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Kidney Biopsy Teaching Case

Cryofibrinogen-Associated Glomerulonephritis

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Cryofibrinogen is an under-recognized cryoprotein. Cryofibrinogen is a cryoprecipitate that develops following plasma refrigeration, but does not occur in cold serum. People with cryofibrinogenemia may be asymptomatic, but this cryoprotein can be associated with thromboembolic disease, particularly affecting the skin. Kidney manifestations are relatively uncommon, but are likely underestimated. We describe clinical features and kidney biopsy results in 2 patients with cryofibrinogen-related kidney disease. Both patients presented with proteinuria and hematuria. One had significant cutaneous ulcers and palpable purpura. Kidney biopsy in both cases showed membranoproliferative glomerulonephritis with no immunoglobulin deposition. Weak segmental capillary wall fibrinogen staining was noted in glomeruli. Immunofluorescence studies following pronase digestion failed to reveal masked immunoglobulin deposits. Ultrastructural studies were distinctive and characterized by organized deposits of large-bore with multilayered tubular structures and fine fibrillary structures in a matrix. To confirm the composition of deposits, we extracted the cryoprecipitate from plasma of a patient and performed ultrastructural studies, which showed identical ultrastructural characteristics to those seen on the kidney biopsy. We also performed proteomic analysis of the cryoprecipitate that confirmed the presence of fibrinogen. Subsequent laboratory evaluation was positive for cryofibrinogen in both patients on multiple occasions. Appropriate therapy was instituted in both patients, which included prednisone, immunosuppressive therapy, and avoidance of cold exposure. In summary, we present clinical, kidney biopsy, and laboratory findings and the treatment and follow-up of cryofibrinogen-associated glomerulonephritis. Awareness of this entity will result in accurate diagnoses, appropriate investigation, and treatment.
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INDEX WORDS: Cryofibrinogen; cryoprecipitate; cryofibrinogenemia; membranoproliferative glomerulonephritis; kidney biopsy; light microscopy; electron microscopy; proteomics; fibrinogen; kidney disease.

INTRODUCTION

Cryofibrinogen is an under-recognized cryoprotein that was first characterized by Korst and Kratochvil.[1] Cryoprotein refers to proteins that precipitate when plasma is stored at 4°C for up to 72 hours. If both serum and plasma form a precipitate upon refrigeration, the responsible proteins are called cryoglobulins. If precipitation forms after plasma refrigeration but does not happen in cold serum, the plasma precipitate is called cryofibrinogen. Whereas cryoglobulins are composed of immunoglobulins and complement factors, cryofibrinogen is made up of fibrinogen, fibrin, and fibrin-degradation products with or without immunoglobulins.[1-3]

Cryofibrinogenemia may be essential (primary) or secondary to infections, solid-organ and hematologic malignancies, autoimmune diseases, or other processes. The exact prevalence of essential (or primary) cryofibrinogenemia is unclear, but it has been identified in up to 2% to 9% of asymptomatic healthy individuals.[4-6] In asymptomatic individuals, cryofibrinogen levels are <50 mg/dL. In symptomatic individuals, cryofibrinogen levels can reach up to 500 mg/dL.[6,7] Clinical manifestations of cryofibrinogenemia are varied and range from being asymptomatic to presenting as a thromboembolic phenomenon. The skin is usually the target organ, with manifestations including cold sensitivity, livedo reticularis, Raynaud phenomenon, and purpura. In more severe cases, skin manifestations included ulcers, gangrene, and ischemia.[4,8] Other sites of thrombosis include lower-limb venous thrombosis, pulmonary embolism, and arterial thrombi.[7]

The kidney is also a target organ for cryofibrinogenemia.[7,9,10] Terrier et al[9] demonstrated the presence of cryofibrinogen in up to 11% of patients admitted for management of kidney disorders and Saadoun et al[7] demonstrated kidney involvement in 13% of patients with cryofibrinogenemia, most of whom had the secondary form. Despite this relatively frequent detection in this subgroup, reports of kidney pathology related to cryofibrinogenemia are very few and lack detail.[11-15] Is this entity less well recognized and therefore unsuspected? In this report, we describe 2 patients with cryofibrinogen-associated

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membranoproliferative glomerulonephritis (MPGN) with the intent to elaborate on pathology and discuss diagnostic challenges.

CASE REPORTS

Clinical History and Initial Laboratory Data

Case 1

A 66-year-old white man was seen in the dermatology clinic because of cold-related cutaneous eruption and subsequent development of skin ulcerations on his lower limbs. The patient recalled developing a severe cutaneous eruption after swimming in a lake in his mid-40s. During the ensuing 20 years, he has had multiple episodes of cold-induced abdominal and lower-extremity eruption requiring less provocation that became more extensive with each episode. At this presentation, the rash was accompanied by ulcers over the left lateral calf (Fig 1). The patient denied having Raynaud phenomenon, urticaria, or livedo reticularis. He reported diffuse arthralgias without arthritis, and painful distal sensory polyneuropathy. A comprehensive review of systems was negative for classic B symptoms of lymphoma, arterial and/or venous thrombotic events, fevers, or myalgias.

The patient had been given the diagnosis of cryoglobulinemic glomerulonephritis (GN) 10 years ago (first biopsy) when he presented with acute kidney injury, hematuria, and proteinuria. Cryoglobulin was detected only at initial diagnosis with a cryocrit of 1.8% (reference range, <0.4%). In the ensuing years, serial cryoglobulin measurements gave negative results. He was treated with monthly intravenous cyclophosphamide for 6 months in combination with high-dose glucocorticoids and eventually was placed on maintenance mycophenolate mofetil therapy. Four years later, an exacerbation of his kidney disease prompted an increase in steroids. A repeat kidney biopsy (second biopsy) was again read as cryoglobulinemic GN, although immunofluorescence study results were negative. His kidney function gradually deteriorated and he was initiated on dialysis therapy.

Other pertinent history included hypertension, hyperlipidemia, monoclonal gammopathy of undetermined significance, gout, obstructive sleep apnea, chronic obstructive pulmonary disease, and congestive heart failure. Medications included allopurinol, amlodipine, pravastatin, calcitriol, furosemide, metolazone, calcium acetate, and diltiazem. The patient had no known allergies. He had a 25 pack-year smoking history until 20 years ago. There was no family history of rheumatic or kidney diseases.

Skin examination showed extensive palpable purpura over the abdomen and proximal thighs. There was a 4 × 3-cm eroded partly ulcerated patch with scalloped borders and surrounding erythema, in addition to a dozen scattered hemorrhagic necrotic papules over the left posterolateral lower leg (Fig 1). Skin biopsy revealed occlusive fibrin thrombi in many vessels (Fig 2A). A few also showed vasculitic changes of the wall.

Laboratory results were within reference ranges for erythrocyte sedimentation rate, C-reactive protein, white blood cells, and platelet counts. The patient had normocytic anemia with a hemoglobin level of 11.4 g/dL. Results for tests including liver function, hepatitis B surface antigen, hepatitis C antibody, antinuclear antibody, antineutrophil cytoplasmic antibody, anticyclic citrullinated peptide, rheumatoid factor, C3 and C4, and antiphospholipid antibodies were negative or within normal range. Serum protein electrophoresis plus immunofixation showed a faint band corresponding to a monoclonal immunoglobulin G (IgG) κ paraprotein; serum free light chain ratio was normal. Coagulation tests and a complete hypercoagulable workup showed no alterations. Bone marrow biopsy and computed tomography did not show evidence of malignancy or hematologic disease. Plasma cryofibrinogen was detectable on 3 different occasions, with cryocrits of 7.3%, 10%, and 12%, respectively. Cryoglobulin determinations were again negative. The 2 prior biopsies were reviewed. The biopsies showed cryofibrinogen-associated MPGN (see Kidney Biopsy section).

Case 2

A 70-year-old man presented with worsening kidney function, proteinuria, and hematuria over 18 months. His medical history is significant for hepatitis B virus carrier status with an undetectable viral load, prostate cancer (status post radical prostatectomy and leuprolide acetate injections), hypertension, osteoarthritis, left pelviureteric junction obstruction (status post renal pyeloplasty), and hyperlipidemia. The patient lived in a warm tropical climate and had no known history of cutaneous rashes, ulcers, or thrombotic phenomenon.

Laboratory investigations showed serum creatinine level of 2.2 mg/dL, corresponding to estimated glomerular filtration rate of 30 mL/min/1.73 m^2 by the 4-variable MDRD (Modification of Diet in Renal Disease) Study equation. Urinalysis showed protein (3+) and blood (2+), and 24-hour urinary protein was quantitated at 8 g. Serologic testing for antineutrophil cytoplasmic antibodies, rheumatoid factor, cryoglobulins, and anticardiolipin antibodies was negative, and C3 and C4 levels were within the reference ranges. Serum electrophoresis and immunofixation studies were negative for monoclonal immunoglobulin.

A kidney biopsy showed a membranoproliferative pattern on injury with organized deposits resembling those described in case 1. The similarities of the ultrastructural deposits in both these cases prompted investigating this patient for cryofibrinogen, which was positive on 3 separate occasions.

Kidney Biopsy

Both cases showed a membranoproliferative pattern of injury with lobular accentuation of capillaries and basement membrane remodeling on light microscopy. Capillary lumina were occluded by macrophages. A rare exudative neutrophil was identified. Scattered intracapillary eosinophilic and fuchsinophilic deposits

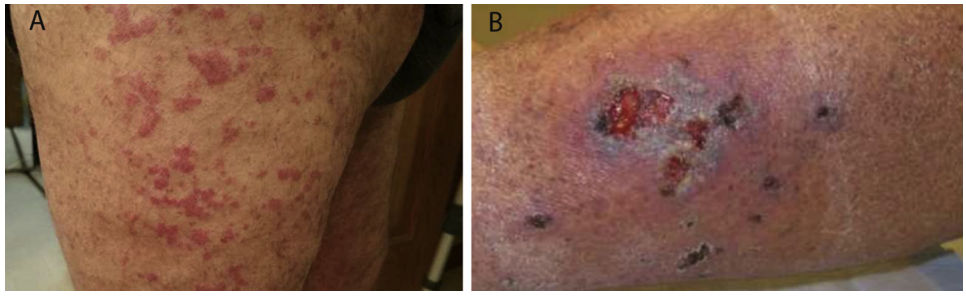

Figure 1. Skin lesions show (A) purpuric rash and (B) ulcers on the calf in patient 1.