

Multiple myeloma presenting with lower extremity gangrene and hyperviscosity syndrome

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ABSTRACT

Hyperviscosity syndrome and cryoglobulinemia associated with lymphoproliferative disorder is a rare but life threatening condition. The delay of diagnosis can lead to severe mutilation and multiple organ damage. The plasma exchange therapy and the targeted treatment of the underlying disorder can lead to significant improvement. We present a patient who developed extensive soft tissue necroses, mimicking the peripheral artery disease. Despite surgical treatment, the skin lesions progressed involving fingers, earlobes and scrotum. Finally, the patient was diagnosed with multiple myeloma and hyperviscosity syndrome. The clinical condition improved after plasma exchange and myeloma treatment with thalidomide and dexamethasone.

Key words: multiple myeloma, hyperviscosity, skin necrosis

Introduction

The extensive lower limb gangrene appearing in the absence of diabetes mellitus or systemic atherosclerosis is a rare condition. Differential diagnosis includes systemic infective diseases, connective tissue diseases, vasculitides or metabolic disorders. (1,2) The aim of this paper is to present a patient who developed extensive soft tissue necrosis as the first manifestation of IgG kappa multiple myeloma associated with cryoglobulinemia (CG) and hyperviscosity syndrome.

Case presentation

A fifty-year old man with a history of smoking, alcohol abuse and significant weight loss (20 kg) over the period of 10 months presented with skin and soft tissue necrosis of the foot, developing after a minor injury of the leg.

Computerized tomography (CT) of the aorta, pelvis and legs did not reveal any significant lesions of the major arteries, but the flow obstruction distal to the posterior tibial artery was described. The transmetatarsal amputation of the right foot was performed. Soon after the amputation, gangrene of the remaining foot, fingers, ears and penis developed, requiring the transmetatarsal amputation of another foot. The patient became lethargic and febrile and was transferred from the regional hospital to the University Hospital Centre Zagreb Medical Intensive Care Unit. At admission, his GCS was 8, axillary temperature was 38°C with radiographic signs of pneumonia. Necrotic skin lesions were present on the earlobes, hands, scrotum, fingers, with large necrotic areas on both legs (figure 1). Femoral and popliteal arterial blood flow was sonographically detectable. Laboratory tests showed anemia, renal lesion, hypercalcemia, coagulopathy

and extremely elevated total protein level (table 1). Electrophoresis of serum proteins with immunofixation detected monoclonal IgG kappa (free light chain IgG kappa 1900.00 g/L (ref 3.30 – 19.40), Ig lambda <1.73 (ref 5.71-26.30). Cryoglobulin was identified in the patient's serum (serum precipitated at 4°C), but cryoglobulin electrophoresis was not performed due to technical issues. Bone marrow was infiltrated with 60-90% plasma cells. Skeletal surveys revealed punched-out lytic lesions of the vertebrae, skull, thoracic cage, pelvis, humeri, femora and tibia. A skin biopsy showed no sign of vasculitis. Diagnosis of multiple myeloma IgG kappa was made and treatment was started immediately. Plasma exchange with 5% albumin substitution was started on the day of admission for hyperproteinemia, cryoglobulinemia and hyperviscosity syndrome (the viscosity of plasma was not measured). The patient became oliguric



Picture1. The extensive lower limb skin necroses present at admission to medical intensive care unit.

and progressively hypoxaemic, requiring mechanical ventilation and renal replacement therapy.

Multiple myeloma treatment with dexamethasone and thalidomide was started on the third day following admission. The patient received a single dose of pamidronate for hypercalcemia. Besides hyperviscosity syndrome, and possible cryoglobulinemia, no other reason for vascular insufficiency was found.

In total, 5 plasma exchange procedures were performed. The patient gradually improved with treatment. He regained consciousness, regression and healing of skin necrotic lesions occurred. His respiratory status improved, allowing for the termination of mechanical ventilation. Serum creatinine decreased and diuresis recovered up to 2000 ml daily without renal replacement therapy. Cryoglobulins could no longer be detected. The patient was transferred to a regional hospital and the continuance of treatment with borthesomybe was planned. Unfortunately, following the transfer, the patient developed another septic episode with fatal outcome.

Discussion

Peripheral artery disease is the most common cause of lower limb soft tissue

disorders. (1) The patient's initial presentation with lower extremity gangrene, together with age and history of tobacco abuse, indicated atherosclerotic arterial ischemia of the lower limb. However, there were no signs of ischemia on other vascular beds (myocardial infarction or cerebrovascular insult) and CT arteriography showed no signs of atherosclerotic arterial disease (vessel wall calcification, multivessel involvement, a mixture of focal and diffuse lesions, or typical ostial and proximal artery locations). (1) The differential diagnosis of peripheral tissue necrosis, the absence of major arterial obstruction or diabetes mellitus is wide and includes vacuillitides such as polyarteritis nodosa, connective tissue diseases (such as Sjogren's Syndrome), systemic lupus erythematosus, pyoderma gangrenosum, infective diseases (such as necrotizing fasciitis), and septic embolism. (2) In patients with end stage renal disease, skin and soft tissue necrosis can rarely appear as a result of calciphylaxis. (2) Skin biopsy, however, revealed only thrombotic occlusions of small vessels without signs of vasculitis. Multiple myeloma and associated hyperviscosity syndrome were diagnosed based on clinical presentation and laboratory results. (3)

Multiple myeloma is a plasma cell neoplasm that is characterized by a single clone of plasma cells producing a monoclonal protein (M-protein). Malignant proliferation of plasma cells produces skeletal destruction, causing bone pain and pathologic fractures. (3) It accounts for 10% of all hematologic malignancies. Diagnostic criteria include the presence of M-protein in serum and/or urine, presence of 10% or more clonal bone marrow plasma cells and related organ or tissue impairment (such as hypercalcemia, renal insufficiency, anemia, and lytic bone lesions on radiographic survey). All of the diagnostic criteria were met in our patient. The M-protein might also lead to hyperviscosity syndrome or recurrent infections through the suppression of normal immunoglobulins.

Cryoglobulinemia is a rare condition, accompanying a broad spectrum of different states and diseases, which is manifested by palpable purpura, progressing to skin and soft tissue necrosis, arthralgia and myalgia. Cryoglobulin consists of immunoglobulins and complement components and precipitates upon refrigeration of serum and plasma. Mixed or polyclonal cryoglobulins (type II and III) can be seen in patients with autoimmune disorders, chronic infections (particularly hepatitis C virus and HIV infection), and lymphoproliferative disorders. Monoclonal cryoglobulin (type I) are often revealed in patients with multiple myeloma or Waldenström's macroglobulinemia. (4) Clinical symptoms result from cryoglobulinemic organ damage, produced by autoimmune-mediated vasculitis or accumulation of cryoglobulins and obstruction of small vessels. The prevalence of clinically-significant cryoglobulinemia has been estimated at approximately 1 in 100,000, and type I CG accounts for 5-25% of all clinical cases. (5) Type I CG classically produces signs related to hyperviscosity and/or thrombosis: Raynaud phenomenon, digital ischemia, livedo reticularis, and purpura may occur. In severe cases, and without treatment, this may progress to gangrene. Neurologic symptoms of

hyperviscosity include blurring or loss of vision, headache, vertigo, sudden deafness, diplopia, ataxia, confusion, and disturbances of consciousness. (5)

Clinically significant type I CG associated with multiple myeloma is sporadically reported in literature in the form of isolated case reports or small retrospective studies, and general treatment recommendations include the treatment of the underlying lymphoproliferative disease. (6,7) A French retrospective study over a 15-year period identified 64 patients with symptomatic type I CG. (8) All patients had either a hematologic malignancy or monoclonal gammopathy of unknown significance. Cutaneous involvement was often present, renal disease was seen in 30% of patients. None of the patients exhibited central nervous system manifestations. Treatment included glucocorticoids, plasma exchange, alkylating agents, rituximab, and other chemotherapy; 10% of patients did not require treatment. Ten-year survival was 87%, with poorer survival rates in patients with hematologic malignancy. Another report from a series of 7 patients with symptomatic type I CG and multiple myeloma noted the benefit of therapies that included drug regimens directed at the myeloma. (9)

Table 1. Laboratory values at admission to medical intensive care unit.

Variable	Reference range	Measured value
ESR	5-28 mm/h	130
Hemoglobin	119 – 157 (g/L)	78
Lukocytes	3.4 – 9.7 ($\times 10^9$ /L)	4.75
Thrombocytes	158 – 424 ($\times 10^9$ /L)	175
Prothrombin time	> 0.70 (s)	0.45
D-dimer	< 0.5 (mg/L)	1.52
fibrinogen	1.8 – 4.1 (mg/L)	2.8
creatinine	63 – 107 (μ mol/L)	221
BUN	2.8 – 8.3 (μ mol/L)	12.5
Na	137 – 146 (μ mol/L)	139
K	3.9 – 5.1 (μ mol/L)	3.0
Ca++	2.14 – 2.53 (μ mol/L)	2.83
Total serum proteins	66 – 81 g/L	99

BUN, blood urea nitrogen; ESR, erythrocyte sedimentation rate

Our patient initially presented only lower extremity skin lesions, more severe and progressive than usually associated with hyperviscosity syndrome. Serum hyperviscosity, hypercalcemia, concurrent sepsis and dehydration all contributed to the renal dysfunction, neurological symptoms and respiratory distress. Daily plasma exchange, accompanied by glucocorticoids and thalidomide as a targeted treatment of multiple myeloma led to a remarkable clinical response, recovery of diuresis, normali-

zation of serum protein level and the disappearance of cryoglobulins.

Conclusion

Hyperviscosity syndrome and cryoglobulinemia associated with lymphoproliferative disorder is a rare but life threatening condition. The delay of diagnosis can lead to severe mutilation and multiple organ damage. The plasma exchange therapy and targeted treatment of the underlying disorder can lead to significant improvement.

REFERENCES

- Weinberg I, Jaff MR. Nonatherosclerotic arterial disorders of the lower extremities. *Circulation* 2012;126:213-222.
- Beitz JM. Calciphylaxis: a case study with differential diagnosis. *Ostomy Wound Manage.* 2003 Mar;49(3):28-38; quiz 39-40.
- Kariyawan CC, Hughes DA, Jayatilake MM, Mehta AB. Multiple myeloma: causes and consequences of delay in diagnosis. *QJM* 2007; 100:635.
- Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc* 2003; 78:21.
- Trejo O, Ramos-Casals M, Garcia-Carrasco M, et al. Cryoglobulinemia: study of etiologic factors and clinical and immunologic features in 443 patients from a single center. *Medicine (Baltimore)* 2001; 80:252.
- Kulger N, Sirvente J, Rigau V, Guillot B. Extensive thrombotic purpura revealing multiple myeloma associated – type 1 cryoglobulinemia. *Br J Hematol* 2011;154 (1).
- Ninomiya S, Fukuno K, Kanemura N, Goto N, Kasahara S, Yamada T, Tsurumi H, Moriwaki H. IgG type multiple myeloma and concurrent IgA type monoclonal gammopathy of undetermined significance complicated by necrotizing skin ulcers due to type I cryoglobulinemia. *J Clin Exp Hematop.* 2010;50(1):71-4.
- Terrier B, Karras A, Kahn JE, et al. The spectrum of type I cryoglobulinemia vasculitis: new insights based on 64 cases. *Medicine (Baltimore)* 2013; 92:61.
- Payet J, Livartowski J, Kavian N, et al. Type I cryoglobulinemia in multiple myeloma, a rare entity: analysis of clinical and biological characteristics of seven cases and review of the literature. *Leuk Lymphoma* 2013; 54:767.