Immunoglobulin G4 related tubulointerstitial nephritis

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ABSTRACT

Tubulointerstitial nephritis is an uncommon manifestation of IgG4 related disease. A case of tubulointerstitial nephritis with special features including isolated renal involvement in this multisystem disorder and the absence of response to steroid therapy in a young male is reported here. There was no nephromegaly, eosinophilia or other organ involvement. The importance of early detection and treatment for preservation of kidney function is highlighted.

Key words: Immunoglobulin G4 related disease, isolated renal involvement, tubulointerstitial nephritis

Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a recently recognized multisystem disorder characterized by a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, storiform fibrosis, tumor-like lesions and in most cases (approximately 70%) elevated serum IgG4 concentrations.[1] Renal involvement is seen in about 15% cases, with tubulointerstitial nephritis (TIN) being the most frequent. We describe a case of IgG4-related TIN in a young male presenting with renal dysfunction.

Case Report

A 42 years male was evalauted for azotemia. He was found to be diabetic 4 years ago on a routine evaluation. He was initially treated with an oral hypoglycemic agent for 2 years and thereafter was on diet control. Serum creatinine was 0.9 mg/dl 2 years ago. On routine check in 4 months prior to presentation, serum creatinine was found to be 4.7 mg/dl. He had been having mild loin pain on both sides for the preceding 1 month and low backache on and off for the past 1 year. Proteinuria was detected 2 months ago. There was no hypertension, hematuria or diabetic retinopathy. He was a tobacco chewer and consumed analgesics occasionally.

On physical examination, blood pressure was 110/80 mmHg. Systemic examination was normal and in particular, no abnormality was found in the salivary and lacrimal glands and there was no lymphadenopathy or organomegaly. There was no edema.

Urinalysis showed trace proteinuria, pH of 6.0, specific gravity of 1.010, 2–4 white blood cells and 4–6 red blood cells per high power field (hpf). 24 h urine protein excretion was 734 mg. Blood urea was 60 mg/dl and serum creatinine 4.9 mg/dl. Other blood tests were: Sodium 143 mEq/L, potassium 3.7 mEq/L, chloride 105 mEq/L, calcium 8.6 mg/dl, inorganic phosphorus 3.5 mg/dl, protein 7.7 g/dl, albumin 4.0 g/dl, uric acid 6.4 mg/dl, alanine amino transferase 18 U/L, alkaline phosphatase 95 U/L, glucose (random) 107 mg/dl, hemoglobin 14.7 g/dl, WBC count 4290/cubic mm (differential count of neutrophils: 57%, lymphocytes: 32%, eosinophils: 3% and monocytes: 8%), platelet count 125,000/mm^3. Antinuclear antibody, antidouble stranded DNA antibody and antiproteinase-3 antibody were negative.

Ultrasonography showed normal sized kidneys with mild increase in cortical echogenicity. There was no dilatation of the pelvicalyceal system. Other organs were normal and there was no lymphadenopathy.

Renal biopsy showed one glomerulus with mild increase of mesangial cellularity and congested capillaries. The glomerular basement membrane was thin. There was diffuse

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interstitial infiltration of lymphocytes and plasma cells along with a large number of eosinophils [Figures 1 and 2]. Focal lymphoid follicle formation was seen. There was much fibrosis with tubular effacement. Trichrome stain showed abundant collagen with focal storiform fibrosis in the interstitium. Immunofluorescence showed no significant deposits. The histopathologic impression was chronic TIN with moderate eosinophilia. This morphology was suspicious of an IgG4 related disorder.

Immunohistochemistry revealed many IgG-positive (168/hpf) plasma cells [Figure 3] with significant number of IgG4-stain positive (60/hpf) plasma cells, representing 36% of the total number of plasma cells [Figure 4]. Serum total IgG was 26 g/L (normal range 6.6–16.9 g/L), and IgG4 level was 8.14 g/L (normal range 0.03–2.0 g/L). No further tests were done.

He was started on prednisolone 40 mg daily. Steroid therapy resulted in worsening of hyperglycemia. Subsequently, dose of prednisolone was tapered by 10 mg every week to a dose of 10 mg daily. Blood glucose was controlled with oral hypoglycemic agent and the last serum creatinine on 13th September was 3.7 mg/dl, when mycophenolate mofetil was added in a dose of 500 mg 2 times daily, as a steroid sparing agent. Further information on this patient is lacking as he was lost to follow-up.

Discussion

Immunoglobulin G4-RD was first described in 2001.[2] The availability of a test to detect specific plasma cells enabled to identify this disease as a separate entity. It had earlier been diagnosed as autoimmune pancreatitis when it involved the pancreas. As different organ involvement with similar histologic features were reported, IgG4-RD was recognized to include entity like idiopathic retroperitoneal fibrosis.[3] Commonest sites of involvement other than pancreas include hepatobiliary tract, salivary gland, orbit and lymph node. Rarely,

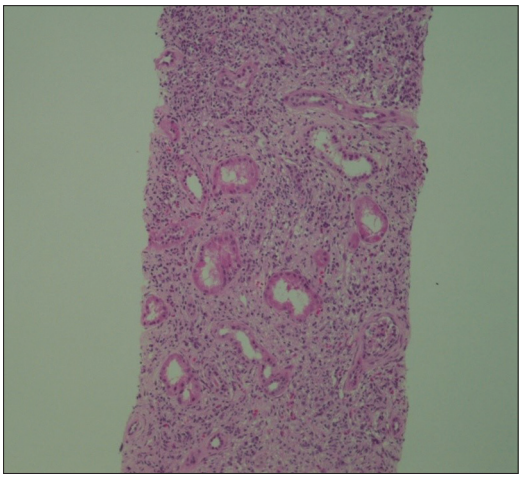

Figure 1: Renal biopsy histopathology under low power magnification

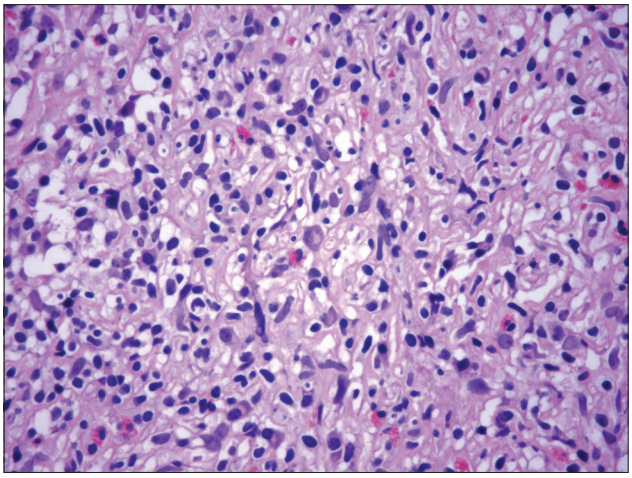

Figure 2: Renal histopathology under high power magnification with interstitial plasma cells, lymphocytes, eosinophils and storiform fibrosis

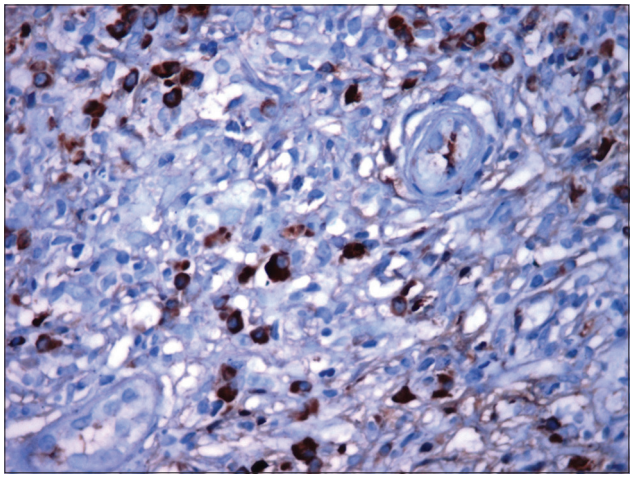

Figure 3: Immunoglobulin G stain positive plasma cells in the interstitium

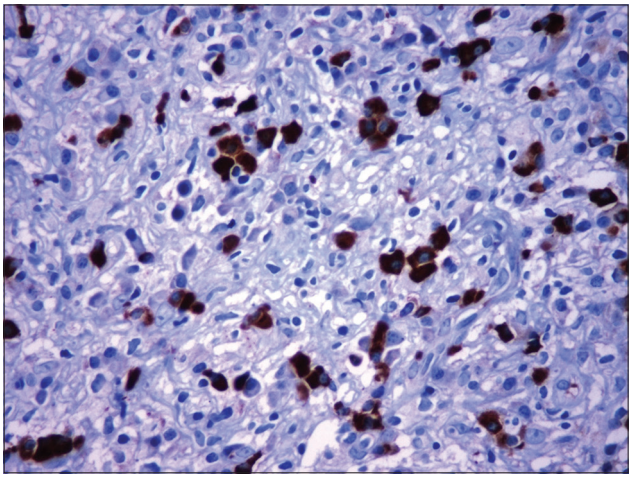

Figure 4: Many immunoglobulin G4 stain positive plasma cells

associated glomerular diseases such as membranous nephropathy, mesangioproliferative glomerulonephritis and focal segmental endocapillary proliferation have been described in IgG4-RD.[4,5] Hydronephrosis secondary to retroperitoneal fibrosis that may represent extra-renal extension of the fibro inflammatory pathology. Rarely, patients show multiple tumor like low density areas on imaging, so called inflammatory pseudotumor.

The etiopathogenesis of IgG4-RD is poorly understood. Several mechanisms such as autoimmunity, innate immunity and allergy have been proposed, but the specific role of IgG4 in the pathogenesis of IgG4-RD remains unclear. The proposed pathogenetic mechanisms, specific pathways and various clinical manifestations are discussed elsewhere.[6]

Glucocorticoid is the first line of therapy. Despite the presence of interstitial fibrosis, there is response to glucocorticoid, which may represent steroid responsiveness of these fibrotic lesions or the patchy nature of inflammatory lesions.[7] However, severe fibrosis leads to organ atrophy. Azathioprine, methotrexate and mycophenolate mofetil are used as steroid-sparing drugs.[8] Rituximab therapy can be used in recurrent or refractory disease.[9]

We have described a case of TIN in a young male who presented with insidious onset of azotemia. The cause of severe azotemia was unclear on clinical evaluation. Renal biopsy showed features of TIN, which was suspicious of IgG4-RD. The confirmation of IgG4-related TIN was made by histochemical staining for IgG4-secreting plasma cells on the renal biopsy. He was treated initially with steroid, following which his renal function showed stabilization and marginal improvement. He developed steroid-related complications necessitating introduction of mycophenolate mofetil for steroid-sparing effect.

Our case highlights the difficulty in diagnosing IgG4-related TIN. Most (70%) of the patients of IgG4-RD and in patients with TIN to the order of 90%[7] have elevated plasma levels of IgG4. The histological features consistent with IgG4-RD are dense lymphocytoplasmacytic tissue infiltrates, storiform fibrosis, obliterative phlebitis and less frequently mild tissue infiltrates. Histological features may differ between different organs, and phlebitis is uncommon on renal biopsy in IgG4-related TIN. Immunohistochemical staining to confirm the presence of IgG4 stained plasma cells is essential for the diagnosis of IgG4-RD, but the mere detection of these cells is not diagnostic of IgG4-RD.[6] The histochemical diagnostic criteria for diagnosis of IgG4-related TIN are (1) number of IgG4 + cells of >10/hpf and (2) the IgG4+/IgG+ ratio of >40%. Our patient had elevated plasma concentration of IgG4 and fulfilled histological and histochemical criteria for IgG4-related TIN. Several others have reported cases of IgG4-related TIN from India.[10-13] It is possible that IgG4-related TIN is underdiagnosed in our country due to the lack of available facilities for histochemical staining.

There were several special findings in our patient as described below. One, the vast majority of patients with IgG4-related TIN are older than 50 years of age and our patient was younger, at 42 years. Although, this disease has been reported in younger patients.[10,12]

Two, our case appeared to have isolated renal involvement in this generally multisystem disorder. He did not have lymphadenopathy, features to suggest involvement of pancreas, salivary glands, retroperitoneum in the form of fibrosis, lymph nodes or orbital involvement. However, we could not definitively exclude the subtle involvement of other organs as we did not perform contrast-enhanced computer tomography (CT) due to significant azotemia. Isolated renal involvement has been reported previously,[12,14] which could be forme fruste presentation in the evolution of this disease over time. Three, he had neither peripheral eosinophilia (seen in about 40%)[15] or nephromegaly (by ultrasonography but CT scan documentation of nephromegaly was not done), which could suggest advanced stage of the disease or hyperechoic areas in the kidney on imaging, which are common findings in IgG4-related TIN. Four, steroid therapy is associated with significant improvement in the recovery of renal function and the effect is seen even when much fibrosis is evident on histology. However, delayed therapy may have less favorable impact on the outcome. Our patient appears to have presented late in the course and it may be a reason for the partial improvement in renal function. This highlights the necessity of early diagnosis in this disease.

Conclusion

Immunoglobulin G4-RD is a recently recognized disease entity with multisystem involvement. TIN in IgG4-RD is uncommon and often unrecognized due to lack of availability of histochemical staining and lack of awareness of this disease among clinicians. Early diagnosis and steroid therapy are critical for a favorable outcome and delay in diagnosis as seen in our case may result in incomplete recovery.

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