Antineutrophil Cytoplasmic Antibody-positive Digital Necrosis in a Patient with Limited Systemic Sclerosis

To the Editor:

Antineutrophil cytoplasmic antibody (ANCA) positivity in the setting of asymptomatic systemic sclerosis (SSc) does not consistently correlate with clinical characteristics. We describe a 31-year-old Latina woman with a 10-year history of limited SSc [sclerodactyly, tight facial skin, antinuclear antibody (ANA)-positive, gastroesophageal reflux disease, Raynaud's phenomenon with no previous digital ulcerations, and without sicca-related symptoms or pulmonary or cardiovascular disease], who presented with severe digital necrosis. Her SSc had been stable under therapy with lansoprazole, hydroxychloroquine, celecoxib, and nifedipine.

Three months before admission, she developed muscle and joint pain in her distal extremities, with temporary relief taking oral and intravenous methylprednisolone. However, the purple discoloration and painful swelling of her toes progressed, and was unresponsive to lidocaine sympathectomies. Subsequently, she developed leg edema and rash, with numbness, tingling, and blistering. Three days before admission, the tips of her fingers and toes turned black.

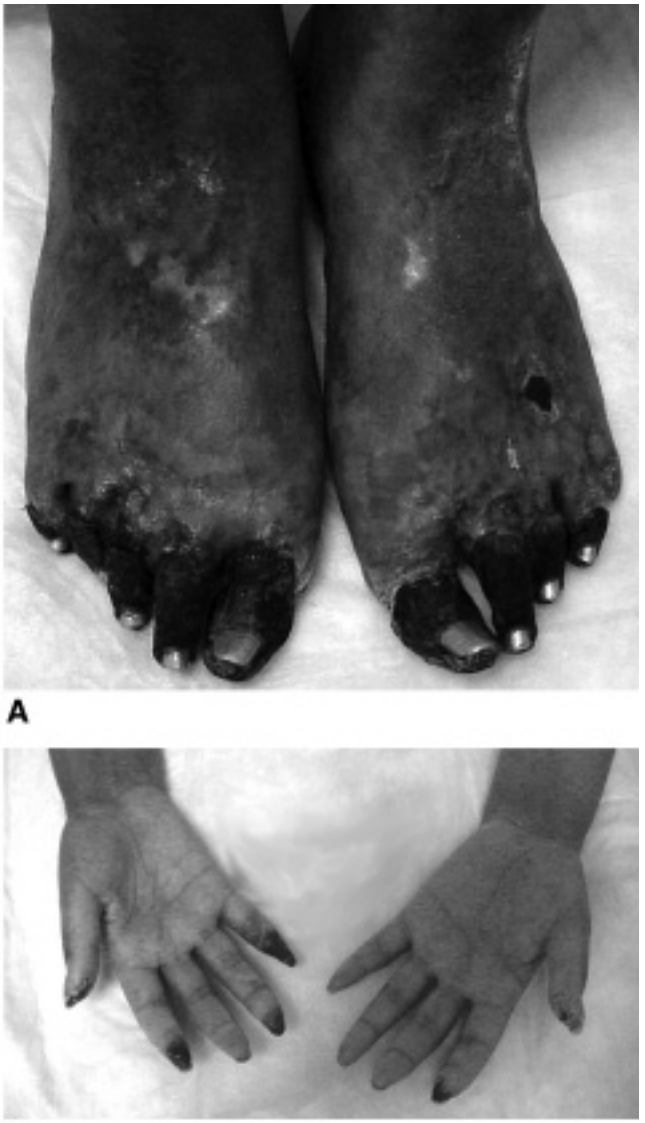

Figure 1. A. Scattered necrotic bullae and blisters on the dorsum of the feet are visible, with necrotic tips of the toes. Aggressive progression of necrosis had occurred within 10 days of the onset of blisters, and within 2 days of the patient noticing ischemia on the tips of her toes. B. Necrotic fingertips, palmar aspect.

Upon admission, her vital signs were stable. Examinations of head, ears, eyes, nose, throat, heart, and lung were normal. There was bilateral edema, cyanosis, and severe tenderness of distal extremities, without synovitis. There was diffuse superficial, livedo-like purpura on her thighs, frank necrosis of the tips of all her toes and 4 fingers, but no ulcerative lesions (Figures 1A, 1B). Her upper arms, thighs, and trunk were spared from lesions or pain.

Initial blood examination results included erythrocyte sedimentation rate (ESR) 96 mm/h, leukocytosis (white blood cells 10.25 μl, 79% polymorphonuclear), ANA titer 1:640, Scl-70 > 6.0 (normal < 1.0), immunofluorescent perinuclear ANCA (p-ANCA) 1:640, myeloperoxidase (MPO) 89 U (normal < 21 U), and rheumatoid factor 157 IU/ml (normal < 25 IU/ml). Tests for hepatitis, cryoglobulins, antiphospholipids, and antibodies to SSA/SSB and centromere were negative. Renal function, C3/C4, and urinalysis were normal.

Bilateral lower extremity computed tomography (CT) angiogram with runoff failed to reveal inflammatory vasculitis, but vessels distal to the dorsalis pedis could not be visualized. A high resolution chest CT scan showed increased reticulations in the left lung with septal thickening, suggestive of early subpleural honeycombing. Pulmonary function testing demonstrated forced vital capacity 88% of predicted and DLCO 21% of predicted. There was no evidence of pulmonary hypertension by echocardiogram. Skin (punch) biopsy of the right shin showed small-vessel vasculitis with fibrinoid necrosis in the vessel wall, leukocytoclasia, and eosinophilia (Figure 2).

After admission, treatment with intravenous (IV) heparin, narcotics, and methylprednisolone at 1 g daily for 3 days was started. IV cyclophosphamide (1 g) was given. IV epoprostenol was titrated up to 8 ng/kg/min for 6 days. Oral vasodilators included sildenafil 20 mg tid and nifedipine 10 mg tid. Vascular surgery consultation advised against any surgical intervention.

After discharge, she received 40 hyperbaric oxygen treatments for her gangrenous digits, IV cyclophosphamide 1 g monthly for 6 months, and oral sildenafil 20 mg tid. Mycophenolate mofetil was then substituted and titrated to 2.5 g orally daily. Over 24 months, all of the 14 necrotizing digits underwent autoamputation. She resumed full-time work as an accountant. Her p-ANCA test remains positive with high anti-MPO titers (76–130 U/ml).

Although the vasculopathy of SSc is usually characterized as a noninflammatory, concentric obliterative process, true inflammatory vasculitis has rarely been reported in the pre-ANCA era[1,2]. More recent reports have described syndromes felt to be related to ANCA-positivity, including rapidly progressive glomerulonephritis[3,4], pulmonary hemorrhage, severe scleroderma[5], and necrotizing vasculitis[6]. Less strong associations include seizures[7], leukocytoclastic vasculitis[8], and interstitial lung disease[9]. Only a few reports have described ANCA-associated digital necrosis[3].

Our patient presented with acute necrosis of 14 digits, resulting in total or partial autoamputation. She had no known vasculitic internal organ involvement or background of Sjögren's syndrome or antiphospholipid antibody syndrome. Serologic screening of asymptomatic patients with SSc has shown a low frequency of ANCA-positivity (10%–13%)[4], but her markedly positive p-ANCA and MPO strongly suggested a true inflammatory digital vasculitis rather than the bland SSc vasculopathy.

ANCA-associated vasculitis (AAV) in the setting of SSc often presents with high ESR and CRP[10]. Either p- or c-ANCA (with/without MPO) may be positive. Higher ANCA titers often correlate with rapid deterioration of organ function and poor outcome[3]. A case series of 50 patients with SSc-AAV suggests that SSc patients with both ANCA and Scl-70 antibodies are at an even higher risk of developing life-threatening AAV, but is inconclusive for SSc disease period and type[5].

The combination of high-dose corticosteroids and cytotoxic immunosuppression (e.g., cyclophosphamide) has been shown to be effective in

several cases of SSc-AAV[6]. Since patients with limited SSc of long duration have much lower risk of renal crisis than patients with early diffuse SSc, weighing the risk to her of digital loss versus renal crisis, our patient was started on therapy of high-dose corticosteroids, cytotoxic therapy, and other treatments within 2 weeks of her fulminant digital infarction. She demonstrated good clinical response to therapy without steroid-induced renal impairment or visceral organ involvement other than her digits.

Because ANCA-positivity in asymptomatic patients with SSc does not consistently correlate with clinical characteristics, we do not recommend routine ANCA screening. However, our experience suggests that when SSc patients present with multiple necrotic digits, vasculitis should be considered. ANCA tests and appropriate biopsies may identify SSc-AAV. Early therapeutic intervention may improve prognosis, especially in life- or organ-threatening conditions.

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REFERENCES

1. Charles C, Clements P. Systemic sclerosis: hypothesis-driven treatment strategies. Lancet 2006;367:1683-91.
2. Herrick A, Oogarah P, Freemont A, Marcuson R, Haeney M, Jayson M. Vasculitis in patients with systemic sclerosis and severe digital ischaemia requiring amputation. Ann Rheum Dis 1994;53:323-6.
3. Endo H, Hosono T, Kondo H. Antineutrophil cytoplasmic autoantibodies in 6 patients with renal failure and systemic sclerosis. J Rheumatol 1994;21:864-70.
4. Herrera-Esparza R, Aguilar JL, Saucedo A, González I, López-Robles E, Avalos-Díaz E. Scleroderma with type III glomerulonephritis and MPO-ANCA antibodies in the serum. J Eur Acad Dermatol Venereol 2005;19:617-20.
5. Rho Y, Choi S, Lee Y, Ji J, Song G. Scleroderma associated with ANCA-associated vasculitis. Rheumatol Int 2006;26:465-8.
6. Locke I, Worrall J, Leaker B, Black C, Cambridge G. Autoantibodies to myeloperoxidase in systemic sclerosis. J Rheumatol 1997;24:86-9.
7. Cheung G, Chew G, Wyndha R, Peters M, Riminton S. Myeloperoxidase-antineutrophil cytoplasmic antibody seroconversion and fulminant vasculitis in Scl-70-positive scleroderma. Intern Med J 2007;37:205-7.
8. Maes B, Van Mieghem A, Messiaen T, Kuypers D, Van Damme B, Vanrenterghem Y. Limited cutaneous systemic sclerosis associated with MPO-ANCA positive renal small vessel vasculitis of the microscopic polyangiitis type. Am J Kidney Dis 2000;36:E16.
9. Hiromura K, Nojima Y, Kitahara T, Ueki K, Maezawa A, Kawai H, et al. Four cases of anti-myeloperoxidase antibody-related rapidly progressive glomerulonephritis during the course of idiopathic pulmonary fibrosis. Clin Nephrol 2000;53:384-9.
10. Casari S, Haeney M, Farrand S, Herrick A. Antineutrophil cytoplasmic antibodies; a "red flag" in patients with systemic sclerosis. J Rheumatol 2002;29:2666-7.

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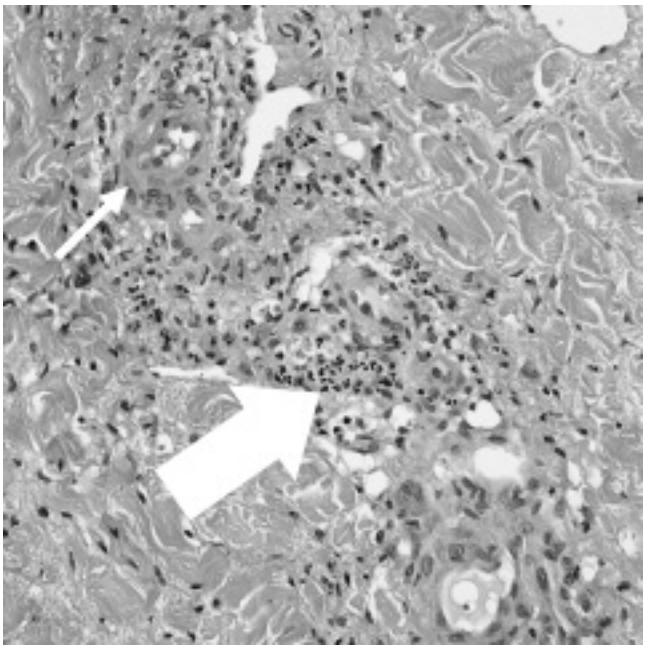

Figure 2. Skin biopsy of the right shin: fibrinoid necrosis can be seen around the blood vessel wall (thin white arrow); an infiltrate of neutrophils, neutrophilic debris, and scattered eosinophils can also be seen (thick white arrow).