

57-year-old woman with purpura fulminans and acute kidney injury

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CLINICAL PRESENTATION

A 57-year-old woman was admitted to Peking University First Hospital with a fever (temperature 38.5°C), and a 5-month history of a systemic purpura-like rash. Four days before admission, the rash worsened after exposure to cold weather for around 4 hours during a trip and involved the skin on her feet, ankles to thighs, buttocks and face (figure 1A–C). She had suffered from repeated but progressive ankle pain and fatigue over the previous 2 years. The initial laboratory investigations showed IgG 18.5 g/L (normal 7.23–16.85) and erythrocyte sedimentation rate (ESR) 41 mm/hour (0–19). The white blood cell count was $10.97 \times 10^9/L$ (normal 3.5–9.5), haemoglobin was 115 g/L (115–140), platelets were $258 \times 10^9/L$ (100–350). The urine albumin-to-creatinine ratio was 414.22 mg/g (<30) and urinary red cell count was 56.9 per high-power field. Serum creatinine (SCr) increased from 37.1 to 155 $\mu\text{mol/L}$ (44–133) the day following hospitalisation, and progressed to above 700 $\mu\text{mol/L}$. Human leucocyte antigen B27, rheumatoid factor and cyclic citrullinated peptide were negative. There was no evidence of coagulation disorder: prothrombin time, activated partial thromboplastin time and Di-Dimer were normal.

FURTHER INVESTIGATIONS

Immunofixation electrophoresis showed monoclonal IgG λ chains in serum and urine (figure 2). Free light chain was measured by immunoturbidimetry (Binding Site kit, Beckman Coulter Unicel DxC 800 automatic analyzer), and the serum free κ chain was 16.4 mg/L (6.29–135) while free λ chain was 357.5 mg/L (313–723), with a $\kappa:\lambda$ free light chain ratio of 0.0158 (0.26–1.65). Cryoglobulin was detected in the blood, following the specific steps of detection recommended in the literature.¹ The cryoprecipitate was further identified as monoclonal IgG λ . Head and pelvis X-rays showed no abnormalities. A bone marrow biopsy showed 5% immature plasma cells, with 2% monoclonal λ light chain restricted plasma cell proliferative disorder with fluorescence in situ hybridisation. Hepatitis B virus antigen and hepatitis C virus antibody were negative. The patient developed repeated symptoms of heart failure and thrombocytopenia to a minimum of $16 \times 10^9/L$. The lactate dehydrogenase concentration was 396 IU/L (110–240, LD-L assay). However, the haemoglobin remained at 110 g/L. Only 0.1% broken erythrocytes were found in a peripheral blood smear. Concentrations of C3, C4 and ADAMTS13 were normal.

Prior to thrombocytopenia, the patient underwent a skin biopsy and a kidney biopsy. The results showed diffuse thrombi formation of dermis microvessels, with a heterogenous substrate containing needle-like crystals plugging the lumen, and a few neutrophils and mononuclear cells infiltrating the perivascular spaces surrounding thrombi (figure 1D,E). For the kidney, the renal arterioles presented obvious swelling with endothelial cells detachment and formation of substantial thrombi containing crystals in the vasculature (figure 3A–C). A mass of neutrophils and mononuclear cells infiltrated the arterioles to form a granuloma-like structure (figure 3D). Glomeruli showed slight endocapillary hypercellularity. Microthrombosis with crystals can be seen in most of the glomerular capillaries. There were also some wrinkled glomeruli, segmental double contours and mild subendothelial space widening. Immunofluorescence microscopy findings revealed deposits of IgM, IgG, C3, κ and λ light chains in glomerular mesangial area, but only the thrombi showed IgG κ restricted

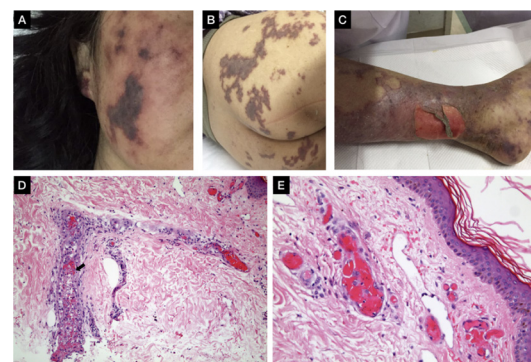


Figure 1 (A–C) Skin signs. (D) Pathological findings of skin biopsy (H&E $\times 200$). The thrombi containing crystals (arrow) plugged the microvascular lumens of dermis. (E) The infiltration of a few neutrophils, lymphocytes and mononuclear cells surrounded the thrombi and in vascular walls suggesting cryoglobulinaemic vasculitis.

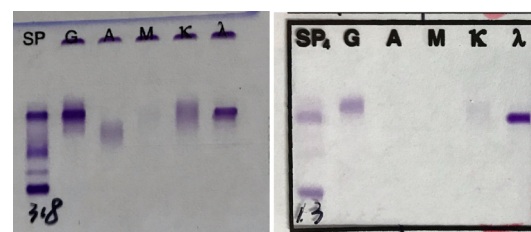


Figure 2 Serum (left) and urine (right) immunofixation electrophoresis.



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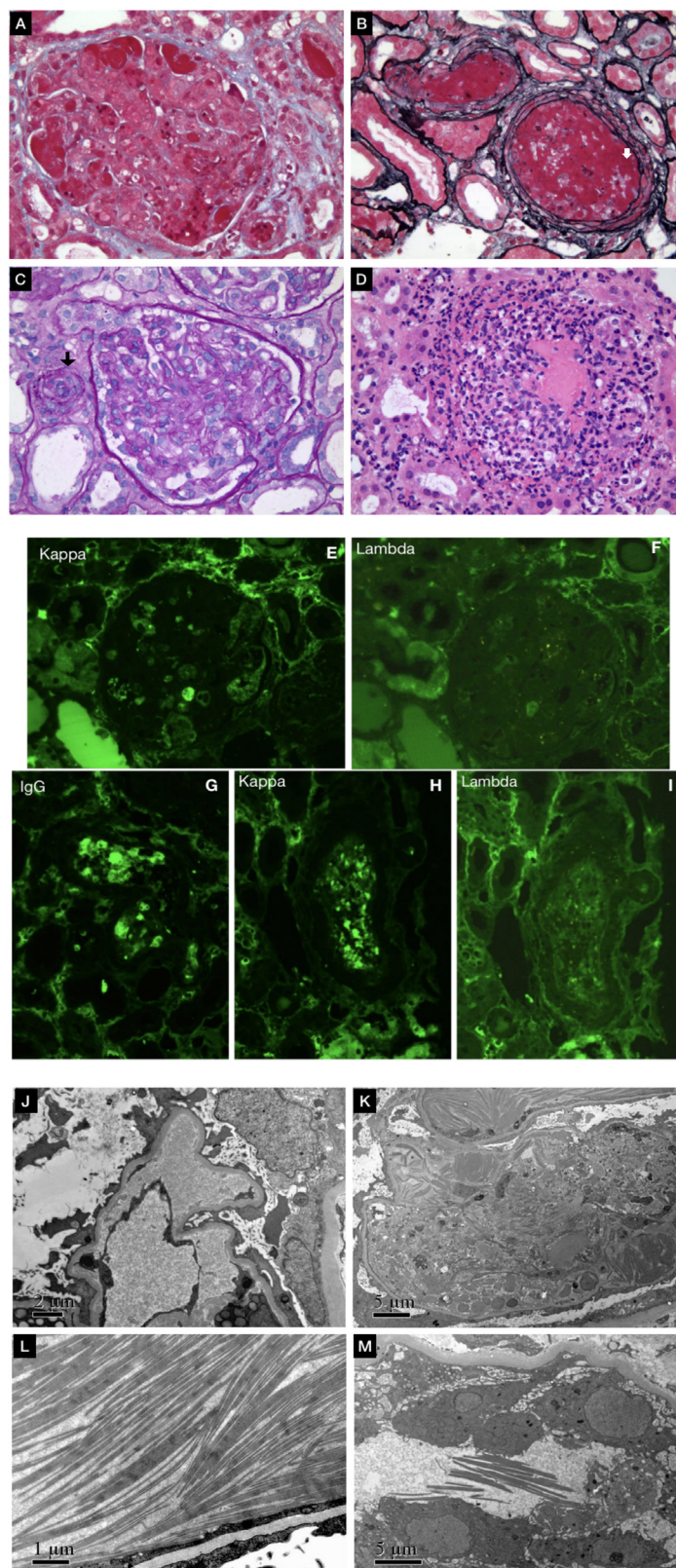


Figure 3 Pathological features of kidney (PASM ×400). The micro-thrombi occluded the glomerular capillary loops with a few neutrophils and mononuclear cells infiltration. (B) The arterioles were occluded by thrombi mixed with cellular debris and crystals (arrow). (C) The swelling of endothelial cells and segmental double contours of glomerular basement membrane in addition to the arteriolar endothelial oedema (arrow). (D) Severe infiltration of neutrophils and mononuclear cells around the thrombi formed a granulomatous inflammation in interlobular arterioles (H&E ×200). (E–I) Immunofluorescence of kidney (×200). Only the thrombi showed IgG κ-restricted staining. The ultrastructure of kidney biopsy was revealed by electron microscopy. (J) The diffuse widening of sub-endothelial areas of glomerular basement membrane, along with extensive effacement of podocyte foot processes. (K) The glomerular capillary loops were filled with crystalloid deposits with some of cellular debris. (L) The intra-capillary crystals were in a rigid stick-like appearance, arranged into the paracrystalline structure. (M) Crystals were seen in a tubular lumen.

staining (figure 3E–I). With electron microscopy, we observed cryocrystalglobulin diffusely filling glomerular capillary loops in a rigid stick-like appearance and arranged into a paracrystalline structure. Similar crystals were seen in some of tubular lumens (figure 3J–M). The pathological findings supported the diagnosis of cryocrystalglobulin-associated vasculitis and crystalline nephropathy.

DISCUSSION

In this patient, cryoglobulinaemia was suspected due to the presence of a common triad of cryoglobulinaemia including purpura, fatigue and joint pain. The occurrence of purpura fulminans after cold weather suggested type I cryoglobulinaemia. Cryoglobulinaemia is a unique model of human disease that combines elements of autoimmune, plasma cell dyscrasia, lymphoproliferative malignancies and non-malignant monoclonal gammopathy (NMMG).¹ Cryoglobulins undergo reversible condensation when changing temperature and concentration, and are associated with the characteristic monoclonal or polyclonal immunoglobulins themselves that induce cryoglobulin precipitate, showing various morphologies under different concentrations and temperatures as crystals, amorphous aggregates and gelatinous forms.² Cryocrystal is a rare form of cryoglobulinaemia.³ In *in vitro* experiments, large crystals are formed at a low supersaturation, while small crystals result at higher supersaturation and lower temperatures. Extracellular crystals take the form of stable, dense, linear or herringbone-like arrays that can be deposited in tissues. The branching structures form a web that ensnares or shears red blood cells, which can trigger haemolysis or thrombosis and cause significant mortality.³

Cryoglobulinaemic organ damage may be produced by two different aetiopathogenic mechanisms: accumulation of cryoglobulins and autoimmune-mediated vascular damage.⁴ Circulating cryoglobulins (mainly monoclonal immunoglobulins or light chains, type I) usually occlude to form hyaline thrombosis and cause capillaritis. Dermatological manifestations including acrocyanosis, skin ulcers, livedo reticularis and cold urticaria,⁴ are more suggestive of type I cryoglobulinaemia. Mixed cryoglobulinaemia involves small and median sized blood vessels, and is closely associated with cold-induced necrotic acral lesions. Other presentation includes joint pain, fatigue and glomerulonephritis. Monoclonal IgG λ chains were detected in both serum and cryoprecipitate, with an increased free λ chains. Combining the above characteristics, with the performance of 5% of immature plasma cells in bone marrow biopsy with no sign of the lymphoproliferative clone, a diagnosis of cryoglobulinaemia by NMMG was made. Histopathology revealed substantial thrombi containing crystals occluded dermis and renal arterioles, as well as glomerular capillary lumen (figures 1D,E and 3A,B). Systemic vasculitis-like changes were shown by thrombotic microangiopathy-like changes (thrombocytopenia, elevated serum lactate dehydrogenase, arteriolar endothelial cell oedema) and inflammatory responses (fever, increased ESR), and leading to acute kidney injury (AKI). These renal pathological manifestations were attributed to the renal injury of NMMG, namely monoclonal gammopathy of renal significance (MGRS).⁵

Most previous case reports described IgG κ associated with crystalloid nephropathy because of its propensity to aggregate into a crystalline structure. However, in the current patient, cryocrystals were formed by monoclonal IgG λ light chains, and presented κ chain restricted staining. It has been reported in the literature that monoclonal crystals lacked immunofluorescence (IF) staining, because the highly organised structure may prevent

combination of antibody to target epitopes. Another possible explanation is that the crystals may be composed of the variable fragments of the monoclonal light chain, and thus cannot be recognised by commercial antibodies. These will lead to a false-negative result.

Treatment of type I cryoglobulinaemia is based on histopathological findings, and should focus on control of the underlying clonal lymphoproliferative malignancies and plasma cells dyscrasia including NMMG, Waldenstrom macroglobulinaemia, low-grade non-Hodgkin's lymphoma, multiple myeloma and chronic lymphocytic leukaemia. A case of NMMG with cryoglobulinaemia that induces kidneys damage should be classified as MGRS,^{5–7} emphasising the significance of organ-saving treatments for this group of patients. Potent chemotherapeutic regimens for haematological malignancies, fludarabine or rituximab-based regimens for NMMG, may help to get better responses. However, a poorer renal outcome was reported when crystals accumulated within the glomerular micro-vasculature.^{6–9} A cohort study from two French University Hospitals emphasised that the occurrence of nephropathy was closely associated with higher mortality in type I cryoglobulinaemia despite involving only 30% of patients.⁹ Specific treatments for cryoglobulinaemia include plasmapheresis.¹⁰ Plasmapheresis removes circulating cryoglobulins and other circulating factors that promote endothelial injury and platelet aggregation. The current patient was treated with steroids, continuous renal replacement therapy and plasmapheresis. Inflammatory markers including ESR improved. The significant improvement in cardiac symptoms occurred once the patient completed plasmapheresis. The patient was transferred back to her home town. She was given daily prednisone 30 mg. The urine output increased to 1500 mL. SCr was initially stable at 351 $\mu\text{mol/L}$ but gradually declined to 95 $\mu\text{mol/L}$ in the following 4 weeks, and further declined to 75 $\mu\text{mol/L}$ 18 months after hospital discharge. Cyclophosphamide 0.2 g per week was used thereafter for a total of 12 times. Prednisone was tapered regularly until drug withdrawal. The patient did not undergo a re-examination of the cryoglobulinaemia due to the lack of testing conditions in the local county hospital, and refused to take a repeated bone marrow test. Her free λ chain decreased to 775 mg/dL. Our patient recovered from inflammation flare of cryocrystalglobulinaemia by steroids and plasmapheresis, and subsequently renal function improved, although monoclonal IgG λ chain could be detected yet.

Take home messages

- ⇒ Type I cryoglobulinaemia is an underlying clonal lymphoproliferative disease with plasma cell dyscrasia and can be induced by non-malignant monoclonal gamma globulin.
- ⇒ The pathogenesis of cryoglobulinaemia mainly involves intra-vascular occlusion and the systemic inflammation induced by cryoglobulin. Cryocrystalglobulinaemia is a rare form of cryoglobulinaemia. The monoclonal crystals may lack immunofluorescence (IF) staining presenting a false-negative result.
- ⇒ The renal manifestations of cryocrystalglobulinaemia include cryocrystal occlusion of renal arterioles and glomerular capillaries, as well as crystalline glomerulopathy, all belonging to monoclonal gammopathy of renal significance.
- ⇒ Plasmapheresis is beneficial to cryocrystalglobulin-related injury remission.

Questions for discussion

1. What features in this patient suggest the diagnosis?
2. What further investigations should be done?
3. How does organ damage occur in this condition?
4. Considering the laboratory evidence of renal failure, what pathological features may be expected?
5. What are the treatment options for the condition?

In conclusion, cryocrystalglobulinaemia can be induced by NMMG. Purpura fulminans and AKI were the results of circulating cryocrystalglobulin occlusion and associated vasculitis. Steroids with plasmapheresis is beneficial to cryocrystalglobulin-related injury remission before initiation of effective chemotherapy.

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