Systemic lupus erythematosus and antineutrophil cytoplasmic antibody–associated vasculitis: An emerging overlap syndrome with cutaneous manifestations

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INTRODUCTION

Systemic lupus erythematosus and antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (SLE/AAV) overlap syndrome is a rare disease originally described in 2008.[1] With only a few reports in the literature, this condition is characterized by aggressive crescentic glomerulonephritis, arthritis, cutaneous involvement, and both antinuclear antibody (ANA) and ANCA. Dermatologic manifestations are common and may occur at initial presentation.[2] Although skin lesions may vary in morphology, the most commonly reported include cutaneous nodules and ecchymoses. Few reports have characterized the cutaneous findings seen in this disorder. We report a young woman with SLE/AAV overlap syndrome who presented with a macular eruption and histopathology findings demonstrating interface dermatitis.

Abbreviations used:

AAV:	antineutrophil cytoplasmic antibody–associated vasculitis
ACR:	American College of Rheumatology
ANA:	antinuclear antibody
ANCA:	antineutrophil cytoplasmic antibody
anti-MPO:	antimyeloperoxidase
MCTD:	mixed connective tissue disease
p-ANCA:	perinuclear antineutrophil cytoplasmic antibody
RNP:	ribonucleoprotein
SLE/AAV:	systemic lupus erythematosus antineutrophil cytoplasmic antibody–associated vasculitis overlap syndrome

CASE

A 40-year-old woman with a history of hypertension presented with headache, right-sided weakness, and acute renal failure. Computed tomography of the head showed subarachnoid hemorrhage caused by aneurysm rupture that was successfully treated with endovascular coil embolization. Renal ultrasound scan found intrinsic renal disease, and rheumatologic workup was significant for positive antimyeloperoxidase (anti-MPO) antibody titer (perinuclear ANCA [p-ANCA]) of 8 IU/mL, ANA with a nucleolar pattern at a titer of 1:640, antichromatin IgG of 1.7 IU/mL and ribonucleoprotein (RNP) antibody of 5.3 IU/mL. Anti-ro, anti-la, anticardiolipin antibody, and lupus anticoagulant were negative. Her creatinine continued to increase (maximum 8.7), and she ultimately required hemodialysis. Renal biopsy with immunofluorescence found pauci-immune crescentic and necrotizing glomerulonephritis. There was no evidence of endocapillary proliferation or immune complex deposition.

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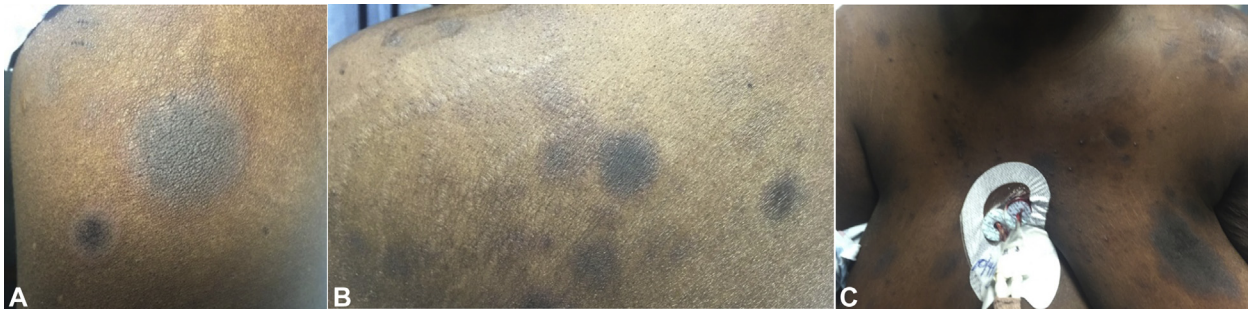

Fig 1. SLE/AAV: clinical photographs. Clinical image of sharply demarcated annular patches with central duskiness and peripheral erythema appear on patient's (**A**) posterior arm, (**B**) upper back, and (**C**) chest.

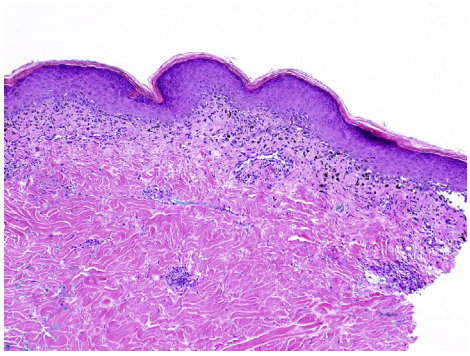

Fig 2. SLE/AAV: examination of punch biopsy specimen from right lateral breast. A punch biopsy section shows lymphocyte-mediated vacuolar interface dermatitis with conspicuous necrotic keratinocytes in the lower epidermis and pigment incontinence. (Hematoxylin-eosin stain; original magnification: ×200.)

During her hospitalization, the patient developed numerous pruritic cutaneous lesions for which the dermatology department was consulted. Physical examination found well-demarcated annular hyperpigmented patches with peripheral erythema and central duskiness on her trunk and extremities (Fig 1). The eruption was not photodistributed. The remainder of her skin and mucosal examination was otherwise unremarkable.

A punch biopsy found interface dermatitis with slight basement membrane thickening and no increased mucin deposition (Fig 2). Direct immunofluorescence from lesional skin on the right arm was positive for granular C3 deposition along the dermoepidermal junction, and IgG demonstrated intraepidermal in vivo ANA. IgA, IgM, and fibrinogen were negative. Based on her clinical and pathologic findings, the diagnosis of SLE/AAV overlap syndrome was made.

Systemic therapy was started primarily to treat her refractory kidney disease and consisted of prednisone, rituximab, hydroxychloroquine, and cyclophosphamide. Additionally, the patient received 1 week of plasma exchange. Cyclophosphamide was poorly tolerated, and she was ultimately transitioned to azathioprine. She was also treated with triamcinolone 0.1% cream twice daily. Her cutaneous involvement and pruritus resolved, although renal failure persisted, requiring continued hemodialysis.

DISCUSSION

Systemic lupus erythematous (SLE) is a chronic autoimmune disease mediated by autoantibody deposition against a variety of targets, including ANA.[3] AAV is a systemic vasculitis mediated by antibodies targeting the granules in polymorphonuclear leukocytes, most commonly anti-MPO or anti-proteinase 3.[4] Although ANCA antibodies occur in approximately 16% of patients with SLE, it is unclear whether this serologic finding is of clinical significance, as few of these patients have concomitant ANCA-associated vasculitis.[5-7] Furthermore, nonspecific assays for ANCAs may cross react with ANAs because of an artifact in ethanol fixation, potentially confounding any true associations.[8]

Distinguishing ANCA vasculitis from SLE vasculitis may, as SLE vasculitis occurs in 11% to 35% of SLE patients, and can manifest in small, medium, and large vessels.[9] SLE vasculitis typically occurs in established SLE patients in the context of a disease flare and is generally mediated by complement and immune complex deposition. The underlying renal histopathology may help to distinguish the diseases. SLE glomerulonephritis often shows immune complex deposition on the glomerular basement membrane.[10] In exception, type IV segmental renal vasculitis does not demonstrate the classic features of lupus nephritis, as it is pauci-immune and resembles ANCA vasculitis both clinically and pathologically.[7,11] These distinct features lead to the

hypothesis of an overlapping syndrome between SLE and AAV.

In 2008, Nasr and colleagues[1] reported a series of 10 patients who presented with severe necrotizing crescentic glomerulonephritis and were all found to be ANCA positive.[1] Renal biopsies exhibited a pattern consistent with lupus nephritis and AAV. The major histopathologic features of these cases (fibrinoid necrosis, absence of significant immune complex deposition, absence of endocapillary proliferation) mirror our patient's renal biopsy. Eight of the 10 patients met American College of Rheumatology (ACR) diagnostic criteria for definite SLE; the other 2 patients met criteria for probable SLE. These findings suggested the existence of an overlapping syndrome of what were previously thought to be 2 distinct diseases. Similar to our case, 7 of the patients carried no previous diagnosis of SLE or AAV. In 2012, another small case series was published of 4 patients with features of both lupus nephritis and AAV, all of whom were positive for anti-MPO (p-ANCA) antibodies, further corroborating the existence of an overlap syndrome.[12]

In a meta-analysis of published literature, Jarrot and colleagues[2] identified 39 patients who met diagnostic criteria for both SLE and AAV, 38 of whom presented with necrotizing crescentic glomerulonephritis.[2] Forty-three percent of these patients had cutaneous lesions. The most commonly reported cutaneous findings were ecchymoses and skin nodules but also included livedo reticularis, Raynaud phenomenon, alopecia, and a malar eruption. There were no descriptions of dusky targetoid patches as were seen in our patient.

Given the small number of reports in the literature, the SLE/AAV overlap syndrome is still being defined but carries features of both diseases. As many as 70% of patients carry no diagnosis of SLE or AAV before presentation.[2,12] Ninety percent of the cases occur in women, with a mean age in the fourth decade.[2,12] The most common features of the overlap syndrome include arthritis, serositis, cytopenias, rhinosinusitis, and pulmonary hemorrhage.[1,2,12] Rapidly progressive glomerulonephritis is an almost universal feature.[1,2,12,13] Several cases report central nervous system vasculitis and thrombotic cerebrovascular events.[2,12,13] We identified no previous reports of cerebral aneurysm or intracranial hemorrhage, as with our patient. The most common systemic treatments are corticosteroids and cyclophosphamide.[1,2,12]

Our patient had 3 ACR criteria for SLE including cutaneous lupus, glomerulonephritis, and elevated ANA titers. Four ACR criteria are typically met before a definitive SLE diagnosis is made. Although elevated double-stranded DNA was absent in our patient, she did have antichromatin IgG, which is a relatively specific marker for SLE although not included in ACR criteria.[14] Other reported cases also met only 3 ACR criteria for lupus when they presented with SLE/AAV overlap syndrome.[1] Although our patient had an elevated RNP, which is a feature of undifferentiated connective tissue disease or mixed connective tissue disease (MCTD) she showed no other features of MCTD such as Raynaud phenomenon or inflammatory myopathy. Rarely, RNP-positive MCTD has been associated with microscopic polyangiitis and rapidly progressive glomerulonephritis.[15] These patients carried a diagnosis of MCTD for between 8 months and 19 years before symptoms of ANCA vasculitis developed.

Our patient's age, gender, and clinical and histopathologic renal disease were all typical of SLE/AAV syndrome. Her treatment plan targeted her ultimately refractory kidney disease, and although her skin lesions improved, it is unclear if one therapy showed superiority over another. Further clinical and pathologic documentation and characterization of SLE/AAV overlap syndrome is important to help elucidate the pathologic mechanisms driving this rare but potentially devastating disease.

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