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CLINICAL NOTES

Long-term remission with rituximab in a patient with severe hepatitis C virus-induced mixed cryoglubulinemia

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ABSTRACT

Mixed cryoglobulinemia (MC) is a small-vessel systemic vasculitis characterized by the presence of cryoglobulins, immunoglobulin complexes that precipitate at low temperatures (< 37 °C) inducing the inflammatory process. The most frequent etiology is hepatitis C infection (HCV) (1). Rituximab (RTX), an anti-CD20 monoclonal antibody, has recently emerged as the treatment of choice for severe MC (2). We present a case of severe hepatitis C virus-induced MC that was controlled and maintained in remission with RTX for 26 months, a remarkable prolonged period of time.

Key words: Cryoglobulinemia. Rituximab. Hepatitis C infection.

CASE REPORT

A 62-year-old woman with genotype 1b chronic hepatitis C was being followed as an outpatient in our hospital. To estimate the grade of fibrosis we performed a percutaneous liver biopsy which revealed both moderated activity and fibrosis (P3, L2, F2). During follow-up, she suffered from an erythematous rash in the distal lower extremities that histologically corresponded to a leukocytoclastic vasculitis. She also began with paresthesias in both feet. The neurophysiological study performed showed symmetric lesions of both motor and sensitive fibers in the lower extremities, all of which was suggestive of multiplex mononeuritis. The most important findings of blood analysis were: Hemoglobin 11.9 g/dL, MCV 85.3, INR 1.34, normal renal function, albumin 3.1 g/dL, total bilirrubin 2.1 mg/dL, ALT 42 U/L, AST 74 U/L, alkaline phosphatase 94 U/L, gammaglutamyl transferase 77 U/L, rheumatoid factor 197 UI/mL, normal immunoglobulins (Ig), positive cryoglobulins, complement component 4 (C4) 6 mg/dL, negative HBV and HAV serology, and HCV viral load of 1,134,990 UI/mL. She was then diagnosed of hepatitis C virus-induced MC with cutaneous (leukocytoclastic vasculitis) and neurological involvement (multiplex mononeuritis). Prior to the initiation of antiviral treatment, our patient was admitted in our hospital due to an acute episode of distal paresis of the right lower extremity associated with pain in the dorsum of the foot and ipsilateral distal lower extremity that prevented her from walking. She also presented with *livedo reticularis* in both lower extremities. The neurological exploration suggested peroneal and fibular nerve damage, which was linked to an exacerbation of her multiplex mononeuritis. Due to the severe of its presentation we started treatment with high dose corticoids (3 daily bolus of 250 mg metilprednisolone followed by 1 mg/kg for a month with progressive withdrawal afterwards), 6 sessions of plasmapheresis and subsequent administration of RTX (four weekly 375 mg/m^2 infusions). At day 2, she began with progressive dyspnea secondary to a massive right pleural effusion that needed drainage with the insertion of a chest tube. Its analysis showed transudate characteristics. In order to clarify its etiology we performed a chest computed tomography, an echocardiogram and an abdominal echography. The first two tests did not reveal any significant alterations while the latter showed signs of chronic liver disease, permeability of mesenteric vessels and splenomegaly as the unique sign of portal hypertension. The lack of any overt cardiovascular disease, the good response to the subsequent administration of diuretics together with the presence of esophageal var-

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ices observed in the upper endoscopy performed, allowed the diagnosis of thoracoascites secondary to her liver disease. The previous finding of grade 2 fibrosis in the liver biopsy was attributed to the sampling error attached to this technique. During her hospitalitation we performed a head MRI that did not show any significant alterations and an electromyogram which located the nerve damage at the right common peroneum nerve. The blood analysis revealed thrombocytopenia of 75,000/μL not previously known and mild proteinuria and microhematuria in the urine test performed without associated renal dysfunction. She had a favorable evolution with an improvement of her paresis, resolution of *livedo reticularis* and negativization of cryoglobulins. The first of the four weekly doses of RTX was administrated the day before her hospital discharge. Two months later, we started antiviral treatment with pegylated interferon and ribavirin, which had to be stopped at week 12 due to a lack of response.

During her subsequent follow-up as an outpatient for 26 months, she has had a favorable evolution with total recovery from her paresis and has not suffered any new exacerbation of MC. As possible adverse effects of RTX, she had two respiratory tract infections that resolved with antibiotic treatment and persistent hypogammaglobulinemia. As far as her liver disease is concerned, she requires diuretic treatment for an appropriate control of thoracoascites. Her Child-Pugh score is 7 points (class B) and after weighing the pros and cons we decided not to initiate a new antiviral treatment with protease inhibitors.

DISCUSSION

Cryoglobulins are classified by the method of Brouet et al. into three types (3): *Type I cryoglobulins* consist of single monoclonal immunoglobulins associated with lymphoproliferative disorders. *Type II cryoglobulins* are composed of monoclonal IgM with rheumatic factor activity and polyclonal IgG. It is the most frequent cryoglobulinemia and HCV represents its main etiological agent. Finally, *type III* cryoglobulins consist of polyclonal IgM and IgG that are mainly associated with immunological diseases, but also with HCV. Globally, HCV represents the cause of MC in 80 % of the cases (1).

Although cryoglobulins can be detected in 36-55 % of HCV-infected patients, only 2-3 % suffers overt vasculitic manifestations (4). Increased duration of HCV infection constitutes a risk factor for its development. It is more common in women and in patients aged 45-65 years. No predominant ethnicity has been described (1).

The disease expression is variable both in the number of organs involved and in the severity of the complications. Although almost any organ can be affected (Table I), the most frequent organs involved are the skin, kidneys, joints and peripheral nerves. Peripheral neuropathy constitutes the most refractory complication to treat (1,4).

Patients with hepatitis C virus-induced MC have a worse prognosis than those with chronic HCV infection without MC (1). In a recent study the survival at 1, 3, 5 and 10 years in patients with HCV-related systemic vasculitis was 96, 86, 75 and 63 % respectively. The main causes of death were severe infections in patients treated with immunosuppressive agents and end-stage liver disease. The major prognostic factors identified in this study were liver fibrosis and vasculitis-related organ involvement expressed by the Five-Factor Score. The latter includes five clinical items, each one resembling the involvement of the following organs: Kidneys, heart, gastrointestinal tract and central nervous system. It is worth mentioning that the prognosis of patients with advanced liver fibrosis at the time of diagnosis of MC relies only on liver disease (5).

Diagnosis is based on clinicopathological and laboratory findings. Besides the presence of cryoglobulins there are other findings that support the diagnosis (1):

- Low C4 and decreased total hemolytic complement levels. C3 is usually mildly decreased or not affected.
- Rheumatoid factor activity.
- Electrophysiological study: Determines the location of the nerve damage.
- Viral serologies (HCV, HCB, cytomegalovirus, Epstein-Barr virus and parvovirus B19) and non-organ-specific autoantibodies to determine the etiology of MC.

Although there is no established therapeutic protocol, a panel of experts of the Italian Group for the Study of Cryoglobulinemia (GISC) promoted a consensus conference to discuss currently used therapies such as glucocorticoids, immunosuppressors, apheresis or biological therapy. Among their recommendations, they proposed RTX as the first line treatment for patients with severe MC (2). The available therapies treat the disease at different levels of the etiopathological cascade (6) (Fig. 1). RTX is a chimeric monoclonal antibody against CD20 antigen, which is selectively expressed on B cells (2). Its union to this antigen triggers B cell death through direct lysis and complement-dependent or antibody-dependent cytotoxicity (7). Moreover, recent investigations suggest additional mechanisms by which RTX could be effective in this disease. Accordingly, RTX seems to restore both B cell and T cell immune homeostasis. As far as the former cell subtype is concerned, in MC there is a reduced size of the global B cell compartment due to a decreased number of naïve B cells that is partially compensated by an increased frequency of immature transitional B cells (7,8). In their study, Holz et al. found an increased susceptibility to apoptosis of the *naïve* B cells that could explain the anomalous distribution described. These same authors also observed a decreased ratio of T1:T2 immature transitional B cells that was related to the increased cryoglobulin levels proper of this disease. After RTX treatment and the recovery of B cells that commenced approximately 6 months after its administration, the different B cell subtypes, the altered T1:T2 ratio, and

Table I. Clinical manifestations of mixed cryoglobulinema (1,4)

Cutaneous manifestations
Palpable purpura
Skin ulcers
Livedo reticularis
Most frequent histopathological pattern: leukocytoclastic vasculitis
Renal involvement
Asymptomatic proteinuria and hematuria
Nephritic or nephrotic syndrome
Variable progression to chronic renal insufficiency
Most frequent histopathological pattern: Type 1 membranoproliferative glomerulonephritis
Neurological manifestations
Sensory or sensory-motor peripheral neuropathy, rarely pure motor neuropathy, often presenting as mononeuritis multiplex
Central nervous system vasculitis
Rheumatologic manifestations
Arthralgias: Most frequent manifestation
Arthritis: Rare, with two types
Non-erosive oligoarthritis involving medium-sized and large joints
Symmetrical polyarthritis mimicking rheumatoid arthritis
Xerostomia/xerophtalmia, but only few fulfill the classification criteria for Sjögren syndrome
Raynaud syndrome
Gastrointestinal manifestations
Abdominal pain and gastrointestinal bleeding secondary to mesenteric vasculitis (20 % of cases)
Cardiovascular manifestations
Myocardial infarction, pericarditis and congestive heart failure secondary to coronary vasculitis
Lung involvement
Asymptomatic (most frequent)
Diffuse interstitial pulmonary fibrosis
Alveolar hemorrhage (rare)

the cryoglobulins levels were restored (7). The influence of RTX treatment on T cell homeostasis is more controversial. Saadoun et al. observed an improvement of the regulation/activation and Th1/Th2 imbalances after RTX administration (8). The use of RTX as the first line treatment in patients with severe MC is based on the recent evidence obtained from several studies published in the last 3 years. The first of these studies compared the efficacy and safety profile of PEG-interferon-ribavirin and RTX and antiviral treatment alone. The combined treatment had a shorter time to clinical remission (5.4 *vs.* 8.4 months; $p < 0.004$), better renal response (80.9 *vs.* 41 %; $p < 0.04$), and higher rates of cryoglobulin clearance (9). Another study with similar design obtained equal conclusions (10). More recently, De vita et al. reported the results of a multicenter trial in which conventional treatment (glucocorticoids, azathioprine or cyclophosphamide, or plasmapheresis) was compared to RTX in patients with severe MC. The primary end point of the study was the survival of treatment at 12 months (i.e., the proportion of patients who continued taking their initial therapy). This survival was statistically higher in the RTX group (64.3 *vs.* 3.5 %, $p < 0.0001$). Other interesting findings revealed by this study were the following (11): a) The median time to relapse after RTX therapy was 1.5 years. This long-term response supports a regimen of retreatment at the time of clinical relapse, rather than a maintenance regimen. The latter could, however, be useful in some patients with very severe CV (severe nephritis, abdominal vasculitis). Data from other studies show that the median duration of the initial response to RTX is approximately 1 year and that retreatment with RTX after a disease relapse is effective in most of the cases; b) RTX was effective even in patients in whom conventional treatment had failed, although with a slightly lower response rate (60.9 *vs.* 71.4 %) and a shorter long-term response (12 *vs.* 18 months). This finding supports an earlier treatment with RTX; and c) patients treated with RTX responded earlier than those treated with conventional treatment. It is generally believed that glucocorticoids and plasmapheresis have an earlier response compared to immunosuppressors such as RTX or cyclophosphamide. Data from other RTX studies reported renal responses within 1-6 months, less than 3 months for skin ulcers and 1-5 months for peripheral neuropathy. The response rates for the renal and neurological involvement were around 90 and 75 %, respectively (2). In the last trial performed by Sneller et al., RTX was again superior to conventional treatment at achieving remission at month 6 (83 *vs.* 8 %, $p < 0.0001$) (12). As far as its safety profile is concerned, RTX infusion reactions represent the most common adverse effect. Other important side effects are HBV reactivation and a greater risk for infections, especially in elderly patients, those who concomitantly receive other immunosuppressors and those who secondary develop hypogammglobulinemia (as is the case of our patient). With regard to its influence on HCV, RTX can increase HCV viral load without significant liver impairment due to the latter or to drug toxicity. With all this evidence, the panel of experts of the GISC proposed RTX as the first line treatment in severe MC. Nevertheless, there is no data to decide whether it is better to start with both RTX and antiviral treatment at the same time or in a sequential manner, generally postponing the antiviral therapy for a month. In our patient, we preferred this last option in order to avoid overlapping toxicities and to control the disease prior to the initiation of antiviral therapy, especially when it has been described that the latter can exacerbate the neurological damage (2). The standard dose and regimen of RTX used in most published MC cases is the one described in our patient.

In conclusion, MC is a disease with variable expression both in the number of organs involved and in the severity of its presentation. Its management should be tailored to each individual patient and discussed in multidisciplinary

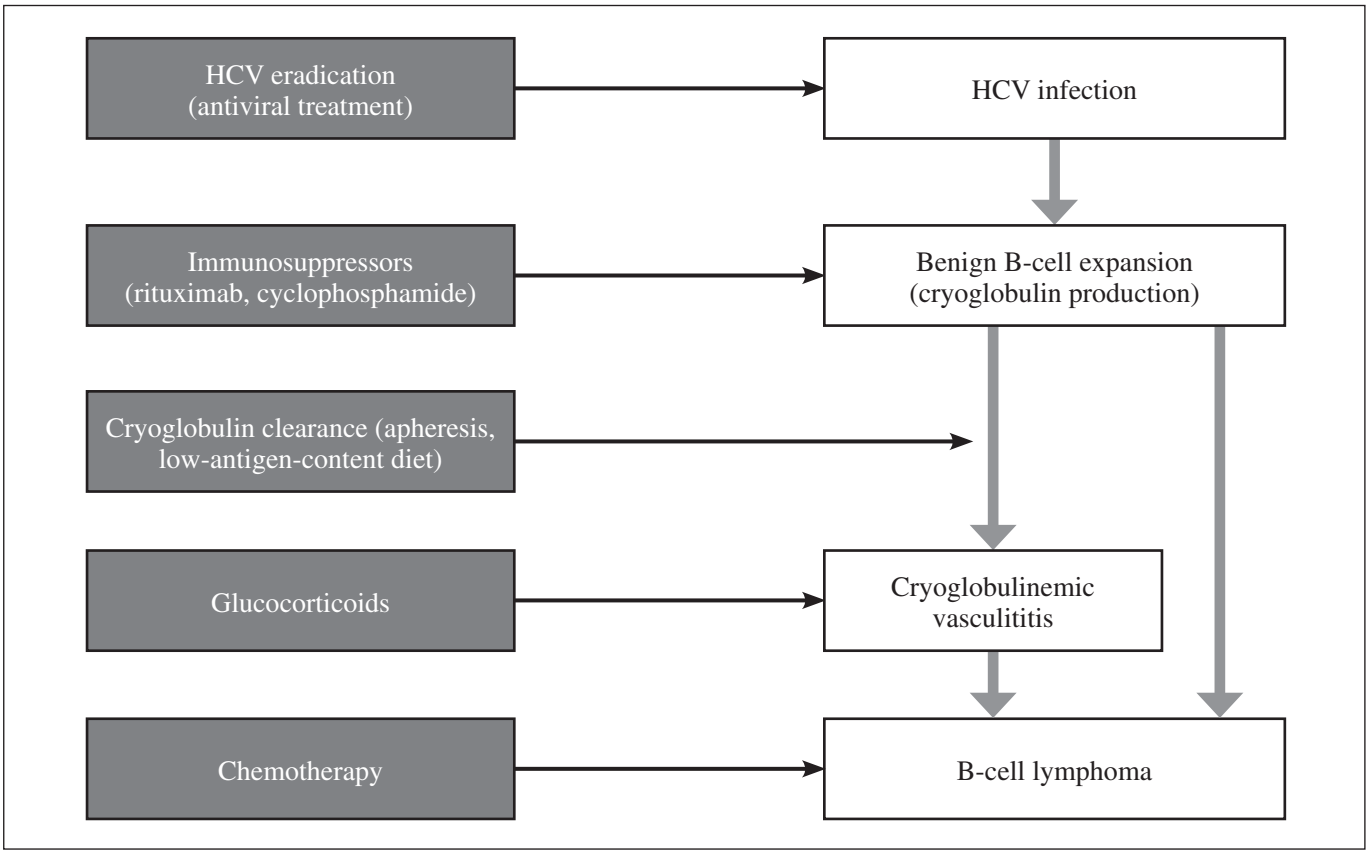

Fig. 1. The available therapies treat the disease at different levels of the etiopathological cascade (6). HCV infection induces a benign B cell expansion that leads to cryoglobulin production. A minority of patients can develop a frank malignant lymphoma on long-term follow-up (< 10 %). The available therapies treat the disease at different levels of the etiopathological cascade.

teams. In this scenario, RTX has emerged as the treatment of choice in severe MC, enabling patients to remain in remission for significant prolonged periods of time, as is the case of our patient.

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