



Case Report

Cryoglobulinemia With Acronecrosis Not Associated With Hepatitis C Infection: A Case Report[☆]

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ABSTRACT

Cryoglobulinemia is a rare disease characterized by the production of monoclonal or polyclonal immunoglobulins that precipitate in cold temperature. While this phenomenon can be observed in a large number of disorders, it has been associated with hepatitis C virus infection in more than 90% of cases. The remaining 10%, called essential cryoglobulinemia, has been characterized by a more severe course and a failure to respond to conventional treatment. This article describes the case of a patient with essential cryoglobulinemia presenting with acronecrosis with a poor outcome, despite treatment, leading to amputation.

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Crioglobulinemia con acronecrosis no asociada a infección por hepatitis C: reporte de un caso

RESUMEN

La crioglobulinemia es una enfermedad rara en la cual se producen inmunoglobulinas monoclonales y/o policlonales que precipitan con el frío. Si bien este fenómeno puede observarse en una gran cantidad de trastornos, se ha asociado más frecuentemente a la infección por el virus de la hepatitis C en más del 90%. El porcentaje restante, llamado crioglobulinemia esencial, se ha caracterizado por curso más severo y falta de respuesta al tratamiento convencional. El presente artículo describe el caso de un paciente con crioglobulinemia esencial que se presenta con acronecrosis, en la que su mala evolución, a pesar del tratamiento, la lleva a la amputación.

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Palabras clave:

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Introduction

Cryoglobulins are circulating immunoglobulins that precipitate in the cold and become soluble again with heat. Cryoglobulinemia is a rare vasculitis affecting arteries of small and medium caliber, and the veins, that is produced by deposition of immune complexes in vessel walls, with subsequent activation of the complement system. This disorder is classified according to the composition of the precipitate in 3 ways: monoclonal cryoglobulinemia (type I), composed of simple monoclonal immunoglobulin, mixed

cryoglobulinemia, consisting of a mixture of polyclonal IgG and monoclonal IgM rheumatoid factor (type II) and the polyclonal variety (type III). This type of classification has a good clinical and etiological correlation. Type I is associated with lymphoproliferative disease and multiple myeloma, while types II and III are associated with connective tissue diseases and infections.¹

The clinical manifestations of cryoglobulinemia symptoms can vary from only general and non-specific to joint pain, renal, neuropathic and skin involvement, which in a few cases can become acronecrosis.²

The association between hepatitis C virus (HCV) and mixed cryoglobulinemia (MC) has been highly evident from the recognition of serological markers for HCV infection, and found in 90% of cases.³ However, there are some cases in which no associated pathology can be determined, so this group is classified as essential⁴ cryoglobulinemia.

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Here we present a case of essential mixed cryoglobulinemia not associated with hepatitis C infection, presented with symptoms of lower limb acrocyanosis, which required amputation of several distal phalanges of the foot, despite an early diagnosis, as a result a poor response to treatment.

Case Report

A 64-year-old woman with a history of hypertension and type 2 diabetes mellitus treated with torasemide 5 mg/day and dietary control, respectively, came to the clinic. She had started her illness with symptoms of joint pain and Raynaud's phenomenon in hands and feet almost 1 year prior. Twenty days before admission she presented fever predominantly during the evening, with an average temperature of 38 °C, which diminished with metamisole, as well as burning sensation in the legs, fatigue and weight loss of 6–7 kg in the past 10 months. Upon examination, the patient was febrile but other vital signs were in the normal, with a good general condition, focused and well hydrated. A cardiac auscultation showed rhythmic sounds, a I-II/VI ejection murmur, but no other abnormalities; peripheral pulses were present. On examination of skin there was discoloration of the lower limbs, mainly on the dorsal aspect of the foot (Fig. 1). The remainder of the examination was normal. During hospitalization, the analysis showed leukocytosis 13 500 cells/mm³ (75% segmented PMN, 15% lymphocytes), Hb 10.8 g/dl, MCV 84.7, platelets 332 000, ESR 54 mm/h and CRP 48 mg/dl. Coagulation studies as well as liver and kidney function were within normal limits. Serologic studies for cytomegalovirus, Brucella and Epstein-Barr as well as Mantoux and serial blood cultures were negative. No alterations of tumor markers, antinuclear antibodies, anti-native DNA, ANCA and rheumatoid factor were seen. After measuring cryoglobulins, a 25%–30% cryocrit was obtained (polyclonal–monoclonal pattern) in separate determinations, always with negative rheumatoid factor without complement consumption and negative analysis for hepatitis B and C. The protein profile showed a monoclonal gammopathy of uncertain significance, but dismissed the presence of a lymphoproliferative process, because of no significant alterations in the CBC, no alteration in the bone marrow study and finally, imaging studies (computed tomography and ultrasound) ruled out the presence of nodal and hepatosplenic involvement. The electromyogram showed signs compatible to severe sensory-motor polyneuropathy with greater lower limb involvement, but the pathological examination of biopsied parts of nervous tissue and vascular alterations were not found. The remaining studies, gastroscopy, abdominal



Fig. 1. Cold induced acrocyanosis in toes of the right foot.



Fig. 2. Amputation of several toes of the left foot.

ultrasound, echocardiogram, visceral arteriography, chest radiography and electrocardiogram, showed no pathological data.

The patient received corticosteroids and cyclophosphamide and remained without fever and showed slight improvement of the dysesthesia in the legs. After discharge, the outpatient controls were carried out for 4 years, and the patient received 8–32 mg methylprednisolone/day depending on the clinical situation. Nevertheless, dysesthesia persisted, with stabbing pain and vascular disorders of the lower limbs, with amputation of the second and fourth left toe injury due to chronic ischemic necrosis (Fig. 2) becoming necessary. Given the poor clinical improvement, additional treatments were tried with prostaglandins, bosentan and rituximab, without satisfactory results. Finally, we had to resort to plasmapheresis associated with rituximab, which maintained the cryocrit at 10% but with only partial control of dysesthesias and vascular abnormalities of the lower limbs.

Discussion

MC is a relatively rare disease associated with many infections or immunological diseases, with an etiology not yet fully explained. It is known that HCV infection plays an important causal role, but the contribution of genetic factors and/or environmental factors is unknown.^{5,6} Since the identification of HCV in 1989, it has been recognized as the cause of about 90% of cases of MC and <5% of cases are now considered essential, in which no causal agent can be determined.⁷ These figures vary a little depending on the prevalence of HCV infection and other demographic aspects.^{3,8}

Essential MC usually has a more aggressive course than those secondary to other diseases, with prevalence of renal, neuropathic and impaired peripheral circulation. Treatment with corticosteroids and immunosuppressants such as cyclophosphamide is unsatisfactory, so the use of anti-CD20 monoclonal antibodies (rituximab), plasmapheresis or drugs still under evaluation as lenalidomide, and alternative therapies is under evaluation.⁴ Plasmapheresis usually provides good results, reducing the levels of circulating immune complexes and cryoglobulins, so it is particularly used in severe complications of essential MC.⁷ This is reflected in this clinical case, where after performing all additional studies to determine any underlying disease, it was concluded that we were dealing with a case of essential MC (type II), presenting with symptoms, such as anemia, joint involvement, and cutaneous vasculitic.

Despite establishing treatment with glucocorticoids, immunosuppressants, vasodilators and rituximab we did not achieve an effective response, as seen in cases of MC associated with HCV infection, so plasmapheresis sessions were begun, associated with rituximab, which achieved partial control of the disease. It was decided that the patient should receive combination therapy with plasmapheresis and rituximab before the winter as a preventive measure of vascular damage.

In terms of clinical manifestations, these can range from a relatively benign course, to dramatic complications that might endanger the life of the patient.^{1,2,9} The main ones are palpable purpura, systemic symptoms, arthralgias, lymphadenopathy, hepatosplenomegaly, peripheral neuropathy, hypocomplementemia, bronchiolitis obliterans, glomerulonephritis, Raynaud's phenomenon, livedo reticularis and acrocyanosis, as well as ulcers and necrosis of the skin.^{5,6} Throughout the progression of our patient, we observed no control of peripheral involvement, which led to necrosis of the second and fourth fingers of the left foot, with subsequent amputation. This severe skin involvement occurs in only about 2% of cases and is due to vasculitis with fibrinoid necrosis and inflammation of the vessel wall and perivascular space, which most often affects the lower limbs, and can evolve to a chronic ulcer and gangrene, as in our patient, as well as cases published in several reviews and case reports.^{2,10,11}

In conclusion, the particularity of this case is the presentation of one of the few cases of MC associated with no underlying disease (non-HCV), being therefore essential, and as mentioned in other

articles, these cases have an abrupt clinical presentation and poor response to conventional therapy.

Conflict of Interest

The authors have no conflict of interest to declare.

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