



CASE REPORT

# Case Report: A case of antiphospholipid-antibody-associated reactive angioendotheliomatosis and panniculitis [version 1; referees: 1 approved, 1 approved with reservations]

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**Abstract**

**Introduction:** Reactive angioendotheliomatosis (RAE) is a benign vascular disorder with a varied clinical presentation that has been associated with a wide range of systemic illnesses. It is characterized histologically by intravascular and extravascular hyperplasia of endothelial cells and pericytes, and this entity only affects the skin. We present the rare case of a woman with both RAE and panniculitis associated with anticardiolipin antibodies in the setting of antiphospholipid syndrome (APLS).

**Case description:** A female in her forties presented for a second opinion of lumps in her skin. The first lump was noted on her right thigh four years prior to presentation, and biopsy demonstrated longstanding septal and lobular panniculitis. Studies that followed this finding revealed a diagnosis of APLS, and the patient had been placed on 400 mg per day of hydroxychloroquine and a daily low-dose of aspirin. She presented with a new subcutaneous plaque on the left lower back, and biopsy of this lesion was suggestive of RAE. She had no history of significant thrombotic events and had never been treated with an anticoagulant. Work-up was negative for other connective tissue diseases that are known for producing subcutaneous nodular lesions.

**Discussion:** RAE is very rare, with less than 50 cases reported in total; five of these in association with APLS. In the context of APLS, RAE is likely a result of the procoagulant state induced by the presence of antiphospholipid antibodies. This case of both RAE and panniculitis associated with anticardiolipin antibodies in the setting of APLS describes rare manifestations of APLS as isolated incidents in a relatively healthy patient.

**Open Peer Review**

Referee Status: ✓ ?

	Invited Referees	
	1	2
<b>version 1</b> published 06 Aug 2014	<span style="color: green;">✓</span> report	<span style="color: green;">?</span> report

- 1 Anne E. Laumann**, Northwestern University Feinberg School of Medicine USA
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**Competing interests:** No competing interests were disclosed.

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## Case

The patient was a 49 year-old Caucasian female legal assistant, with a history of mild hypertension, taking hydrochlorothiazide and metoprolol. Chronic leg pain, panniculitis without known primary explanation, and antiphospholipid antibody syndrome (APLS) presenting for a second opinion of lumps in her skin.

The first lump had been noted on her right thigh four years prior to presentation, when the patient noticed darkening of the overlying skin, giving it a bruise-like appearance, with a central nodule. The area itself was non-tender but was associated with lateral leg pain that, according to the patient, failed to respond to physical therapy and multiple cortisone injections. Biopsy of the thigh nodule demonstrated features of a longstanding septal and lobular panniculitis. The nodule was surgically removed and did not recur. After excision of the nodule, the patient's leg pain decreased, though she felt some residual throbbing, especially at night and with sitting. Approximately six months later she developed two other subcutaneous lumps, on the back and left-lower abdomen. Biopsy of the abdominal lesion was consistent with a lipoma.

Review of systems was unremarkable, as there were no joint pains or swelling of the joints, and no fevers, chills, night sweats, or significant weight change.

Past medical history included hypertension and hypercholesterolemia. The patient had no history of significant thrombotic events and had never been treated with an anticoagulant.

Prior lab investigations, approximately two years prior to presentation in our clinic, revealed an Antinuclear Antibody Test (ANA) that stained positive at dilutions of 1:160 and 1:320, positive anticardiolipin IgM antibody at 93 MPL, and positive Beta-2-glycoprotein 1 IgM antibody at a level greater than 150 MPL. A hematologic panel and coagulation studies were within normal limits. Rheumatologic work-up was also negative for rheumatoid factor, SSA/SSB, and smooth muscle or RNP antibodies. Upon diagnosis of APLS the patient had been placed on 400 mg per day of hydroxychloroquine and 81 mg per day of aspirin.

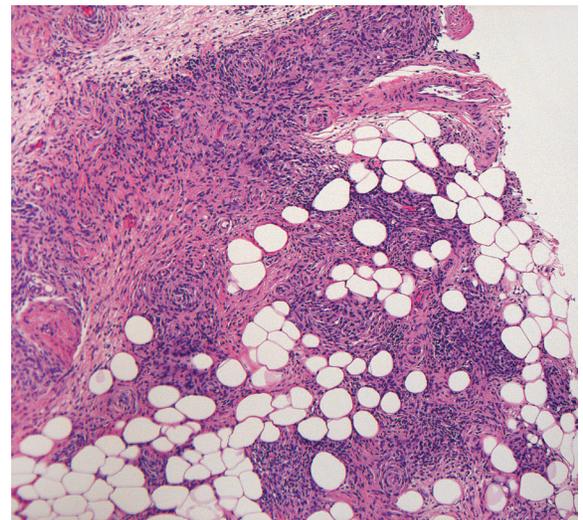
On exam there was a firm subcutaneous plaque on the left lower back, approximately 3×3 cm, with no overlying skin changes (Figure 1), a firm, mobile nodule, approximately 2×2 cm on the left lower quadrant of the abdomen, and a livedo on the extensor surfaces of the upper arms and legs.

A biopsy of the patient's back lesion was reviewed by a dermatopathologist and described as a proliferation of spindled endothelial cells and vessels with concentric wall thickening in the subcutaneous tissue (Figure 2). The spindled cells were highlighted with a CD31 IHC staining (Figure 3), and a Factor XIIIa staining also highlighted many cells within the spindle cell proliferation, confirming their endothelial origin. Additionally, within the dermis there was a perivascular and periadnexal lymphocytic infiltrate. Neither vascular occlusion nor microvascular thrombosis was observed.

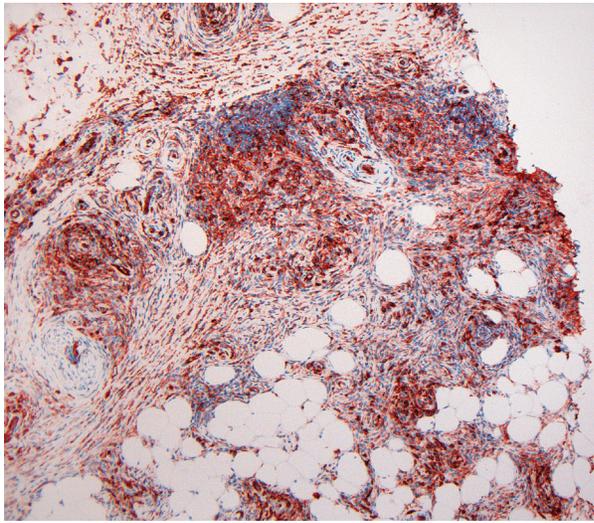
Overall, the spindle cell proliferation within the subcutaneous tissue was thought to be suggestive of a reactive angioendotheliomatosis (RAE). In response to this result, the patient's low dose aspirin and hydroxychloroquine regimen was continued, and she was advised to discontinue oral contraceptive pills (OCPs) given the concern for clotting risk. The patient discontinued OCPs and opted not to have her remaining lesions surgically removed. At six months follow-up, the current lesions have stabilized and no new lesions have developed.



**Figure 1. Clinical photograph of RAE lesion.** This photo shows the firm subcutaneous plaque on the patient's left lower back, approximately 3×3 cm, with no overlying skin changes. On microscopic exam this lesion was found to be RAE.



**Figure 2. H&E stained section of RAE Lesion at 10x.** An H&E staining of the biopsy section of the patient's back lesion demonstrating proliferation of spindled endothelial cells and vessels with concentric wall thickening in the subcutaneous tissue. 10x magnification.



**Figure 3.** CD31-stained section of RAE Lesion at 10x. A CD31 immunohistochemical staining of the patient's back lesion highlighting the spindled cells. 10x magnification.

## Discussion

RAE is a benign vascular disorder with a varied clinical presentation that has been associated with a wide range of systemic illnesses. It is characterized histologically by intravascular and extravascular hyperplasia of endothelial cells and pericytes, and this entity only affects the skin<sup>1</sup>. The intravascular cells are without atypia and have been demonstrated to display reactivity for antibodies to Factor VIII-related antigen, blood group isoantigens A, B, and H, vimentin, and Ulex europaeus I lectin, and negativity for leukocyte common antigen (LCA)<sup>2</sup>. RAE is very rare, with less than 50 cases reported<sup>1</sup>. In contrast, malignant angioendotheliomatosis (MAE), a fatal intravascular lymphoma of B-cell origin, displays reactivity for antibodies to LCA, B-Cell antigens, and vimentin in tumor cells<sup>2</sup>.

Other systemic illnesses that have been associated with RAE include subacute bacterial endocarditis, tuberculosis, lymphoproliferative disorders, liver failure, renal failure, rheumatoid arthritis, cryoglobulinemia, and peripheral vascular atherosclerosis<sup>3</sup>.

Clinically, the presentation of RAE can vary widely, ranging from erythematous or purpuric papules, macules and plaques to ecchymoses, which may exhibit necrosis or ulceration<sup>4</sup>. The lesions have been observed to mimic the following diagnoses: Kaposi sarcoma, morphea, pyoderma gangrenosum, calciphylaxis, angiosarcoma, lichen ruber verrucosus, sarcoid, pyogenic granuloma, eruptive disseminated lobular capillary haemangioma, and lupus panniculitis<sup>4</sup>. The clinical appearance of our patient's back lesion, an indurated, subcutaneous plaque with no change to the overlying skin, led to a differential of lupus panniculitis versus morphea prior to histological diagnosis.

The pathogenesis of RAE remains unclear, although the fact that it is associated with various disparate disease entities suggests multiple pathways leading to a common reactive pattern<sup>3</sup>. Additionally, RAE occurs in the context of conditions that may cause occlusion

of the vascular lumina. This has led to the suggestion that vascular occlusion by thrombi may cause localized hypoxia and acidosis, followed by hyperplasia of endothelial cells and occasionally pericytes, leading to the observed histopathology<sup>5</sup>.

In this case, it is likely that the findings of RAE and panniculitis are both associated with the patient's APLS. Specifically, the pathogenesis of these cutaneous findings has been associated with the presence of anticardiolipin antibodies, which were present in our patient. Localized RAE in the setting of APLS, such as our patient's back lesion, has been previously described in the literature<sup>3</sup>, with the first known case reported in 2000<sup>6</sup> and less than 5 cases reported in total<sup>3,5,6</sup>. In the context of antiphospholipid syndrome, RAE is likely a result of the procoagulant state induced by the presence of antiphospholipid antibodies. A recent report postulates that the anticardiolipin antibody may be the underlying cause for the thrombophilia leading to the finding of RAE, given that a combination of microthrombosis and reactive endothelial-cell proliferation has been reported in association with anticardiolipin antibodies in the literature<sup>5</sup>. The patient's thigh nodule biopsy, which demonstrated panniculitis is also consistent with her diagnosis of APLS. Anticardiolipin antibodies have been associated with septal and lobular panniculitis resembling the features noted in the patient's biopsy<sup>7</sup>. Additionally, previous cases have also reported the association of patients with APLS, thigh nodules with leg pain, and elevated anticardiolipin antibody levels<sup>7,8</sup>. It is unlikely that these cutaneous findings are related to another primary disorder, given the patient's negative work-up and lack of symptoms indicative for systemic lupus erythematosus (SLE), sarcoidosis, fasciitis, or scleroderma/morphea, polyarteritis nodosa, or other connective tissue diseases known for producing subcutaneous nodular lesions.

In conclusion, we report the rare case of a woman with both RAE and panniculitis associated with anticardiolipin antibodies in the setting of APLS. This case adds to the literature by describing these rare manifestations of APLS as isolated incidents in a relatively healthy patient.

## Consent

Written informed consent for publication of clinical details and clinical images was obtained from the patient.

## Author contributions

VW and SS identified this interesting case that warranted reporting. EP prepared the first draft of the manuscript. CS supplied and photographed figures. All authors were involved in the revision of the draft manuscript and have agreed to the final content.

## Competing interests

No competing interests were disclosed.

## Grant information

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*The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*

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# Open Peer Review

Current Referee Status:



Version 1

Referee Report 01 September 2014

doi:10.5256/f1000research.3477.r5732



**Beatrix Volc-Platzer**

Department of Dermatology, Donauspital, Vienna, Austria

In view of the rarity of reactive angioendotheliomatosis this is an important case report to alert clinicians to this disorder and should eventually, be indexed. However, I think that the authors should go into more detail as listed below, and I therefore approve with reservations at the moment.

## Abstract:

**Introduction:** It is not only the clinical presentation that is quite varied, but also the histopathological pattern. Intravascular endothelial proliferation is regarded as "key feature", but other patterns have been described as well. Deposition of fibrin and thrombi are variably found within the endothelial proliferations. Perivascularly, extravasation of erythrocytes and lymphocytes are found... therefore, I suggest adapting the second sentence of the introduction accordingly.

## Case description:

Regarding the case description I have a few suggestions:

- A female patient ....
- ... (APLS) due to ....
- The dose of aspirin should be given as well.
- It should be stated also in the abstract whether - in addition to connective tissue diseases - other potential stimuli of or disease associations with RAE, respectively, have been excluded, e.g. endocarditis, liver or renal disease.

## Case Report:

### Case:

Regarding the case I have a few questions:

- The medication for hypertension is given, but not whether hypercholesterolemia has been treated and, if so, by which medication.
- What was the pattern of ANA staining? In case of positive ANA and in particular with a homogenous pattern, anti-dsDNA-antibodies were negative?
- What are the reference values for antiphospholipid IgM and  $\beta$ 2-glycoprotein 1?
- Have cryoglobulins been tested for?
- I suggest to mention in the text the reason for using hydroxychloroquine (antithrombotic and antihyperlipaemic) in addition to aspirin.
- Figure 1: Is the central pale area a scar after biopsy?

- Histopathology: as far as I see in Figure 2 the main pathology is at the dermal/subcutaneous interface. RAE, however, is found in the superficial dermis or throughout the entire dermis. Histopathology reminds me rather of panniculitis. Is it possible to find another figure showing more of the dermis?
- Immunohistochemical studies have been performed with anti-CD34, vWF, smooth muscle actin for pericytes, and HHV-8.

**Discussion:**

Discussion includes all important features of RAE. However, discussion on histopathological patterns might be extended.

- 1<sup>st</sup> paragraph: ... on various forms of RAE, i.e. diffuse dermal angiomatosis - which might be the main histopathologic differential diagnosis, glomeruloid hemangioma-like, angiomatosis with deposits of cryoglobulin, etc.

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

**Competing Interests:** No competing interests were disclosed.

Referee Report 27 August 2014

doi:[10.5256/f1000research.3477.r5938](https://doi.org/10.5256/f1000research.3477.r5938)

**Anne E. Laumann**

Department of Dermatology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Reviewing this paper has taught me about reactive angioendotheliomatosis, a condition about which I knew little before. As such this is a relevant report for indexation. However, it can be made more concise and some of the grammar can be corrected.

Abstract is excellent, except aspirin was being used as an anticoagulant.

Some suggestions:

**Para 1:** No reason for “The patient was ---” and “ ---with a history of mild hypertension, taking hydrochlorothiazide and metoprolol”. Instead: “A 49 year old female legal assistant with chronic leg pain, panniculitis of unknown cause, and antiphospholipid antibody syndrome (APLS) presented for a further opinion related to lumps in her skin”

**Para 3:** Review of systems revealed no pain or swelling of her joints, no fever, chills, night sweats nor weight change.

**Para 4:** She had known hypercholesterolemia and hypertension, for which she was taking metoprolol and hydrochlorothiazide. She had had no previous significant thrombotic events, but to say she had never had an anticoagulant is not really correct as she was on daily aspirin and in this situation the hydroxychloroquine was being used to help decrease blood viscosity also. May be “anticoagulant” is a question of definition.

**Para 5:** MPL needs defining and the units for Beta-2-glycoprotein need correcting.

Sentence 3: suggest: Rheumatoid factor, SSA/SSB and smooth muscle and RNP antibodies were negative.

**Para 6:** delete “a” prior to “livedo”

**Para 7:** “a dermatopathologist” – presumably one of the authors. IHC needs defining

#### Discussion

**Para 1:** Sentence 3: “without atypia and display” - delete “have been demonstrated to”

**Para 3:** Sentence 2: “Panniculitis” needs correcting

**Para 5:** Sentence 1: delete “patient’s” in – “In this case, it is likely that the findings of RAE and panniculitis are both associated with the APLS.”

Sentence 3: delete “in the literature”. Change: “report” rather than “reported” in “with the first known case reported in 2000”

Sentence 5: delete “in the literature”

Sentence 7: remove “patient’s”

Sentence 8: Only “Additionally” or “also” is needed, not both

Sentence 9: remove “patient’s”. Why do you need “(SLE)” as this is not mentioned again? “Fascitis” should be “fasciitis”.

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

**Competing Interests:** No competing interests were disclosed.

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