CASE REPORT

Membranoproliferative Glomerulonephritis-Like Glomerular Disease and Concurrent Tubulointerstitial Nephritis Complicating IgG4-Related Autoimmune Pancreatits

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Abstract

Autoimmune pancreatitis (AIP) is associated with various types of extrapancreatic organ involvement, and accumulation of IgG4-positive plasma cells in the pancreaticobiliary system as well as in other organs (1-3). Similarly, an elevated level of serum IgG4 and infiltration of IgG4-positive plasma cells into salivary glands have been documented in Mikulicz’s disease and Sjögren’s syndrome. Therefore, conditions like AIP, Mikulicz’s disease and Sjögren’s syndrome are thought to be an IgG4-related systemic disease (4, 5). Lately, tubulointerstitial nephritis (TIN) with a high level of serum IgG4 has been related to IgG4-related systemic disease (6, 7). On the other hand, only a few cases of glomerulonephropathy complicated with IgG4-related systemic disease have been reported. Here, we describe a patient with biopsy-proven membranoproliferative glomerulonephritis-like glomerular disease complicated with IgG4-related TIN, AIP, and idiopathic thrombocytopenic purpura (ITP).

Key words: IgG4, membranoproliferative glomerulonephritis-like glomerular disease, tubulointerstitial nephritis, autoimmune pancreatitis, idiopathic thrombocytopenic purpura

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Introduction

Autoimmune pancreatitis (AIP) is associated with various types of extrapancreatic organ involvement, and accumulation of IgG4-positive plasma cells in the pancreaticobiliary system as well as in other organs (1-3). Similarly, an elevated level of serum IgG4 and infiltration of IgG4-positive plasma cells into salivary glands have been documented in Mikulicz’s disease and Sjögren’s syndrome. Therefore, conditions like AIP, Mikulicz’s disease and Sjögren’s syndrome are thought to be an IgG4-related systemic disease (4, 5). Lately, tubulointerstitial nephritis (TIN) with a high level of serum IgG4 has been related to IgG4-related systemic disease (6, 7). On the other hand, only a few cases of glomerulonephropathy complicated with IgG4-related systemic disease have been reported. Here, we describe a patient with biopsy-proven membranoproliferative glomerulonephritis-like glomerular disease complicated with IgG4-related TIN, AIP, and idiopathic thrombocytopenic purpura (ITP).
Case Report

An 80-year-old Japanese man with histories of tuberculosis and gastric ulcer was admitted to our hospital in March 2004 for the evaluation of an elevated level of serum amylase. He was asymptomatic. On admission, body height was 165 cm, body weight 45 kg, body temperature 36.5°C, and high blood pressure of 160/90 mmHg. Physical examination showed normal lungs, heart, abdomen and central nervous system. Laboratory tests showed leukocyte count 6,100/μL, erythrocytes 384×10⁴/μL, hemoglobin 12.4 g/dL, hematocrit 35.4%, and platelets 10.1×10⁴/μL, with no abnormal lymphocytes. Serum biochemical analyses revealed C-reactive protein 1.9 mg/dL, serum creatinine 1.2 mg/dL, eGFR 43.2 mL/min, blood urea nitrogen 27.0 mg/dL, total serum protein 7.9 g/dL, serum albumin 3.3 g/dL, gamma globulin fraction 43.0%, amylase 135 IU/L (normal value, 27 to 83 IU/L), elastase-1 400 ng/dL, (normal, 70 to 430 ng/dL), and lipase 64 IU/L (normal, 10 to 50 IU/L). Immunoglobulin quantitative analysis showed IgG 3,450 mg/dL (normal, 870 to 1,700 mg/dL), IgM 114 mg/dL (normal, 33 to 190 mg/dL), IgA 274 mg/dL (normal, 110 to 410 mg/dL) and IgG4 subclass 553 mg/dL (normal, 4.8 to 105 mg/dL). Serum levels of C3, C4 and total serum hemolytic activity (CH50) were 46 mg/dL (normal, 86 to 160 mg/dL), 2 mg/dL (normal, 17 to 45 mg/dL), and less than 12 U/mL (normal, 30 to 45 U/mL), respectively. Fluorescent antinuclear antibody (FANA) test was positive at a titer of 1: 80 with speckled and homogeneous patterns. Anti-double-stranded DNA antibody, rheumatoid factor, anti-SS-A antibody and anti-SS-B antibody were negative. HCV, HIV, and HTLV-I antibodies and HBs antigen were negative. On that occasion, urinalysis was within normal ranges. Abdominal ultrasonography and computed tomography (CT) scanning revealed diffuse enlargement of the pancreas with diffuse irregular narrowing of the main pancreatic duct and mild dilatation of the common bile duct. Neither calcification nor cysts were observed in the pancreas (Fig. 1). The ultrasonography also showed atrophic kidneys (right 8.9×5.4 cm, and left 8.9×5.1 cm). During admission, the platelet count decreased from 8.4x10⁴/μL to 1.6x10⁴/μL, and serum platelet-associated IgG (PAIgG) was positive at a titer of 970 ng/10⁷ cells. Based on the above finding, the final diagnosis was AIP associated with IgG4 and concurrent ITP. The patient was treated with 40 mg/day prednisolone for two weeks. The dose was gradually tapered down during the following 16 weeks. Initiation of therapy resulted in increase in CH50 to the normal range, and decreases in IgG and PAIgG to 2,144 mg/dL and 138.3 ng/10⁷ cells, respectively. Follow-up CT study showed a marked decreased in size of the pancreas from 26 mm, 23 mm and 15 mm (pancreas head, body and tail, respectively) to 15 mm, 12 mm and 12 mm (Fig. 1). The patient was discharged and followed-up at the outpatient clinic.

In May 2005, he was re-hospitalized because of hypergammaglobulinemia, hypocomplementemia, and mild renal dysfunction, although he was asymptomatic. The daily proteinuria was 0.4 g and urine sediments containing 22 erythrocytes/high power field (HPF), 4 leukocytes/HPF, and 14 waxy casts/low power field. Other laboratory findings included leukocytes 4,300/μL, erythrocytes 312×10⁴/μL, hemoglobin 9.5 g/dL, hematocrit 30.3%, platelets count 16.9×10⁴/μL, C-reactive protein 4.6 mg/dL, blood urea nitrogen 31.7 mg/dL, serum creatinine 1.4 mg/dL, total protein 8.9 g/dL, albumin 2.7 g/dL, IgG 4,657 mg/dL, IgA 253 mg/dL, IgM...
Clinical course. Treatment with prednisolone (PSL) resulted in a gradual increase in platelet count, and in proportional falls in \( \gamma \)-globulin, IgG and IgG4. 89 mg/dL, IgG4 660 mg/dL, PAlgG 244 ng/10^7 cells, C3 35 mg/dL, C4 less than 1 mg/dL, CH50 less than 12 U/mL. FANA test was positive at a titer of 1: 640 with speckled and homogenous patterns. Anti-double stranded DNA antibody, proteinase-3 antineutrophil cytoplasmic antibody, and myeloperoxidase antineutrophil-cytoplasmic antibody were negative (Fig. 2).

Echo-guided percutaneous kidney biopsy was performed on the 5th hospital day to determine the cause of mild renal dysfunction. The renal biopsy showed widespread and severe interstitial fibrosis accompanied by patchy inflammatory infiltrates consisting mainly of mononuclear cells and plasma cells, with scattered eosinophils. Mononuclear cell tubulitis was also present. The tubules were atrophic with focally thickened basement membranes (Fig. 3A, B, C). Eighteen glomeruli were obtained from the right renal biopsy and subjected to light microscopy. Three of them were global sclerosis. The others showed mild to moderate proliferation of lobular mesangium and abnormal thickening of the glomerular basement membrane (GBM) like double contours with bubble formation. Lobular mesangial proliferation and mesangial interpositions were also noted (Fig. 4A, B). Considered together, the light microscopic findings were consistent with membranoproliferative glomerulonephritis-like glomerular disease.

Immunofluorescence staining was strongly positive for IgG, C3, kappa and lambda light chains with coarse and granular mesangial and peripheral deposits. Weakly positive staining for C1q was found in peripheral GBM (Fig. 5). Unfortunately, electron microscopic analysis could not be performed because of lack of sufficient glomeruli in the specimen. The final diagnosis was membranoproliferative glomerulonephritis-like glomerular disease and tubulointerstitial nephritis, which is compatible with IgG4-related nephropathy.

Following the renal biopsy, the patient was discharged and start of medication at the outpatient clinic was planned. However, the day after discharge, he was admitted a third time for mycoplasma pneumonia and congestive heart failure. He subsequently died in the hospital. Autopsy was not performed.

Discussion

AIP is diagnosed based on the presence of diffuse swelling of the pancreas, diffuse irregular narrowing of the pancreatic duct, high levels of serum \( \gamma \)-globulin, in particular IgG4, and a favorable response to steroid therapy (8-11). IgG4-positive lymphofibroplasmacytic infiltration is found not only in the pancreas, but also in other organs. Therefore, the disease has been regarded as pancreatic involvement of a systemic autoimmune disease (3, 12). The disease has been reported to be associated with Mikulicz’s disease (13), Sjögren’s syndrome (14, 15), hypothyroidism (16), interstitial pneumonia (17, 18), retroperitoneal fibrosis (12), gastric ulcer, sclerosing cholangitis (19) and primary biliary cirrhosis (20). Kamisawa et al (3) were the first to use the term “IgG4-related systemic disease” to describe the systemic nature of the disease (3, 6, 21-23).

Renal lesions of the disease have been reported recently, most commonly they consist of tubulointerstitial nephritis (6, 23, 27-29). Most patients with renal involvement show diffuse interstitial infiltration of T cells and plasma cells, with eosinophils and macrophages (28, 30, 31). Plasma cells infiltrating the interstitium show strong immunoreactivity to IgG4 (21, 28, 30-32). In contrast, glomerulonephritis com-
plicating IgG4-related disease is rare. Some cases with membranous nephropathy, with endocapillary proliferation, capillary wall thickening and crescent formation, or with tubulointerstitial nephritis have been reported (21, 28, 32). In these cases, serum C3, C4 and CH50 were within the normal range or decreased. Autologous antibodies, suggesting systemic lupus erythematosus or Sjögren’s syndrome, such as anti-DNA antibody, anti-SS-A antibody, anti-SS-B antibody, were all negative. Response to steroid therapy was relatively good. In the present patient, the diagnosis of membranoproliferative glomerulonephritis-like glomerular disease was confirmed by renal biopsy. Light microscopy revealed lobular mesangial proliferation, granular deposit in periphery, double contour GBM, severe tubular atrophy and dense interstitial infiltrates of plasma cells, small lymphocytes and eosinophils. We considered that IgG and C3 were positive in mesangium, and C1q was positive along peripheral GBM on immunofluorescence study. In the present case, serum anti-DNA, anti-SS-A, anti-SS-B, and anti-Sm antibodies were negative. However, serum anti-nuclear antibody and platelet-associated IgG were positive, and C3, C4 and CH50 were decreased. We considered that AIP, ITP and interstitial nephritis in this case could be regarded as IgG4-related disease. However, the relationship between glomerulonephritis in this case and IgG4-related systemic disease remains undetermined. At the second admission, one year af-
After the first one, his renal function deteriorated from normal urinanalysis to 0.4 g/day proteinuria and waxy casts in urine sediment, and serum creatinine from 1.2 mg/dL to 1.4 mg/dL. IgG4-related nephropathy could be influential in this relatively rapid progression of renal injury which probably originated as hypertensive nephrosclerosis.

ITP has been described rarely as one of the systemic extrapancreatic lesions associated with AIP. Nishi et al described that autoantibodies against a number of endogenous proteins, such as carbonic anhydrase II (CA II) (24), lactoferrin (25) and pancreatic secretory trypsin inhibitor (26), could be implicated in the pathogenesis of AIP. Among them, CA II is a key enzyme which regulates acidification of the urine and which exists in renal distal tubules. The autoantibody to CA II would cause TIN, and the released CA II in the blood stream would form immune complexes, and would cause systemic autoimmune diseases including ITP. Actually, platelets are abundant in CA II.

In summary, we have described a rare case of membranoproliferative glomerulonephritis-like glomerular disease together with tubulointerstitial nephritis in association with AIP, which all could be regarded as organ expression of IgG4-related systemic disease.

References


