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Case Report
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Clinical Treatment and Observation of a Case of IgG4-Related Nephropathy Combined with Tuberculosis Infection

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Abstract

IgG4-related diseases are a group of chronic, progressive inflammatory diseases with fibrosis and sclerosis of unknown origin. Here, we report a case of IgG4-related nephropathy combined with Tuberculosis (TB) for >1 month in a 69-year-old man with abnormal renal function, which was found on physical examination. He presented with a low level of proteinuria, abnormally high globulin, renal dysfunction and increased kidney size, as well as a positive T-spot test. After renal biopsy of IgG4-related tubulointerstitial nephritis, the patient was finally diagnosed with IgG4-related nephropathy combined with TB, and we followed up the clinical treatment effect.

Keywords: IgG4 related disease; Tuberculosis infection; Biopsy; Glucocorticoid

Introduction

IgG4 related diseases are characterized by a significant increase in serum IgG4 levels and can involve multiple organs, which are often enlarged or nodular and sclerotic due to massive lymphocyte and IgG4-positive plasma cell infiltration with fibrosis [1-4]. The diseases occur mostly in middle-aged and elderly men with a male to female ratio of 2-3:1. Due to the short time of recognition of the disease, no specific incidence has been reported, and an incidence of 2.8/100,000 to 10.8/100,000 has been reported in Japan [5], while epidemiological data are still lacking in China. Clinical data on the effectiveness of treatment and prognosis of the disease are lacking.

Case Presentation

A 69-year-old man was admitted to hospital on June 29th, 2021 because of abnormal renal function. The patient underwent routine physical examination 2 weeks before admission and was found to have abnormal renal function with a blood creatinine of 521 mol/L and urine protein 2+, which was re-examined at a local hospital. The patient had no previous history of hypertension and diabetes mellitus but had undergone internal fixation of left clavicle fracture 7 years ago. The family history was not specific either. The patient's physical examination showed the following: blood pressure 140/70 mmHg, clear consciousness, normal development, good nutrition, no cardiopulmonary abnormalities, soft abdomen, no pressure and rebound pain, and normal muscle strength and tone of the extremities.

Laboratory test results

Hematology results: Hemoglobin was 76 g/L. Urinalysis showed urine protein 1+; 24-h urine protein quantification, 1.96 g/day; renal osmolality, 225 mOsm (freezing point method). Blood biochemistry was as follows: Creatinine, 627 mol/L; uric acid, 441 mol/L; albumin, 30.1 g/L; globulin, 66.7 g/L; blood amylase, 134 U/L (elevated); hematocrit, 120 mm/h. Immune-related tests: Antinuclear antibody: Nuclear granule type 1:320 positive; anti-phospholipase A2 receptor: 1:10 negative; IgG5, 4.6 g/L (elevated); IgG4, 29.6 g/L; complement C3 0.46 g/L (decreased); complement C4, 0.08 g/L; blood light chain lambda, 1,930 mg/dL (increased); blood light chain kappa, 4070 mg/dL (elevated); Coombs test, positive; HLB27, negative. Myocardial markers, and thyroid function, transfusion series, and antineutrophil cytoplasmic antibody were normal. Immunofixation electrophoresis did not show any obvious monoclonal bands. T-cell spotting assay for Tuberculosis (TB) was reactive. Interferon release assay was positive.

Examination results

Ultrasonography was as follows: Right kidney size, 142 mm × 79 mm × 70 mm; left kidney

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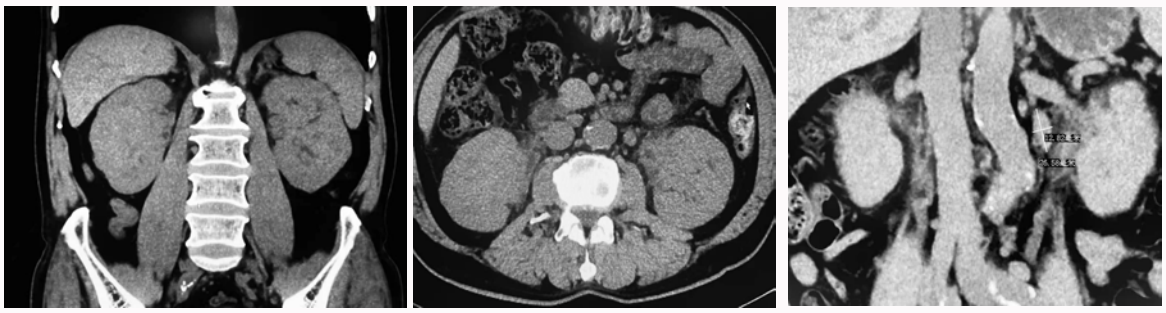

Figure 1: Abdominal CT scan of the patient. CT showed both kidneys enlarged, soft tissue shadow of both renal pelvises, multiple lymph nodes in the hilar region, retroperitoneum, and bilateral groin.

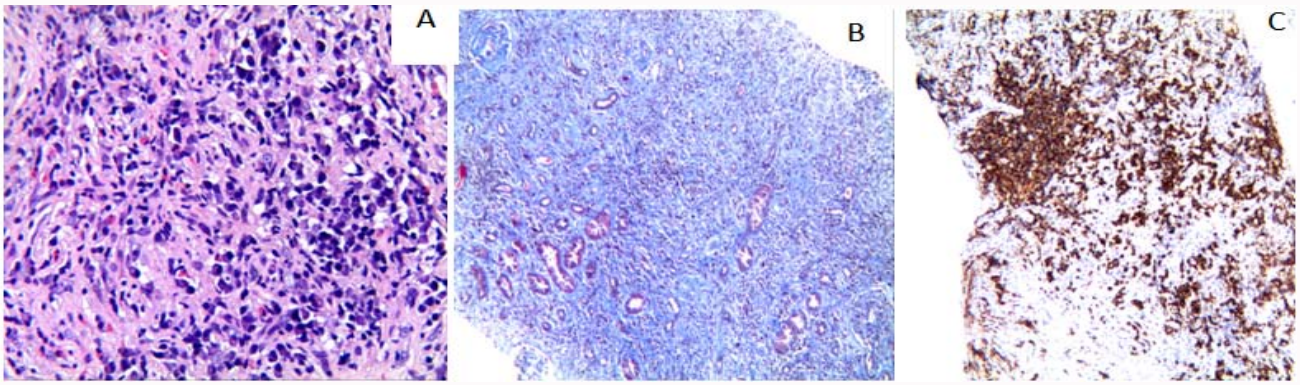

Figure 2: Kidney pathology of the patient. A) PAS staining showed a large number of plasma cell infiltrates in the renal interstitium. B) Masson staining of the renal interstitium revealed matted fibrosis-like changes. C) Immunohistochemical staining showed a large number of IgG4-positive plasma cells.

size, 143 mm × 72 mm × 73 mm; right renal collecting system was separated by 13 mm; left renal collecting system was separated by 10 mm. The bilateral axillary lymph nodes were enlarged, 216 mm hypoechoic on the right side and 2010 mm hypoechoic on the left side, with neat margins and regular shape and general posterior echogenicity. Cardiac ultrasound results were as follows: Ventricular septal thickening, small amount of pericardial effusion. The electrocardiogram was normal. Computed Tomography (CT) showed whole abdomen, both kidneys enlarged, soft tissue shadow of both renal pelvises, and bilateral ureters mildly dilated (Figure 1).

There were multiple lymph nodes in the hilar region, retroperitoneum, and bilateral groin. Cystic foci were found in the liver, complex cysts in both kidneys, and enlarged prostate with calcification were observed. Chest findings showed limited emphysema in the right lung, bronchial dilatation in the lower lobe of the right lung, and focal fibrous sclerosis in both lungs. Enlarged cardiac shadow with pericardial effusion was noted. Calcification of aorta and coronary arteries were also observed. Multiple old rib fractures on both sides, as seen after internal fixation of the left clavicle were noted. Both axillary and mediastinal lymph nodes showed cystic foci in the right lobe of the liver, and large complex cysts in the right kidney. Positron emission tomography-CT results were: (1) both kidneys were enlarged with uneven density and diffusely increased Fluorodeoxyglucose (FDG) metabolism, considering possible inflammation of both kidneys and lymphoma to be excluded. (2) Increased FDG metabolism of prostate lamina, considering inflammation of prostate was observed. (3) Large 2.3 cm diameter lymph nodes in bilateral submandibular, axillary, hilar, mediastinal, retroperitoneal, pelvic and inguinal lymph nodes with increased FDG metabolism, considering the possibility of inflammatory hyperplastic lymph nodes were found. (4) Right middle lobe soft tissue shadow with increased FDG metabolism, considering right middle lobe inflammation; right upper lung alveoli, both middle and lower lungs, and chronic interstitial inflammation under the pleura were noted. (5) A small cyst in the right posterior lobe of the liver was noted. (6) Cervical and lumbar vertebral marginal osteophytes were seen after left internal clavicle fixation.

Renal pathology light microscopy results were as follows: The glomerular lesion was mild, the interstitium was infiltrated by diffuse single nucleated cells and multifocal plasma cells, and matted fibrosis was seen, accounting for 70% of the total area. The walls of small renal vessels were thickened with hyaline degeneration. Immunohistochemistry showed IgG4-positive plasma cells >10/field at high magnification, and immunofluorescence staining for C3c (+) (Figure 2).

The treatment regimen was 24 mg methylprednisolone tablets given orally, and the dose was gradually reduced after 4 weeks. At the same time, isoniazid at 0.3g qd and rifampicin 0.6g qd were given for anti-TB treatment, and supportive treatment such as stomach protection and calcium supplementation were given.

Follow-up of clinical indicators

At present, we have followed the patient for nearly 6 months, and all the indicators have improved. The 24 h urine protein quantification has decreased significantly, while plasma albumin has increased to normal levels. After treatment, renal function recovered well, and blood creatinine decreased from the highest value of 627 mol/L to 179 mol/L. The hemoglobin level also increased significantly,

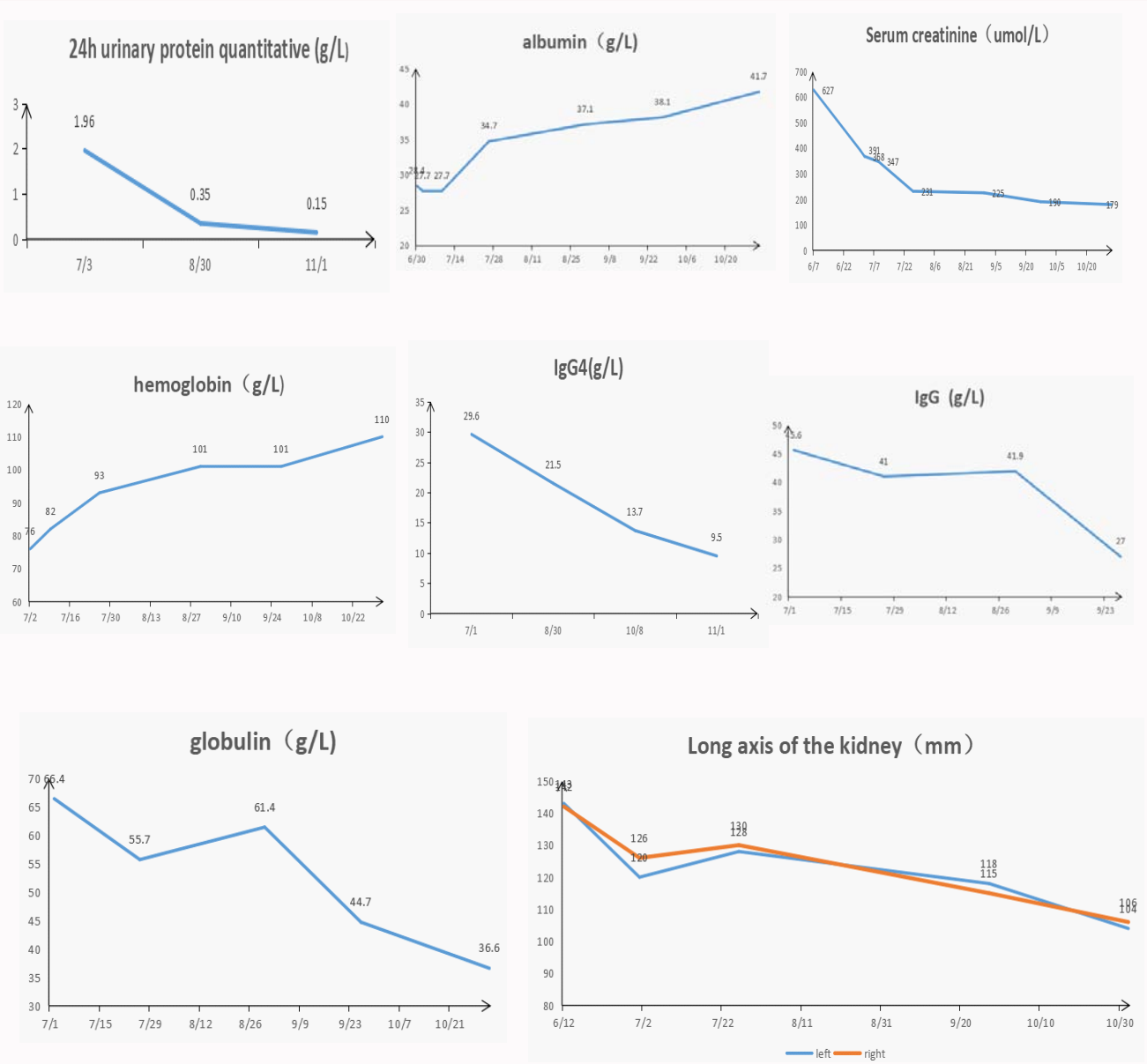

Figure 3: Trend of clinical indicators after the patient was treated. After glucocorticoid treatment, urinary protein decreased significantly, plasma albumin increased, blood creatinine level gradually decreased, and the long axis of the enlarged kidney was significantly reduced. Hemoglobin increased significantly, plasma globulin decreased, and blood IgG and IgG4 both decreased significantly).

globulin level decreased significantly, and IgG and IgG4 decreased significantly. Repeat ultrasound showed that the enlarged kidney had recovered (Figure 3).

Discussion

In 2003, Kamisawa et al. [1] first introduced the concept of IgG4 systemic disease and suggested that it was closely associated with IgG4-positive plasma cells. In 2010, Takahashi et al. [6] officially named such lesions as IgG4-associated diseases. It is now considered that the diseases are immune-mediated fibroinflammatory diseases that can accumulate in multiple organs [7-9]. The common types of presentation are: (1) type 1 (IgG4-associated) Autoimmune Pancreatitis (AIP); (2) IgG4-associated sclerosing cholangitis, which usually occurs in conjunction with type 1 AIP; (3) massive salivary gland enlargement or sclerosing salpingitis, accompanied by lacrimal gland, parotid gland and submandibular gland enlargement; (4) IgG4-associated Mikulicz orbital disease, often with protrusion of the eyeball; and (5) retroperitoneal fibrosis, often with chronic periaortitis, usually involving the ureters, leading to hydronephrosis and renal injury.

The affected organs share a number of key pathological features and prominent clinical and serological similarities, including: swelling of the affected organs, massive infiltration of IgG4-positive plasma cells, and characteristic matted fibrotic changes of varying degrees on histological examination [10-12].

The exact prevalence of IgG4-related diseases is currently unknown. This may be related to the late recognition of the diseases by the medical community. The first international expert consensus on the treatment of the diseases was not available until 2015. The disease was first proposed by Japanese experts, so it is more studied in Japan than in other countries. However, the current epidemiological

research data are mainly from the Japanese AIP data. A 2012 study In Japan showed that about 8,000 people suffered from this disease, which is about 6.27 per 100,000 [5]. Currently, no exact data are available for China. Small clinical samples have been reported subsequently. Raissian et al. [13] studied 35 patients with this disease, with a mean renal creatinine of 309.4 μmol/L before treatment and a mean reduction to 150.3 μmol/L after 6 months of drug treatment, giving a total effective rate of 90.5%. Nineteen of these 35 patients were treated with glucocorticoids and 17 showed effectiveness, but two of them relapsed during hormone reduction. Kawano et al. [14] reported that 38 of 41 patients were treated with hormones, 35 of whom showed effective results, while only three had insignificant results and continued progression of renal function. Of these three cases, one patient reached end-stage renal disease and required long-term maintenance hemodialysis, and the other two showed persistent elevation of blood creatinine. In a study by Saeki et al. [15], 19 of 23 patients were treated with prednisone at doses ranging from 10 mg/day to 60 mg/day, and 18 of them showed significant improvement in renal function, complement levels, and imaging abnormalities after 4 weeks of dosing. All these studies suggest that early diagnosis and treatment with glucocorticoids are effective, but there is a possibility of recurrence during the process of hormone reduction.

According to the 2011 Japanese Society of Nephrology IgG4-RKD diagnostic criteria and the 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-related disease [16], the features of the present patient's medical history include the following: (1) Significantly elevated serum IgG4 levels; (2) renal damage with urinary protein and decreased renal function; (3) renal CT showing bilateral renal enlargement and hypertrophic soft tissue shadow of both renal pelvises; and (4) renal biopsy histological changes-interstitial nephritis changes, such as high infiltration of lymphoplasmacytes, IgG4-positive plasma cells >10/field of view at high magnification, and fibrotic changes.

Therefore, the diagnosis of IgG4-associated nephropathy in our patient was clear. The patient was given 24 mg methylprednisolone orally according to the treatment guidelines. Because the patient had two positive T-SPOT tests with high titers, and although the patient had no TB-related symptoms and no significant abnormalities were seen on chest CT, the possibility of latent TB infection could not be ruled-out, so we also gave him anti-TB treatment. The patient was given isoniazid 0.3 gqd, rifampicin 0.6 gqd [The dosage units are missing.] and received symptomatic supportive treatment. After discharge, the patient was followed up in the outpatient clinic. After treatment, the patient showed a significant reduction in urinary protein, a significant decrease in serum creatinine level, improvement in anemia, and a significant increase in hemoglobin. Immunological indexes such as IgG and IgG4 were significantly decreased, and ultrasound showed that the enlarged kidney was significantly improved. The glucocorticoid dose is being gradually reduced and the chest CT did not show any TB-related infection. The patient is still being followed up [17,18].

Conclusion

In conclusion, IgG4-related diseases have progressive fibrotic lesions that involve multiple organs and tissues throughout the body. Early diagnosis and treatment are important for prognosis. Early application of glucocorticoid therapy can significantly improve the condition of IgG4-related disease, improve the quality of life of patients and delay their progression to end-stage renal failure. We will further follow up the development and treatment efficacy of this case to accumulate experience for clinical diagnosis and treatment of IgG4-related diseases.

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