**CASE PRESENTATION**

A 56-year-old woman with a medical history of hypertension and congestive heart failure (ejection fraction 45%) initially presented to her general practitioner with gradual-onset dyspnea and ankle swelling. She was found to have microscopic hematuria, elevated albumin to creatinine ratio (200 mg/mmol) and an acute kidney injury (creatinine level 290 mmol/L). The work-up for this problem found elevated cryoglobulin levels, with a cryocrit of 1%. She underwent a renal biopsy that was consistent with proliferative cryoglobulin-related membranoproliferative glomerulonephritis (MPGN). Specifically, the pathology showed immunofluorescence strongly positive for immunoglobulin (Ig) M deposits, mesangial endocapillary proliferation, as well as small vessel vasculitic changes.

Work-up for potential precipitants of this patient’s CG was inconclusive and included negative HIV serology, negative hepatitis C serology and unremarkable serum protein electrophoresis (albumin 29 g/L; alpha-1 globulin 5 g/L; alpha-2 globulin 5 g/L; gamma globulin 4 g/L). Rheumatological work-up included a negative antineutrophil cytoplasmic antibody, antinuclear antibody, antidual-stranded DNA antibodies, extractable nuclear antigens, rheumatoid factor, anticitrullinated protein antibody and antiglomerular basement membrane antibody. However, reduced complement levels were noted (C3 0.22 g/L, C4 <0.03 g/L).

The patient was initiated on hemodialysis and was treated with oral cyclophosphamide and prednisone. She was transferred to a tertiary centre for consideration of plasmapheresis. However, before initiating plasmapheresis, her respiratory status acutely deteriorated. She developed hypoxemic respiratory failure and required intubation and ventilation, and admission to the intensive care unit. Before her deterioration, the patient had been clinically stable from a respiratory point of view. Although she required 1 L/min to 2 L/min of oxygen by nasal prongs, she displayed no clinical evidence of worsening respiratory status. A week before her deterioration, an arterial blood gas analysis was performed, which showed a pH of 7.44, pCO₂ 35 mmHg, pO₂ 69 mmHg, bicarbonate 23.8 mmol/L, and an O₂ saturation of 93.6% on 3 L/min by nasal prongs. A chest x-ray at this time showed small bilateral pleural effusions and small bibasilar consolidation.

During this admission, the patient was noted to exhibit extrarenal manifestations of CG including a purpuric rash on her abdomen (Figure 1) and petechiae involving her nail beds (Figure 2). Initial bronchoscopy performed to investigate potential infection as a cause for her respiratory failure revealed normal bronchial mucosa and washings positive for influenza A. Cytology, acid-fast bacilli, Pneumocystis carinii pneumonia, and bacterial and fungal cultures were negative. She was treated with a course of oseltamivir, piperacillin/tazobactam, azithromycin and vancomycin. A bronchoalveolar lavage was not performed on this bronchoscopy.

Despite this broad-spectrum regimen, the patient was slow to improve and continued to require 50% high-flow oxygen by face mask. A follow-up chest radiograph showed bilateral consolidation and her...
Computed tomography scan showed a diffuse alveolar process with evidence of pulmonary hemorrhage in the differential diagnosis (Figures 3A and 3B). Repeat bronchoscopy with sequential sampling revealed progressive bloody returns indicative of diffuse alveolar hemorrhage (Figure 4).

Given that no other etiology for the pulmonary hemorrhage was identified, it was concluded that the underlying CG was the most likely cause. The patient received pulse steroids for three days and underwent seven plasma exchange procedures over the course of two weeks. She was also initiated on rituximab as per the recommendation of nephrology. Her respiratory status improved gradually over the next six days and she was weaned from oxygen.

**DISCUSSION**

Cryoglobulins are immunoglobulins that reversibly precipitate at decreased temperatures (1). Type I cryoglobulins are derived from a single monoclonal immunoglobulin, and are associated with hematological malignancies including multiple myeloma and lymphoma (2). Type II and III cryoglobulins are derived from more than one class of immunoglobulin. Type II CG involves monoclonal and polyclonal immunoglobulins with anti-immunoglobulin G specificity and is frequently associated with chronic infections, most commonly hepatitis C (3). Type III cryoglobulins are mixed polyclonal immunoglobulins directed against other polyclonal immunoglobulins and are found in a variety of chronic inflammatory, autoimmune and lymphoproliferative conditions (2).

CG is associated with a wide spectrum of clinical presentations. Symptoms in type I CG are typically related to increased blood viscosity and precipitated immune complexes. These include Raynaud’s phenomenon, headaches, nosebleeds and ischemic ulcerations (1). Mixed CG typically presents as a nonsystemic small-vessel vasculitis with urticaria, palpable purpura and ulceration. Peripheral neuropathy and arthritis are common systemic manifestations, while hepatosplenomegaly, serositis and glomerulonephritis occur less frequently.

Diffuse alveolar hemorrhage is characterized by bleeding into the alveolar spaces, resulting in hemoptysis as the most common presenting symptom. The work-up and evaluation of diffuse alveolar hemorrhage is described by Ioachimescu and Stoller (4).

Respiratory manifestations are an uncommon consequence of CG, but can include dyspnea, cough, interstitial lung fibrosis and, rarely, acute alveolar hemorrhage (5). Ferri et al (6) analyzed the clinical features of 231 patients with cryoglobulinemia. Mild exertional dyspnea was noted in 15% and 26% of patients at the beginning and end of follow-up, respectively. However, only 2% (four of 210) of patients...
had clinical/radiological evidence of interstitial lung involvement and only one patient was found to have hemoptysis (6).

Bombardieri et al (7) performed lung function studies on 23 patients with mixed CG. The majority (20 of 23) of patients had minimal to absent respiratory symptoms and, of those with severe respiratory symptoms, only one presented with hemoptysis. Notably, 18 of 23 patients had radiographic evidence of interstitial lung disease.

Severe pulmonary involvement, including pulmonary vasculitis and hemorrhage, is uncommonly observed in CG. Amital et al (8) analyzed 125 patients hospitalized with CG over a 23-year period at their centre. Of these, four patients (3.2%) developed alveolar hemorrhage. The authors summarized these cases in addition to the other six cases of CG-associated pulmonary hemorrhage reported in the literature. Of the 10 cases reported, five were type II CG and five were type III. Five patients were found to be hepatitis C positive, one patient had Hodgkin lymphoma and four had no noted concomitant medical condition. Nine of 10 patients had renal pathology including MPGN or glomerulonephritis. Therapies ranged considerably, with patients receiving various combinations of methylprednisone, cyclophosphamide, plasmapheresis, azathioprine, rituximab and hemodialysis. No particular regimen was clearly noted to be superior. Of the patients with available outcome data, six deaths were directly attributable to alveolar hemorrhage.

In our case, a 56-year-old woman was found to have CG with associated hypoxemic respiratory failure and pulmonary hemorrhage. Similar to the cases reviewed by Amital et al (8), she had concomitant renal dysfunction with biopsy-proven MPGN. The immunofixation following her serum protein electrophoresis suggested a polyclonal band consistent with type II CG. The etiology of her CG remains unclear. No evidence of a hematological malignancy was found and she was HIV and hepatitis C negative.

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The clinical significance of the patient’s influenza A infection remains unclear. However, given the immunoglobulin M complexes observed on renal biopsy, it is possible that the acute infection with influenza A virus may have been pathogenic. Four of the patients reviewed by Amital et al (8) were also noted to have experienced a significant clinical deterioration that was associated with a respiratory infection. These authors highlighted the challenge of determining whether the infection occurred secondary to immunosuppression or, rather, precipitated the CG and pulmonary hemorrhage. Unlike the previous cases, our patient responded well to a combination of plasmapheresis, pulse steroids and rituximab.

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