Cryoglobulinaemic vasculitis associated with multiple myeloma

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Abstract

Cryoglobulins are single or mixed immunoglobulins that reversibly precipitate at low temperatures. The clinical manifestations of cryoglobulinaemias vary based on cryoglobulin type. Type I cryoglobulins are associated with plasma cell dyscrasias and lymphoproliferative disorders, and may result in vaso-occlusive phenomena and hyperviscosity syndrome due to high levels of circulating monoclonal cryoglobulin, leading to physical obstruction of vessels. We describe a case of cryoglobulinaemic vasculitis associated with multiple myeloma, complicated by hyperviscosity syndrome.

Introduction

Cryoglobulins are abnormal immunoglobulins that form complexes, which precipitate reversibly at low temperatures and redissolve upon warming. They are made up of monoclonal antibodies, usually of IgM or IgG class, rarely IgA. IgM tends to precipitate at lower temperatures than does IgG cryoglobulin[1].

Cryoglobulinaemias are classified into three types based on their cryoglobulin composition. Type I cryoglobulinaemias are associated with a monoclonal single homogeneous immunoglobulin, usually of IgM or IgG type. These cryoglobulins are present in high concentration, usually greater than 5 mg/ml[1]. Examples of Type I cryoglobulin disorders include multiple myeloma, B cell lymphomas, Waldenstrom's macroglobulinaemia, paroxysmal cold hemoglobinuria and idiopathic nonmalignant monoclonal cryoglobulinaemia.

Type II and III are called mixed cryoglobulinaemias. Type II cryoglobulins are composed of a monoclonal antiglobulin component (usually IgM), and a polyclonal component (IgG). The IgM is associated with a rheumatoid factor like activity. Cryoglobulin concentrations are usually greater than 1 mg/ml. Type III mixed cryoglobulins lack a monoclonal component and consist of two or more immunoglobulins of different classes that are polyclonal. Their concentration is usually less than 1mg/ml. About 30% mixed cryoglobulinaemias are associated with no underlying cause (Essential Mixed Cryoglobulinaemia)[1]. Mixed cryoglobulins are associated with infections such as Hepatitis B and C, infectious mononeucleosis, Cytomegalovirus, HIV, infective endocarditis, leprosy, syphilis, borelliosis, malaria, and Kala-azar; autoimmune disorders like SLE, rheumatoid arthritis and Sjogren's syndrome; lymphoproliferative disorders; and sarcoidosis.

The symptoms of type I cryoglobulinaemia are caused by vascular occlusion resulting from protein precipitation. Clinical manifestations consist of occlusive peripheral vascular phenomena such as Raynaud's phenomenon, acrocyanosis, cutaneous ulcers, gangrene, retinal haemorrhages and arterial thrombosis. Mixed cryoglobulinaemias (type II or type III) are associated with immune complex disease, and are associated with arthritis or arthralgia, vascular purpura, and renal and neurologic symptoms[2].

Herein we report a rare case of cryoglobulinaemic vasculitis associated with multiple myeloma, culminating with vaso-occlusive phenomena and peripheral gangrene.

History

A 64 year old man presented with recurrent painful leg ulceration for 5 years. He had been diagnosed to have cryoglobulinaemic vasculitis in 2002 and had been on long-term oral steroids and intermittent oral cyclophosphamide. Recently he had developed ulcers on the knees, elbows, ear lobes and penis. Pain was characteristically worse on exposure to cold weather. He had small and large joint pain and features suggestive of Raynaud's phenomenon. He had significant weight loss over the last one year. He complained of malaise, myalgia and poor appetite. He did not have neurological symptoms. He had no history of hepatitis.

On examination he was pale, and had necrotic ulcers with punched out edges on legs, ankles (Figure 1), knees and elbows. There were areas of gangrene on legs (Figure 2), earlobes, and penis. He had no lymphadenopathy. There was joint tenderness, but no swelling, effusions or deformities. Cardiovascular, respiratory, abdominal and nervous system examination was normal. Blood pressure was 130/80. No organomegaly was present. Optic fundi were normal.

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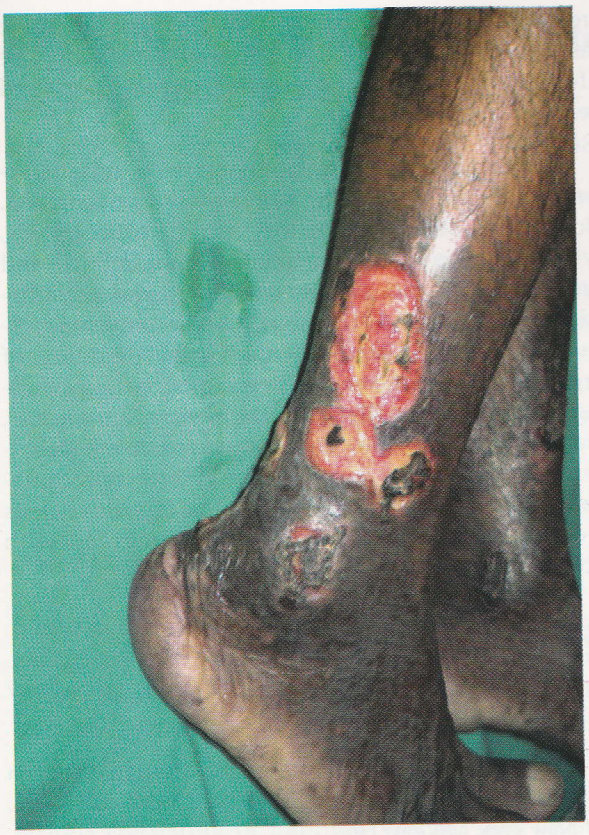

Figure 1. *Vasculitic ulceration on the ankle.*

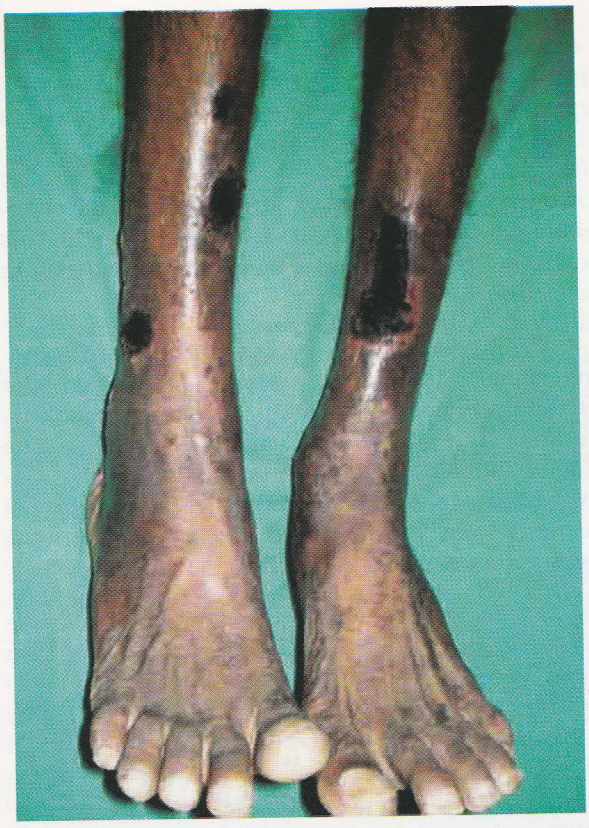

Figure 2. *Areas of gangrene over legs.*

His ESR was 110mm 1st hour. He had hypochromic microcytic anaemia, marked neutrophil leucocytosis, and thrombocytosis (Haemoglobin 8.7g/dl, MCV 62 fl, MCH 23 pg, MCHC 37 mg/dl, WBC 43,800/mm^3, N – 76%, L – 24%, Platelets 494,000/mm^3). Blood picture showed red cell agglutination, few nucleated red cells and neutrophil leucocytosis. Renal and liver functions were normal. Fasting blood glucose was 5.3mmol/l. Skin biopsy showed leucocytoclastic vasculitis. Croglobulins were repeatedly detected from serum. Cryocrit (cryoglobulin titre) was not estimated due to non-availability of facilities. Anti-nuclear factor, rheumatoid factor, Hepatitis B and C serology and HIV screen were negative. Serum proteins were 61 g/l (albumin 32g/l, globulins 29g/l). Serum protein electrophoresis showed polyclonal elevation of gamma globulins. Bence Jones proteins were not detectable in urine. Previous bone marrow examination, done 6 months ago, had showed mild to moderate plasmacytosis. Repeat bone marrow examination was consistent with multiple myeloma (plasma cells accounting for 80% non-erythroid cells). Skeletal survey showed marked osteoporosis. No lytic lesions were present.

Patient was referred for oncologist's opinion. It was decided to treat him with combination of intravenous pulsed corticosteroids, vincristine and cyclophosphamide. Before starting chemotherapy patient developed rapidly spreading, widespread gangrene of the extremities, headache, visual disturbance, confusion, drowsiness, evolving focal neurological signs, dyspnoea, and anuria. Engorgement of retinal vessels and haemorrhages were noted on fundoscopy. Urgent plasmapheresis was considered but patient gradually became comatose and died within a few hours.

Discussion

Cryoglobulins precipitate in the superficial capillaries and subpapillary venules in the coldest parts of the skin, where they produce purpura and microinfacts. The affected areas are painful, and at first show livid purple discolouration, within which dark brown or blackish necrotic patches appear. The lesions are more numerous distally, mostly on lower limbs, and pain worsened by exposure to cold is characteristic. Other dermatological manifestations of cryoglobulinaemias include Raynaud's phenomenon, acrocyanosis, hyperkeratotic spicules in areas exposed to cold, scarring of tip of nose, pinnae, fingertips, and toes, nailfold capillary abnormalities, livedo reticularis, urticarial vasculitis and cold urticaria[3]. In rare instances cryoglobulinaemias can result in gangrene of the extremities[4].

Cryoglobulinaemic vasculitis is associated with a number of infectious, autoimmune and neoplastic disorders. Mortality and morbidity in a patient with cryoglobulinemia often depend on concomitant disease. Patients with plasma cell or lymphoproliferative disorders have an overall worse prognosis[3]. Cryoglobulinaemia may antedate the paraproteinaemia by several years, as illustrated by this example. Close follow up of these patients is therefore necessary.

The mechanisms of cryoprecipitation are poorly understood. Alteration in protein conformation with temperature changes leads to decreased solubility, sludging and subsequent vasculitic damage. The ratio of antibody to antigen in circulating cryoglobulin aggregates or immune complexes affects the rate of clearance from the circulation and the resultant rate and location of tissue deposition[3].

Hyperviscocity syndrome may complicate the course when paraprotein concentration is high enough to increase plasma viscosity sufficiently to impede the microcirculation to tissues. IgM increases viscosity at lower serum concentration than IgG, and within a narrow range, small increases may lead to a great increase in viscosity[5]. The hyperviscosity syndrome encompasses a variety of manifestations attributed to an elevated blood viscosity, including headache, vertigo, nystagmus, hearing loss, visual disturbances, retinal vein congestion, retinal hemorrhages, mucosal hemorrhages, congestive heart failure, and renal impairment[6]. The symptoms are preceded by sequential changes in fundi. Fundal veins become dilated, tortuous and irregular, and finally beaded, with constrictions alternating with dilated segments. Papilloedema, haemorrhages and exudates appear. The Sia water test is a bedside screening procedure for hyperviscosity. The formation of a filmy, white precipitate when a drop of serum is placed in a cylinder of distilled water indicates the need to measure viscosity[6]. The symptoms and signs of hyperviscosity are rapidly improved by plasmapheresis. In some cases removal of as little as 1 litre of plasma may be life saving[5]. Unfortunately our patient perished before plasma exchange.

Treatment of cryoglobulinaemias is unsatisfactory where the underlying cause cannot be removed. Non-steroid anti inflammatory drugs, corticoteroids, cytotoxic drugs such as melphalan, chlorambucil, and cyclophosphamide, plasma exchange, and cryofiltration are used with variable success. Immunosuppressive medications are indicated upon evidence of organ involvement, renal disease, progressive neurologic findings, or disabling skin manifestations[3]. Plasmapheresis is indicated for severe or life-threatening complications related to in vivo cryoprecipitation or serum hyperviscosity. Hepatitis C positive cases are benefited by alpha interferon combined with ribavirin[3].

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