

Extensive leg and foot ulcers as a manifestation of cryoglobulinaemia with accompanying monoclonal gammopathy of undetermined significance

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Abstract

Cryoglobulinaemia is characterized by the presence of cryoglobulins in serum, which precipitate at temperatures below 37°C and dissolve on warming. Cryoglobulins may form immune complexes or circulating aggregates, which induces clinical symptoms of leucoclastic vasculitis or leads to hyperviscosity syndrome. Clinically, cryoglobulinaemia is classified into idiopathic cryoglobulinaemia without any accompanying disease and secondary cryoglobulinaemia, which occurs in association with other diseases, e.g. infectious, lymphoproliferative and connective tissue diseases. Treatment of cryoglobulinaemia depends on a concomitant disease. The aim of the present study was to describe a case of extensive leg and foot ulcers as a manifestation of cryoglobulinaemia accompanying monoclonal gammopathy of undetermined significance.

Key words: ulcers, cryoglobulins, monoclonal gammopathy.

Introduction

Cryoglobulinaemia is the presence of cryoglobulins – plasma proteins in serum, which precipitate and form gels at temperatures below 37°C and dissolve on warming [1]. The proteins in question are composed of monoclonal, polyclonal antibodies and immunoglobulins – the constituents of immune complexes [2]. In 1933, Wintrobe and Bullet first observed serum precipitation in a patient with myeloma whereas the term “cryoglobulin” was introduced by Lerner and Watson in 1947 [3, 4].

The mechanism of formation and precipitation of cryoglobulins has not been fully elucidated. It is thought that temperature-dependent solubility of these proteins is determined by structural changes [5]. Serum cryoglobu-

lins may form immune complexes or circulating aggregates, which results in clinical symptoms of leucoclastic vasculitis or leads to the hyperviscosity syndrome [5].

Clinical symptoms of cryoglobulinaemia have various locations; lesions mostly appear on the skin but other organs and systems may also be affected. The most characteristic symptoms include skin purpura, arthralgia, and weakness, described by Meltzer and Franklin in 1966 and known as the Meltzer triad [6].

Clinically, cryoglobulinaemia is classified into idiopathic cryoglobulinaemia – without any accompanying disease and secondary cryoglobulinaemia – likely to coexist with various diseases. Based on the precipitate composition, three types of cryoglobulinaemia are distinguished:

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- type I – monoclonal, mainly with IgM, less frequently IgG, IgA, light chains, without the presence of rheumatoid factor; this type often accompanies lymphoproliferative diseases, e.g. multiple myeloma, lymphoma, chronic lymphocytic leukaemia or Waldenström macroglobulinaemia;
- type II – mixed – monoclonal-polyclonal immunoglobulins, mainly IgM, less frequently IgG, IgA, with the presence of rheumatoid factor, which accompanies HCV infection, lymphoproliferative and autoimmune diseases; and
- type III – mixed polyclonal cryoglobulinaemia with IgM against IgG and the presence of polyclonal rheumatoid factor, which accompanies HCV, HBV, CMV, EBV infections and autoimmune diseases, mainly lupus erythematosus and Sjögren's syndrome [1, 2, 5, 7].

The aim of the study was to describe a case of extensive leg and foot ulcers with the presence of cryoglobulins accompanied by monoclonal gammopathy of undetermined significance (MGUS).

Case report

A 59-year-old female patient was admitted to the Department of Dermatology, Venerology and Paediatric Dermatology, Medical University of Lublin in December 2009 with a 4-year history of ulcers of both legs. Since April 2008, the patient had been treated for leg ulcers in the course of venous failure at the Surgical Ward of the Public Health Care Institution and the Department of Dermatology of the Military Hospital in Lublin. During hospitalization in the latter institution, numerous examinations were carried out and connective tissue diseases were ruled out. The patient had a history of diabetes and hypertension.

On admission to our Department, the patient was in good general condition although exhausted by the disease, continuous development of new ulcers, severe pain of the lower limbs, and sleepless nights due to pain, which

required narcotic analgesics (other agents were ineffective). Her family history was insignificant. The physical examination of the lower parts of legs, lateral and medial ankle regions of both feet, heels, right great toe and second toes of both feet revealed ulcers, 1 cm to 12-14 cm in diameter, coated with the necrotic, purulent material and surrounded by petechiae. Moreover, the outside edges of both feet and toes were covered with blue-brown spots quickly undergoing necrosis and new ulcers developed (Fig. 1). In the past, she had her fourth finger of the right hand amputated. Ulcers were accompanied by severe pain and the Reynaud's phenomenon. Capillaroscopy showed the pale-pink background, normal number of loops, slightly disorganized loop system in right hand fingers, proper morphology of the majority of loops, single loops slightly branched or curled and slower blood flow with plasma windows in numerous vessels. No dilated loops, megacapillaries, extravasations or thrombotic features were observed. Laboratory tests demonstrated markedly elevated inflammatory factors (CRP 90.5 mg/l, SR 68/h), decreased level of total protein and iron deficiency anaemia; cryoglobulins were found in serum. The remaining biochemical blood tests to assess liver and kidney functions were within normal limits.

A number of laboratory tests were performed due to the presence of cryoglobulins. ANA, pANCA, ANCA, rheumatoid factor, anticardiolipin and thyroid antibodies were not found. Moreover, Sjögren's syndrome was not observed; the Shirmer's test was normal. The levels of C3 – 1.610 g/l and C4 – 0.220g/l, were within normal limits.

Further diagnostic procedures did not reveal the presence of HBV antigen, HCV, HBV, HIV, HIV1/HIV2 antibodies or HCV p24 antigen. The presence of IgG antibodies for CMV was not demonstrated yet the infectious disease physician excluded active CMV infection, hence no further diagnostic procedures and treatment were required. The imaging examinations: thyroid ultrasound, chest HRCT, oesophago-, gastro- and duodenoscopies, CT of the



Fig. 1. Pre-treatment lesions



Fig. 2. State after two cycles of plasmapheresis

abdominal cavity and pelvis minor, as well as mammography were normal. Moreover, tumour markers, CA 19-9, Ca 125, CA 15-3, or CEA, were not found.

The patient underwent protein electrophoresis with immunofixation, which disclosed IgG_κ monoclonal protein, 22.30 mg/l (normal range: 3.3-19.4 mg/l). After the haematology consultation, bone marrow trepanobiopsy was performed. The histopathological evaluation carried out in the Centre of Oncology in Poznań on 18.02.2010 and consulted in Warsaw, showed marrow cellularity suitable for age, with all haematopoietic lines, and the M : E ratio preserved. However, the increased number of plasmatic cells (CD 138+), scattered in small aggregates, was observed. They constituted about 10-15% of all cells and were characterized by monoclonality (secreting IgG_κ) (+).

The bone marrow biopsy findings and IgG_κ monoclonal protein detected in serum electrophoresis and immunofixation led to the diagnosis of monoclonal gammopathy of undetermined significance (MGUS), suggesting a higher risk of developing multiple myeloma. Furthermore, the presence of cryoglobulins was confirmed and type I cryoglobulinaemia was diagnosed [8, 9]. The patient was scheduled for plasmapheresis and underwent two cycles, 5 plasmaphereses each; each plasmapheresis removed 900 ml of plasma; for supplementation, crystalloids and fresh frozen plasma were administered, which improved her general and local condition, relieved pain in lower limbs (Fig. 2). Additionally, Encorton was recommended in the initial dose of 20 mg, increased to 30 mg. After completion of electrophoresis, the patient was treated intravenously with methylprednisolone 3 × 500 mg and cyclophosphamide 1000 mg in monthly cycles – in total 4 pulses. The treatment substantially improved the local lesions; ulcers started to heal, pain was relieved and cryoglobulin test results were negative (Fig. 3). At present, the patient requires further haematological observation and periodic dermatological follow-up.

Discussion

The report presents an interesting case of type I cryoglobulinaemia accompanying monoclonal gammopathy of undetermined significance manifested as long-lasting, extensive ulcers of legs and feet, which caused intensified pain sensations and enormous fatigue. The incidence of this type of cryoglobulinaemia is estimated at 10-15% of diagnosed cases and commonly accompanies lymphoproliferative diseases [1]. In our case, numerous additional tests were performed; serum protein electrophoresis and immunofixation confirmed the presence of IgG_κ monoclonal protein whereas in bone marrow an increased number of IgG_κ positive plasmatic cells (10-15%) was demonstrated, which enabled the diagnosis. The therapy involved two cycles of plasmapheresis, 5 procedures each, which improved the general and local condition of the patient and relieved the pain. It is assumed that plasmapheresis not only removes cryoglobulins, circulating complexes and inflammatory mediators but also modifies the capacity of cryoglobulins to precipitate [10, 11]. The further stage of treatment consisted of cyclic monthly pulses of methylprednisolone and cyclophosphamide; the majority of ulcers healed and healing of the biggest ulcers persisting for over 4 years substantially improved. Moreover, the serum cryoglobulin test was negative and IgG_κ monoclonal protein in serum immunofixation was not detected. The treatment administered was to result in non-specific decrease in production of antibodies [11]. Nonetheless, due to the presence of IgG_κ monoclonal protein in serum and increased percentage of bone marrow plasmatic cells (CD138+) IgG_κ(+), the patient requires further clinical and laboratory observation due to the risk of plasmocytic myeloma or other lymphoproliferative diseases. The factors affecting the development of lymphoproliferative diseases in monoclonal gammopathy of undetermined significance have not been fully known. Genetic factors, angiogenesis in bone marrow and infectious factors are considered to be involved in progression



Fig. 3. State after two cycles of plasmapheresis and pulses of methylprednisolone and cyclophosphamide

of lesions [8]. Serum levels of monoclonal protein, including free light chains (FLC), the type of monoclonal protein (higher risk of myeloma was observed in patients with IgA or IgM gammopathy compared to those with IgG proteins), and percentages of bone marrow plasmatic cells are found useful for prognosis [9].

Skin lesions in cryoglobulinaemia may manifest as extravasations, palpable purpura, urticaria increased by cold, erosions, necrotic changes, ulcers, inflammatory nodules within the subcutaneous tissues and reticular cyanosis [1, 2, 5]. All the manifestations mentioned are frequently triggered by exposure to cold and are mostly located on the lower legs, which are more exposed to low temperatures. Moreover, the Raynaud's phenomenon is

common. Capillaroscopy shows abnormal morphology of vascular loops, shortened capillaries, areas of neoangiogenesis, extravasations, and avascular areas. Disorders of microcirculation observed in capillaroscopy may be related to ischemia associated with rheological disturbances (changes in shape, blood flow, decreased elasticity of vessels) or to the presence of perivascular infiltration [12].

In cryoglobulinaemia, many organs and systems may be affected; wandering arthralgia accompanied by arthritis or otherwise yet without deformities is observed [13]. The involvement of the nervous system manifests as peripheral neuropathies, sensory fibres being more often affected [14, 15]. Respiratory symptoms include dyspnoea,

cough, interstitial infiltrates, and pleurisy. [16]. Moreover, hepatomegaly and splenomegaly as well as abdominal pain are observed. The most serious complication is renal involvement, manifesting as albuminuria, hypertension or acute renal failure [16].

The clinical symptoms listed above are associated with direct occlusion of the vessel's lumen by cryoglobulin particles, which leads to ischemia and necrosis, or with leukoclastic vasculitis with deposition of immunoglobulins in vascular walls and complement activation [17].

In conclusion, it should be emphasized that patients with ulcers and features of skin necrosis accompanied by the Reynaud's phenomenon should be subjected to detailed and multi-directional diagnostic procedures, including cryoglobulin tests and serum protein immunofixation. Further management and therapy depend on the type of cryoglobulinaemia found and require multi-specialist cooperation.

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