IgG4-associated idiopathic tubulointerstitial nephritis complicating autoimmune pancreatitis

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Introduction

It has been well documented that autoimmune pancreatitis (AIP) [1], also known as sclerosing pancreatitis [2], is frequently associated with fibrosclerotic diseases, such as Sjögren's syndrome [3,4], primary biliary cirrhosis [5], primary sclerosing cholangitis [3–5] or retroperitoneal fibrosis [6]. However, as yet, there have been no reports on renal complications of AIP, except for hydronephrosis, caused by retroperitoneal fibrosis. Recently, Hamano et al. [2] reported that the pathogenesis of sclerosing pancreatitis is closely related to the presence of immunoglobulin (Ig) G4. We describe here a patient with AIP in association with tubulointerstitial nephritis (TIN), which is strongly suspected to be induced by immune complexes containing IgG4.

Case

In 1992, a 66-year-old male was admitted to the surgical department of our hospital because of obstructive jaundice. He gave no history of severe abdominal pains or alcohol abuse. Computed tomography (CT) showed the diffuse enlargement of the pancreas with dilatation of the main pancreatic duct, in its body and tail, and mild dilatation of the common bile duct. Neither calcifications nor cysts were observed in the pancreas. Based on a strong suspicion of pancreatic carcinoma, the patient underwent an operation. However, the procedure was changed to cholecystectomy and choledochojejunostomy, because an intraoperative biopsy demonstrated only chronic inflammation featuring diffuse lymphoplasmacytic infiltrations with lymph follicles and marked interstitial fibrosis with acinar atrophy. At the time the patient was without urinary abnormalities, but had an elevation of the gamma globulin fraction to 22.7% (normal: 10.8–19.6%) and a positive serum antinuclear antibody (ANA) test with a titre of 1:640 and a homogeneous pattern. Serum complement levels were not measured.

In June 1996, he was referred to our department because of renal dysfunction. He was on no medications. Urinalysis revealed a mild proteinuria (0.3 g/day) without occult blood or leukocyturia. Serum creatinine was elevated to 2.3 mg/dl (normal: 0.4–1.1 mg/dl). Total serum protein was 8.0 g/dl, the gamma globulin fraction being 38.3%. A fasting blood sugar was within the normal range, but haemoglobin A1c was elevated to 6.5% (normal: 4.3–5.8%). Serum C3, C4 and total serum haemolytic activity (CH50) were decreased to 43.6 mg/dl (normal: 85–160 mg/dl), 3.6 mg/dl (normal: 16–45 mg/dl) and 15 U/ml (normal: 30–40 U/ml), respectively. Serum IgG and the IgG4 subclass were elevated to 2690 mg/dl (normal: 870–1700 mg/dl) and 550 mg/dl (normal: <70 mg/dl), respectively. Circulating immune complexes (CICs) detected by enzyme-linked immunosorbent assay kits using a monoclonal rheumatoid factor (mRF; Nissui Pharmaceutical, Tokyo, Japan) were elevated to 18.9 mg/ml (normal: <4.2 mg/ml). ANA was positive as before, but antibodies to native DNA, Sjögren's syndrome A and Sjögren's syndrome B were all negative. Serum hepatitis B antigen, hepatitis C antibody and cryoglobulin were absent. Schirmer's test showed 15 mm wetting per 5 min in both eyes and sialography using a radioisotope revealed well-preserved function of the glands.

A renal biopsy showed zonal interstitial infiltrations of lymphocytes, predominantly T cells, detected by UCHL1 (DAKO A/S, Glostrup, Denmark), and plasma cells, with a few eosinophils and macrophages accompanying fibrosis with tubular atrophy. Infiltrations of inflammatory cells into the tubular epithelium, so-called tubulitis, were absent. The 12 glomeruli examined revealed mild mesangial proliferation; glomerular capillary walls were not appreciably thickened and no glomeruli showed crescent formation. In interlobular
arteries, a mild thickening of the wall was observed. Direct immunofluorescence showed granular deposits of IgG and C3c along the tubular basement membrane (TBM) in a patchy distribution (Figure 1). IgG4, which was stained using formalin-fixed, paraffin-embedded specimens and the ENVISION system (DAKO A/S), employing sheep anti-human IgG4 antibody (AU009; Binding Site Ltd, Birmingham, UK) and rabbit anti-sheep IgG antibody (Zymed Laboratories, Inc., South San Francisco, CA, USA), was detected along the TBM (Figure 2). In addition, plasma cells infiltrated into the tubulointerstitium and the pancreas showed strong immunoreactivity to IgG4. However, the exocrine pancreas could not be evaluated for IgG4 deposits because of its severe atrophy. In three other patients who had diagnoses of membranous nephropathy, membranoproliferative glomerulonephritis or minimal-change nephrotic syndrome, deposits of IgG4 were observed only in the glomeruli of the patient with membranous nephropathy. Electron microscopic studies showed electron-dense deposits without fibrillar or lamellated structures in the TBM (Figure 3).

After a renal biopsy, our patient received oral prednisolone following three courses of intravenous methylprednisolone pulse therapy. After the initiation of therapy, his CH50 increased to the normal range within 6 months and the ANA test became negative within 3 years. There has been no increase in his serum creatinine up to now. In September 2001, his IgG, IgG4 and CICs decreased to 1940 mg/dl, 149 mg/dl and 3.7 μg/ml, respectively. CT studies revealed marked atrophy of the pancreas.

Discussion

The pancreatic lesions in this patient could be considered as AIP [1] or sclerosing pancreatitis [2], because of the clinicopathological features summarized as follows: (i) no history of acute attacks of pancreatitis; (ii) increased levels of serum IgG; (iii) positive ANA test; (iv) diffuse enlargement of the pancreas in the absence of pancreatic calcification or cyst; (v) lymphoplasmacytic infiltrations with lymph follicles and fibrotic changes; and (vi) improvement of the pancreatic enlargement and serological abnormalities with steroid therapy.

To our knowledge, this is the first case of AIP complicated by renal involvement, histologically confirmed. The renal lesions are characterized by immune complex-mediated TIN. Although TIN with immune-complex deposits may be observed in systemic lupus erythematosus and Sjögren’s syndrome, it is rare to find such deposits in the absence of these autoimmune disorders. This patient had hypocomplementaemia without clinical findings suggestive of the complications of systemic lupus erythematosus or Sjögren’s syndrome.

Clinically, this patient had high serum levels of IgG, especially IgG4, and CICs detected by mRF, all of which decreased at the same time as renal function became stable after steroid therapy. Histologically, positive staining of IgG4 with C3c along the TBM was
observed. In addition, infiltrating plasma cells showed strong immunoreactivity to IgG4. IgG4 has two unique properties [7] that contribute to the pathogenesis of membranous nephropathy [8]. One is the inability to fix C1q, leading to the impaired clearance of immune complexes from the circulation, and the other is low affinity for target antigens, leading to the ability of immune complexes to dissociate, cross the glomerular basement membrane and re-form on the epithelial surface. Based on our findings, the renal lesion of this patient appears to have been induced either by the deposition of CICs containing IgG4 or by the IgG4 subclass of immune complexes formed in situ or both. Although Yoshida et al. [1] have reported a patient with decreased serum levels of both C3 and C4, the cause of hypocomplementaemia in this patient is not clear, because IgG4 has no ability to activate the classical pathway. Some kinds of IgG4 have an Fc-binding reactivity in the constant region [9]. In immune complexes, IgG4 may appear as a rheumatoid factor to other subclasses of IgG that play some part in hypocomplementaemia.

The pancreas of this patient had infiltrations of IgG4-bearing plasma cells. Hamano et al. [2] observed that patients with sclerosing pancreatitis had high serum concentrations of IgG4, CICs and the IgG4 subclass of CICs and that their levels were closely associated with disease activity. They also demonstrated that plasma cells infiltrating into the pancreas had immunoreactivity to IgG4 [6]. Accordingly, sclerosing pancreatitis is strongly suspected to be induced by IgG4 or immune complexes containing IgG4, although IgG4 deposits in the pancreas have not yet been directly demonstrated.

AIP is frequently complicated with fibrosclerotic diseases, such as Sjögren’s syndrome [3,4], primary biliary cirrhosis [5], primary sclerotic cholangitis [3–5] or retroperitoneal fibrosis [6]. Kambham et al. [10] reported immune complex-mediated idiopathic TIN with clinicopathological features similar to those of AIP. Their patients were predominantly older men. Two out of eight of those patients had sclerosing cholangitis. Three out of six patients examined had positive ANA tests and most of the patients had a fair response to immunosuppressive therapy. Histologically, they had lymphoplasmacytic infiltrations and fibrosis. Based on the preceding and the features of our patient manifesting both conditions, AIP and immune complex-mediated idiopathic TIN could be different manifestations of a single disease, the so-called ‘multifocal idiopathic fibrosclerosis,’ and IgG4 could play a pathogenetical role in both conditions.

In summary, we have described here a patient with immune complex-mediated TIN in association with AIP. The renal lesion is strongly suspected to be induced by IgG4 or immune complexes containing IgG4. This case appeared of value in clarifying the pathogenesis of idiopathic TIN.

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References


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