Reactive angioendotheliomatosis associated with antiphospholipid syndrome

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Abstract

Reactive angioendotheliomatosis (RAE) is an uncommon, benign, antiproliferative condition associated with systemic diseases that may cause occlusion or inflammation of the vascular lumina. A link between antiphospholipid syndrome (APS) and RAE has been reported a few times in the literature. Herein, we present a unique case of RAE diagnosed in a patient with primary APS who was well-managed on warfarin and rituximab with no recent thrombotic events. As RAE can precede or follow a diagnosis of APS, the presence of the condition indicates a need to workup for APS and to ensure those with the condition are adequately anticoagulated. However, as demonstrated in this case, the condition can still occur in patients who are adequately anticoagulated.

Keywords: reactive angioendotheliomatosis, antiphospholipid syndrome

Introduction

Reactive angioendotheliomatosis (RAE) is a rare, benign, angioproliferative condition associated with numerous systemic diseases [1]. Four cases in the literature report an association between antiphospholipid syndrome (APS) and RAE [2-5]. Herein, we present a case of RAE diagnosed in a patient with primary APS who was well-managed on warfarin and rituximab with no recent thrombotic events.

Case Synopsis

A middle-aged man with a history of catastrophic primary antiphospholipid syndrome presented with an intermittently pruritic eruption present on the buttocks and posterior legs of unknown duration. The patient reported no known precipitant. The patient was on warfarin at therapeutic levels (target INR 2.5-3.5) and completed two courses of two rituximab infusions (seven months prior and approximately one year prior to presentation). Physical examination revealed diffuse brown-to-violaceous purpuric papules and thin plaques on the posterior legs and buttocks (**Figure 1**).

Two punch biopsies were obtained. Histopathology demonstrated scattered and clustered benign-appearing vessels in the papillary and reticular dermis with intravascular endothelial proliferation (**Figure 2A**, **B)**. These endothelial cells stained positive for CD31 (**Figure 2C)**. An immunohistochemical stain for human herpesvirus-8 (HHV-8) was negative throughout both biopsies. There was surrounding mild chronic infiltrate and hemosiderin laden macrophages. The histologic features were consistent with a diagnosis of RAE.

Case Discussion

Reactive angioendotheliomatosis presents as erythematous-to-violaceous papules, patches, or plaques of varying sizes that can be painful, pruritic, or asymptomatic [6]. Ulceration and necrosis are often present. Reactive angioendotheliomatosis occurs in patients with various underlying systemic diseases that may cause occlusion or inflammation of the vascular lumina. Histopathology of RAE demonstrates a proliferation of pericytes and endothelial cells without cellular atypia within dermal vessels and a surrounding chronic, inflammatory infiltrate [1,6]. The cells stain positive on immunohistochemistry for CD31, CD34, and other endothelial markers. In contrast to malignant

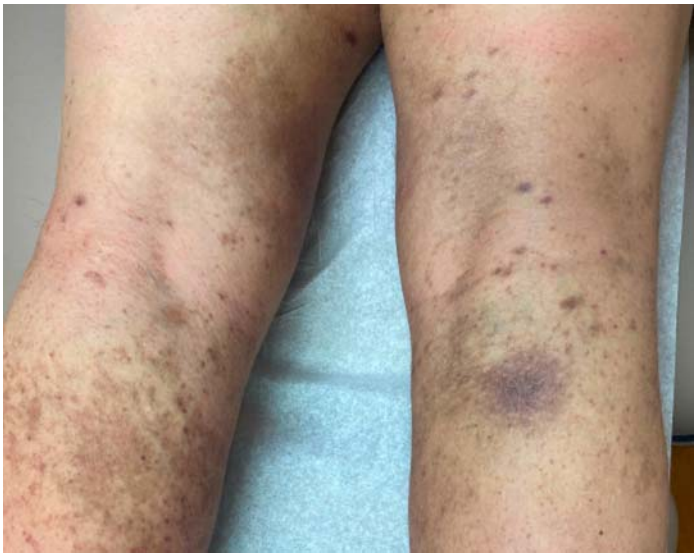

Figure 1. *Diffuse brown to violaceous purpuric papules and thin plaques on the posterior legs.*

angioendotheliomatosis, RAE is negative for CLA as well as B and T cell markers. Microthrombi and vascular occlusion are often present.

The pathophysiology of RAE is unknown but likely involves vascular occlusion or injury that results in local hypoxia and release of angiogenic factors [1,6]. The resulting hyperplasia of endothelial cells may be a stage of angiogenesis or the revascularization of thrombotic vessels. Removal of the hypoxic stimulus through treatment of the underlying systemic condition typically leads to resolution of RAE [6].

Antiphospholipid syndrome is a prothrombotic condition related to an unclear mechanism involving antiphospholipid antibodies. Skin manifestations include livedo reticularis, retiform purpura, subungual hemorrhages, ulcers, and necrosis [7]. These cutaneous lesions show histologic signs of capillary thrombosis and reactive endothelial cell proliferation [8].

There have been reports of RAE occurring in APS. It is believed that the antiphospholipid antibodies bind to resting endothelial cells, inducing their activation and upregulating molecules involved in hypercoagulation [9], thus forming local tissue microthrombi and hypoxia that contributes to the development of RAE. Notably, similar to our patient, two reported cases were stable and therapeutic on warfarin when RAE lesions occurred [3,5]. In one patient, transitioning from warfarin to low weight molecular heparin, oral clopidogrel, and low-dose aspirin resulted in rapid improvement of the lesions [3]. Therefore, even though these patients had no signs of major thrombotic events, they may have still been forming cutaneous microthrombi leading to the development of RAE. Interestingly, one case of RAE preceded the diagnosis of APS and may serve as a heralding sign for the condition [4].

Conclusion

We present a rare case of RAE associated with primary APS. Owing to the hypercoagulable state, patients with APS may be more likely to develop atypical proliferative vasculopathies. Reactive angioendotheliomatosis can either precede or follow a diagnosis of APS. Therefore, the presence of RAE indicates a need for thorough laboratory workup and surveillance for APS. However, as

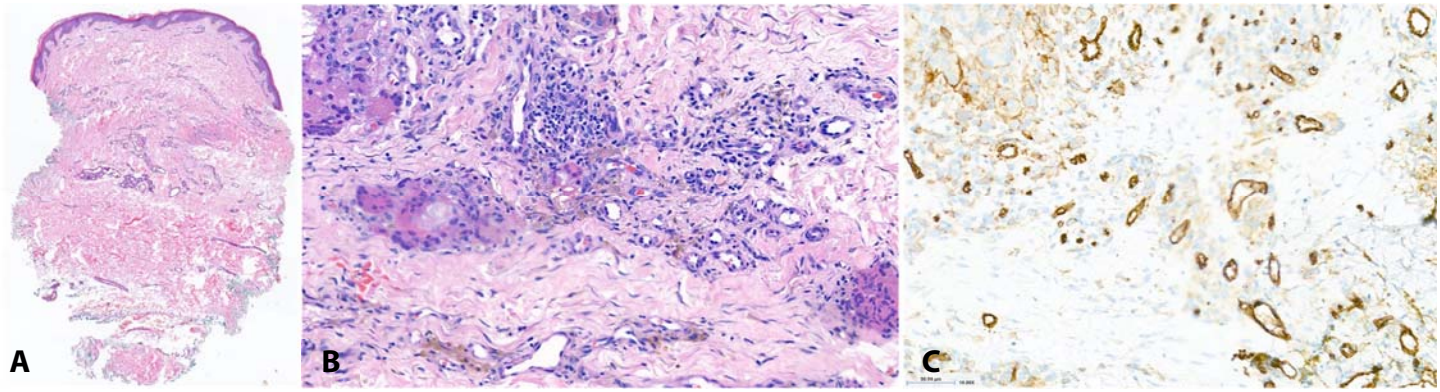

Figure 2. ***A)***, *There are scattered and clustered benign appearing vessels in the papillary and reticular dermis. H&E, 20×.* ***B)***, *Some of these benign appearing dermal vessels have intravascular endothelial proliferation. H&E, 100×.* ***C)***, *A CD31 immunohistochemical stain highlights the endothelial cells, 100×.*

demonstrated in this case, the condition can still occur in patients who are adequately anticoagulated.

Potential conflicts of interest

The authors declare no conflicts of interest.

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