

Antiphospholipid Syndrome in a Patient With Rheumatoid Arthritis

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PRACTICE POINTS

- Antiphospholipid syndrome (APS) is an autoimmune condition defined by a venous and/or arterial thrombotic event and/or pregnancy morbidity in the presence of persistently elevated antiphospholipid antibody titers.
- Cutaneous findings of APS include livedo reticularis most commonly but also anetoderma, cutaneous ulceration and necrosis, necrotizing vasculitis, livedoid vasculitis, thrombophlebitis, purpura, ecchymoses, painful skin nodules, and subungual hemorrhages.
- The various cutaneous manifestations of APS are associated with a range of histopathologic findings, but noninflammatory thrombosis in small arteries and/or veins in the dermis and subcutaneous fat tissue is the most common histologic feature.

Antiphospholipid syndrome (APS) is an autoimmune condition characterized by a thrombotic event and/or pregnancy morbidity in the presence of persistently elevated antiphospholipid (aPL) antibody titers, which are most prevalent in patients with systemic lupus erythematosus but also have been associated with other autoimmune, malignant, and infectious diseases. In contrast to the clear correlation between high aPL antibody titers and thrombotic events in patients with systemic lupus erythematosus, the pathogenic role of these autoantibodies in association with other diseases, such as rheumatoid arthritis (RA), is not as well defined. We report a case of APS manifesting as cutaneous ulceration and necrosis in a patient with severe RA.

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Case Report

A 39-year-old woman with a 20-year history of rheumatoid arthritis (RA) presented to a university-affiliated tertiary care hospital with painful ulcerations on the bilateral dorsal feet that started as bullae 16 weeks prior to presentation. Initial skin biopsy performed by an outside dermatologist 8 weeks prior to presentation showed vasculitis and culture was positive for methicillin-sensitive *Staphylococcus aureus*. She was started on a prednisone taper and cephalexin, which did not improve the lower extremity ulcerations and the pain became progressively worse. At the time of presentation to our dermatology department, the patient was taking prednisone, hydroxychloroquine, hydrocodone-acetaminophen, and gabapentin. Prior therapy with sulfasalazine failed; etanercept and methotrexate were discontinued years prior due to side effects. The patient had no history of deep vein thrombosis, pulmonary embolism, or miscarriage.

At presentation, the patient was afebrile and her vital signs were stable. Physical examination showed multiple ulcers and erosions on the bilateral dorsal feet with a few scattered retiform red-purple patches (Figure). One bulla was present on the right dorsal foot. All lesions were tender to the touch and edema

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Multiple ulcers and erosions on the bilateral dorsal feet (A) and a bulla on the right dorsal foot (B).

was present on the bilateral feet. No oral ulcerations were present and no focal neuropathies or palpable cords were appreciated in the lower extremities. There were no other cutaneous abnormalities.

Laboratory studies showed a white blood cell count of $9.54 \times 10^3/\mu\text{L}$ (reference range, $4.16\text{--}9.95 \times 10^3/\mu\text{L}$), hemoglobin count of 12.4 g/dL (reference range, 11.6–15.2 g/dL), and a platelet count of $175 \times 10^3/\mu\text{L}$ (reference range, $143\text{--}398 \times 10^3/\mu\text{L}$). A basic metabolic panel was normal except for an elevated glucose level of 185 mg/dL (reference range, 65–100 mg/dL). Urinalysis was normal. Erythrocyte sedimentation rate and C-reactive protein level were not elevated. Antinuclear antibodies and double-stranded DNA antibodies were normal. Prothrombin time was 10.4 seconds (reference range, 9.2–11.5 seconds) and dilute viper's venom time was negative. Rheumatoid factor level was elevated at 76 IU/mL (reference range, <25 IU/mL) and anti-citrullinated peptide antibody was moderately elevated at 42 U/mL (negative, <20 U/mL; weak positive, 20–39 U/mL; moderate positive, 40–59 U/mL; strong positive, >59 U/mL). The cardiolipin antibodies IgG, IgM, and IgA were within reference range. Results of β_2 -glycoprotein I IgG and IgM antibody tests were normal, but IgA was elevated at 34 $\mu\text{g}/\text{mL}$ (reference range, <20 $\mu\text{g}/\text{mL}$). Wound cultures grew moderate *Enterobacter cloacae* and *Staphylococcus lugdunensis*.

Slides from 2 prior punch biopsies obtained by an outside hospital approximately 8 weeks prior from the right and left dorsal foot lesions were reviewed. Both biopsies were histologically similar.

Postcapillary venules showed extensive vasculitis with numerous fibrin thrombi in the lumens in both biopsy specimens. The biopsy from the right foot showed prominent ulceration of the epidermis, with a few of the affected vessels showing minimal accompanying nuclear dust; however, the predominant pattern was not that of leukocytoclastic vasculitis. Biopsy from the left foot showed prominent epidermal necrosis with focal reepithelialization and scattered eosinophils. The pathologist felt that a vasculitis secondary to coagulopathy was most likely but that a drug reaction and rheumatoid vasculitis would be other entities to consider in the differential. A review of the laboratory findings from the outside hospital from approximately 12 weeks prior to presentation showed IgM was normal but IgG was elevated at 28 U/mL (reference range, 0–15 U/mL) and IgA was elevated at 8 U/mL (reference range, 0–7 U/mL); β_2 -glycoprotein I IgG antibodies were elevated at 37 mg/dL (reference range, 0–25.0 mg/dL) and β_2 -glycoprotein I IgA antibodies were elevated at 5 mg/dL (reference range, 0–4.0 mg/dL).

The clinical suspicion of a thrombotic event on the dorsal feet, which was confirmed histologically, and the persistently positive antiphospholipid (aPL) antibody titers helped to establish the diagnosis of antiphospholipid syndrome (APS) in the setting of RA. The dose of prednisone was increased from 10 mg daily on admission to 40 mg daily. The patient was started on enoxaparin 60 mg subcutaneously twice daily at initial presentation and was bridged

to oral warfarin 2 mg daily after the diagnosis of APS was established. Oral doxycycline 100 mg twice daily was started for wound infection. The ulcerations gradually improved over the course of her 7-day hospitalization. She was continued on prednisone, hydroxychloroquine, and warfarin as an outpatient and has had no recurrence of lesions after 3 years of follow-up on this regimen.

Comment

Antiphospholipid syndrome is an autoimmune condition defined by a venous and/or arterial thrombotic event and/or pregnancy morbidity in the presence of persistently elevated aPL antibody titers. The most frequently detected subgroups of aPL are anticardiolipin (aCL) antibodies, anti- β_2 -glycoprotein I antibodies, and lupus anticoagulants.¹ Primary APS occurs as an isolated entity, whereas secondary APS occurs in the setting of a preexisting autoimmune disease, infection, malignancy, or medication.² The diagnostic criteria for APS requires positive aPL titers at least 12 weeks apart and a clinically confirmed thrombotic event or pregnancy morbidity.³

About one-third to half of patients with APS exhibit cutaneous manifestations.^{4,5} Livedo reticularis is most commonly observed and represents the first clinical sign of APS in 17.5% of cases.⁶ Cutaneous findings of APS also include anetoderma, cutaneous ulceration and necrosis, necrotizing vasculitis, livedoid vasculitis, thrombophlebitis, purpura, ecchymoses, painful skin nodules, and subungual hemorrhages.⁷ The various cutaneous manifestations of APS are associated with a range of histopathologic findings, but noninflammatory thrombosis in small arteries and/or veins in the dermis and subcutaneous fat tissue is the most common histologic feature.⁴ Our patient exhibited cutaneous ulceration and necrosis, and biopsy clearly showed the presence of vasculitis and fibrin thrombi within postcapillary venules. These findings along with the persistently elevated β_2 -glycoprotein I IgA solidified the diagnosis of APS.

The most common cutaneous manifestations of RA are nodules (32%), Raynaud phenomenon (10%), and vasculitis (3%).⁸ The mean prevalence of aPL antibodies in patients with RA is 28%, though reports range from 5% to 75%.¹ The presence of aPL or aCL does not predict the development of thrombosis and/or thrombocytopenia in RA patients^{9,10}; however, aCL antibodies in RA patients are associated with a higher risk for developing rheumatoid nodules. It is hypothesized that the majority of aCL antibodies identified in RA patients have different specificities than those identified in other diseases that are associated with thrombotic events.¹

Anticoagulation has been proven to decrease the risk for recurrent thrombotic events in patients with APS.¹¹ Patients should discontinue the use of estrogen-containing oral contraceptives; avoid smoking cigarettes; and treat hypertension, hyperlipidemia, and diabetes mellitus, if present. The type and duration of anticoagulation therapy, especially for the treatment of the cutaneous manifestations of APS, is less well defined. Antiplatelet therapies such as low-dose aspirin or dipyridamole often are used for less severe cutaneous manifestations such as livedoid vasculopathy. Warfarin with a target international normalized ratio of 2.0 to 3.0 is most commonly used following major thrombotic events, including cutaneous necrosis and digital gangrene. The role of corticosteroids and immunosuppressants is unclear; one study showed that these therapies did not prevent further thrombotic events in patients with systemic lupus erythematosus.⁴

Conclusion

Although aPL antibodies are most prevalent in patients with systemic lupus erythematosus, an estimated 28% of patients with RA have elevated aPL titers. The aPL antibodies recognized in RA patients are thought to have a different specificity than those recognized in other APS-associated diseases because elevated aPL antibody titers are not associated with an increased incidence of thrombotic events in RA patients; however, larger studies are needed to clarify this phenomenon. It remains to be determined if this case of APS and RA represents a coincidence or a true disease association, but the recognition of the cutaneous and histological features of APS is crucial for establishing a diagnosis and initiating anticoagulation therapy to prevent further morbidity and mortality.

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