

Atypical presentation of pediatric antiphospholipid syndrome



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INTRODUCTION

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by potentially life-threatening recurrent vascular thrombosis, miscarriage, and the presence of antiphospholipid antibodies, including anti-cardiolipin, anti-beta 2 glycoprotein, and lupus anticoagulant. It is additionally associated with false-positive rapid plasma reagin titer. APS can either be primary, presenting in the absence of another autoimmune disorder, or secondary, presenting with another autoimmune disorder. Data on the epidemiology of APS are limited, but 1 study found the annual incidence and prevalence to be 2.1 and 50 per 100,000, respectively.¹ The epidemiology of APS is further limited in pediatric patients, as it is likely underdiagnosed due to a lack of pediatric-specific clinical criteria.² Interestingly, children may have a higher rate of progression from primary to secondary APS.^{3,4} Cutaneous manifestations are common in APS, arising in 18% of cases, including livedo reticularis (LR), Raynaud phenomenon, atrophic blanche, anetoderma, urticaria, malignant atrophic papulosis, purpura fulminans, ulcerative skin lesions, pseudovasculitic lesions,^{5,6} and reactive angioendotheliomatosis.⁷ Although APS has been associated with various skin conditions, it has no established association with eccrine angiomatous hamartomas (EAHs). EAHs are rare, benign, acquired, or congenital neoplasms of eccrine and angiomatous structures, often within the middle or deep dermis, that usually present on the distal extremities with varied clinical features, including

Abbreviations used:

APS:	antiphospholipid syndrome
DRVVT:	dilute Russell viper venom time
EAH:	eccrine angiomatous hamartoma
LR:	livedo reticularis
SLE:	systemic lupus erythematosus

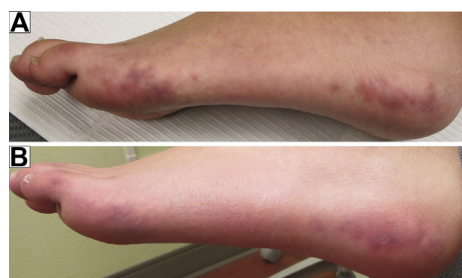


Fig 1. **A**, Left foot rash clinical presentation prior to treatment. **B**, Left foot rash clinical presentation posttreatment.

pain and hyperhidrosis.^{8,9} Herein we report a case of APS presenting as pain within a foot lesion, with changes consistent with EAH on pathology.

CASE REPORT

A 14-year-old girl presented to the clinic with a 2-month history of progressive left plantar foot pain and rash with local cold temperature sensitivity. Prior workup by her pediatrician and podiatrist revealed a positive rapid plasma reagin titer in the absence of sexual activity. On physical examination, a 12 cm × 5 cm, mottled, edematous, tender, and

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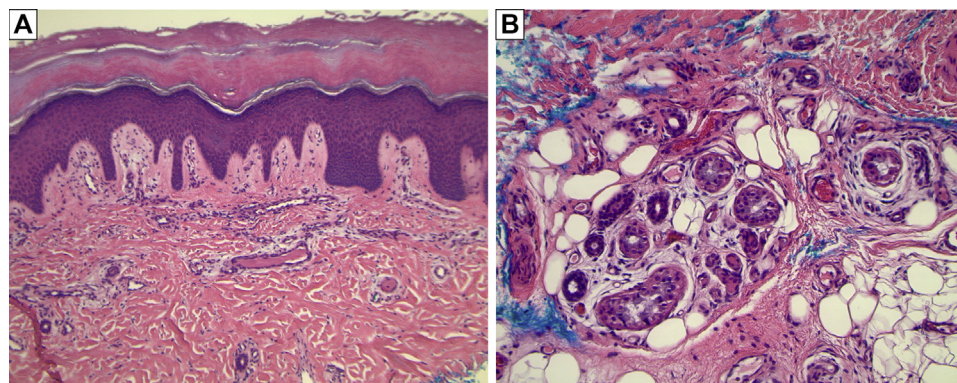


Fig 2. **A**, Hematoxylin-eosin preparation demonstrating dermal microthrombi. **B**, Hematoxylin-eosin preparation demonstrating dermal proliferation of eccrine glands and capillaries. (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**, $\times 200$; **B**, $\times 400$.)

violaceous reticular plaque originating near the heel and extending to the plantar surface of the foot was revealed, consistent with LR (Fig 1, A). Laboratory studies were ordered due to suspicion of APS, and a punch biopsy of lateral calcaneal skin was obtained (Fig 2, A and B).

Laboratory evaluation (Table I) revealed a positive rapid plasma reagin titer, anti-nuclear antibodies, as well as beta-2 glycoprotein IgM, cardiolipin IgG and IgM, anti-smith/ribonucleoprotein, anti-ribonucleoprotein, anti-chromatin, and anti-double-stranded DNA antibodies. Additionally present were elevated gamma gap, erythrocyte sedimentation rate, partial thromboplastin time-lupus anticoagulant, and dilute Russell viper venom time (DRVVT) screen, as well as positive DRVVT mix, DRVVT confirm, and hexagonal phase confirm tests, suggesting the diagnosis of APS. These results remained positive on repeat blood draw.

Biopsy of the lesion revealed a hamartomatous dermal proliferation of eccrine glands and capillaries (Fig 2, B), consistent with an EAH. Also present were microthrombi within some vessels, particularly visible in the superficial and middermis (Fig 2, A), consistent with APS. Due to the patient's risk of thrombosis, she was started on hydroxychloroquine and aspirin, and topical nitropaste was added to be applied to the persistent plaque surrounding the biopsy site, resulting in complete resolution of foot pain within one week. The LR resolved, but a violaceous plaque remained after 2 weeks, further suggesting the presence of the underlying EAH (Fig 1, B). Pediatric hematology, rheumatology, and nephrology were consulted, and rheumatology initiated methotrexate and prednisone, in anticipation of starting rituximab. At the last available follow-up, the patient remained asymptomatic following her first rituximab infusion.

DISCUSSION

EAHs typically arise as a solitary red-blue plaque on a distal extremity and are often diagnosed after presenting with pain or hyperhidrosis.^{8,9} The associated pain within the lesion, which has been attributed to the effects of temperature fluctuations and hormones on the vascular and eccrine tissue as well as fluid retention,⁹ has been reported to resolve with expectant management, excision, or laser therapy.¹⁰ These neoplasms, especially visually occult and asymptomatic variants, can be present for many years prior to symptom onset, as exemplified in this case. This patient likely never noticed the faint discoloration until APS-induced microvascular occlusion occurred, resulting in pain, temperature sensitivity, and LR. Although there is no established link between EAHs and coagulopathy, including APS, APS has been associated with pain within other vascular malformations, such as reactive angioendotheliomatosis.⁷ Mechanistically, one could infer that a site of vascular malformation or proliferation could be an opportune location for APS-induced thrombosis, as abnormal development of these structures may compromise endothelial integrity and alter vascular flow.

This rare, hamartomatous tumor provided us with the opportunity to diagnose APS prior to severe systemic manifestations, which is critical, as children with primary APS may have a higher rate of progression from primary to secondary APS.^{3,4} In one study of 128 adult patients with primary APS, 13% developed secondary APS, including systemic lupus erythematosus (SLE) (8%), lupus-like diseases (5%), and myasthenia gravis (1%).⁴ Although the sample size was substantially smaller, a similar study of 14 children with primary APS found that 21% progressed to secondary APS, including SLE (14%) and lupus-like diseases (7%).³ Although our patient

Table I. Patient laboratory values

Test name	Result	Normal range
Rapid plasma regain	1:1	Nonreactive
Anti-nuclear antibody	1:1280	1:80 or less
Beta 2 glycoprotein IgG	<9	<20 SGU
Beta 2 glycoprotein IgM*	66, 72	<20 SMU
Beta 2 glycoprotein IgA	16	<20 SAU
Cardiolipin IgA	<11	<11 APL
Cardiolipin IgG*	29, 39	<14 GPL
Cardiolipin IgM*	40, 54	<12 MPL
Smith/ribonucleoprotein	2.1	<1.0 AI
Ribonucleoprotein	4.2	<1.0 AI
Chromatin	2.8	<1.0 AI
Rheumatoid factor	<10	<14 IU/mL
Anti-Smith	<1.0	<1.0 AI
Double-stranded DNA	10	<10 IU/mL
Complement, C3	118	90-180 mg/dL
Complement, C4	26	10-40 mg/dL
Complement total (CH 50)	49	31-60 U/mL
Dilute Russell viper venom test screen	96	<45 s
Dilute Russell viper venom test mix	Positive	Negative
Dilute Russell viper venom test confirm	Positive	Negative
Hexagonal phase confirm	Positive	Negative
Partial thromboplastin time-lupus anticoagulant screen	103	<40 s
Erythrocyte sedimentation rate	104	0-20 mm/hr
Creatinine	0.57	0.40-1.0 mg/dL
Total protein	9.1	6.3-8.2 g/dL
Albumin	4.7	3.4-5.4 g/dL
Gamma gap	4.4	<3.8 g/dL

Abnormal values indicated by bold lettering.

*Second listed value is from repeat blood draw.

meets the laboratory criteria for the 2019 EULAR/ACR classification of SLE, including a positive anti-dsDNA antibody test, which is highly specific for SLE, she does not currently meet the clinical criteria for SLE, so her APS remains classified as primary. Treatment of APS typically includes anticoagulation therapy alone.² However, in this case, treatment included escalation to rituximab, as rheumatology's decision was to treat aggressively in an attempt to prevent disease progression.

Despite the lack of association between these 2 diseases, this patient's likely APS-induced pain secondary to microvascular occlusion within this lesion permitted early diagnosis of APS. Though this precocious diagnosis of APS may not stop the potential progression from primary to secondary APS, it will allow the patient to be monitored for manifestations of APS as well as early manifestations of SLE, should they arise.

Conflicts of interest

None disclosed.

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