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CASE REPORT

Type I Cryoglobulinemia With a Fatal Outcome

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PALABRAS CLAVE

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Abstract Type I cryoglobulinemia, a condition associated with lymphoproliferative disorders, is caused by monoclonal immunoglobulins that precipitate at low temperatures. It mostly involves the skin and pathology study shows no signs of vasculitis. Management is usually based on immunosuppressive drugs associated with plasmapheresis for severe disease. The use of rituximab has recently been described for resistant cases. We present an unusual case of long-standing type I cryoglobulinemia associated with a monoclonal gammopathy of uncertain significance. The patient developed extremely severe skin lesions with histological signs of vasculitis. The patient died due to the onset of noncutaneous manifestations of the cryoglobulinemia and complications of the immunosuppressive treatment.

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Crioglobulinemia tipo I de desenlace fatal

Resumen La crioglobulinemia tipo I es un trastorno producido por inmunoglobulinas monoclonales que precipitan a bajas temperaturas. Se asocia a trastornos linfoproliferativos, su clínica es predominantemente cutánea y la anatomía patológica no muestra fenómenos de vasculitis. En su manejo se emplean habitualmente fármacos inmunosupresores junto con plasmaféresis para los casos graves. Recientemente se ha descrito el uso de rituximab para los casos resistentes. Se presenta un caso poco común de crioglobulinemia tipo I de largo tiempo de evolución asociada a una gammopatía monoclonal de significado incierto. El paciente desarrolló lesiones cutáneas de extrema gravedad con fenómenos de vasculitis en la anatomía patológica, y presentó un desenlace fatal secundariamente a la aparición de manifestaciones extracutáneas de la crioglobulinemia y a las complicaciones del tratamiento inmunosupresor.

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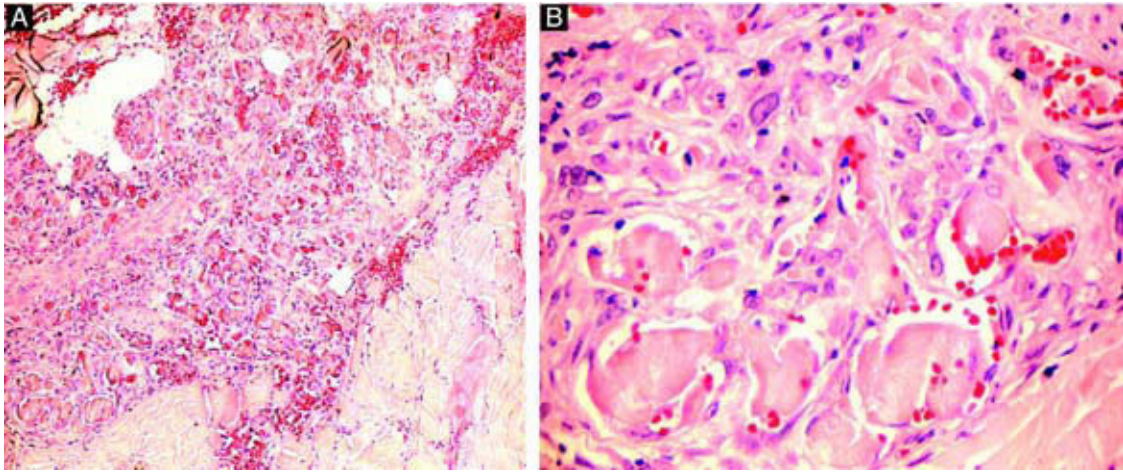


Figure 1 Histologic image of a biopsy sample taken from the thigh showing hemorrhagic areas, multiple hyaline thrombi, and capillary recanalization. Hematoxylin-eosin, original magnification $\times 10$ (A) and $\times 40$ (B).

Introduction

Cryoglobulinemia, a group of disorders characterized by the presence of immunoglobulins that precipitate at low temperatures (cryoglobulins), presents with different degrees of severity and systemic involvement. Three types have been described, depending on whether the immunoglobulins are monoclonal or polyclonal or on whether there is a positive rheumatoid factor. Type I cryoglobulins are monoclonal and are usually only associated with skin manifestations triggered by cold.

Treatment varies according to severity, and includes a range of systemic immunosuppressants (corticosteroids, azathioprine, cyclophosphamide) and plasmapheresis.

In view of the pathophysiology of cryoglobulinemia, rituximab, a monoclonal antibody that induces B-cell depletion and has been successfully used in various autoantibody-mediated disorders, might also be a treatment option for refractory disease.

Case Description

A 65-year-old man was seen in our outpatient clinic in February 2010 seeking urgent attention for multiple painful skin ulcers.

He had been diagnosed with type I cryoglobulinemia in 1988. Specifically, he had monoclonal, kappa light-chain immunoglobulin G (IgG) cryoglobulinemia in association with a monoclonal gammopathy of uncertain significance. Laboratory assays at the time of diagnosis were negative for antibodies against hepatitis viruses B and C, antinuclear antibodies, anti-ds-DNA, anticardiolipin antibodies, protoplasmic-staining antineutrophil cytoplasmic antibodies (ANCA), classical ANCA, and rheumatoid factor. The results for coagulation factor V and proteins C and S were normal. Screening studies, which included a bone marrow biopsy and computed tomography scan of the neck, chest, abdomen, and pelvis, ruled out the presence of associated neoplasms. Several biopsies were also taken from the right

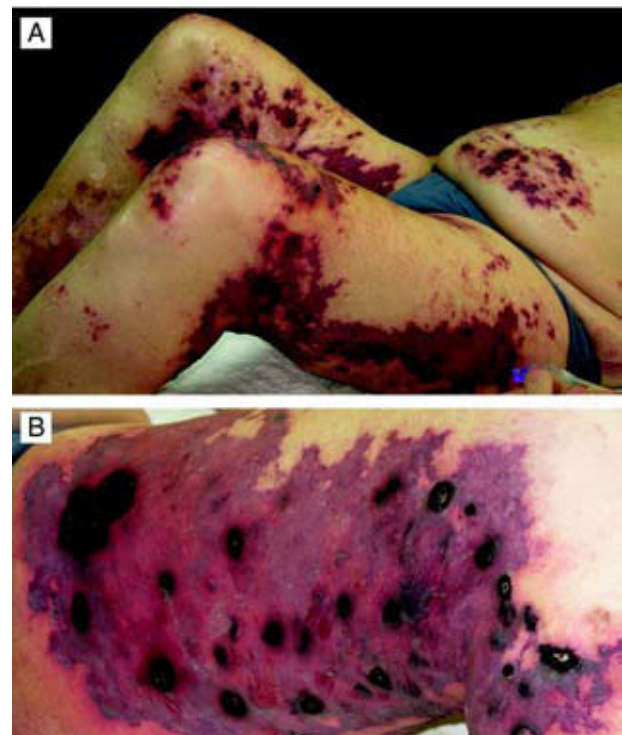


Figure 2 A, Numerous ulcers on the abdomen, buttocks, and legs. B, Erythematous-violaceous ulcers with well-defined borders and central necrosis.

buttock and lumbar region. Histology revealed capillary thrombi and recanalization in all the biopsies (Figure 1), with evidence of leukocytoclastic vasculitis in some of them.

From the time of diagnosis to the visit to our clinic, the patient had been treated with various combinations of immunosuppressants, including corticosteroids (in oral form for maintenance therapy and as bolus and intravenous therapy for flare-ups and during plasmapheresis); methotrexate; mycophenolate mofetil; azathioprine; and



Figure 3 Residual lesions, from previous flare-ups, on the abdomen and flank (A) and on the legs, with amputation of the toes of the right foot (B).

pulse cyclophosphamide therapy. While these treatments had generally kept the disease under control, the patient periodically (every 1 to 2 years) developed flare-ups that required hospitalization.

Physical examination revealed numerous large erythematous-violaceous plaques, which the patient described as painful, on the abdomen, thighs, and legs (Figure 2A). The plaques showed central ulceration and had well-defined borders (Figure 2B). The patient also had hypopigmented scarring lesions caused by previous flare-ups (Figure 3A). The toes on his right foot had been amputated (Figure 3B).

In view of the evident flare-up of the disease and the severity of the patient's condition, the patient was hospitalized, primarily to achieve stabilization and secondarily to start rituximab as a new form of maintenance therapy.

Treatment was initiated with daily plasmapheresis combined with systemic corticosteroids, and morphine was administered via a pump to control the pain. On day 5 of admission, the onset of sepsis with fever, a poor general state, hypotension, and leukocytosis with a left shift required interruption of the plasmapheresis and transfer of the patient to the intensive care unit. Blood cultures and cultures of the plasmapheresis catheter and from 1 of the bleeding ulcers on the hip showed the growth of methicillin-resistant *Staphylococcus aureus*. Treatment was initiated with daptomycin (720 mg twice daily), vancomycin (1 g every 12 hours), vasopressor agents, and intravenous fluid replacement. A day after admission to the intensive care unit, the patient's situation was further complicated by an ischemic stroke and 2 days later, kidney failure requiring dialysis. Finally, on day 8 of admission, the patient developed respiratory distress and died.

Discussion

Cryoglobulins are immunoglobulins that precipitate at low temperatures, with clinical presentations that range from asymptomatic disease to extremely serious conditions. Three types of cryoglobulinemia, which vary according to

their clonality and rheumatoid factor activity, have been described. In type I cryoglobulinemia, the immunoglobulins are mostly IgM, although on occasions they may be IgG or light chains; they are monoclonal and rheumatoid factor is negative. Rheumatoid factor interacts with monoclonal immunoglobulins in type II cryoglobulinemia and with polyclonal immunoglobulins in type III cryoglobulinemia to form immune complexes that trigger the clinical manifestations of the disease. There have been occasional reports of the formation of heterogeneous microaggregates in which the components could not be clearly identified.¹

The case we report is particularly interesting from a clinical perspective but its etiology and pathology are also of interest.

Clinically, type I cryoglobulinemia runs a more benign course than types II or III as it mostly affects the skin. The involvement of organs such as the kidney and the nervous system is rare. Skin manifestations include Raynaud phenomenon, acrocyanosis, purpura, ulcers, and necrosis; the lesions are generally confined to the distal parts of the limbs and are rarely found on the buttocks or the trunk.¹ The skin lesions in our patient were extremely severe and covered as much as 10% of the body surface; they affected not only the thighs but also the buttocks and the abdomen. Another interesting clinical aspect of the case was the fact that the patient experienced an ischemic stroke. While central nervous system manifestations are occasionally reported in type II and III cryoglobulinemia, they are uncommon in patients with type I disease. Given the severity of our patient's condition and the fact that he developed sepsis, we cannot say for certain whether the stroke was caused by the sepsis, the cryoglobulinemia, or both.

Etiologically, types I, II, and III cryoglobulinemia have been associated with lymphoproliferative disorders, autoimmune diseases, and infections² (Table). There have also been reports of essential, or primary, cryoglobulinemia, ie, cases in which no associated diseases have been found. The most common lymphoproliferative disorders associated with type I cryoglobulinemia are Waldenström macroglobulinemia, multiple myeloma, and chronic lymphocytic leukemia.^{3,4} There have only been 2 reports

Table 1 Most Common Disorders Associated With Cryoglobulinemia

| | |
|------------------------|---|
| Hematological diseases | Multiple myeloma, Waldenström macroglobulinemia, chronic lymphocytic leukemia, and monoclonal gammopathy of uncertain significance |
| Infections | Hepatitis C and B virus |
| Autoimmune diseases | Sjögren syndrome, systemic lupus erythematosus, polyarteritis nodosa, rheumatoid arthritis, temporal arteritis, dermatomyositis-polymyositis, Henoch-Schönlein purpura, sarcoidosis |

to date of type I cryoglobulinemia in association with monoclonal gammopathy of uncertain significance.^{3,5} This is an initially benign process characterized by the expansion of a clone of plasma cells or lymphoid cells capable of producing immunoglobulins, with no evidence of malignancy.⁶

Histologically, leukocytoclastic vasculitis is not a common finding in type I cryoglobulinemia as the vascular involvement typically presents as hyaline thrombi without inflammatory phenomena.

The main treatment strategy in cryoglobulinemia is to identify and control the underlying cause and to reserve the use of immunosuppressants (in association or not with plasmapheresis) for refractory cases. Several recent studies have used drugs such as bortezomib⁷ and rituximab^{4,8,9} to treat cryoglobulinemia. Rituximab is an anti-CD20 monoclonal antibody that has shown good results at doses of 375 mg/m² administered intravenously.¹⁰

Given the severity of our patient's condition and the presence of resistance to multiple treatments, we decided to initiate in-hospital treatment with plasmapheresis and systemic corticosteroids and to start rituximab once the patient was stabilized. Unfortunately, he died of sepsis secondary to the immunosuppression typically associated with the standard treatments for cryoglobulinemia.

In conclusion, we have described a case of highly aggressive type I cryoglobulinemia with histopathologic evidence of vascular occlusion and vasculitis and associated with a monoclonal gammopathy of uncertain significance.

Conflict of Interest

The authors declare that they have no conflict of interest.

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