CASE REPORT

A disclosed diagnosis for 24 year's unknown illness

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Accepted 28 August 2017

SUMMARY

IgG4-related disease (IgG4-RD) is a newly described illness over the last several years. A 57-year-old man, who had been followed for chronic kidney disease (CKD), chronic pancreatitis and history of operated cholangitis, was admitted to our hospital for abdominal pain and worsening renal function. Serum levels of IgG and IgG4 were elevated. CT scan showed the characteristic findings of IgG4-related retroperitoneal fibrosis, pancreas and kidney disease. An endoscopic biopsy revealed the finding compatible with IgG4-RD. Steroid therapy led to the remission of his abdominal pain. Patients with CKD of unknown aetiology may have IgG4-RD.

BACKGROUND

IgG4-related disease (IgG4-RD) is newly described illness over the last several years.^{1 2} The disease shares clinical features of neoplasm and autoimmune disease in terms of chronic inflammation with mass formation in multiple organs. A patient with this disease may have lymphadenopathy, autoimmune pancreatitis, sclerosing cholangitis, salivary and lacrimal gland involvement, retroperitoneal fibrosis, aortitis, tubulointerstitial nephritis, lung disease, hypertrophic pachymeningitis or a variety of other organ systems. Tubulointerstitial nephritis is the most common feature of renal involvement, but cases of membranous glomerulonephritis have been also described. Definitive diagnosis of the disease, which is usually made by serological and pathological examinations, is imperative because of its treatability by using steroids and/or immunosuppressive agents. We herein report a Japanese man with a medical history of chronic illnesses of chronic kidney disease (CKD), cholangitis and pancreatitis of unknown aetiology, who was eventually diagnosed with IgG4-RD after a 24-year period of being undiagnosed.

CASE PRESENTATION

A 57-year-old Japanese man, who had been followed up for CKD, chronic pancreatitis and sclerosing cholangitis, was admitted to our hospital because of abdominal pain and worsening renal function. He denied fever, chills, recent weight loss, jaundice or oedema. His CKD was attributed to chronic glomerulonephritis, possibly mild focal segmental glomerulonephritis, based on the results of a renal biopsy which was conducted 24 years earlier. Soon after the time of the renal biopsy, he received a brief trial of oral steroid therapy for the renal disease and the renal function became

improved slightly, but the therapy was discontinued for unknown reasons. Additionally, he had chronic pancreatitis and sclerosing cholangitis and he underwent operation of anastomosis between the common bile duct and the jejunum for his biliary tract disease 18 years ago. He had smoked one pack a day and quitted it 2 years ago. He drank only a little amount of alcohol occasionally. His regular medications included calcium supplements, vitamin D, amlodipine, furosemide, torasemide, ursodeoxycholic acid, silodosin and Chinese herb. His father died of pancreatic cancer.

On physical examination, the temperature was 36.7°C, the heart rate of 89 per minute, the blood pressure of 136/86 mm Hg and the respiratory rate of 20 per minute. He was alert but appeared chronically ill. Abdominal examination showed epigastric tenderness without rebound tenderness or guarding. The remainder of the physical examination was normal.

INVESTIGATIONS

Laboratory results are shown (box 1).

Chest radiograph showed no abnormality. CT scan image of the abdomen revealed periaortic soft tissue lesion suggestive of retroperitoneal fibrosis, multiple mass-like lesions in the pancreas and rim-like soft tissue proliferation around both kidneys suggestive of perinephric lesions (figure 1).

Additional blood test revealed that serum level of IgG was 2015 mg/dL (normal range, 870–1700 mg/dL) and IgG4 was 732 mg/dL (normal range, 4.8–105 mg/dL).

DIFFERENTIAL DIAGNOSIS

A differential diagnosis for the pancreatic lesions included benign or malignant neoplasms, infectious processes or non-infectious inflammatory processes. Based on the family history of pancreatic cancer in his father, a malignant neoplasm was a concern at the time of the current admission. However, multiple combinations of rare inflammatory conditions in his previous and current history had led us to consider a unifying aetiology and to proceed a biopsy for diseased organs. Chinese herb is another cause of CKD, but this was unlikely because effects of Chinese herbs would not account for other organ involvements.

As the kidneys were atrophic, a renal biopsy was not performed. An endoscopic biopsy through the pancreatic duct was conducted, showing numerous lymphocytic infiltration with fibrosis in the pancreatic tissue (figure 2). Histology of the pancreas also showed the characteristic storiform fibrosis, an irregularly whorled pattern of fibrosis. The ratio of

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To cite: Hanai S, Kinjo K, Uezato M, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-221317

Box 1 The laboratory test results of the patient

1. Complete blood count
 - ▶ Haemoglobin 10 g/dL
 - ▶ White cell count 9.47×10^9 per mm^3
 - ▶ Platelet 15.6×10^{10} per mm^3
2. Serum chemistry test
 - ▶ Urea nitrogen 63.3 mg/dL
 - ▶ Creatinine 9.4 mg/dL
 - ▶ Glucose 334 mg/day
 - ▶ Amylase 64 U/L
 - ▶ Lipase 5 U/L
 - ▶ C3 48 mg/dL (normal range, 80–140)
 - ▶ C4 9.0 mg/dL (normal range, 11–45)
 - ▶ Serum complement CH50 16 U/mL (normal range, 30–45)
3. Urinalysis
 - ▶ Protein 2+
 - ▶ Glucose 3+
 - ▶ Occult blood 2+
 - ▶ Pyuria (–)

IgG4 to IgG-positive plasma cells was about 80%. Thus, a definite diagnosis of IgG4-RD was made.

Regarding a cause of his abdominal pain, type 1 autoimmune pancreatitis associated with IgG4-RD was suspected. CKD, sclerosing cholangitis and retroperitoneal fibrosis were also attributed to IgG4-RD.

TREATMENT

The patient was started with oral steroid therapy of prednisolone 30 mg/day.

Figure 1 (A) Contrast-enhanced CT scan showing periaortic soft tissue proliferation, indicating retroperitoneal fibrosis (white arrow). (B) Contrast-enhanced CT scan showing mass-like lesions in the pancreas (white arrows). (C) Contrast-enhanced CT scan showing rim-like soft tissue proliferation around both kidneys suggestive of perinephric lesions (white arrows).

Figure 2 (A) Histology of the pancreas showing storiform fibrosis which is characteristic of IgG4-RD and infiltration of lymphocytes and plasma cells (H&E stain, magnification, $\times 400$). (B) IgG immunostaining showing numerous IgG-positive plasma cells in the pancreas (magnification, $\times 400$). (C) IgG4 immunostaining showing numerous IgG4-positive plasma cells and the ratio of IgG4 to IgG-positive plasma cells is $>80\%$ (magnification, $\times 400$). IgG4-RD, IgG4-related disease.

OUTCOME AND FOLLOW-UP

His abdominal pain disappeared, but the renal dysfunction did not improve and he had to receive regular sessions of haemodialysis therapy. He was discharged on day 46 after the admission. However, unfortunately, he developed ischaemic stroke and was admitted to another hospital, and died.

DISCUSSION

Our case was eventually diagnosed with IgG4-RD many years after the development of CKD, pancreatitis and cholangitis, all of which had been attributed to unknown or other causes at the time of the initial workup. At the current admission, CT scan revealed retroperitoneal fibrosis, the fourth organ involvement. Although a repeat renal biopsy was not performed because of the renal atrophy, underlying renal disease in our patient was considered as IgG4-related kidney disease because of the context of his clinical course and the characteristic findings in the kidneys on CT scan image.

IgG4-RD is a recently elucidated chronic lymphoplasmacytic inflammatory condition involving multiple organs and usually affects men of the middle age. Its aetiology is unknown but it is considered to be an autoimmune disease because patients typically have high serum IgG4 concentration and multiple organ infiltration of IgG4-positive plasma cells and patients usually respond to steroid or immunosuppressive therapies.

In 2001, Hamano *et al* reported the first case of autoimmune pancreatitis with high serum IgG4 concentration.¹ After this report, the growing number of cases have been reported, indicating, worldwide, there have been numerous patients with inflammatory disorders involving various organs and high serum IgG4 concentrations.² Epidemiology of IgG4-RD has not been clearly described. But the number of patients with IgG4-RD are estimated to be approximately 2 cases per $\geq 100\,000$ population, because the estimated total number of those with type 1 autoimmune pancreatitis in Japan was 2.2 cases per 100 000 population.³ IgG4-RD should be distinguished from other inflammatory diseases, especially infection such as tuberculosis, autoimmune disease or malignancy. Its diagnosis basically requires histopathological evidence of infiltration of IgG4-positive plasma cells. Recently, Xia *et al* suggested the diagnostic

value of elevated serum IgG4 concentration and IgG4/IgG ratio for IgG4-RD.⁴ Serum level of IgG4 in our patient was 732 mg/dL, and IgG4/IgG ratio of the patient was 0.36. The data in our patient were compatible with the suggestion of this study. His serum level of complement was low and it was suggested that IgG4-related tubulointerstitial nephritis is distinguished from other organ involvement based on low concentrations of serum complements in patients with IgG4-RD.⁵

Patients who were labelled as having chronic inflammatory disease of unknown aetiology before 2003 were not suspected

of having this entity. There might be some patients with CKD including dialysis patients who might have IgG4-related kidney diseases. Earlier diagnosis and treatment could prevent further multiple organ damages in patients with IgG4-RD.⁵ Thus, if patients have sclerosing cholangitis, pancreatitis or CKD of unclear aetiology, clinicians may need to evaluate for possible IgG4-RD.

Contributors SH, KK and MU: cared the patient. SH, KK and YT: wrote the draft of the manuscript. All authors: contributed to the writing of the final version.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Learning points

- ▶ IgG4-related disease (IgG4-RD) is a chronic inflammatory disorder involving multiple organs such as kidney, biliary tract, pancreas and aorta as in our patient.
- ▶ Treatment for IgG4-RD can be effective and usually employs steroid therapy.
- ▶ In some patients with end-stage renal diseases of unknown cause, IgG4-RD should be considered as possible aetiology.
- ▶ Diagnosis is important even for patients with established kidney failure, because damage to other organs may be treatable.

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