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REVIEW

Mechanisms of hepatic ischemia-reperfusion injury and protective effects of nitric oxide

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Abstract

Hepatic ischemia-reperfusion injury (IRI) is a pathophysiological event post liver surgery or transplantation and significantly influences the prognosis of liver function. The mechanisms of IRI remain unclear, and effective methods are lacking for the prevention and therapy of IRI. Several factors/pathways have been implicated in the hepatic IRI process, including anaerobic metabolism, mitochondria, oxidative stress, intracellular calcium overload, liver Kupffer cells and neutrophils, and cytokines and chemokines. The role of nitric oxide (NO) in protecting against liver IRI has recently been reported. NO has been found to attenuate liver IRI through various mechanisms including reducing hepatocellular apoptosis, decreasing oxidative stress and leukocyte adhesion, increasing microcirculatory flow, and enhancing mitochondrial function. The purpose of this review is to provide insights into the mechanisms of liver IRI, indicating the potential protective factors/pathways that may help to improve therapeutic regimens for controlling hepatic IRI during liver surgery, and the potential therapeutic role of NO in liver IRI.

Key words: Liver; Ischemia-reperfusion injury; Cytokine; Chemokine; Kupffer cells; Mitochondria; Nitric oxide

Core tip: This review provides insights into several key mechanisms of liver ischemia-reperfusion injury, including the effects of anaerobic metabolism and the role of mitochondria, oxidative stress, intracellular calcium overload, liver Kupffer cells and neutrophils, and cytokines and chemokines; and summarizes the protective effects of nitric oxide.

Guan LY, Fu PY, Li PD, Li ZN, Liu HY, Xin MG, Li W. Mechanisms of hepatic ischemia-reperfusion injury and protective effects of nitric oxide. *World J Gastrointest Surg* 2014; 6(7): 122-128 Available from: URL: http://www.wjgnet.com/1948-9366/full/v6/i7/122.htm DOI: http://dx.doi.org/10.4240/wjgs.v6.i7.122

INTRODUCTION

In recent years, liver resection and liver transplantation have been widely adopted in clinical practice for the treatment of liver diseases. Hepatic ischemia-reperfusion injury (IRI) occurs substantially during liver resection or

transplantation and remains a major cause of liver non-function or functional failure following liver surgery. This non-negligible injury has become a bottleneck which has restricted the use of marginal liver donors and the development of extensive liver resection. Hepatic IRI includes both warm and cold IRI - two types that share similar pathophysiological processes. The mechanisms of liver IRI have been widely investigated, but nevertheless remain largely unclear. The factors/pathways have been implicated in the hepatic IRI process include anaerobic metabolism, mitochondria, oxidative stress, intracellular calcium overload, liver Kupffer cells (KCs) and neutrophils, and cytokines and chemokines. More importantly, an effective prevention or treatment method is still lacking. Therefore, an effective method for preventing or minimizing hepatic IRI during liver surgery is urgently needed. A better understanding of the mechanisms in the development of IRI will provide insights into improving the treatment regimen for IRI. In this review, the authors comprehensively discuss the mechanisms of liver IRI and describe the role of nitric oxide (NO) in protecting the liver from IRI.

ANAEROBIC METABOLISM AND ACIDOSIS

IRI exerts wide-ranging metabolic effects on the body. During the state of hepatic ischemia, the metabolic pattern is shifted from aerobic to anaerobic, the redox process of the hepatocytes is blocked, adenosine triphosphate (ATP)-dependent cellular metabolic activities are gradually stopped, and intracellular ATP is rapidly depleted. Conversely, there is accumulation of acidic metabolites, such as lactic acid and ketone bodies, which is caused by enhanced anaerobic glycolysis. This is accompanied by hypofunction of mitochondrial oxidative phosphorylation, resulting in the decrease of pH values between tissues and cells, known as metabolic acidosis. Studies have shown that this change plays a role in protecting the liver cells[1,2]. However, the pH values restore to normal after reperfusion, and further enhance pH-dependent enzyme activation, such as activation of proteases and phospholipases, further worsening the damage of tissues and organs. This is called the pH paradox[3]. The toxicity of acidic metabolites caused by a lower ATP supply mainly impairs the cellular functions of homeostasis, signaling interactions, and sodium/potassium ATPase (Na^+/K^+-ATPase), causing mitochondrial damage and resulting in microcirculation failure and cellular destruction[4].

ROLE OF MITOCHONDRIA

IRI exerts effects not only on the body as a whole, but also at the cellular level. The mitochondria are the location where oxidative phosphorylation mainly takes place, and the mitochondria participate in multiple pathophysiological processes of IRI. A large number of reactive oxygen species (ROS) and reactive nitrogen species are generated in the mitochondria during the state of ischemia. Hypoxia undermines the process of oxidative phosphorylation in cells and obstructs the production of ATP, causing disorders of the cytoplasmic ions such as Ca^{2+}, Na^+, and H^+ in the mitochondria, and finally leads to mitochondrial membrane permeability transition (MMPT)[5]. MMPT is manifested primarily by mitochondrial swelling and the decline of membrane potential[6], which allows soluble molecules of a molecular weight less than 1500 kDa to freely pass through the inner mitochondrial membrane, the so-called "mitochondrial megachannel"[7]. Many studies have indicated that MMPT is related to the process of hepatocyte damage after IRI[5,8].

OXIDATIVE STRESS

IRI has many biochemical ramifications. It has been shown that oxidative stress plays a key role in reperfusion injury. Many highly reactive molecules, such as ROS, are induced during the period of hepatic IRI. ROS include superoxide anions, hydroxyl radicals, and peroxide hydrogen, and mainly act on proteins, enzymes, nucleic acids, cytoskeleton, and lipid peroxides, leading to mitochondrial dysfunction and lipid peroxidation[9]. ROS can also damage endothelial cells and destroy the integrity of the microvasculature. ROS can be reduced or overcome by reducing the blood flow and applying endogenous antioxidants, such as superoxide dismutase, catalase, glutathione, vitamin E, or beta-carotene[10]. On the other hand, application of recombinant adenovirus superoxide has been shown to effectively reduce hepatic IRI in mice[11].

INTRACELLULAR CALCIUM OVERLOAD

Among the biochemical factors affected by IRI, calcium has an especially important role. The electrochemical gradient of the calcium ion plays an important role in maintaining homeostasis of physical calcium (Ca^{2+}). If the calcium level is elevated when ischemia or hypoxia, oxidative stress, toxic substance release or other harmful events occur, this is called Ca^{2+} overload. Intracellular Ca^{2+} overload can activate Ca^{2+}-dependent enzymes such as calpains, protein kinase C, and phospholipase C, and ultimately leads to cell death or apoptosis. Recent studies have shown that the increased amount of intracellular Ca^{2+} is not uniform, but is a local phenomenon. Non-specific calcium channel blockers can inhibit the elevation of intracellular Ca^{2+} and reduce cellular damage, demonstrating that Ca^{2+} influx may play a major role in the IRI process[12,13].

KCS AND NEUTROPHILS

It has been demonstrated that liver KCs and neutrophils are involved in the hepatic IRI process. The KCs mainly mediate liver ischemic injury in the earlier stage of reperfusion (within 2 h) by synthesizing and releasing

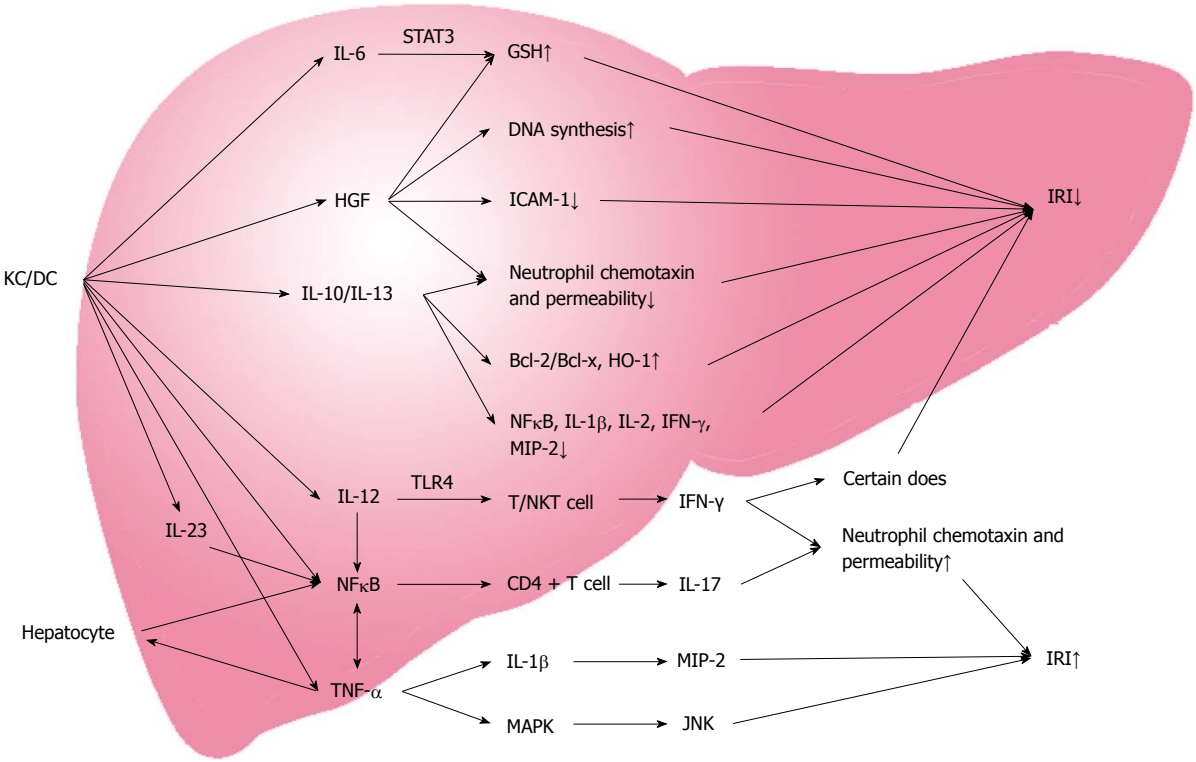

Figure 1 Cytokine network on the regulation of liver ischemia-reperfusion injury. IRI: Ischemia-reperfusion injury; IL: Interleukin; IFN-γ: Interferon-gamma; HGF: Hepatocyte growth factor; MIP: Macrophage inflammatory protein; ICAM-1: Intercellular adhesion molecule 1; NF: Nuclear factor; MAPK: Mitogen-activated protein kinase.

ROS and the pro-inflammatory cytokines tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-1β to further activate liver sinusoidal endothelial cells, enhance the expression of the adhesion molecules intercellular adhesion molecule 1 (ICAM-1)/vascular cell adhesion molecule 1 (VCAM-1), further promote the adhesion, migration, and chemotaxis of neutrophils and endothelial cells, and accumulate and activate neutrophils, resulting in subsequent liver cell damage[14]. Studies have shown that endotoxins are also involved in the process of liver IRI[10,15]. Blocking KC activation by the use of gadolinium chloride or methyl palmitate can reduce acute liver cell injury significantly. Activation of neutrophils can directly damage liver cells by the release of oxidants and proteases after reperfusion. Ultimately, myeloperoxidase (halide form, such as Cl) released from neutrophils changes hydrogen peroxide (H_2O_2) into hypochlorous acid (HOCl), which is a potent oxidant. These oxidants can directly cause liver cell damage and/or induce protease-mediated injury through inactivation of the endogenous anti-protease system[15,16], suggesting that anti-oxidant or anti-protease therapy would be helpful for preventing IRI.

ROLE OF CYTOKINES AND CHEMOKINES

Cytokines play a dual role of anti-inflammatory and pro-inflammatory responses in the process of liver IRI (Figure 1). TNF-α is a key member of the group of endogenous pro-inflammatory and anti-inflammatory molecules, and is a critical factor in triggering the inflammatory cascade. It is secreted by activated KCs and impacts liver tissue and distant organs through paracrine signaling and the endocrine system[17]. TNF-α can bind to the receptors on the surface of liver cells to induce overproduction of the chemokine epithelial neutrophil activating protein-78 (ENA-78) and ROS, activate nuclear factor (NF)-κB, mitogen-activated protein kinase, and c-Jun N-terminal kinase (JNK), and cause liver injury directly[18]. In addition, TNF-α also can upregulate expression of the chemokines ICAM-1, VCAM-1 and P-selectin[19]. Moreover, JNK and ROS can directly act on liver cells to cause liver damage.

In addition to TNF-α, the other important cytokines involved in liver IRI are interferon-gamma (IFN-γ), IL-1β, IL-6, IL-12, IL-23, IL-10, IL-13, vascular endothelial growth factor (VEGF), and hepatocyte growth factor (HGF). These cytokines promote leukocyte activation in the liver after ischemia through various pathways. IFN-γ is mainly produced by T cells and natural killer T cells, and activated by toll-like receptor-4 and IL-12. IFN-γ can either aggravate liver damage or reduce liver damage through enhancing or downregulating neutrophil accumulation and activation in a dose-dependent manner[20]. IL-1β, IL-6, IL-12, and IL-23 are mainly produced by KCs and hepatocytes. IL-1β can upregulate NO synthesis through the protein kinase B (Akt), NF-κB, and inducible nitric oxide synthase (iNOS) pathways. IL-1β can further upregulate leukocyte aggregation and adhesion by activating NF-κB and macrophage inflammatory protein (MIP)-2, thus damaging the liver cells[21]. IL-12 and IL-23 can also increase TNF-α production by activating

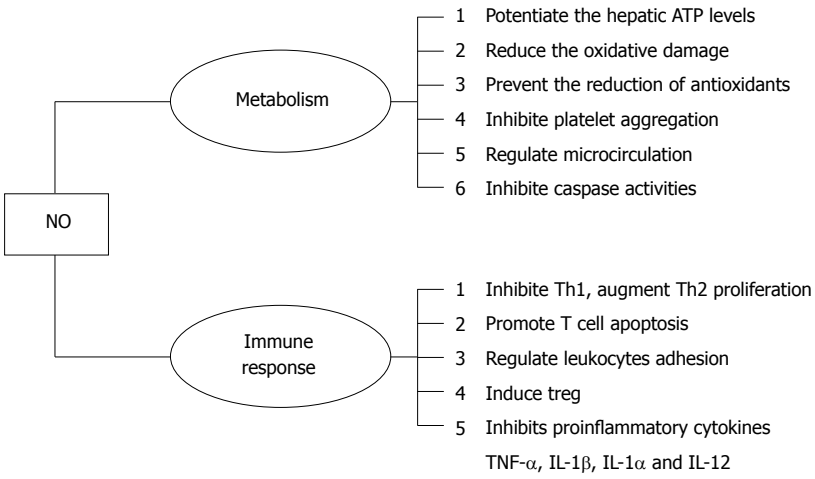

Figure 2 The protective effects of nitric oxide on liver ischemia-reperfusion injury. ATP: Adenosine triphosphate; IL: Interleukin.

NF-κB and signal transducer and activator of transcription (STAT)-4, and further stimulating CD4 T cells to produce IL-17, ensuring the accumulation of neutrophils and aggravating liver damage[22].

On the contrary, IL-6 can activate STAT-3, upregulate glutathione (GSH) expression, and downregulate oxidative stress markers, thus reducing hepatocyte damage and promoting hepatocyte proliferation[23]. IL-10 and IL-13 are mainly produced by KCs and T lymphocytes, and also play a role in alleviating liver damage and promoting liver regeneration. The protective role of IL-10 and IL-13 is mainly mediated by upregulation of heme oxygenase (HO)-1, B-cell lymphoma (Bcl)-2/bcl-x, and downregulation of NF-κB, IL-1β, IL-2, IFN-γ, MIP-2, cytokine-induced neutrophil chemotaxin, E-selectin, and neutrophil aggregation[24,25].

VEGF can be produced by many types of cells including KCs, T cells, sinusoidal endothelial cells and hepatocytes. It plays dual functions in liver IRI. IRI triggers the VEGF receptor and Src tyrosine kinase activation, and upregulates the expression of TNF-α, INF-γ, monocyte chemoattractant protein-1 and E-selectin, all of which result in the accumulation of intrahepatic T lymphocytes, macrophages and neutrophils, producing liver damage. On the other hand, exogenous administration of VEGF can upregulate iNOS production and protect the liver from IRI[26].

HGF is produced by liver non-parenchymal cells, mainly KCs. HGF can increase hepatocyte DNA synthesis, proliferation, and glutathione expression, downregulate the expression of the oxidative stress marker ICAM-1 in sinusoidal endothelial cells, and inhibit cytokine-induced neutrophil chemotaxin and neutrophil permeability, further reducing liver damage and promoting liver cell proliferation[27].

PROTECTIVE ROLE OF NITRIC OXIDE

The effects of NO in protecting the liver from IRI have been studied extensively in recent years. NO is a highly reactive free radical produced from L-arginine and oxygen by nitric oxide synthase (NOS) *in vivo*[28]. Many studies have demonstrated that NO is a versatile signaling mediator involved in a multitude of critical cellular events, such as inhibition of platelet aggregation, regulation of the microcirculation, and inhibition of caspase activities to prevent cell apoptosis[29,30]. It has been shown that both endogenously generated and exogenously administrated NO plays an important role in protecting the liver from IRI[31]. NO has been found to attenuate liver IRI through various mechanisms, including the protection of hepatocytes from apoptosis and the reduction of macrophage infiltration[32]. Complicated mechanisms and numerous molecules are involved in exerting the protective effects of NO against liver IRI, including ATP molecules, endothelin, adhesion molecules, cytokines, free radical species, and antioxidants[33] (Figure 2). NO has been shown to potentiate hepatic ATP levels, reduce oxidative damage, prevent the reduction of antioxidants such as glutathione, and reduce the adverse effects of endothelin during liver IRI[33,34]. Studies have demonstrated that NO affects cellular decisions of life and death by either turning on or shutting off apoptotic pathways, suggesting that NO can function differently depending on the dose and duration of exposure[35,36]. Large amounts of NO may in turn paradoxically damage liver tissue by forming nitrogen peroxide[37], suggesting that the therapeutic safety window of NO is limited.

NO-based therapy has been applied for many years to patients with pulmonary hypertension or cardiopulmonary disorders. The therapeutic application of NO in protecting the liver from IRI has just been emerging. A prospective randomized small group trial with liver transplant patients has demonstrated that NO inhalation in liver recipients during the perioperative period of liver transplantation significantly protects hepatocytes from apoptotic death, accelerates the restoration of liver graft function, and reduces hospital length of stay[38]. Since NO has a very short half-life *in vivo*, it is not an ideal gas

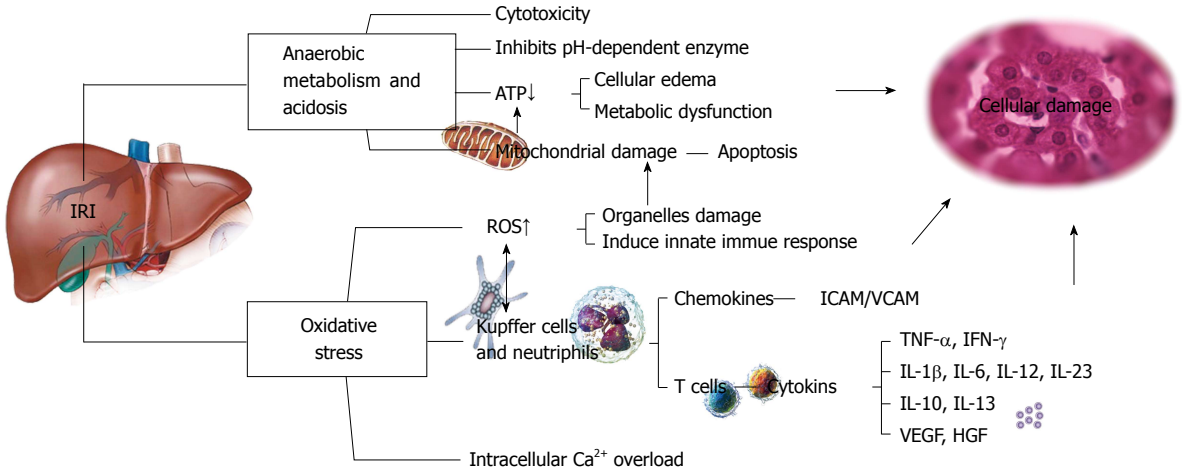

Figure 3 Mechanisms of hepatic ischemia reperfusion injury. ATP: Adenosine triphosphate; IL: Interleukin; ROS: Reactive oxygen species; IRI: Ischemia-reperfusion injury; IFN-γ: Interferon-gamma; ICAM: Intercellular adhesion molecule; VCAM: Vascular cell adhesion molecule; TNF: Tumor necrosis factor.

for the treatment of IRI. NO drugs administered to liver donors, such as organic nitrates and sodium nitroprusside, are now being explored as an alternative choice for NO delivery.

Sodium nitrite, a storage form of NO, can release NO during hypoxia and acidosis[39]. Sodium nitrite has now been identified as an important storage reservior of bioavailable NO in the blood and tissues[40]. The reduction of nitrite to NO has been demonstrated to confer cytoprotection against IRI in the heart, liver, brain, and kidney[40]. Interventions that increase NO production by the use of sodium nitrite before the occurrence of ischemia, either through intraperitoneal injection or oral administration, can mediate significant cytoprotection. This strategy has been demonstrated to potently limit acute IRI in both the heart and liver in murine warm IRI models, with the ability to decrease myocardial infarction and hepatocyte apoptosis[40-43].

NO is also an important effector molecule, produced by KCs and dendritic cells (DCs), and is involved in immune regulation and host innate and adaptive immunity[44]. NO inhibits proinflammatory cytokines, including TNF-α, IL-1β, IL-1α and IL-12, which may induce the inflammatory cascade during liver IRI [24-26,33]. It has been reported that NO exerts multiple effects on immune cells, decreasing the number of T helper (Th)1 cells and augmenting Th2 cell proliferation and their cytokine synthesis, regulating leukocyte adhesion and recruitment to the site of infection[45-47], inhibiting Th1 proliferation, and promoting T cell apoptosis[48,49]. Moreover, NO also contributes to the immunosuppressive function of induced T regulatory cells (Treg)[50]. Therefore, NO is involved in the regulation of liver IRI-associated immune responses. The underlying mechanisms are largely unknown and warrant further investigation.

CONCLUSION

Hepatic IRI is not only a pathophysiological process involving the liver itself, but also a complex systemic process affecting multiple tissues and organs. Hepatic IRI can seriously impair liver function, even producing irreversible damage, which causes a cascade of multiple organ dysfunction. Many factors, including anaerobic metabolism, mitochondrial damage, oxidative stress, intracellular Ca^{2+} overload, cytokines and chemokines produced by KCs and neutrophils, and NO, are all involved in the regulation of liver IRI processes. The most important pathways of liver IRI are initiated by oxidative stress, anaerobic metabolism and acidosis, further resulting in the cellular damage through induction of apoptosis, immune responses, and cytokine regulations (Figure 3). Inhaled NO or NO-producing drugs have shown positive effects on IRI protection in clinical practice, and may be a good choice for liver IRI therapy in the future. Therefore, further exploration of the mechanisms of IRI on animal models focusing on the regulatory pathway of IRI development, with concomitant development of a more effective method of controlling IRI, will help overcome the challenges in the prevention of IRI and therapeutic strategies.

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MINIREVIEWS

Chronic pancreatitis: A surgical disease? Role of the Frey procedure

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Abstract

Although medical treatment and endoscopic interventions are primarily offered to patients with chronic pancreatitis, approximately 40% to 75% will ultimately require surgery during the course of their disease. Although pancreaticoduodenectomy has been considered the standard surgical procedure because of its favorable results on pain control, its high postoperative complication and pancreatic exocrine or/and endocrine dysfunction rates have led to a growing enthusiasm for duodenal preserving pancreatic head resection. The aim of this review is to better understand the rationale underlying of the Frey procedure in chronic pancreatitis and to analyze its outcome. Because of its hybrid nature, combining both resection and drainage, the Frey procedure has been conceptualized based on the pathophysiology of chronic pancreatitis. The short and long-term outcome, especially pain relief and quality of life, are better after the Frey procedure than after any other surgical procedure performed for chronic pancreatitis.

Key words: Chronic pancreatitis; Frey procedure; Surgery; Complication; Outcome

Core tip: The management and the treatment of chronic pancreatitis are challenging. Many surgical procedures were described with 2 different types of concepts: resection *vs* drainage. The Frey procedure is an association of these 2 concepts. This manuscript contains the most recent data about the technique, the short and long-term outcomes of this technique. In addition, there is a review of the literature of series comparing this technique with the other surgical procedures.

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INTRODUCTION

Chronic pancreatitis is a progressive inflammatory disease characterized by debilitating pain and pancreatic insufficiency (nutritional deficiency and glucose deregulation)[1,2]. The enormous personal and socioeconomic impact comprises impairment of quality of life, inability to work and even shortening in life expectancy[3]. Although medical treatment and endoscopic interventions are primarily offered to patients with chronic pancreatitis[4,5], approximately 40% to 75% will ultimately require surgery during the course of their disease[6,7].

Although pancreaticoduodenectomy has been considered the standard surgical procedure for patients with chronic pancreatitis because of its favorable results

on pain control, its high postoperative complication and pancreatic exocrine or/and endocrine dysfunction rates[8,9] have led to a growing enthusiasm for duodenal preserving pancreatic head resection[10,11]. When in 1987 Frey *et al*[12] described a novel hybrid procedure combining local resection of the head of the pancreas and longitudinal pancreatico-jejunostomy, surgeons favorably welcomed it because of its technical feasibility and low surgical risk. Since 1987, numerous studies have analyzed the short and long-term outcome following the Frey procedure and have compared it to other surgical procedures commonly performed for chronic pancreatitis. The aim of this review is to better understand the rationale underlying of the Frey procedure in chronic pancreatitis and to analyze its outcome.

WHY CAN CHRONIC PANCREATITIS BE CONSIDERED A SURGICAL DISEASE?

Mechanisms of pain in chronic pancreatitis

Although pain is the most common symptom (85% of patients)[2] in chronic pancreatitis, its mechanism remains unclear and debated[13-15]. Several concepts have been hypothesized and pain probably results from a combination of them. The intraductal and interstitial hypertension theory is similar to a compartment syndrome[16,17]. Increased ductal pressure related to duct stricture or calculi and intraparenchymal hypertension as a result of fibrosis and edema can activate intrapancreatic nociceptors. The neurogenic theory focuses on intrapancreatic neural damage[18]. Inflammatory mediators from infiltrating lymphocytes are responsible for increased signals along the axons of pain-sensitive neurons, which ultimately can result in a "centrally sensitized" pain state[19]. Traditionally, the head of the pancreas is called the "pacemaker" of pain in chronic pancreatitis. It is often enlarged and can be replaced by an inflammatory mass that can lead to common bile duct or duodenal stenosis[20]. Another explanation to this pain is the compression of adjacent organs by a pseudocyst.

Indications for surgery

Surgical management is usually offered to patients after medical treatment and endoscopic intervention have failed[4,5], and is considered the last option of this step-up approach[21]. Medical treatment for pain related to chronic pancreatitis usually fails, as narcotic dependency occurs in most patients[11]. Longitudinal studies have shown that 40% to 75% of all patients with chronic pancreatitis will require surgery in the course of the disease[7]. The main indications for surgery are intractable pain, non-resolving common bile duct or duodenal stenosis and suspicion of malignancy. The objective of surgery is to relieve intractable pain while preserving pancreatic endocrine and exocrine functions.

Rationale for surgery in chronic pancreatitis

First, surgery has been proved superior to endoscopic treatment in 2 main randomized controlled trials[22,23]. Moreover, several studies have suggested that surgery early in the course of chronic pancreatitis is beneficial in terms of pain control and pancreatic function[21,24]. One experimental and three clinical observational cohort studies have concluded that surgery, especially drainage procedures, can delay the natural course and progressive loss of pancreatic function in chronic pancreatitis. In an experimental model of early *vs* late surgical drainage in pigs, early surgery resulted in less pathological cell damage and better exocrine function[25]. When Nealon *et al*[26] compared the outcomes of conservative treatment *vs* surgery, they reported a delay in pancreatic function impairment after surgical treatment. They concluded that early operative drainage should be performed before the pancreas shows morphological and functional irreversible damage. Ihse *et al*[27] also have recommended surgical treatment to be performed before nutritional or metabolic disorders develop.

Prolonged periods of pain can be associated with peripheral and central nerve sensitization, leading to a permanent state of pain impossible to reverse[19]. A recent observational study suggests that longstanding disease is associated with poor pain control after surgical intervention[28]. In 266 consecutive patients undergoing surgery for chronic pancreatitis, surgery after 3 years of onset of symptoms was independently associated with impaired pain relief and increased rate of endocrine pancreatic insufficiency. A small pilot trial randomized 32 patients with early stage chronic pancreatitis and dilated pancreatic duct between upfront surgical drainage and conservative approach[29]. Significant pain relief was observed in 94% patients in the surgical group compared to 13% patients in the conservative group. New onset pancreatic insufficiency was significantly less frequently observed in the early surgical group compared conservative group. Despite the evidence suggesting a benefit of early surgery, most patients are still managed by a conservative step-up approach. To evaluate the benefits, risks and costs of early surgical intervention, the Dutch Pancreatitis Study Group is currently conducting a multicentric randomized controlled trial (the Early Surgery *vs* Optimal Current Step-up Practice for Chronic Pancreatitis trial) [21].

The role of chronic pancreatitis as a risk factor for pancreatic carcinogenesis has been supported by numerous studies since 1993[30-32]. Lowenfels *et al*[30] published an international cohort study of 2015 patients that reported a cumulative risk of pancreatic cancer in subjects with chronic pancreatitis of 1.8% after 10 years and 4%, after 20 years with a standardized incidence ratio of 14.4. A recent multicentric Japanese study[33] of 506 patients found that the incidence of pancreatic cancer was significantly lower in patients who underwent surgery for chronic pancreatitis than in patients who had a conservative treatment (0.7% *vs* 5.1%, $P = 0.03$, HR = 0.11). Although this study shows a protective effect of surgery in the development of pancreatic cancer from chronic pancreatitis, the exact mechanism remains unclear probably through reduction in pancreatic inflammation.

FREY PROCEDURE: SURGICAL TECHNIQUE

Rationale for the Frey procedure

Based on the pathophysiological mechanisms described above[13-19], two main surgical procedure types have been described in patients with chronic pancreatitis: drainage and resection procedures[11,34,35]. Until the late 80s, pancreaticoduodenectomy was the resection procedure of choice for "head-dominant" disease[11]. The Frey procedure was first described in 1987 by Frey *et al*[12] and combines partial resection of the head of the pancreas (resection) with lateral pancreatico-jejunostomy (drainage). The rationale for this hybrid procedure[12, 36-38] is that it improves the overall pancreatic ductal drainage by decompressing both the duct of Santorini and ducts in the uncinate process. It also allows removal of calculi. Moreover, the partial pancreatic head resection removes what is thought to be the "epicenter" of chronic pain and can relieve symptoms related to ductal stricture.

The Frey procedure was originally applied to patients with an enlarged fibrotic head of the pancreas and an associated dilated main pancreatic duct. It has since then been described in various indications, including patients who have had prior lateral pancreatico-jejunostomy (Puestow or Partington and Rochelle procedures) with no relief of symptoms[38].

Surgical technique

Through a bilateral subcostal incision and after exposure of the pancreas (Kocher maneuver), the main pancreatic duct is located using a syringe aiming toward the tail of the pancreas[12,36-40]. The pancreatic duct is then opened longitudinally (the incision in the tail of the pancreas is extended to within 1-2 cm of the distal portion of the gland and the incision in the head to within 1 cm of the inner aspect of the duodenum). When the main pancreatic duct is exposed, it can be inspected and all calculi removed. The head of the pancreas is partially cored-out while preserving a rim of pancreatic tissue along the inner aspect of the duodenum (to allow blood supply to the duodenum from superior and inferior pancreaticoduodenal arteries), along the pancreatic medial margin (to avoid injuring the superior mesenteric/portal vein) and posteriorly (between the head excavation and the uncinate process and vena cava). During the local excision of the head of the pancreas, the intrapancreatic portion of the common bile duct is freed from inflamed and fibrotic periodical tissue. In about 70% of cases, resection of the fibrotic pancreatic parenchyma is sufficient to relieve a common bile duct stricture. If the obstruction cannot be relieved, a choledocho-duodenostomy or a choledocho-jejunostomy can be performed. The cored-out head of the pancreas and the open main duct are drained into Roux-en-Y limb of jejunum. The Roux-en-Y limb is passed through the transverse mesocolon to lie over the pancreas. A two-layer pancreatico-jejunostomy is performed. The gastrointestinal tract continuity is restored by and end-to-side jejuno-jejunostomy. Owing to the increased risk of pancreatic cancer in patients with chronic pancreatitis, the cored tissue from the pancreatic head is routinely sent for pathological analysis.

Technical key points

Compared to other surgical procedures (especially pancreaticoduodenectomy and Beger procedure), the Frey procedure is easier to perform by avoiding the transsection of the pancreas neck over the superior mesenteric/portal vein.

Although Frey *et al*[37-39] analyzed the relation between weight of the cored pancreatic head tissue and pain relief, this amount of tissue depends on the size of the head of the pancreas, which is highly variable. Some studies suggested that a mean volume percent of head mass resected between 60% and 65% allowed better pain relief. Extensive pancreatic head excision should not be performed as it may lead to increased parenchymal loss and ultimately pancreatic exocrine insufficiency.

Current data suggest that the Frey procedure in small duct chronic pancreatitis is associated with a significantly increased operative time[41]. Difficulty in locating the main pancreatic duct contributes to the delay and intra operative ultrasound in those cases proves useful[42].

Because the Frey procedure can be technically challenging due to major chronic inflammation, it is traditionally performed as an open surgery. Surgeons from John Hopkins recently published a case report describing a total laparoscopic Frey procedure for chronic pancreatitis caused by recurrent pancreatic ductal stones[43]. The laparoscopic approach confers the benefits of magnified visualization while reducing the rate of postoperative wound infection, incisional hernia, bowel obstruction and pain[44]. As laparoscopic Frey procedure is very demanding, the selection of patients that can benefit from it is very important. This approach will less likely be offered to obese patients, as visualization can be impaired by retroperitoneal fat. Similarly, this approach does not fit patients with a highly vascular head of the pancreas because of the increased risk of bleeding.

RESULTS OF THE FREY PROCEDURE

Complications

The Frey procedure can be performed with low mortality (< 2%). The published complication rates range from 7% to 42%[45-50]. The most common complications include hemorrhage, pancreatic fistula and intra-abdominal abscess. Arterial bleeding is the major life-threatening complication (2%-3%). It can occur several days from surgery after erosion of per pancreatic vessels by pancreatic fluid from an anastomotic leakage, or due to the rupture of a pseudoaneurysm[41,49]. Late complications rate after the Frey procedure is high, probably because of comorbidities (alcohol, smoking) in most patients with chronic pancreatitis. The main medical complication is pulmonary infection and/or insufficiency[50]. In 2006, Pessaux *et al*[49]

recommended preoperative respiratory physiotherapy for all patients before the Frey procedure to avoid postoperative respiratory complications.

Short and long-term outcome

Exocrine insufficiency has been described in up to 79% of patients following the Frey procedure, whereas de novo diabetes occurs in only 8% to 34% of patients[45-50].

Keck *et al*[47] showed that 62% of patients were completely pain free 5 years after the Frey procedure. Similarly, Negi *et al*[51] showed that the Frey procedure led to significant and sustained complete or partial pain relief in 75% over a median follow-up of 6 years. This study suggests that the Frey procedure significantly decreases the severity of recurrent exacerbations and also the number of acute episodes requiring hospital readmission. Falconi *et al*[52] reported up to 90% of partially or completely pain-free patients after the Frey procedure. Hildebrand *et al*[53] showed that the indices for global quality of life and for physical and emotional status increased after the Frey procedure.

Factors predicting outcome

Ten to 20% of patients demonstrate persistent pain after the Frey procedure[44-50]. Several risk factors for poor pain relief have been described in the literature, with controversial results[54]. In 1999, Frey and Amikura[38] found that chronic narcotic use, multiple abdominal interventions before pancreatic surgery were associated with poor outcome, whereas Riediger *et al*[55] found that preoperative exocrine insufficiency and postoperative surgical complications were the strongest predictors of poor pain relief. In an Indian study[41], preoperative use of opiates, continuous pattern of pain and postoperative complications were significant predictive factors of failure to achieve complete pain relief after surgery. However, even patients who used opiate medication preoperatively benefited from surgery (significant reduction in pain score, number of pain exacerbation and hospital readmissions). These results suggest that preoperative narcotic use should not be considered a contraindication to the Frey procedure although patients should be referred for surgery early in the course of chronic pancreatitis before drug addiction becomes an issue.

The correlation between main pancreatic duct diameter and pain relief after the Frey procedure remains debated[38,56,57]. A recent study from John Hopkins showed that the degree of pancreatic fibrosis correlated with the resolution of pain in a series of 35 patients treated with the Frey procedure[58]. Their results suggest that pain in patients with extensive pancreatic fibrosis is significantly better relieved by the Frey procedure than in patients with mild or minimal fibrosis. They implied that patients with mild or minimal fibrosis may respond more favorably to other procedures such as total pancreatectomy with islet auto-transplantation. Determination of pancreatic fibrosis extent preoperatively, thanks to improving imaging technologies, might be an important variable to choose the surgical procedure more likely to achieve pain relief. They also found an association between ductal dilation $\geqslant$ 4 mm and better pain relief. However, they believe that the influence of main pancreatic duct diameter on outcome following the Frey procedure may be biased, as ductal dilation is usually the consequence of progressive fibrosis. In these cases, an alternative could be an extended drainage by "V-shaped excision" advocated by Izbicki *et al*[59] and Yekebas *et al*[60] with a partial head resection. This technique seems to be a secure and effective approach for small duct chronic pancreatitis achieving significant improvement in quality of life and pain relief.

Comparison Frey vs other surgical procedures for chronic pancreatitis

Frey procedure *vs* pancreaticoduodenectomy: Operation time is shorter with the Frey procedure, with lower intraoperative blood loss and perioperative transfusion requirements[61]. Chiang *et al*[62], in a prospective study comparing the Frey procedure to pancreaticoduodenectomy found no difference in mortality, morbidity, pain relief or improvement in pancreatic function 3 and 6 mo after surgery. One randomized controlled trial including 61 patients compared the outcome of pancreaticoduodenectomy and Frey procedure[63]. In this trial (follow-up of 2 years), Izbicki *et al*[63] found better results after Frey procedure regarding quality of life, although pain relief was similar after both procedures. Additionally, the rate of complications after the Frey procedure was significantly lower than after pancreaticoduodenectomy (19% *vs* 53%). Farkas *et al*[64] supported those results concluded that the Frey procedure led to better long-term quality of life. In the long-term follow-up study (mean of 7 years) published by Strate *et al*[65], there was no difference between Frey and pancreaticoduodenectomy regarding late mortality, survival rate, exocrine and endocrine insufficiency (although the rates of new onset diabetes after both procedures were twice higher than preoperatively) and need for reintervention. The initial favorable results of quality of life and pain after Frey procedure still existed but were not statistically significant. Interestingly, Aspelund *et al*[66] found however a significantly lower incidence of new onset diabetes after the Frey procedure (8%) than after pancreaticoduodenectomy (25%). A recent randomized controlled trial presented at the European Surgical Association in 2013 reported the 15-year follow-up of the Frey procedure *vs* pancreaticoduodenectomy for chronic pancreatitis[67]. They concluded that long-term pain relief was comparable after both surgical procedures but the quality of life was better after the Frey procedure. Moreover, mean survival was significantly shorter after pancreaticoduodenectomy because of a higher delayed and long-term mortality rate. Regarding weight gain and work rehabilitation, the Frey procedure also showed better outcome than pancreaticoduodenectomy[53] (Table 1).

Frey procedure *vs* Beger procedure: A randomized controlled trial comparing the Frey procedure with Be-

Table 1 Main studies comparing surgical procedures for chronic pancreatitis

Ref.	Year	Study design	Comparison	Median follow-up (in months)
Izbicki *et al*[63]	1998	Retrospective	Frey *vs* PPPD	24
Aspelund *et al*[66]	2005	Retrospective	Frey *vs* PD	36
Hildebrand *et al*[53]	2010	Retrospective	Frey *vs* PD	50
Farkas *et al*[64]	2006	Prospective	Frey *vs* PPPD	24
Chiang *et al*[62]	2007	Prospective	Frey *vs* PD	6
Strate *et al*[65]	2008	Prospective	Frey *vs* PPPD	84
Bachmann *et al*[67]	2013	Prospective	Frey *vs* PD	180
Izbicki *et al*[46]	1995	Prospective	Frey *vs* Beger	18
Strate *et al*[68]	2005	Prospective	Frey *vs* Beger	104
Keck *et al*[47]	2010	Retrospective	Frey *vs* Beger	20.6

PPPD: Pylorus-preserving pancreaticoduodenectomy; PD: Pancreaticoduodenectomy.

ger procedure[46] found that the Frey procedure was associated with a lower complication rate (9% *vs* 15%). In the 8-year follow-up study published by Strate *et al*[68] in 2005, both procedures showed equivalent mortality, pain relief, exocrine/endocrine insufficiency, rate of reintervention and quality of life. Similarly, a study by Keck *et al*[47] including 92 patients showed a trend toward better pain control but similar pancreatic insufficiency rates and weight gain after the Frey procedure when compared to the Beger procedure.

In conclusion, because of its hybrid nature, combining both resection and drainage, the Frey procedure has been conceptualized based on the pathophysiology of chronic pancreatitis. The short and long-term outcome, especially pain relief and quality of life, are better after the Frey procedure than after any other surgical procedure performed for chronic pancreatitis.

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ORIGINAL ARTICLE

Lymphoepithelial cysts and cystic lymphangiomas: Under-recognized benign cystic lesions of the pancreas

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Abstract

AIM: To identify their diagnostic and prognostic clinical characteristics in a large series.

METHODS: Retrospective review of clinicopathologic and imaging characteristics of patients diagnosed with lymphoepithelial cysts and cystic lymphangiomas of the pancreas at Massachusetts General Hospital.

RESULTS: Twelve patients were identified between 1/1/1997 and 8/1/2007. Their median age was 55.5 years (range 19-78 years), and 6 were females. The lesion was incidentally discovered in half of the patients. Contrast enhanced computed tomography demonstrated that the cysts had thin walls, without calcifications, pancreatic duct dilation or pancreatic parenchyma invasion. Endoscopic ultrasound with fine needle aspiration (EUS/FNA) confirmed the diagnosis of a lymphoepithelial cyst in 3 patients, one of whom was spared an operation and continues to do well after 6 years. Eleven patients had a resection: 3 pancreaticoduodenectomies, 7 distal pancreatectomies, and 1 enucleation. The median size of the cysts was 3 cm (range 2-20 cm). At a median follow-up of 57 mo no recurrences or other pancreas-related conditions occurred.

CONCLUSION: Lymphoepithelial cysts and cystic lymphangiomas of the pancreas can be diagnosed with a combination of contrast-enhanced computed tomography scans and EUS/FNA. If the lesion is asymptomatic, an operation might be avoided.

Key words: Lymphoepithelial cysts; Cystic lymphangiomas; Pancreas; Asymptomatic cysts; Benign cystic lesions of the pancreas

Core tip: Lymphoepithelial cysts and cystic lymphangiomas of the pancreas represent rare, benign cystic lesions. The experience with their diagnosis and treatment is limited mostly to case reports. This report describes our experience with twelve lymphoepithelial cysts and cystic lymhangiomas of the pancreas, analyzing their clinicopathologic characteristics, the role of contrast enhanced computed tomography and endoscopic ultrasound with fine needle aspiration for their diagnosis with an emphasis on non-surgical management when a correct diagnosis can be established in an asymptomatic patient.

Konstantinidis IT, Kambadakone A, Catalano OA, Sahani DV, Deshpande V, Forcione DG, Wargo JA, Fernandez-del Castillo C, Lillemoe KD, Warshaw AL, Ferrone CR. Lymphoepithelial cysts and cystic lymphangiomas: Under-recognized benign cystic lesions of the pancreas. *World J Gastrointest Surg* 2014; 6(7): 136-141 Available from: URL: http://www.wjgnet.com/1948-9366/full/v6/i7/136.htm DOI: http://dx.doi.org/10.4240/wjgs.v6.i7.136

INTRODUCTION

The differential diagnosis of cystic lesions of the pancreas includes a variety of inflammatory and neoplastic lesions, some of which have malignant potential, any of which may be symptomatic or not[1].

Among the least known pancreatic cystic lesions are the lymphoepithelial cysts and the cystic lymphangiomas[2]. Their natural history is unknown, but asymptomatic cysts might be left alone if diagnosed accurately. A diagnosis may be possible with a combination of imaging and endoscopic ultrasound with fine needle aspiration (EUS/FNA).

In this study we report our experience with twelve patients diagnosed with lymphoepithelial cysts or cystic lymphangiomas over a period of more than 10 years, focusing on diagnostic evaluation and surgical treatment and exploring the potential of avoiding an operation on asymptomatic patients.

MATERIALS AND METHODS

Study design

Review of a pathology database was performed to identify patients diagnosed with lymphoepithelial cysts and cystic lymphangiomas between 1/1/1997-8/1/2007. A prospectively maintained surgical database since 1/2001 was used to identify the relative frequency of the lymphoepithelial cysts and cystic lymphangiomas among the pancreatic cysts who underwent surgical resection.

Clinical data evaluated included gender, age, presenting symptoms, past medical history, laboratory values, operative procedures and pathology reports. The available computed tomography (CT) scans and endoscopic ultrasound studies performed at the Massachusetts General Hospital were re-reviewed. Pancreatic fistula was defined according to the international study group definition[3]. Operative mortality was defined as death within 30 d of the operation.

Ethics

This study was approved by the institutional review board (IRB) of the Massachusetts General Hospital.

Statistical analysis

Statistical analysis was conducted using SPSS software (version 20.0; SPSS, Chicago, Ill). Continuous variables are shown as median and range. Categorical or dichotomous data are presented in frequencies and percentage (%) as appropriate. This study was approved by the IRB of the Massachusetts General Hospital (MGH).

Table 1 Clinicopathologic characteristics of 12 patients *n* (%)

Factors	LECP (*n* = 8)	Lymphangioma (*n* = 4)
Median age, yr (range)	60.5 (24-78)	37.5 (19-69)
Females	2 (25)	4 (100)
Symptomatic	4 (50)	2 (50)
Abdominal pain	2 (25)	2 (50)
Other (nausea, fever)	2 (25)	0
Operation	7 (87.5)	4 (100)
Distal pancreatectomy	4 (50)	3 (75)
Pancreaticoduodenectomy	2 (25)	1 (25)
Enucleation	1 (12.5)	0
Pathology		
Median size, cm (range)	2 (2-7.6)	10.5 (2.5-20)

LECP: Lymphoepithelial cyst of the pancreas.

Table 2 Diagnostic studies *n* (%)

Factors	LECP (*n* = 8)	Lymphangioma (*n* = 4)
Median CA 19-9, U/mL (range)	35 (3-79)	10 (9-36)
CT characteristics		
Mean size, cm (range)	2.3 (1.5-2.9)	9.2 (2.3-16.5)
Loculations	1 (25)	0
Microcystic	1 (25)	0
Central scar	0	0
Septations	3 (75)	2 (50)
Calcifications	0	0
Mural nodules	0	1 (25)
Thin cyst wall	4 (100)	4 (100)
Pancreatic Duct Dilatation	0	0
Other (vascular invasion, lymphadenopathy)	0	0
FNA	(*n* = 6)	(*n* = 1)
Sufficient	4 (67)	1 (100)
Diagnostic	3 (50)	0

LECP: Lymphoepithelial cyst of the pancreas; FNA: Fine needle aspiration; CT: Computed tomography.

RESULTS

Between 1997 and 2007, 12 patients with cystic lymphangiomas or lymphoepithelial cysts were identified, representing approximately 2% of the pancreatic cystic lesions resected during this period. Median age for these 12 patients was 55.5 years (range 19-78) and 6 (50%) were females. The clinicopathologic data of these patients are shown in Table 1. Half of the patients were asymptomatic. Of the 6 symptomatic patients, 4 presented with abdominal pain (two patients presented with severe, abrupt, abdominal pain and the other two with episodes of right lower and left upper quadrant abdominal pain), 1 with fever, and 1 with nausea. One patient had previously undergone resection of ruptured lymphangiomas at an outside hospital 5 and 10 mo prior to presentation. He underwent a distal pancreatectomy for a second recurrence of a retroperitoneal lymphangioma.

Diagnostic evaluation

The results of the diagnostic evaluation of these patients are shown in Table 2. All of the patients had normal

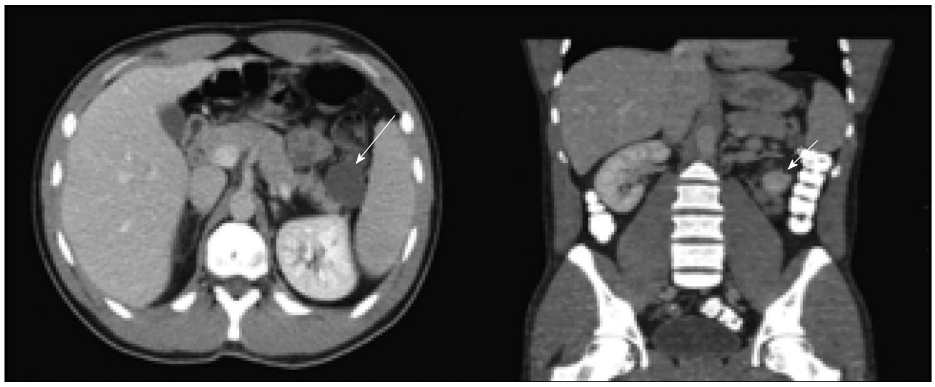

Figure 1 The usual appearance of lymphoepithelial cysts and lymphangiomas on contrast enhanced computerized tomography is that of simple cysts (arrows).

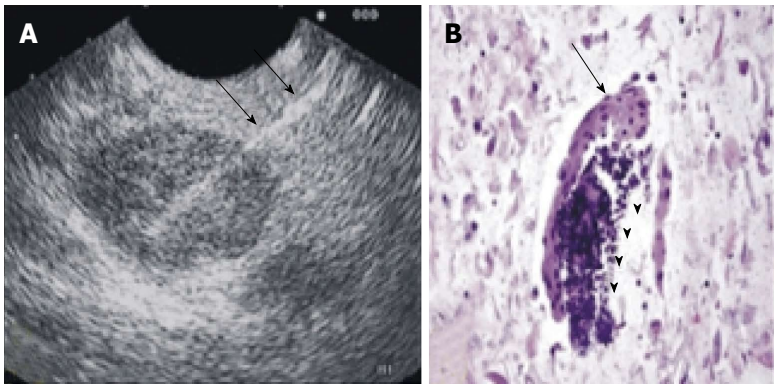

Figure 2 Endoscopic ultrasound guided fine needle aspiration (A) of the cyst with a 22G needle (black arrows) can aid in the correct diagnosis by demonstrating cellular elements characteristic of a lymphoepithelial cyst of the pancreas (B), including squamous (black arrow) and lymphoid subsets (black arrowheads) (HE stain, cell block preparation).

biochemical studies including serum CA 19-9 levels. Abdominal contrast-enhanced computerized tomography (CECT) scans were available for review in 8 (67%) patients. On CT evaluation, lymphoepithelial cysts/lymphangiomas were seen as low attenuation lesions with thin walls without evidence of calcifications, pancreatic duct dilatation, vascular invasion or enlarged lymph nodes (Figure 1). Cyst septa were evident in most of the cysts (62.5%), and there was a mural nodule in one cystic lymphangioma.

Seven patients (58.3%) underwent an endoscopic ultrasound and fine needle aspiration of the cyst (EUS/FNA). Samples were sufficient for cytology evaluation in 71.4% of patients and led to the diagnosis of a lymphoepithelial cyst in 50% of patients who harbored lymphoepithelial cysts based on demonstration of anucleated squamous cells and a lymphoid component (Figure 2). Based on the EUS/FNA results and stable imaging over the course of 6 years one patient was spared an operation. Two other patients were initially spared an operation with the presumptive diagnosis of a benign cyst but both patients eventually underwent a resection due to an increase in cyst size or the suspicion of nodules on subsequent imaging (Figure 3). Histological examination confirmed a lymphoepithelial cyst and a lymphangioma in these cases.

Surgical treatment and outcome

The operations performed included 3 pancreaticoduodenectomies, 7 distal pancreatectomies and 1 enucleation. There was no operative mortality. Pancreatic fistulas developed in two patients after Whipple operations for lymphoepithelial cysts (1 grade A and 1 grade B fistula). At a median follow up of 56.6 mo (range 1-148 mo) no recurrences or other pancreas-related conditions occurred in any of the eleven patients; all of them remain asymptomatic.

Pathologic assessment of the resected specimens confirmed seven lymphoepithelial cysts and four cystic lymphangiomas (Figure 4). The macroscopic appearance of lymphoepithelial cysts demonstrated a cyst filled with characteristic keratinaceous, cheesy material (Figure 5). Cystic lymphangiomas were filled with chylous fluid consistent with lymph. Median size of the cysts at pathologic review was 2 cm, with a range of 1.5 to 7.6 cm for the lymphoepithelial cysts and 10.5 cm for the cystic lymphangiomas (range: 2.5-20 cm). One patient had two lymphoepithelial cyst measuring 1.5 cm and 2 cm in size.

DISCUSSION

The widespread use of abdominal imaging has led to the increasing identification of asymptomatic pancreatic

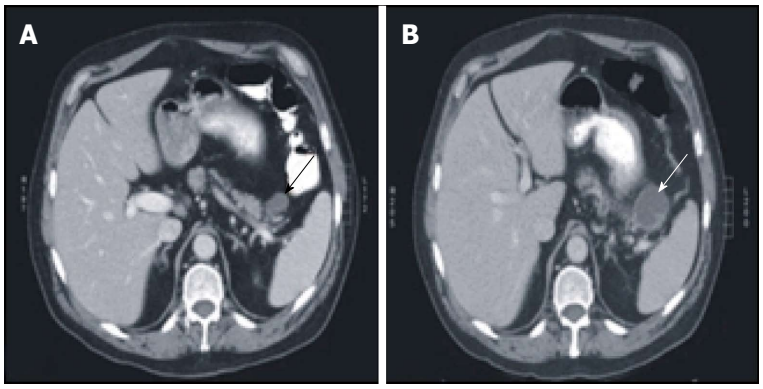

Figure 3 Lymphoepithelial cyst of the pancreas may increase in size during observation. Contrast enhanced computed tomography images demonstrate that the cyst increased from 2.6 cm (A, black arrow) to 4.2 cm (B, white arrow) over a two-month period.

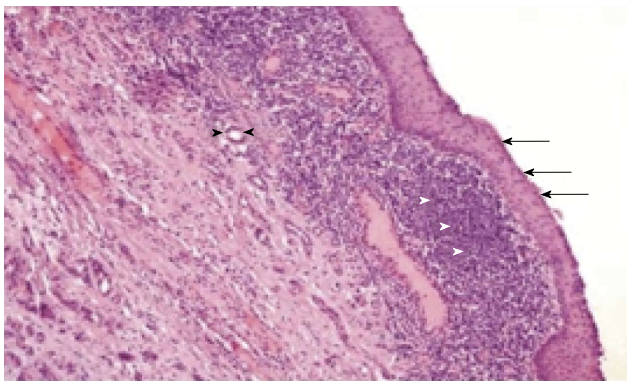

Figure 4 Lymphoepithelial cyst of the pancreas lined by squamous epithelium (black arrows), underlying lymphoid tissue (white arrowheads). Pancreatic ductules are also identified (black arrowheads) (HE stain).

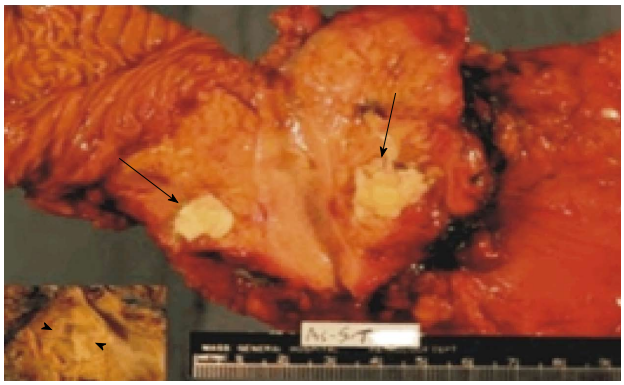

Figure 5 Photo of a transected lymphoepithelial cyst. The characteristic keratinaceous cheesy material is shown (arrows). Inset: the multilocular cyst (arrowheads).

cystic lesions. Seventy-one percent of cysts in a recent report from our institution were serendipitous imaging findings[4]. It becomes likely that uncommon lymphoepithelial cysts and cystic lymphangiomas will increasingly be found incidentally. Although an accurate preoperative diagnosis of pancreatic cysts is not always feasible, criteria associated with an increased risk of malignancy have been established by expert consensus[5] and subsequently validated[6,7] and updated[8]. Establishing a correct diagnosis in a benign asymptomatic cyst can spare the patient a pancreatectomy, which even in specialized tertiary centers carries significant morbidity[9].

This report, representing one of the largest case series describing the clinicopathologic characteristics of lymphoepithelial cysts and cystic lymphangiomas, provides insights into their correct management and spotlights establishment of an accurate diagnosis to avoid an operation in asymptomatic patients. In 3 (50%) of our asymptomatic patients a non-surgical approach was initially chosen on the basis of the probability of a benign lesion in an asymptomatic patient. Two of those eventually underwent resection because of new suspicious imaging findings, but the third continues to do well without intervention during follow-up of 6 years.

Lymphoepithelial cysts of the pancreas are most often found in men in their fifth and six decades of life; 75% of our patients were males who had a median age of 60.5 years. Their characteristic pathologic features are a squamous epithelial lining and surrounding lymphoid tissue, which can be identified on EUS/FNA[1].

Cystic lymphangiomas are benign multicystic lesions that are believed to result from blockage of the lymphatic system and, for unknown reasons, are more common in young females. They can be very large in size and they are frequently located in the peripancreatic tissues in close association with the pancreas. They harbor an endothelial cell lining[10]. In our series four patients were female and had median age of 37.5 years. The largest lesion was 16.5 cm.

The preoperative diagnostic evaluation of the patients in our study included a combination of biochemical and tumor markers, CECT scans of the abdomen and EUS/FNA. Although elevations of serum CA 19-9[11], cyst fluid CA 19-9[12] and persistence of elevated CA 19-9 post-resection[13] have been described in lymphoepithelial cysts, none of our patients had such abnormal levels. Thus, we believe that this marker has no utility in the clinical assessment of these cystic lesions[14]. Consistent with published reports[15], CECT scans in our patients demonstrated cysts with thin walls, without evidence of calcifi-

cations, pancreatic duct dilation or local invasion. Cystic lymphangiomas additionally contain septa, appear multiloculated, and may have papillary projections[16]. A mural nodule (which proved to be an organizing hematoma) was seen in one of our patients who had a lymphangioma. On EUS/FNA lymphoepithelial cysts demonstrate anucleated squamous cells on cytology while their pathology is consistent with a keratinized squamous lining with a lymphocytic infiltrate in the cyst wall[1]. This characteristic, identifiable in 75% of the fine needle aspirations in our study, helps the differentiation from other squamous epithelium-lined cysts (dermoid cysts, splenic epidermoid cysts, squamous cell cancer, primary or metastatic)[12,17-20]. The cyst aspirates may be thick, milky, gray or frothy[2]. Cystic lymphangiomas characteristically contain chylous, milky fluid with a very high triglyceride level, commonly > 3000-5000 mg/dL, consistent with lymph. Cytologic features are consistent with lymphoid tissue[21-23]. They are lined by endothelium with immunohistochemical markers including factor VIII-R Ag, CD 31 and CD 34[10].

Our experience with these uncommon benign pancreatic cysts demonstrates that accurate diagnosis may be feasible through a combination of a contrast-enhanced abdominal CT scan and cyst fluid analyses acquired *via* endoscopic ultrasound and fine needle aspiration. These results can direct the appropriate management strategy, and asymptomatic patients can be spared an operation.

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Part of this work was presented at the 2008 Annual Meeting of the American Pancreatic Association November 6-7, 2008 Chicago Illinois.

COMMENTS

Background

The treatment of pancreatic cysts is a continuously evolving field. Amongst the least well studied pancreatic cystic lesions are lymphoepithelial cysts and cystic lymphangiomas of the pancreas. Familiarity with their correct diagnosis is crucial as they can be followed non-operatively in asymptomatic patients.

Research frontiers

The existing literature on lymphoepithelial cysts and cystic lymphangiomas of the pancreas is limited to case reports. In this report the authors demonstrate our experience with twelve patients, one of the largest single institution experience reported, emphasizing on their correct diagnosis and treatment.

Innovations and breakthroughs

Lymphoepithelial cysts and cystic lymphangiomas of the pancreas can be diagnosed with a combination of contrast-enhanced computed tomography scans and endoscopic ultrasound with fine needle aspiration. Conservative management avoiding a major surgery can be followed as long as the lesions remain asymptomatic.

Applications

The description of the experience with the diagnosis and treatment of these rare pancreatic cystic lesions will aid in their safe management.

Terminology

Lymphoepithelial cysts and cystic lymphangiomas of the pancreas represent rare, benign cystic lesions. Their lining is being characterized by squamous epithelial lining with surrounding lymphoid tissue and endothelial cells respectively.

Peer review

This is a retrospective study regarding lymphoepithelial cysts or cystic lymphangiomas in 12 patients. This is a very uncommon pancreatic pathology and the paper carries a significant number of patients.

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CASE REPORT

Isotretinoin and ulcerative colitis: A case report and review of the literature

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Abstract

This case report describes a case of ulcerative colitis the onset of which occurred after the use of isotretinoin for acne treatment. Our patient, a healthy male young adult, after several months of isotretinoin use, developed gastrointestinal disorders and after thorough medical workup was diagnosed with ulcerative colitis. The literature regarding a possible correlation between isotretinoin use and ulcerative colitis is scarce. Nevertheless, recent epidemiological studies have shed more light on this possible association.

Key words: Ulcerative colitis; Isotretinoin; Acne; Inflammatory bowel disease; Heroin addiction

Core tip: Case reports suggest that isotretinoin administration may trigger inflammatory bowel diseases. This hypothesis has raised great scientific interest and numerous propositions addressing the pathophysiology of this potent association have been made. However, demographic data do not support a correlation between isotretinoin and inflammatory bowel disease. The current case describes a patient who developed ulcerative colitis while on isotretinoin administration. We hope that this case report may contribute to future epidemiological studies with scope to clarify the association between isotretinoin and inflammatory bowel diseases and more specifically ulcerative colitis.

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INTRODUCTION

Ulcerative colitis (UC) is an idiopathic inflammatory bowel disease affecting mostly young adults[1]. Acne is a skin disease that occurs commonly in adolescents and young adults[2]. Isotretinoin is a synthetic analogue of vitamin A and it is approved as treatment of severe acne that is resistant to standard therapy[3]. It has been prescribed to many patients worldwide since its introduction in 1982. Isotretinoin use has some known and well described severe adverse effects. Therefore the onset of ulcerative colitis after isotretinoin use had been reported only in case reports and therefore the risk had not been assessed[4]. Although the association of isotretinoin with

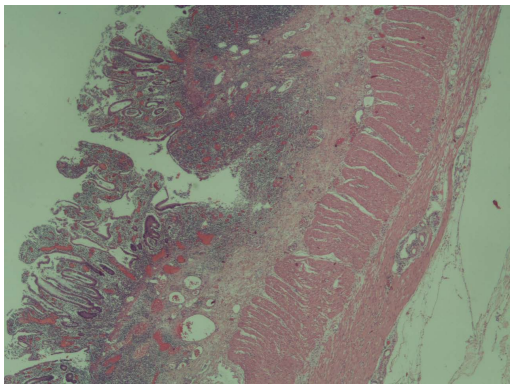

Figure 1 Biopsy from colonoscopy which revealed mucosal inflammation, compatible with ulcerative colitis.

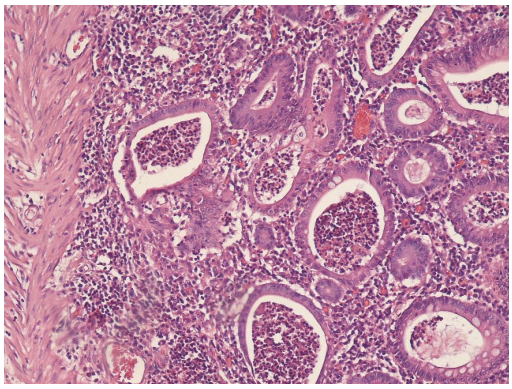

Figure 2 Histopathological image from the excised colon, typical of ulcerative colitis. This image demonstrates marked lymphocytic infiltration (blue/purple) of the intestinal mucosa and architectural distortion of the crypts (right side of the image). The inflammation is shallow and affects only the mucosa sparing the muscularis mucosal (left side).

Table 1 Laboratory findings

Test	Result	Normal lab values
WBC	21.300 per mcL	4-9 × 1000 per mcL
NEU	95%	43%-75%
LYM	1%	11%-49%
CRP	5.9 mg/dL	0.0-0.5 mg/dL
RBC	3.17 × 10^6/UL	3.8-5.3 × 10^6/UL
Hb	9.6 g/dL	13.5-17.0 g/dL
ESR	47 mm/h	M < 50 y.o: 0-15 mm/h
Htc	28%	40.0%-51.0%
Platelets	316 × 10^3/uL	120-380 × 10^3/uL
Alb	1.7 g/dL	3.5-5.5 g/dL
Total protein	4.6 g/dL	6.0-8.0 g/dL

WBC: White blood cells; NEU: Neutrophils; LYM: Lymphocyte; CRP: C-reactive protein; RBC: Red blood cells; ESR: Erythrocyte sedimentation rate.

ulcerative colitis has probably been answered in recent large epidemiological studies[1]. The objective of this case report is to demonstrate a case of a young male who was diagnosed with ulcerative colitis after being treated with isotretinoin for eight months and to review current literature for this association.

CASE REPORT

A 29-year-old male with past medical history of heroin addiction referred to our clinic for surgical treatment of severe ulcerative colitis resistant to conservative treatment and anti-tumor necrosis factor (TNF) therapy. Our patient was diagnosed with acne vulgares in 2007 and was treated with isotretinoin 20 mg two times daily with good results. After eight months of treatment he developed bloody diarrheas accompanied by abdominal pain. No fever or skin rashes or weight loss has been reported and had no medical or family history of gastrointestinal diseases. He was referred to a gastroenterological clinic. He admitted being addicted to heroin since 2004 but had stopped heroin use about 3 mo before this incident. Differential diagnosis on this case proposed that infectious reasons of gastroenteritis and diseases related to drug abuse should be overruled first. In that direction, stool cultures were negative for bacteria and parasites as were examinations for sexually transmitted diseases, hepatitis B, hepatitis C, human immunodeficiency virus infection and endocarditis. Abdominal X-ray was done with no specific findings. Finally colonoscopy was performed and biopsies were obtained. The endoscopic image resembled that of ulcerative colitis. The histological examination defined, from the typical histopathological findings, the diagnosis of UC (Figure 1). Isotretinoin was discontinued and he started treatment with mesalazine for six months with no significant improvement. Therefore was treated with corticosteroids at an outpatient gastroenterological clinic for several months with good clinical results. Mesalazine was used as maintenance treatment. Mild flares were reported rarely in the years that followed.

Soon after the first severe colitis episode he relapsed in his heroin addiction. Fortunately, about a year ago, he entered an anti-addiction treatment program and was treated with methadone.

However five months ago there was a severe relapse of the disease, as depicted by Truelove and Witts severity index. Laboratory findings are summarized in Table 1. The patient had more than 6 bloody diarrheas per day and reported a loss of 15 kg in the precedent two months. The patient required hospitalization for two weeks in a gastroenterological clinic. Stool cultures were negative and he was treated with corticosteroids, antibiotics and parenteral nutrition due to severe malnourishment. In addition, he was treated for his heroin-addiction. There was no clinical improvement and thus rescue therapy with anti-TNF started. The colitis did not respond to infliximab and therefore surgical treatment was proposed. He underwent subtotal colectomy with end ileostomy and mucous fistula of the remaining rectal stump, due to the risk of a vulnerable and unsafe reconstruction. The histopathological findings of the surgical specimens once more confirmed the diagnosis of ulcerative colitis (Figure 2).

During hospitalization he was also assessed by psy-

Table 2 Association between isotretinoin and ulcerative colitis in case control studies

Ref.	Population	UC [RR (95%CI)]
Bernstein *et al*[2]	Residents of Manitoba Canada	1.16 (0.56-2.20)
Crockett *et al*[8]	US health claims database	4.36 (1.97-9.66)
Etminan *et al*[7]	Women using oral contraceptives	1.10 (0.44-2.70)
Alhusayen *et al*[1]	British Columbia residents	1.31 (0.96-1.80)

UC: Ulcerative colitis.

chiatrists for his addiction. He was discharged ten days post-surgery in a significantly improved clinical status. A second restorative operation will be performed later.

DISCUSSION

This case report presented a probable adverse effect of isotretinoin that has been reported rarely by scientists. To the best of our knowledge this is the first case report of ulcerative colitis (UC) related to isotretinoin treatment in Greece. Not many cases of UC after isotretinoin exposure had been reported since its introduction for clinical use in 1982[5]. A possible mechanism is considered to be the prevention of epithelial cell growth and the activation of T-cells. Another theory is that the T-cells that are activated by isotretinoin, express the α4β7 and CCR9 receptors which are crucial to the process of the inflammation in the gastrointestinal system[6]. Several lawsuits have been filled implying correlation between isotretinoin and UC. The fact is that it is not possible to associate adequately isotretinoin isotretinoin and UC based on case reports or small case series. Moreover case reports cannot quantify the risk of UC after isotretinoin treatment[5]. The results from observational studies that followed were still confounding for a positive association. Despite all these, recent epidemiological studies and a meta-analysis suggests that isotretinoin does not increase the risk of UC[7].

Table 2 shows the pooled RR for UC from several large epidemiological studies. Bernstein *et al*[2] found no association between UC and isotretinoin. But Crockett *et al*[8] reported a strong association between them. They also demonstrated that the risk was elevated not only if the dose was increased (OR per 20 mg dose increase: 1.50 95%CI: 1.08-2.09) but also if the therapy with isotretinoin was longer than two months (OR = 5.63, 95%CI: 2.10-15.03). However the recent meta-analysis by Etminan *et al*[7] suggested that there is no correlation between UC and isotretinoin. The pooled RR from their study after the proper adjustment was 1.61 95%CI: 0.88-2.95. Another issue is that the onset of UC is about the same age as acne and UC has also extra-intestinal skin manifestations that can be misinterpreted as acne[9]. Alhusayen *et al*[1] observed that in the subgroup of 12-19 years old; there was a weak but significant association of inflammatory bowel disease and isotretinoin (RR = 1.39; 95%CI: 1.03-1.87). They did not report a separate rate ratio for UC in this subgroup. However their prime outcome was that inflammatory bowel disease was not related with isotretinoin. Moreover the studies that demonstrated a positive correlation between isotretinoin and UC did not address the possibility of previous topical treatment of acne. The main reason was that prior studies have shown that there is no association between UC and topical treatment of acne[10]. Alhusayen *et al*[1] stated that the risk of inflammatory bowel disease after topical acne medication was similar to the risk of isotretinoin. It is still unknown if acne itself is related with inflammatory bowel disease or other inflammatory diseases. Bernstein *et al*[2] concluded also that there is a smaller possibility for patients with known history of inflammatory bowel disease to use isotretinoin for acne treatment than patients from the general population. In addition there is no association from the literature between UC and heroin addiction. Our finding is similar to Papageorgiou *et al*[9] because their patient developed also UC after prolonged therapy with isotretinoin taken twice a day. It is worth of noting that in the majority of previous cases, ulcerative colitis' symptoms developed shortly after the cessation of isotretinoin therapy whereas there are only few cases[11,12], as the present one, addressing to patients who developed symptoms of UC while they were on isotretinoin treatment.

In conclusion recent data from the literature suggest that the risk for UC does not increase with isotretinoin treatment. However, in clinical practice there are significant questions that remain unanswered, such as the risks *vs* the benefits resulting from isotretinoin therapy applied to individuals with positive inflammatory bowel disease family history.

What remains to be investigated further, is the role of isotretinoin as a causative factor in ulcerative colitis or inflammatory bowel disease in general.

COMMENTS

Case characteristics

Bloody diarrheas accompanied by abdominal pain without fever or skin rashes or weight loss in a patient with personal history of heroin abuse.

Clinical diagnosis

Multiple bloody diarrheas per day accompanied by constant abdominal pain that spread in every abdominal region.

Differential diagnosis

Infectious causes of gastroenteritis, diseases related to drug abuse and inflammatory bowel diseases should be considered.

Laboratory diagnosis

Stool cultures and examinations for sexually transmitted diseases, hepatitis B, hepatitis C, human immunodeficiency virus infection and endocarditis were negative, therefore colonoscopy was performed and biopsies were obtained.

Imaging diagnosis

Abdominal X-ray, endoscopy.

Pathological diagnosis

From the endoscopic biopsy the histological findings set the diagnosis of ulcerative colitis (UC).

Treatment

The treatments that the patient underwent were firstly corticosteroids that showed good clinical results with mesalazine as maintenance treatment, thus after a severe relapse of the disease the patient was treated with corticosteroids, antibiotics and parenteral nutrition with no clinical improvement and rescue therapy with anti-tumor necrosis factor (TNF) factors (infliximab) was used, finally he underwent surgical treatment (subtotal colectomy with end ileostomy

and mucous fistula of the remaining rectal stump).

Related reports

UC is a bowel disease that in not quite sure what are its triggering factors. Though many factors are assumed to be associated to the onset of the disease. Some factors are very well studied but others need more research in order to be blamed. The use of isotretinoin, a widely used treatment for acne is associated to UC even though the case reports describing the linkage are few.

Term explanation

Isotretinoin is a medication related to vitamin A used primarily for severe cystic acne and acne that has not responded to other treatments. Anti-TNF therapy (anti-tumor necrosis factor therapy) is a new class of drugs that are approved in treating moderate-to-severe UC. The most common drug used is infliximab, that is a monoclonal antibody that binds to TNF.

Experiences and lessons

UC is a disease that is maybe associated and triggered by more drugs and factors than people already know so in the differential diagnosis of bloody diarrheas in any young patient, should always be the inflammatory bowel diseases.

Peer review

This case report is interesting and well written.

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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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16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flex-

ible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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