

Digital ulcers as presenting symptom of secondary antiphospholipid syndrome



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Key words: antiphospholipid syndrome; digital ulcers; systemic lupus erythematosus.

INTRODUCTION

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder, characterized by thromboembolic events and/or obstetric complications accompanied by antiphospholipid (aPL) antibodies. APS can be primary or secondary to a previously established disease, of which systemic lupus erythematosus (SLE) is the most common, coexisting in approximately 30% to 40% of cases.¹ APS has a heterogeneous clinical presentation and can involve multiple organs, especially the skin. About 40% of patients present with cutaneous manifestations as the first indication of disease.^{2,3} While symptoms such as livedo reticularis and Raynaud phenomenon are common, cases of digital ulcers as the presenting symptom of APS are exceptionally rare.^{2,4} Herein, we report a case of a 31-year-old woman with painful digital ulcers as the first clinical manifestation of APS.

CASE REPORT

A 31-year-old woman with a history significant for SLE complicated by lupus nephritis and Sjögren syndrome presented with skin lesions involving both hands. The patient first noticed dryness and peeling on the fingertips 10 months earlier with subsequent progression resulting in painful ulcers on the bilateral fingers (Fig 1). Skin examination revealed multiple erythematous ulcers with a hyperkeratotic base, located on bilateral distal palmar fingers (Fig 1). Both hands were edematous and tender to the touch. The lesions were confined to her

Abbreviations used:

aPL:	antiphospholipid antibodies
APS:	antiphospholipid syndrome
EULAR:	European Alliance of Associations for Rheumatology
LA:	lupus anticoagulant
LDA:	low-dose aspirin
SLE:	systemic lupus erythematosus

hands. No other new cutaneous manifestations were present at the time. Her current medications included mycophenolate 1500 mg twice daily, prednisone 10 mg, and pulse intravenous cyclophosphamide for lupus nephritis; the patient's renal function was stable. The patient denied a history of smoking or thrombotic events. She had been pregnant 3 times without record of miscarriages or preeclampsia. She denied any symptoms consistent with Raynaud phenomenon. There was no association between skin findings and temperature change. Her other comorbidities included hypertension and a self-reported history of seizure-like episodes; prior electroencephalography failed to detect seizure activity.

Laboratory analysis was notable for leukopenia (white blood cells, $2.4 \times 10^3/\mu\text{L}$), normocytic anemia without evidence of hemolysis (hemoglobin of 10.5 g/dL), and a normal platelet count of $181 \times 10^9/\text{L}$. Coagulation studies including partial thromboplastin time lupus anticoagulant (LA) and dilute viper venom time were normal. LA and

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Fig 1. Digital ulcers in a patient with SLE and positive antiphospholipid antibodies. Ulcers on fingers and palm with scarring at distal tips, along with violaceous patches on the palms and fingers. *SLE*, Systemic lupus erythematosus.

Table I. Patient laboratory evaluation

Test name	Results	
	At presentation	≥ 12 weeks prior
Double-stranded DNA	44 (H)	15 (H)
Complement, C3	98	<40 (L)
Complement, C4	9 (L)	<8 (L)
Beta-2-glycoprotein IgG	<9.4	<9.4
Beta-2-glycoprotein IgM	<9.5	<9.4
Cardiolipin IgG	<9.4	30.8 (H)
Cardiolipin IgM	20.2 (H)	54.7 (H)
Dilute Russell viper venom time	45.8	41.6
Partial thromboplastin time—lupus anticoagulant screen	40.5	42.9

H, High; L, low.

anti-beta-2-glycoprotein I antibodies were not identified. However, elevated levels of anticardiolipin IgM antibodies, which had also been elevated in testing performed 7 months prior, were identified (Table I).

A punch biopsy revealed ulceration in the epidermis with a few thrombi present in small caliber vessels (Fig 2). There was no evidence of vasculitis; these histopathologic findings were reflective of a thrombotic vasculopathy.

The clinical, histopathologic, and laboratory findings in the setting of SLE prompted a diagnosis of APS. Due to the high risk for thrombotic events, the patient was started on aspirin prophylaxis and nifedipine to improve peripheral perfusion.

DISCUSSION

Although common in connective tissue disorders, digital ulcers are rarely seen in SLE, with studies reporting <1% prevalence.^{5,6} The main etiology is attributed to APS.^{5,7} APS is a systemic autoimmune disease of hypercoagulation characterized by recurrent venous and/or arterial thrombosis in the presence of aPL antibodies, namely anticardiolipin, anti-beta-2-glycoprotein I, and LA. APS can present as primary or secondary to other autoimmune disorders, most commonly SLE: approximately 40% of patients with SLE eventually develop APS.¹

Up to 50% of patients with APS will present with cutaneous manifestations as the first indication of disease.^{5,8-10} The most frequent skin finding, livedo reticularis, has been reported in 20% to 40% of all patients with APS.^{9,11} In contrast, digital ulcerations as the presenting symptom in APS are observed in only 1.3% to 1.9% of population.¹² A PubMed literature review focusing on the past 15 years was conducted using search terms “digit, finger, ulcer or necrosis, antiphospholipid.” A total of 62 articles were retrieved. Each article was analyzed for the presence of digital ulcerations and the appropriate clinical context. Most of the results involved ulcers in the context of other conditions such as infections, malignancies, autoimmune, or antineutrophil cytoplasmic antibody–associated vasculitis. A total of 16 publications referenced digital ulcers in the setting of SLE and/or APS. These 16 cases were stratified based on SLE and APL status, with 7 positives for both. Four of the 7 articles presented necrosis and/or gangrene of different body parts, without digital ulcers. In the end, only 2 articles in the past 15 years have described digit ulcerations as the presenting symptom of APS in patients with established SLE. The low number of presentations correlates with studies describing this symptomatology in less than 2% of patients.^{4,12} A breakdown of the literature review is presented in Fig 3.

In the setting of SLE, positivity for aPL can have significant ramifications, emphasizing the importance for early recognition. Patients with concurrent SLE and aPL are more likely to experience organ damage, autoimmune hemolytic anemia, thrombocytopenia, lupus nephritis, and moderate to severe cognitive impairment.¹³⁻¹⁶ The risk of arterial and/or venous thrombosis overall is doubled in patients with SLE and aPL, and there is a 6-fold increased risk for venous thrombosis in patients with SLE and LA.^{13,17}

During evaluation for APS, common practice employs the Sydney classification, which requires 1

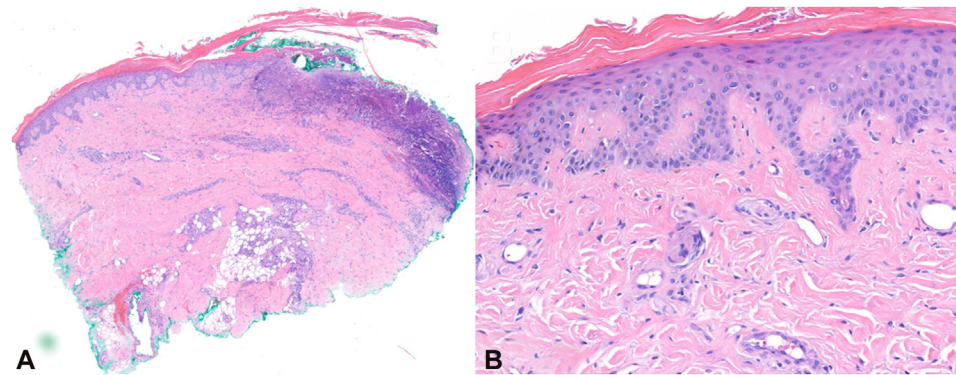


Fig 2. Digital ulcers in a patient with SLE and positive antiphospholipid antibodies. **A**, Ulcer on acral skin with sparse lymphocytic infiltrate (H&E; magnification: 35 \times). **B**, Thrombotic vasculopathy, distant to the ulcer, affecting a capillary (H&E; magnification: 200 \times). *SLE*, Systemic lupus erythematosus.

clinical and 1 lab-based positive result.¹⁸ The patient presented had confirmed vascular thrombosis by histopathology, which met the clinical requirement. For the laboratory criterion, the patient had 2 positive results for IgM class anticardiolipin antibodies, measured over 12 weeks apart. While the first level was high enough to meet criteria, the second level, although elevated, did not meet the described threshold of >40 IgG phospholipid units/mL. However, the Sydney APS criteria were designed to guide research classification and not for clinical purposes.^{18,19} The threshold for positivity (>40 IgG phospholipid or IgM phospholipid units) is based on data available in 2006, and there is no definition available to distinguish moderate-high from low antibody titers.^{18,20} Since 2006, several clinical features not present in the original or revised criteria have been recognized as strongly associated with APS. These so-called “extra-criteria manifestations” are now considered part of the clinical spectrum of APS.²¹ In addition to thrombosis and serologic findings, the patient presented had several of these “extra-criteria” manifestations including hypertension and a history of seizure-like activity. An alternative explanation is “seronegative APS”. Seronegative APS describes patients with clinical manifestations highly indicative of APS in the absence of laboratory criteria.¹⁶ Positivity for these so-called “extra-criteria antibodies” has been reported in 19% to 33% of patients with seronegative APS.¹⁶ The pathogenic role of these alternative antibodies requires further study.

Due to the limited amount of evidence, guidelines for the management of patients with APS have

not been standardized. For primary thrombotic prevention, the use of low-dose aspirin (LDA) is controversial, with evidence showing mixed results.^{22,23} In 2019, the European Alliance of Associations for Rheumatology (EULAR) developed a set of recommendations for the management of APS in adults. These recommendations stratify patients into one of 3 tiers based on aPL titers (low, medium-high, and high risk). For any asymptomatic patient with SLE and aPL positivity and a high-risk designation, LDA is recommended. For patients categorized as low risk, LDA should be considered.²⁴ This recommendation varies slightly from the proposal of the 16th International Congress on Antiphospholipid Antibodies Task Force, which suggested that LDA should be considered on a case-by-case basis.²⁵ In the acute setting, low-molecular-weight heparins, followed by long-term warfarin treatment, is considered standard of care.¹⁶ Warfarin is also recommended for secondary thromboprophylaxis with a goal international normalized ratio of 2-3.²²⁻²⁵ Management of arterial thrombotic events is less established: recommendations include the use of warfarin alone or with LDA.^{24,25} The use of direct oral anticoagulants is contraindicated in patients with arterial thrombotic events, small-vessel thrombosis, aPL-related valvular disease, or triple aPL positivity. Direct oral anticoagulants are not only less effective than warfarin but associated with an increased risk of thrombotic events in patients with a history of arterial thrombosis or triple positive aPL.²⁶ In a randomized trial, 6 of 23 patients with APS on apixaban experienced a stroke compared to 0 of 25 patients on warfarin.²⁷ Rituximab, hydroxychloroquine,

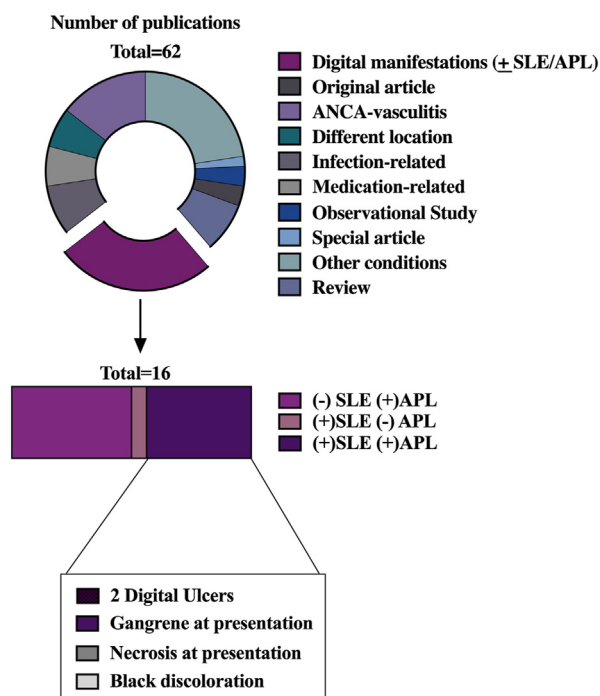


Fig 3. Digital ulcers in a patient with SLE and positive antiphospholipid antibodies. Results of literature review for the past 15 years. PubMed search terms included: “digit, finger, ulceration or necrosis, antiphospholipid.” Results were filtered for language (English) and animal species (human). A total of 62 articles were obtained. Of the 62, only 16 mentioned any digital manifestation in the setting of APL or SLE. These were then categorized by the presence or absence of APL and SLE, yielding 7 (+) SLE and (+) APL. The breakdown of these 7 revealed only 2 articles that described digital ulcers as a presenting symptom of APL in patients with SLE. The remaining 5 involved either gangrene or necrosis as the presenting symptom. Breakdown of the other 46 articles was as followed: 14 articles involved ischemia/necrosis in the setting of other conditions (2 cardiopulmonary, 2 malignancy, 10 autoimmune connective tissue diseases). There were 9 cases related to antineutrophil cytoplasmic antibody–associated vasculitis, 5 due to infections, 4 triggered by medications, and 4 cases not involving the digits. *APL*, Antiphospholipid syndrome; *SLE*, systemic lupus erythematosus.

eculizumab, and statins have been evaluated as alternate or adjunctive therapies and can be considered in cases of catastrophic APS.²⁵

Conflicts of interest

None disclosed.

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