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Type 1 Cryoglobulinemia in Monoclonal Gammopathy Presenting as Acute Renal Failure and Fatal Outcome

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Abstract The cryoglobulinemia , particularly type 1 or monoclonal, is a rare disease with variable severity and diverse clinical manifestations and may lead to death due to multisystem failure and secondary infections. The early recognition and treatment of this disease are essential for a good prognosis. We report a case of cryoglobulinemic disease associated with Monoclonal gammopathy of Undetermined Significance with fatal outcome.

Keywords: *monoclonal gammopathies, cryoglobulinemic vasculitis, cryoglobulinemia, livedo reticularis*

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1. Introduction

The cryoglobulinemic vasculitis (CV) is considered a disease of small and medium vessels by deposits of immune complexes formed from immunoglobulins that precipitate in the cold (cryoglobulins)[1]. There are three types of cryoglobulinemia (CG) according to clonality and immunoglobulin type, being the type 1 or monoclonal, considered extremely rare, accounting for about 6% of the cases [1]. Cryoglobulinemia may be classified based on cryoglobulin composition with the Brouet classification, which is as follows:

-Type I cryoglobulinemia is the result of a monoclonal immunoglobulin, usually immunoglobulin M (IgM) or, less frequently, immunoglobulin G (IgG), immunoglobulin A (IgA), or light chains.

-Types II and III cryoglobulinemia (mixed cryoglobulinemia) contain rheumatoid factors (RFs), which are usually IgM and, rarely, IgG or IgA. These RFs form complexes with the fragment, crystallizable (Fc) portion of polyclonal IgG. The actual RF may be monoclonal (in type II cryoglobulinemia) or polyclonal (in type III cryoglobulinemia) immunoglobulin. Types II and III cryoglobulinemia represent 80% of all cryoglobulins.

We report a case of CV by monoclonal immunoglobulin presenting with systemic manifestation and kidney failure, and histopathological diagnosis of CG.

2. Case Report

The case reported hereafter was authorized for publication with patient consent and approved by the ethics committee in research, as recommended by the CNS. Man, 45 years old, born and living in Fortaleza - Brazil, approximately 1 year before hospital admission began symptoms of asthenia, anorexia, fever and synovitis in small joints of the hands. Ten months afterwards there was worsening of symptoms, associated with reduced urine output, dizziness and blurred vision, livedoid vasculitis, palpable purpura in the lower limbs, and was admitted for etiologic diagnosis. During hospitalization there was a worsening of cutaneous symptoms and has started bilateral epistaxis and drowsiness, compatible with hyperviscosity syndrome.

Table 1. Supplementary tests

Test	Result	Reference
Hemoglobin	8,9 mg/ dl	12,5-15,5 mg/ dl
Leukocytes	6800mm³	4000-10000 mm³
Neutrophil	3200mm³	2000 -7500 mm³
Lymphocytes	2000 mm³	1500-5000 mm³
ESR	55 mm	<10 mm
C -reactive protein	200 mg	< 6 mg
Albumin	3,6 g /dl	3,5 - 5,0
Lactate dehydrogenase	556 U/ fl	200 - 450
Creatinine	2,6 mg/ dl	0,4 -1,1
Bilirubin	1,2 mg/ dl	<1,2 mg/ dl
ANCA	Negative	Negative
ANA	Negative	Negative
Anticardiolipin IGM and IgG	Negative	Negative
Serum Cryoglobulin	Negative	Negative
C3	23 mg/ dl	90-170
C4	0,4 mg/ dl	12-36
Immunofixation	IgG and Kappa	Negative

Initial investigation showed anemia, elevated erythrocyte sedimentation rate and C-reactive protein, increased urea and creatinine (see Table 1). Urinalysis showed hematuria with dysmorphic erythrocyte and proteinuria. Antibody anti-neutrophilic cytoplasm as well as antinuclear, rheumatoid factor and cryoglobulins. Protein electrophoresis showed monoclonal component of 0.36 grams per deciliter, IgG and kappa pattern on immunofixation. Bone marrow aspirate showed monoclonal slight increase of plasma cells (5%).

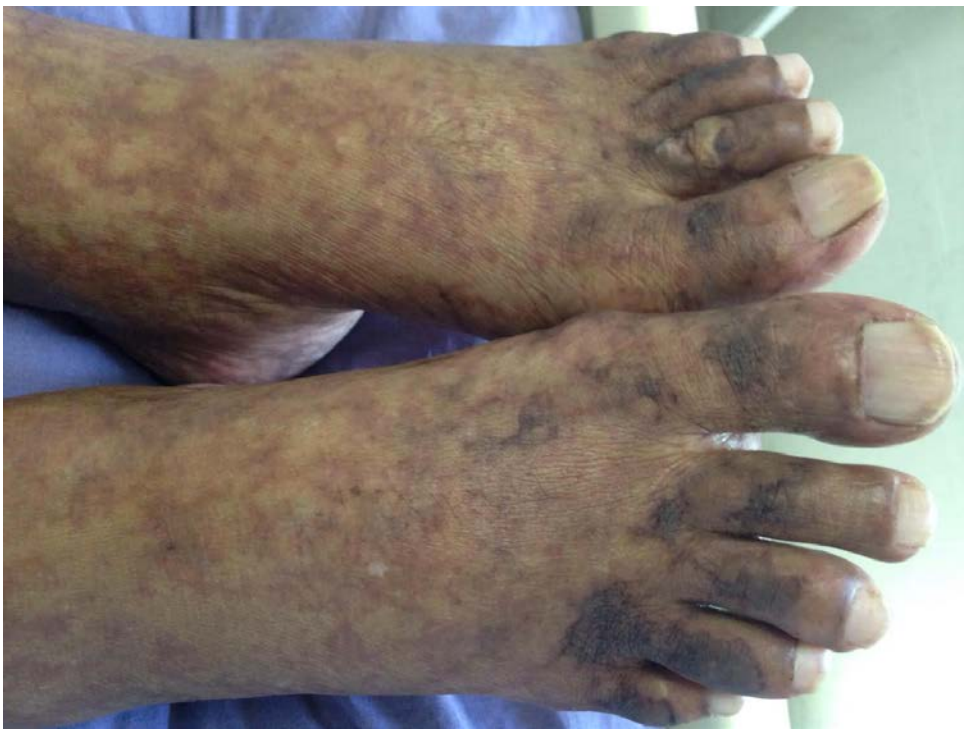

Figure 1. Patient Photography showing livedo and acral necrosis induced by cold

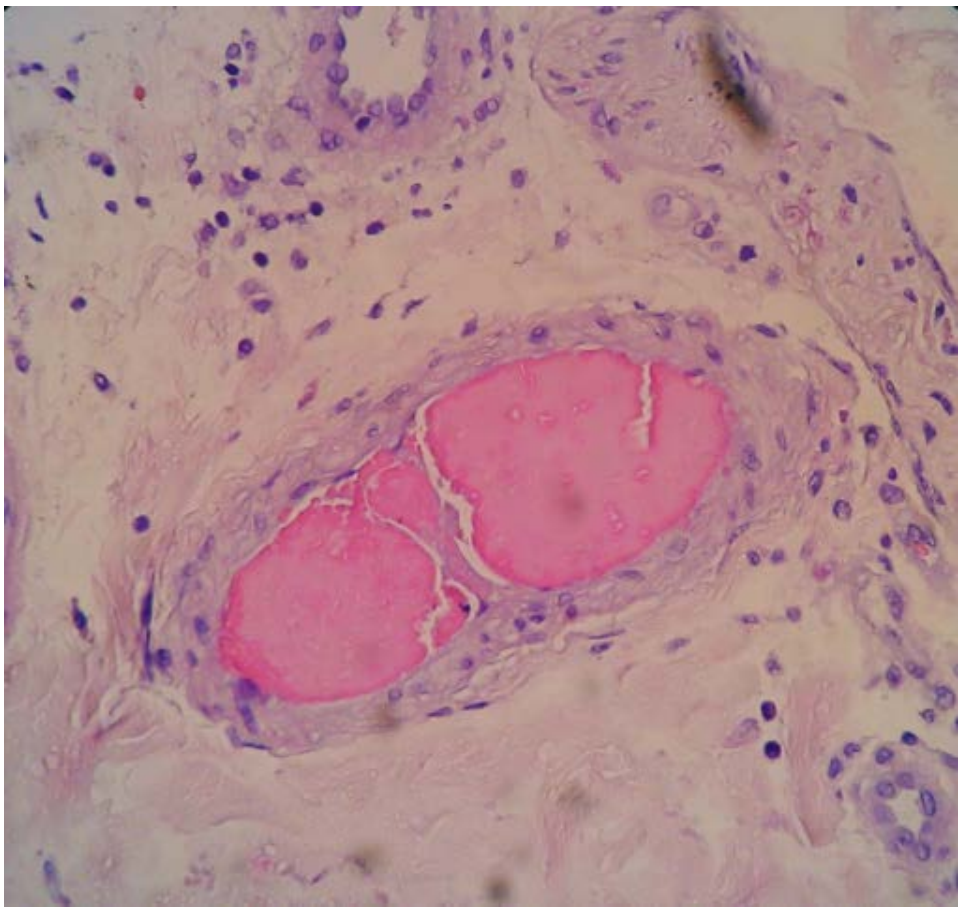

Figura 2. Skin biopsy , H&E 100 x, showing small dermal vessels with homogeneous and eosinophilic content, consistent with intravascular cryoglobulin deposit

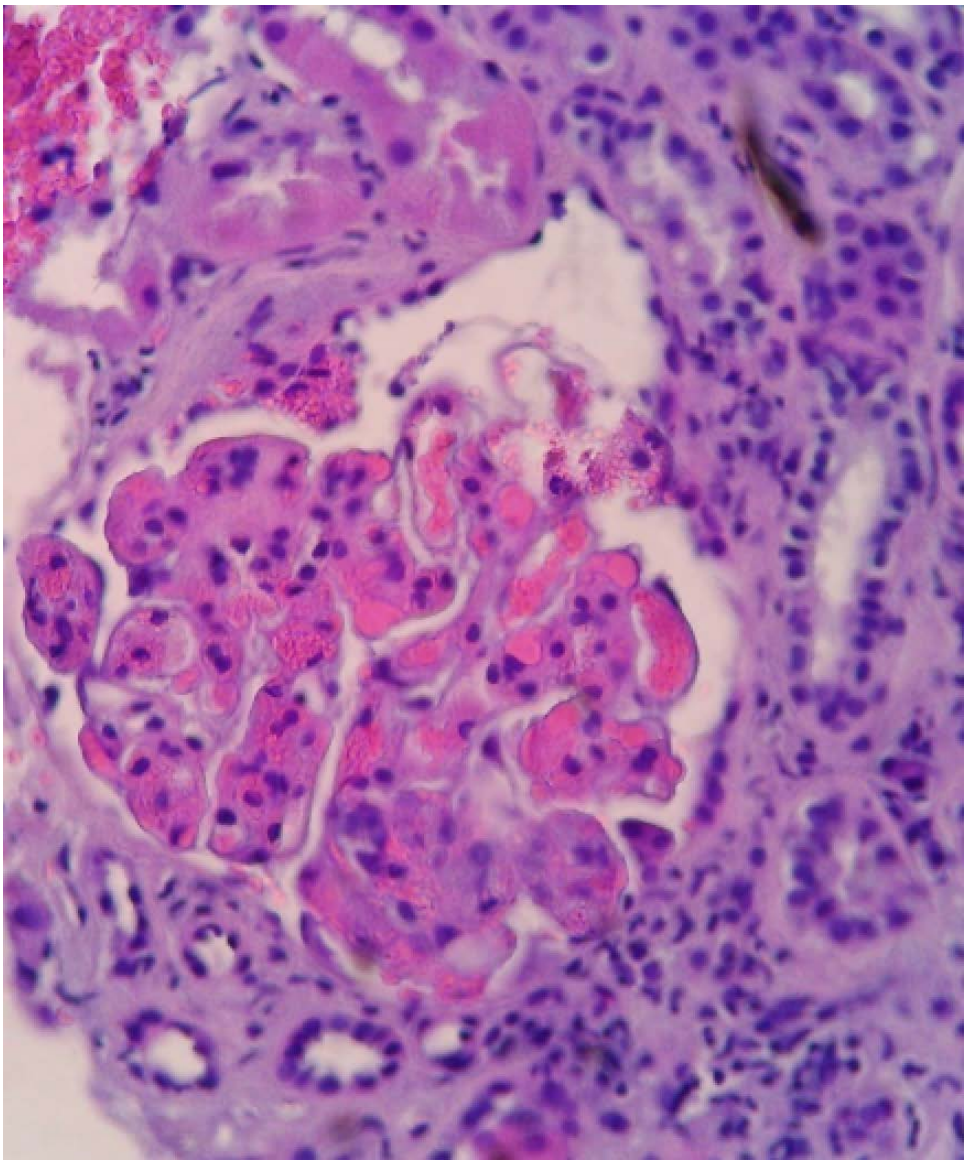

Figure 3. Renal Biopsy, H & E 100x ,showing multiple hyaline pseudothrombi in the glomerular capillaries

It was decided, for diagnostic purposes, perform skin and kidney biopsy, which revealed the presence of hyaline thrombi compatible with cryoglobulinemic vasculitis (Figure 2 and Figure 3)

With the diagnosis of type 1 CG associated with monoclonal gammopathy of undetermined significance, it was decided by immunosuppression with anti-CD20 antibody (Rituximab) and methylprednisolone. On the tenth day post- rituximab patient developed fever and hypotension, and initiated broad-spectrum antibiotics, but eventually developed disseminated intravascular coagulation, and death from circulatory shock.

3. Discussion

Cryoglobulins are immunoglobulins that precipitate in the cold and can be classified according to composition: type 1, monoclonal, type 2, polyclonal and monoclonal and type 3, polyclonal [1,2]. The deposition of these immunoglobulins in vessels and organs causes CV. The classic triad of symptoms described by Melter et al[3] consists of fatigue, arthralgia and palpable purpura, being present in 90% of cases.

The main causes of CG are chronic infections, especially hepatitis C, autoimmune diseases such as lupus erythematosus [1]. The CG Type 1 is considered extremely rare, and less studied, generating diagnostic and therapeutic dilemmas [2,3].

Data from the CryoVas [2] study revealed that the cryoglobulinemia type 1 was often associated with cutaneous necrosis and ulcers, with lower frequency of renal involvement and better prognosis than suggested in previous studies.

A series of 36 cases of type 1 GC has recently been published [3], which showed that the immunoglobulin isotype was IgM in 70% of patients and IgG in 30% . The underlying disease was Gammopathy Moclonal of Undetermined Significance in 36% of cases, Waldestron Macroglobulinemia in 33%, Multiple Myeloma in 11% of cases and non-hodgkin's lymphoma in 16%.

At clinical presentation, 58% of the patients presented skin changes, the palpable purpura was the most common, followed by livedo reticularis , Raynaud phenomenon, inflamatory macules and papules, pigmentary changes and infarction. Peripheral neuropathy occurred in 47% of cases, the predominant form was axonal polyneuropathy (70% of cases in which there neuropathy).

In the kidney, 30% of patients have acute renal insufficiency or proteinuria in the nephrotic range, the main histopathological change is membranoproliferative glomerulonephritis followed by thrombotic microangiopathy [4].

Histopathologic findings can be grouped into five major diagnostic categories: vasculitis; inflammatory or noninflammatory purpura without vasculitis; hyaline thrombosis; postinflammatory sequelae; and coexisting cutaneous disease of unknown significance, such as necrobiotic xanthogranuloma. The presence of hyaline thrombi without vasculitis is highly sugestive of type 1 CG [5].

Treatment of GC type 1 depends on the underlying disease and the severity of the case , the majority of patients with mild cases will be managed symptomatically and with steroids or immunosuppressive agents, patients with severe fulminant illness are treated with cytoreductive therapy, corticosteroids at high doses or anti-CD20 (rituximab) [1-2]. Patients with hyperviscosity syndrome should be handled with plasmapheresis. Some studies suggest that in GC type 1 the use of proteasome inhibitors, such as bortezomib, is more effective than depletion of B lymphocytes [6]

The case shows the importance of an early diagnosis and treatment for the pathology above. There was a 1-year delay in the patient's diagnosis, leading to worsening of performance status and worse tolerability of immunosuppression.

4. Conclusion

Cryoglobulinemic disease by monoclonal imunoglobulin, although rare, should be readily recognized, especially in patients with multisystem involvement, since the introduction of effective therapeutic such as plasmapheresis and immunosuppression can be lifesaving.

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