EXCEPTIONAL CASE

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
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.

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 (IgE/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 |

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

**REFERENCES**

1. Beddhu S, Bastacky S, Johnson JP. The clinical and morphologic spectrum of renal cryoglobulinemia. *Medicine (Baltimore)* 2002; 81: 398–409
2. Herzenberg AM, Telford JJ, De Luca LG et al. Thrombotic microangiopathy associated with cryoglobulinemic membranoproliferative glomerulonephritis and hepatitis C. *Am J Kidney Dis* 1998; 31: 521–526
3. Sethi S, Rajkumar SV, D’Agati VD. The complexity and heterogeneity of monoclonal immunoglobulin-associated renal diseases. *J Am Soc Nephrol* 2018; 29: 1810–1823
4. Amaador K, Peeters H, Minnema MC et al. Monoclonal gammapathy of renal significance (MGRS) histopathologic classification, diagnostic workup, and therapeutic options. *Neth J Med* 2019; 77: 243–254
5. AACR Project GENIE Consortium. AACR project GENIE: powering precision medicine through an international consortium. *Cancer Discov* 2017; 7: 818–831
6. Alchi B, Jayne D. Membranoproliferative glomerulonephritis. Pediatr Nephrol 2010; 25: 1409–1418
7. Okazaki M, Yaomura T, Tsuboi T et al. A case of acute renal failure of multiple myeloma due to monoclonal type I cryoglobulinemia with thrombotic microangiopathy. CEN Case Rep 2015; 4: 174–179
8. Ravindran A, Go RS, Fervenza FC et al. Thrombotic microangiopathy associated with monoclonal gammopathy. Kidney Int 2017; 91: 691–698
9. Néel A, Perrin F, Decaux O et al. Long-term outcome of monoclonal (type 1) cryoglobulinemia. Am J Hematol 2014; 89: 156–161
10. Terrier B, Karras A, Kahn JE et al. The spectrum of type 1 cryoglobulinemia vasculitis: new insights based on 64 cases. Medicine (Baltimore) 2013; 92: 61–68
11. Harel S, Mohr M, Jahn I et al. Clinico-biological characteristics and treatment of type 1 monoclonal cryoglobulinaemia: a study of 64 cases. Br J Haematol 2015; 168: 671–678
12. Sidana S, Rajkumar SV, Dispenzieri A et al. Clinical presentation and outcomes of patients with type 1 monoclonal cryoglobulinemia. Am J Hematol 2017; 92: 668–673
13. Jokiranta TS, Solomon A, Pangburn MK et al. Nephritogenic lambda light chain dimer: a unique human miniautoantibody against complement factor H. J Immunol 1999; 163: 4590–4596
14. Meri S, Koistinen V, Miettinen A et al. Activation of the alternative pathway of complement by monoclonal lambda light chains in membranoproliferative glomerulonephritis. J Exp Med 1992; 175: 939–950