CASE REPORT

Acute alveolar haemorrhage in hepatitis C-related cryoglobulinaemic vasculitis

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SUMMARY

We describe a patient with untreated hepatitis C virus (HCV) infection presenting with pulmonary renal syndrome. He rapidly developed bilateral lung infiltrates and respiratory failure, and bronchoscopy confirmed acute alveolar haemorrhage secondary to cryoglobulinaemic vasculitis. Early bronchoscopy to confirm the diagnosis and consequent institution of immunosuppressive therapy led to excellent outcomes, which otherwise is reported in the literature to carry significant mortality. Therefore, in patients with HCV presenting with bilateral lung infiltrates, physicians must maintain a high degree of clinical suspicion for alveolar haemorrhage secondary to cryoglobulinaemic vasculitis.

BACKGROUND

Acute alveolar haemorrhage as a pulmonary manifestation of cryoglobulinaemic vasculitis is a rare but very poor prognostic sign. We describe a case of hepatitis C virus (HCV)-related cryoglobulinaemic vasculitis presenting as acute alveolar haemorrhage and glomerulonephritis with renal insufficiency. This condition generally carries significant mortality, however, in this case, early bronchoscopy and subsequent institution of immunosuppressive therapy led to excellent outcomes. Therefore, in patients with HCV presenting with bilateral lung infiltrates, physicians must maintain a high degree of clinical suspicion for alveolar haemorrhage secondary to cryoglobulinaemic vasculitis.

CASE PRESENTATION

A 45-year-old man was voluntarily admitted for schizophrenia when routine blood tests revealed non-oliguric acute kidney injury. Other relevant history included untreated hepatitis C infection with Child-Pugh class B cirrhosis and chronic substance abuse. Initial biochemistry revealed creatinine 330 µmol/L (reference interval (RI): 40–120 µmol/L), urea 27.2 mmol/L (RI: 3–7 mmol/L), estimated glomerular filtration rate (eGFR) 18 mL/min (RI: >90 mL/min) and serum albumin 23 g/L (RI: 31–47 g/L). Urinalysis showed moderate haematuria and proteinuria. He was transferred to a tertiary-level hospital, where initial investigations returned negative autoimmune serology and rheumatoid factor. Abdominal ultrasonography revealed evidence of hepatic cirrhosis with ascites, and no hydronephrosis. Coagulation profile was normal, with international normalised ratio of 1.2. He had a protein-to-creatinine ratio of 333 mg/mmol (RI: <30 mg/mmol), and complement levels were low. Cryoglobulin was detected with cryocrit of 1% (RI: <1%). Serology was positive for active HCV. A presumed diagnosis of cryoglobulinaemic glomerulonephritis was made.

Renal function continued to deteriorate, and he developed oliguria, though dialysis was not required. Creatinine peaked at 435 µmol/L, urea 46.2 mmol/L and eGFR 13 mL/min. Concurrently, he became progressively hypoxaemic, requiring oxygen supplementation via nasal prongs. Chest radiographs demonstrated extensive bilateral patchy infiltrates (figure 1). With significant peripheral oedema and over 10 kg above his normal weight, he was initially managed with intravenous diuretics and fluid restriction. CT of his chest revealed bilateral pulmonary infiltrates (figure 2). Given no clinical improvement with diuresis, low grade fevers and very high C reactive protein, he was additionally covered with broad-spectrum intravenous antibiotic therapy though cultures remained negative.

A few days later, the patient had significant radiological and clinical deterioration in respiratory status, requiring high-flow oxygen delivery. Severe vasculitis affecting the pulmonary vasculature was considered, and he underwent bronchoscopy. Bronchoalveolar lavage (BAL) confirmed pulmonary haemorrhage. BAL cultures were otherwise negative. Renal biopsy, which was delayed due to severe respiratory compromise, confirmed cryoglobulinaemic glomerulonephritis (figure 3). While pulmonary cryoglobulinaemic vasculitis requires a tissue biopsy to confirm diagnosis, this was not

Figure 1 Bilateral pulmonary infiltrates on plain chest X-ray.

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Figure 2 Bilateral pulmonary infiltrates on CT.

attained and the diagnosis was strongly suspected based on the blood-stained BAL. Three pulses of 1 g methylprednisolone were administered followed by high-dose oral steroids. There was immediate improvement in renal function and respiratory status, further supporting the presumed diagnosis of cryoglobulinaemic vasculitis. Weekly rituximab was also commenced, 375 mg/m² (800 mg), for a total of four doses.

OUTCOME AND FOLLOW-UP

He was successfully weaned off oxygen supplementation and his renal function improved significantly over the next 14 days,

Figure 3 Renal biopsy. (A) Light microscopy—well-preserved kidney; (B) H&E stain—prominent cellularity and expansion of capillary loops and mesangium consistent with mesangiocapillary glomerulonephritis; (C) double contours of basement membrane consistent with mesangiocapillary pattern; (D) evidence of hyaline thrombus; (E) Masson stain—evidence of cryoglobulin in between vessels.

to creatinine 109 µmol/L, urea 10.9 mmol/L and eGFR 70 mL/min. Gastroenterology follow-up was arranged to commence direct acting antiviral therapy to definitively treat HCV. On 2-month follow-up, he had completed rituximab therapy and his renal function had normalised with creatinine 89 µmol/L, urea 7.6 mmol/L and eGFR 89 mL/min.

DISCUSSION

Cryoglobulinaemia is a pathological condition characterised by the presence of cold-insoluble immunoglobulins in the serum. Brouet's classification differentiates cryoglobulins into three types, based on immunochemical studies.¹ Type 1 is a single monoclonal immunoglobulin, typically associated with haematological malignancies, and is usually asymptomatic or presents with hyperviscosity syndrome. Types 2 and 3, also collectively known as mixed cryoglobulinaemia (MC), have at least two immunoglobulins.² HCV has been recognised as the cause of MC in 80%–90% of cases.³ The proposed stimulant is a HCV glycoprotein which binds peripheral B cells, inducing proliferation of a clone of B cells that produce the immunoglobulin implicated in MC.³ Although overt cryoglobulinaemic vasculitis develops in only approximately 5% of chronic HCV infection, circulating cryoglobulins are detected in 40%–50% of chronic HCV-infected patients.⁴ Immune complexes in the endothelial surface composed of HCV antigens, cryoglobulins and complement cause vascular inflammation, leading to a small to medium vessel vasculitis. This has a wide spectrum of clinical manifestations depending on the organ system involved. Due to the substantial association with HCV infection, MC should always be considered as a possible differential diagnosis when patients with HCV present with symptoms suggestive of vasculitis.

Cryoglobulins have a particular affinity for the renal mesangial matrix and deposit in the glomerulus to cause membranoproliferative GN.⁵ The clinical syndromes associated with this vary, including isolated proteinuria with microscopic haematuria and moderate renal insufficiency, nephrotic syndrome or acute nephritic syndrome.³ Pulmonary manifestations, on the other hand, are a rare consequence of cryoglobulinaemia and can include dyspnoea, cough and interstitial lung fibrosis.⁶ However, the most serious respiratory manifestation remains acute alveolar haemorrhage due to severe vasculitis. This is a rare phenomenon, with only 26 prior cases described in the literature. HCV antibody was detectable in 19 of these cases. Steroids were used in the treatment of all patients, with variable addition of plasmapheresis, cyclophosphamide, rituximab, azathioprine and intravenous immunoglobulin. Half of all reported cases died as a direct result of pulmonary haemorrhage, emphasising there is substantial mortality of acute alveolar haemorrhage in cryoglobulinaemic vasculitis.⁷ Bilateral lung infiltrates associated with dyspnoea, respiratory failure or haemoptysis in patients with hepatitis C infection should prompt investigation for alveolar haemorrhage secondary to cryoglobulinaemic vasculitis. Bronchoscopy should be considered early, as pulmonary haemorrhage on BAL is strongly suggestive of vasculitis, though tissue biopsy is required to confirm the diagnosis. As our case demonstrates, coexisting renal failure with fluid overload and infection can confound the clinical picture. Although our patient did not have haemoptysis, early bronchoscopy and the finding of pulmonary haemorrhage helped in initiating immunosuppressive therapy, resulting in excellent outcomes.

In addition to immunosuppressive therapy, management of HCV-related cryoglobulinaemic vasculitis requires treatment of underlying HCV infection. Infection of peripheral lymphocytes

is implicated as the stimulating factor for the lymphoproliferation that underlies MC. In a cohort of 279 patients with life-threatening cryoglobulinaemic vasculitis, use of antiviral therapy and age were the only variables associated with survival.⁸ Therefore, this is an essential step in management and an important consideration in the era of direct-acting antiviral therapy and increasing cure rate of HCV.

Learning points

- ▶ Mixed cryoglobulinaemia should be considered as a differential diagnosis in patients with hepatitis C virus (HCV) presenting with vasculitic symptoms.
- ▶ Bilateral lung infiltrates with dyspnoea, respiratory failure or haemoptysis in patients with hepatitis C infection should prompt investigation of alveolar haemorrhage secondary to cryoglobulinaemic vasculitis.
- ▶ Early bronchoscopy with bronchoalveolar lavage to confirm the diagnosis and institution of immunosuppressive therapy is crucial for clinical recovery.
- ▶ Acute alveolar haemorrhage due to cryoglobulinaemic vasculitis can rapidly progress to death if untreated.
- ▶ Management of HCV-related cryoglobulinaemic vasculitis requires treatment of underlying HCV.

Contributors TR: collection of case details and reporting of case and discussion. EV: conception, revision and final approval of the version published.

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