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Case Presentation

Reactive angioendotheliomatosis associated with cyroglobulinemia in a marathon runner

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Abstract

We report a case of a 65-year-old marathon runner who presented with painful plaques, which were worse in cold weather and progressed to ulceration. A punch biopsy revealed vascular endothelial hyperplasia and an appearance consistent with reactive angioendotheliomatosis (RAE), a rare, but benign disorder of the skin. Subsequent investigations resulted in the diagnosis of type I cryoglobulinemia; the lesions resolved completely following treatment of the underlying disorder with lenalidomide.

Introduction

Reactive angioendotheliomatosis (RAE) is a rare, poorly defined cutaneous disorder of unknown etiology. The disorder manifests clinically as erythematous, violaceous macules, papules, or plaques on the trunk, limbs, face, and extremities [1]. The diagnosis is confirmed histologically, with characteristic features of proliferation of endothelial cells in dermal and occasionally subcutaneous vessels [2]. There is an absence of cellular atypia, distinguishing the disorder from malignant vascular neoplasms. The pathogenesis of RAE remains uncertain, but there is usually underlying systemic disease [1].

Case synopsis

A 65-year-old marathon runner presented with a twelve month history of intermittent, painful, erythematous plaques symmetrically distributed on the greater helices of the ears, flanks, and lower limbs (Figure 1,2,3). Some plaques progressed to ulceration and necrosis. The lesions were occasionally preceded by pruritus, but there were no other systemic symptoms. The lesions worsened with cold weather and improved with warm weather and protective clothing. The patient had no significant past medical history and was on no regular medications.

The patient was initially thought clinically to have a vasculitis. Two punch biopsies were performed from lesions on the right flank (Figure 4,5,6). The biopsies were similar, showing full thickness epidermal ulceration with a reactive perforating collagenosis-like pattern. There were numerous lobules of thick-walled capillaries in the dermis and this extended into the subcutis. Some vessels displayed endothelial hyperplasia (Figure 5) and organizing fibrin thrombi (Figure 5, 6). There was no evidence of endothelial atypia and no significant inflammatory cell infiltrate.

The patient underwent investigations for an underlying cause, summarized in Table 1. Serum cryoglobulins (monoclonal IgG kappa) were detected, with a cryocrit of <1%. Serum electrophoresis confirmed the finding and free kappa light chains (0.09 g/L) were detected in the urine. The patient was referred to a hematologist and underwent bone marrow biopsy, which revealed a 12% burden of clonal plasma cells. There was no other evidence of organ dysfunction.

A diagnosis of type I cryoglobulinemia was made and thalidomide and dexamethasone were commenced. Thalidomide administration was complicated by bradycardia and treatment was changed to lenalidomide 25mg/day. With treatment, the skin lesions resolved. This was associated with reduced serum free light chains, cryoglobulins, and plasma cells on repeat bone marrow

biopsy. Treatment was discontinued after 18 months. After 24 months of follow up, the patient has no further evidence of RAE and continues to run marathons, including in cold weather.

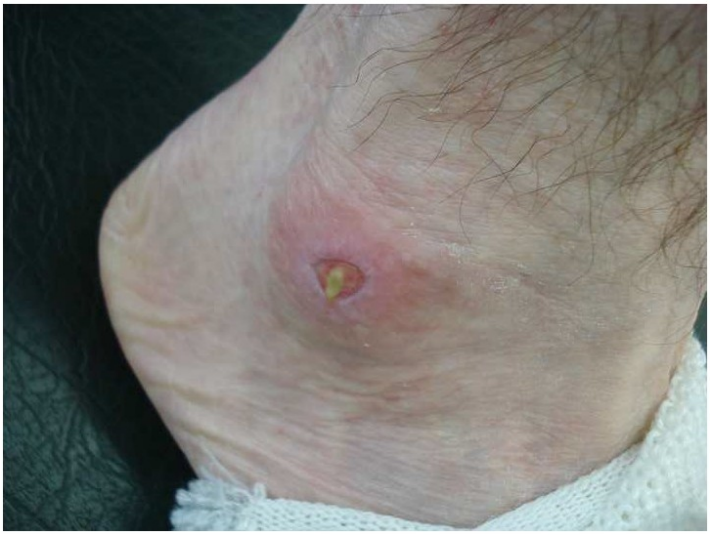
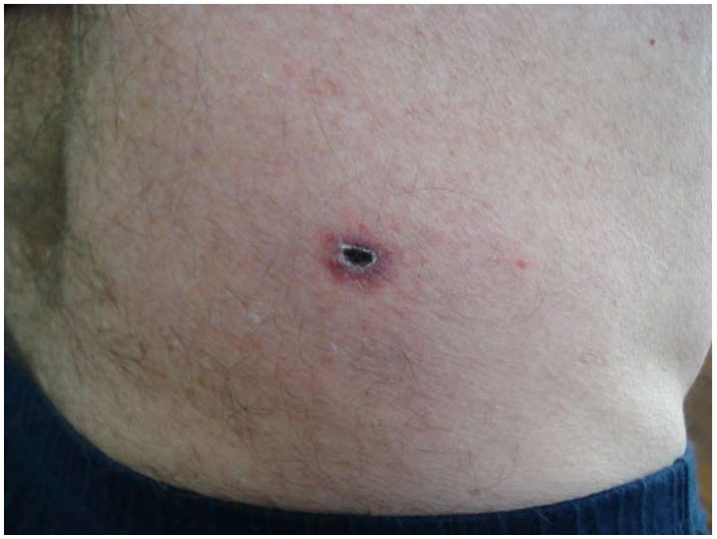

Figure 1 and 2.

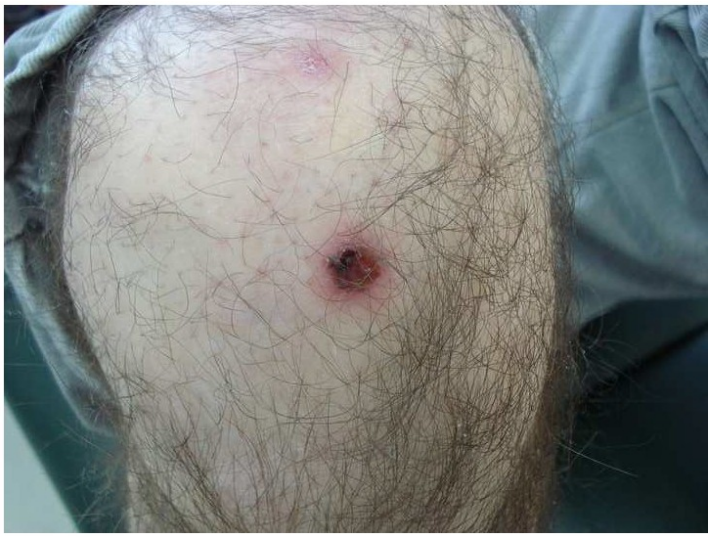

Figure 3.

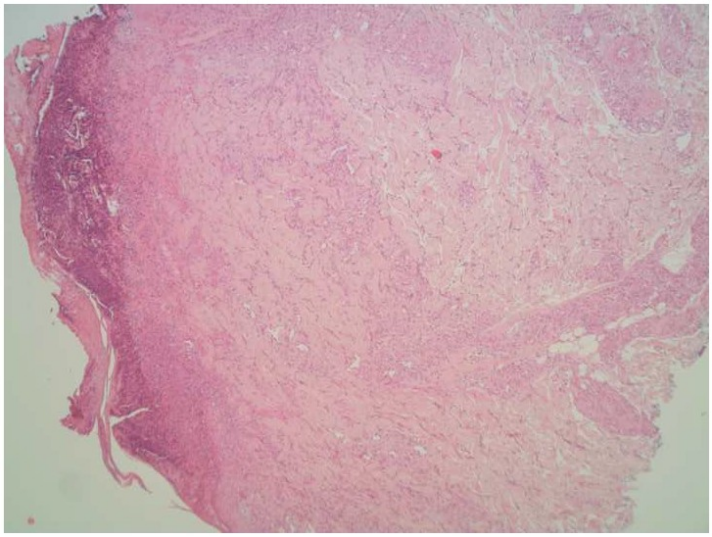
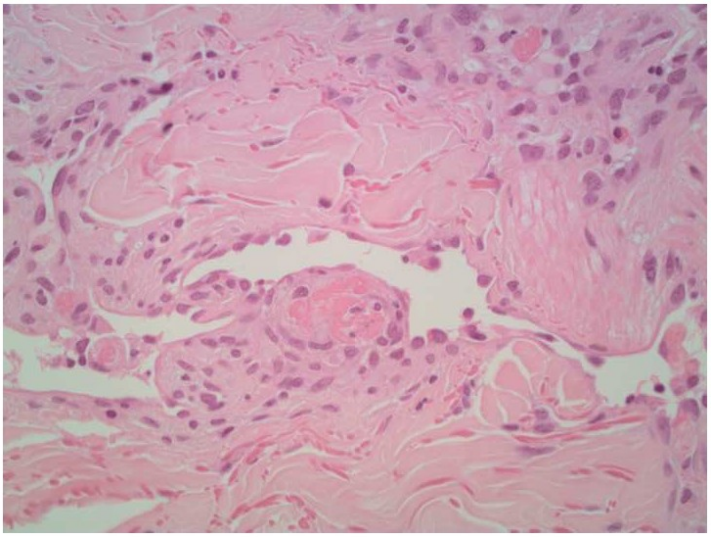

Figure 4 and 5

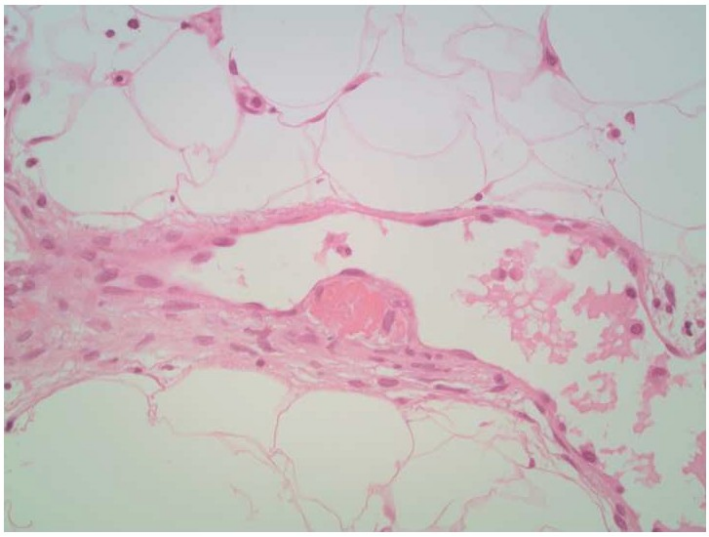

Figure 5

Table 1: Laboratory findings.

Investigation	Result
Full blood examination	Mild neutropaenia (1.7g/L)
Urea, electrolytes, creatinine	Normal
Liver function tests	Normal
Hepatitis serology	Negative
Antinuclear antibodies	Negative
Anticardiolipin antibodies	Negative
Serum cryoglobulins	IgG (kappa) 1g/L, cryocrit <1%
Urine electrophoresis	Free kappa light chains (0.09g/L)
Bone marrow biopsy	12% clonal plasma cells

Discussion

RAE is a rare disorder, which has been reported less than forty times in the literature [4]. It tends to affect males and females equally, and is most common in middle age [1].

RAE has a typical clinical presentation involving erythematous to violaceous macules, patches and plaques distributed over the limbs, face, trunk, and extremities [2]. Ulceration, blistering, and necrosis is uncommon, but may occur as in our case [2]. Systemic symptoms such as weight loss, fever, and malaise may occur [2]. Table 2 displays the differential diagnoses of the disorder.

Table 2: Clinical and histological differential diagnoses of RAE.

Clinical differential diagnoses [1,2]	Histological differential diagnoses[1]
Kaposi's sarcoma	Kaposi's sarcoma

Angiosarcoma	Angiosarcoma
Mycosis fungoides	Spindle cell haemangioma
Sarcoidosis	Glomeruloid haemangioma
Erythema nodosum	Pyogenic granuloma
Systemic lupus erythematosus	Epithelioid haemangioma
Calciphylaxis	Bacillary angiomatosis

RAE has been associated with a variety of disorders including systemic infections, autoimmune disease, lymphoproliferative disorders, peripheral atherosclerosis, renal and hepatic failure, and hypersensitivity reactions [1].Table 3 outlines suggested preliminary investigations and possible findings.

Table 3: Suggested investigations for RAE and possible findings.

Suggested investigations [2]	**Findings**
Full blood count	Anaemia, thrombocytopenia, leukocytosis
Urea, electrolytes, creatinine	Suggestive of renal impairment
Liver function tests	Suggestive of hepatic impairment
Erythrocyte sedimentation rate	Elevated
Lactose dehydrogenase	Elevated
Antinuclear antibody	Elevated
Cold-reactive proteins	Cyroproteinemia, cryofibrinogenemia
Serum protein electrophoresis	Paraproteinemia

RAE can manifest histologically in a variety of ways, but is predominantly characterized by the proliferation of endothelial cells and capillaries either limited to the dermis or extending into the subcutis [1]. Growth patterns can be diffuse, lobular (as in our patient), or mixed [1]. Organizing fibrin microthrombi are common findings. RAE is distinguished from intravascular large B cell lymphoma by the absence of cellular atypia on histology and lack of B or T cell markers on immunostaining [3]. The differentiation of these two disorders is important because they can have a similar clinical appearance, but markedly different prognoses. Intravascular large B cell lymphoma is a multisystem, rapidly progressive disorder with a poor prognosis, whereas RAE is generally benign and self-limiting [3].

The etiology of RAE remains uncertain. Owing to its association with a number of underlying diseases, it seems likely that several different mechanisms lead to a common reaction of cell proliferation and vascular occlusion. Possible pathogenic triggers include circulating immune complexes, cryoproteins, local trauma, and hypoxia [1].

In our patient, RAE was associated with cryoglobulinemia, which has previously been reported in the literature [5,6,7]. It was postulated by LeBoit et al [6] that the deposition of cryoproteins results in vascular occlusion and endothelial proliferation occurs as a response to the hypoxic stimulus. In our patient, the combination of positive cryoglobulins and the clinical presentation of lesions in exposed extremities such as the earlobes supports this finding. However, in cryoglobulinemia associated with RAE, pathology tends to be confined to the dermis [6], but in our patient it included the subcutis. Furthermore, a study by Cohen et al [7] of 72 patients with cryoglobulinemia failed to find an association with vessel proliferation, suggesting that other factors aside from simple cryoglobulinemia may be involved.

Because of the unclear pathogenesis of the disorder, there is no standard treatment. Management regimens have included antibiotics, topical or systemic corticosteroids, surgical excision, laser treatment, and observation; the diagnosis and management of any underlying disease is key [1,2].

The usual clinical course involves stabilization and resolution of the lesions over a period of months to years. However, in some cases the condition can progress or relapse [1,2]. In our patient, treatment with lenalidomide for the underlying disorder resulted in remission.

Conclusion

RAE, although rare, is an important condition to recognize because it is associated with a number of underlying disorders including systemic infections, autoimmune disease, and lymphoproliferative disorders. Our case demonstrates that RAE can be a marker of underlying disease in a patient who otherwise appears healthy.

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