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Teaching Point
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Nephrotic syndrome in Kimura's disease: apropos a case of the glomerular tip lesion in an African-Caribbean male

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Introduction

Kimura's disease is characterized by benign subcutaneous masses located in the head and neck region, often accompanied by regional lymphadenopathy and salivary gland involvement. It is a rare disease that predominantly occurs in young Asian males. Histological analysis shows follicular hyperplasia with eosinophilic infiltration; blood examination usually reveals eosinophilia and elevated concentrations of immunoglobulin E (IgE). The aetiology is still unclear; autoimmune diseases, chronic infections and delayed hypersensitivity reactions are considered as possible causes. Renal involvement including nephrotic syndrome is common [1].

We report an African-Caribbean male who developed nephrotic syndrome due to glomerular tip lesions following uncomplicated surgery for a relapsing left-sided mandibular tumour that was diagnosed as Kimura's disease.

Case report

In 2006, a 56-year-old African-Caribbean male was admitted to our local hospital on Curacao for surgical exploration of a relapsing left-sided submandibular tumour. His medical history was remarkable for relapsing tumours in the head and neck region. The first operation was performed in 1970 when a tumour located below the angle of his right jaw was removed. At that time, no pathological diagnosis was established; Ziehl–Neelsen stain for tuberculosis was negative. He used cocaine intermittently and did not appear for outpatient control. In 2002, he returned with a left-sided elliptic tumour, which had been growing slowly for years. Embolization of a suspected lymphohaemangioma of the neck was performed after angiography. In 2006, he returned again with a relapse on the other side and wanted it removed for cosmetic reasons. On preoperative examination, he had a left-sided, non-tender submandibular tumour of ~10 × 7 × 3 cm that was not fixated to subcutaneous layers or epidermis. The blood pressure was 110/90 mmHg. His creatinine was 100 μmol/L, and dipstick urinalysis showed 2+ proteinuria. The tumour could only be removed partially from the submandibular/submental region, and a partial parotidectomy was performed as well. Microscopic examination revealed marked hyperplasia of germinal centres with interstitial fibrosis (Figure 1A), and extensive infiltration by eosinophils resulting in the formation of eosinophilic abscesses (Figure 1B). Hyalinized vessels were also seen (Figure 1A, insert). These findings are compatible with Kimura's disease (Figure 1).

Three weeks after surgery, he was readmitted to hospital with a nephrotic syndrome. Since discharge, he had been suffering from progressive oedema of the lower limbs without cardiopulmonary complaints. Physical examination revealed a blood pressure of 140/90 mmHg, ascites and extensive pitting oedema of the lower limbs. Laboratory examination showed a creatinine of 299 μmol/L, urea of 49 mmol/L and albumin of 12 g/L; total cholesterol was 16 mmol/L, high-density lipoprotein (HDL) cholesterol 2.1 mmol/L, low-density lipoprotein (LDL) cholesterol 5.6 mmol/L and triglycerides 1.88 mmol/L. His blood showed a marked eosinophilia of 15% (leucocyte count 5.1 × 109/L) and an IgE titre exceeding 3000 IU/mL (normal <300). There was proteinuria of 6.1 g/24 h. Renal ultrasound was unremarkable with normal-sized kidneys. Anti-nuclear factor and anti-double-stranded DNA as well as serology and polymerase chain reaction for human immunodeficiency virus (HIV) remained negative. The

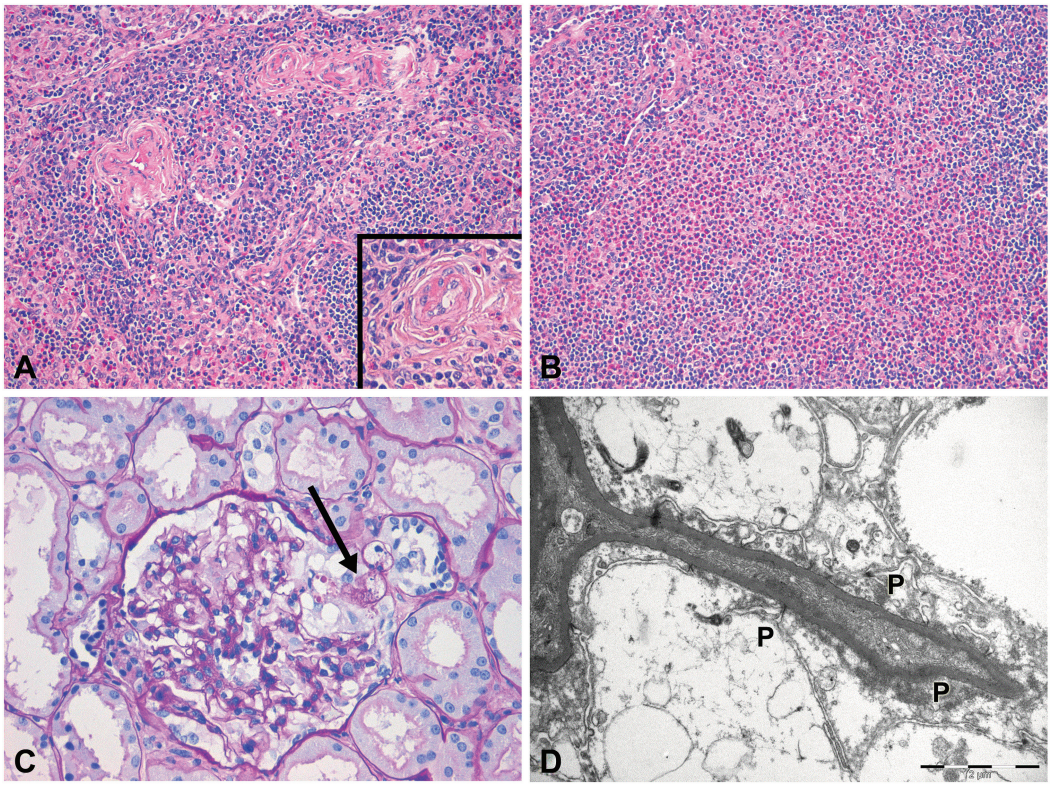

Fig. 1. (**A**). Representative histological picture of the partial parotidectomy showing follicular hyperplasia, interstitial fibrosis and hyalinized vessels (insert, ×40) (H&E staining, magnification ×10). (**B**). Extensive infiltration by eosinophils resulting in the formation of eosinophilic abscesses (H&E staining, magnification ×10). (**C**). One glomerulus showing typical focal and segmental glomerulosclerosis 'tip variant' with foamy macrophage (arrow) (PAS–diastase staining, magnification ×20). (**D**). Electron microscopy showing swelling and effacement of the podocytes (P).

electrocardiogram was normal. Chest X-ray showed a slightly enlarged heart but no signs of pleural effusion. Light microscopy of a kidney biopsy revealed focal segmental glomerulosclerosis (FSGS) with classic 'tip lesion' in 3 out of 10 glomeruli (Figure 1C). Immunofluorescent immunostaining for IgG, IgA, IgM, kappa and lambda light chains, C3c, and C1q showed only non-specific background staining compatible with heavy proteinuria. Electron microscopy showed diffuse effacement and reactive changes of podocytes (Figure 1D).

The patient was treated successfully with high doses of furosemide and prednisone 1 mg/kg and lost 11 kg of fluid. After one-half year of follow-up, he remained in remission with a serum creatinine of 90 μmol/L.

Discussion

Cases of Kimura's disease have been reported sporadically in non-Asian patients with clinical presentations that do not differ significantly from the Asian population. In the largest case series from the USA, 21 cases of Kimura's disease were described with six subjects being of African descent, but unfortunately, no renal involvement was documented [2]. We are not aware of other cases with FSGS in patients with African or Caribbean ancestry and active Kimura's disease.

Kimura's disease is frequently associated with renal involvement. Proteinuria and nephrotic syndrome are the most common presentations of renal involvement in Kimura's disease. Proteinuria is present in 12–16% of patients with Kimura's disease. If present, it leads to nephrotic syndrome in 59–78% of these cases [3,4]. Occasionally, nephrotic syndrome occurs years before diagnosis of Kimura's disease is established.

Various renal pathologies have been associated with Kimura's disease. Membranous glomerulopathy is the most common finding, but mesangial proliferative glomerulonephritis, minimal change disease and IgA-nephropathy have been reported as well [4,5]. FSGS associated with Kimura's disease has only been reported six times previously in the literature, but none of them was of African ancestry [6,7]. FSGS is more common in patients of African ancestry, but the tip lesion as was found in our patient is not typical. Recently, a case of FSGS, albeit a perihilar lesion, related to Kimura's disease was described in a Caucasian male. In this report, an association with B-cell autoreactivity was suggested because of the presence of immune thrombocytopaenia and elevated antinuclear antibodies [8].

However, the precise pathophysiology of proteinuria associated with Kimura's disease is still unknown. Patients with Kimura's disease seem to exhibit a T-helper-2 (Th2) response including up-regulated interleukin (IL)-4, IL-5, IL-13 and IFN-gamma levels, as well as marked eosinophilia and IgE levels [9,10], similar to patients with idiopathic nephrotic syndrome, in particular minimal change disease [11]. T-helper-2 cytokines may have direct effects on podocytes leading to proteinuria [12]. Another explan-

ation might be that the elevated Th2 response may stimulate B-cell differentiation, thereby contributing to autoantibody formation.

Within the spectrum of minimal change disease to focal segmental glomerulosclerosis, the glomerular tip lesion behaves very similar to minimal change disease and often responds well to steroid therapy [13,14]. Kimura's disease is a chronic disorder, with an indolent clinical course. Most cases of Kimura's disease have been treated successfully with corticosteroids. Therapy with cyclosporine or azathioprine may also result in remission [7]. Nevertheless, recurrent relapses and therapy-resistant nephrotic syndrome leading to end-stage renal disease may occur [5]. In one case report, Kimura's disease occurred after renal allograft failure in association with chronic rejection, and a possible relationship with a T-helper-2 dominant immune, casu quo humoral response was discussed as well [15]. It remains purely speculative whether anti-CD20 (e.g. rituximab) or IL-5 antagonist (e.g. mepolizumab) treatment is helpful in relapsing Kimura's disease.

Thus far, only case reports and case series have been published. Well-designed studies on the importance of specific immune therapy in Kimura's disease are hampered by the extremely low prevalence of this disease. Development of an international registry may help to obtain more knowledge about this disease.

Teaching points

(1) Kimura disease occasionally occurs in non-Asian populations.

(2) Nephrotic syndrome is a frequently occurring complication of Kimura's disease.

(3) Glomerular tip lesions tend to behave similarly to minimal change disease and often respond well to steroid treatment.

(4) Patients with Kimura's disease often exhibit an elevated T-helper-2 profile, not unlike other patients with idiopathic nephrotic syndrome.

Conflict of interest statement. None declared.

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