Type I Cryoglobulinemia and Multiple Myeloma
Presenting with Widespread Livedo Reticularis and Skin Necrosis

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Cryoglobulins are reversibly cold-precipitating, circulating immunoglobulins which can lead to clinical symptoms, such as recurrent palpable purpura, polyarthralgia and renal disease. A 65-year-old Taiwanese man presented with widespread, severe livedo reticularis of all four extremities with acrocyanosis, Raynaud's phenomenon, and eventuated in necrosis of auricular helices, scrotum and fingers after repeated cold exposure. Biopsy of livedo reticularis revealed dermal thrombosis with mixed inflammatory infiltrates in and around vessel walls, and biopsy of a gangrenous lesion showed similar occlusive vasculopathy with ischemic necrosis the skin. Further studies confirmed the presence of type I cryoglobulinemia and the diagnosis of IgG-kappa multiple myeloma. Due to the frequent association with underlying hematological disorders, autoimmune diseases and infections, thorough examination in a patient with cryoglobulinemia should be performed. (Dermatol Sinica 23: 17-20, 2005)

Key words: Cryoglobulinemia, Multiple myeloma, Cold intolerance, Gangrene

冷凝球蛋白為可逆性遇冷凝結的免疫球蛋白，常造成症狀如隆起性紫斑、多發性關節痛及腎臟疾病。一個六十五歲台灣男性其皮膚臨床表現為廣泛性及嚴重網狀青斑表現於四肢併肢端發绀、雷諾氏現象，反覆接觸寒冷的環境後導致耳廓、陰囊及手指壞疽性壞死。針對網狀青斑皮膚切片發現真皮層下半部有血管阻塞併混合性發炎細胞浸潤在血管四周及血管內，針對皮膚壞疽部位切片發現阻塞性血管病變併皮膚缺血性壞死。進一步檢查發現患者有第一型冷凝蛋白血症及IgG-kappa多發性骨髓瘤。冷凝蛋白血症常與血液疾病、自體免疫疾病及感染症相關，故詳細的檢查是必須的。(中華皮誌 23: 17-20, 2005)
INTRODUCTION

Cryoglobulins are reversibly cold-precipitating, circulating immunoglobulins which form complexes with other immunoglobulins or proteins. The presence of cryoglobulins in the blood could lead to clinical symptoms precipitated by cold exposure, such as recurrent palpable purpura (100%), polyarthralgia (72.5%) and renal disease (55%), although cryoglobulins at very low levels may be detectable in as many as 51% of normal individuals. Here we present a case of type I cryoglobulinemia with multiple myeloma presenting with extensive livedo reticularis and gangrenous necrosis of the ear helices, scrotum and digits.

CASE REPORT

A 65-year-old Taiwanese man first presented with a 2-week history of asymptomatic reticulate purpuric erythema on the four extremities in August 2002 (Fig. 1). He reported to have similar skin lesions in February 2002. The clinical diagnosis was livedo reticularis. A skin biopsy showed thrombotic occlusion of blood vessels in the lower dermis with a mixed inflammatory infiltrate containing many neutrophils in and around the vessel walls (Fig. 2A). Further laboratory evaluation was suggested but the patient refused and did not return for follow-up. In the next few months, there was worsening of the rash of the digits and ear auricles which eventually became painful, cyanotic with gangrenous changes after exposure to cold fronts in the winter. The occurrence of bone pain brought him back to our oncology clinic in January 2003. Examination revealed extensive reticulated purpura on the lower extremities, scrotum, buttock, hands and neck. Gangrenous...
necrosis was noted on ear helices, scrotum and fingers (Fig. 3). There was no lymphadenopathy or hepatosplenomegaly. A skin biopsy of the gangrenous lesion on the right thigh showed epidermal and dermal ischemia and thrombotic vasculopathy with a relatively sparse infiltrate of inflammatory cells containing neutrophils and nuclear dust (Fig. 2B). Based on the clinical and histopathological findings, cryoglobulinemia or cryofibrinogenemia was suspected. The diagnosis of cryoglobulinemia was confirmed by the presence of cryoproteins in both plasma and serum.

He was admitted to the oncology ward for further evaluation of bone pain. Multiple myeloma was diagnosed based on the findings of elevated IgG of 2680 mg/dl with IgG-kappa monoclonal gammopathy in the serum, free-kappa light chain in the urine, punch-out osteolytic lesions in the skull X-ray, plasmacytosis with plasma cells accounting for 24% of the myeloid cells from a bone marrow aspiration, and a confirmative bone marrow biopsy which showed plasma cell myeloma. Other pertinent laboratory data were as follows: WBC 72700/µl, segment 38%, monocyte 15%, lymphocyte 41%, hemoglobin 10.6 g/dl, platelet 374x10³, ANA 1:40(-), rheumatoid factor <20 U/ml, albumin 3.1 g/dl, globulin 4.2 g/dl, HBs antigen positive, Anti-HCV antibody negative, daily urinary protein loss 0.58 g.

The patient was advised to stay in a warm environment and avoid cold exposure. He received long-term melphalan 2 mg/day with prednisolone to treat multiple myeloma. The skin lesions resolved gradually and did not recur in the ensuing 16 months during which time the serum IgG was reduced to 1050 mg/dl and remained stable.

**DISCUSSION**

By 1974, Brouet et al. popularized a system to classify cryoglobulinemia by the components of the cryoprecipitate. Type I cryoproteins consist of self-aggregate, single monoclonal immunoglobulins, usually IgG or IgM. They are usually (>70%) associated with immunoproliferative diseases, mainly multiple myeloma and Waldenstrom’s macroglobulinemia. In type II and type III cryoglobulinemia, there are immune complexes consisting of rheumatoid factors of monoclonal IgM (type II) or polyclonal IgM (type III) that form complexes with polyclonal IgG. Type II cryoglobulinemia is usually associated with macroglobulinemia, lymphoproliferative disorders, autoimmune diseases and chronic HCV infection. Type III cryoglobulinemia is associated with chronic infections and autoimmune diseases. The close association of HCV infection with mixed cryoglobulinemia, which accounts for 43% to 85% of the cases of mixed cryoglobulinemia, has been addressed recently, although no significant difference was found in the clinical presentation and outcome between HCV⁻ and HCV⁺ patients with cryoglobulinemia. Our patient had IgG monoclonal gammopathy in the serum associated with multiple myeloma, and negative rheumatoid factors and anti-HCV antibodies. The findings are consistent with type I cryoglobulinemia.

Purpura is the most frequent symptom of cryoglobulinemia, which is found in about 90% of all patients, followed by hepatosplenomegaly,
REFERENCES


