Hepatitis C-associated cryoglobulinaemia presenting with refractory hypertensive crisis and acute pulmonary oedema

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We report two elderly women who presented with hypertensive crisis and acute pulmonary oedema, which responded poorly to antihypertensive therapy. The patients were later diagnosed as having hepatitis C virus-related cryoglobulinaemia. ***(MJA 2005; 182: 38-40)***

Acute pulmonary oedema is a well-known complication of severe hypertension,[1] but, to our knowledge, has never been reported in association with mixed cryoglobulinaemia. We report two patients with severe hypertension who presented with pulmonary oedema which was not controlled until cryoglobulinaemia was diagnosed and treated with plasmapheresis and methylprednisolone.

Clinical records

Patient 1

Presentation: A 66-year-old woman presented to our emergency department in late February (winter) with severe dyspnoea of 2 hours' duration. She had a 10-year history of hypertension, and had had a stroke 3 months before, but had recovered. Over the previous month, her blood pressure had been over 210/120 mmHg, and she had intermittent dyspnoea, orthopnoea and leg oedema. On examination, she was orthopnoeic, with blood pressure of 218/124 mmHg, regular pulse of 126 bpm, and respiratory rate of 36 breaths per minute. She had engorged jugular veins, bilateral chest crackles, hyperpigmentation of the legs and marked bipedal pitting oedema. A chest radiograph showed diffuse haziness over both lungs. Electrocardiography (ECG) showed inverted T waves in leads V_4 to V_6. Oxygen saturation was 77% while breathing 100% O_2 (reference range [RR], 95%–100%).
Initial management: The patient was intubated and mechanically ventilated. Her central venous pressure was 13 cmH_2O (RR, 3–11 cmH_2O), and pulmonary wedge pressure was 19 mmHg (RR, 6–12 mmHg). She was treated with intravenous glyceryl trinitrate and diuretics, but over the next 48 hours her blood pressure fluctuated between 300/130 mmHg and 200/90 mmHg, and pulmonary oedema persisted.

After 2 days, the patient was extubated. Over the next 24 hours, she developed massive bilateral pleural effusions and numerous petechiae over the legs. Echocardiography revealed a normal left ventricular (LV) ejection fraction (72%) and diastolic dysfunction. Radionuclide angiography confirmed these findings. Laboratory tests showed hypoalbuminaemia, proteinuria (daily protein loss, 9.3 g), haematuria with granular casts, impaired renal function, anaemia and thrombocytopenia (Box 1). Nephrotic syndrome was diagnosed.

1 Blood test results before diagnosis of cryoglobulinaemia

Test	Patient 1	Patient 2	Reference range
Serum albumin (g/L)	24	24	32–45
Serum urea nitrogen (mmol/L)	13.9	36.8	2.9–8.2
Serum creatinine (μmol/L)	230	412	53–106
Haemoglobin (g/L)	59	98	120–160
Platelet count (10^9/L)	105	69	150–450
Complement 3 (g/L)	0.62	0.30	0.79–1.19
Complement 4 (g/L)	0.02	0.07	0.17–0.37
Rheumatoid factor	1:10 240	> 1:20 480	< 1:40

Further tests revealed a decreased serum concentration of complement components C3 and particularly C4, and markedly raised concentration of rheumatoid factor. However, tests were negative for antinuclear (ANA), anti-double-strand-DNA (anti-ds-DNA), antiglomerulo-basement-membrane and antineutrophil-cytoplasmic antibodies. A cryoglobulin test was positive (Box 2). Immunofixation electrophoresis of the cryoprecipitates showed monoclonal IgM/kappa and polyclonal IgG. A test for hepatitis C virus antibodies (anti-HCV) was then performed and was positive.
Diagnosis: On Day 27 of admission, the patient was diagnosed with type II mixed cryoglobulinaemia associated with HCV infection. At that time, her blood pressure was still fluctuating between 230/130 mmHg and 180/100 mmHg, and pulmonary oedema and massive pleural effusions persisted, despite vigorous antihypertensive therapy with frusemide, intravenous glyceryl trinitrate, an α-adrenergic blocker and angiotensin-converting enzyme inhibitors. Repeated thoracocentesis was required to release massive effusions (initially transudative, but later haemorrhagic). Renal biopsy revealed diffuse glomerulonephritis with crescent formation.
Management: Plasmapheresis was started on Day 27, along with pulse therapy of intravenous methylprednisolone (500 mg daily for 3 days). After five courses of plasmapheresis in 12 days, the hypertension and pulmonary oedema were controlled.

The patient was discharged from hospital on Day 57 of admission. At discharge, serum creatinine level was 141 μmol/L (reference range [RR], 53–106 μmol/L), and she was taking prednisolone (25 mg), diltiazem (180 mg), spironolactone (75 mg) and doxazosin (8 mg) per day.

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Patient 2

Presentation: In February, 2 years after Patient 1, a 77-year-old woman presented to our emergency department with a 1-day history of severe dyspnoea and orthopnoea. She had had hypertension for 3 years. On several occasions during the previous month, her blood pressure had risen to 200/120 mmHg. On examination, she was stuporous, with blood pressure of 200/110 mmHg, regular pulse of 112 bpm, and respiratory rate of 36 breaths per minute. She had engorged jugular veins, bilateral chest crackles, hepatomegaly, ascites and bipedal oedema. A chest radiograph showed bilateral diffuse haziness, and ECG showed a generalised low QRS complex. Blood gas analysis showed pH, 7.43 (RR, 7.35–7.45); $PaCO_2$, 3.9 kPa (RR, 4.7–5.3 kPa) and PaO_2, 11.2 kPa (RR, 12.7–13.3 kPa) while breathing oxygen through a mask.

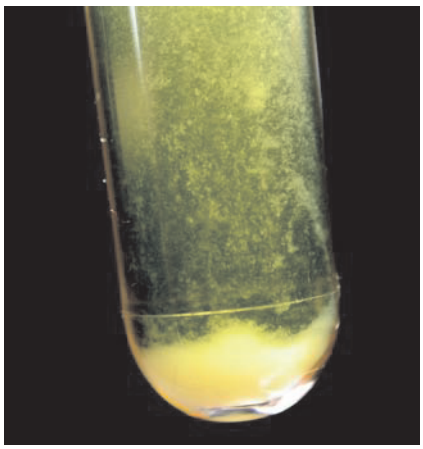
Initial management: The patient was intubated and mechanically ventilated. Central venous pressure was 12 cmH_2O. Echocardiography revealed concentric LV hypertrophy, normal LV ejection fraction, but impaired LV diastolic function. Blood pressure fell to 170–200/90–100 mmHg in 2 days, after diuretic and nitroprusside therapy, but pulmonary oedema and respiratory failure did not decrease, even after haemodialysis. She had massive ascites, bilateral pleural effusions, hypoalbuminaemia, proteinuria (daily protein loss, 3.5 g), haematuria, poor renal function, anaemia and thrombocytopenia (Box 1). Nephrotic syndrome was diagnosed.

Levels of both C3 and C4 were markedly low. ANA and anti-ds-DNA antibodies were negative, but rheumatoid-factor titre was markedly high. Cryoglobulin tests on Days 14 and 16 of admission were positive. Immunofixation electrophoresis of serum cryoprecipitates showed polyclonal IgG. HCV tests were negative for anti-HCV antibody but positive for serum HCV RNA.

Diagnosis: The diagnosis of type III mixed cryoglobulinaemia associated with HCV infection was thus established on Day 16 of admission. At that time, the patient was still being mechanically ventilated and needed repeated thoracocentesis (effusions were initially yellow, but later became haemorrhagic). Computed tomography of the head showed multiple ischaemic infarcts.

Management: Plasmapheresis and methylprednisolone pulse therapy (1 g intravenously daily for 3 days) were started on Day 17 of admission. The patient was extubated the next day and discharged from hospital 2 weeks later, after two courses of plasmapheresis. Serum creatinine level at discharge was 291.5 μmol/L.

2 Cryoglobulin test



Cryoglobulin particles float in the serum and precipitate at the bottom of the test tube at 4°C. The particles dissolve on rewarming of serum to body temperature.

Discussion

Hypertensive crisis with rapid-onset pulmonary oedema has been associated with coronary artery disease,[2] renal artery stenosis[3,4] and phaeochromocytoma,[5] but a search of English-language articles in PubMed revealed no previous reports of an association with mixed cryoglobulinaemia. The latter is characterised by the presence of cold-precipitable cryoglobulins in serum. Underlying diseases include autoimmune and infectious diseases, especially hepatitis C.[6-9] "Mixed" indicates that the cryoglobulins in these patients contain either monoclonal plus polyclonal immunoglobulins (type II cryoglobulinaemia), or polyclonal immunoglobulins (type III cryoglobulinaemia).[7] In hepatitis C, cryoglobulins usually contain anti-HCV antibody, HCV RNA and IgM rheumatoid factor (ie, anti-IgG autoantibody).[9]

Cryoglobulins often trigger the formation of immune complexes, leading to immune-complex-type vasculitis, and produce cutaneous, vasomotor, renal and neurological symptoms.[7-9] In our patients, factors precipitating the acute pulmonary oedema included hypertensive crisis, renal insufficiency and probably coronary insufficiency. The hypertensive crisis and pulmonary oedema had abrupt onset, progressed rapidly to respiratory failure, were accompanied by nephrotic syndrome, and responded poorly to antihypertensive and diuretic therapy.

Our patients had had moderate hypertension for 3–10 years before their blood pressure suddenly rose markedly 2 to 3 months before the development of pulmonary oedema. Hypertension has been found in 37% of patients with cryoglobulinaemia.[6] When the underlying disease of cryoglobulinaemia (eg, hepatitis C) flares up, levels of cryoglobulins (which contain HCV-RNA) increase, resulting in higher levels of circulating immune complexes, acute vasculitis and raised blood viscosity. These factors all precipitate the abrupt rise in blood pressure and pulmonary oedema, and explain the failure of conventional antihypertensive agents.

Treating cryoglobulinaemia in our patients decreased renal vasculitis and ischaemia, fluid overload, and ultimately hypertension and pulmonary oedema. Coronary vasculitis, found at autopsy in 22% of patients with mixed cryoglobulinaemia,[6] could contribute to pulmonary oedema. However, both our patients had a normal LV ejection fraction, suggesting that neither had significant coronary vasculitis.

In both patients, acute pulmonary oedema developed in winter. Whether cold weather worsens hypertension by precipitating more cryoglobulins and increasing viscosity awaits further observation.

In our patients, the initial features that led to the suspicion of vasculitis were petechiae, proteinuria and haematuria. Further testing revealed decreased complement levels (especially C4). These and other manifestations, including oedema, ascites, recurrent pleural effusions, cerebral infarction and glomerulonephritis, were caused by circulating cold-precipitable immune complexes and resulting vasculitis.[6-9]

Chronic HCV infection stimulates B-cell clones to proliferate and produce cryoprecipitable IgM antibody with rheumatoid-factor activity[10] — an important laboratory index of HCV-related mixed cryoglobulinaemia. However, Patient 2 was negative for anti-HCV antibody, possibly because the sensitivity of the anti-HCV immunoassay, although high, is still suboptimal,[11] or because the anti-HCV antibodies were concentrated in cryoprecipitates, and therefore not detectable by the serum assay.[7]

In both patients, the refractory hypertension and pulmonary oedema responded to plasmapheresis and methylprednisolone therapy. Conventional treatment of mixed cryoglobulinaemia aims

to reduce circulating immune complexes through immunosuppression and plasmapheresis.[8] Although immunosuppressive therapy alone could ameliorate vasculitis,[12] plasmapheresis has shown hypotensive effect in immune-complex nephritis, including mixed cryoglobulinaemia.[13] It also reduces plasma viscosity and improves perfusion of the affected organs,[14] thus helping in patients with hypertension, encephalopathy or severe renal impairment.

Neither patient had a history of blood transfusion, surgery, intravenous drug use or tattooing. They probably acquired HCV infection through non-sterile injections or acupuncture in local clinics, the most common source of HCV infection in Taiwan.[15,16]

With the increasing prevalence of hepatitis C,[17] knowledge of its extrahepatic manifestations is important. Our two patients illustrate the association with mixed cryoglobulinaemia presenting with hypertensive crisis and acute pulmonary oedema.

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(Received 9 Jun 2004, accepted 5 Oct 2004) ❑