glomerulosclerosis in a patient with polycythemia rubra vera. Nephron 1995;69:361.
9. Ulusoy S, Ozkan G, Sönmez M, Mungan S, Kaynar K, Cansiz M, et al. Absence of hypoalbuminemia despite nephrotic proteinuria in focal segmental glomerulosclerosis secondary to polycythemia vera. Intern Med 2010;49(22):2477-80.
10. Au WY, Chan KW, Lui SL, Lam CCK, Kwong YL. Focal segmental glomerulosclerosis and mesangial sclerosis associated with myeloproliferative disorders. Am J Kidney Dis 1999;34:889-93.
11. Landolfi R, Di Gennaro L, Falanga A. Thrombosis in myeloproliferative disorders: pathogenetic facts and speculation. Leukemia 2008;22(11):2020-8.

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Tubulointerstitial nephritis and sclerosing cholangitis associated with autoimmune pancreatitis

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To the Editor:

Autoimmune pancreatitis (AIP) is a form of chronic pancreatitis caused by an autoimmune inflammatory process with lymphocyte infiltration and fibrosis that lead to organ dysfunction,[1] related to high levels of IgG4 and anti-carbonic anhydrase II antibodies.2,3 This disease frequently produces extra-pancreatic manifestations as well, such as sclerosing cholangitis and tubulointerstitial nephritis.[4]

Sclerosing cholangitis associated with AIP produces imaging test results and a clinical presentation similar to that of primary sclerosing cholangitis (PSC), but has a dramatic response to steroid treatment.[5]

Here, we describe the case of a patient with repeated episodes of pancreatitis and cholangitis who was managed as a case of PSC with no response, and who developed tubulointerstitial nephritis with renal biopsy findings suggestive of an autoimmune process, with resolution of gastrointestinal and renal manifestations through the administration of steroids.

CASE REPORT

Our patient was a 37-year old male who sought treatment in March 2006 for jaundice, fever, and abdominal pain; we first suspected an episode of cholangitis, but an endoscopic retrograde cholangiopancreatography and p-ANCA tests due to suspected PSC were negative, leading to the suspicion of microlithiasis.

In May of 2006, we performed an endoscopic sphincterotomy. Eight days later, the patient showed another episode of cholangitis. We considered the possibility of acalculous gallbladder disease as the cause for the recurring cholangitis; a cholecystokinin scintigraphy was compatible with this diagnosis, and we performed a laparoscopic cholecystectomy, but 15 days later the patient returned with yet another episode of cholangitis.

We returned to the suspected diagnosis of PSC, and performed a liver biopsy that revealed acute cholangitis with minimal foci of fibrosis. In early 2007, we administered a magnetic resonance cholangiography that revealed constrictions that were compatible with the diagnosis of PSC, with no possibility of performing a surgical intervention.

We managed the patient as a case of PSC, administering ursodeoxycholic acid and low doses of antibiotics (ciprofloxacin), and yet the patient continued to suffer repeated episodes of cholangitis.

In October 2007, the patient sought treatment for fever and abdominal pain; we started treatment with ciprofloxacin and requested an abdominal contrast tomography based on the patient's creatinine value of 8.7mg/dl. In May 2007, the patient's creatinine value was 1.2mg/dl.

The patient was evaluated in nephrology, and the only finding was paleness.

Laboratory analyses revealed creatinine: 7.6mg/dl, blood urea nitrogen (BUN): 46, normal sodium and potassium levels, pH: 7.32, bicarbonate: 16, Hb: 9.7g/dl, urinalysis with glycosuria (50mg/dl) and no hyperglycaemia.

A renal ultrasound revealed normally sized kidneys with increased bilateral echogenicity.

The patient was diagnosed with acute renal failure secondary to tubulointerstitial nephritis due to the consumption of quinolones.

After antibiotic treatment was removed and the patient was hydrated on the following day, creatinine decreased to 5.5mg/dl and BUN to 36mg/dl. Serum complement was normal, anti-nuclear antibodies (ANA) and serological tests for syphilis (VDRL) and human immunodeficiency virus (HIB) were negative; 24-hour proteinuria was 580mg. The patient was discharged with a creatinine value of 2.2mg/dl.

Twenty days later, the patient returned again for treatment for fever, diarrhoea, and oedema. Upon hospitalisation the patient had a creatinine value of 15mg/dl, potassium at 5.8mEq/l, and urine cytochemistry revealed leukocyturia, proteinuria (25mg/dl), glycosuria (50mg/dl), and haematuria (erythrocytes: 6 per field). A physical examination revealed no pathological findings. We considered this to be an exacerbation of the previous case of renal failure; due to the suspicion of tubulointerstitial nephritis, we started treatment with prednisone and took a renal biopsy.

The renal biopsy revealed: acute tubulointerstitial nephritis; immunofluorescence revealed: IgG ++ (interstitial), IgA and IgM +++ (interstitial), k and lambda chains: absent, C3: +++ peripheral, M and Bowman's

capsule, and absence of C1q. We interpreted these findings as histological changes corresponding to acute tubulointerstitial nephritis due to hypersensitivity to medications as opposed to autoimmune.

We continued to treat the patient with steroids, and upon discharge, creatinine was at 3.6mg/dl.

Since starting the patient on steroids, no further episodes of cholangitis or pancreatitis were produced, which led to the diagnosis of AIP with sclerosing cholangitis and tubulointerstitial nephritis as extra-pancreatic complications.

We did not measure IgG4 levels, since the patient had already received steroid treatment.

The first outpatient follow-up consultation revealed creatinine at 1.6mg/dl. The steroid treatment was progressively decreased, and the patient is currently on a regimen of 5mg prednisone every other day indefinitely. Follow-up measurements of creatinine revealed values ranging from 1.4mg/dl-1.7mg/dl.

The last follow-up session in December 2010 showed the patient's creatinine value to be 1.43mg/dl, and no new episodes of cholangitis or pancreatitis have occurred.

DISCUSSION

In 1961, Starles made the first description of chronic pancreatitis with autoimmune manifestations; later, in 1995, this form of pancreatitis was labelled by Yoshida as "autoimmune pancreatitits".[6]

Although the number of reports of this disease has recently increased, and some studies report a prevalence of 5% among patients with chronic pancreatitis, the true incidence of AIP remains unknown.[7]

AIP is frequently associated with rheumatoid arthritis, Sjögren's syndrome, and inflammatory bowel disease; it is also common to encounter hypergammaglobulinaemia and elevated IgG4 levels, anti-carbonic anhydrase II, and lactoferrin auto-antibodies, which suggests an autoimmune disease, although its pathogenesis is still unkown.[1-3]

The extra-pancreatic autoimmune manifestations of AIP include sclerosing sialadenitis, retroperitoneal fibrosis, interstitial pneumonitis, sclerosing cholangitis, and tubulointerstitial nephritis.[4,8]

As regards sclerosing cholangitis associated with this type of pancreatitis, diagnosis is hindered by the fact that this condition shares many imaging test, cholangiography, and clinical findings with PSC; several authors have reported that the appearance of this disease in patients older than 60 years of age, with elevated levels of IgG4, and a dramatic response to steroid treatment all favour the diagnosis of AIP-associated sclerosing cholangitis as opposed to PSC.5

Various diagnostic criteria have been suggested for AIP; these include the revised Japan criteria, which place special emphasis on imaging test findings, the Mayo Clinic criteria (HISORT), which involve the use of histological, imaging test, and serology findings, as well as the manifestations in other organs and response to steroids, and the Italian criteria, which give greater importance to histological findings; however, no unified international consensus exists regarding which diagnostic criteria to use.[9]

As yet, few cases of tubulointerstitial nephritis have been reported in association with AIP; generally, these are observed in male patients older than 50 years of age, with mononuclear cell infiltrates that are positive for IgG4 in the renal interstitium, and with clinical and serological (decreased IgG4 levels) evidence of response to steroid treatment.[8,10]

Despite the lack of information regarding IgG4 levels in our patient, there were elements to suggest sclerosing cholangitis and tubulointerstitial nephritis associated with AIP: frequent episodes of cholangitis with magnetic resonance cholangiography findings that initially produced the suspicion of PSC, but the patient showed little response to normal treatment and had no auto-antibodies (p-ANCA, ANA), which are present in 85% of all patients with this pathology; this was supported by the repeated episodes of pancreatitis with evidence of diffuse growth of the pancreas, and resolution of symptoms through treatment with steroids.

The renal biopsy findings, specifically those from immunofluorescence testing, favoured the diagnosis of an autoimmune mechanism responsible for producing the tubulointerstitial nephritis observed in this patient.

Conflicts of interest

The authors declare that they have no conflicts of interest related to the contents of this article.

1. Finkelberg DL, Sahani D, Deshpande V, Brugge WR. Current concepts Autoimmune pancreatitis. N Engl J Med 2006;355:2670-6.
2. Okazaki K, Uchida K, Ohana M, Nakase H, Uose S, Inai M, et al. Autoimmune-related pancreatitis is associated with autoantibodies and a Th1/Th2- type cellular immune response. Gastroenterology 2000;118:573-81.
3. Aparisi L, Farre A, Gomez-Cambronero L, Martinez J, De Las Heras G, Corts J, et al. Antibodies to carbonic anhydrase and IgG4 levels in idiopathic chronic pancreatitis: relevance for diagnosis of autoimmune pancreatitis. Gut 2005;54:703-9.
4. Ohara H, Nakazawa T, Ando T, Joh T. Systemic extrapancreatic lesions associated with autoimmune pancreatitis. J Gastroenterol 2007;42 Suppl 18:15-21.
5. Nishino T, Oyama H, Hashimoto E, Toki F, Oi I, Kobayashi M, et al. Clinicopathological differentiation between sclerosing cholangitis with autoimmune pancreatitis and primary sclerosing cholangitis. J Gastroenterol 2007;42:550-9.
6. Song Y, Liu QD, Zhou NX, Zhang WZ, Wang DJ. Diagnosis and management of autoimmune pancreatitis: Experience from China. World J Gastroenterol 2008;14(4):601-6.
7. Lin LF, Huang PT, Ho KS, Tung JN. Autoimmune Chronic Pancreatitis. J Chin Med Assoc 2008;71(1):14-22.
8. Uchiyama-Tanaka Y, Mori Y, Kimura T, Sonomura K, et al. Acute Tubulointerstitial Nephritis Associated With Autoimmune-Related Pancreatitis. Am J Kidney Dis 2004;43(3):18-25.
9. Nishimori I, Onishi S, Otsuki M. Review of diagnostic criteria for autoimmune pancreatitis; for establishment of international criteria. Clin J Gastroenterol 2008;1:7-17.

10. Yoneda K, Murata K, Katayama K, Ishikawa E, Fuke H, Yamamoto N, et al. Tubulointerstitial nephritis associated with IgG4-related autoimmune disease. Am J Kidney Dis 2007;50(3):455-62.

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Acute kidney injury induced by allergic conditions-associated renal cholesterol crystal embolism

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Dear Editor,

Cholesterol crystal embolism (CCE) is characterized by multi-system organ dysfunction resulting from occlusion of arteries by atheromatous plaque. Most CCE occur following vascular surgery or radiological procedures, and the CCE which occur without history of interventional operation or surgery is often called "spontaneous CCE".[1] However, CCE is commonly accompanied by eosinophilia which is an important characteristic of allergy. Although eosinophilia is generally considered as the secondary reaction after CCE occurring, allergic disease has been proved to be the risk factor of atherosclerotic disease.[2-4] So the relationship between CCE and allergy is still deserved to discuss. Here we describe a case of CCE which occurred after the attack of allergic disease. The patient had a long history of allergic disease (allergic asthma and eczema) over 20 years and an acute attack of eczema and asthma before kidney function decreasing. Satisfactory treatment was obtained with only corticosteroid. This case is a direct proof that allergy is not only the secondary reaction, but also be one of the important precipitating factors of CCE.

One month before admission, a 71-year-old male presented with asthma and eczema. Then he had lower limb edema, anorexia, and toe pain. He had a long history of eczema and asthma over 20 years, with no history of chest pain, anticoagulant therapy, cardiac catheterization, or angiography. Urinary sediment showed BLD±, PRO±. Blood chemistry showed renal function insufficiency (BUN: 118.8mg/dL, Cr: 4.28mg/dL). Blood routine showed anemia (90g/L), thrombocytopenia (81x10^9/L; normal range, 100 to 300x10^9/L) and eosinophilia (absolute eosinophil count, 1.6x10^9/L; normal range, 0 to 0.5x10^9/L). Immunological examination showed increased IgE level (3080IU/mL; normal range, 0 to 165IU/mL). The symptoms got worse gradually and the serum Cr had increased to 6.72mg/dL before admission. On admission, the patient presented with marked lower-extremity pitting edema with bilateral pre-tibial skin eczema. Feet pulses were preserved. The skin temperature of the first one-third of the dorsal feet decreased. Cyanosis was present in the toes with overt tenderness.

On admission, serum creatinine had increased to 7.88mg/dL. Urinalysis showed slight proteinuria (272mg/24h) and increased N-acetylglucosaminidase (29.9U/gCr; normal range, 2-21.6U/gCr). IgE level was very high (3650IU/mL). Doppler ultrasonic imaging study of arteries revealed atherosclerosis and small mural plaques of bifurcations for the common carotid artery, the internal carotid artery and the proximal and middle vertebral artery.

Percutaneous kidney biopsy was performed. The results revealed as follows (Figure 1 A). Among all 12 glomerulus, 5 glomerulus showed ischemic global sclerosis and 2 glomerulus showed ischemic atrophy. Others showed diffuse slight to mild proliferation of glomerular mesangial cells. Multifocal tubular atrophy and interstitial fibrosis were present and accompanied by focal infiltration of mononuclear cells, neutrophils and eosinophils in the interstitium. The most noticeable changes were found within the small arteries, arterioles and vascular pole of the glomeruli presenting with cholesterol crystal gaps. On immunofluorescence, mesangial deposits of FRA (+) were present while IgA, IgG, IgM, C3, and C1q were weak or negative.

Although the creatinine clearance rate (Ccr) was as low as 7.3ml/min/1.73m^2, hemodialysis was not administered immediately because of no oliguria. Intravenous methylprednisolone was administered at a dose of 40mg/day. Three days later, the patient's general condition improved dramatically. Pain of toes was obviously relieved and no further cutaneous lesions appeared. One week after treatment, the skin temperature of feet increased and the cyanosis turned shallower than before. Blood routine showed eosinophil count decreased to 0.18x10^9/L. Serum creatinine and IgE decreased to 5.57mg/dL and 2970IU/mL, respectively. Oral triamcinolone was given at a dose of 24mg/day. Three weeks after treatment, serum creatinine decreased to 4.26mg/dL. Pre-tibial skin eczema and pain of toes diminished. The temperature of feet skin recovered. Five weeks after treatment, serum creatinine decreased to 2.69mg/dL. Eosinophil count turned normal. Steroids were tapered 10 % every 2-4 weeks. Triamcinolone has been tapered to 4 mg/day for maintenance treatment without CCE relapse so far. The serum creatinine of the patient was 2.81mg/dL during last visit (Figure 1 B).

The relationship between CCE and autoimmunity is an interesting issue. Details of the inflammatory response have been documented in animal models that cholesterol emboli could not only mechanically occlude the vessel but also