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Contents

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MINIREVIEWS

CASE REPORT

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Bimonthly Volume 10 Number 5 September 25, 2021

Contents

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MINIREVIEWS

Serum phosphate and chronic kidney and cardiovascular disease: Phosphorus potential implications in general population

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Abstract

It has already been established that in end-stage renal disease, hyperphosphatemia causes soft tissue calcification including vascular calcifications. It has also been supported that there is a connection between increased serum pho-sphate and morbidity in subjects, who suffer from renal disease. However, studies in these populations conferred mixed results. Several warnings are included in the role of serum phosphorus on cardiovascular disease in normal populations. Homeostasis of serum phosphate is obtained by the cooperation between regulatory hormones, cellular receptors and bone metabolic factors. There is the probability that one or more phosphate regulatory factors, rather than phosphate directly, may be responsible for observed associations with calcifi-cation and cardiovascular events in normal populations. Experimental studies have shown that the restriction of dietary phosphate prevents the pro-gression of kidney dysfunction, although high dietary phosphate aggravates the renal function. In the current review, we discuss the role of serum phosphorus on progression of renal dysfunction and cardiovascular outcomes in chronic kidney disease patients and its involvement in important health risks in the general population.

Key Words: Phosphorus; Renal insufficiency; Chronic; Dialysis; Cardiovascular diseases

Core Tip: Disordered phosphorus homeostasis in chronic kidney diseases is associated with bad outcomes including cardiovascular morbidity/mortality and progression of renal dysfunction in end-stage of renal disease. Potential health consequences in cardiovascular and kidney disease could be developed in subjects with a high intake of dietary phosphorus despite the apparently normal renal function, due mainly to abnormalities in metabolism and in regulatory factors, rather than to serum phosphorus itself. The maintenance of serum phosphorus in normal range should be obtained.

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INTRODUCTION

High serum phosphate concentrations have been connected to adverse health outcomes in chronic kidney disease (CKD) including cardiovascular disease, progre-ssion of kidney disease and all-cause mortality[1-3]. Hyperphosphatemia in CKD has been also associated with the development of secondary hyperparathyroidism, which is responsible for bone disease implicating the stimulation of regulatory hormones such as fibroblast growth factor-23 (FGF23) and parathyroid hormone (PTH), which in turn may promote left ventricular hypertrophy[4,5]. The kidneys are unable to regulate the serum phosphorus concentrations despite the wide fluctuations in dietary phosphorus intake[6]. In a normal kidney function the phosp-horus urinary excretion is increased independently of dietary intake and phosphorus absorption from the gastrointestinal tract and fasting serum phosphate is maintained within a tight range. Therefore, elevation of serum phosphate due to reduced urinary excretion is a main manifestation of advanced renal failure. Previ-ously, we considered the importance of serum phosphate in elderly patients with type 2 diabetes mellitus (T2DM) and we observed the high serum phosphate to be associated with both low estimated glomerular filtration rate (eGFR) and albuminuria, despite the fact that high serum phosphorus levels were found to be non-significant risk factor for the occurrence of T2DM[7]. A positive phosphate balance occurs in the early stage of renal dysfunction, serum phosphate levels mainly increase in advanced stages of CKD and remain elevated in patients in the end-stage renal disease (ESRD) without dialysis treatment (Figure 1).

In the meantime, phosphate is needed in mineralization and bone growth and phosphorus intake is obtained by a rich diet in meat, grains, and dairy products. However, it has been shown that the elevation of serum 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] concentrations due to low dietary calcium intake is inhibited by high phosp-horus intake. Moreover, phosphorus intake may be a major source of acid load in the body[8-10]. Therefore, there remains the question whether high phosphorus intake adversely affects bone mass rather than improves bone function. Kidney Disease Improving Global Outcomes (KDIGO) clinical guidelines recommended the maintenance of serum phosphate concentrations within the normal laboratory range in dialysis patients using dietary phosphate restriction or intestinal phosphate binders in order to achieve a such as goal[11]. Several studies have also considered the effectiveness of these approaches in patients with CKD stages 3–5 before the initiation of dialysis[12-17]. It should initiate interventions in early stages of CKD including the control of phosphorus and the use of vitamin D analogs, thus the development of parathyroid hyperplasia and the skeletal complications of CKD to be prevented[18]. Vitamin D analogs are used to suppress hyperparathyroidism having lesser toxicity on calcium and phosphorus than calcitriol. However, it is important that PTH is not over-suppressed, because the decrease of bone turnover to abnormally low levels includes the risk for adynamic renal bone disease, which is combined by exacerbation of extra-skeletal deposition of calcium in blood vessels and other tissues.

In the current review, we discuss the role of serum phosphorus on progression of renal dysfunction and cardiovascular outcomes in CKD patients and its involvement in potential health risks in the general population. We also report evidence for the relationship between dietary phosphate intake and adverse outcomes in these populations.

RELATIONSHIP BETWEEN SERUM PHOSPHORUS AND PROGRESSION OF KIDNEY DYSFUNCTION

Many years ago, experimental studies showed that the restriction of dietary phosphate prevents the progression of kidney dysfunction, although high dietary phosphate aggravates the renal function[19,20].

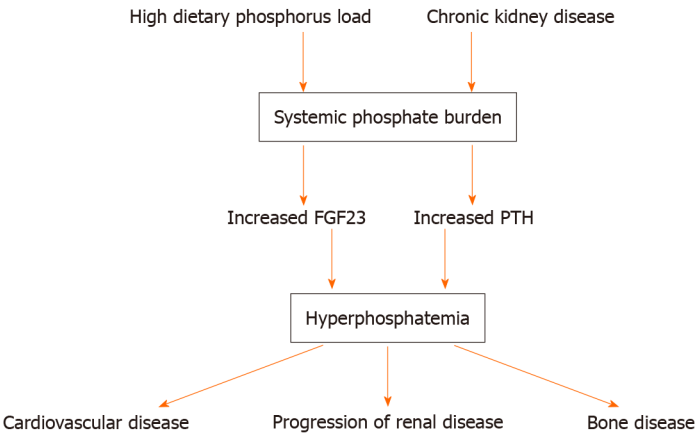

Figure 1 Influence of hyperphosphatemia on different organs/tissues.

However, few clinical studies were conducted to the effect of serum phosphorus concentrations on the rate of CKD progression. It has been shown that in CKD patients serum phosphorus concentrations > 4 mg/dL were associated with an increased risk of ESRD development in both National Health and Nutrition Examination Survey (NHANES) participants and in a United States veterans with CKD study[21,22]. In the Ramipril Efficacy In Nephropathy (REIN) Study, an independent risk of elevated serum phosphorus for exacerbation of renal function in patients with proteinuric CKD was found, although a restriction of the risk was shown caused by the renoprotective action of ramipril[23]. Elevated baseline serum phosphate concentrations were found to be independently related to progression of renal disease in a post hoc analysis of the African American Study of Hypertension and Kidney Disease (AASK) Study[24]. Large study including almost 100000 patients showed that increased serum phosphate concentrations were combined with high incidence of ESRD[25]. Controversially, the Kidney Early Evaluation Program (KEEP) Study did not show an independent association between serum phosphorus concentrations and exacerbation of renal function in ESRD adjusting for demographic and clinical characteristics in multivariable analysis, despite there being a higher prevalence rate of cardiovascular disease (CVD) among patients with higher serum phosphorus[26]. The above studies were different regarding follow-up time and, particularly in the KEEP study, the measurements of serum phosphorus became the baseline and an averaged over time value was not used.

The positive association between serum phosphorus and progression of kidney disease may be attributed to the extension of endothelial dysfunction to the glomerular endothelium, due to acute phosphorus loading, in addition to phosphorus-induced calcification. Another proposed potential mechanism includes the injury of podocytes and overexpression of pituitary-specific positive transcription factor 1 (Pit-1) transporter in rats caused by the elevation of serum phosphorus[27].

Fibroblast growth factor 23 (FGF23) is a hormonal factor, which is significantly involved in maintenance of serum phosphate balance. FGF23 concentrations increase progressively starting in the early CKD as a physiologic adaptation to serum phosphate homeostasis. Eventually, the elevated FGF23 concentrations play an important role on bone disease of these patients[28]. ESRD incidence has also been associated with increased concentrations of FGF23. Studies including participants with mild CKD showed that the risk of all-cause mortality and progression to ESRD was higher in combination with increased FGF23[29,30]. However, a more complicated relationship between FGF23, phosphorus and CKD progression was suggested, due to the association remained stable despite adjustment for phosphorus concentrations.

Accounting for the daily fluctuation of phosphorus, it seems that vascular calcification, endothelial dysfunction, injury of podocytes and high FGF23 result in progression of renal disease, due to high serum phosphorus.

In Figure 2, mechanisms which are connected to the relationship between serum phosphorus and the progression of renal dysfunction are shown.

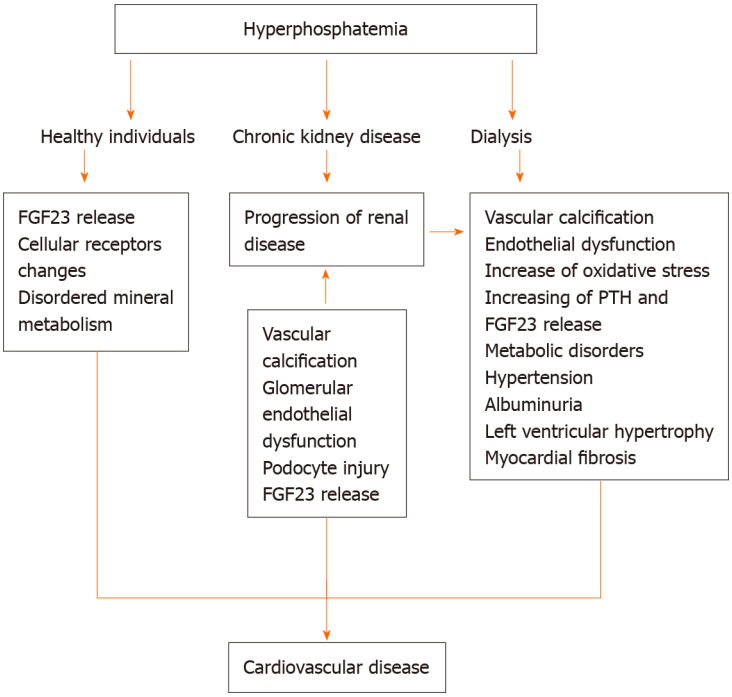

Figure 2 Actions and pathophysiological implications of hyperphosphatemia in different populations.

SERUM PHOSPHATE AND CARDIOVASCULAR DISEASE IN ADVANCED CHRONIC KIDNEY DISEASE

The patients in advanced CKD present increased calcifications, even those at a young age[31]. It has already been established that in ESRD patients, hyperphosphatemia is the reason of soft tissue calcification including vascular calcifications. Loss of the smooth muscle phenotype, expression of bone-specific markers and mineralization of the extracellular matrix was caused by the addition of exogenous phosphate to cultured vascular smooth muscle cells[32,33]. These processes collectively have as an effect calcification of the medial blood vessel wall (Mönckeberg's arteriosclerosis) resulting in the loss of normal vessel compliance. It has been shown that inferior epiga -stric arteries removed from ESRD patients undergoing renal transplantation presented medial arterial calcification in a 44% prevalence rate[34,35].

High evidence connecting phosphate overload with medial arterial calcification in renal failure was provided by animal models.

Moreover, it has been highly supported that extended vascular calcification, especially coronary artery calcification may play a potential role in the disproportionately increased prevalence rate of CVD in this population of patients[36]. Many years ago, an independent association between serum phosphate ≥ 5.5 mg/dL and all-cause and cardiovascular mortality in hemodialysis patients was shown[37]. Another large study including > 40000 hemodialysis patients showed that serum phosphorus concentrations ≥ 5 mg/dL were associated with a high risk of death[38]. However, such an association is not restricted to hemodialysis patients in different countries. A serum phosphate concentration > 3.5 mg/dL was independently associated with mortality and this risk was linearly elevated with an increase in concentration equal to each 0.5 mg/dL in a large retrospective study including 6730 CKD patients from Veterans Affairs Medical Centers[3]. An Italian study including > 1700 CKD patients showed a significant relationship between serum phosphorus and the likelihood of death[39]. Furthermore, the evidence for significant relationship between higher serum phosphorus and mortality in CKD patients was confirmed by a meta-analysis including 47 studies and 327644 CKD participants[40].

Currently, a multinational, randomized controlled large simple trial including a total of 3600 adult ESKD patients receiving dialysis is ongoing with primary endpoints the cardiovascular death, non-fatal major cardiovascular or peripheral arterial events (ClinicalTrials.gov Identifier: NCT03573089). The participants were randomized either to intensive (≤ 1.50 mmol/L) or liberalized (2.0-2.5 mmol/L) serum phosphate target. The choice and dose of phosphate binders is at the treating physician's discretion and local practice to achieve and maintain serum phosphate concentration within the

required target range according to randomization.

Furthermore, HiLo is currently running as another multicenter, cluster-randomized clinical trial of approximately 4400 patients with ESRD undergoing hemodialysis with a primary hypothesis the targeting serum phosphate levels of < 5.5 mg/dL to be compared to less stringent control of serum phosphate to target levels of > 6.5 mg/dL having as a goal the reduction of all-cause mortality and all-cause hospitalization among these patients (ClinicalTrials.gov Identifier: NCT04095039). Secondarily, this trial will test if less stringent control of serum phosphate results in increased serum albumin and protein catabolic rate (PCR), as markers of diet and nutrition.

The main mechanism for the relationship between hyperphosphatemia and adverse cardiovascular outcomes has been attributed to vascular calcification caused by phosphorus, but there may be additional potential explanations including acute endothelial dysfunction particularly in cases of an acute elevation of serum phosphorus. It has been used a diet containing either low (400 mg) or high (1200 mg) phosphorus and serum phosphate concentrations were measured before and 2 h after the meals in combination with flow-mediated dilation of the brachial artery measurement. It was found that the high dietary phosphorus load increased serum phosphorus at 2 h (by an average of 0.8 mg/dL) and significantly decreased flow-mediated dilation (by an average of 4.5%)[41]. Such a finding supports that a significant elevation of serum phosphorus, due to oral phosphorus loading, may be important in the pathogenesis of CVD. We recently considered the importance of serum phosphate in elderly patients with T2DM, strongly related to endothelial dysfunction, *vs* non-diabetes mellitus in relation to renal function[7]. We enclosed 110 subjects and 29 of the participants had T2DM (a ratio equal to 26.4%). We found high serum phosphate to be associated with hypertension, albuminuria, smoking, low estimated glomerular filtration rate (eGFR) and metabolic disorders including higher body mass index (BMI), higher serum glucose and higher uric acid levels, possibly due to phosphorus contribution to diabetes mellitus-induced endothelial dysfunction and/or vascular calcification.

In vitro experiments also showed that high phosphorus loading inhibited nitric oxide (NO) production due to increased reactive oxygen species release and endothelial NO synthase inactivation *via* conventional protein kinase C (PKC), resulting in impaired vasodilation[41].

Furthermore, there are reports that phosphorus might result in direct actions on the myocardium, causing fibrosis[42]. Although one such as conception was supported by *in vitro* studies, direct clinical evidence has been provided by studies, which have connected hyperphosphatemia with left ventricular hypertrophy in CKD[43] and ESRD patients[44]. A relationship between high serum phosphorus and arterial compliance, which may indirectly result in left ventricular hypertrophy, has also been reported[45].

High FGF23 concentrations have been already found to be a significant risk factor for adverse outcomes including death in patients with CKD[29,46,47]. Higher risk of heart failure, stroke, and death among individuals with preserved renal function were also associated with increased FGF23 concentrations[48].

According to the above, calcification of the medial blood vessel wall (Mönckeberg's arteriosclerosis), endothelial dysfunction and inhibition of nitric oxide (NO) production caused by increased reactive oxygen species release, mainly in cases of acute overload of phosphorus, are involved in the pathophysiological mechanisms of CVD in advanced CKD due to phosphorus. Regulatory factors of serum phosphorus including FGF23 are also implicated in bad outcomes in these patients and high phosphorus may have an additional direct action on myocardium inducing fibrosis (Figure 2).

SERUM PHOSPHATE AND CARDIOVASCULAR DISEASE IN EARLY RENAL DYSFUNCTION AND IN GENERAL POPULATION

A connection between increased serum phosphate and adverse outcomes in patients who suffer from mild to moderate renal dysfunction or even in subjects who have apparently a normal kidney function has been supported. However, studies in these populations conferred mixed results. Among 3490 male United States veterans with stage III–IV CKD it was demonstrated that there is a significant relationship between higher serum phosphate concentrations and mortality and incident myocardial infarction[3]. Controversially, another previous study did not find any adjusted association of serum phosphate concentrations with all-cause mortality or progression of

renal dysfunction among 10672 individuals who had early CKD in the community-based Kidney Early Evaluation Program (KEEP)[26]. Different demographic characteristics, causes of CKD, comorbidities and the timing of serum phosphate measurements, which vary throughout the day as 1.0 mg/dL, may have contributed to heterogeneous associations[49]. Data from the CARE (Cholesterol And Recurrent Events) study showed an independent association between increased phosphorus and risk of mortality in subjects who had underwent a myocardial infarction[50]. It is worth mentioning that most of the enrolled patients in this study had baseline serum phosphate in normal range and the baseline eGFR was more than 60 mL/min per 1.73 m^2. Supportively, a number of large epidemiological studies have suggested that mild elevations of serum phosphorus even within the normal range are associated with the risk of CVD including cardiovascular events, vascular calcification and cardiac valve calcification in general population[51-54]. Interestingly, a previous study found that the risk of mortality increases by 1.09 (HR: 1.09; 95%CI: 1.06, 1.84) per every 1.0 mg/dL increase in serum phosphorus considering the relationship between elevated serum phosphorus concentrations over time and mortality in participants with eGFR > 60 mL/min per 1.73 m^2[25]. Another study found that young men and women with relatively high serum phosphate concentrations (> 3.9 mg/dL) had a greater pre-valence rate of coronary artery calcification 15 years later[55].

Many warnings are included in the role of serum phosphorus on CVD in normal populations. Phosphate homeostasis is obtained by regulatory hormones, cellular receptors and bone metabolic factors[56-58]. Common genetic variants located within or near multiple genes of mineral metabolism have been identified, which were associated with serum phosphate concentrations among 16264 individuals without apparently kidney dysfunction[59]. It is probable that one or more regulatory factors of phosphorus, rather than phosphate directly, may be responsible for observed associations with calcification and cardiovascular events in normal populations.

On the other hand, in early CKD and general populations the range of serum phosphate concentrations is typically found within or just above the normal laboratory range. In experimental models higher concentrations of phosphorus were used to induce calcification, ruling out the manifestation of calcification to be a plausible mechanism for the observed associations between serum phosphorus and cardiovascular events in normal populations. Coronary artery calcium represents calcified atherosclerosis rather than medial arterial calcification in normal populations in contrast to advanced renal disease population of patients[60].

Findings related to the risk due to high phosphorus were shown to be controversial in early stages of CKD, because of different demographic characteristics, causes of CKD, comorbidities and the timing of serum phosphate measurements, which vary throughout the day. One or more phosphate regulatory factors including FGE23 and/or cellular receptors, due to genetic variants linked to multiple genes of mineral metabolism, rather than serum phosphate itself directly, are responsible for observed associations between high serum phosphate and both calcification and cardiovascular events in normal populations.

In Figure 3, potential mechanisms which are involved to the relationship between serum phosphorus and cardiovascular disease in different stages of renal dysfunction are shown.

IMPORTANCE OF DIETARY PHOSPHORUS INTAKE

Previous studies have supported that the elevated dietary phosphorus intake is connected to endothelial dysfunction[41] and increased FGF23 concentrations[61]. Particularly in subjects with a normal kidney function it has been shown a significant relationship between high FGF23 Levels and acute oral phosphorus loads[62]. In disagreement, in the Chronic Renal Insufficiency Cohort (CRIC) Study an association between dietary phosphorus intake and FGF23 concentrations was not found[63]. It seems that the interrelation between FGF23 and phosphorus intake is influenced by the kidney function and a preserved kidney function rather than CKD is required thus the association between them to be significant. Moreover, the usage of foods containing inorganic phosphorus additives confuses the results, because inorganic phosphorus is not captured completely by dietary surveys resulting in invalid findings regarding the association between FGF23 and dietary phosphorus intake. On the other hand, a strong, independent association between dietary phosphorus intake and left ventricular mass assessed by magnetic resonance was shown in MESA (Multi-Ethnic Study of Atherosclerosis) Study[64]. Increased oral phosphorus load was also found to

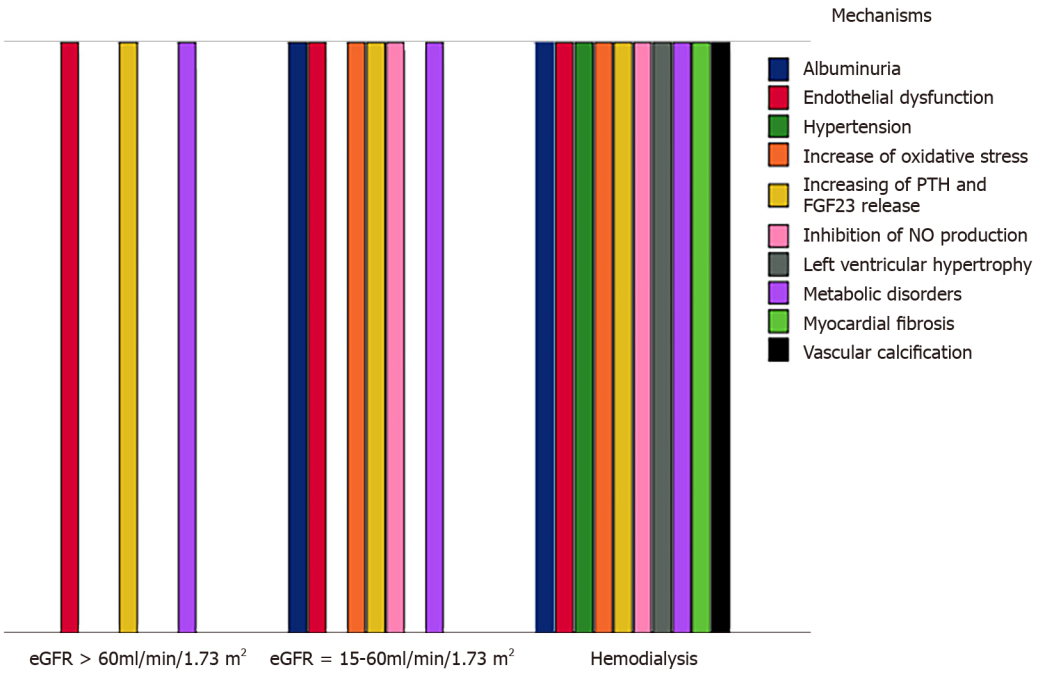

Figure 3 Mechanisms, which are involved to the relationship between serum phosphorus and cardiovascular disease in different stages of renal dysfunction.

promote the generation of tumors and a significant association between phosphorus and cancer may occur[65].

According to above discussed, the elevated intake of dietary phosphorus seriously disrupts phosphate homeostasis in healthy individuals. A disordered phosphorus homeostasis has potential health consequences in bones, cardiovascular, and kidney disease, even in the presence of reserved kidney function. Furthermore, the increased serum phosphorus, even without elevated oral phosphorus intake, as in advanced CKD patients, may be linked to worse outcomes.

The dietary phosphorus intake is reflected by the serum phosphate concentrations in dialysis patients. It has been established that a significant fall in serum phosphorus is clearly obtained by the restriction of dietary phosphorus or the use of oral phosphate binders[66]. Therefore, serum phosphate levels could be used as a marker of dietary intake in this population. However, a such as relation has not been completely established in CKD patients without dialysis or in normal population, despite a cross-sectional study in NHANES III which showed a mildly significant association between dietary and fasting serum phosphorus concentrations[67]. Since kidney function maintains the balance of serum phosphorus independently on phosphorus intake, fasting serum phosphorus is a very poor indicator of dietary phosphorus intake in normal population or in patients without dialysis. In these subjects repeated measurements of serum phosphorus throughout the day could reflect the wide fluctuation in phosphorus intake.

Moreover, it has been shown a circadian variation of serum phosphorus in healthy subjects and in patients with early renal failure[49,68]. The phosphorus concentrations might vary to 2 mg/dL during a 24-h time. It has been proved that the lowest serum phosphate concentration is in morning specimens and the least difference in serum phosphate concentrations on high- compared with low-phosphate diets also to be at this time of day, without an increase of urine phosphate excretion, PTH or FGF23 to be combined[49]. The mechanisms for phosphorus circadian variation phenomenon are still unclear. Nevertheless, the high variation of serum phosphorus during daytime, due to high oral phosphate load, could result in adverse outcomes, even in normal kidney function[41]. Other factors which influences the relation between dietary phosphorus intake and serum phosphate levels may be the use of foods with additives containing inorganic phosphate and the different bioavailability of phosphorus from various food sources. Phosphorus in meat can be absorbed more than the same amount of phosphorus in cereals. The ratio between calcium and phosphorus dietary intake is also other confounder in the relation between intake and serum phosphorus concentrations.

Table 1 Dietary phosphorus recommendations

Dietary phosphorus recommendations
Restricting dietary phosphorus intake in dialysis patients, thus serum phosphate levels to be maintained within normal range with the use of intestinal phosphate binders or intensive hemodialysis
Restricting dietary phosphorus intake in adults CKD stages 3-5, thus serum phosphate levels in repeated measurements to be maintained within normal range with the use of intestinal phosphate binders
Consideration of bioavailability of phosphorus sources (animals, vegetables, additives) in patients with CKD stages 1-5
Control of serum phosphorus to be in normal range in healthy individuals
Prescribing a high phosphorus intake (diet or supplements) in adult kidney transplant recipients with hypophosphatemia, because a severe drop in serum phosphorus 1.5 mg/dL or below can cause neuromuscular disturbances, due to impaired cellular metabolism

CKD: Chronic kidney disease.

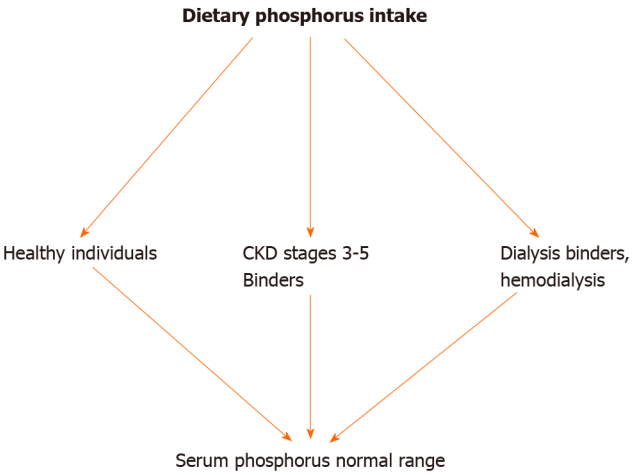

Figure 4 Phosphate control is schematically depicted in different populations.

Although many observational studies have been conducted on the relation between serum phosphorus concentrations/dietary intake and outcomes, it still remains undetermined whether phosphorus is a real toxin or is a simple marker for adverse events. The cause for this would be the lack of a reasonable approach. However, clinical studies including The Modification of Diet in Renal Disease (MDRD) study observed a significant reduction in the risk of ESRD or death with reduced dietary protein intake and, by extension, reduced intake of dietary phosphorus, as the main intervention[69,70]. Even though the comparisons of randomized groups in previous studies do not prove a beneficial cause effect of either protein restriction or phosphorus restriction on morbidity/mortality, such a restriction should be recommended, thus serum phosphorus could be retained within normal range for the reduction of risk for cardiovascular events and the protection of renal function.

In Table 1, recommendations of dietary phosphorus are listed and in Figure 4, phosphate control in different populations of patients are included.

CONCLUSION

Disordered phosphorus homeostasis in CKD is associated with bad outcomes including cardiovascular morbidity/mortality and progression of renal dysfunction in ESRD. Elevated intake of dietary phosphorus seems to disrupt phosphate homeostasis even in healthy individuals, due mainly to abnormalities in regulatory factors including FGE23 connected to genetic variants of mineral metabolism multiple genes, eventually resulting in potential health consequences in bones, cardiovascular, and kidney disease. Therefore, the maintenance of serum phosphorus in normal range should be obtained. However, further studies are still required to clarify the underlying pathophysiologic mechanisms and, particularly, to define interventions,

which would attenuate the adverse outcomes due to phosphorus.

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MINIREVIEWS

Trends in pediatric nephrotic syndrome

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Abstract

Nephrotic syndrome (NS) is relatively common in children, with most of its histological types being minimal changed disease. Its etiology has long been attributed to lymphocyte (especially T-cell) dysfunction, while T-cell-mediated vascular hyperpermeability increases protein permeability in glomerular capillaries, leading to proteinuria and hypoproteinemia. Based on this etiology, steroids and immunosuppressive drugs that are effective against this disease have also been considered to correct T-cell dysfunction. However, in recent years, this has been questioned. The primary cause of NS has been considered damage to glomerular epithelial cells and podocyte-related proteins. Therefore, we first describe the changes in expression of molecules involved in NS etiology, and then describe the mechanism by which abnormal expression of these molecules induces proteinuria. Finally, we consider the mechanism by which infection causes the recurrence of NS.

Key Words: Nephrotic syndrome; Gene; Immunity; Viral infection; Children

Core Tip: There is no doubt that some vascular hyperpermeability factor is involved in the incidence of proteinuria in idiopathic nephrotic syndrome (INS). However, no etiological molecule has been identified in INS as a factor for increasing the permeability of renal glomerular capillaries with reproducibility and clinical consistency. In addition, since the onset is sometimes observed in the family, there is high incidence of INS in East Asian children and there is the association of steroid-sensitive NS in childhood in Japan with the *HLA-DR/DQ* region, it is highly possible that some genetic factors are involved in the onset of NS. In our opinion, INS is a multifactorial disease in which immunological stimuli, trigger the production of substances that impair podocytes, resulting in dysfunction of the slit membrane and cause proteinuria.

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INTRODUCTION

Nephrotic syndrome (NS) is a chronic kidney disease that is relatively common in children, with an annual incidence of 2 to 7 *per* 100000 in the pediatric population[1]. An epidemiological study of pediatric idiopathic NS (JP-SHINE study) was conducted in Japan, and found an incidence of 6.49 *per* 100000, which is 3 to 4 times that reported for Caucasians[2]. The male-female ratio was 1.9%, and 32.7% of patients had frequent recurrences during the 1- to 4-year observation period, which was similar to previous reports[2].

NS is classified into idiopathic (INS), secondary, and congenital depending on the cause and timing of proteinuria. INS accounts for 90% of NS in children. Furthermore, since more than 80% of INS in children is minimal change NS (MCNS), more than 70% of NS in childhood is MCNS. This epidemiology differs strongly from that in adults[1].

Focal segmental glomerulosclerosis (FSGS) is the second most common disease in pediatric INS after MCNS. However, the difference between MCNS and FSGS has been debated for many years, with no conclusions being reached[3,4]. It remains unclear whether they are distinct due to differing etiologies or stages/severity (early/mild for MCNS and advanced/severe for FSGS). The etiology of MCNS and FSGS has not yet been concluded.

TOPICS IN NS

Relationship between INS and T-cell function

Regarding INS etiology, the involvement of T-cell dysfunction proposed by Shalhoub [5] in 1974 has long been supported[5]. In this study, steroid therapy showed a rapid and significant effect in INS patients, whose lymphocytes released vascular hyperpermeability factors into the culture supernatant. Additionally, INS patients were in remission when they suffered from measles, and malignant lymphoma patients often had INS. Finally, the recurrence of INS patients was significantly higher during upper respiratory tract inflammation.

From these observations, it was concluded that lymphocytes (mainly T cells) in INS patients are dysfunctional and overproduce vascular hyperpermeability factors. These factors have been thought to increase vascular protein permeability in renal glomerular capillaries and lead to proteinuria[6,7].

In fact, when the supernatant from immortalized T cells from NS patients is administered to rats, it effaces foot processes and causes proteinuria, but the normal control T-cell supernatant does not show such changes[8].

T cells include helper T cells (CD4 antigen-positive) that are presented with antigens from monocytes and macrophages and regulate immune responses, and killer T cells (CD8 antigen-positive) that damage virus-infected cells. Furthermore, helper T cells include Th1 and Th2 cells, which differ in cytokine secretion and effector functions. Th1 cells produce interleukin (IL)-2, interferon (IFN)-γ and tumor necrosis factor (TNF)-α, and Th2 cells produce IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13. So, far, many groups have investigated the dynamics of blood cytokine levels in MCNS patients[9].

It has been reported that there is no significant difference between cytokine levels in remission in MCNS patients and controls, but IL-4 and IL-13 levels are elevated at the onset of NS, that is, Th2-dominant fluctuations are observed. On the other hand, there have been some reports denying these fluctuations, and no consensus has been reached[10,11].

Reasons for the different observations may be differences in patient backgrounds, lack of standardization of analysis methods (such as sampling and timing), and there are no suitable *in vitro* cultured cells or *in vivo* animal models. At present, there is no established evidence that Th1 or Th2 dominance causes NS. Yap *et al*[12] found the elevated mRNA expression of IL-13 in the T cells of NS patients[12]. After that, an increase IL-13 concentration in blood and T-cell were confirmed by other groups[13, 14].

IL-13 receptors are expressed in glomerular epithelial cells, and the addition of IL-13 to cultured glomerular epithelial cells reduces barrier function[15]. Furthermore, since strong expression of IL-13 in rats causes MCNS-like nephropathy[16], it is possible that an increase in IL-13 in MCNS patients has an effect on the pathology. However, there is a report that the blood concentration of IL-13 is not necessarily high in MCNS patients[17], and future examinations of cytokine concentration in the renal region are necessary.

It has been reported that the expression of a molecule called c-mip (c-maf inducing protein) is increased in MCNS T cells[18]. Subsequent analysis revealed that c-mip expression was increased not only in T cells but also in glomerular epithelial cells when NS recurred[19]. Mice in which c-mip is overexpressed in glomerular epithelial cells show proteinuria, with c-mip modifying the tyrosine kinase signal by the slit membrane. C-mip has been suggested as a mediator causing glomerular epithelial cell damage in MCNS[19].

There have also been reports of the effectiveness of TNF-α inhibitors in nephrotic patients[20] and of nuclear factor-κB (NF-κB) pathway activation in the blood cells of MCNS patients[21], but the number of cases was small, and then no further examinations have been reported.

The CD25- and CD4-positive regulatory T-cell population has an inhibitory effect on the immune response and specifically expresses the transcription factor Foxp3. The forkhead box P3 (*FOXP3*) gene is thought to be the master gene in regulatory T-cell development and function. Examination of recurrence of MCNS revealed that the number of suppressive T cells was the same as normal, but the regulatory T cells of ability to suppress T-cell proliferation was reduced at the time of MCNS recurrence [22]. In addition, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome, multiple endocrine disorders and digestive diseases caused by mutations in the *FOXP3* gene are complicated by NS. A relationship between MCNS and regulatory T cells has been strongly suggested, while epigenomic changes in the lymphocytes of MCNS patients are also being investigated[23]. Changes in histone methylation[24] and DNA methylation[25] in MCNS have been reported, but there is currently no data on whether these are related to changes in lymphocyte function leading to MCNS. Since steroids induce epigenetic changes, this field is expected to gain interest, specifically in understanding the mechanism of steroid sensitivity in MCNS.

Relationship between INS and B cell function

Although the function of B cells in MCNS is extremely poorly understood compared to that of T cells, rituximab (a human monoclonal antibody against the B cell antigen CD20) is clinically effective against frequently relapsing NS. That is, it became clear that depletion of B cells is a treatment for MCNS[26]. However, it is unclear whether this arises from an effect of rituximab on B cells or a change in T-cell function mediated by B cells.

On the other hand, rituximab binds to acid sphingomyelinase-like phosphodiesterase 3b (SMPDL-3b), a protein expressed in glomerular epithelial cells. Serum from NS patients reduces SMPDL-3b expression levels in cultured glomerular epithelial cells, induces cytoskeletal changes, and reduces the filtration barrier function, whereas rituximab increases SMPDL-3b expression level and suppresses the changes obtained with NS patient serum[27].

This suggests that rituximab may exert a proteinuria-suppressing effect directly on glomerular epithelial cells without the intervention of immune cells. However, the extent of involvement of this mechanism in the clinical effects of rituximab is unknown at this time.

Other factors

Hemopexin: Hemopexin is a blood factor potentially associated with MCNS. It is an enzyme involved in heme metabolism, and its administration to rats induces reversible proteinuria[28]. Hemopexin activity is increased in MCNS patients[29], and since hemopexin acts on the cytoskeleton of glomerular epithelial cells *via* nephrin *in vitro* [30], it may be involved in MCNS. However, this report included a small number of cases, and it is unclear whether its observations can be generalized.

Angiopoetin-like 4: In 2011, Clement *et al*[31] found an increase in Angiopoetin-like 4 (Angptl4) levels in the blood of MCNS patients[31]. Angptl4 expression is also enhanced in epithelial cells in the glomeruli of MCNS patients, and proteinuria occurs when Angptl4 is strongly expressed specifically in glomerular epithelial cells in mice [31]. Therefore, it was suggested that an increase in Angptl4 Leads to MCNS, but this possibility has now been refuted. Subsequent analysis revealed that mice expressing

Angptl4 in the liver did not exhibit proteinuria, and that Angptl4 in the blood acted on glomerular endothelial cells and had a proteinuria-lowering effect[32]. Interestingly, Angptl4 levels are elevated by lowering blood albumin, but Angptl4 suppresses lipoprotein lipase activity, which suppresses the conversion of triglycerides to free fatty acids and causes hyperlipidemia[32]. Therefore, Angptl4 may play a role in NS hyperlipidemia.

CD80: CD80 (B7-1) is a membrane protein that is expressed on activated B cells and antigen-presenting cells. It binds to CD28 on CD4 + T cells in response to T-cell receptor activation and promotes T-cell proliferation. Thus, interaction co-stimulation signaling between CD80 and CD28 mediates the interaction between T cells and B cells or antigen-presenting cells and regulates the adaptive immune response. On the other hand, cytotoxic lymphocytes-associated antigen-4 (CTLA-4), which is a negative co-stimulatory receptor, also binds to CD80 as a ligand, but its affinity is ten times higher than that of CD28 and CD80, and therefore strongly inhibits the binding of CD28 and CD80.

Animal experiments have shown that when glomerular epithelial cells are stimulated and injured, they express CD80[33]. Urinary CD80 levels increase during recurrence of MCNS, which is not seen in FSGS patients or those in remission, suggesting that changes in CD80 expression may be specific to MCNS[34]. The addition of serum from MCNS patients to cultured podocytes has been shown to increase CD80 expression *in vitro*[35], suggesting that there is a close relationship between MCNS and CD80 expression. It is believed that these are not only involved in the onset and recurrence of MCNS, but are also potential biomarkers for differentiating MCNS from FSGS.

A two-hit hypothesis has been proposed, whereby the induction of CD80 expression by a serum stimulus is the first hit, and the subsequent decrease in CTLA4 expression that suppresses the CD80 signal is the second hit[36].

Abatacept is a chimera of CTLA4 and IgG that binds to CD80 and suppresses the CD80-CD28 signal, attenuating the immune response. Therefore, several groups have recently investigated whether suppressing CD80 on glomerular epithelial cells by abatacept leads to an attenuation of proteinuria. Yu *et al*[37] reported the administration of abatacept to 5 FSGS patients [4 rituximab-resistant and 1 steroid-resistant NS (SRNS)] and the improvement of nephrotic-level proteinuria in all of them[37].

On the other hand, Garin *et al*[38] reported that abatacept had a temporary inhibitory effect on proteinuria in MCNS patients, whereas there was no change in proteinuria in FSGS patients despite a decrease in urinary CD80 antigen[38]. Another group has reported that abatacept has a poor effect on proteinuria in FSGS patients [39]. Future cases need to be collected to analyze the involvement of CD80 and abataept on NS.

Genetic factors

More than 50 genes mutated in hereditary podocytopathies have been identified (Table 1). The causative gene of congenital and SRNS is being elucidated. Depending on the gene mutated, NS can be roughly classified into three types for convenience: congenital NS developing symptoms early in life (*NPHS1, NPHS2, NPHS3, CD2AP, MYO1E, PTPRO etc.*), NS with an adult onset in the form of autosomal dominant inheritance (*TRPC6, ACTN4, INF2 etc.*), and NS with symptoms in other organs (*WT1, LAMB2, LMX1B, MYH9 etc.*). Many of these genes encode proteins that are strongly expressed in glomerular epithelial cells, so these genetic diseases are considered podocyte diseases. In Western studies, two-thirds of infant NS cases developing within the first year of life are explained by four gene mutations (*NPHS1*, 24%; *NPHS2*, 38%; *LAMB2*, 5%; and *WT1*, 3%). It has also been reported that in steroid-resistant congenital NS that develops under 2 years of age, mutations in 24 of the currently known genes are found in nearly 90% of cases[40]. The analysis of more than 2000 cases of SRNS found that 30% of cases were explained by 27 known genes[41].

It is important to understand to what extent genetic background is involved in the onset of steroid-sensitive NS (SSNS) and MCNS. Familial onset of SSNS is rare, in fact, it was reported that the onset of SSNS in the sibs is 3%[42]. Certainly, the frequency of known genetic abnormalities in SSNS is extremely lower than that in SRNS. For example, the analysis of 38 SSNS patients did not find any genetic abnormalities[43]. Minor nephrin abnormalities have been reported in siblings with proteinuria[44]. In addition, a mutation in *LMX1B*, the causative gene of Nail-Patella syndrome, has been found in patients with proteinuria without extrarenal symptoms[45]. Furthermore, a gene mutation in *EMP2* was found by analysis of familial SSNS that developed in early

Table 1 Genetic forms of podocytopathies

Gene	Inheritance	OMIM ID	Pathology	Function	Features
NPHS1	AR	602716	FSGS/MCD	Slit membrane	Congenital. Finish type
NPHS2	AR	604766	FSGS/MCD	Slit membrane	Develop ESRD in the first or second decades
CD2AP	AR	607832	FSGS	Slit membrane	Severe early-onset SRNS
CRB2	AR	609720	FSGS	Slit membrane	Child onset SRNS
FAT1	AR	600976	FSGS	Slit membrane	First or second decade onset SRNS. Tubular ectasia, haematuria and facultative neurological involvement
TRPC6	AD	603652	FSGS	Slit membrane	Both child and adult onset SRNS
MYO1E	AR	601479	FSGS	Actin binding	Child onset SRNS
PLCE1	AR	608414	FSGS/MCD	Actin binding	Infantile to child onset SRNS
INF2	AD	613237	FSGS	Actin binding	Complicated by Charcot-Marie-Tooth disease
ACTN4	AD	604638	FSGS	Actin binding	Adult onset SRNS
MYH9	AD	160775	FSGS/MCD	Actin binding	Complicated by Epstein syndrome
ANLN	AD	616027	FSGS	Actin binding	Both child and adult onset SRNS
KANK1	AR	607704	MCD	Actin regulation	
KANK2	AR	614610	MCD	Actin regulation	Early-onset SSNS
KANK4	AR	614612	FSGS	Actin regulation	Early-onset SRNS
ARHGDIA	AR	601925	FSGS/DMS	Actin regulation	Onset age is younger than 3 yr
ITSN1	AR	602442	FSGS/MCD	Actin regulation	SSNS
ITSN2	AR	604464	FSGS	Actin regulation	SSNS
MAGI2	AR	606382	MCD	Actin regulation	SSNS
TNS2	AR	607717	FSGS/MCD	Actin regulation	SSNS
DLC1	AR	604258	FSGS	Actin regulation	SSNS
ARHGAP24	AD	610586	FSGS	Actin regulation	
LAMB2	AR	609049	DMS/FSGS	Integrin and laminin	Pierson syndrome
ITGA3	AR	605025	FSGS	Integrin and laminin	Infantile onset SRNS. Congenital interstitial lung disease and mild epidermolysis bullosa
ITGB4	AR	147557	FSGS	Integrin and laminin	Congenital or infantile onset SRNS. Epidermolysis bullosa and pyloric atresia
WT1	AD	256370	DMS/FSGS	Nucleus	Denys-Drash syndrome. Frasier syndrome. Wilms tumor
LMX1B	AD	161200	FSGS/MCD	Nucleus	Nail-patella syndrome
SMARCAL1	AR	606622	FSGS	Nucleus	Schimke immunoosseous dysplasia
NUP93	AR	614351	FSGS	Nucleoporins	Child onset SRNS
NUP107	AR	607617	FSGS	Nucleoporins	Child onset SRNS
NUP205	AR	614352	FSGS	Nucleoporins	Early onset SRNS
XPO5	AR	607845	FSGS	Nucleoporins	Speech development delay
COQ2	AR	609825	FSGS/CG	CoQ10 biosynthesis	Early-onset NS
COQ6	AR	624647	FSGS	CoQ10 biosynthesis	Early-onset NS. Hearing loss
PDSS2	AR	610564	FSGS	CoQ10 biosynthesis	Leigh syndrome
MTTL1	AR	590050	FSGS	CoQ10 biosynthesis	

SGPL1	AR	603729	FSGS	S1P metabolism	Hyperpigmentation, increased ACTH, hypoglycemia, and hypocalcemia with seizures, ichthyosis, primary hypothyroidism and developmental delay
SCARB2	AR	602257	FSGS	Lysosome	Progressive myoclonic epilepsy

FSGS: Focal segmental glomerulosclerosis; MCD: Minimal change disease; ESRD: End-stage renal disease; ACTH: Adrenocorticotropic hormone; SRNS: Steroid-resistant nephrotic syndrome; DMS: Diffuse mesangial sclerosis; CG: Collapsing glomerulopathy.

childhood[46]. *EMP2* is expressed in glomerular epithelial and endothelial cells, regulates the expression of the membrane protein caveolin, and its mutation is thought to cause morphological changes to epithelial cells. Additionally, mutations of the kidney ankyrin repeat-containing proteins 1, 2 and 4 known as the cause of SRNS have also been found in SSNS patients[47].

Ashraf *et al*[48] focused on a family with SSNS and performed a whole exome analysis of its members. A novel causative gene, called *ITSN2*, was identified in this family. By combining this result with those from the genomic analysis of NS families with a blood relative, six novel causative genes were identified. The 17 families with mutations in this gene had an NS which was partially sensitive to steroid treatment. Interestingly, all identified genes were involved in the same pathway (Rho signaling) and were found to interact with each other. This pathway also includes genes involved in SRNS, which is indicative of a common mechanism in SSNS and SRNS. In addition, this study suggested that steroids also act on this signaling pathway[48].

These facts suggest that gene mutations affect glomerular epithelial cell function.

Large-scale studies have begun on not only causative genes whose mutations determine the onset of disease, but also polymorphisms in susceptibility genes that increase the risk of onset. In the case of diseases affected by multiple susceptibility genes, the magnitude of the risk of developing the disease is expressed by the "odds ratio." Specifically, it is expressed as a numerical value indicating how many times the risk of developing the disease is higher in a person who has a susceptibility gene than that of a person who does not have the susceptibility gene.

Genome-wide association studies (GWAS) are comprehensive analyses of the single nucleotide polymorphisms (SNPs) an individual has in their genome. A GWAS was performed in less than 200 cases of acquired NS in Japan, and an SNP in the intron of *GPC5*, which encodes Glypican-5, was found to correlate with NS onset. Glypican-5 is expressed in glomerular epithelial cells and its specific knockdown in these cells turns mice resistant to the development of experimental proteinuria. It is believed that the expression levels of this gene define susceptibility to glomerular epithelial cell damage [49].

In a GWAS of about 200 childhood-onset SSNS cases, the proportion of *HLA-DQA1* polymorphisms on chromosome 6 was significantly increased in SSNS (odds ratio 2.1) [50]. Jia *et al*[51] performed a GWAS using an SNP array optimized for Japanese patients, including 224 pediatric SSNS patient and 419 healthy subject control specimens. As a result, SNPs showed a significant genome-wide association in the *HLA-DR, DQ* region of the short arm of chromosome 6. This result was also confirmed in another cohort consisting of 213 pediatric SSNS patients and 710 healthy controls[51].

A GWAS using an SNP array optimized for Japanese patients was performed on 987 pediatric SSNS patients and 3206 healthy controls. As a result, in addition to the *HLA-DR, DQ* region, variants (polymorphisms) showing a significant genome-wide association with the *NPHS1-KIRREL2* region of chromosome 19 19q13.12 were identified. Furthermore, the relationship between multiple *NPHS1* variants and glomerular *NPHS1* mRNA expression was investigated. The expression of *NPHS1* mRNA from chromosomes having haplotypes with these risk variants was reduced. It has been clarified that *NPHS1* is involved in expression regulation[52].

Although polymorphisms in the multiple susceptibility genes do not cause the disease, they can have a significant impact on the risk of developing NS. These macroscopic genome analyses, which are expected to gain popularity in the future, are effective not only for clarifying the dynamics of susceptibility genes but also for establishing the genetic differences found in populations such as specific ethnic groups and races.

Mechanism of glomerular epithelial cell damage in NS

As mentioned above, various genetic abnormalities can cause NS. It has also been suggested that changes in circulatory factors and local tissues may be involved in the onset of non-genetic NS. Despite these various causes, changes in glomerular epithelial

cells are common throughout NS. In particular, fusion of the foot process is observed in most cases, and basement membrane detachment, vacuolar degeneration, and inclusion body formation are strongly associated with barrier rupture.

Glomerular epithelial cells receive chemical or mechanical stimuli from the glomerular blood vessels and Bowman's cavity to transmit intracellular signals[53]. These signals control the development, morphogenesis, and maintenance of morphology of glomerular epithelial cells, and are closely related to proteinuria[54].

Slit membrane complexes such as Nephrin, Neph1, and Podocin play a major role in controlling the cytoskeletal structure of glomerular epithelial cells, and various adapter proteins are used in the intracellular region of slit membrane proteins, due to stimulation-dependent phosphorylation[55,56]. The slit membrane functions as a conversion point for receiving extracellular signals such as humoral factors[19,57]. This signaling system is extremely important for executing reversible morphological changes in epithelial cells and as the point of action of NS drugs.

Significance of viral infection in the onset and recurrence of INS in children

There are many reports on the immunological background of INS patients and abnormalities in renal glomeruli. In recent years, there have been an increasing number of research papers on relationship between upper respiratory tract infection (URI) and the onset and recurrence of INS.

In children, it has been known for over 30 years that the onset and recurrence of INS are observed in URI. Specifically, about 70% of INS recurrences are triggered by URI [58]. Despite interesting findings reported in recent years, the molecular mechanism that links URI to the onset and recurrence of INS has not been elucidated.

Involvement of Toll-like receptors in INS pathology

Innate immunity plays an important role in the initial recognition of pathogens (*e.g.*, bacteria, viruses, and parasites), phagocytosis or digestion, and the subsequent induction of an inflammatory response and the induction of acquired immunity. Macrophages, neutrophils, and phagocytes such as dendritic cells play a central role in this process. These cells express pattern recognition receptors (PRRs) that recognize pathogen-associated molecular patterns (PAMPs) and transmit activation signals through PRRs. The Toll-like receptor (TLR) family of PRRs, consist of 13 types reported in humans, each of which recognizes different PAMPs such as proteins lipids, and nucleic acids of bacteria, viruses, and parasites. TLRs have specific signaling pathways depending on the adapter molecule which lead to the induction of differential gene expression patterns. The main signal transduction pathways are the MyD88-dependent and TRIF-dependent pathways. The former is involved in the induction of the inflammatory response through NF-κB activation, and the latter activates the IFN regulatory factor (a transcription factor) which finally induces type I IFN and is involved in the antiviral response.

There are some reports that the expression of TLR-3 and TLR-4 in peripheral blood mononuclear cells (PBMC) is enhanced at the time of INS onset or recurrence[59,60]. Mishra *et al*[60] compared the mRNA expression levels of TLR-3, TLR-4, and CD80 using PBMC of 40 SSNS cases (25 of whom were initial or recurrent and 15 were in remission; histological type was mainly MCNS), 30 cases of SRNS (tissue type was mainly FSGS) and 23 control children. The mRNA expression levels of these molecules were increased in patients with initial and recurrent SSNS. On the other hand, patients with SRNS displayed a decreased expression compared to those of normal controls [60].

TLR-3 is localized in the cell and recognizes viral double-stranded RNA, while TLR-4 is present on the cell surface and recognizes sugars, lipids, and proteins derived from the virus[61]. Therefore, the fact that the expression of these TLRs is enhanced is consistent with the fact that many INS recurrences are triggered by URI.

Involvement of alveolar surfactant protein in recurrence of INS

When MCNS patients relapse with URI, their levels of pulmonary surfactant proteins surfactant protein A (SP-A) and surfactant protein D (SP-D) in the serum increase. As a result of activating signal-regulatory protein-α (SIRPα), structural changes (such as disappearance of podocyte foot protrusions) occur, resulting in the appearance of proteinuria[62].

This inference is based on the elevation of SP-A and SP-D levels in the serum collected at the time of recurrence of MCNS patients. SIRPα is stimulated by adding the MCNS patient's serum at the time of recurrence to cultured podocytes, and protein phosphatase non-receptor type 1 is released, which dephosphorylates nephrin, activates podocyte NF-κB, promotes CD80 and pro-inflammatory cytokine production,

and causes structural podocyte changes. SIRPα is a transmembrane protein that contains a tyrosine phosphorylation site in the cytoplasmic region and is expressed in dendritic cells, macrophages, nerve cells, and microglia. SIRPα is also expressed in podocytes, and it was clarified that it is involved in the regulation of podocyte structure and function as one of the major tyrosine phosphorylated proteins in renal glomeruli[63-65].

In addition, SP-A and SP-D, which are mainly produced by alveolar type II epithelial and Clara cells, are known as useful biomarkers of interstitial pneumonia, but they are also SIRPα agonists[66]. Therefore, a hypothesis that SP-A and SP-D serum levels increase during URI causing abnormalities SIRPα in podocytes and leads to recurrence of INS can be formulated.

Certain viruses that are prone to the onset and recurrence of INS in children

Approximately 85% of microorganisms that cause URI, the so-called cold syndrome, are viruses. The main causative viruses are rhinovirus and coronavirus, followed by RS virus, parainfluenza virus, and adenovirus. It is well known that pediatric INS patients are prone to recurrence when suffering from cold syndrome. There were various studies examining the link between recurrence and the causative virus such as RS virus, influenza virus A and B, parainfluenza virus, varicella herpes zoster virus, and adenovirus, but it was unclear whether a specific pathogen was involved in recurrence. In 2017, two facilities reported that infection with a specific virus was involved in recurrence. Lin *et al*[67] proposed the hypothesis that rhinovirus (HRV) infection leads to increased expression of CD80 in the renal podocytes of patients and causes recurrence[67]. Lin *et al*[67] examined 32 MCNS patients who relapsed during URI due to HRV, using PBMC and renal biopsy tissue, and compared the patients with CD80-positive T cells of PBMC to control children with PBMC. The ratios of CD80-positive T cells to CTLA-4 positive T cells and the ratios of Th17 to Treg increased at the time of recurrence in MCNS when compared to those in control children, but they normalized during the remission period. Furthermore, in an immunostaining study using renal tissue of MCNS patients who underwent renal biopsy at the time of recurrence, CD80 was strongly expressed renal glomeruli, but CTLA-4 was weakly expressed. It is speculated that HRV infection increases the CD80 CTLA-4 ratio of PBMC in MCNS patients, resulting in an increase in the Th17 Treg ratio. As a result, the expression of CD80 in podocytes is enhanced and structural podocyte changes occur, leading to recurrence[67].

The Epstein-Barr (EB) virus is a double-stranded DNA herpesvirus found in cultured cells of Burkitt lymphoma that frequently occurs in children in equatorial Africa. It is also called human herpesvirus type 4. A characteristic of herpesviruses, including EB virus, is that they cause latent infections centered on B lymphocytes[68]. Dossier *et al*[69,70] have proposed the etiologic significance of the EB virus in INS because of findings of infection and reactivation of the EB virus in pediatric patients with initial INS[69,70]. According to them, about half of children with INS have amplification of EB virus DNA. This amplification occurs in a locus with a previously reported monobasic polymorphism in children with SSNS (6p21.32), associated with the ability to produce EB virus nuclear antigen 1. Additionally, depletion of B cells with rituximab relieves INS, but the cells that are persistently infected with EB virus are B cells. These facts were cited as the basis for the EB virus etiology[70].

On the other hand, it is a well-known fact that pediatric INS resolved due to viral infections, such as influenza and measles[71,72].

It has been reported that CD25, CD4, Foxp3, and regulatory T cells (Tregs) levels increase in the blood during measles, and that changes in the T-cell-producing cytokine balance during measles are involved in NS remission[73]. An increase in the number of Tregs was observed in response to intercurrent influenza B virus infection and prednisolone administration, along with a parallel decrease in the amount of proteinuria[74]. Moreover, both influenza virus infection and glucocorticoid (GC) administration, which is the key treatment for INS, increase the number of Tregs[75, 76]. Therefore, it may be hypothesized that Tregs play an important role in INS pathogenesis in patients with INS complicated by influenza B and measles infections.

New insights in the drugs of MCNS

(1) GC: Approximately 80% of pediatric MCNS patients are in remission with GC, but how GC improves MCNS remains unclear. GC may act directly on podocyte receptors to suppress the appearance of proteinuria. In fact, dexamethasone has a significant effect on the structure and function of human podocytes[77], and has been shown to suppress the intracellular signaling of podocyte NFκB[78]; (2) Cyclosporine (CsA): The suppression of intracellular signal transduction of activated T cells was thought to be a

possible mechanism of CsA in MCNS. CsA acts on the calcineurin-dependent dephosphorylation of synaptopodin in podocytes to stabilize the actin cytoskeleton and reduce proteinuria[79]; and (3) Rituximab (RTX): RTX, a monoclonal antibody that acts against the B cell surface antigen CD20, is also highly effective in MCNS. However, its mechanism of action is not well known.

It speculated that the depletion of B cells may reduce self-reactive T cells through cell-cell interactions[80]. Fornoni *et al*[27] indicated that RTX not only recognizes CD20 on the surface of B cells, but also binds to and protects podocyte SMPDL-3b preventing the destruction of the actin cytoskeleton and suppressing proteinuria[27].

Why don't we still understand the cause of MCNS?

Among the genetic abnormalities identified for congenital NS and SRNS, many have been found to be explained by glomerular epithelial cell abnormalities, however, many aspects of MCNS pathogenesis remain unknown. There are various possible reasons for this. (1) Factors other than the currently analyzed blood factors; (2) Involvement of not one but multiple factors (Genetic, immunological or circulatory factors *etc.*); and (3) Caused by a combination of such factors (*e.g.*, glomerular epithelial cell factor + immunological factor, T cell factor + B cell factor,1st hit + 2nd hit, *etc.*)

Considering these problems, carrying out comprehensive analysis, such as analysis of genome, epigenome, proteome, and transcriptome using a large cohort will be essential for future studies. Additionally, clarifying the genetic background of patients with a familial history may provide an opportunity to approach the more common cause of idiopathic INS.

CONCLUSION

There is no doubt that some vascular hyperpermeability factor is involved in the incidence of proteinuria in INS. However, no etiological molecule has been identified in INS as a factor for increasing the permeability of renal glomerular capillaries with reproducibility and clinical consistency.

In addition, since the onset is sometimes observed in the family, there is high incidence of INS in East Asian children[2] and there is the association of SSNS in childhood in Japan with the *HLA-DR DQ* region[51], it is highly possible that some genetic factors are involved in the onset of NS.

In our opinion, INS is a multifactorial disease in which immunological stimuli, trigger the production of substances that impair podocytes, resulting in the dysfunction of the slit membrane and causing proteinuria.

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CASE REPORT

Lemierre's syndrome caused by *Klebsiella pneumoniae:* A case report

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Abstract

BACKGROUND

Lemierre's syndrome is a disease that causes anaerobic sepsis, internal jugular vein thrombosis, and septic embolism in the lungs and other organs after acute oropharyngeal infection. It was named after André-Alfred Lemierre in 1936.

CASE SUMMARY

Here, we have reported a case of Lemierre's syndrome in a 56-year-old female patient who presented with a sore throat. The patient had septic shock, had not voided, and had severe hyperglycemia at the time of her visit. Imaging tests revealed bilateral pneumonia, pleural effusion, pulmonary embolism, and renal vein thrombosis. The patient was admitted to the intensive care unit and placed on mechanical ventilation due to acute respiratory distress syndrome. Continuous renal replacement therapy was administered to treat renal failure with anuria. *Klebsiella pneumoniae* was cultured from blood and sputum samples. After reviewing various results, the patient was ultimately diagnosed with Lemierre's syndrome. The patient was treated with appropriate antibiotics and thrombolytic agents. She was discharged from the hospital after recovery.

CONCLUSION

Lemierre's syndrome is associated with a high mortality rate. Therefore, clinicians should be familiar with the signs and symptoms of this disease as well as the preemptive examinations, procedures, and treatments.

Key Words: Lemierre's syndrome; *Klebsiella pneumoniae*; Diabetes Mellitus; Pulmonary embolism; Septic pneumonia; Case report

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Core Tip: Lemierre's syndrome is mostly caused by Fusobacterium. However, we present a rare case of Lemierre's syndrome caused by *Klebsiella pneumoniae* in a patient with poor glycemic control. Uncommon in Lemierre's syndrome, renal vein thrombosis and acute kidney injury occurred, continuous renal replacement therapy was performed, and mechanical ventilation was performed for serious pulmonary complications. The incidence of Lemierre's syndrome decreased after antibiotics were developed. However, when Lemierre's syndrome occurs, the mortality rate from its complications is high, so we want to emphasize that patients with systemic symptoms accompanied by fever and sore throat should be suspicious of Lemierre's syndrome.

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INTRODUCTION

Lemierre' syndrome, also known as postanginal sepsis, was first named in 1936 after the French microbiologist André-Alfred Lemierre. This syndrome is characterized by anaerobic sepsis and blood clots in the internal jugular vein (IJV) after acute oropharyngeal infection. It also causes septic embolism in the lungs and other organs [1].

Lemierre's syndrome is typically caused by *Fusobacterium necrophorum*, which is a part of the normal flora of the oropharynx. However, the recent development of various antibiotics and advancements in medical care have led to diversified and antibiotic-resistant strains.

Therefore, after referring to the current literature, we have reported a single case of Lemierre's syndrome caused by *Klebsiella pneumoniae* (*K. pneumoniae*). In accordance with the course of this disease, pulmonary embolism, occurring after oropharyngeal infection, developed into acute respiratory distress syndrome.

CASE PRESENTATION

Chief complaints

A 56-year-old female patient presented to the emergency department of our institution with sore throat, dyspnea, abdominal pain, and diarrhea.

History of present illness

The patient was unable to eat due to a sore throat and had been unable to take her diabetes medication for 5 d prior to the visit.

Subsequently, the patient visited the hospital with abdominal pain, diarrhea, and shortness of breath.

History of past illness

The patient had been prescribed medication for diabetes and hypertension 2 years previously. She also had a history of a canceled surgery for chronic right-sided otitis media.

Personal and family history

The patient had diabetes, hypertension, and chronic otitis media.

Physical examination

At the time of admission, the patient's blood pressure, pulse rate, respiratory rate, body temperature, and oxygen saturation level were 11.3/7.8 kPa, 104, 22, 36 °C, and 90%, respectively. The patient was conscious. Swelling and redness were observed in the left neck and both tonsils. Rales were auscultated throughout the chest. Auscultation of the abdomen revealed a normoactive bowel sound with no tenderness.

No urine was produced after catheter insertion.

Laboratory examinations

Blood tests revealed an evaluated white blood cell count (16.47 × 10^3/μL), anemia (hemoglobin level, 7.2 g/dL; hematocrit level, 24.4%), renal failure (blood urea nitrogen, 78.8 mg/dL; creatinine level, 4.22 mg/dL). The patient was hyperglycemic, with a glucose level of 32.6 mmol/L. The patient had uncontrolled diabetes, with a glycated hemoglobin level of 11%. The C-reactive protein level was also elevated at 207.58 mg/dL. An arterial blood gas test revealed acidosis of pH 7.27. Additionally, a pCO_2 level of 25 mmHg, a pO_2 level of 83 mmHg, and a bicarbonate level of 11.5 mEq/L indicated metabolic acidosis.

The anion gap was 21.5 mEq/L, and the serum lactate level was 1.8 mmol/L. Therefore, a provisional diagnosis of lactic acidosis was established. Urine ketone was present in trace amounts. Spot urine microalbumin/creatinine ratio was 123.6 mg/gCr.

Imaging examinations

Chest radiography showed multiple patchy infiltrations in both lungs (Figure 1).

Chest computed tomography (CT) revealed peribronchial consolidation and ground-glass opacity with cavitary nodules in both lungs. Pulmonary thromboembolism (PTE) in the segmental and subsegmental pulmonary arteries of the right lower lobe was suspected (Figure 2).

Abdominal computed tomography showed extensive thrombosis in the left renal vein, extending to partial thrombosis in the suprarenal inferior vena cava (IVC).

A neck angio CT was performed on the third day to assess left neck swelling. A 13 mm × 10 mm nodular lesion was observed on the left parotid gland (Figure 3).

Further diagnostic work-up

For further evaluation, blood, sputum, and urine cultures, hypercoagulability test were performed.

The hypercoagulability test showed decreased protein S activity and less free protein S antigen but normal total protein S antigen, protein C activity, and protein C antigen. The von Willebrand factor and factor V Leiden were normal, and lupus anticoagulant level was elevated. However, anticardiolipin and anti-β2 glycoprotein-1 antibodies were absent.

Additionally, the following findings were noted: prothrombin time, 14.5 s; antithrombin III, 72.1; D-dimer, 2.01; and fibrinogen, 926.1. These results did not meet the diagnostic criteria for disseminated intravascular coagulation.

On the fourth day of hospitalization, as pneumonia was worsening, sputum analysis was performed using bronchoalveolar lavage.

A fine-needle aspiration biopsy of the nodule on the left parotid gland was performed on day 14. The nodule was found on neck angio CT. Biopsy results indicated that the nodule consisted of inflammatory cells. Although there was a possibility of cervical lymphadenopathy, the mass was not removed and was closely observed.

The patient had a history of discontinued treatment for chronic right-sided otitis media. Therefore, she underwent otoscopy after being transferred to a general hospital unit. Chronic otitis media with cholesteatoma was suspected. An additional temporal bone was identified on CT. The focal bone defect was suspected to be the right tegmen mastoideum. Therefore, surgical therapy was considered after the acute inflammation was controlled.

Follow-up chest CT was performed as there was no further clinical improvement in pneumonia. Progression of invasive aspergillosis was observed.

Microbiological identification of the causative agent

K. pneumoniae was identified on culture of blood samples taken immediately after admission and on culture of sputum samples extracted *via* bronchoscopy. Except for piperacillin and ampicillin, the bacteria were susceptible to other antibiotics.

Aspergillus niger (*A. niger*) was identified on a follow-up sputum culture. The (1-3)-β-D-glucan assay confirmed the presence of invasive *Aspergillus*.

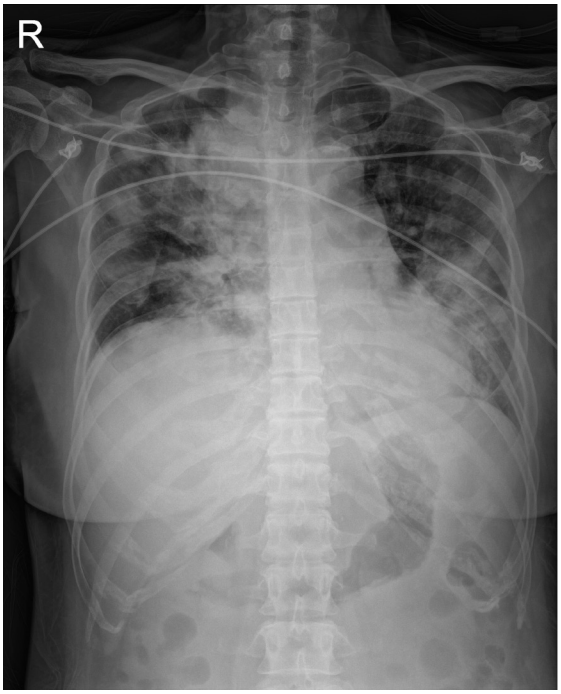

Figure 1 Chest radiography showed multiple patchy infiltrations at both lungs.

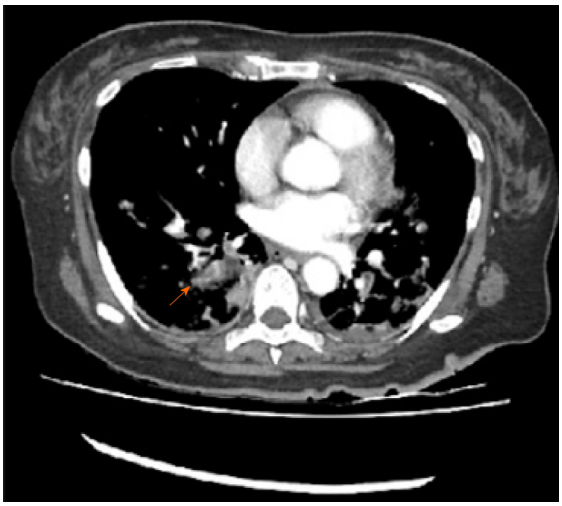

Figure 2 Computed tomography scan of the chest showed suspicious pulmonary thromembolism in segmental and subsegmental pulmonary arteries of right lower lobe (orange arrow).

FINAL DIAGNOSIS

The final diagnosis was Lemierre's syndrome due to *K. pneumoniae.*

TREATMENT

After admission, the patient was transferred to the intensive care unit to undergo treatment for anuria and metabolic acidosis. After continuous renal replacement therapy and administration of a large amount of fluid, the patient started to urinate on the first day of hospitalization. Acute renal failure improved on the second day. However, oxygen demand gradually increased, and pneumonia was aggravated in both lungs on chest radiographs. Therefore, mechanical ventilation was initiated.

Piperacillin-tazobactam and levofloxacin were used as empirical antibiotics. They were used to simultaneously manage *Streptococcus pneumoniae* and *Pseudomonas spp.*,

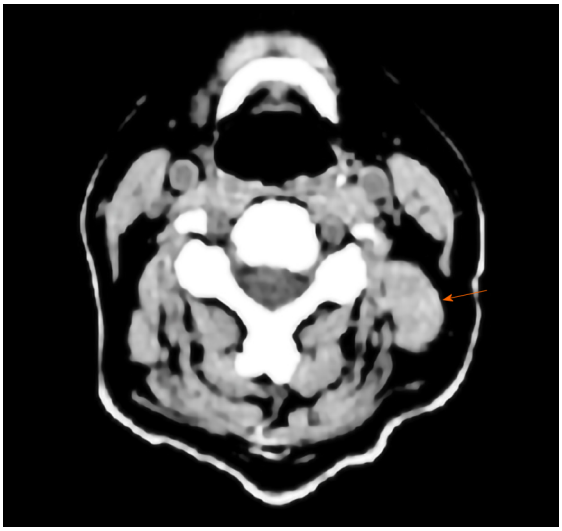

Figure 3 Computed tomography scan of the neck showed the 13 mm × 10 mm size nodular lesion (orange arrow) in left parotid gland.

the causative agents of severe community-acquired pneumonia. These antibiotics were selected based on previous reports of fluoroquinolone combination therapy leading to a better prognosis than β-lactam alone in severe cases[2].

Enoxaparin, a low-molecular-weight heparin, was initiated on the second day to treat the pulmonary thromboembolism.

However, the patient's clinical condition further deteriorated due to pneumonia. Therefore, on the fourth day, the initial antibiotics were replaced with vancomycin and meropenem.

As there was no improvement in pneumonia after the antibiotics were changed, mechanical ventilation was continued. On the ninth day, vancomycin was discontinued due to a lack of evidence of a gram-positive bacterial infection. Amikacin was added to meropenem. On day 13, improvement was seen in pneumonia. The patient's oxygen demand decreased, and therefore, she was weaned from mechanical respiratory support. She was subsequently transferred to a general hospital unit.

Moreover, *A. niger* was isolated in a follow-up sputum culture. Therefore, we started administering amphotericin following consultation with the infectious disease medical staff.

Subsequently, the patient recovered gradually, amphotericin was switched to itraconazole and low-molecular-weight heparin was switched to apixaban. She was ultimately discharged from the hospital.

OUTCOME AND FOLLOW-UP

Leukocytosis occurred on the 12th day after discharge; therefore, the patient was re-hospitalized. There was suspicion of an abscess in the right lung field. An air-fluid level was identified (Figure 4).

A. niger was not identified in the follow-up culture performed after hospitalization. *K. pneumoniae* susceptible to third-generation cephalosporins was identified, consistent with the initial culture result. Therefore, during hospitalization, piperacillin-tazobactam was administered. The patient was discharged with a prescription of cefditoren and itraconazole.

Itraconazole was discontinued after 3 mo. The lung lesion with bilateral ground-glass opacity on radiography did not improve. Therefore, the patient continued taking cefditoren and received continuous respiratory rehabilitation treatment. To reduce the risk of PTE recurrence, apixaban was administered for ≥ 6 mo.

DISCUSSION

In 1989, Sinave *et al*[3] summarized the key symptoms of Lemierre's syndrome and suggested the following diagnostic criteria: (1) Primary infection of the oropharynx; (2)

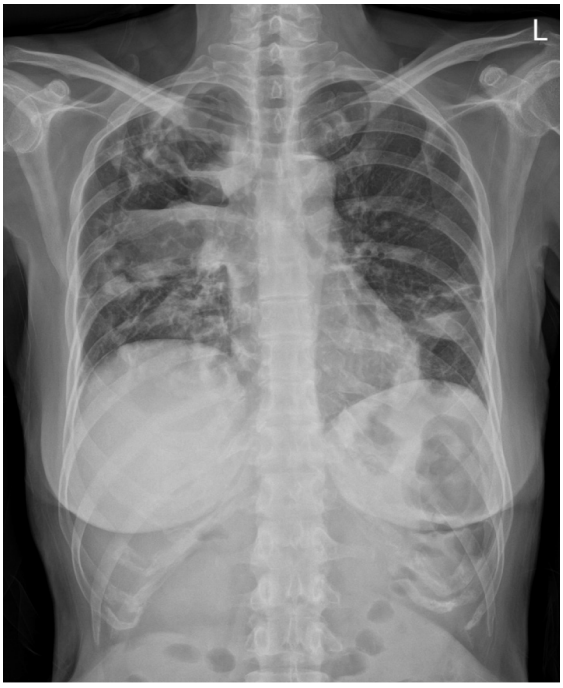

Figure 4 Chest radiography showed large cavitary consolidation with internal air-fluid level in right upper and middle lobes.

Sepsis with at least one bacteria identified on a blood culture; (3) Clinical or imaging findings of IJV thrombosis; and (4) At least one metastasis.

Lemierre's syndrome was a common disease until the development of antibiotics. However, recently it has become a rare disease and has been called the "forgotten disease"[1].

This disease occurs mainly in adolescents and young adults. However, its cause has not been clearly established.

In young adults, pharyngitis symptoms are observed during the initial stages of the disease. In contrast, elderly individuals manifest early metastatic complications, such as pneumonia and brain abscesses. This suggests that infection of the IJV causes complications in other organs through blood circulation. In recent studies, 7% cases of Lemierre's syndrome progressed to septic shock[4]. Pulmonary impairment was the most common metastatic complication, leading to pneumonia, pulmonary embolism, pleural effusion, pneumothorax, and thoracic empyema. A total of 10% cases required mechanical respiratory assistance for acute respiratory distress syndrome. This was the case in our study.

Less than 5% patients receive renal replacement therapy for acute renal failure[4]. However, for 2 d, our patient underwent continuous renal replacement therapy for acute kidney injury caused by septic shock and renal vein thrombosis.

Lemierre's syndrome is primarily caused by *Fusobacteria*, which are a part of the normal flora in the oropharynx, genitourinary tract, and gastrointestinal tract. Among the 13 species of *Fusobacterium*, *F. necrophrum* is the most common pathogen[5]. In other case reports, *Bacteroides* spp., *Streptococcus* spp., *Enterococcus* spp., *Peptostreptococci*, and *Proteus mirabilis* have been identified as pathogens.

In the present case, *K. pneumoniae* was the causative pathogen. However, *K. pneumoniae* has rarely been reported as a cause of Lemierre's syndrome in previous case reports. Based on some retrospective studies, only 2.5% cases have been reported to be caused by *K. pneumoniae*[6].

In a study published in 2015, eight of nine patients with Lemierre's syndrome associated with *K. pneumoniae* had poorly controlled diabetes[7].

Similarly, our patient had poor blood glucose control with a glycated hemoglobin level of 11% and a serum glucose level of 32.6 mmol/L at the time of admission.

Patients with type 2 diabetes mellitus are vulnerable to infection because of the decreased activity of neutrophils[8]. The underlying mechanism of the increased susceptibility of patients with type 2 diabetes mellitus to *K. pneumoniae* is as follows. The hypermucoviscosity phenotype of *K. pneumoniae*, especially K1/K2 isolates, is resistant to phagocytosis[9]. Poor glycemic control significantly reduces phagocytosis of virulent K1/K2 *K. pneumoniae*. Additionally, Lin *et al*[10] showed that older patients

with poor glycemic control had decreased phagocytosis activity.

Beta-lactamase-resistant beta-lactam antibiotics are recommended for typical Lemierre's syndrome. Beta-lactamase produced by *F. necrophorum* may lead to therapy failure[7].

Therefore, treatment should be changed from empirical antibiotics to targeted antibiotics based on the results of the blood culture and antibiotic susceptibility analysis.

If *K. pneumoniae* is the likely cause of Lemierre's syndrome, drugs that can also treat gram-negative aerobic rods should be used until the causative pathogen is identified. Additionally, the appropriate drug must be selected based on the susceptibility data of *K. pneumoniae* in the region and the risk of an Extended-spectrum beta-lactamases-producing strain[11,12].

In our patient, IJV thrombosis was not observed. Instead, pulmonary thromboembolism, partial thrombosis of the suprarenal IVC, and extensive thrombosis of the left renal vein were observed.

The hypercoagulability test results led to the suspicion of protein S deficiency. However, protein S deficiency is difficult to diagnose solely based on the results obtained once in the acute phase[13].

We have scheduled another test for the protein S deficiency diagnosis 3 mo later. Since prolonged prothrombin time and decreased antithrombin III levels are common in sepsis, the result was considered to be non-specific.

We compared the hypercoagulability properties of *F. necrophorum* and *K. pneumoniae* because they are related to the pathogenesis of Lemierre's syndrome.

F. necrophorum produces a component of the cell surface called hemagglutinin, which forms thrombi[4]. Russo *et al*[14] have suggested that this is because *K. pneumoniae* causes more frequent metastatic spread in the K1/K2 group. Another possibility is increased capsule production in the hypervirulent type.

Although the hypothesis has not been tested, it appears that the mucoviscosity of the strain's thick capsules persists in the bloodstream and causes greater aggregation of bacterial cells to form thrombi[14].

The role of anticoagulation for IJV thrombosis is controversial. As Lemierre's syndrome has a low incidence rate, there is a lack of controlled investigations for anticoagulation treatment.

Also, anticoagulation medication was introduced to prevent respiratory failure and propagation of the septic thrombus to the intracranial sinuses.

There is no clear evidence to outline the appropriate duration of anticoagulation treatment. Previously reported findings suggest a duration of 4 wk to 6 mo[15]. Schubert *et al*[16] analyzed 23 patients diagnosed with septic thrombosis of the IJV from 1998 to 2010. The primary infection site in 11 patients was the middle ear[16]. Otitis is a common disease. However, it can progress to systematic infection by forming septic thromboses in the IJV. Therefore, source control is fundamental even if it is a local infection.

In addition, the incidence rate of Lemierre's syndrome is increasing again in recent years. The development of various antibiotics and advancements in medical care have led to the emergence of various new pathogenic strains and multidrug-resistant strains. The syndrome may be fatal as it is accompanied by numerous systemic complications. Therefore, Lemierre's syndrome must be suspected in cases of fever or throat pain associated with infections of the oropharynx and middle ear. Preemptive examinations, consultation with other specialists, appropriate procedures, and targeted treatments are essential.

CONCLUSION

The primary site of infection in Lemierre's syndrome is the oropharynx. Oropharyngeal infections cause IJV thrombosis and anaerobic sepsis. The disease typically manifests as sore throat, a symptom of oropharyngeal infection. This can lead to metastatic complications and death. Lemierre's syndrome is a rare disease[17]. Therefore, it is difficult for doctors with no experience with this syndrome to suspect it [5]. In addition, symptoms of oropharyngeal infection are often resolved when the patient visits the hospital. This disease should be considered in the differential diagnosis when systemic complications caused by upper respiratory tract infection are suspected.

Atypical Lemierre's syndrome should be suspected in cases in which a typical causative strain is not identified or cases of thromboembolism at a site other than the

IJV thrombosis. After diagnosis, it is essential to assess whether surgery or intervention is necessary through active consultation with other specialists. Appropriate antibiotic treatment according to the causative strain must be initiated.

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