

Painful Purpuric Ulcers of the Legs: A Tell-Tale Sign of Systemic Disease?

A 71-year-old Chinese man presented with acute, painful and progressive purpuric patches with haemorrhagic bullae on the lower limbs. These lesions ulcerated and were very slow to heal with eschar formation (Fig. 1). His past medical history included hypertension. He denied any new medications, contactants or illicit drug use. A skin punch biopsy was taken from the foot lesion (Fig. 2). What is your diagnosis?

- A. Pyoderma gangrenosum
- B. Cholesterol crystal embolism
- C. Cutaneous polyarteritis nodosa
- D. Cryoglobulinaemia with occlusive vasculopathy secondary to multiple myeloma
- E. Angioimmunoblastic T-cell lymphoma

Findings and Diagnosis

The images (Figs. 1A-B) show purpuric patches with necrotic centre over both feet along with a few overlying

bullae on initial presentation. Despite optimal wound care, these progressed to slow-healing ulcers with thick eschar formation at day 30 (Fig. 1C) compared to day 10 of admission (Fig. 1D).

Investigations revealed normochromic, normocytic anaemia (Hb, 10.7 g/dL; normal, 14-18 g/dL) and markedly raised erythrocyte sedimentation rate at 105 mm/hr (1-10 mm/hr). Skin biopsy for histology showed epidermal necrosis and the superficial and deep vessels were thrombosed and occluded by hyaline deposits with paucity of inflammatory infiltrate which was consistent with occlusive vasculopathy (Fig. 2). Screening for thrombotic disorders, autoimmune diseases and infective causes including human immunodeficiency viruses, hepatitis B and C were unremarkable.

Subsequently, rouleaux formation was noted in the complete blood count. Thereafter, elevations were noted in serum creatinine of 108 $\mu\text{mol/L}$ (CrCl, $\sim 51 \text{ mL/min}$) and serum calcium of 2.72 mmol/L (2.15-2.58 mmol/L,



Fig. 1. A: Top view of purpuric patches with necrotic centre over both feet with a few overlying bullae. B: Lateral view of purpuric patches. C: Slow-healing ulcers on the right foot with thick eschar formation at day 30. D: Ulcers at day 10 of admission.

Answer: D

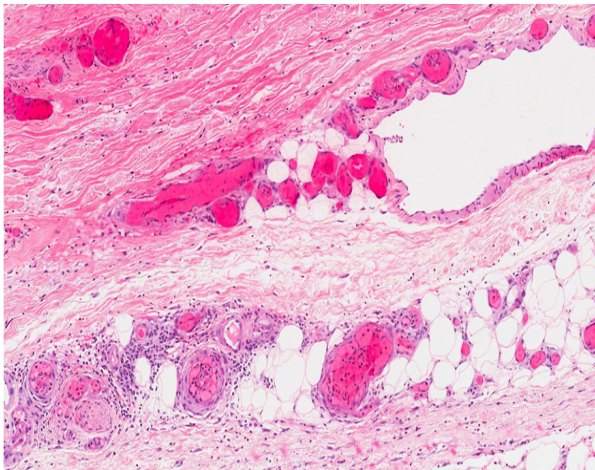


Fig. 2. Histopathology of occlusive vasculopathy shows superficial and deep vessels are thrombosed and occluded by hyaline deposits with paucity of inflammatory infiltrate (haematoxylin and eosin stain, original magnification $\times 100$).

adjusted). Total protein was raised at 109 g/L (65–82 g/L) with hypoalbuminaemia at 22 g/L (38–48 g/L). Multiple myeloma was thus suspected. Serum protein electrophoresis showed an M-spike of 6 g/dL (0.7–1.6 g/dL) with a monoclonal gammopathy of IgG kappa in immunofixation electrophoresis. Serum IgG was markedly elevated at 62.7 g/L (8.5–19.5 g/L) while other immunoglobulins were suppressed.

There were no lytic bone lesions on skeletal survey. Biopsy of the bone marrow confirmed a plasma cell dyscrasia with increased plasma cells of 66% which was consistent with multiple myeloma. Cryoglobulin test was also positive. A diagnosis of type I cryoglobulinaemia with occlusive vasculopathy secondary to multiple myeloma was made. Patient was started on chemotherapy of lenalidomide and dexamethasone with improvement of the skin lesions.

Discussion

Multiple myeloma is characterised by a clonal proliferation of plasma cells that produce a monoclonal immunoglobulin. These plasma cells infiltrate into bone and organs leading to anaemia, hypercalcaemia, renal failure, bone pain, weight loss and neuropathy. Rarely, skin lesions in multiple myeloma patients may develop secondary to associated disorders such as cryoglobulinaemia. The prevalence of clinically significant cryoglobulinaemia is approximately 1 in 100,000.¹ Type I cryoglobulinaemia (10–15% of patients) results from cold precipitable monoclonal immunoglobulins that increase blood viscosity and lead to occlusion of vessels. It is associated with an underlying plasma cell dyscrasia or lymphoproliferative disorder.

Skin involvement is characterised by the cardinal sign of cold occlusion—that is, purpura (often retiform)

and necrosis—leading to ulceration and even gangrene in severe cases. Other cutaneous findings include Raynaud's phenomenon, acrocyanosis and livedo reticularis. Histologically, skin lesions demonstrate occlusive vasculopathy with bland eosinophilic hyaline thrombi within blood vessels in the dermis and minimal inflammatory infiltrate.²

The above skin features can occur in other instances. They can be distinguished based on clinical history and investigations. Cholesterol crystal embolism is iatrogenic in the majority of cases (with angioplasty being the most common event that triggers it) and manifests as a classic triad of livedo reticularis, renal failure and eosinophilia.³ Skin biopsy would reveal cholesterol clefts in the lumina of small arteries and arterioles. History of recent vascular surgery should raise suspicion of this cause.

As a form of vasculitis of the small- and medium-sized arteries of the dermis and subcutis, cutaneous polyarteritis nodosa usually presents as painful nodules, livedo reticularis and ulcers of the legs. Bullae, cutaneous necrosis and digital gangrene occur less frequently.⁴ Characteristic leukocytoclastic vasculitis with fibrinoid necrosis in the dermal vessels confirms the diagnosis. Possible infectious triggers include hepatitis B and C, streptococcal infection and tuberculosis.

Pyoderma gangrenosum is an ulcerative neutrophilic dermatosis that often presents as violaceous papules or nodules that result in ulcers with undermined edges and is associated with inflammatory bowel disease, arthritis and myelogenous leukaemia.⁵ It usually remains a clinical diagnosis of exclusion with non-specific histological findings that may include a necrotic or ulcerated epidermis and a diffuse infiltrate of neutrophils, lymphocytes and histiocytes in the dermis, sometimes with vasculitis.

Angioimmunoblastic T-cell lymphoma is an aggressive peripheral T-cell lymphoma characterised by fever, weight loss, night sweats, general lymphadenopathy, hepatosplenomegaly and polyclonal hypergammaglobulinaemia. Skin manifestations include maculopapular eruption (most common), erythroderma, nodules, palpable purpura and urticarial plaques.⁶ Histologically, a dense superficial and deep infiltrate of atypical lymphoid cells is seen on skin biopsy.

Treatment for cutaneous occlusive vasculopathy is targeted at the underlying aetiology. In this case, the pathogenesis is likely related to the monoclonal cryoglobulins produced by the overproliferating plasma cells of multiple myeloma—precipitating as hyaline thrombi—which occlude the dermal blood vessels and result in acral ischaemia and necrosis.⁷ Hence, management and prognosis should be tailored to control plasma cell lymphoproliferative disorder. Indeed, clinical improvement in cutaneous lesions has been reported 6 to 8 weeks after chemotherapy is started for multiple myeloma.^{2,8} Plasmapheresis may also be used to quickly control severe cryoglobulinaemia symptoms at onset.^{2,8}

Conclusion

Our patient had cutaneous lesions comprising painful, progressive purpuric patches that became slow-healing ulcers with eschar formation. Differential diagnoses of thrombotic disorders, autoimmune or vasculitic diseases, infection and malignancy were considered. Ultimately, investigations revealed an underlying multiple myeloma and associated type I cryoglobulinaemia. The learning point here is that cutaneous occlusive vasculopathy may manifest as an early sign of underlying haematologic malignancy such as multiple myeloma with cryoglobulinaemia. As such, a malignancy screen should be performed. A high index of suspicion is required and clues to the association include slow healing or progressive necrotic ulcers despite optimal standard treatment, or abnormal laboratory markers such as raised serum protein, erythrocyte sedimentation rate, creatinine, hypercalcaemia and/or anaemia. Prompt recognition and treatment of the underlying multiple myeloma will help prevent disease progression.

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