

BRIEF ARTICLES

Reactive Angioendotheliomatosis: A Case Report

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ABSTRACT

Reactive angioendotheliomatosis (RAE) is a rare, typically self-limiting, angioproliferative disease that is commonly seen in patients with a variety of inflammatory and systemic diseases. RAE can clinically present as ulcerated, single or multifocal, violaceous papules or plaques. We report a case of a 59-year-old male with a complicated cardiac history who presented with biopsy-proven RAE on the thigh. The differential diagnosis of RAE can include Kaposi sarcoma and angiosarcoma, as well as other non-malignant cutaneous diseases. These diagnoses must be excluded before correctly diagnosing and treating RAE. We review the common presentation of RAE along with criteria to exclude other possible diagnoses that can resemble RAE.

CASE REPORT

A 59-year-old gentleman presented with a lesion on his left thigh that had been present for three months (Figure A). The lesion was initially described as a spontaneous lemon-sized pink area that later progressed to an increasingly painful plaque with central crusting. Prior to examination in our office, he was evaluated by vascular surgery due to left lower extremity pain. Ultrasound performed by vascular surgery showed left iliac artery stenosis and partial occlusion. Patient was scheduled for vascular intervention pending evaluation and clearance by dermatology for the new onset skin changes. He had no history of similar lesions in the past, but did have a previous history three years prior of a left femoral-

tibioperoneal trunk bypass. Within the past three months, the patient's medical history had also been complicated by cerebrovascular accident, myocardial infarction, and acute pancreatitis. While the cause of the pancreatitis was not definitively determined, the patient did have a history of alcohol abuse and hyperlipidemia.

On physical examination, the patient had a large pink-red plaque on left medial thigh with a small amount of scaling, and central white induration with a thicker dark brown crust. The right lower extremity was clear. Laboratory findings revealed a low hemoglobin of 11.7 (reference range, 12.0-17.0 g/dL), elevated platelets of 418 (reference range, 149-390 thousands/uL), elevated fibrinogen of 503 (reference range, 227-495 mg/dL), and an elevated

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erythrocyte sedimentation rate of 36 (reference range, 0-11 mm/hr). Two punch biopsies were obtained to aid with diagnosis, one from the central white indurated area and one from the peripheral pink-red zone (Figures B and C). Histopathologic examination of both biopsies from the left thigh revealed an ill-defined dermal-based proliferation of poorly formed slit-like vascular spaces that percolated through reticular collagen bundles, surrounded adnexal structures and extended into the subcutis. The vascular spaces were lined with flattened, bland endothelial cells without cytologic atypia or mitotic activity. CD31 and CD34 immunostains highlighted the patchy vascular proliferation. HHV-8 immunostain was negative.

Following this initial evaluation in our office, the patient was lost to dermatologic follow up. However, a review of a shared electronic medical record revealed that less than two months later, he had a revascularization procedure of the left femoral and left iliac arteries. Patient was discharged to short term rehabilitation. Patient did have complications shortly thereafter with wound healing requiring wound debridement and a wound vacuum device. Patient did not respond to requests to contact the office.

DISCUSSION

Reactive Angioendotheliomatosis (RAE) is a rare, benign condition that presents with a cutaneous vascular proliferation and tends to occur in patients with coexistent systemic diseases.¹ Clinical presentation typically includes erythematous macules, purpuric papules, and purpuric plaques, which can be ulcerated.¹ Although lesions tend to favor the limbs, they can also present on the face or trunk.¹⁻³ RAE has been reported in all age groups and is equally common in both males

and females.² Review of systems may be positive for constitutional symptoms, such as fevers and weight loss.^{2,3} Laboratory results may demonstrate an elevated erythrocyte sedimentation rate.² Coexistent diseases are broadly reported in the literature and include infectious diseases, systemic diseases, hematologic disorders, monoclonal gammopathies, and vascular abnormalities.

While the pathogenesis is unknown, changes in portal and systemic hemodynamics, as well as a response to local hypoxia, have been suggested. This is further supported by cases of RAE that improve after arterial bypass procedures, corroborating the notion that local tissue hypoxia may have been an inciting agent leading to induction of angiogenesis.¹ Another theory is that deposition of complement and immunoglobulins may induce vascular injury and reactive angiogenesis.¹ Furthermore, association with underlying systemic infections suggest that RAE can represent a hypersensitivity response of endothelial cells to foreign antigens.¹ This hypersensitivity response leads to deposition of immunoglobulins in capillaries in the skin leading to thrombi, ensuing local hypoxia and, again, subsequent angiogenesis.¹⁻³

On histopathology, RAE demonstrates a benign intraluminal proliferation of endothelial cells that may occlude the vascular lumen.⁴⁻⁶ In addition, the vessels are usually dilated.⁴ The upper subcutaneous fat might demonstrate vascular occlusion with cells and fibrin.² The intravascular cells are positive for factor VIII-related antigen, CD31, and CD34.⁴

Initially, RAE was divided into benign and malignant variants. The malignant variant, incorrectly named malignant

angioendotheliomatosis, has now been redefined as angiotropic large cell lymphoma/intravascular large B-cell lymphoma, an intravascular type of malignant lymphoma.³ Angiotropic large cell lymphoma is a rare extranodal lymphoma characterized by neoplastic lymphocytes in the lumina of blood vessels that can present similar to RAE: erythematous, violaceous plaques with ulcerated nodules.⁹ Angiotropic large cell lymphoma will show atypia of intraluminal cells in skin biopsy specimens and intrasinusoidal infiltration of lymphoid cells in bone-marrow specimens.^{3,9} Angiotropic large cell lymphoma is mostly of B-cell origin (positive for CD20 and CD79a immunomarkers) but rare cases can demonstrate a T-cell or NK-cell phenotype (positive for CD2 and CD3; negative for CD4 and CD5; variable expression of CD56, EBV and CD30).^{2,13}

In addition, RAE must be distinguished from intralymphatic histiocytosis and intravascular papillary endothelial hyperplasia on histopathology. Intravascular papillary endothelial hyperplasia is a nonneoplastic reactive process that arises within blood vessels after vascular trauma. This vascular injury results in thrombus formation, inflammation which facilitates endothelial cell proliferation.¹⁰ Histologically, intravascular papillary endothelial hyperplasia demonstrates thin-walled dilated blood vessels with a thrombus and hyaline papillary fronds lined by endothelial cells.³ Intralymphatic histiocytosis is a disorder defined by the accumulation of histiocytes within lymphatic vessels and clinically presents as asymmetric plaques, nodules or macules.¹¹ Intralymphatic histiocytosis shows intraluminal proliferations with occlusion whereas RAE shows intraluminal glomeruli-like tufts of capillaries.³ The majority of the intraluminal cells expresses positive CD68 and negative CD31/CD34

with marked dermal edema and perivascular inflammatory infiltrate.^{4,11}

Other important clinical entities to consider include Kaposi's sarcoma and angiosarcoma. Kaposi sarcoma (KS) presents initially as erythematous, violaceous bilateral and symmetric patches, typically on the lower extremities.⁷ KS can range from an isolated cutaneous involvement to a rapidly progressive cutaneous, mucosal, and visceral disseminated disease.⁷ Histopathology varies depending on the phase of the disease. Early KS resembles granulation tissue and small vessel-like proliferation.⁷ As the lesions progress, endothelialized vessels with slit-like spaces cuffed by oval and spindle cells infiltrating dermal collagen bundles will evolve. HHV-8 has been closely linked with all types of KS.⁷ Angiosarcoma is a malignant neoplasm derived from vascular endothelial cells that presents as a hematoma-like lesion, sometimes as a consequence of radiation therapy or chronic lymphedema, around the eighth decade of life.⁸ The majority of cases involve the upper extremity of women who have undergone radical mastectomy for the treatment of breast cancer but can also be seen on the sun exposed head and neck of elderly males.^{8,12} This diagnosis can be excluded by its distinct histopathological features, which include irregular, anastomosing vascular structures with pleomorphic and hyperchromatic atypical endothelial cells.⁸

Figure A. Clinical Presentation of left thigh of 59-year-old male showed reactive angioendotheliomatosis presenting as progressively enlarging, tender, erythematous plaque with central ulcerations.



Figure B. H&E of Biopsy 2 at 4x. Showing poorly-demarcated dermal based proliferation of slit-like vascular spaces throughout reticular collagen bundles.

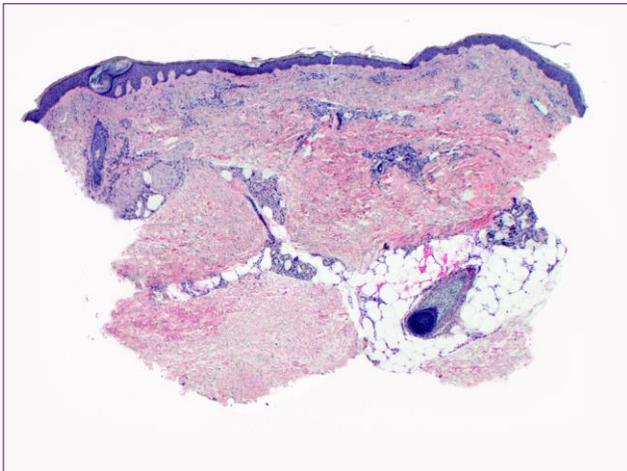
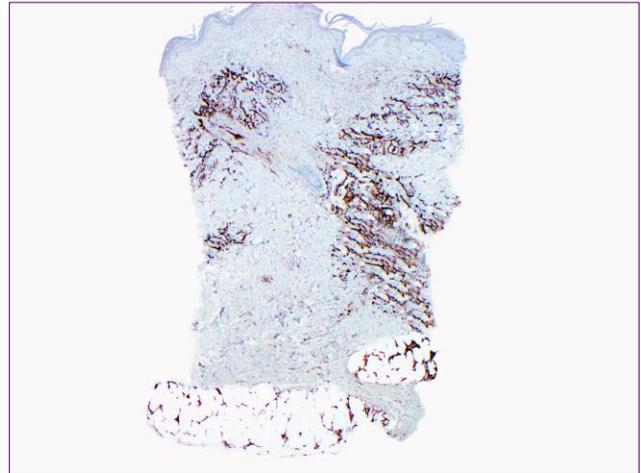


Figure C. H&E x 4x. CD34 stain showing patchy proliferation of capillaries throughout the dermis.



CONCLUSION

RAE is typically self-limiting with a favorable prognosis.¹ Therapy, if needed, is directed at the underlying systemic disease. However, no specific treatment is currently available. Consideration can be made for antibiotics for infections and systemic steroids for their suppressive role on neoangiogenesis when no apparent cause can be found.³ In all, RAE is a rare reactive endothelial proliferation associated with numerous conditions in response to an unknown inciting stimulus.

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