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Clinical Report

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Recognizing isolated IgG4-related nephropathy

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Abstract
IgG4-related tubulointerstitial nephritis is an uncommon cause of renal impairment. It has been associated with dysfunction in a number of other organs giving rise to the term IgG4-related systemic disease; organ involvement can occur metachronously, hence, making it more difficult to identify patients. The exact cause of this condition remains unknown. Here, we present a case of isolated renal involvement which demonstrates how particular biochemical, radiological and histopathological changes should raise the suspicion of IgG4-related nephropathy, especially when there is an absence of clues from any other organ.

Keywords: IgG4-related systemic disease; isolated renal involvement; tubulointerstitial nephritis

Introduction

IgG4-related disease is a relatively new term coined to encompass a little known condition of unknown aetiology, characterized by multi-organ tissue infiltration by IgG4+ plasma cells [1]. The first affected organ identified was the pancreas [2], but it is now increasingly apparent that a variety of organs may be affected, including the salivary glands, retroperitoneum, aorta, thyroid, lungs, kidneys, lymph nodes, periorbital tissue, skin, pericardium, breast, prostate and thyroid glands [3].

The case below demonstrates the importance of recognizing the biochemical, radiological and histological features representative of renal IgG4 disease, when there is no obvious extra-renal involvement.

Case report

A 29-year-old man of Indian extraction, born and raised in London, initially presented to physicians in Beijing where he had been teaching art for the past 18 months. Whilst his complaints of sinusitis, lethargy and wheeze were being investigated, he was found to be hypertensive with a creatinine level of 262 µmol/L, an active urinary sediment and a protein creatinine ratio of 237 mg/mmol. There was no notable past medical history and no regular medication use. His hepatitis B, C and HIV status were all negative and his chest radiograph was normal. Immunology revealed a positive PR3 with normal ANF, complements and a negative anti-GBM titre. His renal ultrasound scan (USS) demonstrated a 9.1 cm right kidney and an 11.7 cm left kidney with multiple hyper-reflective foci in the renal cortices. He proceeded to have a renal biopsy in China which was reported to contain 20 glomeruli, of which 11 were sclerosed. There was focal segmental increase in the mesangial matrix and cellularity, with diffuse tubular atrophy, interstitial fibrosis and inflammatory cell infiltration. Electron microscopy (EM) was not performed. The nasal polyp biopsy showed only non-specific inflammatory changes. A diagnosis of chronic tubulointerstital nephritis (TIN) with glomerular sclerosis was made and the patient was prescribed losartan 50 mg od and amlodipine 5 mg od.

After 3 months, the patient returned to the UK and presented himself to a nephrologist. His creatinine was stable at 248 µmol/L with a normal full blood count, lipid profile, coagulation screen, fasting glucose and electrolytes. His urinary protein excretion at this time was 0.35 g/24 h. His total immunoglobulin levels showed an IgG of 22.18 g/L (8.0–18.0 g/L) but normal IgA and IgM levels. Another USS again revealed irregular renal outlines with focal hyper-reflective areas (Figure 1).

The lobulated renal outlines raised the suspicion of a possible infiltrative or infective process and a magnetic resonance imaging (MRI) scan was arranged. This showed areas of high T2 signal change throughout the parenchyma, conforming to lobular boundaries with some sparing of the lobules and with no other abdominal abnormalities. A micro-bubble contrast USS demonstrated uniform enhancement throughout the cortical medullary areas without evidence of abnormal washout and with symmetrical cortical perfusion. The irregular outline was, therefore, thought secondary to long standing fibrosis or scarring and the patient returned to China.

The patient presented again 4 months later, asymptomatic but with an increased creatinine level of 310 µmol/L, which prompted a repeat biopsy. This contained eight glomeruli showing only minor ischaemic changes. In the interstitium, there was extensive storiform fibrosis with a mixed chronic inflammatory infiltrate containing

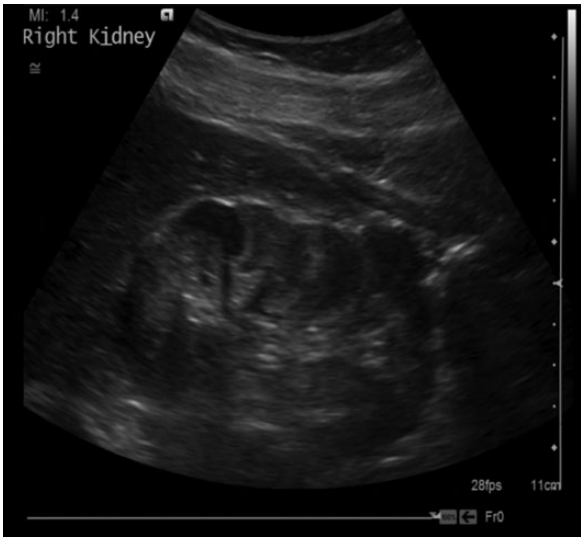

Fig. 1. A 9.7 cm Right kidney with focal hyper-reflective areas scattered patchily throughout the cortex, possibly demonstrating some mass effect. This has resulted in an irregular renal outline with a solid rather than a cystic appearance.

prominent plasma cells and scattered eosinophils. The majority of the plasma cells stained for IgG4 on immunohistochemical staining. EM showed small electron dense deposits on tubular basement membranes.

The patient's immunoglobulin subclasses were measured at this point and showed a markedly elevated total IgG4 subclass only, at 19.8 g/L (0.8–1.4 g/L). He was, therefore, diagnosed with IgG4-related TIN and treatment with 40 mg of oral prednisolone was initiated (Figure 2).

Discussion

The initial suspicion of IgG4-related renal disease may arise following the finding of an active urinary sediment, radiological abnormalities or reduced renal function and this may then prompt a renal biopsy. An accurate diagnosis is very important as this disease is often acutely sensitive to steroids [4]; however, there is not always a sustained response and there have been reports of rituximab being used for refractory disease [5].

Most case reports of renal involvement in IgG4-related disease are from Asia and in 2011, the All Japan IgG4

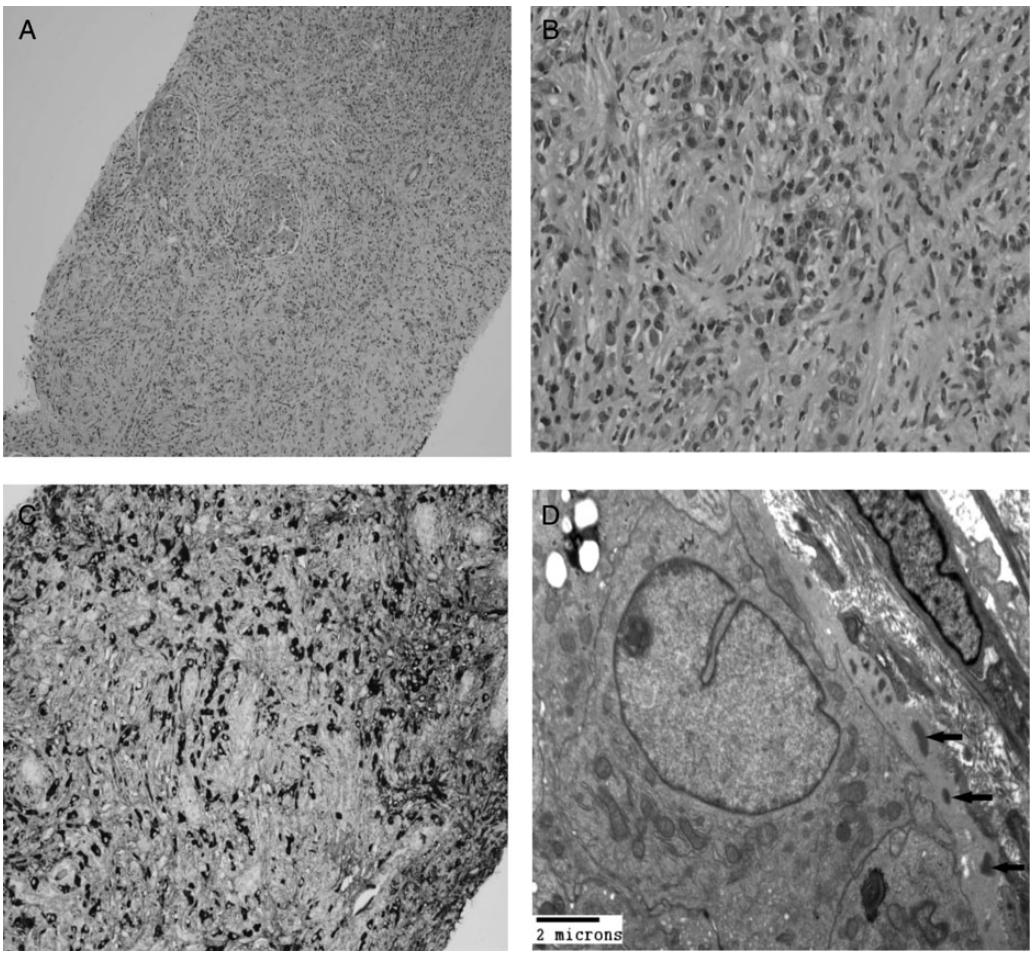

Fig. 2. Kidney biopsy. (**A**) A low power view shows two congested but otherwise normal glomeruli. There is extensive tubular atrophy with storiform interstitial fibrosis and a chronic inflammatory infiltrate (H&E). (**B**) At higher power, the interstitial infiltrate is seen to contain many plasma cells and scattered eosinophils (H&E). (**C**) Immunohistochemistry demonstrates that most of the plasma cells contain IgG4 (immunoperoxidase stain for IgG4). (**D**) EM shows electron dense deposits within a tubular basement membrane (arrows) consistent with immune complex deposition (×8000).

team proposed a set of organ-specific diagnostic criteria to aid recognition of this syndrome [6]. Although IgG4 levels are deemed neither necessary nor sufficient to secure a diagnosis, elevated levels are useful as a serological disease marker [1, 6].

The radiological findings on USS and MRI, described in our case report, are typical of renal involvement. Nunokawa *et al*. have coined the term 'Renal Rim Sign' to describe the peri-renal soft tissue rim found on computed tomography contrast studies which they say reflects the plasma cells, lymphocytes and fibrosis found on histopathological examination of the interstitium [7]. The characteristic renal biopsy appearances were well illustrated by this case with an interstitial infiltrate containing IgG4+ plasma cells and the presence of immune complexes on tubular basement membranes. In some cases, membranous nephropathy is also seen [8].

Our patient requires long-term follow-up, not only to monitor for extra-renal involvement but also to ensure a sustained response to steroid treatment, largely guided by changes in creatinine. Whether or not changing IgG4 levels can aid prognosis or determine treatment strength or duration remains unknown. After 2 months of a reducing steroid regimen, the patient now has a creatinine level of 233 µmol/L.

Conflict of interest statement. None declared.

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