

RESULTS: Seventy per cent of evaluated individuals in the DS and AA group were male; presented mean age of 18.6 (SD ± 7.2) years and 70% were Caucasian. We observed involvement of the scalp, with a single lesion in 10% and multiple in 90% of subjects. It was observed that there is no significant difference in the frequency distributions of the alleles HLA loci A, B, C, DRB1 and DQB1 of subjects studied. However, according to Fisher's exact test, there is a trend (P = 0.089) of DS group to present higher proportions of HLA-A 36 and HLA-B 15 than the AA group and AA and DS group.

CONCLUSION: There was a tendency for the DS group, to present proportion of HLA-A 36 and HLA-B 15 higher than the AA group and group of individuals with AA and DS. However, there was no significant difference in the frequency distribution of the alleles.

Key words: Down syndrome; Alopecia areata; Human leukocyte antigen antigens; Immunology; Genetic

Core tip: The prevalence of alopecia areata (AA) in down syndrome (DS) individuals ranges from 1% to 11%, higher than in general population. The frequency distribution of human leukocyte antigen alleles in the groups was heterogeneous; there was a tendency of alleles A-36 and B-15 in DS group. The cause of AA in DS remains unknown.

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INTRODUCTION

Down syndrome (DS) is the most frequent chromosomal anomaly and common cause of mental retardation[1,2]. The prevalence of DS is approximately 1:770 births, with a slight preponderance in the male gender[3].

This syndrome presents an increased prevalence of autoimmune disorders[4]. The prevalence of alopecia areata (AA) in DS ranges from 1% to 11%, more frequent in this group than the general population[5-11]. Some studies conducted with DS patients with and without AA showed changes related to the immune system. There are few studies involving the histocompatibility antigens (HLA), DS and AA[12-14].

The purpose of this study was to describe HLA alleles (loci A, B, C, DRB1 and DQB1) in individuals with DS and AA.

MATERIALS AND METHODS

A cross-sectional study was conducted, in which 109 individuals were evaluated; 10 individuals with DS without AA (Group A) and 10 individuals with AA without DS (Group B), 10 individuals with DS and AA (Group C) and their families (Figure 1). The individuals were matched by gender and age. The clinical research protocol was approved by the Ethical Research Committee of the Martagão Gesteira Pediatric Institute (IPPMG) and all participants or their caregivers signed the informed consent.

All DS individuals were diagnosed clinically, most by cytogenetic analysis, and presented a documented medical history of AA or presented alopecia at the time of a consultation at the Medical Genetics Service. AA was considered to be hair loss leading to a "flaw" on any hairy body surface.

All the participants of the study were submitted to anamnesis and clinical exam to confirm DS and/or AA diagnosis by a clinical geneticist and by a dermatologist respectively. Exclusion criteria included: trichotillomania and presence of polycystic ovaries (evaluated by pelvic ultrasound in post-menarche female DS and/or AA patients).

The following data were computed: (1) gender and age; (2) cytogenetic exam; (3) ethnic group; (4) clinical picture of AA; (5) family history of AA; (6) HLA alleles; and (7) evaluation of family.

The HLA typing was performed using commercial kits: LABType® Typing sequence specific oligonucleotide probes (SSO) Tests (One Lambda, Inc. CA, United States), which are based on the use of SSO which are connected on the microbeads encoded by fluorescence identifying alleles encoded by the DNA sample.

A descriptive analysis with measures of central tendency and frequency distribution was made and an inferential analysis on exploratory level was made by Fisher's exact test to compare categorical data between the three groups by ANOVA and Kruskal-Wallis test for numerical data. Nonparametric test was used because the variables were not normally distributed (Gaussian), due to the dispersion of the data and rejection of the hypothesis of normality according to the Kolmogorov-Smirnov test. The criterion for determination of significance level was 5%.

RESULTS

Table 1 provides the frequency (*n*) and percentage (%) of categorical variables and disease according to demographic groups (A, B and C) and the corresponding descriptive level (*P* value) of Fisher's exact test. The age in months and the number of family members were expressed as mean, median and standard deviation and compared by Kruskal-Wallis ANOVA.

Table 2 provides the frequency (*n*) and the percentage (%) of the loci of HLA-A, B, C, DQB1 and DRB1 alleles, in the groups (DS, AA and DS + AA) and corresponding descriptive level (*P* value) of Fisher's exact test.

Regarding the relatives evaluation of first and second degrees, it was observed that the majority of alleles showed a low frequency. We emphasize some alleles such as HLA-C 07 (21/55), HLA-DQB1 03 (28/55) and HLA-DQB1 06 (22/55) which had a high frequency (> 50%) in the first-degree relatives of all groups.

DISCUSSION

This study reflects an unpublished investigation in patients with DS. However, there was no statistical significance in the distribution of HLA in DS with or without AA. Although the sample size reflected a small number of patients, in general, the groups did not differ (Table 1), reflecting the selection criteria used. Several studies have focused on the association of HLA and AA; some of them correlating prognosis, extent, chance of recurrence and family history with HLA[15-17]. These studies report that HLADQB1*03 allele was presented in 80% of all patients with AA, independently of the phenotype, and in 92% of individuals with total or universal AA. It was also demonstrated that the frequency of HLA-DRB1*1104 was increased in all sorts of AA[15,16]. These data were not reported in this study.

Although the literature reports that the AA in individuals with DS is more common in females[5,18], the sample was predominantly male (70.0%). Schepis *et al*[19] (2005) studied individuals with DS and AA, and also identified more men with AA (92.3%). Concerning the 352 DS cases recorded in IPPMG, 15 of them presented AA; the most frequently occurrence of AA in males was not significant ($P > 0.05$). AA can occur as a single and self-limited episode, but also can recur in DS patients[20,21]. In this study, 90% (9/10) individuals with DS and AA had

Table 1 Demographic and disease variables according the group *n* (%)

Variable	Category	DS group (A)		AA group (B)		DS + AA group (C)		*P* value[1]
Gender	Male	7	(70.0)	7	(70.0)	7	(30.0)	1.000
	Female	3	(30.0)	3	(30.0)	3	(30.0)	
Age, mo	Avarage ± SD (median)	224.1 ± 86.0 (233.5)		217.3 ± 90.2 (197.0)		224.3 ± 86.9 (223.5)		0.970[2]
Clinical presentation	1 lesion S			1	(10.0)	1	(10.0)	Descrip-tive
	1 lesion S/cilium			1	(10.0)	0	0.0	
	Lesions S			6	(60.0)	9	(90.0)	
	Lesion S/total			1	(10.0)	0	0.0	
	Lesion S/total/eyebrow			1	(10.0)	0	0.0	
Family history of alopecia	Yes	0	0	2	(20.0)	0	0	0.230
	No	10	(100.0)	8	(80.0)	10	(100.0)	
Karyotype	free trisomy	7	(100.0)			6	(85.7)	0.500
	Translocation	0	0			1	(14.3)	
Ethnic group	Caucasian	6	(60.0)	3	(30.0)	7	(70.0)	0.270
	Non-Caucasian	4	(40.0)	7	(70.0)	3	(30.0)	
Family (*n*)	0	0	0	2	(20.0)	1	(10.0)	Descrip-tive
	1	3	(30.0)	5	(50.0)	3	(30.0)	
	2	2	(20.0)	1	(10.0)	0	0.0	
	3	2	(20.0)	1	(10.0)	0	0.0	
	4	0	0.0	1	(10.0)	2	(20.0)	
	5	1	(10.0)	0	0.0	2	(20.0)	
	6	1	(10.0)	0	0.0	1	(10.0)	
	7	1	(10.0)	0	0.0	1	(10.0)	
Family (*n*)	Avarage ± SD (median)	3.1 ± 2.2 (2.5)		1.4 ± 1.3 (1)		3.4 ± 2.5 (4)		0.085[2]

[1]Fisher exact test; [2]Kruskal-Wallis ANOVA. S: Scalp; DS: Down syndrome; AA: Alopecia areata.

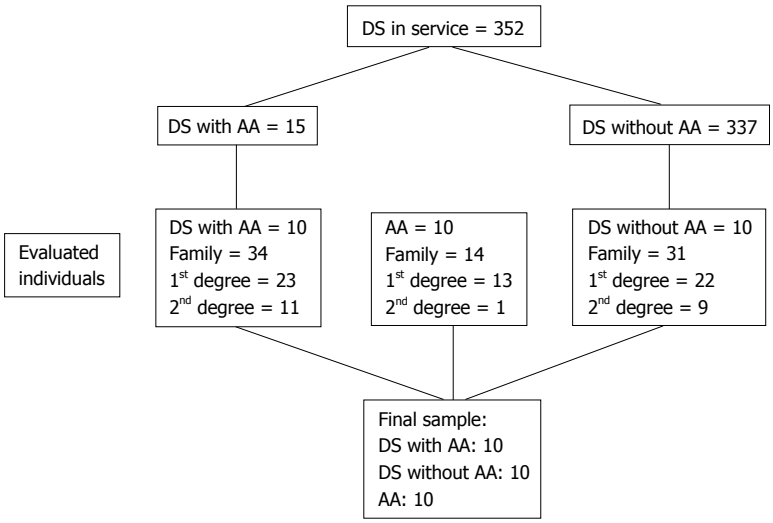

Figure 1 Structure of selected sample. DS: Down syndrome; AA: Alopecia areata.

more than one lesion on the scalp, and 10% (1/10) presented single lesion on the scalp. This finding was similar which is reported in the literature[19]. AA can affect any hairy area and the most affected is scalp (90%)[22-25]. All evaluated individuals presented scalp lesion.

Regarding family history, it is present in 10%-25% of cases of AA[10,26]. In this study we observed two cases (20%) of family history (first degree relative) in AA without DS group.

Genetic studies of AA have focused on HLA antigens due to immunological aspects of the disease[15,17,27,28]. Some have demonstrated that major complex of histocompatibility genes are the major determinants for diseases mediated by T cells, including AA[29,30]. In this study, no significant difference was observed at the level of 5% on the proportion of HLA-A between groups. According to Fisher's exact test, there is a trend ($P = 0.089$) of the DS group, present proportion of HLA-A 36 (30%) higher than the AA (0%) and DS with AA (0%) group. Xiao *et al*[17] (2006) evaluated Chinese individuals, 192 with AA and 252 controls and found higher frequency of HLA-A*02 and A*03 in patients than in controls. Despite not being the same allele, we can see that the distribution is in fact heterogeneous.

In the same study[17], comparing patients and controls, a higher frequency of HLA-B*18 and HLA-B*27

Table 2 Distribution of the most frequent human leukocyte antigen A, B, C, DQB1 and DRB1 alleles

Alleles	DS group (A)		AA group (B)		DS + AA group (C)		*P* value[1]
HLA-A 02	4	(40.0)	3	(30.0)	5	(50.0)	0.890
HLA-A 24	1	(10.0)	0	0.0	3	(30.0)	0.290
HLA-A 36	3	(30.0)	0	0.0	0	0.0	0.089
HLA-B 15	4	(40.0)	0	0.0	1	(10.0)	0.094
HLA-B 35	1	(10.0)	2	(20.0)	3	(30.0)	0.850
HLA-B 44	0	0.0	2	(20.0)	4	(40.0)	0.120
HLA-B 53	3	(30.0)	1	(10.0)	1	(10.0)	0.570
HLA-C 02	4	(40.0)	0	0.0	2	(20.0)	0.120
HLA-C 07	4	(40.0)	3	(30.0)	5	(50.0)	0.890
HLA-C 15	1	(10.0)	3	(30.0)	0	0.0	0.290
HLA-DQB1 02	6	(60.0)	3	(30.0)	4	(40.0)	0.530
HLA-DQB1 03	2	(20.0)	6	(60.0)	5	(50.0)	0.270
HLA-DRB1 01	1	(10.0)	2	(20.0)	3	(30.0)	0.850
HLA-DRB1 03	4	(40.0)	3	(30.0)	2	(20.0)	0.880
HLA-DRB1 04	0	0.0	1	(10.0)	2	(20.0)	0.750
HLA-DRB1 11	1	(10.0)	3	(30.0)	3	(30.0)	0.640
HLA-DRB1 13	3	(30.0)	2	(20.0)	4	(40.0)	0.880

[1]Fisher Exact test. HLA-A 01, -03, -11, -23, -25, -30, -31, -32, -33, -66, -68, -80. HLA-B 07, -08, -13, -14, -27, -37, -40, -42, -48, -49, - 50, -51, -52,- 57, -58, -81. HLA-C 01, -03,- 04,- 05, -06,- 08, -14,-16,-17. HLA-DQB1 04, -05, -06. HLA-DRB1 01, -07, -08, -10, -12, -15, -16 alleles had a frequency less than 1 and were not included in the Table 2. HLA: Human leukocyte antigen; DS: Down syndrome; AA: Alopecia areata.

was found in patients. In this study there was no significant difference at 5% in the proportion of HLA-B and between groups. According to Fisher's exact test, there is a trend (P = 0.094) in DS group presenting a higher proportion of HLA-B 15 (40%) than the others groups. There is few published data on HLA-C and AA. It was described in literature the highest frequency of HLA-Cw*0704 in patients with AA. In this study, it was observed that there is no significant difference at 5%, proportion of HLA-C, HLA-DQB1 and HLA-DRB1 alleles between groups.

This finding was different from some studies reported in the literature, conducted in patients with AA without DS, which showed a predisposition to develop AA in cases with HLA-DRB1*03, HLA-DRB1*04, HLA-DQB1*06, HLADRB1*13, HLADRw52a, DQ7, HLADQB1*03, HLA-DRB1*11[15-17,27,31,32].

Different HLA types are found in the population and it is rare to find two individuals having the same HLA[33]. The frequencies of alleles tend to be different among populations racially and ethnically distinct. The Brazilian population is genetically very different and it is justified by the contribution of three groups: Caucasians, Africans and Native Americans[34]. This fact may explain the heterogeneous distribution in this study and the differences found in earlier studies.

This study was conducted with a small sample. Moreover, it was difficult to collect some relatives of the subjects, especially the second degree, who refused to participate. These two factors were found limitations in this research.

In a conclusion, The frequency distribution of HLA alleles (loci A, B, C, DRB1 and DQB1) was heterogeneous in the three groups, with no significant difference in the proportion. There was a trend (P = 0.089) of the DS group to present higher proportion of HLA-A 36 than the others groups and a trend (P = 0.094) of the DS group to present higher proportion of HLA-B 15 than the others groups. HLA-C 07, HLA-DQB1 03 and HLA-DQB1 06 alleles showed high frequency (> 50%) in first-degree relatives of the total sample.

This study was conducted with a small sample. We suggest further studies with larger sample.

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COMMENTS

Background

The prevalence of alopecia areata (AA) in down syndrome (DS) individuals ranges from 1% to 11%, higher than in general population.

Research frontiers

This study was undertaken to describe human leukocyte antigen (HLA) alleles in individuals with DS and AA, and try to explain the higher prevalence of AA in these individuals.

Innovations and breakthroughs

The frequency distribution of HLA alleles in the groups was heterogeneous; there was a tendency of alleles A-36 and B-15 in DS group. The cause of AA in DS remains unknown. The authors suggest further studies with a larger sample.

Peer review

The work presented in the paper provides an indication that individuals with Down syndrome exhibit a higher prevalence of AA than the general population. In spite a small sample size, the manuscript provides some interesting insights into the immune system disturbances in DS individuals.

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OBSERVATIONAL STUDY

He had always wanted to ask an andrologist but had never done so

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Abstract

AIM: To understand and analyze what young Italian males attending high school would like to ask andrologists but do not know how to or do not have the courage to do so.

METHODS: As part of our "Androlife" campaign, we invited 1565 students attending the last year of high school to participate in our research. Firstly, they attended a lesson on general and andrological health and then, on a voluntary basis, they responded to a survey and were subjected to a preventive andrological visit.

RESULTS: The data analysis showed that the main topics in which young people are interested are: sexual activity and sexuality, sexually transmitted diseases, andrological health and fertility, and lifestyle.

CONCLUSION: This study highlights that young people are very interested in sexual health issues and that they have specific needs and interests with regard to sexual health information. Public education campaigns such as Androlife should be supported and further improved on the basis of the advice received by young participants. Sexual and reproductive health education targeting adolescents and young adults represent the basis both for wellness and for fertility preservation, and thus benefits of increased support to educational campaigns would be apparent not only in terms of individual health but also in terms of cost reduction in public spending.

Key words: Men's health; Adolescence; Prevention; Education; Sexual health; Andrologist

Core tip: This article considers the questions young people are most frequently asking. It can be considered an innovative paper because in Italy and other countries many of these topics are considered taboo. Moreover, in this article we underline that the benefits of increased support for educational campaigns would be apparent not only in terms of individual health but also in terms of cost reduction in public spending.

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INTRODUCTION

Sexual health, sexual disorders and everything related to sex have often been considered a taboo topic in Italy for many reasons, including cultural, social and religious factors. Furthermore, while the specialist in gynecology is now both well known and readily accepted, the specialist in andrology is not yet fully established among the public. However, both in Italy and all over the world, societies are becoming increasingly aware that men as well as women need sexual health care services, while at the same time services that are available are underutilized[1].

The absence of a referring specialist for men adds to the lack of heath education and prevention programs with the result that young people, particularly males, often are not knowledgeable of diseases and risk factors related to sexual health. This situation inevitably leads to difficulties in implementing preventive measures. Moreover, the difficulty that young people encounter in talking to parents and seeking medical attention for sex-related problems motivates adolescents to attempt to solve problems by using the web or by relying on word of mouth and often on urban myths. Consequently, if the user is unable to select and identify the correct information there exists a major risk that not only problems are seldom solved, but also that they are often aggravated[2]. However, the tendency to high-risk behavior and to low utilization of sexual health services is not only characteristic of young males but also extends to adult men, and it may contribute to lower male life expectancy[3]. Some authors have already taken into account social, behavioral and psychosocial factors associated with sexual activity among young adolescents in order to create effective and enforceable prevention programs[4-6], and in many countries these programs have already been activated[7-9]. In Italy, male sexual health has received growing attention in recent years and a previous study on young men has identified a number of risk factors for adolescents, highlighting a strong influence of body mass index (BMI) on skeletal proportions and penis length and identifying a large proportion of subjects with testicular hypotrophy at risk of future fertility problems[10]. A strong impetus to andrological health prevention was given by the campaign "Androlife". This was a project aimed mainly at young people with the aim of providing information, promoting prevention and collecting data. In this project, an anonymous questionnaire was administered to young participants selected among high school students. This paper focuses on just one section of this survey. In particular, we wanted to understand and analyze what young Italian males attending high school would like to ask andrologists but do not know how to or do not have the courage to do so.

MATERIALS AND METHODS

Androlife campaign

Androlife is a project that has the following objectives: (1) to sensitize and to inform young people on general and andrological health; (2) to promote primary prevention of diseases, especially concerning the male reproductive system; (3) to collect information on the habits, lifestyles, general and sexual health status of young people through an anonymous questionnaire; and (4) to highlight pathological conditions detectable by a free medical examination performed only in volunteers.

To achieve these objectives the "Androlife team" organized social and cultural events, free clinics dedicated to andrological prevention, and interventions by specialists in high schools for students in their final year in order to inform, educate and provide a free medical preventive evaluation for those who wished it.

Patients and setting

A total of 1565 students attending the final year of high school in 2012-2013 in the Veneto Region of North-East Italy were enrolled in the study. All students, aged 18-19 years, attended an informative session held by a physician of the University of Padua. Of all participants, 1492 agreed to complete an anonymous survey. On a voluntary basis, 1083 participants then elected to undergo an on-site clinical examination. The study was approved by the local Ethics Committee with the protocol number 2208P.

Information session

The sessions focused on 5 main topics: sexually transmitted diseases, andrological diseases, lifestyle, drugs and alcohol and cybersex. For each topic, the specialist explained the risk factors, how to prevent them, how to take care of one's own health, the forms of self examination such as testicular self-examination, and possible solutions to existing problems. Students could also ask questions in public and/or ask further information in private on the topics covered.

Survey

The anonymous survey included a general family history and a number of questions on lifestyle, with particular attention to smoking, diet, physical activity and the use and, or, abuse of drugs. Moreover, a large section focused on sexual activity, such as number of partners, sexual orientation, use of condoms, and use and/or abuse of pornography on the web. Finally, the last section of the survey contained an empty space where each participant was invited to write questions they might have wanted to ask an andrologist but had never done so. This section represented the topic of this paper.

Visit

On-site clinical examination was aimed at collecting anthropometric and penile measurements that included: height, weight, BMI, waist circumference, arm span, pubis-to-floor and crown-to-pubis length, penis length, penis circumference and testicular examination.

RESULTS

Among 1492 subjects who completed the survey, 1184 provided a question that they had always wanted to ask a specialist but had never done so. Of these, 793 (67%) claimed to already know the word andrologist, but only 274 (23.1%) had already undergone an andrological check. After collecting all the questions, we clustered them into four main groups, taking into account the frequency with which questions were asked (Table 1): 475 (40.2%) adolescents had asked questions about sexuality and sexual activity, 242 (20.4%) about sexually transmitted diseases, 216 (18.2%) about andrological health and fertility, and 142 (12%) about lifestyle. A further 109 (9.2%) questions did not fit into one of these groups and were combined into a generic group. The first 3 clusters were further divided into subgroups. The first cluster on

Table 1 The main and most frequent questions of 1184 young Italian men *n* (%)

Sexuality and sexual activity	Masturbation	Is masturbation normal?
475 (40.2)	223 (46.9)	Can a frequent masturbation cause damage to the penis and/or to the body?
		Can masturbation be useful before a sexual intercourse?
		Can masturbation have negative effects on sports performance?
		Can masturbation reduce the risk of prostate cancer?
	Sexual intercourses	Which are the safest contraceptive methods?
	199 (41.9)	The oral sex cause oral cancer?
		Can anal sex be risky?
		What is the right age for the first sexual intercourse?
	Drugs for sex	Are there effective drugs to treat premature ejaculation?
	53 (11.2)	At what age can you use phosphodiesterase inhibitors?[1]
		Are there drugs to help penis growth?
		Are web products, to improve sexual performance, effective and safe?
Sexually transmitted diseases	HIV	Is HIV treatable?
242 (20.4)	95 (39.3)	Is a single sexual intercourse, with an HIV positive subject, enough to acquire the infection?
		Is HIV transmissible through masturbation?
		Why there is no cure for HIV?
	HPV	Is HPV a virus that can also affect men?
	79 (32.6)	How is HPV transmitted?
		Is it possible, and how, heal from HPV infection?
	Generic questions	Is the birth control pill effective against STD?
	68 (28.1)	Is sexual intercourse the only way of transmission of STD?
		What should you do in case of STD?
		Can those who have never had sexual intercourse have a STD?
Andrological health and fertility	Varicocele	How can I know if I have a varicocele?
216 (18.2)	91 (42.1)	Which are the effects of varicocele?
		Is always necessary to operate in case of varicocele?
		After the operation, may varicocele recur?
	Testicular tumours	Which are the symptoms of testicular cancer?
	80 (37.1)	Is it possible to prevent testicular cancer?
		Is it possible to heal from testicular cancer?
		Does testicular cancer always cause infertility?
	Generic questions	Does andropause exist? What age?
	45 (20.8)	Which are the consequences of testicular trauma?
		Is short frenulum dangerous?
		Can you return fertile after vasectomy?
Lifestyle	Can illicit drugs and alcohol interfere with sexual health?	
142 (12)	Does physical activity improve andrological health?	
	Is the use of androgens helpful or harmful to the andrological health?	
Generic questions	Can virginity be established for a man?	
109 (9.2)	Can web pornography cause addiction?	
	Has the partner a role in sexual desire?	
	To keep your cell phone in your pocket can damage fertility and or sexuality?	
	How can an issue of sexual orientation be addressed?	

[1]Students did not know the active ingredient of these drugs and, in the questions, they used the most famous trade names. HIV: Human immunodeficiency virus; STD: Sexually transmitted disease; HPV: Human papillomavirus virus.

sexuality and sexual activity was divided into masturbation, sexual intercourse and drug use for sex; the sexually transmitted diseases group into human immunodeficiency virus, human papillomavirus virus and into a third generic group; andrological health and fertility was divided into varicocele, testicular tumors, and a final generic one. Table 1 shows the main and most frequent questions that young men provided in the survey, while in Table 2 we have given short answers to the received questions.

DISCUSSION

Sexuality and sexual activity

The issue of sexuality is still a difficult topic to discuss with young people, and too little is being done to provide correct information to adolescents who are just starting to explore their sexuality. In this context, the Androlife campaign intended to be helpful to the largest number of young men not only in giving information but also in facilitating the promotion of health, and in particular andrological health. This campaign, aimed at high school students, highlighted, on the one hand, much interest and active participation by adolescents in the topic, and, on the other hand, a fundamental difficulty in dealing with these issues and a fundamental lack of knowledge of many basic facts on the part of the participants. The worst consequences are a lack of preventative measures, and a reliance on the web for addressing problems, with the result that such problems are not always approached properly, nor are they effectively solved. In this paper we have considered the main topics on which young men would like to receive information or clarification but do not know how to or where to find it. In particular, the largest number of questions was related to masturba-

Table 2 Answers to the most frequent questions of young Italian men

Sexuality and sexual activity	Yes, masturbation is normal
	Masturbation doesn't cause damage to the penis and/or to the body
	There is no evidence that masturbation is useful before sexual intercourse
	There is no evidence that masturbation has negative effects on sports performance
	It has not been demonstrated that masturbation reduces the risk of prostate cancer
	The safest considered contraceptives are condoms, the contraceptive pill and intrauterine devices
	The risk of cancer caused by oral sex is related to the transmission of HPV
	Anal sex can be risky due to the transmission of STD
	There isn't a "right age" for the first sexual intercourse because everyone reaches maturity at different ages
	There are effective drugs to treat premature ejaculation, but not all cases require drug treatment
	The clinic, not the age determine the use of phosphodiesterase inhibitors
	Drugs are useful for the growth of the genitals only in the case of some diseases (*e.g.*, certain hormone deficiencies)
	Is not safe, and often even effective, to rely on the web to improve sexual performance
Sexually transmitted diseases	HIV is treatable but not curable
	Even a single sexual intercourse, with an HIV positive subject, is enough to acquire the infection
	HIV is transmissible through masturbation only if the biological produced fluids come into contact with wounds
	The complexity of the virus causes the current treatment options to treat but not to heal from infection by HIV
	Yes, HPV can also affect men
	HPV is transmitted through all forms of sexual activity
	It is possible heal from HPV infection reducing risk factors (smoking, unprotected sex, low hygiene...)
	The birth control pill is absolutely not effective against STDs
	Sexual intercourse is not the only way of transmission of STD
	In case of STDs the first thing to do is consult a doctor as soon as possible
	STDs can also be present in people who have not had sex but have been in contact in other ways (*e.g.*, transfusions with infected blood)
Andrological health and fertility	A varicocele can be diagnosed by clinical examination or ultrasound
	A varicocele may be asymptomatic, present with scrotal symptoms or pains, and in some cases worse spermatogenesis and testicular function
	It is not always necessary to operate in the presence of a varicocele
	In some cases, after operation, varicocele may recur
	Symptoms of testicular cancer: presence of a mass, change in size, change in texture, scrotal and/or inguinal pain, scrotal weight feeling
	It is necessary to prevent testicular cancer
	Yes, it is possible to heal from testicular cancer
	If early treated, testicular cancer not always cause infertility
	There is no well-defined andropause but fertility and sexual potency decrease with age
	Severe testicular trauma may have consequences on testicular function and fertility
	A short frenulum is not dangerous and it is easily solved
	Regaining fertility after vasectomy is sometimes possible but difficult
Lifestyle	It is well established that drugs and alcohol negatively interfere with sexual health
	Physical activity is necessary to maintain and improve andrological health
	If not necessary, the use of androgens is harmful to the andrological health
Generic questions	Male virginity can not be established
	Yes, web pornography can cause addiction
	Yes, also the partner plays a very important role in sexual desire
	To date there are conflicting data on the role of cell phone on fertility and or sexuality
	It is good to deal with issues relating to sexual orientation with trained and professional doctors and psychologists

HIV: Human immunodeficiency virus; STD: Sexually transmitted disease; HPV: Human papillomavirus virus.

tion, denoting ignorance in this respect and highlighting widespread beliefs in popular myths. In fact, many young males are not aware of the fact that masturbation is integral to normal sexual development and that it represents a dynamic process during adolescence, and only compulsive masturbation should be considered a problem[11,12]. The other issue of great interest was, unsurprisingly, sexual intercourse. Interestingly, the main concern in this regard, was in contraceptives and methods for optimal performance, as well as about oral and anal sex while the risk of sexually transmitted disease (STD) did not seem to be prominent. Although previous studies have highlighted that there are a number of different pathways that may lead to either voluntary or involuntary adult sexual inexperience[13], it is more likely that many of the concerns voiced by the participants arise from actual voluntary practice, considering the growing proportion of adolescents engaged in oral and anal sex practices[14].

Sexually transmitted diseases

In our opinion, what should be worrisome is the lack of interest and concern displayed by the participants in STDs. In fact, the questions show that adolescents are poorly informed about the transmission pathways, consequences, and possible treatments for infections, and at the same time, they do not seem to give considerable thought to these issues. This observation is in agreement with the data collected by other authors who have highlighted the need for effective interventions to reduce adolescent STD infection[15]. Moreover, STDs also represent

the most significant modifiable risk factors for this age group with regard to fertility[16]. This topic does not seem to be a priority for adolescents, but this may only be the consequence of a lack of sexual health education and not of indifference toward these issues.

Andrological health and fertility

STDs do not seem to be of great interest, but when made aware of these issues, students expressed the will to learn more both in terms of the most common diseases and of those they are more afraid of, such as varicoceles and testicular tumors. A varicocele is one of the most common pathologies but despite numerous studies concerning its evaluation and treatment, uncertainties remain. Both overtreatment and undertreatment are particularly costly. Expensive ultrasound, office visits and surgery must be avoided in those who do not need these treatments, while a careful follow-up and eventual intervention must be guaranteed to subjects who may be in need of them[17]. Another disease of great interest to students is testicular cancer, which represents the most common malignancy in young men, with the highest incidence among men in Nordic countries. Known risk factors are cryptorchidism, a previous history of testicular cancer and a family history of testicular cancer, and early detection and appropriate treatment are the only methods to decrease mortality[18,19]. In fact, if adequately treated and followed up it represents the most curable solid tumour and survival rate exceeds 90% in young males[20]. Unfortunately, the majority of young males is not aware of this information, which is critical for successful health prevention. Therefore, this survey, in accordance with data collected by other authors, underscores the continued need for comprehensive sexual and reproductive health education for adolescents and young adults[21].

Lifestyle

A widespread social problem all over the world is the use and abuse of alcohol and illicit drugs[22]. This represents the main topic of lifestyle in which young people are involved and on which they focus their interest, and prevention and treatment efforts would benefit from more careful attention in preventive health programs. Another matter to consider is physical activity during adolescence. The long-term benefits of habitual physical activity are recognized[23], but it is necessary to inform adolescents about the risks of using doping substances, particularly considering the increased consumption of such substances by young people who practice sport[24,25].

Generic questions

In the last cluster, we collected less frequent but perhaps more topical and current questions asked by the participants. In addition to the issue about the possible negative effects of the use of mobile phones on fertility, questions asked by participants were commonly questions to which there are conflicting answers[26], and questions on topics of interest concerning web pornography and sexual orientation. Web pornography is a phenomenon of such increasing interest as to be defined by some authors as the new sexual revolution[27]. To date, a number of studies have highlighted the reasons why web pornography has such widespread use, and considered the characteristics of this new form of sexuality[28,29]. However, no one has yet taken into account the possible negative effects of the use or abuse of web pornography in terms of an increase or decrease in interest in real sexuality and in real sexual intercourse. Sexual orientation represents a difficult topic for adolescents to bring up, particularly because of the family and social context in Italy. It is demonstrated that homosexual young people face different developmental challenges during adolescence than those faced by heterosexual youths or individuals who recognize their homosexual orientation later in life[30]. Though sexuality has acquired new dimensions in many countries including Italy, religions and cultures consider sexuality almost exclusively as focused on reproduction[31]. Hence, there exists a difficulty for young people to deal with the issue of sexual orientation and therefore, the necessity to provide an adequate and qualified service for information and assistance. In conclusion, this study highlights not only that young people are very interested in general health issues, but also that they have very specific needs and interests on sexual health and sexual health information. In our opinion, public education campaigns such as Androlife should be increased in number and frequency and improved on the basis of the view of young participants. Sexual and reproductive health education and promotion for adolescents and young adults represents the basis both for wellness and for fertility preservation. Finally, the benefits of increased support for educational campaigns would be apparent not only in terms of individual health but also in terms of a reduction in public spending costs.

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COMMENTS

Background

Sexual activity, sexual health and sexual disorders are open issues and current problems especially among adolescents.

Innovations and breakthroughs

This study highlights not only that young people are very interested in general health issues, but also that they have very specific needs and interests on sexual health and sexual health information.

Applications

This is an interesting and meaningful topic which brings attention to the health care providers and raises public awareness for the importance of education in reproductive health.

Peer review

This is an interesting and meaningful topic.

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SYSTEMATIC REVIEWS

Reporting of dental status from full-arch radiographs: Descriptive analysis and methodological aspects

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Abstract

AIM: To identify standards, how entities of dental status are assessed and reported from full-arch radiographs of adults.

METHODS: A PubMed (Medline) search was performed in November 2011. Literature had to report at least one out of four defined entities using radiographs: number of teeth or implants; caries, fillings or restorations; root-canal fillings and apical health; alveolar bone level. Cohorts included to the study had to be of adult age. Methods of radiographic assessment were noted and checked for the later mode of report in text, tables or diagrams. For comparability, the encountered mode of report was operationalized to a logical expression.

RESULTS: Thirty-seven out of 199 articles were evaluated *via* full-text review. Only one article reported all four entities. Eight articles reported at the maximum 3 comparable entities. However, comparability is impeded because of the usage of absolute or relative frequency, mean or median values as well as grouping. Furthermore the methods of assessment were different or not described sufficiently. Consequently, established sum scores turned out to be highly questionable, too. The amount of missing data within all studies remained unclear. It is even so remissed to mention supernumerary and aplased teeth as well as the count of third molars.

CONCLUSION: Data about dental findings from radiographs is, if at all possible, only comparable with serious limitations. A standardization of both, assessing and reporting entities of dental status from radiographs is missing and has to be established within a report guideline.

Key words: Research design; Guideline; Dental radiography; Epidemiology; Public health; EQUATOR

Core tip: Full mouth dental radiographs are in worldwide daily use and contain various informations about dental and oral health of adult patients. This is why it is often used for epidemiologic research or to augment clinical data. But, when reported, data is presented in multifarious ways. Thus no or only little comparison of research outcome is possible. Existing standards of evaluation and reporting should be fixed in a reporting guideline regarding: number of teeth and implants; caries, fillings and restorations; root-canal fillings and apical health; alveolar bone level. Application of sum scores turned out to be very questionable.

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INTRODUCTION

Beside diagnosis support, X-rays are an established method to follow up treatments with surrogate characteristics, such as: bone loss in implantology, periodontology and maxillo-facial surgery, or apical flare up and loss of teeth in endodontology, or caries prevalence in operative dentistry.

Moreover, it is used for assessment of skeletal changes focussing orthodontic or temporo-mandibular-disorders. It is even possible to find approaches of forensic medicine, *i.e.*, for non-invasive age determination *via* orthopantomograms.

The quality of panoramic radiographs has enhanced during the last years. Namely their sensitivity and specifity to diagnose findings, as mentioned before, is considered to be satisfying. Problems of underestimation are discussed commonly. Nevertheless, determining oral health by radiographic presentable dimensions of the dental status is possible. That is why panoramic radiographs are often used for epidemiologic and retrospective analysis of dental status and oral health respectively. Recently, a review subsumed the competence and application of panoramic radiographs for epidemiologic studies of oral health[1]. However, it remains uncertain, whether standards are established to report radiographic findings which describe dental status or oral health data in general. No results, neither in Pubmed/Medline, EQUATOR-Network (www.equator-network.com) or Cochrane Library could be identified searching a relevant guideline. Therefore, this systematic review was launched, to find out, which approaches are commonly used, to assess and report the entities: decay, missing, restorative, endodontic and periodontal status as surrogate dimensions of oral health (Table 1).

MATERIALS AND METHODS

Search and identification/inclusion and exclusion

A Medline/PubMed search was performed for articles reporting findings from full arch radiographs, focused on oral health and dental status of adults. This search was conducted in November 2011. No time limit was set. Panoramic X-ray or a full-mouth radiographic survey with periapical radiographs of all remaining teeth were definied as "Full arch radiograph". In the following, the term "radiograph" will be only used in this sense.

To find and include such papers the following search-string was constructed stepwise and applied finally as: ("radiographic study" or "panoramic") and ("oral health" or "dental status" or "dental health" or "dentition") not (children OR review OR edentulous)

The following inclusion and exclusion criteria were set for a full text review of findings: All peer-reviewed reports with dental findings obtained from full arch radiographs are included, even if there had been additional clinical examination or patient chart reviews. These reports had to focus on at least one surrogate of "dental status" or "oral health" (Table 1), whereas reports handling edentulous or partially edentulous patients were disregarded.

Only articles written in English were included. Studied cohorts had to be of adult age, respectively the mean age had to be at least 18 years.

If it was not determinable in the abstract, which kind of radiography was applied or which variables of dental status were reported, the article was included to full-text review.

Excluded was all literature handling radiometric issues only [*i.e.*, bone density, cephalometric angles of jaw and joint, subjected to soft-tissues (carotis, lymphal-nodes)] or focusing on specific teeth/tooth types only (such as caries in third molars) as well as anthropologic analysis. Articles were also excluded, if they turned out to report on the basis of bitewing radiographs or specific single radiographs to fulfill their objective.

Definition of variables of interest

Every previously included paper was reviewed towards the report of at least one out of the following eight variables (I a-Ⅳ), which reflect the surrogates listed in Table 1. If inclusion was validated, information about: (1) Bibliography and focus of study; (2) Number of patients studied and country of origin; (3) Number and kind of radiographs studied was noted first. Then the materials and method section (MMS) and results were checked for the following 8 variables of interest: I a: remaining/missing teeth (also included in DMFT/S); I b: implants or implant-loss; Ⅱ a: fillings (also included in DMFT/S); Ⅱ b: decay/caries (also included in DMFT/S); Ⅱ c: restorations (*i.e.*, crowns); Ⅲ a: root canal treatment; Ⅲ b: apical status; Ⅳ: alveolar bone level on teeth or implants.

These variables were recorded by their mode of report. Further statistical analyses applied to these variables within the articles were disregarded, due to the different focus of the studies. Regarding the application of these variables, it was noted if additional arrangements, exclusion or inclusion criteria towards the report were mentioned by the authors. For example: how to handle the "third molars", supernumerary teeth or teeth not depicted clearly on radiographs.

If a variable was mentioned in the section "methods" but not reported, it was mentioned not reported "(NR)". If a variable was not mentioned within the method section, it was noted as not defined "(ND)". Furthermore it was recorded, if the authors applied a special method of evaluation and how it was described or whom they cited. A "?" was assigned to indicate an assumption by the reviewers throughout the data, whenever there was no clear statement within the context of the article. For lon-

Table 1 Entities of dental status and their surrogates in oral health: Left column notes the entities of dental status, which can be assessed from a full-arch radiograph

Focused entities	Subject of clinical dentistry	Surrogate of oral health
Alveolar bone loss, furcation and vertical bony defects	Periodontology, implantology	Periodontitis/inflammation, risk of tooth loss
Fillings/inlays	Operative dentistry	Oral hygiene, caries, decay, risk for massive fillings/partial crowns
Massive filling/partial crown	Operative dentistry, prosthodontics	Risk of root canal treatment, risk for crown-treatment
Crowns and fixed dental prosthesis/ pontics	Prosthodontics, periodontology	Massive decay (even of healthy teeth), risen risk for caries and endodontic problems, risk for bone loss and fracture (missing teeth), missing teeth
Root canal filling and root posts	Operative dentistry, endodontology, prosthodontics	High number of life events of intervention, risk of tooth loss by fracture/ inflammation, need for crown
Apical lesion	Endodontology, oral surgery	High risk of tooth loss, poor root canal treatment, inflammation
Missing teeth	Prosthodontics, implantology	High number of life events of interventions, former inflammations, trauma, hypodontia, malocclussion
Implants	Periodontology, prosthodontics	Missing teeth, higher risk for inflammation (periimplantitis), occlusal rehabilitation
Edentoulism	Prosthodontics, oral surgery	High number of life events, no further risk of odontogenic inflammation (caries, periodontitis, apical lesions)

Their possible relation as a surrogate of oral health is shown in the right column. The involved subjects of Dental Medicine are noted in the middle column. Reading the table from top to down, it has to be considered, that surrogates include content of cells above.

gitudinal studies, the different comparisons between the dates of results were not considered, as far as no other way of report was applied. Information about removable dentures had been neglected, because these are generally not allowed to be seen on radiographs at all. If results of a study or cohort were published twice, first, the longer observation period and, secondly, the higher impact factor in year of publication gave favor for inclusion.

Operationalization of findings

The report of variables I to Ⅳ was reduced to a simple logic expression. Every expression, shown in Table 2, can be translated with the following "keys-words" and abbreviations: "ND" or "NR" indicates "not defined" or "not reported".

"N" = "number"; "[]" = "of/in"; "()" = "expressed as"; "/" = "by presenting values"; "," = "and"; "+" = "with"; "G" = "in group (s)"; "F" = frequency, "%" = percentage, "SD" = standard deviation, "Q" = quartiles, "rg" = range, "al" = "all patients/teeth/surfaces", "tot" = "total", "pat" = "patient(s)", "grades" = "declared graduation or scaling of measurements", "FDP" = "fixed dental prosthesis".

Variable I refers to "r" = remaining, "m" = missing or "f" = lost/failed teeth. Variables Ⅱ-Ⅳ always refer to affected patients, teeth, lesions, surfaces or sites. Following groups were standardized: age, gender, jaw, tooth-type, age-group, grades (of a previously defined classification).

If authors introduce special groupings (*i.e.*, diseased/ healthy, baseline/follow-up and so on), it was abbreviated "spec" for "special". This was mandatory due to the different outcome-variables of the studies.

For dental terms following abbreviations were used: "ABL" = "alveolar bone level/loss", "apH" = "apical health", "RCF" = "root canal filled", "FDI" = "FDI-tooth code", "FDP" = "fixed dental prosthesis".

Two examples of this operationalization: The following expression in the column "Ⅱb Caries/Decay": "N[surface](mean, SD)[pat]/G[age, gender]" is translated to "The number of carious surfaces is expressed as mean and standard deviation in a patient, by presenting values in groups of age and gender".

Another exemplary expression in the column "Ⅲa RCT" is "N[pat + teeth](F)" translated to "Number of patients with affected teeth is expressed as frequency".

Subsumption

All included papers were ordered according to their objective. Bibliography as well as number and origin of patients were described by frequency distributions. To discuss the consistency, the findings were subsumed for all papers towards each entity of interest. Therefore cited methods of radiographic evaluation were full-text reviewed, as far as these were written in English or German and obtainable *via* library services.

RESULTS

Following Figure 1, thirty-seven studies were evaluated and can be found in Table 2.

The years of publication of all results are shown in Figure 2. In whole 27447 (median = 191) X-rays have been evaluated and reported within 37 studies including 27772 (median = 215) patients. Figure 3 shows the shares of patients towards their origin. Ninety-four percent of the patients studied were from United States and Europe.

For nine journals no Impact Factor (IF) was noted at *Journal Citation Report* (JCR) of "Web of Knowledge" (www.webofknowledge.com). The 5-year IF in 2010 of all JCR-listed and evaluated journals was median = 2.23, range: 0.89-6.39, SD = 1.16. So the included articles represent an extract of high ranked journals, regarding an average IF of about 1.3 (median = 1.2, mean = 1.5) for

Table 2 Evaluated articles and encountered mode of report: All full-text reviewed articles are sorted by the year of publication

Ref.	Number of X-rays evaluated	Ⅰa: Number of teeth	Ⅱa: Fillings	Ⅱb: Caries	Ⅱc: Restorations	Ⅲa: RCF	Ⅲb: apF	Ⅳ: ABL
Helenius-Hietala *et al*[17] 2011[b]	212	N[r-teeth](mean,SD)[pat]	ND	N[pat] (mean)/G[spec]	ND	ND	NR	mm(mean,SD)/pat; meanABL[pat]/G[spec]; N[teeth+G[ABL]] (mean,SD)/G[spec]
Yoshihara *et al*[40] 2011[a]	177	N[r-teeth](mean,SD)[pat]/G[spec,gender]	ND	ND	ND	ND	ND	ND
Andersen *et al*[28] 2011[b]	52	N[r-teeth](mean,SD, median,Q)[pat]/G(age)	ND	ND	ND	Combined: N[teeth](mean,SD,median,Q)[pat]/G[age]; N[teeth](F,%)[toothtype]/G[age]		ND
Seppänen *et al*[18] 2011[b]	84	N[r-teeth](median,rg)[pat]	ND	N[pat](F,%)[all pat], G[spec]	ND	ND	ND	N[pat](F)[ND]/G[spec]
Willershausen *et al*[9] 2011[d]	2374?	N[r-teeth](mean?)/G[age,spec], N[m-teeth](mean)/G[age]	N[teeth](mean,SD)[pat]/G[spec], N[pat](%)/G[age]	N[teeth](mean,SD)[pat]/G[spec], N[pat](%)/G[age]	N[teeth](mean,SD)[pat]/G[spec]; N[pat](%)/G[age]	N[teeth](mean,SD)[pat]/G[spec], N[pat](%)/G[age]	ND	ND
Kirkevang *et al*[22] 2009[b]	470	N[r-teeth](median,rg)[pat]/G[age]	N[teeth+1,2,3 surfaces](median,range)[pat]/G[age,toothtype]	N[teeth](median,rg)[pat]/G[age,tooth-type]	ND	ND	ND	ND
Saeves *et al*[10] 2009[d]	93	N[m-teeth](mean)[pat]/G[age,spec]	N[teeth](mean)[pat]/G[age,spec]	ND	"Some"	N[teeth](%)[all teeth]; N[pat](F)[spec]	ND	ND
Tarkkila *et al*[13] 2008[b]	161	N[r-teeth](mean,SD)[pat]/G[spec]	Combined with clinical examination: N[DMFT,DT,FT](mean,SD)[pat]/G[spec]		ND	NR	NR	ND
Buhlin *et al*[49] 2007[b]	51	N[r-teeth](mean,SD)[pat]/G[spec,all]	N[DMFS](mean,SD)[pat]/G[spec,all]; N[DMFT](mean,SD)[pat]/G[spec,all]		ND	ND	N[lesions](F,%)[pat]/G[spec]	N[pat](F,%)/G[grade]
Nalçaci *et al*[26] 2007[d]	190	N[r-,m-teeth](mean,SD)[pat]/G[gender,tooth-type]	N[teeth](median,SD)[pat]/G[gender,all]	N[teeth](median,SD)[pat]/G[gender,all]	N[FPD](F,%)/G[gender,jaw] N[teeth](SD,median)[pat]	N[teeth](median,SD)[pat]/G[gender,all]	N[teeth](median,SD)[pat]/G[gender,all]	N[pat](median, SD)[ND ABL]/G[gender]
Huumonen *et al*[3] 2007[b]	95	N[m-teeth](F)/G[spec]	ND	N[teeth](F)/G[spec]; N[findings?](F)/G[spec]	ND	N[teeth](F)/G[spec]	N[teeth](F)/G[spec];	N[pat](F)/G[spec]
Jansson *et al*[36] 2006[c]	191?	N[r-teeth](mean,SD)[pat]/G[spec]	ND	ND	ND	ND	ND	N[pat](F)/G[spec]
Tabrizi *et al*[11] 2006[c]	20	N[r-teeth](F,mean,SD)[pat]	N[DMFS,DMFT](mean,SD)[pat]/G[spec]		Included to DMFT?	ND	ND	ABL(mean)[pat]
Skudutyte-Rysstad *et al*[30] 2006[d]	146	ND	ND	ND	ND	N[pat+tooth](F,%)[all]; N[pat]/N[teeth](F); N[teeth](F,%)/G[spec]	N[pat+tooth](F,%)[all]; N[teeth](F)[grade]; N[pat]/N[teeth](F); N[teeth](F,%)[all]/G[spec]	ND
Peltola *et al*[31] 2006[a]	307	NR *via* DMFT	NR *via* DMFT N[pat](F)[DMFT = 0]/G[spec]	N[lesions](mean,SD)[pat]/G[spec]	ND	N[teeth](mean,SD)[pat]/G[spec]	N[lesions](mean,SD)[pat]/G[spec]	NR

Ma *et al*[2] 2005[a]	1232	N[pat+m-teeth](%)/ G[tooth-type]; N[m-teeth](%)[tooth-type]	ND	ND	ND	ND	ND	ND
Olze *et al*[14] 2005[d]	275	NR	NR	NR	ND	ND	ND	ND
Cabrera *et al*[4] 2005c	1417	N[pat](F)/G[m-teeth,spec]	ND	ND	ND	ND	ND	ND
Rosenquist *et al*[5] 2005[b]	452	N[pat](F)[G[m-teeth]/ G[spec]		N[pat](F)[G[m-teeth]/G(spec)		ND	N[pat](F)[teeth]/G[spec]	N[pat](F)[grade]/G(spec)
Montebugnoli *et al*[44] 2004[c]	113	NR *via* pantomography index	ND	NR *via* Pantomography index	ND	ND	NR	NR
Abou-Raya *et al*[46] 2002[a]	50	N[pat+m-teeth](%)/ G[spec]	ND	NR *via* Pantomography index	ND	ND	NR *via* pantomography index	NR *via* pantomography index
Enberg *et al*[21] 2001[a]	137?	N[r-teeth] (mean,SD)[pat]/ G[gender,age,spec]	ND	N[teeth](mean,SD)[pat]/ G[gender,age,spec]	ND	N[teeth](mean,SD)[pat]/ G[gender,age,spec]	N[teeth](mean,SD)[pat]/ G[gender,age,spec]	N[teeth](F,%)[pat]/ G[gender,age-group,spec]
Närhi *et al*[6] 2000[a]	396	N[pat+r-teeth]; N[r-teeth] (mean,SD)[pat]/ G[gender,jaw,spec]	ND	N[teeth]; N[teeth] (mean,SD)[pat]/ G[gender,spec]	ND	absN[teeth], N[teeth](mean,SD)[pat]/ G[gender,spec]	N[teeth], N[teeth](mean,SD)[pat]/ G[gender,jaw,spec]	N[teeth](mean,SD)[pat,grade] /G[gender, spec]
Aartman *et al*[43] 1999[a]	211	N[r-teeth] (mean,SD)[pat]/ G[spec]	ND	N[teeth](mean,SD) [pat]/ G[spec]	ND	N[teeth](mean,SD)[pat]/ G[spec]	ND	ND
Taylor *et al*[38] 1998[b]	362	N[r-teeth?](median)/ G[spec]	ND	ND	ND	ND	ND	N[pat](F,%)[grades]/G[spec, age-group];
Grau *et al*[48] 1997[c]	126	NR *via* pantomography index	ND	NR *via* pantomography index	ND	NR *via* pantomography index	NR *via* pantomography index	NR *via* pantomography index
Peltola *et al*[19] 1993[c]	990?	N[pat](%)[DMFT = 0]	N[DMF](mean,SD)[pat]/ G[age]	N[teeth](mean,SD,rg)[pat]	ND	N[pat](%)	N[pat](%)	N[pat+ND G[ABL]](F,%)
Hakeberg *et al*[33] 1993[c]	180	N[m-teeth] (mean,SD,rg)[pat]/ G[spec,gender,age]	N[surfaces](mean,SD,rg)[pat]/G[spec, gender,age]	N[surfaces](mean,SD,rg) [pat]/G[spec,gender,age]	ND	N[m-teeth] (mean,SD,rg)[pat]/ G[spec,gender,age]	N[lesions](mean,SD,rg)[pat] /G[spec,gender,age]	N[lesions](mean)[pat]/ G[grade,spec]
Corbet *et al*[24] 1992[b]	165	N[m-teeth] (mean,SD)[pat]/G[age]; N[m-teeth](%)[FDI]	ND	ND	N[pontics,cantilever,crowns](%)[FDI]; N[FPD](%)[units]; N[units,retainers](mean,SD)[all FPD]	ND	ND	ND
Lindqvist *et al*[15] 1989[d]	50	N[r-teeth](mean,rg)[pat]		N[pat+"seriously decayed teeth"](F,%)		N[teeth,pat](F); N["Inadequate" RCF](F,%)	N[pat](F)/G[lesions]	N[pat](F,%)/ G["periodontits"]; N[pat?](F)[spec]
Stermer Beyer-Olsen *et al*[37] 1989[c]	141	ND	ND	ND	ND	N[teeth](F), N[pat](F,%)	N[teeth,RCF-teeth](F), N[pat](F,%)	N[pat](F,%)
Grover *et al*[7] 1982[a]	5000	N[pat](F,%)/G[m-teeth]		Combined for all carious as N[findings,pat](F,%)		ND	N[findings,pat](F,%)	N[pat+G[periodontits]](F,%)
Langland *et al*[16] 1980[b]	2921	ND	ND	N[pat+lesion?](F,%)	N[pat+FPD](F,%)	N[pat+tooth](F,%)	N[pat+lesion?](F,%)	N[pat+G[periodontits]](F,%)
Meister *et al*[25] 1977[b]	5783	ND	ND	ND	N[pat+FPD](F,%)	ND	N[findings](F,%)	N[pat+G[periodontits]](%)

Pelton *et al*[20] 1973[d]	200	ND	ND	N[findings](F)/ G[jaw,spec]	ND	ND	ND	ND
Christen *et al*[27] 1967[b]	1338	ND	ND	ND	"Many ill fitting crowns"	ND	N[pat+tooth](F)	N[pat+"gross periodontits"](F,%)
Lilly *et al*[8] 1967[d]	1285	N[pat](F,%)/G[r-teeth]	ND	ND	ND	N[teeth](F)/G[tooth-type]; N[pat,canals](F)	N[teeth](F)G[spec]	ND

The date is followed by a discretionary index for the 5 year Impact Factor of the journal in 2010 (a < 1.5; b < 3; c > 3; d: None). Please see caption: Operationalization of findings in "Materials and Methods" section to decipher content in columns Ⅰa-Ⅳ. Column Ⅱb "Implants" is not shown for a comprehensive view and due to the lack of noteworthy reports. RCF: Root-canal-fillings; apF: Apical findings; ABL: Alveolar bone loss; ND: Not defined; NR: Not reported.

Dental Journals listed in the JCR in 2011.

All modes of report are shown-according to the scheme of operationalization-in Table 2. The following subheadings subsume these findings and focus on the methodic of radiographic assessment.

Missing/remaining teeth and implants

Thirty/37 (81%) of all studies reported remaining and/or missing teeth. Four articles intended a report of these values within their material and method section, but did not so. Beside mean-and median values, two artificial approaches were found: Ma *et al*[2] reported the prevalence of missing tooth types (first molars). Other authors gave the number of absolute frequency of missing teeth within their studied cohort[3]. In addition to this the following groupings were found: "< 10 missing teeth"[4], "0, 1-5, 6-14, 15-20, > 20 missing teeth"[5], "1-7, 8-20, 21-32 teeth"[6], "1-2, 3-5, 6-9, 10-14, 15-20, 21-27 missing teeth"[7], "0, 1-11, 21-12, 22-27, 28-31, 32"[8].

This approach of grouping allowed the authors mentioned above to report only the "number of patients" within their established groups. Before 1990 absolute frequencies were reported more frequently. Due to the variety of dentition, especially existence of 3rd molars, the problem of report is thoroughly discussed below.

Only 3 articles considered and reported dental implants. That is why this column is not shown in Table 2. The modes of report were: "N[pat + implants](%)/G[age]"[9], "N[implants](F)[all pat]/G[spec]"[3] and worded "some"[10].

Caries, fillings and restorations

Due to the clinical DMFT-index decayed (carious) and filled (restored) teeth are often pooled and mixed up. Six authors did so-three out of these using the DMFT/DMFS-Index[11-13]. Overall 19 out of 37 papers mentioned to evaluate "carious problem", "-lesions", "-teeth" or "defective teeth". One did not report their announced findings[14] and two remained unclear[15,16]. Four authors got more specific towards their assessment by mentioning the following criteria: "deep caries cavities"[17], "carious pulpal exposure lesions"[18], "lesions clearly perforating the enamel and clear radiolucencies under old fillings were recorded. Enamel caries was excluded"[19], "gross carious lesions … in posterior teeth"[7].

Pelton *et al*[20] classified caries lesions within a reliability study of panoramic and periapical radiographs as "C1: radiographically viewed that involved the enamel, but did not penetrate the dentin; C2: … involved the enamel and the dentin, but not the pulp; C3: … said to involve the pulp".

Two other authors explained more concrete: "Caries was judged to be present in the radiograph when a clearly defined reduction in mineral content of the proximal, occlusal, and/or restored surfaces was evident"[6], and "(Caries was) present when the lesion reached the dentin proximally or occlusally or was found at restored surfaces"[21].

Kirkevang *et al*[22] used a method published by Wenzel[23] described as follows: "A surface was assessed as having a caries lesion if a radiolucency, exhibiting the shape of a caries lesion and observed at a caries-susceptible site", and augmented with "extended into dentine; radiolucencies confined to the enamel were ignored".

In the same article Kirkevang *et al*[22] gave concrete information about fillings: "Registrations were performed on mesial, distal and occlusal or incisal surfaces. Fillings in pits and fissures in oral and buccal surfaces were not registered".

Tabrizi *et al*[11] stated "Restorations and dental caries were also calculated for each participant", but owes the data by presenting only DMFT-values.

Reporting is also structured by using absolute frequencies of patients with "lesions"[18,19], or "affected teeth" in all patients[3]. In addition to this, following groupings were found: "0,

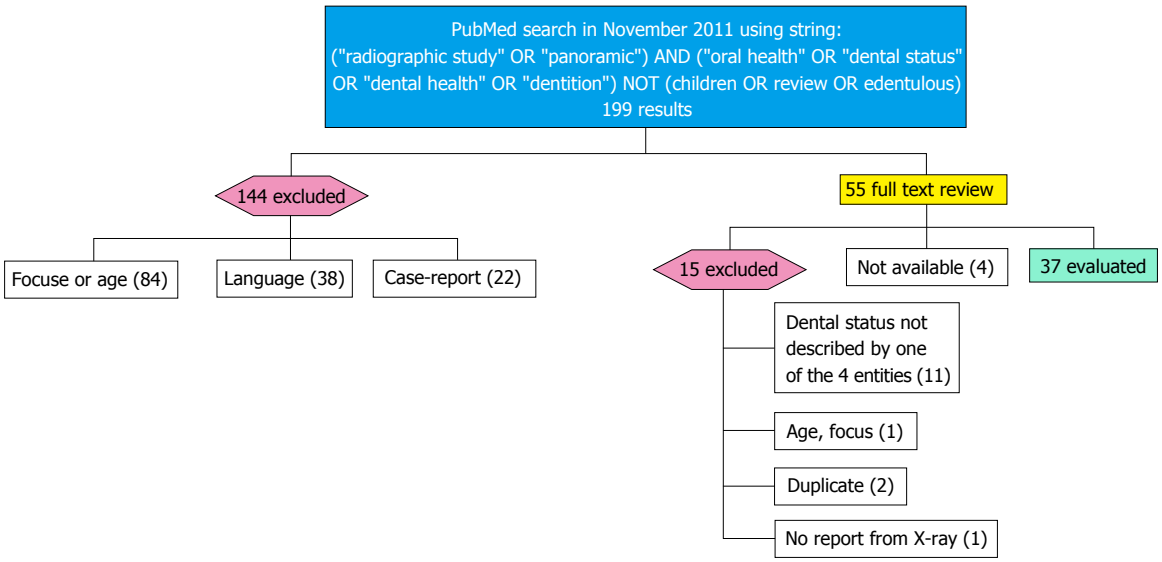

Figure 1 Flow chart of review strategy and finally evaluated articles: The flow chart shows the systematic exclusion of search results towards the finally evaluated studies. The primary reasons for exclusion are mentioned including the number of concerned articles.

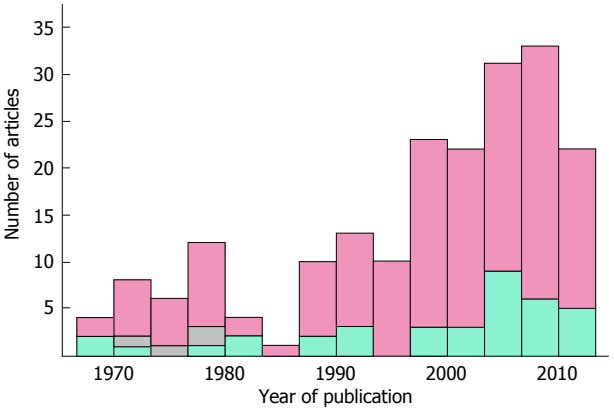

Figure 2 Distribution of included and excluded articles: Distribution of the 37 evaluated (green) and 159 excluded (red) studies of the search results ordered by their date of publication. Shaded fractions represent the 4 articles which were not available as full text version.

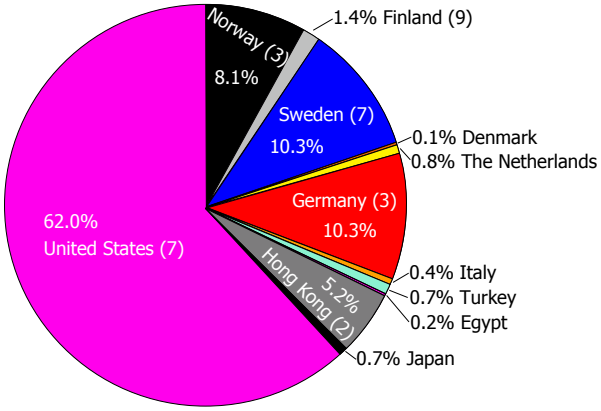

Figure 3 Shares of patients in the 37 evaluated studies with respect to the country of origin: The number of contributing studies is noted in brackets behind the country. Preponderance of United States is due to two reports of "mass X-ray evaluation" in the years 1977 and 1982. If these two are left out of consideration the median value of studied subjects in a paper is 212 (mean = 485).

< 5, > 5 defective teeth"[5], "0, 1-2, ⩾ 3 carious lesions"[19]. Restorations were reported six times[9,10,16,24-26], but 2 articles did insufficiently[10,27]. Within three out of seven articles restorations, fillings and decay were merged[5,11,15].

Root canal fillings and apical health

Identification of root canal filled teeth was taken for granted in 15 out of the 18 papers. Within 3 papers it was clarified in more detail within the MMS as "ongoing or completed root canal treatment, …, pulp amputation", "teeth with pulp amputation, endodontic fillings, or both"[3,6,21]. One article merged root canal fillings and apical health[28].

Seventeen further articles focused on apical health. The periapical index (PAI) by Orstavik *et al*[29] was used for diagnosis of periapical health by only three authors, who regarded the PAI-scores 3-5 as positive finding[3,28,30].

For Peltola *et al*[31] "A radiolucency measuring > 2 mm in the apical bone was considered to be an apical rarefaction". Nalçaci *et al*[26] cited Soikkonen *et al*[32] method: "A periapical lesion, interpreted as apical periodontitis, was recorded if there was a clearly discernible local widening of the apical periodontal membrane space". But, this approach is not described within this referred citation (handling edentulous patients at all). Hakeberg *et al*[33] divided "Periradicular destructions … into three different classes according to size; 1 = pathologically altered lamina dura and radiolucency less than 2 mm, 2 = radiolucency of 2-10 mm, 3 = radiolucency > 10 mm"[33], and set grade 2 as cut-off for affection. The earliest grading found was in Lilly *et al*[8] 1967: "less than 5 mm and 5-10 mm apical translucency"[8].

The remaining five articles only mentioned to evaluate "apical radiolucencies"[17], "periapical lesions"[5], without further criteria or mentioning additions like: "radicular cysts as well as sclerotic periapical lesions indicating con-

densing osteitis"[6,21], or "sign of osteolysis"[12].

Alveolar bone level

The most various methods in assessment and reporting were found for alveolar bone level.

Metric measurements were used by five authors[6,7,17,21,33]. In addition to this following groupings were found: "≥ 6 mm, ≥ 4 mm"[17], "> 1-3 mm, > 3-6 mm, > 6 mm"[6], "< 2 mm, 2-4 mm, > 4 mm"[33]. "< 4 mm = moderate periodontitis, > 4 mm = severe periodontits"[7].

To relativize metric measures the following formula for alveolar bone loss is used: "total bone height divided by total root length [the distance from the radiographic apex to the cemento-enamel junction (CEJ)] multiplied by 100.", and applied *i.e.*, by Tabrizi *et al*[11].

Rosenquist[5,12] decided to use a modified criterion of Lindhe[34]: "< 1/3 of the root length, > 1/3 of the root length, and horizontal loss supporting tissues, > 1/3 of the root length, angular bony defects and/or furcation involvement" which is similar to Nyman *et al*[35] cited by Tabrizi *et al*[11]. Two authors used a relative root length, but went for an overall approach and added a criterion for "diseased" *via* their amount of findings: "≥ 30% of the sites with ≥ 1/3 bone loss"[36] and "including one or more teeth"[37].

Semiquantitative approaches were found specified: "classified as extension to: (1) to the coronal third of the root; (2) the middle third of the root; and (3) the apical third of the root"[18,21]. Graduations apart from thirds exist also: *i.e.*, as an ordinal scale with five grades: "0%, 1%-24%, 25%-49%, 50%-74%, or ≥ 75%"[38] or with only one cut-off point as: "one-fourth or more of the normal bone height"[37].

A direct measurement of ABL-percentages was developed by Schei *et al*[39] and used by only one author[38].

For two authors "A healthy horizontal bone level was considered to be 2 mm"[21,31]. Huumonen *et al*[3] graded into "(1) No bone loss, bone level within 2-3 mm of the cemento-enamel junction area; (2) Slight bone loss, bone level at the cervical third of theroots; and (3) Moderate to advanced bone loss, bone level between the middle third of the roots at or beyond the apex"[3]. Slightly different graduation-starting out the same with level 0-Nalçaci *et al*[26] continues: "(1) Moderate bone loss, bone level at the middle third of the roots; (2) Advanced bone loss, bone level at the apical third of the roots; and (3) Severe bone loss, bone level at or beyond the apex", but did not mentioned a cut-off. So it remains unclear (ND) what the reported "horizontal bone loss" is intended to be.

In three cases the results were presented with previously not defined expressions like "periodontal problem"[18] or undefined graduations like "Slight marginal bone loss … and vertical bone loss"[19]. The definition lacks what exactly is supposed to mean "affected" in this context. Likewise less helpful is a more historical graduation we came over: "If considerable bone loss was seen, this was called 'gross periodontal disease'. If there was pronounced 'arclike' bone loss limited to the molar and incisor regions, this was designated as periodontosis"[25].

One methodical article on forensics was coping with the calculation of DMFT and DFT-Index. They stated within their material and method section to grade ABL of 2nd premolars towards the criteria "0, less than half of first third, up to third of root, more than a third". But the findings were not reported at all[14].

DISCUSSION

The diversity of assessments and report modes is found to be alarming. The applied search strategy covers only a small, but high-ranked, sample of articles handling radiographic findings. It has to be assumed, that diagnosis and report of the entities studied here are not standardized at all, as it is for clinical dental status, namely the DMFT-, CPITN-, PI-, or BOP-Index for example.

In the following, each above mentioned and studied entity is discussed critically towards assessment and report. Further consequences are subsumed.

Number of teeth and implants

The method to identify teeth from a radiograph is quite simple. Not so the communication of amounts and values.

Commonly, every time when the descriptive level of absolute frequencies (*i.e.*, number of affected patients) is not used, the calculation has to be relative to a standardized data-set (*i.e.*, all patients studied, all patients with root canal treatment). It gets even more complicated, if the complete dentition is handled as an entity: When median-or mean values are used, the calculation base has to be clear. For the first: including the third molars to the calculation, or not? For the second: how to handle missing or supernumerary teeth? For the third: are edentulous patients excluded[17,40], or included to the calculation-or have there been other selection criteria like "at least 15 remaining own teeth"[9]?

Unfortunately this was not clear for 9 out of the 37 studied papers. Twenty-three included, 4 excluded, the third molars for evaluation. Two articles presented both approaches. Due to the variety of third molars dental history (retention, extraction) it make sense-similar to DMFT Index-to exclude these, if these are not primary focus of a study. Please follow the subheading "report of values" below, where more inherent details are addressed.

Against the backdrop of costly dental implants as a routine therapy after about 40 years now, their presence in oral status should be reported. Their number can give not only important dental input, but also ideas towards the financial background of an individual patient, a group, a whole cohort or even the social system.

Carious lesions, fillings and restorations

The detection of carious lesions within radiographs is discussed and researched by operative dentistry, foremost. Searching "detecting caries and X-ray" *via* Pubmed/Medline results around 100 findings. The definitions used by the authors studied herein are inconsistent. This is why

a clear statement which definition can be used as a gold standard to assess a tooth as affected by caries, would be favorable. We found the approach of Pelton and Bethart the most reproducible[20].

As fillings are made from radiopaque resin, cement, compomer, or metal, these can be easily seen on radiographs. If a restoration material is only slightly radiopaque, like silicate ceramic, the used adhesive composite or luting cements is clearly visible. However, the size of restorations can only be guessed, due to the 2-dimensional projection. But, the amount of decay could be derived from the ratio of filling and remaining coronal tooth substance.

These remarks are valid for fixed restorations (crowns, pontics) too. For all of these 3 findings, the mode of report as a comparable number and the report of missing values has to be standardized.

Root canal fillings

Root canal fillings can be recognized just as easily as a tooth or restoration itself can be, because radiopaque materials are used around the world very commonly. Two authors judged the quality of root canal fillings[3,30]. If the quality or length of root canal fillings should be regarded or not, remains to be discussed by endodontologist. Works about the potential already exist[41]. Furthermore the existence of root canal posts has to be taken into account. Some of these are either not radiolucent (Fiberposts) or radiopaque and due to their form not possible to distinct from a perfect root canal filling.

Regarding the reporting mode as frequency or percentage is same as discussed for missing/remaining teeth. Furthermore reporting authors should care about the problem that the number of teeth is easier to compare than the number of roots or even root canals. Moreover the values of root canal treatments should be reported separately from apical affection(s) of a tooth or root.

Apical health

Beside the controversy of detection capability with periapical and panoramic radiographs (augmented with the problem: digital *vs* analog), the key point is to diagnose the affection in awareness of healthy variations-without a clinical examination. This is analog to the detection of caries. The method of the PAI by Orstavik *et al*[29] is a good example for standardization and should be used more often. This 5-grade assessment tool is based on standardized pictures. It might be most reliable if used with a cut-off at Grade 3.

Confusing is the usage of "lesion" or "finding" in contrast to "affected tooth", because *i.e.*, a lower first molar may have 2 apical or carious lesions (mesial and distal), but is only 1 affected tooth. As for the above-mentioned root-canal fillings, at this point of time no consensus could be found. But, we found one possibility for clarification: "For multi-rooted teeth, the root presenting the highest PAI-score and the quality of the corresponding root filling was used"[30].

Alveolar bone loss

The "radiographic alveolar bone loss" is one classical research dimension of periodontology and implantology. Thereby it has been of interest for ages-expressed in hundreds of publications. Thus radiographic assessment of this entity is just as many-faceted. Two general approaches could be identified: metric measuring and proportions of bone height towards root length. The latter might be the better choice due to the variety of root length by anatomy and radiographic projection. Moreover, approaches including the age dependence of bone loss are described[42].

Beside bone level, furcation and vertical defects might be taken into account, too. The authors do not want to judge, which way is the best. But, even if a standard can be found in the future, also the cut off values for healthy and affected shall be defined by the authorities (see caption "grading and cut-offs"). Until then, the authors find the relative approach coping with the "first third of the root", described by Nyman *et al*[35], the most reliable.

Missing values/misinterpretation

Depiction problems of X-rays may lead to missing values, because it is not always possible to state a finding (*i.e.*, the vertical alveolar bone height by overlapped projection of two teeth, carious lesion at a filling by a "burn out" artifact). Only 5 papers mentioned depiction problems right in their material and methods section as follows: "If the image of the permanent teeth was blurred, supplementary digital intraoral radiographs were taken of these teeth"[28], "For areas poorly visible in the panoramic radiograph, intraoral radiographs were made"[6,26,37], "A tooth was judged as non-measurable if the CEJ or bone crest could not be identified properly because of overlapping caries or restorations. In cases where any one of the dental or bony landmarks could not be identified on one aspect (mesial or distal), the tooth was excluded"[11]. Projection artifacts may also lead to misinterpretation, which is mostly ruled out by the use of 2 examiners and/or reliability assurance. Such problems were solved differently: "In case of disagreement between the observers, their mean is used in the calculation"[43].

"Only panoramic radiographs that displayed the whole dentition without asymmetry, distortion or error in patient positioning were included"[2], "The radiographs were assessed twice, the first time by each dentist separately and next time by all in cooperation"[10].

One article announced within materials and method section: "Missing values were registered with suitable so-called 'missing values"[9], but-it was true for all articles above mentioned, these values were not reported.

One of the articles revealed depiction problems while studying the X-rays and stated: "A total of 54 teeth, most often maxillary pre-molars, were excluded"[11].

Discussions about sensitivity and specifity of panoramic radiographs were only anecdotal, not concrete. Montebugnoli *et al*[44] dropped an important sentence, which was unfortunately not discussed further or towards their findings: "Other factors that could affect the outcomes include differences in the way of measuring … dental status (the measures used to assess the oral status seem to be related to the strength and significance of the

associations reported)"[44].

Beside this, Langland *et al*[16] mentioned within their comparative study in 1980: "Discrepancies in the percentages of periodontal disease may be attributed to variance in the classification of each disease entity each year …."[16] and also Grover *et al*[7] did so in 1982: "Several discrepancies in findings … explained by variance … in diagnostic methods". One author explicitly complained about the absence of guidelines and stated: "We found it difficult to clearly define what a short root was and how to define early obliteration of the pulp. There are no guidelines in the literature, which defined what is a short root, and what is obliteration. For that reason it was difficult to compare our data with earlier studies"[10].

In summary, it has to be pointed out again, that panoramic radiographs can be regarded as sufficient diagnosis instrument. During the past 5 years digital imaging made great strides. But, sufficient comprehensive data about quality progress is not published yet. Nonetheless, the assessment of dental findings within a radiograph is restricted by anatomical deviations of oral structures, such as dislocation or rotation of teeth. That implies missing data are common in radiographic based studies-especially for alveolar bone loss, apical health and caries. The option of an "indiscernible/unclear" criteria will reduce bias since firstly, no accidental attribution as "affected" or "healthy" have to take place, secondly an idea about overall image quality is given.

Such missing values may be handled statistically, but have to be reported and how these were regarded in calculation.

Report of values: Mean and median, absolute frequencies and percentages

The number of remaining and missing teeth is reported most frequently (see caption "missing/remaining teeth and implants"). But even in this case, comparability is difficult due to the different modes of reporting. 4 authors decided for the report of median-number, 16 for mean, 6 for absolute frequencies. The same utilization can be found across the other studied entities: caries, root-canal-filled teeth, apical lesions and even alveolar bone level.

For the report of frequencies the use of median values can be assigned as the better choice due to its lower susceptibility towards extreme single values and the non-normal distribution of remaining and missing teeth in patients. To clarify the distribution of data we recommend the report of both: mean and medium value, augmented with SD, range and quartiles.

Dichotomization, groups, grades and cut-offs

A grouping of age, findings, measures are often necessary for further analyses, especially to calculate odd-ratios or only to compare such "self-made" groups. Grouping with a cut-off allows additionally to report absolute and relative frequencies of teeth or patients, instead of mean or median values. Examples for the last mentioned would be "1-10 missing teeth" or "< 20 remaining teeth". Especially the rationales behind the cut-offs points are questionable. Sometimes these are set following previous analysis of the same sample, such as: "Each group comprised one-third of the dentate subjects in the baseline study"[6], or "Each dental index was dichotomized at the mean value"[44]. It can also be empirical reasons as: "The cut-off point (< 45 and > 45 years) was selected in accordance with the introduction of a new social-security law"[21]. However, cut-off points for "healthy" and "diseased" varied, especially if diagnosis of alveolar bone height and apical lesions are dichotomized for analyses, graphic art and report.

With such intervention to data, these are not universally valid anymore. Further comparability is hindered, if the crude data are not available from the paper.

The DMFT and other sum scores

Three authors reported DMFT-values[11-13]. One team reported only the number of patients (one time as percentage, one time as an absolute frequency) with a DMFT value of zero[19,31]. The DMFT would be helpful for a comparison with existing epidemiological data, but it hinders to extract missing/remaining teeth if only given as a sum score. If not separated by the author, no more information can be extracted from the DMFT; the DMFS is even worse. Furthermore alveolar bone level and apical health are not covered within this (exclusively) clinical index.

Within our review other indices could be found: six authors cited Mattila *et al*[45]: "Association between dental health and acute myocardial infarction" and their sum score of a "Total Dental Index" or "Pantomographic Index"[6,12,18,46]. This is also cited as panoramic tomography score, which is "the sum of radiolucent periapical lesions, third-degree caries lesions, vertical bone pockets, radiolucent lesions in furcation areas[47]" and was applied by Montebugnoli *et al*[44]. Even if published and cited in high-ranked journals, we found this system neither comprehensible in development nor validated for multipurpose application. Its focus is both: infective oral lesions in a combination of oral and radiographic evaluation as well as from radiographic assessment itself. Furthermore the description of index does not contain either methods of oral nor radiographic assessment for its entities. Despite of this fact, the sum of total dental index (TDI) can reach values "between zero and 10"[45]. Nevertheless, the scale of this cited index varies between publication due to modification by the authors: "0-14"[48], "0-8"[49], "0-10"[18,50], 0-15[6]. Seppänen *et al*[18] used a classification of the sum scores "good, moderate and poor" which was not established by Mattila *et al*[45] 1989 as cited in this very article. Montebugnoli *et al*[44] decided to dicromize "each dental index … at the mean value". Buhlin *et al*[49] separated the index according to the statement "TDI of 0 or 1 are considered to have good oral health and those with TDI 4-8 have poor". Especially these inconstancies left this tool highly questionable. However, further investigation is needed for a concluding evaluation of this approach. Beside, and discussed for the DMFT, a sum score-with such complexity of terms-might not be

useful for report. Foremost because, the values of each contained entity are not given to the reader and for future comparison.

Limitations of this report

This report is only based on articles indexed at PubMed/Medline. The variety of applied approaches was expected to grow if further databases (*i.e.*, EMBASE or MEDPILOT) are searched. Although this might harden the presented conclusion, it would not rise the informative content of this report.

Detailed information about type of X-ray and films used as well as acts of calibration of examiners was not included to this review. We took into account, that journal reviewers have already checked the applied intervention and found these appropriate. Furthermore, the widespread use of dental radiographs implies standardization on a reasonable level and quality. Findings in adults were favored, due to the variety of radiographic studies and dentition in children and adolescents. The variety of the mixed dentition is in fact a problem of standardization. The authors are aware that for every entity studied within this review, hundreds of other articles exist and there might be even standards scientists agree on. But, this can only be figured out by further systematic reviews-one for each entity and a final harmonization in a reporting guideline. Such a general guideline would support the authors preparing their studies and manuscripts as well as the scientists to compare data.

Only one article covered all entities studied in this review[26]. Nevertheless, all researches would have been enabled to report all these entities. Evidently it is often not of interest to report about *i.e.*, alveolar bone loss while presenting results about the prevalence of apical lesions. Nonetheless, such data would contrast and illustrate findings by thorough information about the studied cohort. More accompanied information could be conveyed about dental status of studied subjects. Thus, comparability and multi-variate analyses would be simplified generally. The authors think it would be worthwhile to have an easy reporting system of all entities. Today's possibilities to provide such data digital *via* online publication would enable authors and publishers to share data without expensive printed pages.

There are established but not generally accepted and enforced standards to assess and report findings from radiographic surveys. Thereby comparability of published findings is only possible with chief limitations. There is need to agree on standardized assessment and diagnosis first, and about the mode of report secondly. An easy and validated multi-term report-system of dental status would allow a widespread application, especially for dental public health and epidemiology. In consequence: there is need for a reporting guideline.

COMMENTS

Background

Reporting standards are necessary to compare research outcomes especially in medical science. Full-mouth radiographic surveys allow information about the dental status. These are: number of teeth, caries, fillings/restorations, root canal treatments/filling, apical health and alveolar bone loss. But findings have to be evaluated and reported in such a way, that a comparison between published results is possible. There is no reporting guideline, yet. Which mode of report could be proper is neither finally discussed nor published. The paper shows shortcommings in current acquisition and presentation of data, hereinafter it recommends suitable methodical approaches.

Research frontiers

Dental radiology, epidemiology, research methodology in dentistry and medical statistics for oral health variables.

Innovations and breakthroughs

Only 8 out of 37 scientifically papers are at the maximum comparable towards 3 out of 7 entities of dental status. Evaluation of radiographs differ is widely. Reporting with statistical tools like mean and median or grouping and dichotomization did not allow further comparison, due to a lack of raw data. Also sum scores or indices like Decayed, Missing and Filled Teeth (DMFT) impede comparability of data. Thus no standard could be identified. Besides, missing values are underreported.

Applications

A guideline of standards for evaluation, report and cut-off points is needed. So far it can be advised, that: (1) depicting problems and resulting missing values are reported; (2) it must be stated, if third molars are included or not when reporting the number of missing or remaining teeth; (3) implants should be taken into account; (4) sum scores are only present with crude data of the study. In case of DMFT the decayed teeth, missing teeth, filled teeth and decayed and filled teeth should be given separately, too; (5) apical health should be evaluated with a validated tool preferably the Peri-Apical-Index; (6) alveolar bone loss should be evaluated and reported in exact percentage or "in thirds" (Lindhe) not in absolute millimeters; (7) all distributions of data are presented with mean and medium value, augmented with SD, range and quartiles; and (8) the reader is given the rational for grouping or a cut-off point if data is dichotomized.

Terminology

"Full-arch radiographs" are radiographs taken mostly in dental office and depicting all teeth (including the complete root) of a human dentition. Mostly a so called "panoramic radiograph" is taken; but also a survey with intraoral radiographs can be applied. "Apical health" describes the situation around the tip of the tooth root inside the bone of the jaw. This area might be retreat for bacteria causing a painless infection, which is relevant for systemic health and inflammation parameters. Such infections can be detected by radiographs. "Alveolar bone loss" describes the loss of jaw bone around teeth. The amout of lost bone correlates with the infection of tissues around teeth, which is a multifactorial disease promoted by bacteria. As seen in the radiograph the occurrence of a a so called "periodontitis" (inflammation of the gums) can be anticipated by the loss of bone. "DMFT" is the World Health Organization-standard to report a clinically assessed dental status. It is namely the sum of Decayed, Missing and Filled Teeth in a dentition. "Reporting guideline" is a standardization for scientific reporting of findings. Today many such guideline exists in Medicine (www.equator-network.com).

Peer review

It is a well organized and written paper.

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CASE REPORT

Chemotherapy induced Takotsubo cardiomyopathy

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Abstract

Chemotherapy has been linked with Takotsubo cardiomyopathy. Most of the literature on chemotherapy associated Takotsubo cardiomyopathy is on the drug 5-fluorouracil. In this report, we describe the case of a 55-year-old Asian male who developed Takotsubo cardiomyopathy while receiving dual chemotherapy with cytarabine and daunorubicin for acute myeloid leukemia. To our knowledge, it is the first case of Takotsubo cardiomyopathy associated with daunorubicin and/or cytarabine.

Key words: Takotsubo cardiomyopathy; Chemotherapy; Cytarabine; Daunorubicin

Core tip: In this case report, we describe first case of Takotsubo cardiomyopathy associated with daunorubicin and/or cytarabine.

Goel S, Sharma A, Garg A, Chandra A, Shetty V. Chemotherapy induced Takotsubo cardiomyopathy. *World J Clin Cases* 2014; 2(10): 565-568 Available from: URL: http://www.wjgnet.com/2307-8960/full/v2/i10/565.htm DOI: http://dx.doi.org/10.12998/wjcc.v2.i10.565

INTRODUCTION

Chemotherapeutic drugs have a wide range of cardiotoxic effects. Recently, there have been case reports of chemotherapy [namely 5-fluorouracil (5-FU)] induced Takotsubo cardiomyopathy (TC)[1-5]. However, to the best of our knowledge, there has been no published literature on cytarabine and/or daunorubicin causing TC. In this report, we describe the case of a 55-year-old Chinese male who developed TC while receiving dual chemotherapy with cytarabine and daunorubicin for non M3 acute myeloid leukemia.

CASE REPORT

A 55-year-old male with past medical history of diabetes mellitus (type Ⅱ) presented to our hospital with complaints of pleuritic chest pain with non-productive cough and fever (Tmax 101.2 °F) for 3 d. Chest X-ray showed right-sided lung infiltrates. Patient was admitted to the medical floor with the diagnosis of community-acquired pneumonia and was started on moxifloxacin. The patient's blood work showed an incidental finding of 12% blast cells with a total white cell count of 9.9. Electrocardiogram performed on the day of admission revealed sinus tachycardia with abnormal R wave progression. Echocardiogram showed ejection fraction (EF) of 60%-65%, with normal chamber size and mild diastolic dysfunction. Three sets of cardiac enzymes including cardiac Troponin I and creatine kinase-MB were negative. Patient was evaluated by the hematology and oncology team for the incidental finding of blast cells on peripheral blood smear. The next day, as per the hematologist's recommendation, the patient underwent a bone marrow biopsy which showed the presence of pro-myelocytes, suggestive of M3 acute myeloid leukemia. The patient was started on All Trans-Retinoic Acid induction chemotherapy regimen. Prophylactic valacyclovir, omeprazole and intrave-

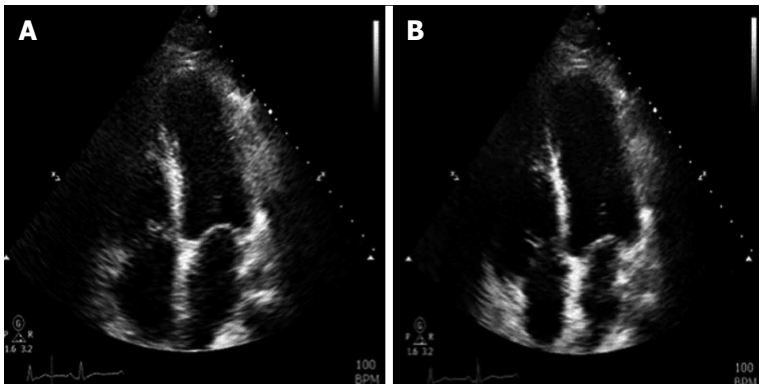

Figure 1 Echocardiogram showing ballooning of the apex with hyper contracted basal segment at end systole (A) end diastolic phase (B).

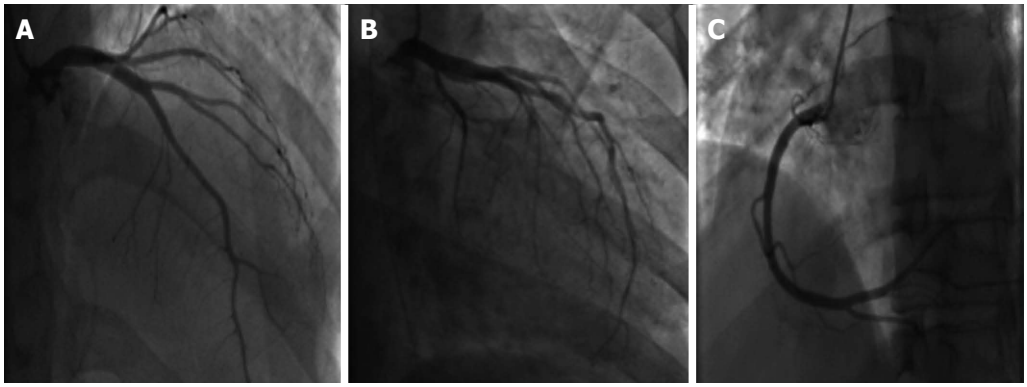

Figure 2 Coronary angiogram showing clean coronaries with thrombolysis in myocardial infarction 3 blood flow left main and left anterior descending (A), left circumflex (B) and right coronary artery(C).

nous (*iv*) fluids were also started.

Two days after the initiation of chemotherapy, fluorescent *in situ* hybridization results demonstrated a negative translocation of chromosomes 15, 17, thus confirming the diagnosis of non-M3. As a result, the chemotherapy regimen was changed to cytarabine 100 mg/m^2 and daunorubicin 60 mg/m^2. On day 6 of chemotherapy with cytarabine and daunorubicin, the patient began to experience non-radiating sub sternal chest pain associated with palpitations. Electrocardiogram obtained at that time showed sinus tachycardia of 170 bpm with ST segment elevation in leads I, aVL, V5, V6; consistent with anterolateral wall ST elevation myocardial infarction (STEMI). The patient was transferred to the cardiac intensive care unit (CCU) with a diagnosis of STEMI. Cardiac enzymes were obtained which showed Cardiac Troponin I of 8.54 upon initial transfer to the CCU, reaching a maximum of 38.64 after 18 h (normal values 0-0.1 ng/mL). Given the patient's immunocompromised state, cardiac catheterization was deferred and he was managed medically with aspirin, clopidogrel, rosuvastatin, and aggressive *iv* hydration. Echocardiogram done on day 6 of chemotherapy showed an EF of 30%-35% with segmental wall motion abnormalities: mild anterior, septal, apical, inferior and lateral wall hypokinesia, with normal diastolic function consistent with mid-left anterior descending artery occlusion (Figure 1). On day 20 of admission, patient underwent an elective cardiac angiogram, which showed non-obstructive coronary vasculature, mildly decreased left ventricular systolic function, EF of 50% with mild anterolateral and anterobasal hypokinesia (Figure 2).

DISCUSSION

This case report demonstrates a strong causal relationship between chemotherapy and the development of TC as evidenced in the patient's presentation on day 6 of chemotherapy induction. Symptomatic recovery of the patient after supportive medical management, with the concomitant discontinuation of the chemotherapeutic agent, also strengthens this causal relationship. The patient's repeat echocardiogram (performed 2 wk after discontinuation of the chemotherapeutic agents) showed a complete recovery of the EF with no wall motion abnormalities. In addition, a coronary angiogram demonstrated non-obstructed coronary vasculature. Given the patient's clinical presentation and the diagnostic evidence obtained, there is no alternative justification for the clinical course observed other than Takotsubo cardiomyopathy. This is the first case report of daunorubicin and/or cytarabine induced TC.

Most of the literature on chemotherapy associated TC is published on the drug 5-FU, a widely used chemotherapeutic agent for solid tumors. One case report from

Japan described daunorubicin-induced TC in a patient with refractory multiple myeloma[6]. However, to our knowledge, this is the first case report of daunorubicin and/or cytarabine induced TC in the United States.

Chemotherapy induces increased sympathetic tone with resulting elevation of cytokine, free radical, prostaglandin, catecholamine and growth factor levels. The excess of these modulators can potentiate worsening adrenoreceptor sensitivity, and can contribute to the clinical presentation of TC[1-5]. Daunorubicin belongs to the anthracycline class of chemotherapeutic agents, which remains among the most active anti-cancer drugs for solid tumor and hematologic malignancies. The exact pathogenic mechanisms responsible for the underlying cardiotoxic effects of anthracycline agents has yet to be elucidated. The current postulated mechanism supports the role of free radical induced cardiac damage (known to be caused by the excessive production of hydrogen peroxide, hydroxyl radicals and reactive oxygen species)[6-10]. These free radicals promote lipid peroxidation which contributes to cell membrane damage, and thus results in the activation of pro-apoptotic enzymes, such as Bax, Cytochrome-c and caspase-3, in myocyte mitochondria, triggering apoptosis and resulting in cardiac myocyte cell death[6-10]. Cardiac myocytes are more susceptible to lipid peroxidation due the presence of a high mitochondrial density with resultant high-energy requirements and the lack of anti-oxidant enzymes, which are required for the detoxification of superoxide anions and hydrogen peroxide. As a result of this cardiac myocyte susceptibility, a dose-related and irreversible loss of cardiac myocytes occurs, resulting in cardiomyopathy[11]. Though the exact mechanism of cardiotoxicity caused by cytarabine has yet to be elucidated, it is postulated that this drug can result in a hypersensitivity reaction or possible immune-mediated damage of cardiac myocyte[12].

In conclusion, we suggest that physicians be vigilant when treating patients with daunorubicin and/or cytarabine and should be aware of a possible association of these chemotherapeutic agents with TC.

COMMENTS

Case characteristics

A 55-year-old male receiving treatment with Daunorubicin and Cytarabine for non M3 acute myeloid leukemia (AML) experience non-radiating sub sternal chest pain associated with palpitations on 6th day after chemotherapy.

Clinical diagnosis

Acute coronary syndrome.

Differential diagnosis

ST segment elevation myocardial infarction (STEMI), non-STEMI, Unstable Angina, Aortic Dissection, Pulmonary embolism, cardiomyopathy, Ventricular wall rupture.

Laboratory diagnosis

Cardiac troponin I and creatine kinase-MB elevation with continued uptrend, consistent with myocardial ischemia.

Imaging diagnosis

Electrocardiogram-anterolateral STEMI; Echocardiogram (ECHO) at day 6 of therapy-ejection fraction (EF) of 30%-35% with segmental wall motion abnormalities; repeat ECHO (two weeks later)-Normalization of EF and no wall motion abnormalities; cardiac catheterization (two weeks later)-clean coronaries. Pt diagnosed with Takotsubo cardiomyopathy.

Treatment

Due to patient's immunocompromised state, he was medically managed with aspirin, clopidogrel, rosuvastatin, and aggressive intravenous hydration in cardiac intensive care unit.

Related reports

Patient initially thought to have acute coronary syndrome but was eventually found to have Takotsubo cardiomyopathy. Patient had clean coronaries on Cardiac catheterization and on repeat ECHO, his EF normalized and wall motion abnormalities resolved.

Term explanation

Non M3 AML-According to French-American-British classification acute myeloid leukemia are sub grouped in to 8 categories M0-M7. This classification guides the therapy and prognosis in patients diagnosed with AML.

Experiences and lessons

Vigilance should be observed while treating patients with daunorubicin and/or cytarabine.

Peer review

This is first case report of takotsubo cardiomyopathy associated with daunorubicin and/or cytarabine.

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CASE REPORT

Intensive outpatient comprehensive behavioral intervention for tics: A case series

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Abstract

Recent randomized clinical trials have established the efficacy of Comprehensive Behavioral Intervention for Tics (CBIT) in treating children and adults with Tourette syndrome and persistent tic disorders. However, the standard CBIT protocol uses a weekly outpatient treatment format (*i.e.*, 8 sessions over 10 wk), which may be inconvenient or impractical for some patients, particularly patients, who are required to travel long distances in order to receive care. In contrast, an intensive outpatient program may increase accessibility to evidence-based behavioral treatments for Tourette syndrome and other persistent tic disorders by eliminating the necessity of repeated travel. This case series evaluated the use of an intensive outpatient program CBIT (IOP CBIT) for the treatment of 2 preadolescent males (ages 10 and 14 years) with Tourette syndrome. The IOP CBIT treatment protocol included several hours of daily treatment over a 4-d period. Both children evidenced notable reductions in their tics and maintained treatment gains at follow-up. Moreover, both patients and their parents expressed treatment satisfaction with the IOP CBIT format. This case series addresses an important research gap in the behavioral treatment of tic disorders literature. The patients' treatment outcomes indicate that IOP CBIT is a promising treatment that warrants more systematic investigation.

Key words: Tourette syndrome; Tics; Habit reversal; Intensive outpatient; Behavior therapy

Core tip: Comprehensive Behavioral Intervention for Tics (CBIT) is an empirically supported treatment for individuals with Tourette syndrome. However, the standard, weekly outpatient format of CBIT may preclude some from receiving care. This is the first case series to examine the treatment outcomes of intensive outpatient CBIT (Intensive Outpatient Program CBIT) in children. Despite marked differences between the two boy's presentations, outcomes for both cases were positive.

Blount TH, Lockhart AT, Garcia RV, Raj JJ, Peterson AL. Intensive outpatient comprehensive behavioral intervention for tics: A case series. *World J Clin Cases* 2014; 2(10): 569-577 Available from: URL: http://www.wjgnet.com/2307-8960/full/v2/i10/569.htm DOI: http://dx.doi.org/10.12998/wjcc.v2.i10.569

INTRODUCTION

Tourette syndrome (TS) is a disorder characterized by multiple motor tics and at least one vocal tic that occur regularly and are present for at least 12 mo[1]. On average, tics emerge between the ages of 3 and 8 years, peak between 10 and 12 years, and decrease in adulthood[2,3]. An estimated 60% of children with Tourette syndrome also

meet diagnostic criteria for at least one psychological disorder, with attention deficit hyperactive disorder (ADHD) being the most common comorbid condition[4], followed by obsessive compulsive disorder (OCD), social anxiety, depression, and externalizing behaviors[4-6].

Standard treatments for tourette syndrome and persistent tics

Historically, pharmacologic interventions have been used as the first-line treatment for symptom management in Tourette syndrome patients[7]. However, medications require long-term continuous use and are associated with negative side effects that frequently lead to discontinuation of treatment (for review, see[7-9]). Alternatively, behavioral interventions reduce concerns regarding negative side effects and potential long-term consequences of prolonged medication use. A number of behavioral interventions have been examined (for review, see[10]) with habit reversal therapy[11] garnering the most support (for review, see[12]). Habit reversal consists of awareness training, contingency management, relaxation training, competing response training, social support, and generalization training.

Comprehensive Behavioral Intervention for Tics (CBIT)[13] is a multiple-component behavioral treatment for Tourette syndrome and persistent tic disorders that expands on the original habit reversal therapy protocol and includes additional emphasis on psychoeducation, functional interventions, and relapse prevention. Recently, two large randomized controlled trials examined the efficacy of CBIT compared to supportive therapy in adults and children diagnosed with Tourette syndrome and persistent tic disorders. The child study (n = 126; mean age 11.7 years) found that CBIT was superior to a psychoeducation and supportive therapy comparison condition in reducing tics (52.5% *vs* 18.5%, respectively)[14]. The adult study (n = 122; 16-69 years) also found superior results for CBIT, with 38.1% of the participants who received CBIT *vs* 6.4% in the psychoeducation and supportive therapy condition experiencing a significant improvement in their tics symptoms at post-treatment[15]. Importantly, both adults and children in the CBIT condition maintained treatment gains and reported decreased psychological symptoms at the six-month follow-up.

Taken together, these findings indicate that CBIT produces similar outcomes as medication without the side effects and that patients continue to experience benefits after treatment is completed[14]. In response to mounting evidence, CBIT is now considered a first-line treatment for persistent tic disorders in Europe[12] and Canada[16].

Rationale for intensive outpatient CBIT

The standard outpatient CBIT protocol is comprised of eight sessions that are completed over 10 wk, followed by three monthly booster sessions. However, weekly sessions may be inconvenient or impractical for some patients depending on the complexity of their symptoms or their accessibility to care. Instead, these patients may benefit from an intensive outpatient program (IOP) that compresses CBIT into a week-long protocol. An IOP can help extend treatment catchment areas and compensate for the current lack of CBIT providers. Importantly, IOP also allows for patients to practice CBIT without the distraction of school or work. This is particularly relevant to the use of the competing response procedure, which is to be implemented upon the detection of a premonitory urge to tic or the actual occurrence of a tic. The IOP CBIT allows patients to dedicate time specifically to detecting urges and tics and implementing the competing responses without the distractions of day-to-day life. To date, no studies have been published evaluating the effectiveness of an IOP CBIT. However, Flancbuam *et al*[17] presented a case study detailing the outcome of a 25-year-old male diagnosed with TS who traveled to the United States in order to receive seven sessions of adapted CBIT over two weeks[13]. The patient reported notable decreases in tic frequency and subjective distress and high treatment satisfaction at posttreatment, although he also reported a lapse in his tic symptoms when he returned home.

Little is known about the benefits of IOP CBIT, but there is precedence for treating children with an IOP behavioral program. For example, Whiteside and colleagues[18] present a case series of three adolescents who received 10 sessions of exposure and response prevention for OCD over five days. Each of the three adolescents experienced a decrease in OCD symptoms at posttreatment, and two maintained gains after three months. Moreover, an IOP (one session) protocol has been used to treat specific phobia in children and has demonstrated efficacy in three randomized controlled trials (for review, see[19]).

Goals of the case series

The current case series addresses an important limitation in the literature by examining whether IOP CBIT can help quickly reduce tic severity in two youth diagnosed with TS. Although the boys in the case series differed markedly by age, ethnicity, psychological symptoms, behavioral distress, and tic severity, and although they were treated by different treatment teams (see Table 1), both evidenced a notable reduction in tics and maintained their treatment gains. The patients and their parents provided written informed consent for this case series.

CASE REPORT

Patient A

Patient A (see Table 1) was a 10-year-old Asian-American male in the fourth grade. He was placed in the gifted-and-talented program and advanced mathematics. He maintained good grades but had occasional behavioral problems at school. He had several friends and was involved in piano, karate, and chess.

Patient A's tics were first noticed by his second grade teacher when he was 7 years old. He was evaluated by a neurologist and a psychologist a year prior to receiving IOP CBIT. Both diagnosed him with Tourette syndrome.

Table 1 Summary of patient information

	Patient A	Patient B
Age (yr)	10	14
Ethnicity	Asian-American	African-American
Academic history	4th grade Gifted and talented	9th grade Dysgraphia, low-intellectual functioning, and disorder of written expression
Psychological history	Tourette syndrome	Tourette syndrome, ADHD, specific phobia, anxiety, insomnia, and stuttering
Tic interference	Minimal	Significant
Type (number) of tics	Motor (5)	Motor (6) and vocal (4)
Treatment teams	Psychologist, psychology postdoctoral fellow, and psychology intern	Psychologist and two psychology postdoctoral fellows
Length of treatment	4 d, 8 treatment sessions	4 d, 3 treatment sessions

ADHD: Attention deficit hyperactive disorder.

Table 2 Patient A and B's outcome assessment scores

Measures	Baseline	1 wk posttreatment	1 mo follow-up	7 mo follow-up	Baseline		1 wk posttreatment		1 mo follow-up		6 mo follow-up	
	Patient A				Patient B							
	M	M	M	M	M	P	M	P	M	P	M	P
YGTSS												
Total	15	9	6	5	21	18	15	13	11	12	14	13
Number	2	1	1	2	5	4	4	4	2	2	2	2
Frequency	4	4	2	2	3	3	3	3	2	2	2	3
Intensity	4	3	2	1	4	4	2	2	3	4	2	4
Complexity	3	0	0	0	4	3	2	2	2	3	4	3
Interference	2	1	1	0	5	4	4	2	2	1	4	1
CGI-SI	4	3	2	2	5		3-4		3		4	
CGI-I		1	1	1	-		2		2		3	

M: Motor tic; P: Phonic tic; YGTSS: Yale Global Tic Severity Scale (Clinical Cut-off: 14), YGTSS subscales are out 5, with 0: None, 5: Severe; CGI-SI: Clinical Global Impressions-Severity of Illness (0: Not assessed; 1: Normal; 2: Borderline; 3: Mild; 4: Moderate; 5: Mark; 6: Severe; 7: Extreme); CGI-I: Clinical Global Impression-Improvement (0: Not assessed; 1: Very much improved; 2: Much improved; 3: Improved; 4:Minimal improvement; 5: No change; 6: Minimal worse; 7: Much worse; 8: Very much worse).

The neurologist recommended medication, which his parents decided against, and the psychologist recommended yoga and family therapy. They attended two sessions of family therapy but discontinued treatment after deciding that it was not helpful. After researching behavioral treatments on the Internet, Patient A's mother contacted one of the authors (ALP) to inquire about receiving CBIT for her son. Since the family would be required to travel to another city to receive CBIT, the staff and his mother agreed to use an IOP CBIT protocol. The patient presented for care in March 2013. At baseline, he and his mother reported that he experienced frequent facial tics that interfered with piano practice and chess competitions, but the tics did not interfere with his academic or social functioning. However, his mother was concerned that he would have tic-related social difficulties when he started middle school the following year.

Baseline assessment

A baseline assessment was conducted by a master's level independent evaluator (IE), who was not involved in the patient's treatment. The Yale Global Tic Severity Scale (YGTSS)[20] and the Clinical Global Impression Scale (CGI)[21] were administered at baseline, posttreatment, and follow-up and were the main outcome measures for treatment (see Table 2). The YGTSS, a semi-structured clinical interview, is routinely used in the TS literature and has well established psychometric properties (*e.g.*,[14, 20, 22,23]). It provides a Total Motor Tic Score (range: 0-25), Total Phonic Tic Score (range: 0-25), Total Tic Score (range: 0-50); past studies have used YGTSS Total Scores greater than 13 as a cut-off for clinically significant tics (> 9 if patient has only motor or vocal tics; *e.g.*,[14]). A decrease of 4 points on the YGTSS is considered clinically meaningful in children[14]. The YGTSS was conducted by the IE and was completed by the patient with the help of his mother. The CGI-S and CGI-I scales are well-established rating tools applicable to all psychiatric disorders[21]. The CGI-S scale is used to assess treatment response in patients. The CGI-S requires the clinician to rate the severity of the patient's illness at the time of the assessment, relative to the clinician's past experience with patients who have the same diagnosis. The CGI-I requires the clinician to rate how much the patient's illness has improved or worsened relative to a baseline state.

The IE also administered the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version[24], a semi-structured clinical interview designed to determine present episode and lifetime history of psychiatric illness based on the diagnostic criteria of the

Table 3 Overview of Patient A's treatment schedule

	Day 1	Day 2	Day 3	Day 4
Session	1:90 min	3:60 min	5:60 min	7:60 min
Number	Review history	Review OOSAs	Review OOSAs	Review OOSAs
	Treatment rational	Inconvenience review	Inconvenience review	Inconvenience review
	Psychoeducation	Review treatment tic 1	Review treatment tic 1-3	Review treatment tic 1-3
	Tic hierarchy	Functional intervention	Functional intervention	Functional intervention
	Introduce function-based interventions	Competing response tic 2	Competing response tic 2	Competing response tic 2 Review relaxation
	Introduce reward program	Reward review	PMR	Relapse prevention
	Teach tic monitoring		Reward review	Reward review
Lunch (2 h)	Monitor tic 1	Monitor tics 1, 2	Monitor tics 1-3	Monitor tics 1-3
	Functional assessment	Practice CRs 1, 2	Practice CRs 1-3	Practice CRs 1-3
Session	2:90 min	4:60 min	6:60 min	8:60 min
Number	Review OOSAs	Review OOSAs	Review OOSAs	Review OOSAs
	Inconvenience review	Inconvenience review	Inconvenience review	Inconvenience review
	Functional assessment and treatment tic 1	Review treatment tic 1 and 2	Review treatment tic 1-3	Review treatment tic 1-3
	Competing response tic 1	Functional intervention tic 3	Functional intervention tic 2	Functional intervention
	Reward review	Competing response tic 3	Competing response tic 2	Competing response tic 2
		Introduce relaxation	Review relaxation	Review relaxation
		Diaphragmatic breathing	Reward review	Relapse prevention
		Reward review		Reward review
OOSAs	Practice CR for tic 1	Practice CRs tics 1-3	Practice CRs tics 1-3	Posttreatment assessment
	Monitor 30 min	Monitor 30 min	Monitor 30 min	
		Relaxed breathing	Relaxation	

CR: Competing response; OOSA: Out of session assignment; PMR: Progressive muscle relaxation.

Table 4 Patient's A tic symptom hierarchy tracker ratings

	S1	S3	S4	S5	S6	S7	S8	1 mo	6 mo
Eye Blink	6	6	4	4	3	1	2	0	1
Upper Lip	4	4	4	1	1	0	1	0	0
Facial Grimace	6	6	0	1	1	0	0	0	0
Neck Jerk	9	3	2	1	1	0	1	1	0
Nose Flair	4	4	0	0	0	0	0	0	0

Session 2 (S2) scores were not recorded; Subjective Unit of Distress Scale range from 0 to 10, with 0: No Distress; 10: Extreme distress.

Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision[25]. In addition, the patient completed the Premonitory Urge Scale[26], the Child Yale-Brown Obsessive Compulsive Scale[27,28], and the ADHD Interview[29] at baseline. These commonly used measures were selected to provide a comprehensive evaluation of the patient's tic-related symptoms and psychiatric functioning.

The assessment confirmed a diagnosis of Tourette syndrome with evidence of clinically meaningful motor tics. He had a history of vocal tics but was not experiencing them at the time of the assessment. He did not endorse OCD symptoms and reported only minimal ADHD symptoms. Patient did not meet diagnostic criteria for other Axis I diagnoses.

Formulation, rationale, and treatment plan

Environmental and social factors are believed to play a significant role in tic manifestation[22]. CBIT is an evidence-based behavioral treatment that recognizes and targets these factors. The patient completed eight sessions (60 to 90 min each) of CBIT over four consecutive days (see Table 3). The protocol was administered by a treatment team, including two licensed psychologists and a pre-doctoral psychology intern.

Course of treatment

Psychosocial and tic history were gathered and treatment rationale was provided in Session 1. Consistent with the CBIT manual, Session 1 focused on information gathering and providing a treatment overview and rationale. Patient A's mother was already well versed on TS. Patient A and his mother identified five current motor tics (neck jerk, eye blink, upper lip tic, facial grimace, and nose flair) that occurred in isolation and as a single complex tic (see Table 4). Tic monitoring and the role of social support to encourage skill use were introduced and a reward program was established to reinforce treatment compliance.

The Tic Hassle worksheet[30], the functional assessment procedure, and the competing response procedure were introduced in Session 2 and were conducted each session for the remainder of treatment. The Tic Hassle worksheet uses a Subjective Units of Distress Scale (SUDS), in which patients verbally rate their level of distress on an 11-point scale, with 0 representing minimal distress and 10 representing extreme distress. In Session 2, Patient A identified neck pain (SUDS = 9), people noticing (SUDS = 3), his grandfather staring at him (SUDS = 4), interruption of piano practice (SUDS = 6), and increasing the time it takes to complete school work (SUDS = 5) as tic hassles. By the end of the eighth session, he no longer experienced distress from these hassles. Patient A and his mother had difficulty completing the functional

assessment for the individual tics throughout treatment. They reported that the tics occurred with equal frequency across all settings and denied consequences following tic occurrence. Moreover, due to the format of treatment, they had little to no opportunity to implement relevant function-based interventions at home.

Competing response training focused on one tic at a time, starting with his most distressing tic (*i.e.*, neck jerk tic). This component of treatment requires that patients become more aware of their tics and premonitory urges. Consequently, Patient A was asked to describe his tic and its corresponding premonitory urge, identify each time he engaged in the tic during the training, and then identify each time he experienced the premonitory urge. Next, the patient and the provider collaboratively selected an appropriate competing response. Effective competing responses are physically incompatible with and less conspicuous than the tic, can be performed for at least 60 s, and do not disrupt normal activity[13]. For example, the competing response for the patient's neck jerk tic involved having him gently move his chin forward and focusing on one spot each time he experience the tic or the premonitory urge. Self-monitoring indicated that his neck jerk tic occurred frequently (30 times in 5 min). By Session 4, he described decreased neck pain, and his mother reported a notable decrease in the neck jerk tic. The competing response training was implemented for his eye-blink and lip tics in Sessions 3 and 4, respectively. His competing responses included slow, rhythmic blinking for the eye tic and pursing his lips gently together for the lip tic. He demonstrated quick mastery over the lip tic but continued to have difficulty with his eye-blink tic. Consequently, the eye-blink tic remained the focus of CBIT for Sessions 5 to 8. By Session 8, both he and his mother reported improvement in his eye-blink tic, although his mother still occasionally had to prompt him to engage in his competing response.

Relaxation training was initiated in Session 4, and relapse prevention was discussed in Sessions 7 and 8. Since they had previously disagreed about what constituted a tic, both the patient and his mother were asked to discuss how they would handle new tics should they emerge. Ways to communicate about potential tics were explored, and a plan for this type of conversation was developed. At the end of treatment, both Patient A and his mother expressed high treatment satisfaction.

Patient B

Patient B (see Table 1) was a 14-year-old African-American male. He participated in a home school program in which he attended classes several times per week outside his home and was also involved in track and field. At the time of the intervention, Patient B had not shared information about his diagnosis with peers. As a result, he often suppressed his vocal and motor tics when around peers and then released his urges to tic at home. At intake, Patient B's vocal and motor tics had occurred for approximately six months. He had already been evaluated by pediatric neurology and developmental pediatrics and was prescribed methylphenidate for ADHD, clonidine for tics, and melatonin for sleep. Patient B completed an magnetic resonance imaging and electroencephalography with pediatric neurology, and it was determined that he did not present with epilepsy or other neurological concerns. When the tics were unresponsive to medication intervention, Patient B and his family were referred for behavioral treatment. Patient B's psychological history was positive for developmental delays, ADHD, and learning difficulties, with no prior history of tics. He had previously undergone treatment for specific phobia and stuttering.

Patient B presented for behavioral treatment in Spring 2012. Given the severity of his behaviors at his initial appointment (*i.e.*, grabbing his mother's arm, punching the floor, and difficulty starting and stopping movements), consultation with ALP was sought regarding the appropriateness of outpatient services. It was determined that he might benefit from an intensive outpatient treatment protocol, which started in Summer 2012.

Baseline assessment

A baseline assessment of Patient B's current functioning was conducted by a master's level IE, who was not involved in the treatment delivery, and included the YGTSS[20] and the clinician-rated CGI[21] and the Hopkins Motor/Vocal Tic Scale (HMVTS)[31]. Only the YGTSS and CGI were used as outcome assessments, and additional information about their psychometric properties can be found under Patient A's baseline assessment section. The assessment confirmed the diagnosis of TS and indicated that Patient B was experiencing clinically significant vocal and motor tics (as defined[14]). Specifically, Patient B and his parents reported six motor and four vocal tics, which significantly interfered with family interactions and had begun to interfere with his peer relationships.

Formulation, rationale, and treatment plan

The treatment team met with Patient B and his family to discuss treatment options including IOP CBIT. The family had already exhausted many other options in the community with little to no success, and his parents were hopeful that this alternative approach would alleviate his symptoms. Given the severity of his symptoms, Patient B continued to take clonidine during his participation in IOP CBIT.

Patient B and his parents attended one baseline assessment session and three IOP CBIT sessions over the course of four consecutive days. Although only three IOP CBIT sessions were conducted, the total amount of time spent for the intervention was comparable to that of the standard eight session CBIT protocol. During the course of treatment, Patient B's parents observed through a one-way mirror. Treatment was administered by a team consisting of a board certified child and adolescent psychologist and two child and adolescent postdoctoral fellows (see Table 5 for a summary of the specific treatment schedule).

Table 5 Overview of Patient B's treatment schedule

	Day 1	Day 2	Day 3	Day 4
Session Number	S1: (1.5 h) Baseline assessment Meet therapists Introductions Treatment overview	S2: (3.5 h) Psychoeducation Introduce relaxation Stress *vs* relaxation Relaxation postures PMR + 12 Diaphragmatic breathing Visual imagery Awareness training Psychoeducation about tics Rationale for treatment Tic Sx hierarchy Feedback about assessment	S3: (3.5 h) Review relaxation OOSAs Tic hassles form Competing responses Inconvenience review Review tic 1 and 2 Competing responses 1, 2 Review treatment tic 1 Practice relaxation Competing response 1 and 2 Assign homework	S4: (3.5 h) Competing response Inconvenience review Relaxation practice Review OOSAs Review CR for all tics Summarize progress Emphasize social support Reward review
OOSAs		Practice relaxation Practice PRM + 12 Practice visual imagery	CR tics 1-2 Monitor 15 min, 3-4x F(x) based interventions Relaxed breathing	F(x) based interventions Relaxation Family and social support

PMR: Progressive muscle relaxation; Sx: Symptoms; CR: Competing response; OOSA: Out of session assignment; F(x) = Function.

Course of treatment

During the baseline assessment, Patient B and his parents identified six current motor tics (grabbing/touching, putting napkins in mouth, full-body twitches, open mouth with head nodding, "closing" self into small spaces, tapping surfaces) and four vocal tics (screaming, humming, repeating self, and "Aahh" sounds). The treatment agenda, rationale, tic monitoring, and family support were discussed with Patient B and his parents.

CBIT was initiated in Session 2. The treatment team provided psychoeducation about tic disorders, the rationale for competing response training, awareness training, and the stress and relaxation responses. The team also engaged the patient in several relaxation strategies and progressive muscle relaxation, which yielded a notable decrease in his tics. A hierarchy of the patient's current tics was developed. Patient B was assigned relaxation and tic monitoring homework, which was reviewed at the start of the next session (see Table 5).

The following day, Patient B reported some benefit with homework while his mother reported a reduction in the severity and intensity of the grabbing tic in public places. Session 3 focused on completing the tic hassles worksheet[30], in which Patient B described the grabbing tic and vocal tic as most bothersome. He identified arm pain (SUDS = 9), parental dependence (SUDS = 11), and annoying others (SUDS = 7) as tic hassles. Patient B reported that his vocal tic was embarrassing (SUDS = 10). Competing response training was implemented with one tic at a time, starting with the most distressing tic (grabbing), followed by the vocal tic. For the grabbing tic, Patient B was asked to practice squeezing his hands together and pushing them down as a competing response. For the vocal tic, Patient B was instructed to clench his teeth and push his tongue against the roof of his mouth as his competing response.

On Day 4, the treatment team reviewed the homework, in which the patient's mother observed only one vocal tic during several discrete tic observation periods. Patient B reported not having any tics or urges while at a friend's house, and he stated that he did not feel as though he was suppressing his tics. Because Patient B was still reporting some difficulty identifying premonitory urges, a token economy was also implemented during the session whereby Patient B earned points towards a desirable reward for detecting a premonitory urge by notifying the provider (*i.e.*, raising his finger) and engaging in the appropriate competing response. Patient B responded positively to the token economy and was motivated to identify premonitory urges. He was also able to resist the urge to tic or engaged in the tic for markedly less time compared to pretreatment. At the end of the session, Patient B and his mother reported improvement in the awareness of his tics and premonitory urges. The treatment team also practiced relaxation strategies, summarized treatment progress, and discussed relapse prevention during the last part of the session. Providers emphasized the importance of ongoing social and family support.

Over four days of assessment and treatment, behavioral improvement was observed and noted by all three providers, Patient B, and his parents. Patient B reported feeling skeptical at the beginning of the week about whether this treatment would be effective, but at the last session he stated, "I stand corrected." Patient B was able to control his tics by either stopping them from occurring, notifying providers when he was about to have one, and/or decreasing the length of time spent engaging in specific tic behaviors. Overall, Patient B and his parents verbally reported high treatment satisfaction.

Results

Patient A: By the end of treatment, Patient A and his mother reported a clinically meaningful decrease in his tic severity as assessed by the YGTSS and the CGI. Importantly, his tic severity scores had decreased further by the

one-month follow-up (see Table 2). Following their one-month follow-up assessment, Patient A and his mother attended a 60-min booster session, in which his mother reported that she only occasionally noticed a slight eye-blink tic. Patient A disagreed with his mother that this was a tic. He also reported that although he still experienced an urge to tic, the urge was less severe and occurred less frequently. Both Patient A and his mother reported continued treatment satisfaction with IOP CBIT at follow-up. Patient A and his mother reported continued treatment gains at the seven-month follow-up and high treatment satisfaction. More specifically, he reported that he continued to occasionally experience a slight eye tic. However, both he and his mother agreed that the tic was not noticeable to others and did not cause him interference. No new tics emerged from the time of treatment completion through the seven-month follow-up period.

Patient B: The YGTSS (see Table 5) and HMVTS were administered by the same IE and completed by Patient B with the help of his parents at one week, one month, and six months. Overall, the assessments revealed clinically meaningful improvement in Patient B's functioning (see Table 2). At the one-week follow up, there was an overall reduction in number of tics (10 *vs* 2). The parents reported that Patient B had not engaged in the grabbing tic in the previous week, that he was more aware of the urge to grab, and that he was able to apply a more appropriate competing response (*i.e.*, walking away, distraction, breathing). During follow-up interviews, Patient B was observed using several appropriate competing responses (*i.e.*, crossing his arms, sitting on his hands) in reaction to the urge to grab others. Patient B also reported feeling "a lot better," stating, "I don't really tic as much." He also reported that the duration of his tics had decreased, that he was less bothered by his tics, and that the tics were less noticeable to others in public. The parents confirmed his impressions. Patient B was also provided with additional suggestions on competing responses to use for the remaining tics. The treatment team reviewed the follow-up plan with parents, which included booster sessions.

At the one-month follow-up, the YGTSS revealed that treatment gains had been maintained, and Patient B demonstrated a reduction in tic number, frequency, and interference of both motor and vocal tics. By the six-month follow-up, Patient B was exhibiting a slight increase in the frequency of vocal tics and an increase in the complexity and interference of motor tics (see Table 2); however, Patient B admitted to not practicing the breathing and relaxation strategies. Therefore, booster sessions were scheduled to review IOP CBIT components.

Although Patient B's presentation at six months post-treatment revealed some regression (as seen in Table 2), the family expressed their appreciation for Patient B's progress and his ability to function better at home and at school. The family also stated that the tics had become "so subtle" that he was no longer concerned or upset by them.

DISCUSSION

The current case series describes the implementation of an intensive outpatient behavioral treatment with two preadolescents who presented with Tourette syndrome. Despite their different presentations, both patients demonstrated treatment gains following the IOP CBIT intervention. The generalizability of the current case series is unknown at this time. However, IOP CBIT may be appropriate for individuals who present with moderate to severe tics, those who are experiencing clinically significant impairment in daily academic and social functioning, and for individuals and their families who desire to experience a quick reduction in motor and/or vocal tics. On the other hand, individuals who might not be good candidates for CBIT include those with oppositional and/or defiant behaviors, since adherence to the treatment protocol would likely prove to be a challenge. In addition, because it is important for individuals with Tourette's to receive adequate psychosocial support in monitoring and reducing their tics, those with chaotic or limited family and social support systems may find this protocol challenging.

It should be noted that many individuals with Tourette syndrome experience a waxing and waning of symptoms over time and that many tics resolve on their own[2,3]. Although CBIT is not a cure for Tourette syndrome, based on the current case series, individuals who follow the treatment protocol can expect to learn tools and skills to better manage their tics, understand their premonitory urges, reduce the negative impact of the tics on their lives, and experience improvement in their overall academic and social functioning[14].

Limitations and future directions

Despite addressing an important gap in the literature pertaining to the use of an intensive outpatient CBIT approach with children and adolescents, there are several limitations to the current case series that should be noted. First, an intensive treatment approach requires a time commitment from parents and patients that would likely require a parent to request time away from work and/or a child to be absent from school. This might present a financial challenge for some parents and possibly create academic stressors for some children. It also raises the question about the most convenient time to deliver an intensive outpatient intervention for children and adolescents. That is, Patient A received his treatment during a planned school break, while Patient B was seen during the summer. Clinicians should consider and discuss the time commitment it takes for families to participate in this type of intensive treatment approach.

Second, both patients received treatment at academic medical centers without individual fee-for-service costs as a part of psychology internship and postdoctoral training programs. It is possible that many families might find paying out-of-pocket for an intensive outpatient treatment to be a financial burden. Moreover, with the increased limitations placed on behavioral health services by managed

care organizations, insurance companies might be unable or unwilling to pay for an intensive outpatient program. Future research should examine the generalizability of a comprehensive behavioral intervention for TS in the community at large. Third, receiving treatment as part of a research study or through a military treatment facility would also facilitate access to services for this population. While members of the current treatment teams received training, consultation, and/or supervision from one of the leading researchers (ALP) in the field of TS, accessibility of behavioral health providers who are trained in CBIT might be more limited in other geographical areas. Both families reported feeling grateful that they had access to the current treatment teams. Agencies and educational institutions would greatly benefit the community by offering more training opportunities for behavioral health providers in the treatment of TS. The Tourette Syndrome Association has sponsored many CBIT training programs.

Finally, the intensive outpatient program implemented in the current treatment protocol might compromise the external validity of the intervention. Both patients received the intensive treatment at a much faster pace compared to traditional therapy, creating an artificial environment in which to practice the skills learned. This limited both patients' ability to practice the functional based interventions in their everyday environments at a more natural pace. Future research should continue to examine the generalizability and long-term benefits of IOP CBIT. Future research should also consider a single subject research design or an experimental research design to include a control group receiving traditional weekly CBIT with the experimental group receiving IOP CBIT over 3-4 d.

The current case series adds an important piece to the scientific literature on the behavioral treatment of Tourette syndrome and persistent tic disorders by demonstrating that Cognitive Behavioral Intervention for Tics employed as part of an intensive outpatient program can reduce tic severity. The use of an intensive outpatient program incorporating Comprehensive Behavioral Intervention for Tics appears to offer several benefits. First, the patients in this case study were able to make notable progress over the span of 1 wk *vs* 10 wk. Additionally, IOP CBIT allows patients to focus almost exclusively on developing and practicing their competing responses without the interference of work or school. IOP CBIT also expands the potential treatment catchment areas, which would make CBIT more accessible to a wider range of patients who would otherwise be limited by geography or expense. Importantly, an IOP CBIT has the potential to help compensate for the current lack of CBIT providers.

COMMENTS

Case characteristics

Both Patients A (10-year-old male) and B (14-year-old male) experienced multiple tics that were consistent with Tourette syndrome.

Clinical diagnosis

Patients A and B both met diagnostic criteria for Tourette syndrome.

Differential diagnosis

Patients A and B were both assessed for attention deficit hyperactive disorder and obsessive compulsive disorder.

Treatment

Patients completed intensive outpatient Comprehensive Behavioral Interventions for Tics (CBIT).

Related reports

Although previous studies support the use of CBIT, when delivered in eight weekly sessions, more research is needed to determine whether an intensive outpatient format can improve tic management in children with a persistent tic disorders; however, the treatment outcome of these two cases are promising.

Experiences and lessons

This case series represents the first report of treatment outcomes following an intensive outpatient CBIT protocol for children. Although future research is required before more definitive conclusions can be reached, the findings of this case series suggest that Intensive Outpatient Program CBIT may reduce tic symptoms in children with Tourette syndrome.

Peer review

This is a template for a valuable modification of CBIT for those who desire thorough management in a short period of time. This represents a promising approach that merits confirmation by other investigators in other settings.

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CASE REPORT

Challenging rescue of a 4 years old boy with H1N1 infection by extracorporeal membrane oxygenator: A case report

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Abstract

Introduction: World Health Organization announced on April 2009 a public health emergency of international concern caused by swine-origin influenza A (H1N1) virus. Acute respiratory distress syndrome (ARDS) has been reported to be the most devastating complications of this pathogen. Extracorporeal membrane oxygenator (ECMO) therapy for patients with H1N1 related ARDS has been described once all other therapeutic options have been exhausted. Here, we report the case of a child (German, male) with H1N1-associated fulminate respiratory and secondary hemodynamic deterioration who was rescued by initial emergent ECMO established through a dialysis catheter and subsequent switch to central cannulation following median sternotomy. This report highlights several important issues. First, it describes a successful use of a dialysis catheter for the establishment of a veno-venous ECMO in an emergency case by child. Second, it highlights the importance of a closely monitoring of clotting parameters during ECMO therapy and third, if severe respiratory failure is complicated by cardiogenic shock, veno-atrial ECMO support *via* median sternotomy should be considered as a viable treatment option without further delay.

Key words: Airway; Circulatory temporary support; Coagulants; Extracorporeal membrane oxygenation; Infection

Core tip: Here, we report the case of a child with swine-origin influenza A-associated fulminate respiratory and secondary hemodynamic deterioration, who was rescued by initial emergent extracorporeal membrane oxygenator (ECMO) established through a dialysis catheter and subsequent switch to veno-atrial ECMO (VA-ECMO) *via* central cannulation. This report highlights several important issues. First, it describes a successful use of a dialysis catheter for the veno-venous ECMO-establishment in an emergency case by child. Second, it highlights the importance of a closely monitoring of clotting parameters and third, if severe respiratory failure is complicated by cardiogenic shock, VA-ECMO support *via* median sternotomy should be considered as a viable treatment option without further delay.

Papadopoulos N, Martens S, Keller H, El-Sayed Ahmad A, Moritz A, Zierer A. Challenging rescue of a 4 years old boy with H1N1 infection by extracorporeal membrane oxygenator: A case report. *World J Clin Cases* 2014; 2(10): 578-580 Available from: URL: http://www.wjgnet.com/2307-8960/full/v2/i10/578.htm DOI: http://dx.doi.org/10.12998/wjcc.v2.i10.578

INTRODUCTION

Establishment of extracorporal membrane oxygenation (ECMO) through percutaneous placement of cannulas in

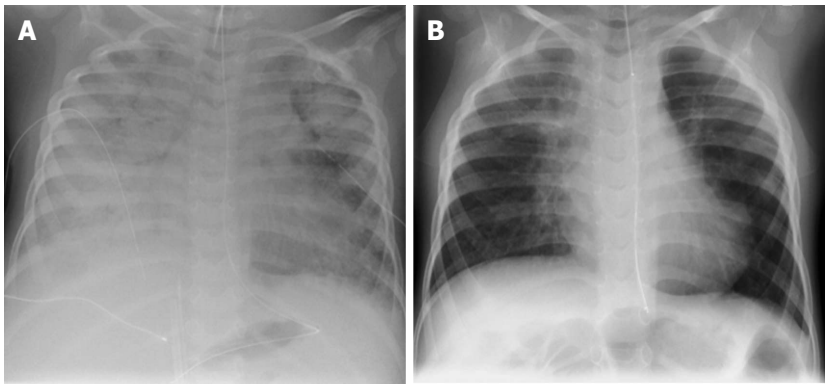

Figure 1 Anterior-posterior chest radiograph. A: Postintubation anterior-posterior chest radiograph of a 4 years old boy before Extracorporeal membrane oxygenator (ECMO) support with acute respiratory distress syndrome caused by proven novel 2009 H1N1 influenza virus; B: Anterior-posterior chest radiograph of the same patients after successful veno-atrial ECMO weaning and successful decanulation.

children can be difficult because of the small vessel size[1]. Median sternotomy may be necessary in selected cases to cannulate the ascending aorta and right atrium for sufficient ECMO flow[1,2].

CASE REPORT

A 4 years old German boy presented in our emergency room with a 24 h history of shortness of breathe following several days of an influenza-like illness. At presentation, he suffered from respiratory failure requiring urgent intubation and mechanical ventilation. After his admission to our intensive care unit the initial chest radiograph revealed bilateral patchy infiltrates (Figure 1A). H1N1 influenza virus was confirmed by the reverse transcriptase-polymerase chain reaction assay of respiratory secretions. Bacterial cultures were negative. He was treated empirically with Oseltamivir. Within 24 h after hospital admission the patient had severely impaired gas exchange despite maximum respiratory support on the ventilator. For this reason high frequency oscillation ventilation (HFOV) was initiated. Since there was no improvement of the respiratory situation within 4 d of HFOV-treatment, veno-venous ECMO (VV-ECMO) had to be established.

Because of the small vessel size of the child, save cannulation sites for percutaneous placement of the ECMO cannulas were limited and included the internal jugular veins and the femoral veins. Placement of a cannula through the jugular vein was not successful. The child was in critical clinical condition and we decided to start VV-ECMO support *via* an 11 Fr dialysis catheter (Dolphin Protect, Gambo, Hechingen, Germany) placed into the left femoral vein. We established ECMO outflow of oxygenated blood *via* the arterial lumen and inflow of deoxygenated blood *via* the venous lumen of the dialysis catheter. We connected ECMO-tubes with the dialysis catheter *via* a connector (1/4 × LLm, Maquet GETINGE GROUP, Hirrlingen, Germany). ECMO circuit consisted of a Quadrox id pediatric (Maquet Cardiovascular, Wayne, NJ, United States) polymethylpentene oxygenator and a Rotaflow (Maquet Cardiovascular) centrifugal pump. This setting allowed for a flow of 400-milliliter per min. Despite the rather low circuit flow, the combination of VV-ECMO and HFOV allowed for an immediate improvement of oxygenation and weaning of vasopressor support.

Three days later, following an initial course of stabilization a sudden exchange of the VV-ECMO-system had to be performed due to massive clot-formations in the oxygenator. Notably there was an exponential elevation of fibrinogen and D-Dimer, as a result of disseminated intravascular coagulation (DIC), which could be detected from the establishment of the VV-ECMO support on until the system change. In order to avoid further clotting formations continuous application of heparin directly in the venous cannula of the new ECMO circuit has been established.

One day after the system change a sudden hemodynamic instability required high inotropic and vasopressor support. Therefore we decided to switch the VV-ECMO to veno-atrial ECMO (VA-ECMO). In order to reliably maintain adequate flow in this critical situation we performed a median sternotomy and established VA-ECMO support *via* the right atrial appendage and the ascending aorta. A Bio-Medicus (Medtronic, Inc., Minneapolis, MI, United States) arteria cannula was used as the return cannula for oxygenated blood. For venous drainage a multiport Bio-Medicus (Medtronic, Inc.) cannula was used. Circuit flow of 1.2 liters min^{-1} led to a stabilization of the hemodynamic situation with immediate weaning from the vasopressor and intotropic support.

VA-ECMO was provided for a total of 10 d and could afterwards be successfully explanted. The patient could be successfully decannulated and control chest radiograph showed normal lung morphology (Figure 1B). The 4-year-old boy could be discharged from the hospital after a total of 38 d with full resolution of symptoms.

DISCUSSION

This report highlights several important issues. First, it describes a successful use of a dialysis catheter for the establishment of a VV-ECMO in an emergency case, in which, due to the small vessel size of the child, the

percutaneous placement of routine ECMO cannulas was not possible. Second, as clotting formations in the ECMO-oxygenator is a possible and devastating complication especially in critically ill patients with H1N1 infection suffering a DIC, it is vital that clotting parameters, especially fibrinogen and D-Dimer, of such patients are closely monitored. Third, if severe respiratory failure is complicated by cardiogenic shock, VA-ECMO support *via* median sternotomy should be considered as a viable treatment option without further delay[3-9].

COMMENTS

Case characteristics

The 4 years old patient presented in the emergency room with the main symptom of dyspnoea.

Clinical diagnosis

Clinical diagnosis of acute respiratory failure leads to an urgent intubation and mechanical ventilation of the young boy.

Differential diagnosis

Bacterial infection could be excluded once the bacterial cultures were negative.

Laboratory diagnosis

Swine-origin influenza A (H1N1) influenza virus was confirmed by the reverse transcriptase-polymerase chain reaction assay of respiratory secretions.

Imaging diagnosis

After his admission to the authors intensive care unit the initial chest radiograph revealed bilateral patchy infiltrates.

Pathological diagnosis

Within 24 h after hospital admission the patient had severely impaired gas exchange despite maximum respiratory support on the ventilator.

Treatment

For this reason high frequency oscillation ventilation (HFOV) was initiated. Due to the fulminate respiratory and secondary hemodynamic deterioration, initial emergent veno-venous extracorporeal membrane oxygenator (VV-ECMO) (extracorporeal membrane oxygenator) established through a dialysis catheter and subsequent switches to veno-atrial ECMO (VA-ECMO) through central cannulation following median sternotomy, has to be performed.

Term explanation

ECMO therapy for patients with H1N1 related acute respiratory distress syndrome (ARDS) has been described once all other therapeutic options have been exhausted. This report highlights several important issues. First, it describes a successful use of a dialysis catheter for the establishment of a VV-ECMO in an emergency case by child. Second, it highlights the importance of a closely monitoring of clotting parameters during ECMO therapy and third, if severe respiratory failure is complicated by cardiogenic shock, VA-ECMO support *via* median sternotomy should be considered as a viable treatment option without further delay.

Peer review

This manuscript lights on the problem of the ECMO cannulation in emergency and in the pediatric patient, and indicate as a solution the use of the dialysis catheter instead of the double lumen pediatric ECMO's cannula.

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CASE REPORT

Left ventricular pseudoaneurysm formation: Two cases and review of the literature

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Abstract

Left ventricular wall rupture (LVWR) comprises a complication of acute myocardial infarction (AMI). Acute LVWR is a fatal condition, unless the formation of a pseudoaneurysm occurs. Several risk factors have been described, predisposing to LVWR. High index of suspicion and imaging techniques, namely echocardiography and computed tomography, are the cornerstones of timely diagnosis of the condition. As LVWR usually leads to death, emergency surgery is the treatment of choice, resulting in significant reduction in mortality and providing favorable short-term outcomes and adequate prognosis during late follow-up. Herein, we present two patients who were diagnosed with LVWR following AMI, and subsequent pseudoaneurysm formation. In parallel, we review the aforementioned condition.

Key words: Pseudoaneurysm; Left ventricle rupture; Myocardial infarction

Core tip: Ventricular wall rupture (LVWR) comprises a complication of acute myocardial infarction. Acute LVWR is a fatal condition, unless the formation of a pseudoaneurysm occurs.

Petrou E, Vartela V, Kostopoulou A, Georgiadou P, Mastorakou I, Kogerakis N, Sfyrakis P, Athanassopoulos G, Karatasakis G. Left ventricular pseudoaneurysm formation: Two cases and review of the literature. *World J Clin Cases* 2014; 2(10): 581-586 Available from: URL: http://www.wjgnet.com/2307-8960/full/v2/i10/581.htm DOI: http://dx.doi.org/10.12998/wjcc.v2.i10.581

INTRODUCTION

Cardiac rupture as a pathophysiological entity was first described by Harvey[1] in 1647. It is a complication of acute acute myocardial infarction (AMI) with an overall incidence of 6.2%[2,3]. It represents the second cause of death after cardiogenic shock, and accounts for as much as 15% of in-hospital mortality[4-6]. Rupture may involve any cardiac structure, *i.e.*, atria, ventricles, interatrial or interventricular septum, papillary muscles or chordae tendineae, or one of the heart valves. Left ventricular wall rupture (LVWR) occurs up to 10 times more frequently than septal rupture, affecting up to 11% of patients after AMI and is almost invariably fatal, with death occurring within minutes after the development of chest pain[6]. In contrast, subacute LVWR and containment by false aneu-

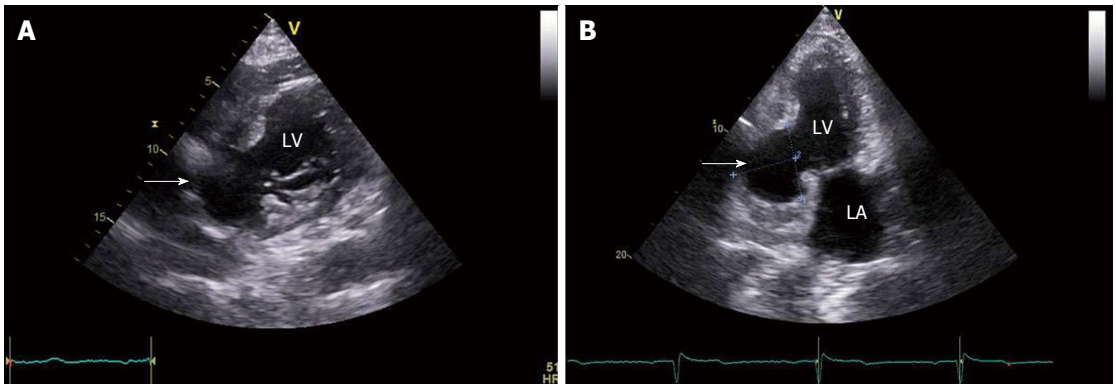

Figure 1 Echocardiography: Parasternal short axis and 2-Chamber view of the left ventricle posterior wall pseudoaneurysm (A and B, arrows). LA: Left atrium; LV: Left ventricle.

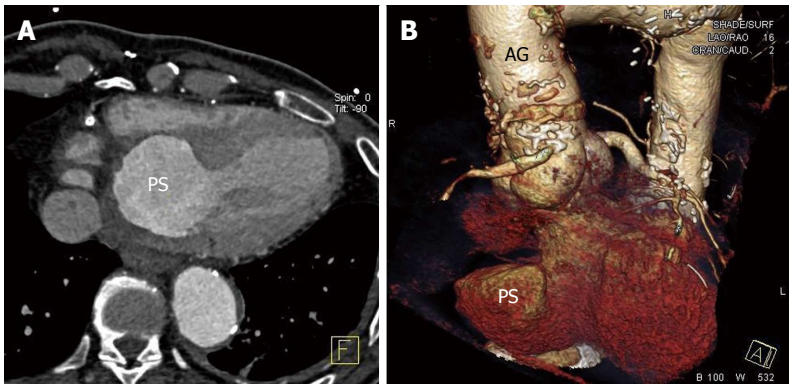

Figure 2 Cardiac computed tomographic angiography (A) and volume rendering (B): Left ventricle posterior wall pseudoaneurysm. PS: Pseudoaneurysm; AG: Aortic graft.

rysm formation of the pericardial layers may lead to patient's survival for hours or even days, but rarely weeks[7-9].

CASE REPORT

Case 1

A 62-year-old man was referred for echocardiographic evaluation. Two weeks ago, he had been admitted to another hospital for a non-ST segment elevation myocardial infarction for which he had undergone coronary arteriography. Coronary angiography revealed a 60% occlusion of the left anterior descending artery (LAD), a totally occluded right coronary artery (RCA), and a totally occluded left internal mammary artery (LIMA) graft to the LAD. The patient's history included coronary artery bypass grafting operation, with a LIMA graft to the LAD, and an ascending aorta replacement with an aortic graft (Hemashield straight tube, Boston Scientific) due to aneurysm, twelve years earlier. Moreover, nine years ago, he had undergone percutaneous coronary angioplasty and had received a drug-eluting stent to the RCA. Echocardiography revealed rupture of the left ventricular posterior wall which was contained by pericardium, thus forming a sizeable pseudoaneurysm (Figure 1). There was no significant pericardial effusion and the overall systolic function of both ventricles was found within normal limits. Based on the echocardiographic diagnosis the patient was admitted to our hospital for further investigation and treatment. The patient's admission 12-lead surface electrocardiogram (ECG) showed ischemic changes in the inferior leads (Ⅱ, Ⅲ, aVF). Cardiac computed tomographic angiography (Figure 2A) and volume rendering technique (Figure 2B) confirmed the presence of a pseudoaneurysm, with 50 mm × 50 mm dimensions, at the posterior wall of the left ventricle. The patient was referred to Surgery and a surgical repair of the defect with application of a Dacron patch with continuous suture was performed. Repeat echocardiography demonstrated a well-placed patch at the site of the rupture, enforcing the walls of the pseudoaneurysm. The patient had an uneventful postoperative recovery and was discharged on day 6 with explicit instructions and medication.

Case 2

An 86-year-old man presented with exertional dyspnea of five months duration. He had a history consistent with chronic atrial fibrillation under acenocoumarol and atenolol, and dyslipidemia under simvastatin. He had no history of documented coronary artery disease the 12-lead ECG showed Q waves in leads Ⅲ and aVF. He was hemodynamically stable with normal vital signs. The echocardiographic study demonstrated a pseudoaneu-

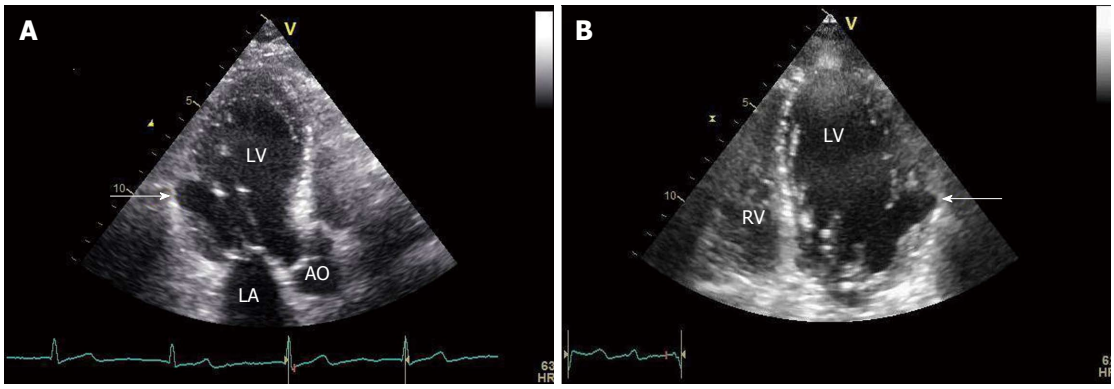

Figure 3 Echocardiography: Modified 4- and 3-Chamber view of the left ventricle lateral wall pseudoaneurysm (A and B, arrows). RV: Right ventricle; LA: Left atrium; AO: Ascending aorta; LV: Left ventricle.

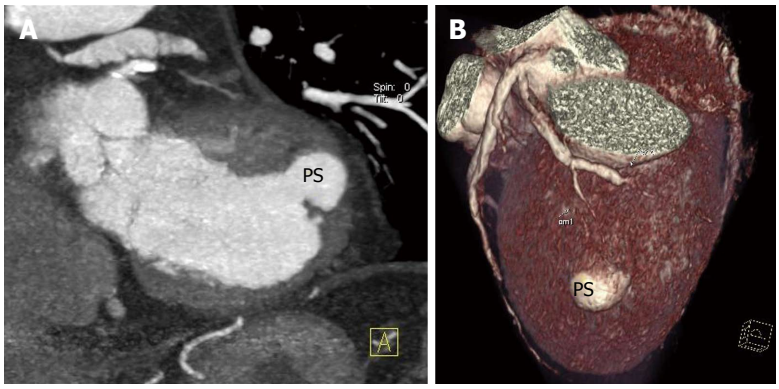

Figure 4 Cardiac computed tomographic angiography and volume rendering: Left ventricle lateral wall pseudoaneurysm (A and B). PS: Pseudoaneurysm.

rysm at the akinetic basal inferior lateral wall of the left ventricle, close to the base of the anterolateral papillary muscle (Figure 3). The overall function of the left ventricle was preserved. Cardiac computed tomographic angiography and volume rendering technique revealed significant atherosclerosis and coronary arteries narrowing. The echocardiographic findings were confirmed; a circular opacified 19 mm × 16 mm protrusion originating from the lateral wall of the left ventricle was observed (Figure 4). The patient's clinical condition and echocardiographic findings remained stable over his 3 years follow-up.

DISCUSSION

Time of occurrence and factors related to LVWR in AMI

The traditional risk factors for LVWR include older age (> 60 years), female sex, first lateral or anterior wall AMI, severe one-vessel coronary artery disease with lack of collateral circulation, and absence of previous angina[4,10,11]. On the contrary, the presence of multivessel disease may exert a protective effect, probably linked to development of greater collateral circulation[12]. Furthermore, it has been reported that the majority of patients with LVWR had suffered ST segment elevation AMI, with positive cardiac biomarkers, and a higher heart rate, lower blood pressure, and higher GRACE risk score at admission than patients without LVWR[13-15]. Chronic hypertension and diabetes mellitus do not seem to modify the incidence of LVWR[16], and contrary to a previous report[17], steroid use and late thrombolysis do not appear to increase the risk of LVWR[18,19]. Concerning thrombolysis, three mechanisms have been proposed as been responsible for occurrence of LVWR: hemorrhage to the ischemic zone resulting in loss of muscular tissue strength[20,21], increased collagen degradation and synthesis restrain by thrombolytic agents[22], lymphocytic migration to the infarct zone initiating absorption of collagen and proteolysis[21]. Depending on the time of its occurrence, LVWR may be classified as early, when it develops within the first 48 h post-AMI, or late, when it occurs beyond 48 h post-AMI. The early form represents 40%-50% of cases[23], however it is generally accepted that the true proportion is likely to be higher when including patients who die suddenly from LVWR before reaching hospital[24].

Differentiating true aneurysm from pseudoaneurysm

Rarely, LVWR is contained by an adherent pericardium, creating a pseudoaneurysm. Differentiation between left ventricular aneurysm and pseudoaneurysm is difficult, yet it is the most important task to carry out in order to facilitate therapeutic decision making. Pericardial friction rub, decreased heart sounds, sinus bradycardia or junctional rhythm, are all signs of pseudoaneurysm[25]. However, chest pain, dyspnea and hypotension, as well as persistent

ST segment elevation in the area of AMI on the surface ECG, are common for both true aneurysm and pseudoaneurysm[26]. Thus, distinguishing between these two entities is very difficult merely on a clinical basis, because many characteristics are common. Especially concerning electrocardiographic predictors of LVWR and aneurysm or pseudoaneurysm formation, a deviation of the ST segment or T wave, or both, from the usual evolutionary pattern after AMI has been observed[27]. Furthermore, differing opinions exist concerning the most common site of LVWR. Some reports indicate the anterior wall as the most frequent site of aneurysm and pseudoaneurysm formation, where areas more recent series have observed a predominance of lateral and posterior wall ruptures[27].

Imaging modalities in the diagnosis of LVWR in AMI

The most available and sensitive diagnostic tool to establish the different types of cardiac rupture is echocardiography[28]. In patients with LVWR the most frequent echocardiographic finding is pericardial effusion; in fact, the absence of pericardial effusion has a high negative predictive value and excludes cardiac rupture in patients with AMI[29]. However, in our cases no pericardial effusion was found. The presence of pericardial effusion has a low positive predictive value for LVWR as it may be present in 28% of patients with AMI without cardiac rupture[30]. The absence of pericardial effusion in our patients could be due to the lack of rupture of the left ventricular wall. The presence of echogenic masses in the effusion fluid is a relevant sign, particularly in patients with subacute LVWR, since these signs may be found in fibrinous pericarditis associated with AMI[31]. Direct visualization of the myocardial tear, true aneurysm or pseudoaneurysm is diagnostic, however, it is possible in only one third of LVWR cases[32]. Recently, cardiac magnetic resonance (CMR) imaging, especially with contrast enhancement, has emerged as a valuable diagnostic tool providing visualization of the entire heart, and clear differentiation of structures such as the pericardium, myocardium, thrombus and epicardial fat[33], as well as the pathological scar tissue substrates for life-threatening ventricular arrhythmias in AMI patients[34]. CMR can provide morphological definition of LVWR and pseudoaneurysm location, extension and relation to adjacent structures. Furthermore, CMR has an enormous value in differentiating between left ventricular aneurysms and pseudoaneurysms, in stable patients, with the ability to obtain cross sectional views in any plane[35].

We presented two patients who survived LVWR following an AMI. The patients' survival was clearly due to the containment of the rupture by the pericardial sac and the formation of the pseudoaneurysm. As LVWR usually leads to death, emergency surgery is the treatment of choice regardless the patient's condition. Surgical repair, enforcing the pericardial layers at the ventricular locus resistentiae minoris, results in significant reduction in mortality and provides favorable short-term outcomes and adequate prognosis during late follow-up[36]. Interestingly, our second patient survives for 3 years after diagnosis without surgery. Early diagnosis of LVWR is based on clinical suspicion. Echocardiography is of paramount importance, while computed tomography and CMR can be used to confirm diagnosis in stable patients.

COMMENTS

Case characteristics

Two patients who were diagnosed with left ventricular wall rupture (LVMR) following acute myocardial infarction (AMI), and subsequent pseudoaneurysm formation.

Clinical diagnosis

Variable clinical presentation, ranging from asymptomatic forms of the condition to more typical angina pectoris or dyspnea.

Differential diagnosis

Cardiac ischemia, pulmonary disease and heart failure are the main differential diagnoses.

Laboratory diagnosis

There are no specific laboratory findings in the condition described. However, negative cardiac enzymes could exclude novel myocardial infarction.

Imaging diagnosis

Echocardiography is the most useful and available imaging method in the diagnosis of left ventricular aneurysm and pseudoaneurysm formation. Computed tomography and cardiac magnetic resonance are complementary modalities, however of paramount importance in differentiating between the two aforementioned entities.

Treatment

Surgery is the treatment of choice for post-myocardial infarction left ventricular pseudoaneurysms.

Related reports

Left ventricular rupture and pseudoaneurysm formation have been described in the literature. However, long-term follow-up in an untreated patient (the authors' second case) is quite rare.

Term explanation

LVWR following an AMI and containment by false aneurysm formation of the pericardial layers may lead to patient's survival for hours or even days, but rarely weeks.

Experience and lessons

LVWR may be a rare condition in the era of primary percutaneous interventions, however it should always be a consideration in post-myocardial infarction patients.

Peer review

This is an interesting manuscript.

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CASE REPORT

Importance of defining the best treatment of a genital gunshot wound: A case report

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Abstract

Twenty percent of genital traumas are caused by penetrating injuries; accordingly gunshot and stab wounds have increased in the last couple of years around the globe, even in Colombia. A 67-year-old male patient was admitted to the emergency room because he received multiple gunshot wounds. On physical examination, multiple wounds on his penis with loss of tissue in the foreskin, glans, anterior urethra (distal third) and cavernous corpora were found. The urologist performed a partial penectomy with a penis reconstruction, he debrided the cutaneous flap of the dorsal foreskin and its glans, sutured the distal cavernous corpora and dissected the urethra. Penetrating genital injuries are extremely important due to their impact on the functional, psychological and the aesthetic consequences. It is necessary to define the best possible treatment to minimize the damage.

Key words: Genital; Penile; Injuries; Trauma; Amputation

Core tip: Genital injuries are a common problem in civil war. For example, in developing countries its incidence is increasing, so it is of vital importance to notice how to focus the clinical case and how to treat patients with this condition. The impact on functional and aesthetic aspects calls our attention to treat these patients correctly.

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INTRODUCTION

Twenty percent of genital traumas are caused by penetrating injuries[1-3]; with traumatic amputations-as part of genital traumas-usually happening in acute psychotic events[4-6]. In only a small percentage they are caused by agricultural and industrial accidents or even by gunshot or stab wounds[4-6]. Due to a raise of civil war conflicts, gunshot and stab wounds have increased in the last couple of years, especially in Columbia[7], making this type of injuries prevalently seen at Hospital Universitario del Valle (Cali, Colombia). In both males and females, the penetrating genital injuries occur with other associated injuries in 70% of cases[8,9].

It is therefore important to know that the injured persons will have a different degree of damage and that the urologists will have to determine the probability of reattaching the part of the amputated or reconstructing the injured penis[4].

The purpose of this report is to describe an interesting case of a genital gunshot wound associated with a literature review to support the case and treatment, according to CARE guidelines for Case Reports.

CASE REPORT

A 67-year-old male patient was admitted to the emergen-

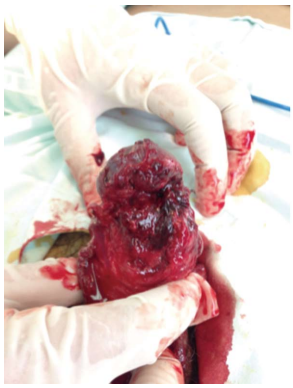

Figure 1 Glans and cavernous corpora injured.

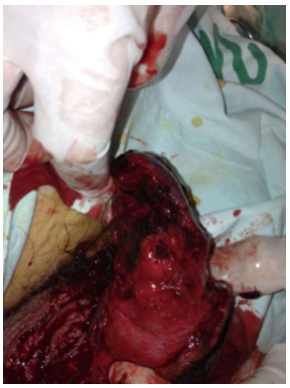

Figure 2 Injured urethra.

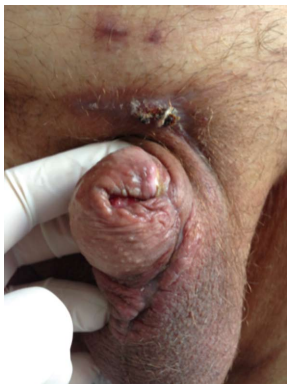

Figure 3 Left sided retraction.

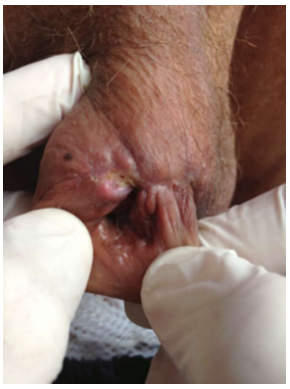

Figure 4 Mild meatus stenosis.

cy room because he received multiple gunshot wounds. On physical examination, a suprapubic and multiple wounds on his penis were found, with loss of tissue in the foreskin, glans, anterior urethra (distal third) and cavernous corpora on the left side (Figures 1 and 2). Because of the extent of injuries and the inability to have a permeable urinary tract, a suprapubic tube (cystostomy) was placed and a surgical cleansing and debridement were performed.

On the next hospitalization day, he was taken to the operating room, where following conditions were found: devitalized glans with some necrosis areas, loss of the pendulous urethra up to its middle third, and a partial loss of its foreskin, but with some good cutaneous flap remaining. The urologist decided to perform a partial penectomy with a penis reconstruction, he debrided the cutaneous flap of the dorsal foreskin and its glans, sutured the distal cavernous corpora and dissected the urethra. Following the reconstruction a urethral Foley catheter was placed.

Three days after his admission, on his second postop day, he was managed as an outpatient due to good clinical status.

As an outpatient, two months later, he showed up with good clinical status, the surgical wound was healed but some left-sided retraction of the neomeatus was found (Figures 3 and 4).

DISCUSSION

In an emergency room, a patient with multiple injuries or even with isolated genital damage requires prompt assessment and course of action[3]. Sometimes it is important to assess the range, caliber and type of weapon to evaluate the amount of the damage, before the treatment can be initiated[1]. Primarily physicians should focus on life threatening conditions and their treatment; and only then focus on genital and associated trauma. The surgical approach will depend on the site of the damage but a lateral or a sub-coronal degloving should supply a good exposure[3].

The first principles of caring of genitalia are debridement of devitalized tissue, preservation of as much viable tissue as possible, diversion of urine, hemostasis and removal of foreign bodies if necessary[3]; the conservative management is election for most cases[10]. If some tissue is not completely viable, the conservative management is encouraged for a delayed penile repair, perhaps 4 wk after trauma[3]. A tunica albuginea defect could be repaired easily but if bigger damage is found, the surgeon should use an autologous or xenograft[3].

When loss of genital skin is mild to moderate, reconstruction with the same skin is preferable but when an extensive injury is encountered, a full-thickness skin graft should be established for reconstruction[10,11]. This could

be taken from the abdomen, buttock, thigh or axilla, depends of the preference of the surgeon[11].

According to the grade of damage, there are a variety of treatments, for example: closure of residual stump, surgical reanastomosis or total phallic substitution with reconstruction[4,12].

The penis and the amputated part should be washed out and debrided with saline or ringer solution[3,13] in every case. If replantation is attempted, it should be done within 24 h with proper maneuvers and conservation of the amputated part (usually the glans) because success has been reported within this time[14] and this could be performed in a micro or non-microvascular approach with better results in the first one[3].

Particularly in this case, the patient had a genital gunshot wound with loss and devitalized tissue: the glans, the urethra and the cavernous corpora, so the replantation was not indicated, then the second choice of treatment was used as literature says: a closure of the penile stump was performed (cavernous corpora) and the urethra was spatulated as in a standard partial penectomy[4]. The phallic substitution with reconstruction is usually recommended for patients with a good mental status and after the episode has passed and the patient is stable[4], but this is not going to be discussed in this article.

The postoperative management should include: antibiotics for the risk of infection, a Foley catheter for the urethral reconstruction, and some dressings over the penis[4]. These recommendations are based on descriptive studies due to the lack of clinical trials to assess the best treatment possible.

Based on the aesthetic and functional results the patient could need a second or third surgery accompanied by the plastic surgeon[4,15], for example, this patient will need a reconstructive surgery to place the parts where they go and also perhaps an urethral reconstruction to assure the functional status.

It is important to recognize the need to interact with different specialists for example the plastic surgeon, the psychologist/psychiatrist, and the urologist for sure[4]. This is not something easy to treat, so the general physician, the urologist and every doctor involved in the treatment should recognize, diagnose and treat according to the damage to minimize the sequels.

This case allows us to recognize and to keep in mind how important and relevant these injuries are due to their impact on the functional, psychological and the aesthetic consequences. It is necessary to wash out and debride the injured tissue and consequently, defining the best possible treatment to minimize the damage.

COMMENTS

Case characteristics

A male patient received multiple gunshot wounds.

Clinical diagnosis

Multiple wounds caused tissue lost in the foreskin, glans, anterior urethra and cavernous corpora.

Differential diagnosis

There are not differential diagnosis, but according to the findings urologists need to check for damage to the urethra, glans and cavernous corpora.

Treatment

The treatment offered to this patient was a partial penectomy along with penis and urethral reconstruction.

Term explanation

Partial penectomy: to take a part of the penis off. Cystostomy: to put a suprapubic tube to permit drainage of urine from the badder.

Experiences and lessons

The author confirmed how important and relevant these injuries are due to their impact on the functional, psychological and the aesthetic consequences.

Peer review

This paper is well-written, and this case report is informative for readers.

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CASE REPORT

Bladder paraganglioma: A report of case series and critical review of current literature

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Abstract

Extra-adrenal chromaffin cell-related tumours or paragangliomas are rare, especially in the bladder. In this article, we reported three different clinical cases of bladder paraganglioma, followed by a review of current literature on the pathophysiology and management of bladder paraganglioma. Case 1 involved a 23 years old female patient who complained of a 10-year history of micturition-related headaches, palpitations and diaphoresis; while in case 2, a 58 years old female patient presented with history of painless haematuria and an incidentally diagnosis of a functioning paraganglioma during endoscopic transurethral resection of bladder tumour; and lastly in case 3, a 54 years old male renal transplant recipient was referred to the urology outpatient with a suspicious bladder mass found incidentally on routine transplant workshop.

Key words: Bladder paraganglioma; Bladder mass; Catecholamine and its metabolites; Nuclear imaging

Core tip: Bladder paraganglioma is a rare condition and patients can present with various clinical presentations. Biochemical profiling and nuclear imaging study can assist in the identification of this lesion. Preoperative care with volume hydration and adrenergic blockade are often necessary and surgery remains the only cure for these patients.

Ranaweera M, Chung E. Bladder paraganglioma: A report of case series and critical review of current literature. *World J Clin Cases* 2014; 2(10): 591-595 Available from: URL: http://www.wjgnet.com/2307-8960/full/v2/i10/591.htm DOI: http://dx.doi.org/10.12998/wjcc.v2.i10.591

INTRODUCTION

Paragangliomas are rare tumours that arises from extra-adrenal paraganglia and consists of specialized neural crest-derived cells (catecholamine-secreting chromaffin cells)[1]. Of all chromaffin cell-related tumours, paraganglioma accounts for less than a quarter of cases[1,2]. The sympathetic paraganglia are symmetrically distributed along the paravertebral axis and small sympathetic paraganglia can also be found in other organs such as the bladder. Primary paraganglioma of the urinary bladder is very rare making up less than 0.05% of all bladder malignancy. Paragangliomas can present with clinical symptoms secondary to catecholamine hypersecretion or mass effect, incidental finding on radiographic imaging, and/or on routine family screening for hereditary paraganglioma. We explore three different clinical cases of bladder paraganglioma that were treated at our institution.

CASE REPORT

Case report 1

A 23 years old female was referred by her general practitioner with history of urinary urgency and an incidental finding of bladder mass on urinary tract ultrasound.

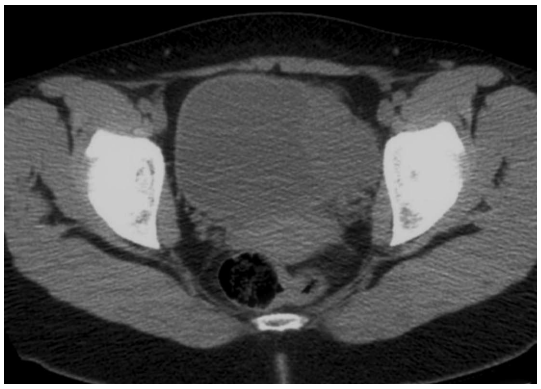

Figure 1 Computer tomography showing an avidly enhancing mass in the left urinary bladder wall.

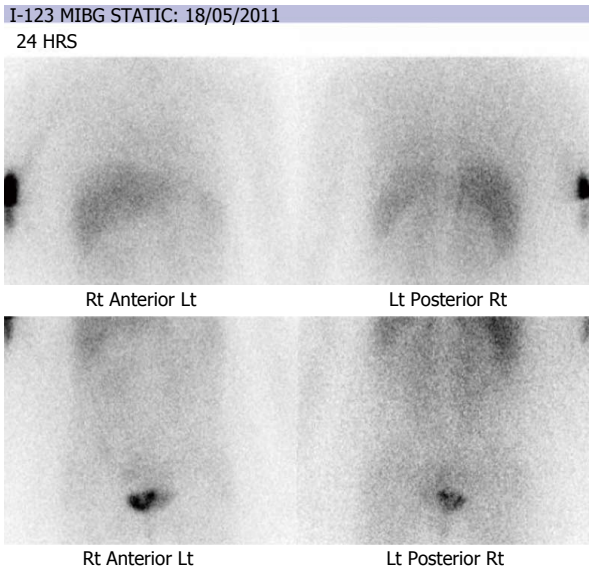

Figure 2 Iodine-123-meta-iodobenzylguanidine scintiscan showing intense tracer uptake in the left side of the bladder consistent with bladder paraganglioma as well as injection artefact in the right cubital fossa. I-123 MIBG: Iodine-123-meta-iodobenzylguanidine.

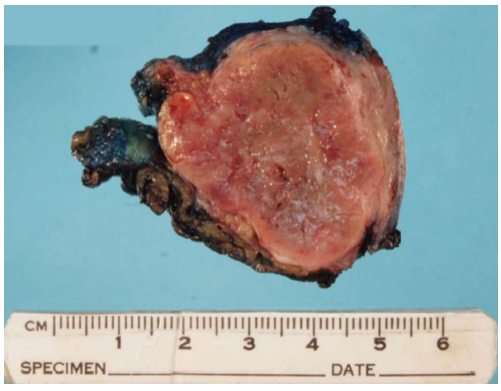

Figure 3 Macroscopic view of bladder paraganglioma. The tumour is red-brown in colour and well-circumscribed.

When enquired further, she described a long-standing history of episodic severe throbbing headaches lasting few minutes, dating back to as early as the age of 12 years. These paroxysmal attacks of headache coincided with her bladder emptying and over the last few years, she also experienced palpitations, nausea, sweat and facial pallor post-micturition. In addition, she recalled the presence of microscopic hematuria in her urine dipstick since the age of 12 years. She has been diagnosed with borderline hypertension in her late teens but is not on antihypertensive medication. There was no family history to suggest a hereditary endocrine disorder.

Urinary tract ultrasonography revealed a large vascular soft tissue mass on the left bladder wall and her urine cytology revealed mildly atypical urothelial cells in two out of three samples. There was a marked elevation of urinary noradrenaline (4748 nmol/dL, Reference: [50-600]) and its metabolites on 24 h urine collection. Plasma metanephrine was also significantly elevated (8500 pmol/L, reference < 900 pmol/L). Staging computed topography of the abdomen and pelvis showed a 6.2 cm × 4 cm × 4.9 cm solid and enhancing, loculated mass near to the left vesicoureteric junction (Figure 1). Following consultation with the endocrinologist, alpha (α)-adrenergic and beta (β)-adrenergic blockade was achieved with a combination of phenoxybenzamine and metoprolol for a minimum of 2 wk prior to surgery. During this time, further imaging with Iodine-123-meta-iodobenzylguanidine (I-123 MIBG) scintiscan confirmed the presence of bladder phaeochromocytoma without metastatic disease (Figure 2).

A formal rigid cystoscopy, left retrograde pyelogram and examination under anesthesia were performed and showed a firm, irregular, well circumscribed lesion in the left bladder that was not fixed to the pelvis and a normal distal left ureter configuration. She was hypertensive intraoperative and required α-adrenergic blockade with phentolamine. Discussion ensued about her condition and she underwent partial cystectomy 2 wk later with volume hydration and antihypertensive medication. A combination of adrenergic blockade with phentolamine, esmolol and metaraminol were utilised intraoperatively during her partial cystectomy.

The histopathology of the bladder wall specimen sections showed a 35 mm × 32 mm well-circumscribed, lobulated, red-brown tumour (Figure 3). Microscopically, the tumour was composed of nests of cells with eosinophilic cytoplasm and round nuclei with vesicular chromatin. It was encapsulated with no evidence of extracapsular invasion and surgical margins were clear (Figure 4). The tumour cells stained positive for chromogranin, patchy for S-100 and negative for cytokeratin consistent with urinary bladder paraganglioma.

Further immunohistochemistry on the tumour specimen revealed the tumour was negative for succinate dehydrogenase subunit B (SDHB). She was subsequently discharged and remained asymptomatic at 36 mo of follow up.

Case report 2

A 58 years old female underwent a routine uneventful resection of bladder mass found during investigation for

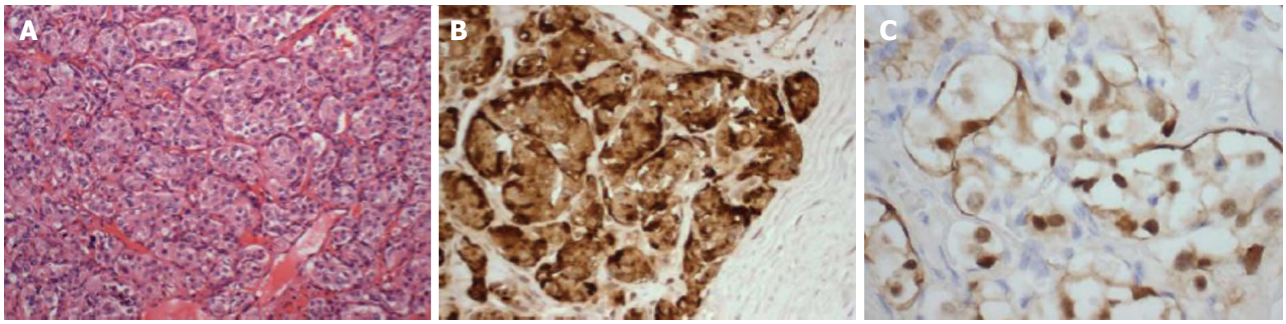

Figure 4 Haematoxylin and eosin staining of bladder paraganglioma tumour (A) showing characteristic nests of cells with eosinophilic cytoplasm and round nuclei. Chromogranin staining (B) was strongly positive, whilst S100 staining (C) was positive in patches.

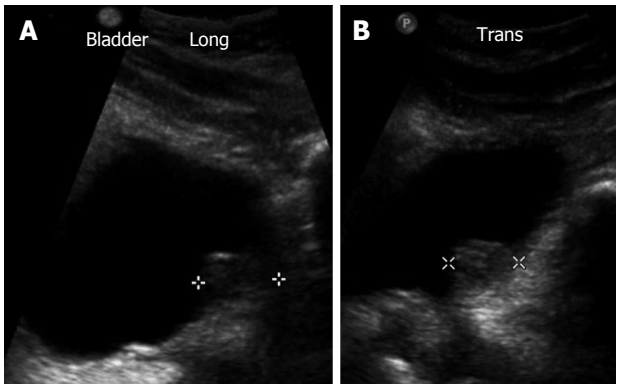

Figure 5 Longitudinal and transverse views of a paraganglioma protruding into the bladder.

painless macroscopic haematuria. The histopathology of this mass showed solid nests of plump epithelial cells with granular to foamy cytoplasm and enlarged, moderate pleomorphic nuclei. Immunohistochemical staining was strongly positive for chromogranin, neuron-specific enolase (NSE), synaptophysin and protein gene product 9.5, consistent with a neuroendocrine tumour. On retrospect history, she had been taking atenolol and oxazepam for her moderate hypertension and anxiety disorder. Given that the patient's younger sister had a history of poorly controlled hypertension, both sisters underwent genetic testing and von Hippel Lindau (VHL), SDHB and succinate dehydrogenase screening, but were negative.

Further investigations showed an elevated creatinine ratio of urinary normetanephrine (0.40 mmol/mmol creatinine) and metanephrine (0.13 mmol/mmol creatinine), and an increased 24-h excretion of normetanephrine (3.2 μmol/24 h). Nuclear imaging study with I-123 MIBG scan showed a discrete round focus on the left side of the bladder with no further evidence of metastases.

The patient was commenced on phenoxybenzamine and propranolol preoperatively for 2 wk and underwent open partial cystectomy and re-implantation of her left ureter. Intra-operatively the patient remained haemodynamically stable. Histopathology confirmed bladder paraganglioma with multiple nodules found predominately within the muscularis propria but not extending into the peri-vesicle soft tissue and a clear of the surgical margins. The tumour showed focal moderate nuclear pleomorphism with no lymphovascular invasion. She remained asymptomatic with normal imaging test at 60 m of follow up.

Case report 3

A 54 years old male renal transplant recipient for end-stage renal failure (secondary to Alport's syndrome) was referred for investigation of an asymptomatic bladder mass. After having undergone a left sided radical nephrectomy for papillary renal cell carcinoma 12 mo earlier, this bladder mass was discovered on surveillance urinary tract ultrasonography (Figure 5). He underwent routine cystoscopy which revealed a submucosal polyp at the anterior bladder suspicious for urothelial tumour and this bladder "tumour" was completely resected.

Histological examination revealed tumour cells arranged in nested architecture with circumscribed margin and focal areas of smooth muscle invasion. Interestingly the immunohistochemistry staining of the tumour cells were positive for synaptophysin and chromogranin but negative for cytokeratin.

The patient subsequently underwent an I-123 MIBG scan and metastatic disease was excluded. Serum and urinary catecholamines were negative too. Follow-up flexible cystoscopy at 1 year post-resection showed no evidence of disease recurrence.

DISCUSSION

Bladder paraganglioma is rare and accounts for less than 1% of all catecholamine secreting neoplasms and only 0.5% of all bladder tumours[3]. They are thought to arise from embryonic rests of chromaffin cells within the bladder wall and often occur in young women in their second to fourth decade of life[4]. Paragangliomas that secrete catecholamine may give rise to clinical presentation similar to a hyperfunctioning adrenal phaeochromocytoma. Episodic symptoms may occur in spells or paroxysms, and can be highly variable. The position of these tumours within the bladder results in characteristic symptom complex related to micturition or over-distension of the bladder with catecholamine release. The majority of patients will experience micturition related hypertension, cold

sweats, palpitations, headaches, dizziness and sweating much like the Case 1 in our series[5]. Systemic catecholamine secretion occurs with increased bladder pressure after bladder contraction, triggering these sympathomimetic attacks[6]. These symptoms may also be precipitated by defaecation, sexual activity, ejaculation or bladder instrumentation. Approximately 55%-60% of patients will also experience painless haematuria, although it is mostly microscopic in nature[7]. While hematuria is commonly reported in patient with bladder mass, this is not specific for paraganglioma. Only a minority of patients will experience weight loss, nausea, tremor, postural hypotension, syncope, chest pain, blurred vision, laryngismus, high blood sugar levels or symptoms associated with catecholamine cardiomyopathy[5].

Suspected cases of paragangliomas should first be investigated by measuring the level of catecholamine and its metabolites such as metanephrine and vanillylmandelic acid secretion in either the blood or urine. The measurement of serum adrenaline and noradrenaline can be costly and is usually unnecessary[8]. The majority of paragangliomas are not hormonally active, thus preoperative catecholamine levels maybe normal[1,8]. Bladder paraganglioma can often be difficult to distinguish radiologically from other bladder lesions[8]. The use of intravenous contrast may precipitates a hypertensive crisis although non-ionic contrast is reported to be safe[9]. In contrast to the hyperintense T2 signalling on magnetic resonance imaging with adrenal phaeochromocytoma, paraganglioma is likely to be homogenous on T2 signal[10]. Both I-131 MIBG and ^{18}F-fluorodeoxyglucose, positron emission tomography are useful for localization of potential metastatic disease. I-123 MIBG can be used as an alternative to I-131 MIBG for accurate preoperative localization of small lymph node[11].

As many as half of the cases of paraganglioma share a genetic basisa and can be related to a number of hereditary conditions including VHL, neurofibromatosis type 1, Carney triad, Multiple Endocrine Neoplasia types 2a and 2b and familial paraganglioma[1]. Therefore, genetic testing should be offered in cases of young patient (under 50 years old) with a positive family history or with history of bilateral, extra-adrenal or multifocal phaeochromocytoma, a positive genetic mutation as well as those tumours with negative SDHB staining[12].

Since paraganglia are distributed throughout the bladder wall, paraganglioma can be found in any part of the bladder. These tumours are mostly well circumscribed and usually form nodules or small mass. Placing the tumour in a Zenker's fixative will turn the tumour black; a positive chromaffin reaction. Histologically, paraganglioma is often misdiagnosed as urothelial carcinoma[13] and paraganglioma may mimic high grade urothelial carcinoma with a nest pattern. Features of paraganglioma include zellballen architecture where tumour cells are arranged into nests and lobules, a delicate fibrovascular stroma and eosinophilic cytoplasm. Immunohistochemistry is usually positive for NSE, chromogranin and synaptophysin and negative for cytokeratin. There are no definitive characteristics which reliably distinguish benign from malignant tumour, and desmoplastic reaction is often absent[12]. The distinction between benign and malignant paraganglioma has long been contentious, with the only widely accepted and definitive proof of malignancy being metastasis to other organs. Some histological features such as tumour necrosis, a mitotic rate greater than 3/30 high power field, capsular invasion, large nests with central degeneration, a lack of hyaline globules, a high nuclear/cytoplasmic ration, monotony of a cytological pattern and spindle cells patters are suggestive of increased malignant predilection[14]. Immunohistochemistry stains are often useful in helping to establish the diagnosis and those with SDHB negative-stain may indicate a succinate dehydrogenase subunit-mutated tumour. Urothelial carcinoma and carcinoid tumours are positive for cytokeratin, while melanoma cells show positivity for S100, HMB45 and Melan A stains.

Complete surgical removal of the tumour is the treatment of choice[1,4,6]. If the paraganglioma is a catecholamine secreting tumour, the effects of excess circulating catecholamines should be reversed prior to surgical extirpation. Combined preoperative α- and β-adrenergic blockade are required to control the blood pressure in order to prevent intra-operative hypertensive crisis. An α-adrenergic blockade should be commenced prior to β-adrenergic blockade, to allow for volume expansion of the contracted blood volume and a liberal salt diet and adequate hydration are also advised. Once adequate α-adrenergic blockade is achieved, β-adrenergic blockade can be initiated. Localised tumours can be removed in partial cystectomy while transurethral resection is adequate in superficial and small bladder lesion[8]. Postoperative 24 h urinary catecholamine and its metabolites should be conducted at week 2 and if the levels are normal, the resection of paraganglioma is considered complete.

As discussed earlier, malignant phaeochromocytoma remains a challenging entity to diagnose and treat. Up to 15% of bladder paraganglioma can become metastasis, and metastasis is the only reliable indicator of malignancy. Young age, extensive local disease and micturition attacks are risk factors for malignancy while features such as vascular invasion, a deeply invasive growth patterns and recurrence are often poor prognostic signs. Metastatic potential is often unclear and thus long-term annual follow up is suggested[15]. In patients with metastatic disease, complete cystectomy and pelvic lymph node dissection is the preferred option[16]. Nuclear imaging such as I-131 MIBG radiotherapy has also been shown to be useful for palliative control of tumour function in metastatic disease, but the current chemotherapy and radiotherapy treatment options are limited[17].

Bladder paraganglioma is a rare condition and patients can present with various clinical presentations. Biochemical profiling and nuclear imaging study can assist in the identification of this lesion. Preoperative care with volume hydration and adrenergic blockade are often nec-

essary to control the blood pressure and to prevent intra-operative hypertensive crisis. Surgical extirpation remains the only cure for these patients and further research into this rare condition is warranted.

COMMENTS

Case characteristic

All patients presented with bladder mass with various clinical symptoms.

Clinical diagnosis

Bladder paraganglioma is diagnosed through biochemical hormonal profiling and nuclear imaging study.

Differential diagnosis

Urothelial cancer, benign bladder lesion.

Laboratory diagnosis

Measurement of catecholamine and its metabolites levels such as metanephrine and vanillylmandelic acid secretion in either the blood or urine.

Imaging diagnosis

Nuclear imaging study using iodine-131-meta-iodobenzylguanidine and ^{18}F-fluorodeoxyglucose, positron emission tomography.

Pathological diagnosis

Features of paraganglioma include zellballen architecture where tumour cells are arranged into nests and lobules, a delicate fibrovascular stroma and eosinophilic cytoplasm. Immunohistochemistry is usually positive for neuron-specific enolase, chromogranin and synaptophysin and negative for cytokeratin.

Treatment

Preoperative care with volume hydration and adrenergic blockade are often necessary to control the blood pressure and to prevent intra-operative hypertensive crisis. Surgical extirpation remains the only cure.

Related reports

Bladder paraganglioma is a rare condition and patients can present with various clinical presentations. Malignant phaeochromocytoma remains a challenging entity to diagnose and treat, and further research into this rare condition is warranted.

Experiences and lessons

This case series highlights the various clinical presentation of bladder paraganglioma and provides a clinical review of the current literature on management of this rare condition.

Peer review

This is a well-written report of three cases of bladder paraganglioma. Bladder paraganglioma is very rare. Their pathological diagnosis is quite proper and clinical practice is also well-summarized.

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CASE REPORT

Haemostatic management for aortic valve replacement in a patient with advanced liver disease

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Author contributions: Weinberg L and McCall P were the principal anaesthetists who managed the case; both were responsible for the planning and writing of the case report; Kearsey I and Tjoakarfa C were responsible for all the data collection, collation of pictures and the writing of the case report; Matalanis G and Galvin S were the cardiac surgeons that performed the operation and were responsible for the writing of the case report; Carson S was the clinical perfusionist that managed the case and was responsible for the writing of the case report; McNicol L and Bellomo R were responsible for the co-management of the patient in the preoperative and postoperative period and were responsible for the writing of the manuscript.
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Abstract

Redo-sternotomy and aortic valve replacement in patients with advanced liver disease is rare and associated with a prohibitive morbidity and mortality. Refractory coagulopathy is common and a consequence of intense activation of the coagulation system that can be triggered by contact of blood with the cardiopulmonary bypass circuitry, bypass-induced fibrinolysis, platelet activation and dysfunction, haemodilution, surgical trauma, hepatic decompensation and hypothermia. Management can be further complicated by right heart dysfunction, porto-pulmonary hypertension, poor myocardial protection, and hepato-renal syndrome. Complex interactions between coagulation/fibrinolysis and systemic inflammatory response syndrome reactions like "post-perfusion-syndrome" also compound haemostatic failure. Given the limited information available for the specific management and prevention of cardiopulmonary bypass-induced haemostatic failure, this report serves to guide the anaesthesia and medical management of future cases of a similar kind. We discuss our multimodal management of haemostatic failure using pharmacological strategies, thromboelastography, continuous cerebral and liver oximetry, and continuous cardiac output monitoring.

Key words: Cardiac surgery; Liver failure; Coagulopathy; Cardiopulmonary bypass

Core tip: Cardiac surgery in patients with advanced liver disease is associated with significant morbidity and mortality. Refractory coagulopathy is common and requires a proactive multidisciplinary haemostatic management strategy. Given the limited information available for the specific management and prevention of cardiopulmonary bypass induced haemostatic failure, this report serves to guide the anaesthesia and medical management of future cases of a similar kind. We discuss our multimodal management of haemostatic failure using pharmacological strategies, thromboelastography, continuous cerebral and liver oximetry, and continuous cardiac output monitoring.

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agement for aortic valve replacement in a patient with advanced liver disease. *World J Clin Cases* 2014; 2(10): 596-603 Available from: URL: http://www.wjgnet.com/2307-8960/full/v2/i10/596.htm DOI: http://dx.doi.org/10.12998/wjcc.v2.i10.596

INTRODUCTION

Redo-sternotomy and aortic valve replacement (AVR) in patients with advanced liver disease is rare and associated with a prohibitive morbidity and mortality. Refractory coagulopathy is common and a consequence of intense activation of the coagulation system that can be triggered by contact of blood with the cardiopulmonary bypass (CPB) circuitry, CPB-induced fibrinolysis, platelet activation and dysfunction, haemodilution, surgical trauma, hepatic decompensation and hypothermia. Management can be further complicated by right heart dysfunction, porto-pulmonary hypertension, poor myocardial protection, and hepato-renal syndrome. Complex interactions between coagulation/fibrinolysis and systemic inflammatory response syndrome (SIRS) reactions like "post-perfusion-syndrome" also compound haemostatic failure.

We present a patient with critical aortic stenosis who underwent redo-sternotomy and AVR prior to being listed for orthotopic liver transplantation. In this context, there is little information on the specific management of CPB-induced haemostatic failure. Therefore, we discuss our multimodal management of haemostatic failure using pharmacological strategies, thromboelastography (TEG), continuous cerebral and liver oximetry, and continuous cardiac output monitoring.

CASE REPORT

A 46-year-old male (weight 68 kg, height 183 cm) presented to our institution with acute pulmonary oedema secondary to severe aortic stenosis. The patient consented for a redo-sternotomy and AVR, with an estimated perioperative mortality of 50%. Previous cardiac history included open valvotomy *via* median sternotomy for a congenital calcified bicuspid aortic valve at age 6. The patient had a 10-year history of chronic liver disease secondary to alcohol abuse, with a Child Pugh Score of 8 (Child Class B), and a Model for End-Stage Liver Disease (MELD) Score of 12. The liver disease was further complicated by severe portal hypertension with ascites, thrombocytopaenia, oesophageal varices and portal hypertensive gastropathy. Two years prior, he underwent an emergency laparotomy for bleeding umbilical varices, which required intensive care unit (ICU) admission and an 8-unit red blood cell transfusion for hemorrhagic shock.

On this admission a transthoracic echocardiogram revealed preserved systolic left and right ventricular function, a severely calcified bicuspid valve (aortic valve area: 0.7 cm^2; mean aortic valve pressure gradient of 60 mmHg), moderate aortic regurgitation, mild mitral regurgitation, moderate pulmonary hypertension and a dilated ascending aorta (5.4 cm). Other cardiovascular risk factors included IgA nephropathy (creatinine 110 μmol/L, estimated glomerular filtration rate 73 mL/min per 1.73 m^2). There was no history of smoking or diabetes. The pulmonary oedema settled with conservative medical therapy. A coronary angiogram and right heart catheter study revealed no occlusive coronary artery disease, with a cardiac index of 3.4 L/min per square meter and a pulmonary artery pressure of 71/30 mmHg (mean 33 mmHg). Preoperative investigations including TEG are summarised in Tables 1-3. A detailed perioperative haemostatic coagulation strategy was formulated by a team composed of anaesthetist, haematologist, cardiac surgeon and intensivist.

The day before surgery, terlipressin [1 mg intravenous (*iv*) every 6 h] was commenced. Prior to induction of anaesthesia, an 8-French Rapid Infuser Catheter (Arrow) was inserted into each arm. Invasive monitoring included a 20 Gauge arterial line, 4-lumen central venous catheter, continuous cardiac output and continuous mixed venous oximetry measured with a fiberoptic pulmonary artery catheter (Edwards Lifesciences, Irvine CA) (Figure 1). External defibrillator pads were applied as a safety precaution. Bispectral index monitoring and cerebral and hepatic tissue oxygenation (Invos, Somanetics®) were measured with a cerebral/somatic oximeter, by placing disposable transducers over the right and left forehead (Figure 1), and on the skin overlying the lower right costal margin (Figure 2). The oximeters provided real-time monitoring of brain and liver oxygen saturations, measuring oxygen consumption and delivery. This allowed for detection and correction of cerebral and hepatic oxygen desaturation to optimise haemodynamic intervention. Tranexamic acid (1 g *iv* load then 500 g/h infusion) was commenced to minimize fibrinolysis during and after CPB. Octreotide (100 mcg bolus, then 25 mcg/h) was commenced to control portal hypertension and minimise hepatic ischaemia reperfusion injury from CPB. Vancomycin (1 g *iv*) and ceftriaxone (1 g *iv*) were administered for antimicrobial prophylaxis.

Redo-sternotomy was performed using an oscillating saw while lifting up the sternal wires. Dense adhesions of the right ventricle and posterior table of the sternum precluded access to the heart for central venous cannulation. Consequently, the femoral artery and vein were cannulated and the venous cannula carefully positioned using transoesophageal echocardiography guidance in the right atrium. After careful dissection around the heart and full heparinisation, the standard on-pump AVR technique was applied. A second venous cannula was added *via* the superior vena cava to the venous circuit to allow venous drainage, further minimizing hepatic congestion. After aortic cross clamp, pulsatile CPB was established, complete with haemofiltration to prevent fluid overload and maintain electrolyte neutrality. During CPB the patient was severely vasoplegic requiring escalating doses of noradrenaline (20 μg/min *iv*) and vasopressin (0.4 IU/min *iv*) to maintain a mean arterial pressure of 50 mmHg. Optimal pump flow rates and vasopressor use were

Table 1 Perioperative laboratory values and heparinase thromboelastography results

	Ref. ranges	Pre-operative	Pre-CPB	Rewarming Haemostatic intervention: FFP 15 mg/kg	Immediately post separation from CPB Haemostatic intervention: Protamine 500 mg; DDAVP 0.3 mg/kg; Concentrated fibrinogen 4 g; Platelets 2 pooled doses; 2 units packed RBC	15 min post separation from CPB Haemostatic intervention: Prothrombine × 1000 IU; then continuous infusion at 100 IU /h	30-min post separation from CPB Haemostatic intervention: Nil	Arrival intensive care unit
R (min)	4-8	6.4	5.0	6.7	6.9	28.9	7.8	6.7
K (min)	0-4	2.0	1.8	1.8	1.8	4.9	1.5	1.6
Angle (deg)	47-74	62.7	63.5	65.6	65.2	49.6	68.5	65.5
MA (mm)	54-72	53.7	61.9	61.3	57.6	71.8	69.0	70.1
LY30 (%)	0-8	0.7	0.3	0.0	0.0	1.4	0.0	0.0
INR	-	1.3	1.2	1.4	1.7	1.5	1.4	1.4
PT	11-15 s	13 s	14 s	15 s	19 h	17 h	16 h	16 h
APPT	22-38 s	36 s	39 h	> 200 h	49 h	50 h	45 h	38 s
Fib clauss	2.0-4.0 g/L		2.3 g/L	1.3 L	2.6 g/L	2.0 g/L	1.6 L	1.8 g/L
D-dimer	< 0.23 mg/L	1.05 h	Not measured	0.94 h		1.15 mg/L	Not measured	Not measured
Hb	130-180/L	90 L	83 L	73 L	55 L	85 L	Not measured	71 L
WBC	4.0-11.0 × 10^9	3.9 L	4.2 × 10^9	10.8 × 10^9	8.2 × 10^9	11.7 h	Not measured	9.4 × 10^9
Platelets	150-400 × 10^9	76 L	64 L	57 L	140 L	120 L	Not measured	73 L

The thromboelastography was performed after each of haemostatic interventions described. CPB: Cardiopulmonary bypass; FFP: Fresh frozen plasma; DDAVP: Desmopressin acetate; INR: International normalised ratio; PT: Prothrombin time; APPT: Activated partial prothrombin time; WBC: White blood cells; RBC: Red blood cells; MA: Maximum amplitude; K: Clot formation time; R: Reaction time.

Table 2 Perioperative arterial blood gases

	Ref. ranges	Pre-operation	Pre-cardiopulmonary bypass	Rewarming	Post separation	Closure	Post-op day 1	Post-op day 2 (venous)
pH	7.35-7.45	7.34[1]	7.32[1]	7.37[1]	7.24[1]	7.34[1]	7.34[1]	7.33[1]
pCO_2 (mmHg)	35-45	37	38	35	50[2]	42	39	45
pO_2 (mmHg)	80-110	105	230[2]	388[2]	385[2]	404[2]	111[2]	33[1]
HCO_3^- (mmol/L)	-	19	19	20	20	22	20	23
Base excess (mmol/L)	-3/+3	-6[1]	-6[1]	-4[1]	-6[1]	-3	-5[1]	-2
O_2 sat (%)	> 94	98	100	100	100	100	100	56[1]
Na^+ (mmol/L)	135-148	132[1]	132[2]	136	138	138	138	130[1]
K^+ (mmol/L)	3.5-5.3	4.0	4.0	4.9	3.9	3.9	4.6	4.5
Cl^- (mmol/L)	95-106	107[1]	107[2]	106	108[2]	108[2]	106	99
Ionised Ca^{2+} (mmol/L)	1.13-1.32	1.16	1.07[1]	0.92[1]	0.83[1]	1.06[1]	1.10[1]	1.10[1]
Haemoglobin (g/L)	120-180	80[1]	78[1]	71[1]	77[1]	86[1]	71[1]	63[1]
Glucose (mmol/L)	0.0-5.0	5.9[2]	6.3[2]	8.3[2]	6.2[2]	3.8[1]	8.0[2]	8.9[2]
Lactate (mmol/L)	3.9-5.8	0.9	0.6	4.0[2]	2.9[2]	2.0[2]	1.5	1.3

[1]Value below reference range; [2]Value above reference range.

Table 3 Perioperative renal function and liver function tests

	Ref. ranges	Pre-op	Arrival in ICU	Day 1 post op
Urea (mmol/L)	3.2-7.3	8.7[2]	6.3	7.6[2]
Creatinine (μmol/L)	62-106	110[2]	91	125[2]
Albumin (g/L)	35-52	31	25[1]	36
Globulins (g/L)	25-35	46[2]	19[1]	20[1]
Bilirubin (μmol/L)	< 18	40	35[2]	47[2]
ALP (IU)	40-130	99	51	49
ALT (IU)	< 41	30	21	22
GGT (U/L)	< 60	100[2]	40	40

[1]Value below reference range; [2]Value above reference range. ICU: Intensive care unit; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transpeptidase.

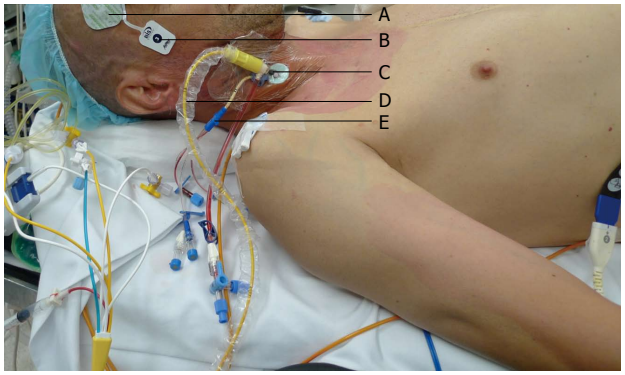


Figure 1 Monitoring used for redo-stenotomy and aortic valve replacement. A: Cerebral oximeter (Invos, Somanetics®); B: Bispectral index; C: 9 French Internal jugular sheath; D: Continuous cardiac output and mixed venous oximetry measured with a fiberoptic pulmonary artery catheter (Edwards Lifesciences, Irvine CA); E: 4-lumen central venous catheter.

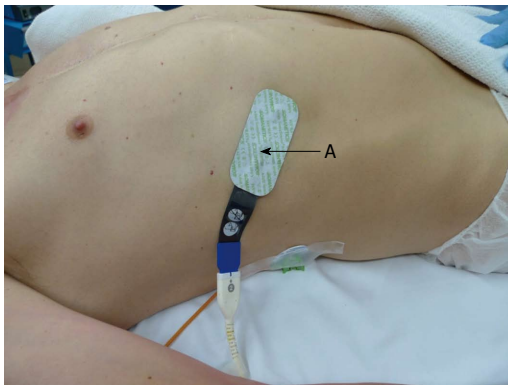


Figure 2 Hepatic tissue oxygenation measured by positioning an oximetry disposable transducer between the ribs and over the liver. A: Hepatic oximeter (Invos, Somanetics).

guided by cerebral and liver oximetry. There was excellent correlation between cardiac output, mixed venous saturations and cerebral and liver oximetry throughout the case (Figures 3 and 4). In response to progressive refractory vasoplegia, methylene blue (1 mg/kg *iv*) was administered, which rapidly re-established an acceptable mean arterial pressure. The noradrenaline and vasopressin requirements were weaned to 3 μg/min and 0.05 IU/min

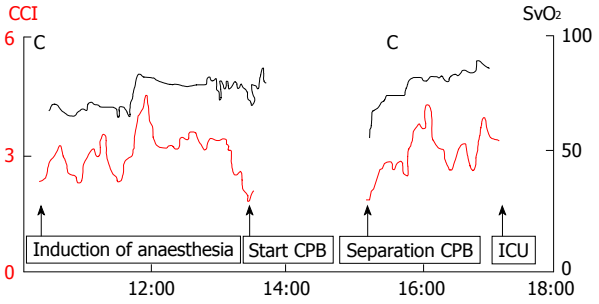


Figure 3 Intraoperative continuous cardiac index and mixed venous oxygenations tracings measured from the pulmonary artery catheter displayed on a Vigilance™ Monitor (Edwards Lifesciences, Irvine CA). ICU: Intensive care unit; CPB: Cardiopulmonary bypass; CCI: Continuous cardiac index.

respectively. A 25 mm Mitroflow® aortic pericardial valve (Sorin, Milan, Italy) was inserted without complication.

Prior to separation from CPB, a rewarming heparinase TEG was performed (Table 1, Figure 5). Desmopressin acetate (0.3 mcg/kg *iv* over 20 min) was administered to increase the plasma levels of factor Ⅷ and von Willebrand factor to minimize post-operative blood loss. Based on the rewarming TEG (Table 2 and Figure 5), fresh frozen plasma (15 mg/kg) was added to the CPB circuit to avoid volume overload and right ventricular distension during bypass separation. Glyceryl trinitrate (5 μg/min *iv*), and frusemide (20 mg *iv*) were administered to further reduce right ventricular preload and hepatic congestion.

After successful separation from CPB, haemostatic management focused on minimizing intraoperative bleeding and maintaining normothermia. Protamine (500 mg *iv*) was given to reverse the effects of heparin and correct activated clotting time to baseline values, followed by two bags of pooled platelets and *iv* administration of concentrated fibrinogen (4 g *iv*) (Riastap®, *iv* Behring, Australia). The dose of fibrinogen was calculated according to the patient's body weight (68 kg) and his estimated blood volume (4.8 L). Based on a preoperative haemoglobin of 9.8 g/L, a haematocrit of 30% of plasma volume (3.4 L), and a preoperative fibrinogen level of 2.5 g/L, we calculated that a dose of 4 g of fibrinogen would be needed to increase plasma fibrinogen levels by an estimated 1.2 g/L. With haemodilution on bypass, we expected the fibrinogen to fall by approximately 1-1.5 g/L. Following administration of concentrated fibrinogen, a heparinase TEG revealed significant prolongation of the R-time, confirming an underlying coagulopathy (Figure 5). Human prothrombin complex® (500 IU *iv* bolus, then 100 IU/h *iv* infusion) (CSL Behring, Australia) was administered, which corrected the R-time and improved haemostasis (Figure 5). Calcium chloride (1-2 g *iv*) was also administered. The total CPB time was 141 min and aortic cross-clamp time 61 min. Temporary epicardial pacing wires were not used to avoid the small risk of cardiac bleeding on wire removal additional. A topical haemostatic matrix (FLOSEAL™, Baxter, Pty) was used to control bleeding

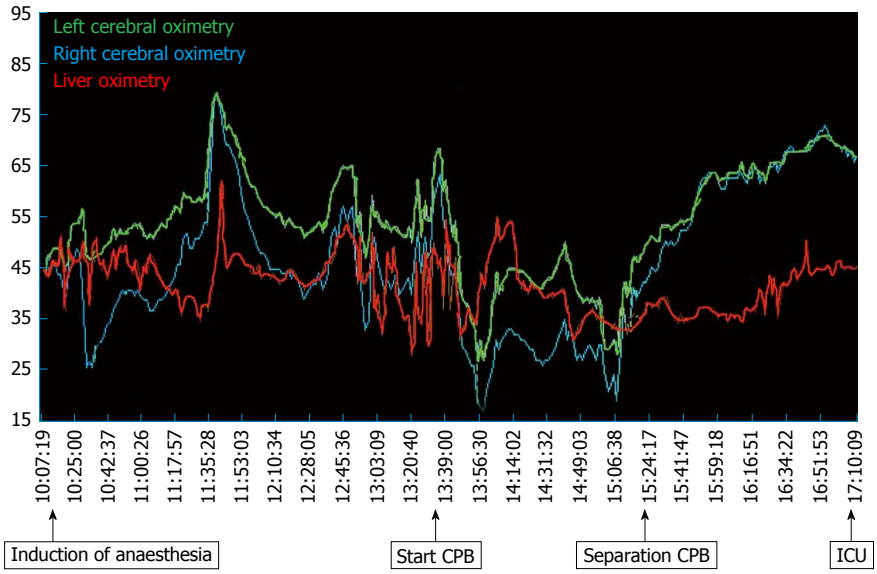


Figure 4 Cerebral and hepatic tissue oxygenation tracings measured with a cerebral/somatic oximeter (Invos Somanetics®) throughout the surgery and during cardiopulmonary bypass. ICU: Intensive care unit; CPB: Cardiopulmonary bypass.

from the suture lines, and thrombin dried powder (GELFOAM®, Baxter, Pty) was applied to the bone marrow of the sternum, which allowed sternal closure with minimal bleeding. Mediastinal and bilateral pleural drains were placed so that volume losses could be measured in ICU, and collection of blood around the heart avoided during the postoperative period.

In ICU, the octreotide (25 mcg/h *iv*) and prothrombinex (100 IU/h *iv*) infusions were continued for 8 h. Haemodynamic stability was maintained and the noradrenaline and vasopressin infusions weaned after 6 h, and the patient was extubated. Terlipressin (1 mg *iv*) was continued every 6 h for a further 24 h. The patient was transferred to the ward the following day, and discharged home ten days later without complications. There were no further requirements for coagulation or blood product intervention. Postoperatively, renal, haematological and liver function tests remained stable, and are summarised in Tables 1-3.

Three months post discharge, and at the time of writing, the patient continues to make satisfactory cardiac progress and is currently awaiting liver transplantation.

DISCUSSION

This case illustrates that redo-sternotomy and aortic valve AVR in the setting of advanced liver disease is feasible but requires careful planning. The central management decisions for such cases include to either (1) replace the valve first and then proceed with liver transplantation at a later date; (2) offer a combined procedure, *i.e.*, AVR and liver transplantation simultaneously; and (3) proceed with liver transplantation first, and then replace the valve at a later stage. In the case described here, after extensive multidisciplinary discussion a consensus was reached that the risks of liver transplantation in the setting of uncorrected symptomatic severe aortic stenosis were prohibitive. In view of the bicuspid valve and dilated ascending aorta, a transcatheter AVR was not a consideration. A combined AVR and liver transplant was considered but there were concerns that there may be further cardiac decompensation during the waiting period. Given that the patient was progressively symptomatic, a redo-sternotomy and AVR was considered to afford the best chance of survival, with activation for liver transplantation initiated at a later stage if the outcome was successful.

As shown in this case, redo cardiac surgery provides several technical challenges that distinguish it from primary cardiac surgery. These obstacles include repeat sternotomy, injury to the heart during dissection, quality and availability of conduits if required, a calcified ascending aorta, and more-advanced coronary disease involving the native vessels. As a result, operative mortality in most reoperations is 3 to 5 times that for a primary AVR. Adding in the ensuing complications of advanced liver disease, perioperative mortality increases with an estimated perioperative risk of mortality of 50%[1]. Each patient's condition and presentation is unique, and thus requires individualized management delivered by a multidisciplinary team. Consideration must be given to the sequence of procedures, cardiac surgical technique, and management of anticoagulation.

Combined cardiac and liver transplantation was first reported by Starzl *et al*[2] in 1984, but has remained uncommon because of the unique medical and surgical challenges it poses . In two descriptive reports of outcomes in patients with advanced liver cirrhosis undergoing cardiac surgery[3,4], hepatic decompensation, respiratory and renal failure, gastrointestinal haemorrhagic events, sepsis and mediastinitis were among the most common postoperative complications. The association of MELD scores and Child-Turcotte-Pugh classification, and adverse outcomes is less clear. In the study by Filsoufi *et al*[4], mortality rate increased significantly according to the

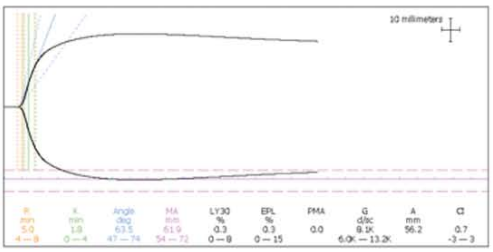
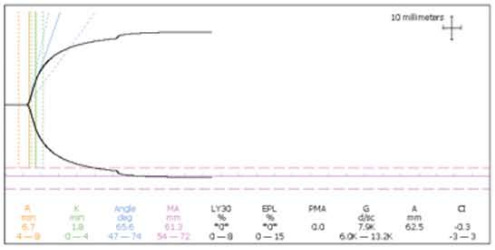
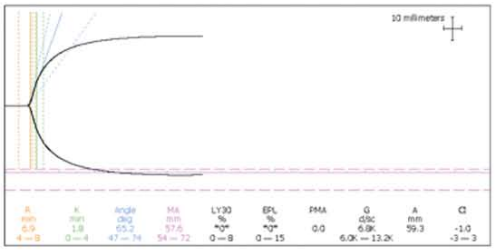
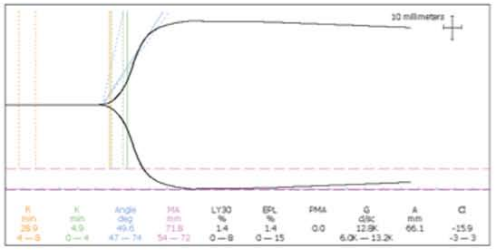
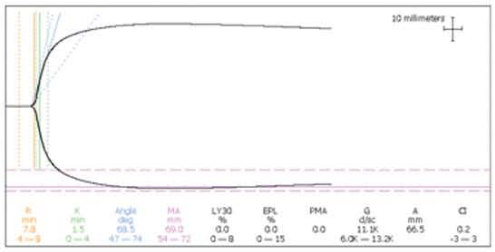
Pre-induction of anaesthesia	(1) Pre-med: morphine intramuscular 15 mg (2) 3 L central venous catheter, continuous pulmonary artery catheter, 8-f rapid infuser catheter peripheral access (3) Tranexamic acid *iv*: 1 g load then 500 g/h infusion to stop at surgical closure (4) Octreotide *iv* 100 mg bolus intravenous, followed after 2 h by a continuous infusion of 25 mg/h for 12 h (5) Terlipressin *iv* 1-2 mg administered every 6 h for 12 (6) Vancomycin *iv* 1 g/ceftriaxone 1 g *iv* antibiotic prophylaxis	
During CPB	(1) TOE guidance of venous lines to ensure excellent drainage and minimal hepatic congestion (2) Pulsatile flow (3) Haemofiltration (4) Noradrenalin commenced for vasoplegia (5) Vasopressin *iv* 0.1-0.4 IU/min commenced for vasoplegia (6) Methylene blue *iv* 1.5 mg/kg administered for refractory vasoplegia unresponsive to above	
Rewarming	(1) DDAVP *iv*: 0.3 μg/kg over 20 min (2) 4 unit FFP directly into the CPB circuit ensuring ACT > 600 s haemofiltering and removing fluid to minimise increasing portal pressures and unnecessary volume load when separating from CPB (3) Glyceryltrinitrate *iv* 5 μg/min to reduce preload to right heart pressures and minimise hepatic congestion (4) Calcium chloride 1-2 g	
After separation from CPB	(1) Protamine *iv* 500 mg, guided by ACT (2) Concentrated fibrinogen: 4 g (3) Prothrombinex *iv* 500 IU load followed by 100 IU/h infusion (4) Platelets: 2 pooled bags (10 units) (5) Frusemide *iv* 20 mg	
Prior to transfer to ICU	(1) Octeotide *iv* 25 mg/h for 6-12 h (2) Terlipressin *iv* 1-2 mg 4-h for 12-24 h (3) Prothrombinex at 100 IU/h for 6-12 h If bleeding still refractory: consideration of: (1) ± Cryoprecipitate 1 bag per 10 kg body weight (2) ± Recombinant activated factor Ⅶ (45-90 μg/kg) if ongoing haemostatic failure observed (3) Additional products based on clinical picture, TEG and laboratory coagulation results	

Figure 5 Perioperative thromboelastrography tracings observed in this case with corresponding haemostatic management action or planned strategy. DDAVP: Desmopressin acetate; FFP: Fresh frozen plasma; CPB: Cardiopulmonary bypass; TEG: Thromboelastography; TOE: Transoesophageal echocardiography; *IV*: Intravenous; ACT: Activated clotting time.

Child-Turcotte-Pugh classification (class A, 10%; B, 18%; and C, 67%). The reported mortality of redo cardiac surgery was approximately 50%[3]. Similarly, the rate of complications was higher in class B (50%) and C (100%) compared to class A (20%). Suman *et al*[5] reported that a cutoff Child-Pugh score > 7 had a sensitivity and specificity of 86% and 92% for mortality, although there was no association between mortality and MELD scores. In contrast, Morimoto *et al*[3] reported that Child-Pugh class score did not correlate with hospital mortality, although MELD score was significantly higher in patients who died immediately post cardiac surgery. To date, there have been several reports of combined AVR and liver transplantation[6]. Postoperative outcomes are variable; the majority of cases have been successful however, mortality due to clotting disturbances has also been reported. As a result, careful preoperative preparation must be conducted in such highly complex cases to prevent catastrophic

outcomes.

As seen in this case, a common yet serious complication of CPB is vasoplegic syndrome, a post-perfusion syndrome characterised by low systemic vascular resistance, significant hypotension, and a high cardiac output. It has an incidence of 5%-25% and a mortality rate as high as 25%[7]. In this case, we used the standard first line vasoactive treatment (noradrenaline and vasopressin) to maintain a mean arterial pressure of 50 mmHg[8]. However methylene blue was required during CPB to reduce the severity of vasoplegia. Use of methylene blue had been used effectively for the treatment of refractory vasoplegia in two randomised control trials[9,10], acting through its inhibitory effect on cyclic guanosine 3',5'-monophosphate-mediated vasodilatation. Despite restoring vascular tone intraoperatively, discontinuation of vasopressin has been associated with postoperative refractory vasoplegia, therefore in the case described here, vasopressin was for continued for 6 h postoperatively.

AVR performed in the context of advanced liver disease added an additional layer of complexity in preventing further decline of hepatic and renal function. The patient's history of significant portal hypertension justified the use of both terlipressin and octreotide to prevent variceal beeding[11-13]. Terlipressin has also been shown to improve hepatorenal syndrome, thought to be due to arteriolar vasoconstriction in the splanchnic area, which was an important consideration for the patient's underlying IgA nephropathy. Its effects are mediated *via* V1 receptors on vascular smooth muscle[13]. In animal models, octreotide has been shown to improve hepatic ischaemia-reperfusion injury by down-regulating inflammatory cytokines (tumor necrosis factor alpha and interleukin-1 beta) and inhibition of hepatocellular apoptosis[14], and in this case, served an added benefit when separating from bypass.

Coagulopathy is a frequent occurrence during CPB and is due to a number of factors including excessive fibrinolysis, platelet dysfunction, coagulation factor consumption, and coagulation factor dilution from intravascular volume replacement. We used a variety of multimodal pharmacological agents to prevent intraoperative and postoperative bleeding. Hypofibrinogenemia is common in cardiac surgery, which was minimized preoperatively with tranexamic acid, and intraoperatively with concentrated fibrinogen[15,16]. Desmopressin acetate[17,18], Human Prothrombin-X complex[19] and protamine were also implemented as described previously.

In this case, we employed several haemostatic and haemodynamic monitoring methods to guide our management. TEG, commonly used in cardiac surgery, is a useful tool in denoting a patient's clotting profile at landmark time points to influence specific pharmacologic decisions[20,21]. Figure 5 summarizes consecutive TEG readings and the subsequent interventions undertaken. It should also be noted that TEG requires trained personnel to operate and therefore poses as a limiting factor for its use[20]. Additional haemodynamic monitoring included pulmonary artery catheter sampling of mixed venous blood (SvO_2) and tissue oximetry. Intraoperatively, we were primarily concerned about the key factors that influence oxygen delivery, namely haemoglobin, oxygenation, and cardiac output. Continuous liver, cerebral and mixed venous oximetry enabled immediate detection of adverse changes, prompting correction and subsequent visualization of improvements of haemodynamic trends. Continuous recordings of cardiac output and global oxygenation status are presented in Figure 3. The brain and liver tissue oxygenation tracings are shown in Figure 4. In the context of low liver oximetry, in addition to the aforementioned factors that influence tissue oxygenation, hepatic congestion secondary to the outflow obstruction was also carefully monitored. Then, depending on the determined underlying cause, suitable corrections were made in the form of red cell transfusion, adjustment pump flow rates, and ensuring adequate venous drainage at all times. Although hepatic oximetry is predominantly used in the paediatric setting[22,23], we justified its use to intensively monitor the already compromised liver, and guide therapy as above. Interestingly, the liver oximeter tracing tracked the cerebral oximeter tracing very accurately (Figure 4), providing reassurance of continual intact hepatic perfusion.

In conclusion, we report a case of AVR in a patient with advanced liver disease. Given the limited information available for specific management and prevention of haemostatic failure, this report serves to guide future cases of a similar kind.

COMMENTS

Case characteristics

A 46-year-old male with a history of chronic liver disease secondary to alcohol abuse, presents with acute pulmonary oedema secondary to left ventricular failure.

Clinical diagnosis

Severe aortic stenosis.

Differential diagnosis

Non cardiogenic causes of pulmonary oedema include pulmonary contusion, acute respiratory distress syndrome, transfusion-related acute lung injury, aspiration, hypertensive crisis, upper airway obstruction, and neurogenic causes (seizures, intracranial haemorrhage).

Laboratory diagnosis

Plasma creatinine 110 μmol/L; albumin 31 g/L; bilirubin 40 μmol/L; haemoglobin 90 g/L; prothrombin time 1.3 s; platelets 76 ($\times 10^9$).

Imaging diagnosis

Transthoracic echocardiogram a severely calcified bicuspid valve, with an aortic valve area of 0.7 cm^2; mean aortic valve pressure gradient of 60 mmHg with moderate pulmonary hypertension.

Treatment

The patients underwent redo-aortic valve replacement requiring aggressive haemostatic therapy for coagulopathy and refractory vasoplegia.

Related reports

Combined cardiac surgery in patients with advanced liver disease.

Experiences and lessons

Cardiac surgery in patients with advanced liver disease is associated with significant morbidity and mortality. Refractory coagulopathy is common and requires a proactive multidisciplinary haemostatic management strategy.

Peer review

Weinberg *et al* present an interesting and complex case report of a patient with critical aortic stenosis and advanced liver disease who underwent redo-

sternotomy and aortic valve replacement prior to being listed for orthotopic liver transplantation.

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CASE REPORT

Liver abscess caused by *Burkholderia pseudomallei* in a young man: A case report and review of literature

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Abstract

Pyogenic liver abscess is a common entity in Indian subcontinent and is mostly caused by gram negative bacteria. Melioidosis is not commonly seen in India and only a few cases are reported. It can give rise to multiple abscesses at different sites including liver. We report a case of isolated liver abscess caused by *Burkholderia pseudomallei* (*B. pseudomallei*) in a 29-year-old recently diagnosed diabetic, immunocompetent male. Diagnosis was made by imaging and culture of pus aspirated from the abscess and he was treated with percutaneous pigtail catheter drainage followed by antibiotics (meropenem and trimethoprim-sulphmethoxazole). Melioidosis is an emerging infection in India and has high mortality rate, so early diagnosis and prompt management is warranted which requires clinical vigilance and an intensive microbiological workup. Clinicians should be aware of isolated liver abscess caused by *B. pseudomallei* in appropriate clinical settings.

Key words: Liver abscess; Diabetes; *Burkholderia pseudomallei*; Emerging infection; India

Core tip: Liver abscess due to *Burkholderia pseudomallei* (*B. pseudomallei*) is extremely rare and is mostly reported from Taiwan. In India, most of the reports of are from southern coastal India and this entity is exceedingly rare in eastern India. The actual magnitude of this emerging infection may be under reported due to non-availability of confirmatory tests. Accurate diagnosis is necessary as outcome is fatal with ineffective treatment. We report a case of multiple liver abscesses caused by *B. pseudomallei* in a 29-year-old diabetic male, who was referred as a case of recurrence of pyogenic liver abscess which was previously caused by pseudomonas not responding to antibiotic therapy and aspiration. Diagnosis was made by imaging and culture of aspirated pus revealed *B. pseudomallei* and he was treated successfully with surgical drainage and prolonged course of intravenous and oral antibiotics. So, in a case of pyogenic liver abscess not responding to conventional antibiotics, *B. pseudomallei* should always be thought as a possibility which can be identified by its characteristic appearance on culture and microscopy or direct immunofluorescence testing as well as unique imaging features.

Pal P, Ray S, Moulick A, Dey S, Jana A, Banerjee K. Liver abscess caused by *Burkholderia pseudomallei* in a young man: A case report and review of literature. *World J Clin Cases* 2014; 2(10): 604-607 Available from: URL: http://www.wjgnet.com/2307-8960/full/v2/i10/604.htm DOI: http://dx.doi.org/10.12998/wjcc.v2.i10.604

INTRODUCTION

Liver abscess is the commonest intra-abdominal abscess, which may be of biliary tract origin (commonest) or hematogenous spread from a distant site, and rarely traumatic. Pyogenic liver abscess is a rare but potentially lethal condition, with a reported incidence of 20 per 100000 hospital admissions in a western population[1]. Both gram positive and gram negative aerobes and anaerobes have been found on culture of aspirated pus, among them *Escherichia coli* (*E. coli*) is cultured most frequently in Western countries[2] and Klebsiella in Asian countries[3].

Burkholderia pseudomallei (*B. pseudomallei*), a category Ⅱ bioterrorism agent, is the causative organism melioidosis and is endemic in Southeast Asia and northern Australia[4]. *B. pseudomallei* is found in soil and water and infection occurs by inoculation, inhalation, or ingestion[4]. Melioidosis is most commonly known to present as pneumonia followed by abscesses in the skin. Abscesses in internal organs like spleen, kidney, prostate and liver have also been reported as part of disseminated disease. Isolated liver abscess in melioidosis is a rare clinical condition.

Cases of melioidosis have been reported from southern coastal part of India, but melioidosis causing liver abscess is rare. In cases of liver abscess not responding to conventional anti-microbial the possibility of melioidosis should always be kept in mind. Because of high relapse and mortality rate, early diagnosis and prolonged treatment is a must in this case.

CASE REPORT

A 29-year-old male was referred to us with high grade fever for 20 d and cough for 2 wk. He had no history of tuberculosis, foreign travel or animal exposure and is farmer by occupation. He had a pyogenic liver abscess by *Pseudomonas aeruginosa* along with pancytopenia about one year back. On admission patient was toxic with high grade fever (37.7 ℃-39.4 ℃) with a pulse rate of 126/min and blood pressure of 100/76 mmHg. Liver was enlarged, tender with a liver span of 15 cm and spleen was just palpable. There was no free fluid in abdomen clinically.

Investigations revealed hemoglobin 10.3 gm/dL, total leucocyte count of 9400/μL, neutrophil 88%, lymphocyte 10%, eosinophil 2% and platelet count of 175 × 10^9/μL. Fasting plasma glucose was 164 mg/dL and HbA1c was 8.1%. So he was newly diagnosed of having diabetes mellitus and started on treatment with insulin. Renal function and liver function tests were within normal limits. Human immunodeficiency virus serology was negative. Acid fast bacilli were not found in sputum and sputum culture showed no growth of any pathogenic organism. Chest radiograph showed elevation of right dome of diaphragm (Figure 1A). Abdominal ultrasound revealed hepatomegaly with a large hypoechoic space occupying lesion (88 mm × 91 mm) in right lobe of liver with splenomegaly. Contrast enhanced computed tomography of abdomen showed hepatomegaly with loculated hypodense lesion (8.5 cm × 7.4 cm) in the anterior part of right lobe (Figure 1B), and multiple small hypodense lesions with confluence in the posterior part of right lobe (Figure 1C). Pus was aspirated from the abscess which on culture showed dry, wrinkled colonies (Figure 2A) on 5% sheep blood agar and McConkey's agar after 48 h of incubation at 37 ℃. Gram-negative, oxidase-positive, motile, aerobic bacilli with typical bipolar "Safety pin" appearance (Figure 2B) was seen on gram stain suggestive of *B. pseudomallei*, which was identified by Vitek 2 compact system. Culture sensitivity was done, which was sensitive to ceftazidime, piperacillin-tazobactum, meropenem, trimethoprim-sulphmethoxazole and minocycline.

Patient was treated with percutaneous catheter drainage, antibiotics and strict glycemic control. Intravenous meropenem was continued for two weeks followed by trimethoprim-sulphmethoxazole for 20 wk after which follow up computed tomography (CT) scan showed complete resolution of the liver abscess.

DISCUSSION

Liver abscess is a common entity in India; among which pyogenic liver abscess is a rare variety. Ascending infection from biliary tract is the most common cause, followed by hematogenous spread[4]. *E. coli*, is the most often cultured bacteria, accounting for about 33% of the cases followed by streptococcal group[5].

Melioidosis varies from asymptomatic infections and localized skin abscess without systemic illness to fulminant diseases with abscesses involving lungs and other internal organs especially when the host immunity is compromised. Cases of isolated liver abscess are not very common and rarely reported. It is an environmental saprophyte and is endemic in Southeast Asia and northern Australia. In India it is found in southern parts in the states of Karnataka, Tamil Nadu, Kerala and Maharastra[6]. Twenty eight cases of septicemic melioidosis were reported from a tertiary care hospital in south India between 1993 and 2002[7] and it is an emerging infection in India. Liver abscess caused by *B. pseudomallei* is rare and only 9 cases have been reported in India[6,8-10] till now, and few cases have been reported in Taiwan[11-13]. Gopalakrishnan *et al*[14], in a series of 32 cases of culture proven Melioidosis found localized infections in 14 patients but did not encounter even a single case of liver abscess.

The most important risk factors are diabetes, renal disease, liver cirrhosis, thalassemia, alcoholism, use of immunosuppressive agents, cystic fibrosis and kava (a Hawaiian drink) consumption[15]. The presenting symptoms may vary from fever, dry cough due to irritation of diaphragm by abscess, abdominal pain, localized swelling to septicemia shock. Lung is most commonly involved in melioidosis. Abscess in other internal organs such as liver and spleen may be a presenting feature in an immunocompromised host. The risk factor for our patient was diabetes but isolated liver abscess without any other organ involvement has seldom been reported previously.

A positive culture of *B. pseudomallei* from the aspirated pus from liver abscess is the definitive diagnosis. It is

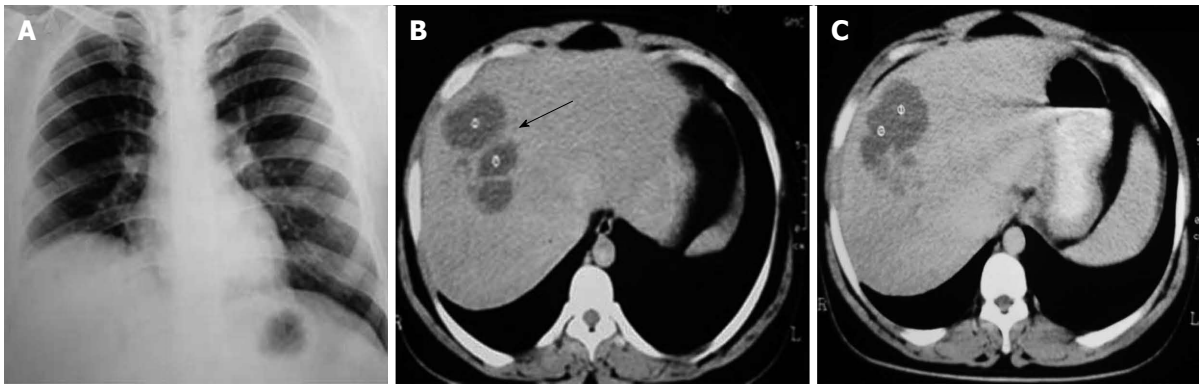

Figure 1 Computed tomography. A: Chest radiograph shows elevation of right hemi-diaphragm; B: Contrast enhanced computed tomography of upper abdomen shows one loculated hypodense lesion (8.5 cm × 7.4 cm) with irregular inner margin noted in the right lobe of liver (black arrow); C: Multiple small hypodense lesions with confluences also seen in posterior part of right lobe.

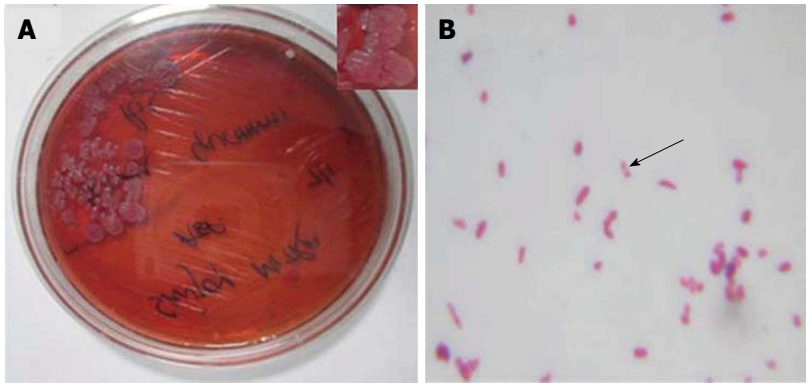

Figure 2 Identification of bacteria. A: Showing dry wrinkled colonies on 5% sheep blood agar (48 h of incubation at 37%). Inset: colonies in enlarged view; B: Gram negative oxidase positive bacillus with typical bipolar "safety-pin" appearance on gram stain (black arrow).

difficult to differentiate *B. pseudomallei* from other gram negative bacilli. Direct immunofluorescence microscopy is 98% specific and 70% sensitive compared to culture[7]. Chest radiograph may show elevation of right dome of diaphragm as in our case. CT scan findings will include liver abscesses with a "honeycomb" pattern of multiseptate, multiloculated lesions and a "necklace sign" with multiple peripheral radial loculations contained within the larger hypodense honeycomb lesions[16]. These findings were shown in a retrospective study in a small number of cases of liver abscess with melioidosis.

B. pseudomallei is characteristically resistant to penicillin other than ureidopenicillins, ampicillin, first- and second-generation cephalosporins, gentamicin, tobramycin, streptomycin and macrolides. It is only susceptible to chloramphenicol, tetracyclines, trimethoprim-sulfamethoxazole, ureidopenicillins, third-generation cephalosporins, carbapenems and amoxicillin-clavulanate[14]. The antibiotic of choice for melioidosis is ceftazidime (40 mg/kg every 8 h)[17]. Imipenem or intravenous amoxicillin-clavulanate is the alternative choices[18]. Parenteral antibiotics should be continued for at least 10-14 d, or until patient is able to take oral medications. Oral maintenance therapy for at least 20 wk with amoxicillin-clavulanate (amoxicillin 27 mg/kg per day divided into three doses) or trimethoprim-sulfamethoxazole (trimethoprim 8 mg/kg per day and sulfamethoxazole 40 mg/kg per day) should be given in patients with abscess for complete resolution[14]. Patients need to be followed up for at least 6 mo after complete resolution of abscess.

In conclusion, *E. coli* is the commonest cause of pyogenic liver abscess in India, but *B. pseudomallei* should also be kept in mind because of its rising incidence and misdiagnosis can lead to treatment failure and high mortality rate. Diabetes and immunosuppressed state are the important risk factors. Prolonged treatment with antibiotic is necessary for complete resolution in *B. pseudomallei* liver abscess. Liver abscess in a diabetic not responding to aminoglycosides and penicillins should be dealt with rigorous attention or otherwise the outcome will be fatal.

COMMENTS

Case characteristics

A 29-year-old farmer presented with high grade fever and cough for 3 wk.

Clinical diagnosis

High grade pyrexia, tachycardia, just palpable splenomegaly and tender hepatomegaly.

Differential diagnosis

An infectious etiology common in tropical countries such as pyogenic liver abscess, malaria, tuberculosis and an immunocompromised state [*e.g.*, human

immunodeficiency virus (HIV)] have been considered.

Laboratory diagnosis

Mild anemia, neutrophilia, fasting hyperglycemia, raised glycosylated hemoglobin was present whereas sputum for Acid-fast bacilli, HIV serology, blood for malaria parasite were negative.

Imaging diagnosis

Chest X-ray, abdominal ultrasound and abdominal contrast enhanced computed tomography were done which showed elevated hemidiaphragm on X-ray and hypodense loculated lesion in right lobe of liver on ultrasound and tomography.

Pathological diagnosis

Aspirated pus from the abscess inoculated on 5% sheep blood agar and McConkey's agar showed gram-negative, oxidase-positive, motile, aerobic bacilli with typical bipolar "Safety pin" appearance on gram stain suggestive of *Burkholderia pseudomallei* (*B. Pseudomallei*), later confirmed *via* automated Vitek-2 compact system and was sensitive to ceftazidime, piperacillin-tazobactum, meropenem, trimethoprim-sulphmethoxazole and minocycline.

Treatment

Patient was treated with percutaneous catheter drainage, strict glycemic control with insulin, intravenous meropenem for 2 wk followed by trimethoprim-sulphmethoxazole for 20 wk which led to resolution of abscess.

Term explanation

"Safety Pin" appearance: bipolar staining of *B. Pseudomallei* on gram stain as if the organism resembles a "Safety Pin", "Necklace sign" on computed tomography scan: multiple peripheral radial loculations contained within the larger hypodense honeycomb lesions of liver abscess.

Experiences and lessons

Isolated liver abscess due to *B. Pseudomallei* can occur specially in immunosuppressed and diabetic patients who need prolonged treatment with antibiotics for resolution and misdiagnosis may lead to treatment failure and high mortality rates.

Peer review

This paper is interesting and it could be accepted pending review.

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4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

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5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/

ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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