Type-I Cryoglobulinaemia Associated to Monoclonal Gammapathy of Undetermined Significance

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Abstract: Cryoglobulins are immunoglobulins that undergo reversible precipitation at cold temperatures. Monoclonal type-I cryoglobulinaemia is the least frequent and is associated to hematological diseases such as multiple myeloma, Waldenström’s macroglobulinaemia, chronic lymphocytic leukaemia and lymphoma. We describe the case of a 60-year-old female patient, who suffered from burning pain in her feet for ten months before her admission. The patient presented intermittent distal cyanosis that progressed to digital ischaemia. She also reported paresthesia in her hands, difficulty in writing, and a 26-kg-weight loss. At the physical examination, it was identified livedo reticularis, palpable purpura, and painful ecchymotic lesions in her calves and feet. Moreover, peripheral pulses were palpable and symmetrical. It was observed an atrophy of the right first dorsal interosseous and both extensor digitorum brevis, as well as a distal bilateral apal aesthesia and allodynia. Both Achilles reflexes were absent. Laboratory tests revealed anemia, high erythrosedimentation rate and C-reactive protein. Serum protein electrophoresis showed a monoclonal IgG-Kappa gammopathy. The results also evidenced the presence of Bence-Jones proteinuria. The bone marrow biopsy revealed less than 10% of plasma cells, and skin biopsy informed leukocytoclastic vasculitis. The patient was treated with high-dose intravenous steroids and cyclophosphamide. The treatment showed that the skin lesions had improved, pain disappeared and motor deficit stopped its progression.

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Introduction
Cryoglobulins are immunoglobulins that precipitate with cold and can be monoclonal or polyclonal. Type-I cryoglobulinaemia is the least common form of presentation. It is monoclonal and is usually associated with lymphoproliferative diseases such as multiple myeloma, Waldenström macroglobulinaemia, chronic lymphocytic leukemia and lymphoma (Ramos-Casals et al., 2012; Ramos et al., 2017). It follows the description of the case of an adult patient who developed ischemia, digital and peripheral vasculitis neuropathy secondary to type-I cryoglobulinaemia related to monoclonal gammopathy of undetermined significance (MGUS). The established immunosuppressive therapy achieved a clear improvement of symptoms.

Case report
A 60-year-old woman who, 10 months before her admission, started feeling burning pain in both soles and intermittent distal cyanosis in both lower extremities, which were exacerbated by standing and exposition to cold, was admitted. In the last month it evolved with a persistent blueish coloration in the 3rd to 5th toes of the right foot, with necrotic lesions. She reported paresthesia in both hands and difficulty in writing and fine mobility in the right hand for the last month. She noticed a twenty-six-kilogram weight loss for the last 6 months, related to a hypocaloric diet. She denied fever, arthralgia and colour changes in the hands or face. Nor did she refer any other relevant symptoms in her past personal and familiar history.

On physical examination, it was found a presence of livedo reticularis, palpable purpura and ecchymotic lesions, painful at palpation, in both the anterior and medial legs (Figure 1). The third right toe showed bluish colour and distal necrosis. Peripheral pulses were present. No edema was found.

Figure 1 – Distal necrosis of the third toe; purpuric lesions in the left lower limb.
The neuromuscular examination showed loss of strength in the right interosseous muscles (MRC scale 3/5); the strength was normal at the remaining muscles; hyporeflexia in the right upper limb and both lower limbs, as well as bilateral indifferent plantar reflexes. She presented atrophy of the first right dorsal interosseum and both extensor digitorum brevis muscles; she described allodynia in legs and feet.

Stein Weinstein’s monofilament test was positive on both soles of the feet. The rest of the physical examination, including the fundus and the capillaroscopy, was normal.

The electromyogram determined the existence of a sensory-motor axonal neuropathy in the lower limbs, with denervation, associated with the dysfunction of A-delta fibers (abnormal silent cutaneous period). In the upper extremities, a multiple axonal mononeuritis was evident.

Imaging studies of the chest, abdomen and pelvis showed no pathological findings, except for signs of hepatic steatosis. Arterial and venous Doppler ultrasounds of both lower extremities was normal.

The presence of osteolytic lesions in the skull or long bones was not evident. Renal function and urinary sediment were normal. Total body positron emission tomography showed no abnormalities.

In the admission laboratory Hb (hemoglobin) 10.4 g/dl (reference value (RV) = 12.0–16.0) compatible with anemia of chronic disorders; erythrosedimentation > 120 mm/h (VR < 30) and C-reactive protein 3.83 mg/dl (RV < 0.3 mg/dl). The rest of the laboratory showed no relevant findings.

Antibodies against HIV, hepatitis B and C were negative. VDRL (venereal disease research laboratory test) was not reactive.

The C4 fraction of the complement decreased: 4 mg/dl (RV = 16.0–47.0) and the C3 fraction was normal.

Figure 2 – Left: cryoglobulin precipitation from serum; right: immunofixation, monoclonal IgG-Kappa type-I cryoglobulin.
The electrophoretic proteinogram showed a monoclonal component of 1.9 g/dl in the gamma fraction. Serum electro immunofixation determined an IgG-Kappa monoclonal gammopathy. Proteinogram with immunofixation of the urine showed Bence Jones proteinuria of the Kappa type. The quantification of serum immunoglobulins by immunoturbidimetry resulted in: IgG 1,530 mg/dl (RV = 658–1,837), IgA 45 mg/dl (RV = 71–360) and IgM 87 mg/dl (RV = 40–263).

The determination of serum cryoglobulins was positive: cryocrite 16% (RV < 0.5). Immunoochemical typing of purified cryoglobulin (immunofixation): monoclonal IgG-Kappa type-I cryoglobulin (Figure 2). The viscosity of the serum was normal. The PCR for hepatitis C virus in the cryocrit sample was negative.

The determination of rheumatoid factor, antinuclear antibodies (FAN/AAN-IFI-Hep-2, linear immunoassay), Anti DNA, Anti-Sm, Anti-U1snRNP, Anti-Scl-70, Anti-SSA/Ro (52), Anti-SSA/Ro (60), Anti-SSB/LA, Anti-Cemp-B, anti-Histones, Anti-Rib-P and ANCA were negative.

The myositis profile of the antibodies was negative: method: linear immunoassay. Substrate: highly purified or recombinant antigens (Anti-jo-1, Anti PM/Scl-100, Anti PL-12, Anti Mi-2, Anti Ku (p70/80), Anti SRP, Anti PL-7) antibodies.

The determination of the antiganglioside-IgG/IgM-ELISA antibodies (Anti GM1, anti-Asialo GM1, anti-GM2, anti-GD1a, anti-GD1b and anti-GQ1b) was negative. The anti-MAG-IgM-ELISA antibody (myelin-associated glycoprotein) was negative.

A bone marrow biopsy puncture was performed: it showed abnormalities of the plasma cells compatible with monoclonal gammopathy of uncertain importance.

The skin biopsy revealed leukocytoclastic vasculitis.

The diagnosis was a type-I cryoglobulinaemia vasculitis associated with a monoclonal gammopathy of undetermined origin (MGUS): immunosuppressive treatment was initiated with high-dose corticosteroids and intra-venous cyclophosphamide. The skin lesions improved, burning pain in the lower extremities subsided and the progression of motor involvement stopped.

Discussion
The patient began her disease with dermatological and neurological manifestations that worsened with cold, due to a type-I cryoglobulinaemia, associated with an IgG-Kappa MGUS. This entity corresponds to 22% of all patients with cryoglobulinaemia, followed by multiple myeloma and Waldenström macroglobulinaemia. Cutaneous involvement due to vascular purpura and peripheral neuropathy are the most frequent manifestations (Sidana et al., 2017).

The clinical manifestations are due to deposits of immune complexes in the vascular wall of the skin, joints, the peripheral nervous system or the kidney. Capillaries, arterioles and cryocrite are primarily involved, but small and medium-sized arteries can also be affected (Damoiseaux and Cohen Tervaert, 2014).

The most frequent cutaneous sign (in 80–90% of patients) is palpable purpura, which always begins in the lower extremities; the trunk and upper extremities are...
less involved. Raynaud’s syndrome and acrocyanosis can occur (Cacoub et al., 2015). In our patient, all of them were dermatological manifestations, in addition to ulceration and necrosis in the third toe of the left foot, which are the most frequent signs in this type of cryoglobulinaemia (Kolopp-Sarda and Miossec, 2018). Histopathological lesion of the skin was compatible with leukocytoclastic vasculitis: this manifestation is not frequent in type-I cryoglobulinaemia, albeit it has been reported (Echeverría et al., 2011).

Neuropathy associated with cryoglobulinaemia is found in 7–17% of symptomatic patients. It consists of an axonal damage secondary to necrotizing vasculitis or intraneuronal infiltration of cryoglobulins. Most vasculitis neuropathies are multiple mononeuritis or symmetric motor-sensory neuropathy. In some patients, the presence of anti-GM1 or anti-sulfatide antibodies (Thomas et al., 1992) may be detected. Painful neuropathies secondary to cryoglobulinaemia might also be caused by other contributing factors, such as the increased expression of proinflammatory cytokine genes or nerve growth factor (NGF).

In summary, there is a reduction in the density of intraepidermal nerve fibers in this painful neuropathy (Blaes, 2015; Hsu et al., 2017). The patient described had an axonal neuropathy with concomitant involvement of the small fibers in the lower extremities; and in the upper extremities, a multiple mononeuritis of the axonal type. Anti-GM1 antibodies were negative and the presence of anti-sulfatide antibodies could not be determined.

Our patient was diagnosed with IgG-Kappa MGUS, without anti-MAG antibodies. These antibodies are more frequently associated with IgM MGUS and cause a paraproteinemiceous demyelinating neuropathy, by interfering with the signalling between the axon and the Schwann cell: a reduction in the phosphorylation of neurofilaments and a reduction in the axonal caliber is generated, thus reducing the efficiency of nerve (Ramos et al., 2015; Talamo et al., 2015). MGUS is considered a premalignant condition, as it is associated with lymphoproliferative disorders such as multiple myeloma, Waldenström macroglobulinaemia, chronic lymphocytic leukaemia and lymphoma (Kagaya and Takahashi, 2005).

Type-I cryoglobulins lack rheumatoid factor (FR) activity and do not readily activate complement. In this case report, complement C4 was greatly diminished and C3 was normal, typical of mixed cryoglobulinaemia.

The association of corticosteroids and cyclophosphamide led to the improvement of the skin and the peripheral neurological syndrome, with a decrease in painful symptoms. In the largest study of type-I cryoglobulinaemia associated with MGUS, most patients received this treatment scheme. Other treatments performed in that study were rituximab or only corticosteroids. The improvement was 57% in those patients with MGUS IgG and 86% in those with IgM MGUS (Sidana et al., 2017).

In conclusion, we present the case of a woman with type-I cryoglobulinaemia associated with IgG-Kappa MGUS, which manifested mainly with peripheral neuropathy and dermatological lesions, without renal complications.
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