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Solving the Puzzles of Rheumatic Diseases

S. Louis Bridges Jr., MD, PhD
Editor

As we send this issue to press in October 2020, clinicians and patients at HSS have transitioned to a "new normal" after the disruptive emergence of COVID-19 earlier this year. During my first few weeks at HSS, I have been deeply impressed by the dedication of our faculty, staff, and trainees to safety amid this unprecedented challenge. Our rheumatology faculty and staff have inspired me by their commitment to improving the lives of patients affected by rheumatic diseases, as demonstrated by the cases presented in this issue.

In Case 1, **Caroline H. Siegel, MD**, and **Doruk Erkan, MD, MPH**, discuss the treatment of a man with pain and cyanosis of the digits caused by antiphospholipid syndrome. In Case 2, **Diane Zisa, MD**, and **Kyriakos A. Kirou, MD, DSc, FACP**, review the case of a woman with systemic lupus erythematosus whose nephritis and cutaneous vasculitis were refractory to treatment. In Case 3, **Kimberly Showalter, MD, MS**, **Jessica K. Gordon, MD, MS**, and **Bella Mehta, MBBS, MS**, present the case of a woman with Sjögren's syndrome with rapidly progressive interstitial lung disease. And in Case 4, **David R. Fernandez, MD**, and **Linda A. Russell, MD**, discuss the progression of a 32-year-old woman's dermatomyositis—a rash that resolved during pregnancy, only to recur postpartum, along with fatigue and weakness.

We are eager to hear from readers. Please let us know your thoughts on these cases and the treatments presented. We welcome your comments at **complexcases@hss.edu**.

With best wishes,

A. Louis Bridges Jr., MD, PhD

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Physician-in-Chief
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In This Issue

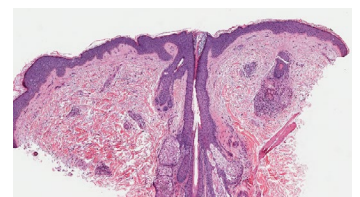# Case 1 Case presented by Caroline H. Siegel, MD, and Doruk Erkan, MD, MPH

Management of Diffuse Peripheral Ischemia in Antiphospholipid Syndrome: Anticoagulation, Immunosuppression, Vasodilation, or All Three?

Case Report A 39-year-old man with a history of well-controlled type 1 diabetes mellitus (T1DM) since childhood and migraine presented with 1 week of pain and cyanosis of the fingers of the left hand and toes of both feet. Although he had no history of Raynaud's phenomenon, warm temperature yielded transient improvement. He had primary antiphospholipid syndrome (APS), diagnosed 6 years prior on the basis of unprovoked lower extremity deep vein thrombosis and persistent antiphospholipid antibodies (positive lupus anticoagulant test, high-titer anticardiolipin antibody [aCL] immunoglobulin [Ig] G, and high-titer anti-β2-glycoprotein I antibody [aβ2GPI] IgG). He was on warfarin (target international normalized ratio [INR]: 2.5–3), aspirin 81 mg daily, atorvastatin 10 mg daily, and verapamil 240 mg daily. Two weeks prior to presentation, his INR had increased to 7 while on antibiotics for sinusitis; it nadired at 1.3 a week later after warfarin was held.

On physical examination, he had distal cyanosis in the left hand and both feet (Fig. 1). Laboratory test results were notable for platelet count of 94 K/µL (normal: 150-450 K/µL), INR of 1.8, one-time troponin elevation to 0.19 ng/mL (normal: ≥ 0.04 ng/mL), and elevated serum transaminases, which peaked at 3 times the upper limit of normal and then trended down over 1 week. Serum levels of complement components 3 and 4 were normal, and aCL IgG was >150 GPL and aβ2GPI IgG was >150 SGU. Antineutrophil cytoplasmic antibodies were negative. Glycosylated hemoglobin (HbA1c) was 6.8% (normal: ≤ 5.6%). Transthoracic and transesophageal echocardiography did not identify valvular vegetations. Magnetic resonance angiography (MRA) of the left hand revealed severe occlusive arterial disease with extensive collateralization (Fig. 2).

Due to concern for APS-associated microvascular disease evolving to catastrophic APS (CAPS), he was started on methylprednisolone 125 mg twice daily, hydroxychloroquine 200 mg twice daily, and intravenous (IV) heparin. Aspirin and atorvastatin were continued; verapamil was switched to nifedipine 60 mg daily. Four days after admission, rituximab 1 g IV was given (repeat dose 2 weeks later). We initiated sildenafil 20 mg 3 times daily, with partial improvement in the cyanosis of the left second finger. One week later, the

patient underwent a left upper extremity nerve block with marked but temporary benefit. Intravenous immunoglobulin (IVIG) 2 g/kg was administered over 5 days and platelet count normalized. The patient also received IV epoprostenol with no immediate response; this was discontinued after 12 hours due to flare of migraine, and sildenafil was increased to 40 mg 3 times daily.

By the time of discharge, methylprednisolone had been tapered to 10 mg twice daily and warfarin was resumed. Aspirin, atorvastatin, hydroxychloroquine, nifedipine, and sildenafil were continued. The pain and cyanosis in the left hand had resolved except in the gangrenous distal second finger; his toes remained dusky.

Discussion Patients with APS may experience a spectrum of thrombotic manifestations: moderate-to-large vessel disease, microvascular disease, and CAPS [1]. Our patient presented with ischemic digits due to microvascular disease and unexplained mild transaminase and troponin elevations but did not meet CAPS classification criteria [2].

While anticoagulation is the mainstay of treatment for moderate-to-large vessel thrombosis in APS, microvascular APS and CAPS require additional modalities. First-line therapy for CAPS includes anticoagulation, glucocorticoids, IVIG, and/or plasma exchange [1]. For microvascular APS and CAPS, adjunctive therapies include statins and hydroxychloroquine [1]. Rituximab may be effective in patients with microvascular manifestations [3]. The optimal management of peripheral ischemia in APS is not well established.

Our patient's clinical presentation was atypical. Microvascular APS leading to diffuse peripheral ischemia is rare, especially without meeting CAPS classification criteria [4]. Longstanding T1DM likely contributed to the chronic arterial disease seen on MRA. Although he had no known T1DM-related microvascular complications, peripheral microvascular disease can develop before retinopathy and may not correlate with the degree of glycemic control [5]. Prior infection and subtherapeutic INR level may have triggered this patient's acute presentation. Vasospasm seemed to play a role as well, perhaps causing steal phenomenon in the context of underlying arterial occlusions. Thus, in addition to anticoagulation

and immunomodulation, we optimized his calcium channel blocker, added a phosphodiesterase 5 inhibitor, and pursued trials of a prostaglandin and chemical sympathectomy.

In conclusion, for this complex case of refractory peripheral ischemia in a patient with APS and T1DM, we used an aggressive multimodal treatment strategy to maximize perfusion to multiple digits at risk of infarction. ■

Case images on the next page

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Figure 1

Palmar aspect of the left hand showing duskiness of all fingertips, with severe cyanosis involving the distal half of the second finger.

Dorsal aspect of the left the hand showing cyanosis of the distal second finger.

Duskiness of all toes of the left foot distally.

Duskiness of all toes of the right foot distally, with more significant cyanosis involving the distal half and proximal lateral aspect of the fourth toe.

Figure 2

MRA of the left hand showing severe occlusive arterial disease, predominantly affecting the arteries arising from the radial aspect of the deep palmar arch, with extensive collateral circulation. There is significant occlusion of blood flow to the distal second finger.

Case 2 Case presented by Diane Zisa, MD, and Kyriakos A. Kirou, MD, DSc, FACP

Relapsing Lupus Nephritis and Cutaneous Vasculitis: A Race to Contain B Cells

Case Report A 45-year-old woman with a history of systemic lupus erythematosus (SLE) since 2006 came to HSS in 2014 for continued management of SLE. Disease manifestations included arthritis, alopecia, Raynaud's phenomenon, lymphadenopathy, pericarditis, and mononeuritis multiplex. She also had a recurrent erythematous, tender rash on her lower legs; a biopsy revealed leukocytoclastic vasculitis (LCV) with deposits of immunoglobulin M (IgM) and to a lesser extent IgA and C4d within the microvasculature, consistent with an SLE-associated immune complex-mediated vasculitis. Positive serologies included antinuclear antibody, anti-Smith, anti-Ro, anti-La, and anti-RNP antibodies; low levels of serum complement component 3 and 4 (C3 and C4) were found. Results were negative for anti-dsDNA antibodies, antiphospholipid antibodies, anti-neutrophil cytoplasmic antibodies (ANCA), rheumatoid factor, and cryoglobulins. She was treated with corticosteroids (CS), hydroxychloroquine, azathioprine, tacrolimus, and belimumab. Severe flares of the disease required high-dose CS therapy.

Despite this treatment, she developed progressive disease in 2018, with palpable purpura extending to her proximal legs, arms, and trunk (Fig. 1). In the following months, she developed new nephrotic-range proteinuria and microscopic hematuria. A kidney biopsy showed diffuse class IV glomerulonephritis with prominent intra-capillary hyaline "thrombi" and IgM and IgG mesangial and subendothelial deposits. She received pulse-dose and high-dose oral CS and mycophenolate mofetil (MMF) 3000 mg/day, with partial improvement in kidney function and proteinuria.

However, the rash remained active, causing severe pain and ulceration (Fig. 2A), despite treatment with MMF, CS, diuretics, and wound care. Two doses of rituximab 1000 mg separated by 2 weeks were added to her regimen, resulting in marked improvement in skin lesions and proteinuria and successful tapering of CS. Unfortunately, the nephritis and cutaneous vasculitis flared again 5 months later, coinciding with B-cell repletion and a decrease in C3/C4 levels, just before her next scheduled dose of rituximab. This pattern continued (Fig. 3), despite addition of weekly belimumab. The refractory left leg skin ulcer eventually healed (Fig. 2B).

Discussion Vasculitis occurs in 11 to 20% of SLE patients, most frequently as a small vessel LCV manifesting as cutaneous lesions [1]. The development of cutaneous vasculitis in patients with SLE has been demonstraed to correlate with increased SLE activity overall, therefore warranting additional therapy for disease control [1].

This case highlights the role of B-cell targeted therapies for both cutaneous vasculitis in SLE and lupus nephritis. The presence of immune complexes in the skin and kidney biopsies, as well as the profound serum C3/C4 level drop coinciding with the vasculitic and nephritic flares, suggested a dominant role of the autoimmune B-cell pathway in causing these manifestations. The therapeutic approach thus shifted to B-cell targeted agents with complementary mechanisms of action: an anti-CD20 antibody, rituximab, and an antibody against soluble B-lymphocyte stimulator (BLyS), belimumab [2]. The patient's condition improved with this combination, but the disease predictably flared when CD19/CD20 B-cell subsets repopulated just prior to the next dose of rituximab. Efforts to preempt flares now involve accelerated dosing of rituximab to every 4 months.

We are unsure why this patient's disease remained refractory. Transient and/or incomplete B-cell depletion is thought to contribute to resistant disease by selecting for potentially more pathogenic B-cell clones [2]. Additionally, while rituximab results in near complete depletion of circulating B-cells, those in tissues remain relatively unaffected [2]. Thus, future therapeutic considerations for refractory cases may include achieving a more durable B-cell depletion in peripheral blood and tissue with alternative anti-CD20 antibodies, such as obinutuzumab, which is currently under investigation for use in patients with lupus nephritis [3]. Other therapies for refractory SLE under investigation include Bruton's tyrosine kinase (BTK) inhibitors and plasma cell-targeted agents such as proteasome inhibitors [4, 5]. ■

Case images on the next page

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Figure 1

Representative vasculitic lesions on the patient's trunk.
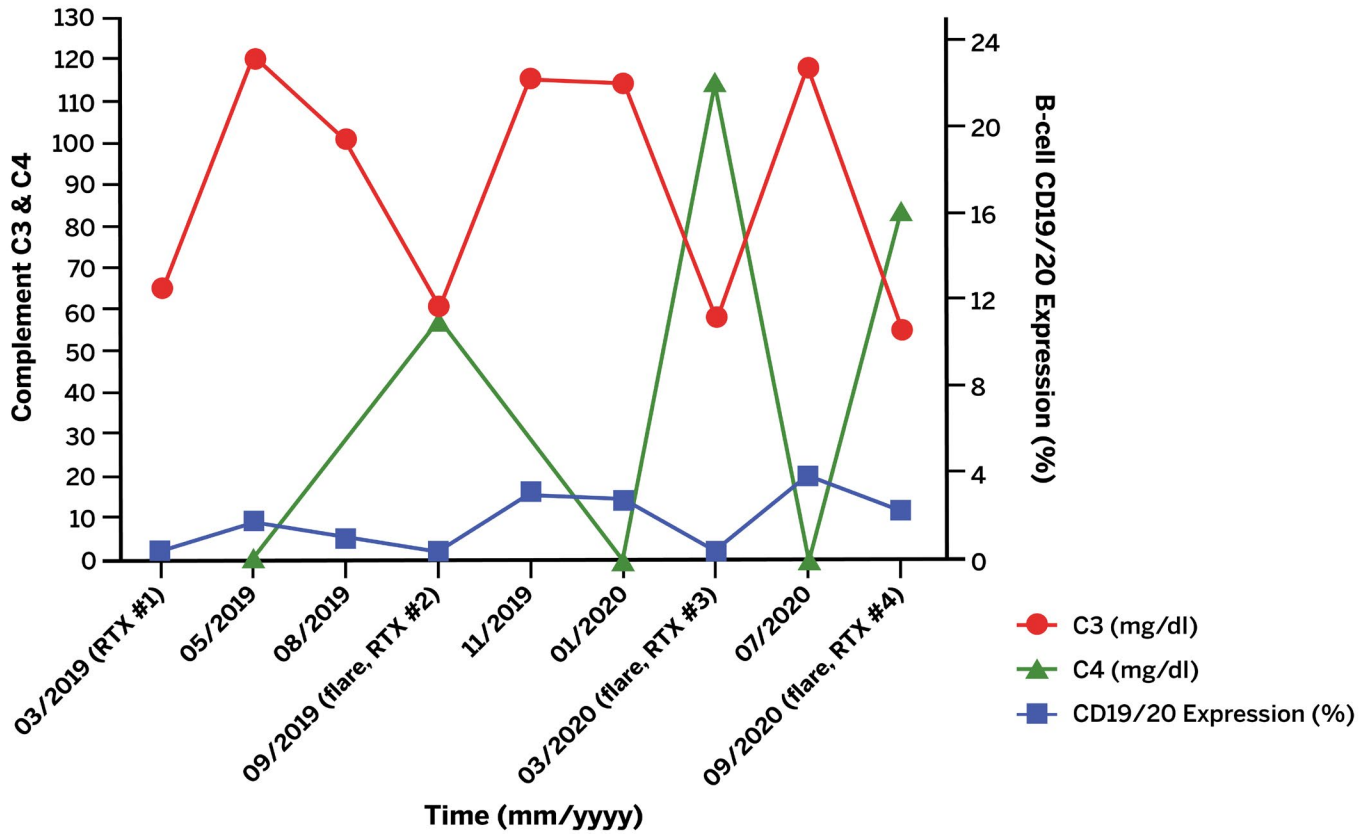
Figure 2A

Figure 2B

Ulcerated lesion on lower extremity (A) that resolved after initiation of rituximab, belimumab, and local wound care (B).

Figure 3

Laboratory data trend of complement levels and B-cell CD19/CD20 expression as a function of time. Time points marked by "flare" signify a flare of patient's rash and nephritis. "RTX" indicates rituximab was administered at this time point.

Case 3
Case presented by Kimberly Showalter, MD, MS, Jessica K. Gordon, MD, MS, and Bella Mehta, MBBS, MS

Sjögren's Syndrome-associated Interstitial Lung Disease Treated with Immunosuppression

Case Report A 39-year-old woman with former tobacco use (4.5 pack-years) presented with rapidly progressive interstitial lung disease (ILD). Two years prior, the patient developed subacute exertional dyspnea and cough, for which she received antibiotics without improvement. One year later, she developed diffuse arthralgias (hands, wrists, knees, ankles), xerophthalmia, xerostomia, and worsening dyspnea. Computed tomography (CT) scan of the chest revealed extensive peripheral honeycombing, traction bronchiectasis, and lower lobe predominant ground-glass opacities (Fig. 1). Laboratory testing was notable for positive antinuclear antibody (1:320, speckled) and Sjögren's syndrome A (anti-SSA) autoantibody. Other laboratory results were unremarkable including rheumatoid factor and serum antibodies to Sjögren's syndrome B (anti-SSB), anti-Smith, anti-RNP, anti-double-stranded DNA, anti-topoisomerase, anticentromere, RNA polymerase III, myeloperoxidase, serine proteinase 3, anti-Jo-1 (and extended myositis panel), and cyclic citrullinated peptide. Evaluation for infectious etiologies (HIV, tuberculosis, and pulmonary bacterial, viral, and fungal pathogens) was unremarkable.

Pulmonary function testing (PFT) demonstrated restrictive lung disease with reduced %-predicted forced vital capacity (FVC) to 32% and normal FEV1/FVC ratio. There was no evidence of pulmonary hypertension on right heart catheterization. A lung biopsy was obtained that demonstrated fibrosing and cellular interstitial pneumonitis with a usual interstitial pneumonia (UIP) pattern. Prednisone (10 mg twice daily) and hydroxychloroquine were initiated without symptomatic improvement. She left the country for 3 months, during which time her shortness of breath slowly worsened. Upon returning, she was hospitalized with acute hypoxemic respiratory failure with FVC decline to 29% predicted and an increasing exertional oxygen requirement (2 L/min to 4 L/min). Repeat infectious work-up was unremarkable and imaging revealed no pulmonary embolism. She was referred both for pulmonary transplantation and rheumatology evaluations.

Additional immunomodulatory medications were added: mycophenolate mofetil (MMF) (increased over 8 weeks to 3 g daily) and rituximab (1 g intravenously for 2 doses, 14 days apart). She also began pulmonary rehabilitation. Subsequently, her joint pain resolved, dyspnea improved, and exertional oxygen requirement decreased to 2 L/min. Her %-predicted FVC improved slightly: 30% and 32% after 6 and 12 months, respectively. Currently, lung transplantation is on hold due to symptomatic improvement.

Discussion Approximately 10 to 20% of individuals with Sjögren's syndrome (SS) have clinically relevant pulmonary involvement, defined by respiratory symptoms with PFT and/or chest radiographic abnormalities [1]. Common symptoms include dyspnea, cough, and sputum production. Common histopathologic findings include non-specific interstitial pneumonitis, bronchiolitis, and usual interstitial pneumonia [2]. Factors associated with increased risk of lung disease include male sex, older age, history of tobacco use, hypergammaglobulinemia, lymphopenia, and presence of rheumatoid factor, anti-SSA, or anti-SSB antibodies [1, 3]. Importantly, the presence of ILD is associated with a 4-fold increased risk of death at 10 years [4].

To date, no controlled trial has been conducted in SS-ILD. Prednisone (1 mg/kg) is recommended as initial treatment, and MMF, azathioprine, rituximab, and cyclophosphamide have also been used [1, 5, 6]. MMF was studied in 125 patients with connective tissue disease (CTD)-ILD (5 with SS). Among individuals with UIP, MMF was associated with PFT stability over a median of 2.5 years [6]. Rituximab was evaluated in a retrospective cohort study of SS-ILD (n = 10) [5]. There was no significant 6-month improvement in FVC; however, there was mild improvement in diffusing capacity for carbon monoxide (7%-predicted) and significant improvements in patient reported outcomes. Lung transplantation is considered in patients with advanced pulmonary involvement. A retrospective study of 67,621 patients showed no difference in post-transplantation

mortality between those with non-scleroderma CTD-ILD and idiopathic pulmonary fibrosis [7]. ◼

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Figure 1

Chest CT scan without contrast demonstrates extensive peripheral areas of honeycombing, areas of traction bronchiectasis, and scattered ground-glass opacities with a lower lobe predominance.

Case 4 Case presented by David R. Fernandez, MD, PhD, and Linda A. Russell, MD

The Use of Autoantibody Testing in a Postpartum Patient at Risk of Malignancy-Associated Dermatomyositis

Case Report In May 2019, a 32-year-old woman developed a rash on her face, chest, and knuckles, initially thought to be contact dermatitis. She saw a second dermatologist to evaluate persistent symptoms, who found positive results on antinuclear antibody (ANA) testing. She was referred to rheumatology, but additional lab testing was unrevealing. She learned she was pregnant, and the rash resolved spontaneously 4 weeks into the pregnancy. She delivered a heathy son at 40 weeks' gestation. Approximately 8 weeks postpartum, the rash on her face, chest, and knuckles recurred. About 4 and a half months postpartum, she developed fatigue and weakness of her proximal arms and legs, and came to HSS for evaluation. She had no shortness of breath or dysphagia.

The patient had a prior uncomplicated pregnancy, no prior surgeries, and no family history of autoimmunity but did have a first-degree relative with a *BRCA* mutation. She was breastfeeding and planned to wean in the setting of possibly needing additional medications. She was married, with 2 young children, and worked full-time.

Her physical exam was notable for erythema of her cheeks and upper chest and erythematous papules over the metacarpophalangeal joints consistent with Gottron's papules. She could not abduct her shoulders above 90° against gravity, although she could stand from a seated position without using her arms.

Laboratory testing showed a white blood cell count of 3.3 cells/mm^3 and elevated levels of aspartate aminotransferase (45 U/L), creatine kinase (CK, 665 U/L), aldolase (10.6 U/L), and lactate dehydrogenase (LDH, 324 U/L). An ANA test was positive in a speckled pattern at a 1:320 dilution, while tests of anti-Jo-1, anti-RNP, and anti-dsDNA antibodies were negative, complement C3 and C4 were normal, and erythrocyte sedimentation rate was normal. Myositis autoantibody profiling was positive for p155/140 (TIF-1γ). A skin biopsy result was consistent with dermatomyositis (Fig. 1). Pulmonary function testing and echocardiography were normal.

She was started on high-dose prednisone, with rapid, significant partial improvement in strength and skin disease. Azathioprine 50 mg daily was then added. Over the next several weeks, her strength continued to improve and the rash to fade, and CK and LDH levels fell. Intravenous immunoglobulin (IVIG) 2g/kg monthly was added for additional steroid sparing and symptom control, and she noted further skin improvement. A second series of IVIG doses was unfortunately associated with development of aseptic meningitis requiring hospitalization.

Malignancy screening was performed. Computed tomography (CT) scanning of the chest/abdomen/pelvis was normal. Esophagogastroduodenoscopy and colonoscopy revealed features of celiac disease and lymphocytic colitis. Mammography showed changes consistent with lactation. Genetic testing disclosed no *BRCA 1/2* mutations but did show a mutated checkpoint kinase 2 (*CHEK2*) allele, which is associated with an increased risk of ovarian, colon, and breast cancer.

Discussion Pregnancy outcomes in myositis are variable, but generally good outcomes are associated with good disease control prior to pregnancy, as in other rheumatic diseases such as lupus [1]. It has long been recognized that a subset of patients with rheumatoid arthritis do particularly well during pregnancy, achieving reduced disease activity, or even remission, though they may flare again postpartum. Our case demonstrates this spontaneous improvement phenomenon manifesting in dermatomyositis, which has been described in a small Spanish case series [2] but is nonetheless very rare.

Anti-TIF-1γ antibodies are specific to patients with dermatomyositis, most commonly patients with malignancy-associated dermatomyositis. In a recent large study, 38% of patients positive for anti-TIF-1γ developed cancer, versus 15% of patients who were anti-TIF-1γ negative [3]. While our patient did not exhibit signs of malignancy after comprehensive screening, the risk of an occult malignancy emerging remains elevated in patients with anti-

TIF-1γ for 3 years after dermatomyositis disease onset [3]. Ongoing screening is merited over that period in these patients. However, the risk of malignancy in this context is also tightly related to age. Juvenile dermatomyositis poses essentially no risk of malignancy, and malignancy risk remains low but not nonexistent in those under 40 years of age [3,4]. Our patient will continue with intensive lifelong screening for malignancy based on the presence of a heterozygous mutation in the tumor suppressor gene *CHEK2*, which has been implicated in increased risk of several cancers, including breast cancer [5].
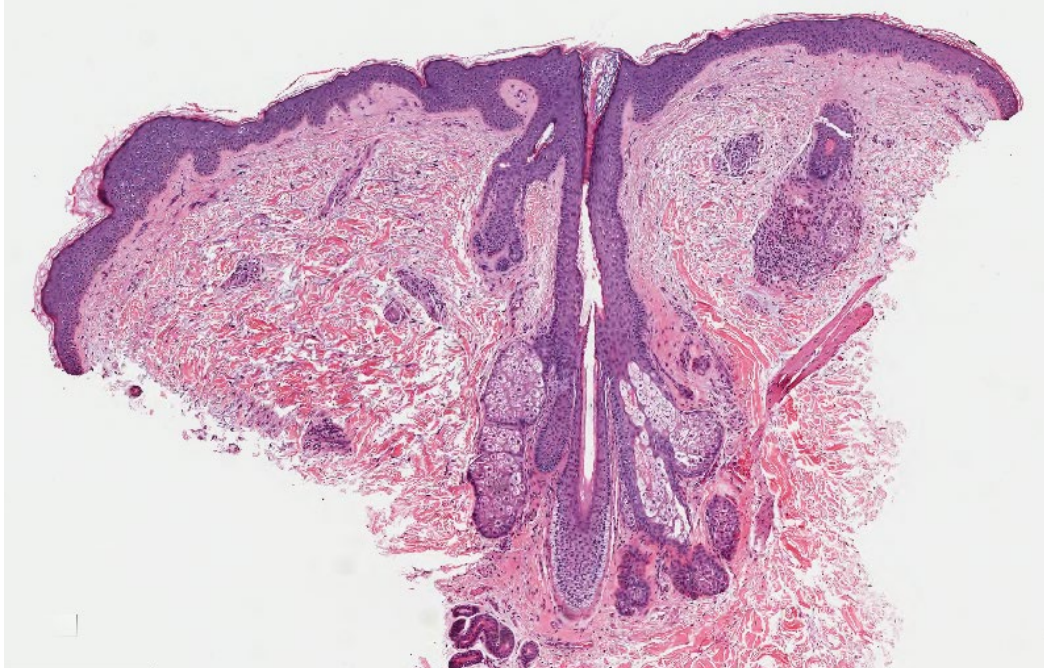
This case illustrates several interesting features of rheumatic disease during pregnancy, as well as the use of autoantibody testing to identify patients at high risk of malignancy-associated dermatomyositis, who would benefit from more prolonged surveillance. ■
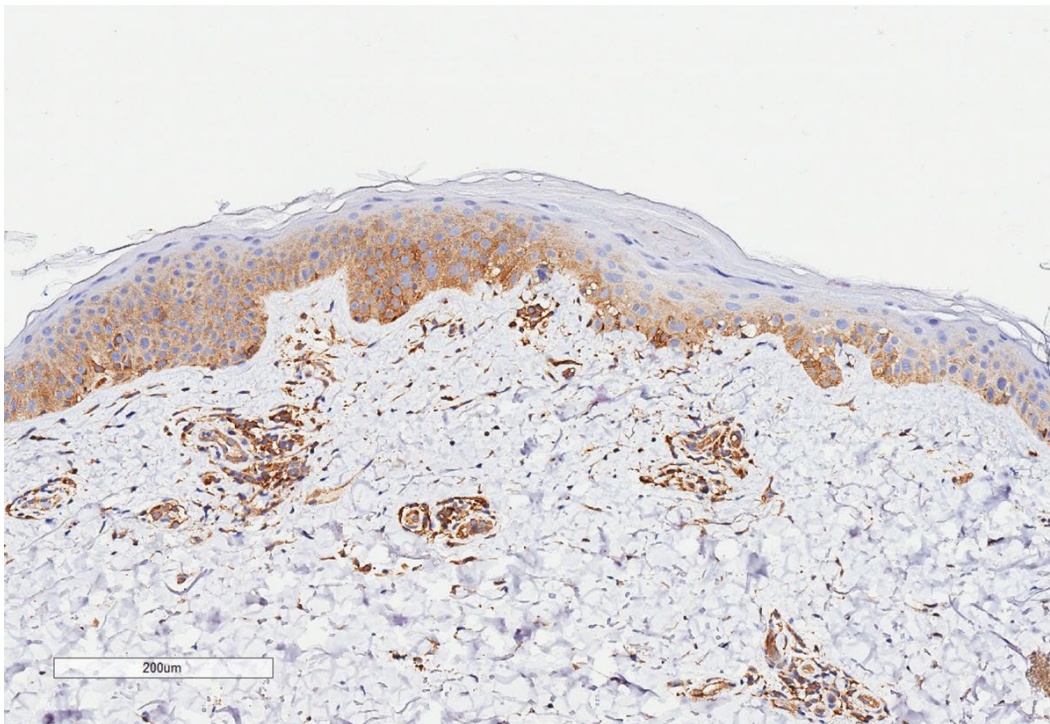
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Figure 1

Hematoxylin and eosin staining of biopsy demonstrates dermatomyositis.

MxA staining, which binds to endothelial cells.

Grand Rounds from HSS

Management of Complex Cases

HSS Education Institute