Glomeruloid reactive angioendotheliomatosis in a woman with systemic lupus erythematosus and antiphospholipid syndrome mimicking reticular erythematous mucinosis

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Key words: antiphospholipid syndrome; glomeruloid pattern; lupus erythematosus; reactive angioendotheliomatosis; reticular erythematous mucinosis.

INTRODUCTION

The umbrella term "cutaneous reactive angiomatoses" was introduced in 2003 to include uncommon angioproliferative (capillary) cutaneous conditions, which present with variable clinical features and involve patients with a variety of underlying systemic conditions.[1] Histologically, these disorders are characterized by different patterns of intravascular or extravascular lobular or diffuse hyperplasia of endothelial cells, pericytes, and, sometimes, histiocytes, mostly throughout the dermis.[1] The first condition to be described was reactive angioendotheliomatosis (RAE), which is usually associated with prothrombotic conditions.[1] We report a case of RAE in its rare glomeruloid variant, occurring in a woman with systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS), which is notable because it mimics reticular erythematous mucinosis (REM).

Abbreviations used:

APS: antiphospholipid syndrome
RAE: reactive angioendotheliomatosis
REM: reticular erythematous mucinosis
SLE: systemic lupus erythematosus

CASE REPORT

A 71-year-old woman with a 3-year history of SLE and autoimmune hepatitis in the context of APS presented with an asymptomatic rash on the chest for 8 months, expanding slowly. She reported 4 spontaneous miscarriages in her 30s and a leg deep venous thrombosis 6 years before. She was taking 12.5-mg prednisone, 1.5-mg mycophenolate mofetil, and 400-mg hydroxychloroquine. Physical examination revealed an eruption consisting of erythematous macules merging into a reticulate pattern with slightly purpuric hue on the central part of the chest and base of the neck (Fig 1).

The woman had thrombocytopenia (70,000 cells/μL), antinuclear antibodies (ANA) with a homogeneous pattern and a titer of 1/320, anti-double–stranded DNA antibodies, and she also tested positive for anti-β2-glycoprotein (IgM, 36 IU/mL; IgG, 24 IU/mL [normal range < 20 IU/mL]). Tests for anticardiolipin antibodies, lupus anticoagulant, rheumatoid factor, antineutrophil cytoplasmic antibodies, cryoglobulins, and Protein C and S were negative. The levels of C3 and C4, prothrombin time, activated partial thromboplastin time, and D-dimer were within the normal ranges.

Histopathology of an incisional biopsy showed an expansion of the dermal vasculature in the superficial and mid-dermal layer related to an intravascular proliferation of small-to-enlarged cells and closely spaced capillaries, which filled and occluded the vascular lumina in a glomeruloid pattern (Figs 2 and 3). Intravascular thrombi with erythrocytes and scanty lymphocytic infiltrate were observed. No significant cellular atypia was present. Immunohistochemistry with CD31 outlined the intraluminal vascular spaces and the endothelial

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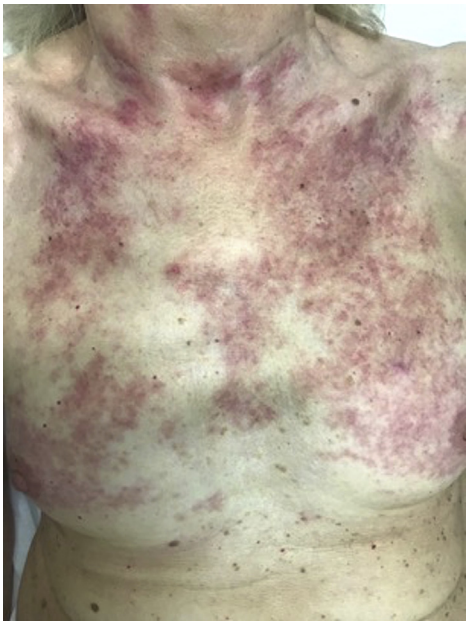

Fig 1. RAE. A clinical presentation of the reticular eruption. *RAE*, Reactive angioendotheliomatosis.

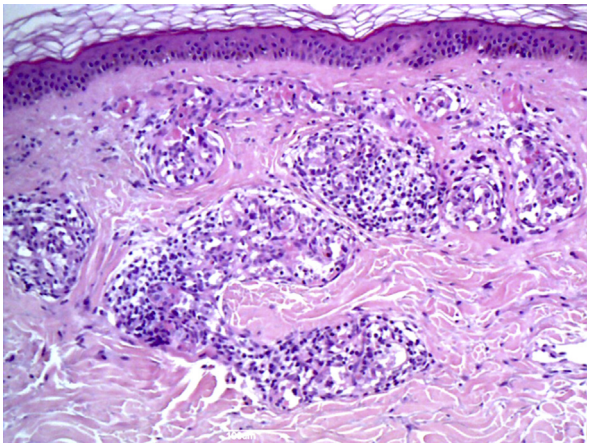

Fig 2. RAE. Histopathologic findings with dilated dermal vessels filled with intravascular proliferation of endothelial cells and closely spaced capillaries occluding the vascular lumina (hematoxylin-eosin stain; original magnification: ×100.) *RAE*, Reactive angioendotheliomatosis.

cells (Fig 4), while D2-40 immunostaining for lymphatics was negative. The patient was given 150 mg of cardio aspirin and 400 mg of pentoxiphylline twice a day in addition to her lupus therapy. No improvement was noted after one year of follow-up.

DISCUSSION

We here describe a case of angioendotheliomatosis with typical clinical and histopathologic findings. Originally, 2 variants of angioendotheliomatosis were considered: a benign or reactive form (RAE) and a malignant angioendotheliomatosis.[2] In fact, the latter corresponds to intravascular, angiotropic lymphoma.[2] RAE is a rare condition, affecting women and men equally, and has been reported in all age groups. The clinical features are nonspecific, presenting with polymorphous erythematous purple-brownish macules and papules or purpuric plaques and occasionally ulcerated lesions with a wide distribution. RAE has been especially associated with infectious and autoimmune diseases, inflammatory and (sub) occlusive vasculopathies, and hemolymphoproliferative disorders, many of which have partial or complete luminal obstruction by thrombi or abnormal proteins in common.[1,3] The association of RAE with previous concomitant SLE and APS has been reported in 2 cases (Table I),[4-7] while 2 further cases developed in

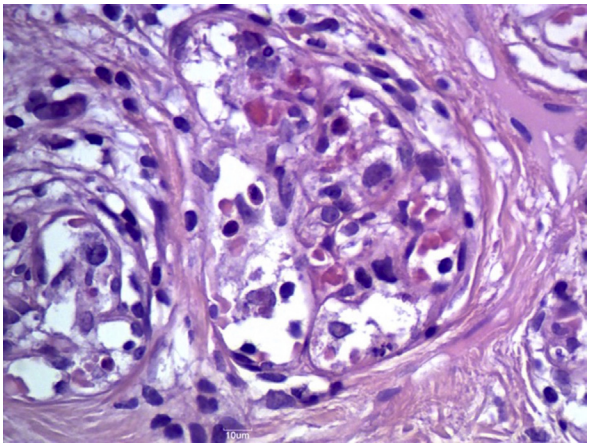

Fig 3. RAE. Closely packed capillaries within pre-existing dilated vascular spaces resembling renal glomeruli, with intravascular thrombi and erythrocytes (hematoxylin-eosin stain; original magnification: ×200.) *RAE*, Reactive angioendotheliomatosis.

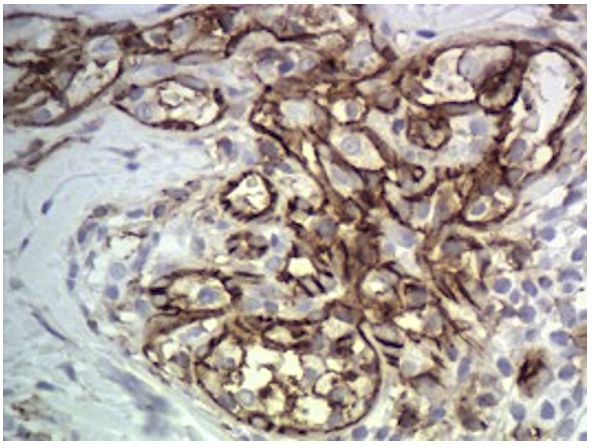

Fig 4. RAE. Immunostain positivity for CD31. *RAE*, Reactive angioendotheliomatosis.

Table I. Characteristics of RAE associated with SLE and/or APS

Reference	Clinical presentation	Sex	Age	Association	Histopatologic pattern	Therapy and outcome
Tahi et al, 2003[5]	Indurated erythematous purpuric plaques on lower chest, abdomen, and upper thighs	Man	31 years	SLE and APS	Glomeruloid RAE with intravascular thrombi	Subcutaneous enoxaparin, oral clopidogrel, and low-dose aspirin. Rapid improvement and complete resolution. Follow-up not provided.
Creamer et al, 2000[6]	Purpuric lesions on neck, chest, and abdomen, evolving to areas of full thickness necrosis	Woman	50 years	SLE and APS	Expansion of dermal microvasculature by intravascular cellular proliferation and focal thrombosis	Reinstating warfarin therapy. Slow healing of the necrotic lesions. Follow-up not provided.
Nikam et al, 2015[4]	Indurated purpuric, scaly plaque of the plantar surface, extending from the second to the fourth toe web spaces and in a livedo-like pattern on the dorsal aspect of the right foot	Woman	In her 30s	Primary APS	Expansion of dermal vasculature due to intravascular cellular proliferation, with intravascular thrombi	Pentoxyphyllin, low-dose aspirin. After 6 months, the lesions regressed in size with a reduction of symptoms. No follow-up provided.
Kawaoka et al, 2008[7]	Asymptomatic flat-topped violaceous or purpuric papules and plaques over the elbows, thighs, and buttocks	Woman	51 years	Primary APS	Diffuse dermal angiomatosis; no intravascular thrombi	No improvement with oral and intralesional steroids, cryotherapy, and alitretinoin gel 0.1%. Two sessions of long-pulsed dye laser (595 nm) with satisfactory results. No follow-up provided.
Current case	Erythematous macules merging into a reticulate pattern on the central part of the chest and the base of the neck	Woman	71 years	SLE and APS	Glomeruloid RAE with intravascular thrombi	Pentoxyphyllin, low-dose aspirin. No improvement at 1-year follow-up.

APS, Antiphospholipid syndrome; *RAE*, reactive angioendotheliomatosis; *SLE*, systemic lupus erythematosus.

patients affected with primary APS, not fulfilling the criteria for SLE.[4] Our case confirms a higher prevalence among women, although age was more advanced, and presentation differed from the prevalent indurated purpuric plaques reported in previous observations. The diagnosis relies on histopathology, showing proliferation of endothelial cells within the lumina of dermal vessels with intravascular thrombi. In the glomeruloid variant, many closely packed capillaries were observed within pre-existing dilated vascular spaces, resembling the structure of renal glomeruli.[8] The pathogenesis remains unclear but possibly relies on different stimuli causing dermal vessel (sub) occlusion. Local hypoxia is a potent mediator of angiogenic cytokines synthesis, such as vascular endothelial growth factor, which induces endothelial cell proliferation to restore an adequate blood circulation.[1,9] The main histologic differential diagnosis is intralymphatic histiocytosis, which is characterized by the accumulation of macrophages within D2-40-positive lymphatic vessels and can be associated with systemic diseases, particularly rheumatoid arthritis.[1,9]

While histology was very specific, the clinical presentation in our patient was rather peculiar, and we considered the differential diagnosis of REM,

acute cutaneous lupus erythematosus, and retiform purpura.[10-13] REM was plausible, typically affecting the midline of the chest or the upper portion of the back of young and middle-aged women. However, intravascular proliferation is not a histopathology finding in REM, showing a perivascular and periappendageal, predominantly lymphocytic infiltrate with dilated capillaries in the superficial and deep dermis. The abundant dermal mucin deposition is another diagnostic clue in REM. Although LES developed in a patient with reticular lesions, clinically and pathologically consistent with REM, no link appears to exist between the 2 conditions. The relationship of REM with lupus tumidus is also a matter of debate.[10,11] The hypothesis that the neck and widespread symmetric macules eruption could represent acute cutaneous lupus erythematosus was supported by the hematologic test results, which did not confirm active disease. Moreover, histopathology in lupus erythematosus shows interface dermatitis of vacuolar type.[12] Retiform purpura is a clinical pattern, characterized by nonblanchable, hemorrhagic branched patches or plaque, which can occur in a variety of vascular disorders, leading to wall vessel damage and/or lumen occlusion, with analogies to angioendotheliomatosis. It is usually related to infections, disseminated intravascular coagulation, purpura fulminans, and APS. Histopathology, however, occlusive nonvasculitic vasculopathy is observed.[12]

In summary, we have presented a case of cutaneous glomeruloid RAE in a woman with SLE and APS clinically mimicking REM. This variant should be added to the polymorphous clinical presentations already reported and emphasizes the protean manifestations of the disease, the diagnosis of which relies on appropriate histopathologic examination. Due to its potential association with life-threatening prothrombotic systemic disorders, it appears crucial to perform exhaustive investigations when a diagnosis of RAE is made.

Conflicts of interest

None disclosed.

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