CASE REPORT

A case of acute renal failure of multiple myeloma due to monoclonal type I cryoglobulinemia with thrombotic microangiopathy

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Abstract The term cryoglobulinemia (CG) is used to refer to vasculitis due to so-called mixed cryoglobulins containing immune complexes. Although most cases of monoclonal CG, called type I CG, are asymptomatic, purpura, skin ulcers, and renal failure develop in some cases. Hematological disorders are the underlying diseases in most cases, on which the therapeutic strategies available and the prognosis of patients depends. We here report a case of a 47-year-old man who had pain in both his ankles, with palpable purpura and epistaxis, and presented with acute renal failure. Monoclonal immunoglobulin (Ig) G- κ protein was detected and cryoglobulin was also positive. Renal biopsy revealed emboli with a fibrillar structure in the glomeruli and renal tubule lumina. The complication of thrombotic microangiopathy (TMA) occurred during the course. Therefore, plasma exchange and hemodialysis were added to methylprednisolone pulse therapy. The treatment was successful, dissipating the purpura. However, the purpura relapsed and renal dysfunction progressed when

the administration of oral steroids was tapered. Bone marrow biopsy was performed again, which indicated an increase in abnormal plasma cells. The patient was finally diagnosed as multiple myeloma. Then, bortezomib-dexamethasone therapy was initiated. This is the first case of type I CG with monoclonal IgG complicated by TMA during the course; it provides insight into the pathogenesis of renal dysfunction associated with type I CG.

Keywords Cryoglobulinemia · Acute renal failure · Monoclonal gammopathy of undetermined significance · Multiple myeloma · Thrombotic microangiopathy

Introduction

The precipitation of blood proteins at temperatures lower than 37 °C is referred to as cryoglobulin. Cryoglobulinemia (CG) is characterized by conditions such as palpable purpura, arthritis, and glomerulonephritis. Type I CG consisting of monoclonal immunoglobulin is often asymptomatic, but sometimes produces signs related to thrombosis, such as Raynaud's phenomenon, livedo reticularis, purpura, skin ulcers, and neurologic symptoms without evidence of vasculitis. Most patients have hematological diseases, including Waldenström's macroglobulinemia, monoclonal gammopathy of undetermined significance (MGUS), and multiple myeloma, as underlying diseases. Thus, the prognosis of patients and therapeutic strategies available largely depend on the underlying diseases [1]. Types II and III CG consist of mixed immunoglobulins, which form immune complexes when they contain cryoglobulins with rheumatoid factor activity, and cause cryoglobulinemic vasculitis, such as palpable purpura, arthralgia, and myalgia. Mixed CG generally results from chronic inflammatory states, including

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connective tissue diseases, and viral infections, such as hepatitis C virus (HCV).

Renal lesions associated with essential cryoglobulinemia, including mixed cryoglobulinemia, have been pathologically characterized by membranoproliferative glomerulonephritis (MPGN) [2, 3]. However, in terms of renal lesions in type I CG, few large-scale studies have been conducted [1, 4]. Electron microscopic images of CG are characterized by fine fibers arranged in parallel and various forms, such as fingerprint and microtubule structures.

Acute renal failure (ARF) of cryoglobulinemia arises mainly with mixed CG (types II and III CG) associated with hepatitis C. Another case of infection-triggered ARF with mixed CG has been presented [5]. However, ARF in type I CG is a rare entity [6, 7] and, furthermore, ARF with thrombotic microangiopathy (TMA) (excluding the drug-induced type and anti-phospholipid antibody syndrome) has not yet been described.

Case report

The patient was a 47-year-old Japanese male without any past or family history. He had pain in both his ankles with palpable purpura and epistaxis, and was admitted to our hospital. He had an intermittent fever of 38 °C approximately 1 month prior to his admission.

On admission, his height and body weight were 173 cm and 69.4 kg. His blood pressure was 141/90 mmHg and body temperature was 36.5 °C. Palpable purpura was found on both ankles. Laboratory test results were as follows: serum creatinine (Cre), 1.82 mg/dL (normal range 0.6–1.1 mg/dL); serum urea nitrogen (UN), 18 mg/dL (normal range 8–22 mg/dL); sodium, 140 mEq/L (normal range 138–146 mEq/L); potassium, 4.0 mEq/L (normal range 3.6–4.9 mEq/L); chloride, 104 mEq/L (normal range 99–109 mEq/L); calcium, 9.0 mg/dL (normal range 8.7–10.3 mg/dL); phosphate, 2.7 mg/dL (normal range 2.5–4.7 mg/dL); total protein, 8.2 g/dL (normal range 6.6–8.3 g/dL); serum albumin, 3.3 g/dL (normal range 3.8–4.8 g/dL); serum IgG, 2893 mg/dL (normal range 870–1700 mg/dL); serum IgA, 210 mg/dL (normal range 110–410 mg/dL); serum IgM, 47 mg/dL (normal range 33–190 mg/dL); C3, 146 mg/dL (normal range 55–120 mg/dL); C4, 11 mg/dL (normal range 20–55 mg/dL); and CH50, 65 U/mL (normal range 35–45 U/mL). Other laboratory data were as follows: leukocyte count, 8100/μL (normal range 3500–8500/μL); erythrocyte count, $388 \times 10^4/\mu\text{L}$ (normal range $430\text{--}570 \times 10^4/\mu\text{L}$); hemoglobin, 13.1 g/dL (normal range 13.5–17.0 g/dL); and platelet count, $25.3 \times 10^4/\mu\text{L}$ (normal range $15\text{--}35 \times 10^4/\mu\text{L}$). Urinalysis showed proteinuria of 0.28 g/day and 10–19 red blood cells per high-power field. Urinary β-2 microglobulins (β-2MG) and *N*-acetyl-β-D-

glucosaminidase (NAG) were 515 μg/L (normal range 0–150 μg/L) and 29.6 U/L (normal range 0–11 U/L), respectively. Cryoglobulins were positive, and serum and urine immunoelectrophoresis showed the presence of monoclonal IgG-κ. Bence-Jones protein was also positive in the urine. Skin (lower leg purpura) and nasal septum biopsies revealed thrombi in the lumina of the small blood vessels. Bone marrow aspirate clot showed 3 % plasma cells (light chain κ-positive and λ-negative). No significant accumulation was detected by PET-CT in the bones or lymph nodes throughout the body. The diagnostic criteria of multiple myeloma were not met; therefore, the patient was diagnosed with MGUS.

Renal biopsy was performed on day 6 when the Cre was 4.55 mg/dL (Fig. 1) and exhibited an extensive number of glomerular capillary thrombi along with tubular casts. Twenty glomeruli were detected on light microscopy. Of these, global sclerosis was found in two glomeruli and segmental thrombi in six glomeruli. Endocapillary proliferation and mesangiolysis were identified in some of the remaining glomeruli. The renal tubule lumen was partially filled with needle-like structures, and in the interstitium, there were moderate fibrotic changes. Needle-like and granular structures in the renal tubule lumen were stained deep red with Masson trichrome stain. Immunohistochemistry results showed that IgG and IgA were positive in the glomerular capillary thrombi, and that IgM was weakly positive in the periphery of thrombi (Fig. 2). As for light chain, κ light chain was positive in the glomeruli and tubules, but λ was negative (Fig. 3). Electron microscopy displayed a massive fibrillar structure 60 nm in size mainly occupying the glomerular lumen, which was partially invaginated into the endothelial basement membrane (Fig. 4).

Initially, the patient was thought to have vasculitis on admission. Treatment was started with oral prednisolone (PSL) (70 mg/day). However, renal function rapidly deteriorated (Cre 9.5 mg/dL and UN 104 mg/dL). Therefore, on day 9, hemodialysis was started. Furthermore, on day 19, hemoglobin was decreased to 8.7 g/dL, lactate dehydrogenase (LDH) rose from 166 to 312 IU/L (normal range 119–229 IU/L) and haptoglobin dropped to 0 mg/dL, accompanied by thrombocytopenia (platelet count, $6.3 \times 10^4/\mu\text{L}$). Red cell fragmentation was seen on peripheral blood smear. These findings were complicated by TMA. All the listed data, including lowering of the activity of a disintegrin-like and metalloprotease with thrombospondin type 1 motifs 13 (ADAMTS13), anti-phospholipid antibody, direct and indirect Coombs test, and coagulation test related to disseminated intravascular coagulation (DIC) were negative. Plasma exchange (a total of five times) was added to the 3-day methylprednisolone (mPSL) pulse (1 g/day) therapy, which produced a rapid

Fig. 1 Light microscopic images (**a, b** Periodic acid-Schiff stain, $\times 400$; **c, d** Masson trichrome stain, $\times 400$). Unstructured embolus-like substances lacking cellular components were observed in the glomerular capillary (arrows in **a, c**). Neither mesangial matrix

expansion nor mesangial proliferation was observed. No crescent was formed. A needle-like structure strongly stained with Masson trichrome stain occupied the renal tubular lumen (arrows in **d**)

response. Hemodialysis was subsequently discontinued on day 30. Purpura on the lower leg disappeared and his renal function improved (Cre 1.7 mg/dL); he was then discharged from the hospital. However, 2 months later, when PSL was reduced to 12.5 mg/day, Cre deteriorated (4.8 mg/dL) and lower leg purpura and epistaxis relapsed. The patient was readmitted. Laboratory investigation on the second admission yielded the following results: Cre, 4.8 mg/dL; UN, 54 mg/dL; calcium, 9.5 mg/dL; phosphate, 4.2 mg/dL; serum IgG, 2643 mg/dL; serum IgA, 72 mg/dL; and serum IgM, 39 mg/dL. Other laboratory data were as follows: leukocyte count, $12,000/\mu\text{L}$; erythrocyte count, $343 \times 10^4/\mu\text{L}$; hemoglobin, 10.7 g/dL; and platelet count, $19.7 \times 10^4/\mu\text{L}$. Urinalysis showed proteinuria of 30 mg/dL and 20–29 red blood cells per high-power field. Urinary β -2MG and NAG were 429 $\mu\text{g/L}$ and 9.7 U/L, respectively. Bone marrow biopsy revealed the novel symptom of an increase of abnormal plasma cells. The patient was diagnosed with multiple myeloma. Four cycles of bortezomib-dexamethasone therapy were conducted, which improved his serum creatinine from 5.8 to 1.8 mg/dL without side effects.

Discussion

We encountered a case of ARF with lower leg purpura and pain in both ankles. Monoclonal IgG- κ was detected in the blood and urine of this patient, and he tested positive for cryoglobulin. Although clonal analysis of cryoglobulins unfortunately could not be performed because of insufficient samples, both the clinical course and the subsequent pathological findings consistently indicated type I CG.

Many patients with detectable type I CG are asymptomatic. A previous study of 64 cases of type I CG pointed out that skin symptoms were the most common (55 cases; 86 %), followed by purpura (44 cases; 69 %) and peripheral neuropathy (28 cases; 44 %). Renal failure was less common than expected (19 cases; 30 %) compared with types II and III CG. Of 19 cases of renal involvement, 18 were MPGN, the most pathological characteristic of type I CG [1]. In general, patients with MPGN have substantial proteinuria, occasionally reaching the nephrotic range, and the renal insufficiency progresses relatively slowly for years. However, in the present case, the patient had mild proteinuria (1 g/day or less) during the course and

Fig. 2 Immunohistochemistry images **a** IgG, $\times 400$; **b** IgA, $\times 400$; **c** IgM, $\times 400$). The thrombi were strongly reactive with IgG, moderately with IgA, and mildly with IgM

remained non-oliguric; nevertheless, he fell into ARF, which required hemodialysis.

ARF in CG sometimes occurs in mixed CG and seldom in monoclonal CG. As for ARF in type I CG, a few cases of both Waldenström's macroglobulinemia and angioimmunoblastic T cell lymphoma containing monoclonal IgM cryoglobulin have been documented [6, 7]. Moreover, it is well known that monoclonal IgM in Waldenström's macroglobulinemia per se causes thrombosis, even if cryoglobulin is negative [8]. However, CG in multiple myeloma due to monoclonal IgG is recognized to be uncommon and moreover ARF in CG of multiple myeloma is even rarer [4]. Thus, our case is extremely unusual, especially in regard to the type of cryoglobulin. The patient described here did not have monoclonal IgM, but IgG cryoglobulin, which has less aggregation capacity than IgM. Another case of ARF with glomerular capillary light chain thrombi has been reported previously [9].

Renal biopsy demonstrated thrombi in the glomerular and renal arteriole lumina, with only mild mesangial proliferation and the absence of crescent formation. These findings of embolization were the same as those from pathological biopsies of the nasal mucosa and lower leg

purpura. In immunohistochemical staining, at first, we obtained only negative results for glomerular staining with IgG, IgA, IgM, C3, C4, κ and λ light chain in immunofluorescence. Because the disease was distributed focally, thrombus might not have been included in the fresh cryosection of immunofluorescence. Instead, we performed immunoenzyme staining using an epon-embedded specimen; in this case, the thrombi were reactive for not only IgG but also others (IgA and IgM), although monoclonal IgG was detected in this patient. In terms of light chains, positive staining of κ light chain and negative staining of λ light chain proved the monoclonality. It has been observed in previous studies that multiple immunoglobulins showed positive staining even if a patient had monoclonal immunoglobulin [6, 8]. The authors assumed that the reasons why other immunoglobulins stained positive in thrombi might be either the trapping of immunoglobulins and complement or local immune activation [8]. Electron microscopic images showed needle-formed crystals approximately 60 nm in width in the glomerulus, which corresponded to the diameter of previously reported cryoglobulins [10, 11]. The needle-like structures that occupied renal tubules were stained with κ light chain called Bence-

Fig. 3 Immunohistochemistry images (**a, c** κ light chain, $\times 400$; **b, d** λ light chain, $\times 400$). In the glomerular and renal tubule lumina, thrombi were stained with κ light chain, but not with λ light chain

Fig. 4 Electron microscopic images (**a** $\times 3,000$; **b** $\times 20,000$). A large amount of fine fibrous dense matter occupied the glomerular lumen (arrows in **a**). This dense matter contained a cylinder-like structure of approximately 60 nm in width (**b**)

Jones protein. Although the needle-like structures did not fully morphologically accord with the cast nephropathy in which glassy, fracturing casts exist, the tubular damage

considerably affected renal failure. Hypercalcemia, which occasionally causes ARF in multiple myeloma, did not exist in this case in all periods. On day 6, we performed

renal biopsy. After that, the renal insufficiency continued to worsen during a very short period, and then we postulated that more thrombi might have formed after the renal biopsy. ARF was thought to be attributable to nephropathy with a combination of glomerular thrombosis and tubular injury, as opposed to nephritis with glomerular inflammation.

Furthermore, after the development of ARF, anemia along with thrombocytopenia and decreased haptoglobin resulted in TMA. TMA is a feature of a number of clinical disorders including hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), malignant hypertension, systemic lupus erythematosus (SLE), pregnancy, and renal transplantation [12]. To the best of our knowledge, type I monoclonal CG accompanying TMA has never been reported. Only two reports exist concerning mixed CG, in which CG and TMA occurred concurrently [13, 14]. In both cases, patients had massive proteinuria and renal biopsies revealed typical MPGN. The authors assumed the participation of anti-phospholipid or other HCV-associated antibodies, or of heat-insoluble cryoglobulinemia, in generating TMA. Our case was characterized pathologically by thrombosis with faint inflammation, and was apparently different from typical MPGN seen in mixed CG. Thus, we speculate that the TMA in our case did not have an immunological or inflammatory cause, but was instead due to a mechanical or physical factor secondary to severe embolisms, like malignant hypertension. As the patient underwent both mPSL pulse therapy and plasma exchange at almost the same time, it was unclear which therapy was more effective. In cases of TTP, plasma exchange is useful because it can remove unusually large von Willebrand factor multimer (UL-VWFM), inflammatory cytokines, autoantibodies of ADAMTS13 and also replenish ADAMTS13 and normal VWFM. In the present case, ADAMTS13 activity was normal at 85 %. We considered that, upon using PSL as an anti-inflammatory approach, plasma exchange could control the activity of disease effectively, mainly by direct removal of CG. The precise reason why TMA developed in our patient but not in others was unclear, but one possibility was the property of clonality of CG, which provides fulminant symptoms under special circumstances. The accumulation of more cases is necessary to understand the pathogenesis of this rare ARF accompanying TMA in type I CG.

In summary, we encountered a case of ARF due to embolism in type I CG followed by TMA. Pathologically, fibrillar structures were deposited in the glomerular and renal tubule lumina. Plasma cell dyscrasia as an underlying disease was initially MGUS, and was finally diagnosed as

multiple myeloma. Renal failure recovered reversibly by bortezomib-dexamethasone therapy. Type I cryoglobulinemia patients rarely exhibit ARF. Therapeutic strategies for the underlying diseases, particularly hematological disorders, are important.

Conflict of interest The authors declare that no conflict of interest exists.

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