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Exceptional Case

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Monoclonal gammopathy of renal significance presenting with cryoglobulinaemia type I–associated severe thrombotic microangiopathy

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ABSTRACT

We report a 53-year-old man who presented with acute renal failure. His medical history revealed a spondyloarthropathy, for which secukinumab was started recently, and a monoclonal gammopathy of unknown significance. Kidney function deteriorated despite the withdrawal of secukinumab and dialysis was started. In the serum, type 1 cryoglobulins were present and a kidney biopsy showed ischaemic glomeruli, with thrombosis of the larger interlobular arteries. Other causes of thrombotic microangiopathy were excluded. Bone marrow immunophenotyping showed 1% monoclonal plasma cells. A diagnosis of monoclonal gammopathy of renal significance was made. Haematological treatment resulted in haematological and renal response.

Keywords: acute renal failure, cryoglobulinaemia, monoclonal gammopathy of renal significance, thrombotic microangiopathy

INTRODUCTION

Cryoglobulinaemia is defined by the presence in serum of immunoglobulins that precipitate with cold temperature and dissolve with rewarming. Kidney involvement occurs in 20–30% of patients with cryoglobulin-associated systemic disease and usually presents with proteinuria or acute kidney injury [1, 2]. Histologically, the most frequent pattern of injury (occurring in >95% of patients) is membranoproliferative glomerulonephritis. In a few patients, kidney biopsy shows a thrombotic microangiopathy (TMA) picture, with thrombi in the glomerular capillaries, in electron microscopy (EM) characterized by the subendothelial deposition of fluffy material [2–4].

We report a patient with cryoglobulinaemia type I, who presented with acute kidney injury, caused by thrombi in the larger intrarenal arteries, in the absence of glomerular abnormalities.

CASE REPORT

A 53-year-old male patient presented with acute renal failure. His detailed medical history is given in the Supplementary data, online Appendix. In brief, the patient was known for 5 years with a monoclonal gammopathy of unknown

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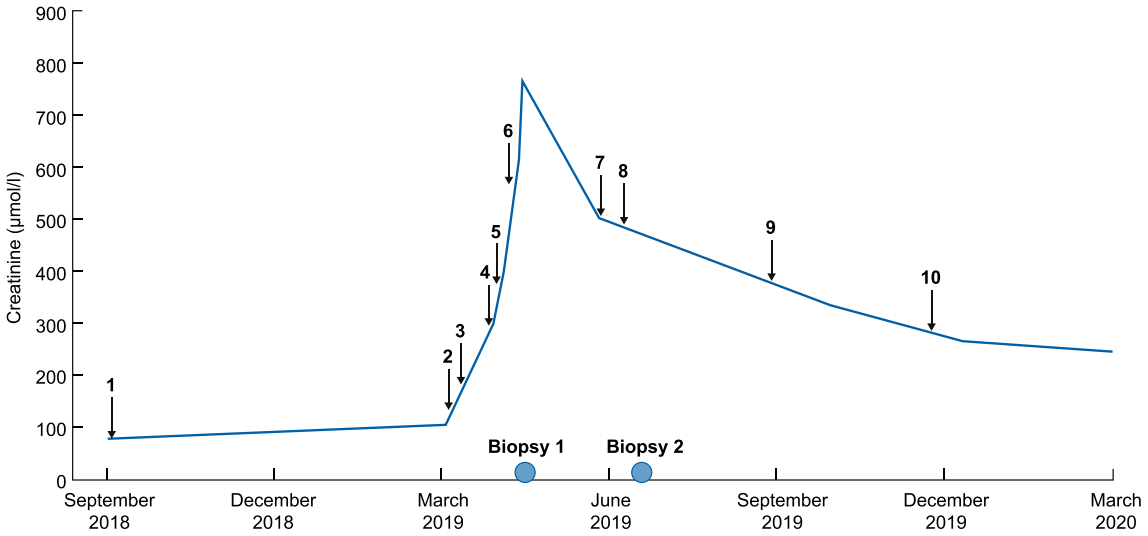

FIGURE 1: A course of serum creatinine. 1. Chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) and, previous use of methotrexate, etanercept and leflunomide. 2. Start secukinumab. 3. Stop NSAIDs and secukinumab. 4. Start methylprednisolone (3 times). 5. Start haemodialysis and start plasmapheresis (7 times). 6. Start bortezomib and dexamethasone (3 cycles). 7. Stop haemodialysis. 8. In partial remission, added cyclophosphamide to bortezomib dexamethasone (3 cycles). 9. Very good partial response. 10. Autologous stem cell transplantation.

Table 1. Results of laboratory tests and imaging studies at diagnosis

Laboratory test	Result	Normal range
Haemoglobin (g/dL)	9.4	13.5–17.4
Thrombocytes (10^9/L)	143	150–400
Erythrocyte sedimentation rate (mm/h)	25	<15
Lactate dehydrogenase (U/L)	297	<250
Haptoglobin (g/L)	0.66	0.3–1.6
C3 (mg/L)	1199	700–1500
C4 (mg/L)	91	100–400
CH50 (%)	16	67–149
C1q (IE/mL)	61	81–128
IgG lambda M-protein (g/L)	7.9 g/l	–
Bence jones (urine)	Not present	–
Free light chain lambda (mg/L)	91.3	5.7–26.3
Free light chain kappa (mg/L)	36.7	3.3–19.4
Cryoglobulins type 1 (g/L)	2.5	–
Antinuclear antibodies	Negative	–
Anti-neutrophil cytoplasmic antibody	Negative	–
IgG anti-β2 glycoprotein (U/mL)	<7	<10
IgG anti-cardiolipin (U/mL)	<10	<40
IgM anti-cardiolipin (U/mL)	<10	<40
Anti-glomerular basement membrane antibody	Negative	–
Lupus anticoagulant (LAC)	Negative	–
Hepatitis C	Negative	–
ADAMTS13 (%)	80	>50
Ultrasound abdomen	Normal-sized kidneys	
Echocardiogram	No cardiac hypertrophy	
PET-CT scan	No abnormalities	

significance (MGUS), stable immunoglobulin G (IgG) lambda concentration of ∼5 g/L and spondyloarthropathy. His anti-rheumatic therapy was changed and secukinumab was added (Supplementary data). Laboratory tests at that time showed a slightly increased creatinine (Figure 1). After 2 weeks, a further increase was noted, necessitating hospital admission. The patient presented a 4-month history of general fatigue, mild dyspnoea and cough and loss of appetite and weight (4 kg). There was no fever or night sweats and no skin or joint complaints. Physical examination revealed hypertension (blood pressure of 190/110 mmHg). There was no oedema or cardiac murmur. There were no skin or joint abnormalities.

Relevant laboratory findings and results of medical imaging are presented in Table 1. Kidney function deteriorated

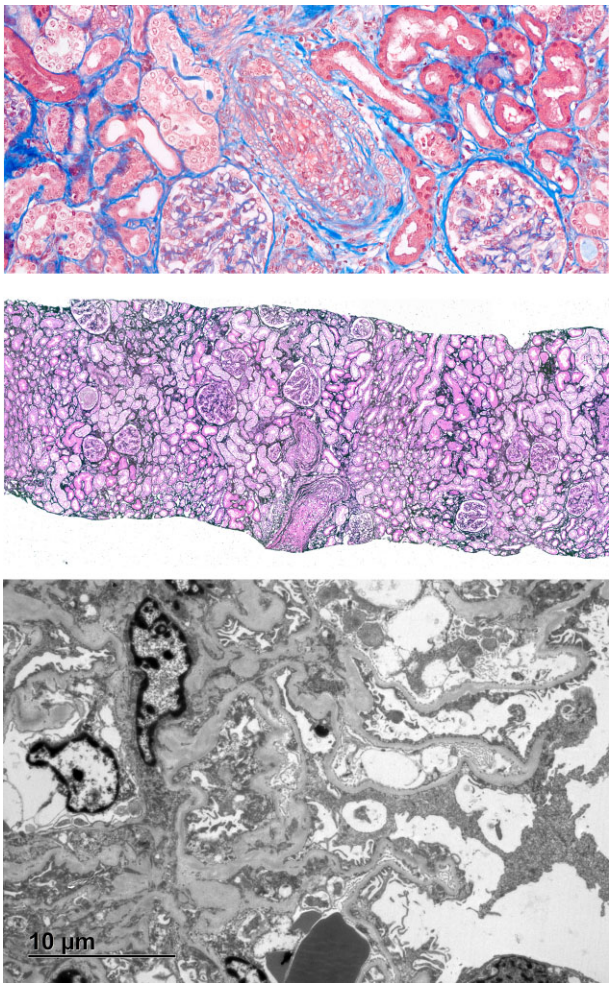

FIGURE 2: Biopsy at diagnosis. Light microscopy showed overall well-preserved renal architecture without significant interstitial fibrosis/tubular atrophy. There were no glomerular abnormalities and also small vessels were unremarkable (no glomerular or arteriolar thrombi). Interlobular arteries frequently showed severely narrowed and sometimes occluded lumens due to intimal thickening/intimal proliferation. Occasionally, luminal fibrin thrombi with nuclear debris were present. True necrotizing changes of the vessel wall were not seen and the pattern of injury was therefore considered most consistent with thrombotic micro-angiopathy rather than vasculitis. There was tubulopathy, probably due to ischaemia. EM showed glomerular ischaemia but no signs of endothelial injury and no deposits. IF microscopy (not shown) was negative for IgG, kappa, lambda and C3.

despite the withdrawal of secukinumab and dialysis was started (Figure 1). A kidney biopsy was performed, showing thrombi in the larger renal arteries, in the absence of glomerular abnormalities (details in Figure 2). No cause of the thrombosis was found after a thorough diagnostic workup (Table 1). Therefore a presumptive diagnosis of large vessel TMA due to monoclonal IgG type I cryoglobulinaemia was made. Haematological evaluation revealed a mild plasmacytosis in the bone marrow biopsy, plasma cells were monoclonal and there was lambda light chain restriction. Directed by the presence of cryoglobulins, initial treatment consisted of methylprednisolone and plasmapheresis after haematological evaluation, followed by clone-directed treatment with bortezomib and dexamethasone. After three cycles this treatment was intensified with cyclophosphamide in view of ongoing TMA in a second biopsy (details in the Supplementary data). Thereafter, a haematologic very good partial response was reached after a total of six treatment cycles. Kidney function improved (Figure 1). The patient received consolidation therapy with high-dose melphalan and autologous stem cell transplantation and achieved complete haematological remission. At the last follow-up, renal function was stable (Figure 1).

DISCUSSION

Our patient presented with acute kidney injury attributed to glomerular hypoperfusion due to thrombotic obstruction of the intrarenal arteries. Our case is notable since there was no evidence of glomerular involvement; specifically, there were no double contours and both immunofluorescence (IF) and EM were unremarkable. Other causes of TMA were excluded. We considered the role of secukinumab highly unlikely (detailed clinical course provided in the Supplementary data).

In the serum cryoglobulins, type I was present and we consider this the likely cause of the kidney injury. Admittedly we cannot exclude that the TMA was caused by the mere presence of a monoclonal Ig and independent of the cryo-activity. An association between an M-protein and TMA has been suggested and possible mechanisms have been discussed (details in the Supplementary data). In the absence of a haematological malignancy, this patient thus presented a rare variant of monoclonal gammopathy of renal significance. The favourable response to clone-directed therapy supports the role of the monoclonal Ig. Our case report suggests that an M-protein can contribute to TMA, with mere manifestations in the larger arteries. The role of cryoglobulins deserves further study. Importantly, the presence of thrombi in the arteries, in the absence of glomerular injury, negative IF and EM should lead to a search for a monoclonal Ig and testing for cryoglobulins.

SUPPLEMENTARY DATA

Supplementary data is available at *CKJ* online.

PATIENT CONSENT

The patient gave informed consent to publish this case.

CONFLICT OF INTEREST STATEMENT

The results presented in this article have not been published previously in whole or part.

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