

CASE REPORT

Resolution of neurological deficits secondary to spontaneous intracranial haemorrhage and posterior reversible encephalopathy syndrome (PRES) in a patient with hepatitis C-associated cryoglobulinaemia: a role for plasmapheresis

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SUMMARY

Essential mixed cryoglobulinaemia or type II cryoglobulinaemia is an important extrahepatic manifestation of chronic hepatitis C. Cryoglobulinaemia results in the deposition of immune complexes in small or medium-sized blood vessels leading to palpable purpura, arthralgia, renal disease and peripheral neuropathy. Posterior reversible encephalopathy syndrome (PRES) is a distinct phenomenon characterised by vasogenic oedema in the posterior circulation of brain. Cryoglobulinaemic vasculitis leading to spontaneous intracranial haemorrhage and PRES syndrome is rarely reported in the medical literature. In this report, we present an unusual case of spontaneous intracranial haemorrhage and PRES secondary to hepatitis C-associated cryoglobulinaemia presenting as right dense hemiplegia. Prompt institution of plasmapheresis resulted in successful resolution of symptoms in our patient, followed by full neurological recovery. To the best of our knowledge, this case describes the first successful use of plasmapheresis in alleviating neurological complications resulting from cryoglobulinaemic vasculitis and PRES secondary to chronic hepatitis C.

BACKGROUND

Chronic hepatitis C is the leading cause of type II cryoglobulinaemia and accounts for 90% of cases. On the other hand, approximately 40–65% of patients with chronic hepatitis C have detectable cryoglobulin levels.¹ Type II cryoglobulinaemia is characterised by a mixture of polyclonal immunoglobulins and monoclonal immunoglobulins, either IgM or IgA, with rheumatoid factor (RF) activity. In patients with chronic hepatitis C, the production of IgM anti-IgG with RF activity together with decreased liver clearance contributes to increased levels of circulating cryoglobulins. These cryoglobulins bind complement in the vessel wall and mediate inflammatory cascades, resulting in vasculitis. In fact, several inflammatory markers including interleukin (IL)-1 β , IL-6 and tumor necrosis factors- α are significantly elevated in patients with chronic hepatitis C-associated cryoglobulinaemia. The most common clinical manifestations of cryoglobulinaemic vasculitis consist of cutaneous palpable purpura, membranoproliferative glomerulonephritis,

arthralgia or arthritis and peripheral neuropathy. Central nervous system (CNS) and pulmonary involvement are rare complications. CNS manifestations reported in the literature include cerebral ischaemia and haemorrhage as result of CNS vasculitis. Treatment of hepatitis C-associated cryoglobulinaemia is directed towards the underlying aetiology using antiviral therapy. Type II cryoglobulinaemia often follows a chronic smouldering course but occasionally can be rapidly progressing with life-threatening manifestations in some individuals. Such patients may require prompt institution of plasmapheresis with/without immunosuppressants.

CASE PRESENTATION

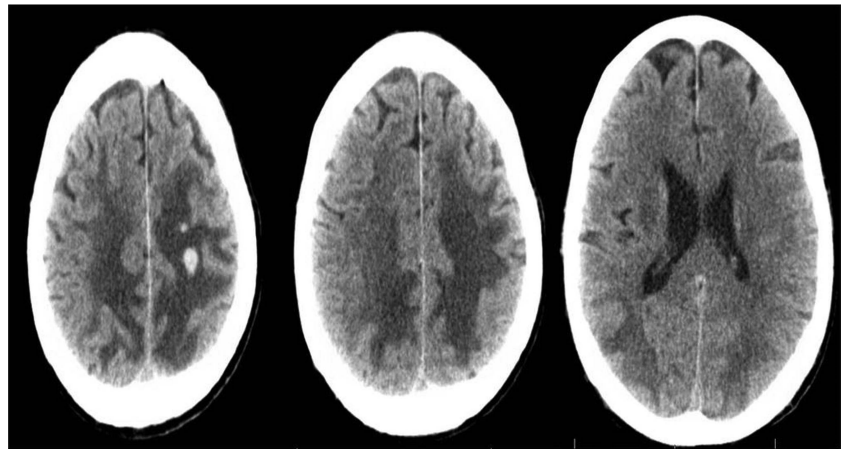
A 58-year-old Caucasian man with a medical history significant for chronic hepatitis C (genotype 3a, log hepatitis C virus (HCV) 5.06 IU/mL), type II cryoglobulinaemia, membranoproliferative glomerulonephritis, chronic obstructive pulmonary disease, depression, hypertension and degenerative lumbar disease presented with gradual onset of occipital headache, difficulty in coordination and right-sided weakness involving face, upper and lower extremities over a 1-week duration. He reported no known drug allergies, and current medications included nifedipine, hydralazine, cyclobenzaprine and morphine sulfate. Social history was significant for smoking of 15 pack-years, no alcohol or illicit drugs use. Family history was unremarkable. Review of systems was negative except for easy bruising and skin rash over bilateral lower extremities. Initial vitals demonstrated blood pressure of 148/97, pulse rate 74, respiratory rate 20, temperature 36.3°C and body mass index 21 kg/m². Physical examination was remarkable for being alert, awake and in no apparent distress. Pupils were equal and reactive along with no visual field defect and intact extraocular movements. Right-sided facial weakness was noted with forehead sparing. Right haemiparesis was noted with power of 2/5. Bilateral sensation was intact for pin-prick, light touch and vibration. Deep tendon reflexes were exaggerated on the right side. Extensor plantar reflex (Babinski sign) was present on the right side. Chest, heart and abdominal examinations were unremarkable. Palpable purpura was also noted over bilateral lower extremities.



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Figure 1 CT of the head demonstrating white matter oedema in bilateral parieto-occipital lobes with bleeding at presentation.

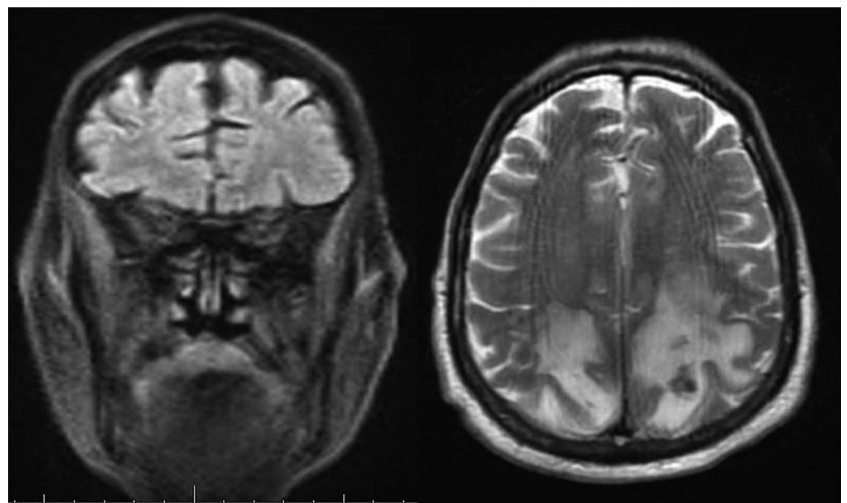


INVESTIGATIONS

Laboratory investigations showed haemoglobin 9.7 g/dL, mean corpuscular volume 87.2, white cell count 7700/dL and platelet count 81 000/dL. Sodium was 138 meq/dL, potassium 4 meq/dL, chloride 110 meq/dL, bicarbonate of 22 meq/dL, blood urea nitrogen 29 mg/dL, creatinine 1.3 mg/dL, estimated glomerular filtration rate 40 mL/kg/min, serum glutamic oxaloacetic transaminase 66 U/L, serum glutamic pyruvic transaminase 76 U/L, alkaline phosphates 110 U/L, albumin 3.1 g/dL, albumin/globulin ratio was reversed (0.9, normal 1.1–1.8), elevated erythrocyte sedimentation rate of 66, total bilirubin 0.4 mg/dL, prothrombin time 14 s, international normalised ratio of 1.1, RF was positive (3360 IU/mL), antinuclear antibodies screen was negative, complement C3 was low (73.6 mg/dL, normal range 88–201 mg/dL), complement C4 was low (1.8 mg/dL, normal range 16–47 mg/dL), cryoglobulin was positive, IgM κ monoclonal gammopathy and polyclonal IgG.

An initial head CT without contrast demonstrated multiple hyperdensities within bilateral posterior frontal lobes, the largest measuring 9.2×8.6 mm on the left side with no midline shift. Periventricular and deep white matter bilateral posterior hypodensities were also noted (figure 1). Subsequent MRI of the brain demonstrated subcortical haemorrhagic foci that were predominantly isointense on T1 and hypointense on T2. Extensive vasogenic white matter oedema was noted in bilateral occipital and parietal lobes, consistent with posterior reversible encephalopathy syndrome (PRES; figure 2).

Figure 2 MRI of the brain demonstrating subcortical oedema with tiny bleeding on T2 and fluid-attenuated inversion recovery images.



TREATMENT

Patient's clinical status deteriorated over the next 48 h, with increasing confusion, progressive weakness and low haemoglobin (7.7 g/dL), increased bruising but stable platelet count (80 000/dL). He was started on urgent plasmapheresis.

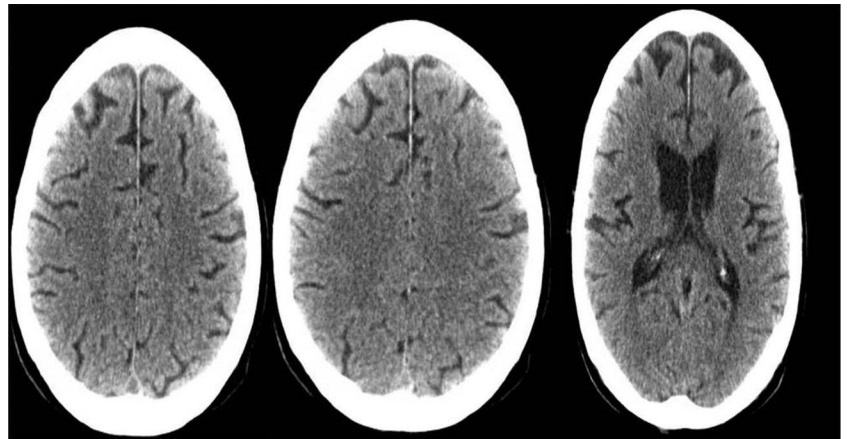
OUTCOME AND FOLLOW-UP

By day 5, the patient demonstrated significant neurological recovery with rapid resolution of neurological deficits. He later on completed a 10-day course of plasmapheresis and was clinically stable. He was advised to start anti-hepatitis C viral therapy with pegylated interferon- α and ribavirin as an outpatient. Repeat head CT showed significant resolution of haemorrhagic foci and vasogenic oedema over the posterior lobe (figure 3).

DISCUSSION

Hepatitis C is the common cause of type II or mixed cryoglobulinaemic vasculitis. It has been estimated that up to 50% of patients with mixed cryoglobulinaemia have HCV antibodies and usually they have more severe manifestations.² Active hepatitis may or may not be present in patients with mixed cryoglobulinaemia syndrome as evidenced by normal aminotransferase levels in a subset of patients. It is also important to know that majority of patients with hepatitis C associated cryoglobulinaemia do not develop vasculitis. In a study of 127 patients with chronic HCV infection, it was noted that 69 patients (54%) had circulating cryoglobulins and only 18 patients (26%) had clinical

Figure 3 CT of the head at same levels after treatment with plasmapheresis demonstrating resolved oedema and bleeding.



symptoms consistent with cryoglobulinaemic vasculitis.³ Patients with cryoglobulinaemia had a longer duration of disease and higher prevalence of cirrhosis. Therefore, HCV infection should be ruled out in patients with type II cryoglobulinaemia. On the other hand, serum cryoglobulins should be tested in patients with HCV who present with unexplained arthralgia, renal disease and vasculitic skin lesions especially over the lower extremities.

Type II cryoglobulinaemic vasculitis is characterised by small vessel leucocytoclastic vasculitis mediated by deposition of antigen–antibody complexes in small arteries, small arterioles and capillaries. This inflammation can lead to the destruction of the vessel wall which is associated with neutrophil debris and hypocomplementaemia. The clinical presentation of cryoglobulinaemic vasculitis varies from mild clinical symptoms such as arthralgia and purpura to life-threatening complications such as rapid progressive glomerulonephritis and wide spread vasculitis.⁴ Ferri and colleagues demonstrated in a review of 231 patients that purpura (81%), weakness and fatigue (80%) and arthralgia (72%) were the most common manifestations of type II cryoglobulinaemic vasculitis. Meltzer's triad (purpura, weakness and arthralgia) can be present in up to 80% of patients. Peripheral neuropathy (58%), renal involvement (30%), liver involvement (77%) and Raynaud phenomena (36%) were also documented.

Histologically, membranoproliferative glomerulonephritis is the most common pattern of renal involvement in up to 80% of these patients. Furthermore, the presence of renal disease is a major contributing factor in the long-term prognosis. Rarely, pulmonary involvement and CNS involvement (attention deficit, cognitive impairment and high frequency of MRI abnormalities) can be associated with type II cryoglobulinaemic vasculitis. A previous report of a 63-year-old woman who presented with acute severe encephalopathy secondary to HCV-associated cryoglobulinaemia showed marked improvement after starting plasma exchange.⁵ The patient remained in remission with maintenance therapy consisting of low-dose daily prednisone and cyclophosphamide for 6 months after the initial presentation.

PRES is characterised by vasogenic oedema predominantly localised in the posterior cerebral hemispheres. PRES can occur in a variety of clinical settings although the most common include hypertensive crises, pre-eclampsia and immunosuppressive therapy. Chawla *et al*⁶ have reported a case of PRES in a patient with chronic liver failure secondary to hepatitis C. Chronic HCV, PRES and cryoglobulinaemic vasculitis have been independently associated with spontaneous intracranial

haemorrhage.^{7–9} The combination of all three factors can increase the odds of intracranial haemorrhage as seen in our patient.

The treatment of type II cryoglobulinaemic vasculitis is directed towards the underlying aetiology, which is a chronic HCV infection in majority of patients. In patients with rapid progressive and life-threatening complications due to vasculitis, addition of immunosuppressive therapy with high-dose pulse steroids, rituximab or cyclophosphamide with or without plasmapheresis has been reported.^{10–11} Plasmapheresis is also indicated for patients with cryoglobulin hyperviscosity syndrome. Although plasmapheresis is an accepted modality for treating cryoglobulinaemic vasculitis, there are no large multicenter randomised controlled trials to support its use.¹² The majority of evidence to support the use of plasmapheresis comes mostly from a small number of case reports and case series; based on mechanistic basis that plasmapheresis removes circulating cryoglobulins with the exception of patients with decompensated cirrhosis, all patients with type II cryoglobulinaemia associated with HCV should be treated with antiviral therapy. It is recommended that antiviral therapy be delayed by one to four months in patients who require immunosuppressive therapy including plasmapheresis.^{10–13–14} Our patient was referred for institution of antiviral therapy at the completion of his plasmapheresis sessions which lasted for 4 weeks.

In summary, we report a case of spontaneous intracranial haemorrhage and PRES secondary to HCV-associated cryoglobulinaemia, resulting in focal neurological deficits, which was successfully managed by prompt institution of plasmapheresis. Chronic hepatitis C, cryoglobulinaemia and PRES have been previously demonstrated to be independent risk factors for intracranial haemorrhage. In this setting, plasmapheresis can be highly effective in providing complete resolution of neurological deficits as seen in our patient.

Learning points

- ▶ Intracranial haemorrhage and posterior reversible encephalopathy syndrome can be manifestations of cryoglobulinaemic vasculitis in hepatitis C virus infection.
- ▶ Type II cryoglobulinaemia often follows a chronic smouldering course but can have rapid life-threatening complications.
- ▶ Plasmapheresis can be highly effective in providing complete resolution of neurological deficits in cryoglobulinaemic vasculitis.

Contributors DA and HIB wrote the case; BT and GB reviewed and edited it.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Cicardi M, Cesana B, Del NE, *et al.* Prevalence and risk factors for the presence of serum cryoglobulins in patients with chronic hepatitis. *J Viral Hepat* 2000;7:138–43.
- 2 Cacoub P, Fabiani FL, Musset L, *et al.* Mixed cryoglobulinemia and hepatitis C virus. *Am J Med* 1994;96:124–32.
- 3 Lunel F, Musset L, Cacoub P, *et al.* Cryoglobulinemia in chronic liver diseases: role of hepatitis C virus and liver damage. *Gastroenterology* 1994;106:1291–300.
- 4 Saadoun D, Delluc A, Piette JC, *et al.* Treatment of hepatitis C-associated mixed cryoglobulinemia vasculitis. *Curr Opin Rheumatol* 2008;20:23–8.
- 5 Lidove O, Cacoub P, Maisonneuve T, *et al.* Hepatitis C virus infection with peripheral neuropathy is not always associated with cryoglobulinaemia. *Ann Rheum Dis* 2001;60:290–2.
- 6 Chawla R, Smith D, Marik PE. Near fatal posterior reversible encephalopathy syndrome complicating chronic liver failure and treated by induced hypothermia and dialysis: a case report. *J Med Case Rep* 2009;26:6623.
- 7 Aiba T, Watanabe T, Koike T, *et al.* C-type hepatitis in spontaneous intracerebral hemorrhage. *No To Shinkei* 1996;48:1116–19.
- 8 Hefzy HM, Bartynski WS, Boardman JF. Hemorrhage in posterior reversible encephalopathy syndrome: imaging and clinical features. *AJNR Am J Neuroradiol* 2009;30:1371–9.
- 9 Chen WH, Lin HS, Kao YF. Type II cryoglobulinemia and brain hemorrhage. *Clin Appl Thromb Hemost* 2008;14:241–4.
- 10 Madore F, Lazarus JM, Brady HR. Therapeutic plasma exchange in renal diseases. *J Am Soc Nephrol* 1996;7:367–86.
- 11 Guillevin L, Pagnoux C. Indications of plasma exchanges for systemic vasculitides. *Ther Apher Dial* 2003;7:155–60.
- 12 Poynard T, Leroy V, Cohard M, *et al.* Meta-analysis of interferon randomized trials in the treatment of viral hepatitis C: effects of dose and duration. *Hepatology* 1996;24:778–89.
- 13 Campise M, Tarantino A. Glomerulonephritis in mixed cryoglobulinaemia: what treatment? *Nephrol Dial Transplant* 1999;14:281–3.
- 14 Cacoub P, Saadoun D, Limal N, *et al.* PEGylated interferon alfa-2b and ribavirin treatment in patients with hepatitis C virus-related systemic vasculitis. *Arthritis Rheum* 2005;52:911–15.

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