CASE REPORT

Mixed cryoglobulinemia: a diagnostic and therapeutic challenge

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SUMMARY

Mixed cryoglobulinemia is frequently secondary to hepatitis C virus infection. Diagnosis and therapeutic management are challenging, depending on the spectrum and severity of manifestations, as well as on the presence of comorbidities. We describe a case of a 79-year-old woman with a non-cirrhotic hepatitis C virus infection presenting with weakness, arthralgias, purpuric rash with left leg ulcerative lesions, bilateral peripheral sensorimotor polyneuropathy, renal impairment and cardiac failure. The investigation was compatible with a severe type II mixed cryoglobulinemia with multisystemic involvement, including a low-grade B cell lymphoma and concomitant intestinal tuberculosis. Initial management with immunosuppressive therapy with glucocorticoids to control symptoms and simultaneous tuberculosis treatment was required. Unavailability of adequate antiviral treatment led to the need to control the severity of systemic manifestations with rituximab, before the effective aetiological treatment with sofosbuvir and ledipasvir was possible, allowing the definitive resolution of the disease.

BACKGROUND

Hepatitis C virus (HCV) infection is a chronic multi-systemic inflammation disease with well-known hepatic manifestation and a range of extrahepatic manifestations that can affect the autoimmune, metabolic, neurological and cardiovascular systems.^{1,2}

Cryoglobulinemic vasculitis is a systemic inflammatory syndrome characterised by the presence of circulating immunoglobulins (Ig) that precipitate at low temperatures and redissolve with rewarming. This condition can be classified in three serological categories: type I, with monoclonal Ig, and types II and III, the mixed cryoglobulinemia, with a polyclonal IgG and a monoclonal or polyclonal IgM rheumatoid factor, respectively. Mixed cryoglobulinemia is often associated with viral infections, mainly HCV.^{3,4} Cryoglobulins are found in 25%–30% of patients with HCV, but only 10%–15% of these patients develop clinically significant disease, with different ranges of symptoms.⁵ The spectrum of manifestations ranges from mild to severe disease, which may include typical purpuric skin lesions, other organ involvement and lymphoproliferative disorders.⁶

CASE PRESENTATION

We report a case of a 79-year-old woman with hepatitis C (genotype 1b, Metavir score 1), diagnosed by

the age of 75 and under follow-up due to the low fibrosis stage and advanced age. The patient had a history of arterial hypertension, blood transfusion following a spleen fracture and IgG kappa monoclonal gammopathy of undetermined significance (MGUS).

The patient presented at the outpatient clinic with a long-term history of progressive weakness and arthralgias, associated with bilateral lower limb purpuric rash and ulcerative lesions on the left leg (figure 1A), peripheral oedema and progressive dyspnoea over the previous 3 months, followed by diarrhoea with sporadic hematochezia in the previous 2 weeks. The patient was admitted at our department for investigation.

Symptomatically the patient showed Meltzer's triad, composed of purpuric lesions, arthralgias and weakness. The initial laboratory investigation revealed a positive rheumatoid factor (470 IU/mL), positive cryoglobulins (cryocrit 2%, IgG polyclonal and IgM monoclonal), hypocomplementaemia (C4: 3.6 mg/dL, C3: 70 mg/dL) and decreased renal function (creatinine of 1.34 mg/dL and a glomerular filtration rate (GFR) of 58 mL/min).

The diagnosis of type II mixed cryoglobulinemia was made, and all systems were explored in detail to determine its involvement.

Cryoglobulinemia presented with cutaneous involvement, with the physical examination showing purpuric papules of the lower extremities with deep ulceration of the left ankle and foot (figure 1A) and bilateral leg hyperpigmentation (figure 1B). During the hospitalisation, a thorax, abdomen and back cold urticaria episode was observed (figure 1C). A cutaneous biopsy was performed and the histology revealed leucocytoclastic vasculitis (figure 2A).

Musculoskeletal manifestations were expressed with arthralgias, predominantly in the ankles, knees, proximal interphalangeal and metacarpophalangeal articulations, with exacerbation on exposure to cold temperature.

Renal impairment, over the previous 3 months, with an increase of serum creatinine from basal levels of 0.86 mg/dL up to 1.3–1.4 mg/dL (GFR 58 mL/min) was associated with microscopic haematuria and proteinuria (397 mg/24 hours).

The patient presented an insidious mild confusional state, as well as symmetric peripheral hypoesthesia, which were investigated, respectively, with MRI, showing focal white matter hypersignal, and electromyography, evidencing bilateral peripheral motor polyneuropathy.

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Figure 1 Cutaneous lesions: (A) Deeper ulcers in the left leg, (B) cutaneous hyperpigmentation and (C) back with cold urticaria.

Dyspnoea for moderate exertion, bilateral lower extremities oedema and diffuse crackles at pulmonary auscultation, an elevated NT-pro N-terminal brain-type natriuretic peptide (BNP) (3000 pg/mL) with a cardiac ultrasound with absence of cavity dilation, preserved global systolic function, mild mitral, tricuspid and aortic valve insufficiency, and pericardial effusion without haemodynamic repercussion evidenced a state of cardiac failure.

To rule out the hypothesis of progression of MGUS, a bone biopsy was performed, revealing a low-grade B cell lymphoma (10% of the total cell count) (figure 2B).

The patient reported gastrointestinal symptoms during the previous 2 weeks, namely diarrhoea (4–6 bowel movements per day), associated with hematochezia. The bacterial and parasitological cultures were negative and the ileocolonoscopy revealed normal intestinal mucosa. CT scan revealed a parietal thickening of the distal ileum and caecum. Ileal histology showed chronic inflammatory infiltrate with granuloma (figure 2C), while Ziehl-Neelsen colouration demonstrated acid-alcohol-resistant bacillus (figure 2D). The diagnosis of intestinal tuberculosis was established, with the exclusion of systemic involvement, namely respiratory and ganglionic involvement (negative expectoration, blood and bone marrow cultures).

TREATMENT

The patient had a type II mixed cryoglobulinemia secondary to HCV and an intestinal tuberculosis. Initial immunosuppressive therapy with methylprednisolone (7.5 mg/kg 3 days) and subsequent prednisolone (1 mg/kg) during 4 weeks, with gradual tapering, was done to control systemic manifestations. Complete symptomatic resolution was observed, after 4 months, with remarkable cutaneous ulcer resolution (figure 3), normal mental status and renal function improvement, with estimated GFR (eGFR) of 74 mL/min and no proteinuria (<105 mg/24 hours). Concomitant tuberculosis treatment was made (2 months of isoniazid 300 mg, rifampicin 600 mg, ethambutol 1200 mg and pyrazinamide 500 mg, followed by 4 months of isoniazid 300 mg and rifampicin 600 mg).

Although the patient had been proposed for HCV treatment in a regimen without interferon, this therapeutic was not available at the time. Three months after stopping corticotherapy, the patient had symptoms recurrence — one ulceration in the dorsal

left foot, arthralgias and dyspnoea for moderate exertion, with eGFR of 55 mL/min and proteinuria (306 mg/24 hours). Oral corticosteroids were not effective in the reduction of symptoms (namely due to the presence of ulceration worsening) and a new cycle of methylprednisolone (7.5 mg/kg, 3 days) and posterior prednisone (1 mg/kg) was required. A special request for HCV treatment with new direct-acting antivirals (DAA) in a therapeutic regimen without interferon was denied again.

After this, it was impossible to taper prednisolone below 20 mg, and the patient was admitted as an inpatient to start immunosuppressive treatment with rituximab (375 mg/m² = 700 mg; four weekly infusion and two additional doses monthly) with a remarkable improvement (figure 4) and allowing tapering of prednisolone (5 mg/day). Prophylaxis with lamivudine 150 mg/daily (HBcAb-positive, HBsAb-negative, HBsAg-negative, with undetectable hepatitis B DNA) and sulfamethoxazol 800 mg + trimethoprim 160 mg three times a week (pneumocystis prophylaxis) was made.

After 2 months of rituximab interruption, the new DAA for HCV treatment was approved in our country, and the patient underwent treatment with sofosbuvir 400 mg and ledipasvir 90 mg daily, during 12 weeks, with sustained virological response (SVR) at 12 weeks. There was no further need for treatment with immunosuppressive agents.

OUTCOME AND FOLLOW-UP

Twelve weeks after treatment completion, the patient had SVR, shows no skin lesions or arthralgias, and had a normal renal function (proteinuria <105 mg/24 hours, no microscopic haematuria and GFR of 78 mL/min). At 1 year follow-up, the patient remains totally asymptomatic, has negative cryoglobulins, normal C3 and C4 levels and undetectable HCV RNA.

DISCUSSION

This patient had a type II mixed cryoglobulinemia with multi-systemic involvement (cutaneous, musculoskeletal, renal, neurological and cardiac), a low-grade B cell lymphoma (both secondary to HCV) and an intestinal tuberculosis. The primary therapeutic goal in this patient was to control severe vasculitic features (renal, neurological and extensive cutaneous

Figure 2 Histology: (A) Cutaneous histology showing leucocytoclastic vasculitis on H&E staining, (B) bone marrow histology with clusters of CD20+ cells, (C) ileum histology with lymphoid inflammatory infiltrate with granulomas on H&E staining, and (D) Ziehl-Neelsen staining showing *Mycobacterium bacillus*.

Figure 3 Evolution of cutaneous lesions during corticosteroid treatment: (A) After 72 hours of methylprednisolone, (B) after 1 month of prednisolone 1 mg/kg, (C) after 2 months of tapering prednisolone and (D) after 1 month of prednisolone suspension.

Figure 4 Evolution of cutaneous lesions during treatment with rituximab: (A) After first dose of rituximab, (B) after four doses of rituximab and (C) after completion of the treatment with rituximab.

involvement) with pulsed doses of glucocorticoids.⁵ Simultaneously, intestinal tuberculosis was diagnosed and treated accordingly.

After controlling systemic manifestations, the goal was to treat the aetiological factor, HCV. In 2014, in our country, the available treatment was interferon with ribavirin (with or without first-generation protease inhibitors). Given the low response rates of interferon/ribavirin in symptomatic patients with cryoglobulinemia, especially in patients with renal and neurological impairment, and considering the fact that the patient was highly symptomatic (which would probably be associated to poor tolerance to the expected adverse effects) and was a genotype 1 (requiring longer treatment courses), a request for new DAA treatment without interferon was performed.^{7,8} Treatment with interferon-free DAA has shown to be safe and well tolerated, and allows for shorter treatment courses, with low discontinuation rates and high rates of SVR, which in patients with cryoglobulinemia can be as high

as 83%–100%.^{8–11} The patient was informed of the treatment options and decided to wait for the approval of treatment with new DAA.

While waiting for the treatment, the patient needed an additional cycle of pulsed corticotherapy, which was insufficient to resolve the symptoms. At this time, it was necessary to act on a pathogenic feature, the B cell expansion, and to start immunosuppressive treatment with rituximab, a monoclonal antibody against CD20.^{5,12} This agent led to a significant improvement and was important to control the leg ulcers, the neuropathy, the nephropathy and probably the non-Hodgkin's lymphoma.^{12,13}

When the symptoms were once again controlled, it was possible to treat HCV, thus controlling the disease and curing the patient. The treatment of this patient with cryoglobulinemic vasculitis was challenging and required the management of conflicting situations, namely autoimmune manifestations, lymphoproliferative disorder, HCV infection and other infections that had to be weighed in order to achieve the primary goal of curing the patient.

Contributors MKT wrote the manuscript and followed the patient. LC critically revised the manuscript. TBC followed the patient and critically revised the manuscript. CC critically revised the manuscript.

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Learning points

- ▶ Although the presence of circulating cryoglobulins is frequent in patients with hepatitis C virus, the development of a symptomatic cryoglobulinemia is quite uncommon.
- ▶ Mixed cryoglobulinemia is an immunocomplex-mediated condition that can lead to a wide spectrum of multisystemic manifestations, including cutaneous, musculoskeletal, renal, neurological, cardiac, haematological, pulmonary and gastrointestinal symptoms.
- ▶ Therapeutic management may include aetiological, pathogenic and symptomatic treatment options, which must be individualised for each patient, according to the severity of each manifestation of the disease.
- ▶ In patients with severe disease manifestations, initial immunosuppressive therapy should be performed, followed by treatment of the underlying condition.
- ▶ Whenever immunosuppressive agents are used, it is important to consider the reactivation of latent infections, namely hepatitis B.

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