Successful Treatment of Multi-system IgG4-related Disease with Cyclophosphamide: A Case Report
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ABSTRACT
Immunoglobulin G4-related disease (IgG4-RD) is increasingly recognized as an autoimmune disease, involvement of multi-organ or system, which is characterized by tissue infiltration of IgG4-positive plasma cells and elevated serum IgG4. We reported a case of 54-year-old man with a medical history of uarthritis, virus B hepatitis, autoimmune pancreatitis, cholecystitis, pulmonary lesion and acute renal failure. The patient was diagnosed with multi-system IgG4-RD based on histological analysis of the renal biopsy revealed IgG4-positive plasmacyte infiltration, elevated serum IgG4(6.95g/L). Corticosteroids (methylprednisolone 250mg/d for 3 days subsequently 40 mg/d) and cyclophosphamide (0.8g iv per month) were used. Not only the IgG4 levels returned to normal but also patient’s renal dysfunction and pulmonary lesions relieved after treatment.

Keywords: Cyclophosphamide, IgG4 related disease, kidney, lung, pancreas

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INTRODUCTION

IgG4 related disease (IgG4-RD) is a multi-organ immune-mediated condition that mimics many malignant, infectious, and inflammatory disorders (1). Many organs or systems can be involved, including pancreas, gall bladder, bile duct, salivary glands, thyroid gland, lymphnodes, kidney, lung, liver, retroperitoneum and aorta (2). The etiology and mechanism of this disease is unclear (3). The clinical manifestations are protean, without characteristic symptoms and signs at the early stage, which leads to misdiagnose. Tissue biopsy is the gold standard for diagnosis (1). The current treatment for IgG4-RD is corticosteroids and rituximab. Cyclophosphamide had been reported to treat IgG4-RD, however, the result was not satisfactory (4, 5). In this report, we describe an IgG4-RD patient with multiple organs involvement successfully treated with combination of corticosteroids and cyclophosphamide.

CASE REPORT

A 54-year-old Chinese man had a past medical history of uarthritis and virus B hepatitis. He was admitted to hospital with the chief complaint of stomachache and jaundice in April 2014. Abdominal ultrasonography and magnetic resonance cholangiopancreatography (MRCP, Figure 1 C, E) indicated swelling of pancreas, expansion of common bile duct and pancreatic duct, irregularity of renal shape with bilateral, multiple renal parenchymal nodules on both T1 and T2 weighted images. Blood examinations revealed serum direct bilirubin (DB) 114.0 umol/L, indirect bilirubin (IB) 28.2 umol/L, alanine aminotransferase (ALT) 117 IU/L, aspartic aminotransferase (AST) 97 IU/L, serum
creatinine (sCr) 210mmol/L, amylase (AMY) 142IU/L, lipase (LPS) 416.1IU/L. He was diagnosed as autoimmune pancreatitis, cholecystitis and renal failure. Laparoscopic cholecystectomy and corticosteroids therapy (methylprednisolone 250mg/d for 3 days) were applied, which relieved liver and renal dysfunction partly (sCr 135mmol/L). After discharge from hospital the patient began to complain of fever, cough and expectoration. Chest computed tomography (CT) scan showed multiple patchy shadows, nodules, fibrous stripes in bilateral lungs (Figure 1A). Blood tests indicated sCr elevated to 209mmol/L. He was then diagnosed as pulmonary infection and chronic renal insufficiency. Multiple antibiotics were used, which relieved pulmonary lesion partly. However, biochemical test showed continuous deterioration of renal function (sCr 309umol/L). Therefore he was admitted in Dec 2014. Physical examination showed hypertension (BP 150/95mmHg) and moist rales in bilateral lungs. Heart and abdomen findings were non-remarkable. Lab tests suggested sCr 340umol/L, eGFR 16.67ml/min/1.73m2, Hb 125g/L and ALT 18 IU/L. Urine protein was 0.68g/24h. Autoimmune antibodies are negative. Complements C3 and C4 were decreased. Serum IgG (31g/L) and IgG4 (6.4g/L) levels were elevated significantly. Renal biopsy showed tubulointerstitial nephritis characterized as diffused renal tubules atrophy with inflammatory cell infiltration. Immunohistochemistry stain indicated IgG4 positive plasma cells infiltration (Figure 2). The patient was diagnosed with IgG4 related disease involved kidney, pancreas and lung according to diagnostic criteria (6).
Figure 1: Radiographic images: CT scan showed (A): multiple patchy infiltrating shadows, nodules in right lung; (B): absorption of lung lesion after treatment; MRI scan showed: (C and E) Irregularity changes of renal shape and with bilateral, multiple renal parenchymal nodules on both T1 and T2 weighted images; (D and F) relief of renal lesion after treatment.
Figure 2: Pathology images: Pathological change of renal biopsy indicated tubulointerstitial nephritis characterized as diffused renal tubules atrophy with inflammatory cell infiltration (plasma cells and lymphocytes). Fibrosis is arranged in a storiform pattern. Immunohistochemical stain showed IgG4-positive plasma cells per high-power field exceed 10 cells. A: PAS stain (400×), B: PASM stain (400×), C: Masson's trichrome stain (400×), D: IgG4 immunohistochemical stain (400×).

Corticosteroids therapy (methylprednisolone 40mg/d) was applied thereafter. One month later, sCr and IgG4 levels were decreased (from 430umol/L to 296umol/L and from 6.4g/L to 4.3g/L, respectively). Chest CT scan showed remarkable improvements of pulmonary and renal lesions(Figure 1 B, D, F). However, the sCr level at the follow up in the 2nd month increased (from 296umol/L to 340umol/L). In order to achieve better immunosuppressive effect, high dose corticosteroid (methylprednisolone 250mg/d for 3 days followed by 40mg/d) and cyclophosphamide (0.8gi.v. per month) was used. In the most recent follow up (June 2015), his renal function was significantly recovered (sCr 133umol/L) and IgG4 decreased to
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normal (0.691g/L) (Figure 3).

**Figure 3**: Clinical course of the patient. (MEP: Methylprednisolone, CYC: Cyclophosphamide)

**DISCUSSION**

The epidemiology of IgG4-RD remains uncertain. A recently review (2) reported that 74% cases were from Japan. Meanwhile the authors had noted that IgG4-RD had been reported in almost all racial and ethnic groups. The etiology and mechanism of the disease were unclear. It may involve complex genetic susceptibility factors and immune abnormality (3).

IgG4-RD is characterized by elevated serum IgG4 and infiltration of IgG4 positive plasma cells into multi-organs, especially kidney. The IgG4 related renal disease is characterized as hypergammaglobulinemia, renal dysfunction, hypocomplementemia and
mild proteinuria (7). Contrast enhanced CT scan can indicate multiple or isolated low-density lesions including characteristic mass-like lesions beyond the outline of the kidney (8). Renal pathologic changes are generally interstitial nephritis, especially “bird’s eye” fibrosis (7).

Although cases of multiple organs involvement had been reported previously (9-14), the current case was a rare case with pancreas, lung and kidney involvement. During the treatment of the patient, his lung lesions had been misdiagnosed as infection, which delayed the optimal timing of treatment. The radiological presentations of IgG4 related lung lesions were diversified, thickening of the bronchovascular bundle as characteristic lesion by CT (15). But the radiographic change similar to bacterial or fungal infection with lungs of this case was rare in IgG4-RD. The doctors need to timely identify the disease, when it is difficult to determine the etiology of lung infection, especially clinical manifestations combined multiple organ involvement.

Although corticosteroids had been considered as the first-line therapy of IgG4-RD, no standard treatment was recommended. Because almost all treatment strategies were from case reports or retrospective analyze of small cohort, no randomized clinical trials have been done. Immunosuppressive agents, including rituximab, azathioprine, cyclosporine A, methotrexate, mycophenolate, cyclophosphamide or bortezomib, were used for recurrent or refractory cases to achieve additional immunosuppression and sparing the effects of long-term corticosteroids (4, 16-19). A prospective, open-label trial16 indicated rituximab may be an effective treatment for IgG4-RD, even without corticosteroids. In the previous report, cyclophosphamide failed to treat IgG4-RD4, (5). However, in this case, cyclophosphamide combined with corticosteroids successfully achieved recovery of
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pulmonary lesion and kidney dysfunction along with satisfactory decrease of serum IgG4 level without severe adverse effect. We found that reason may be the shorter disease duration and lower immunoglobulin level of our case. Therefore, based on the experience from this case, we think cyclophosphamide could be recommended for IgG4-RD patients with severe multiple organs involvement. However, large-scale and multicenter clinical trials should be adopted to further confirm its effectiveness and safety.

CONCLUSION

IgG4-RD is a chronic progressive autoimmune disease, eventually leading to tissue fibrosis and organ dysfunction, which affect the prognosis of patients. In order to delay the progress of the disease, early diagnosis and timely treatment are critical. Doctors need to raise awareness of the disease, especially in those with symptoms and signs of multiple organs involvement. Biopsy of lesions is the gold standard of diagnosis, which should be performed timely in patients suspected with this disease. Corticosteroids combined with cyclophosphamide may be a reasonable alternative in the treatment of IgG4-RD.

Conflict of Interest

The authors declare that they have no conflict of interest.

Informed consent

Informed consent was obtained from the patient.
REFERENCES


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