

CLINICAL CARE CONUNDRUM


Cracking the Case

The approach to clinical conundrums by an expert clinician is revealed through presentation of an actual patient's case in an approach typical of morning report. Similar to patient care, sequential pieces of information are provided to the clinician who is unfamiliar with the case. The focus is on the thought processes of both the clinical team caring for the patient and the discussant.

This icon represents the patient's case. Each paragraph that follows represents the discussant's thoughts.

Jennie Wei, MD, MPH^{1*}, Patrick P. Kneeland, MD², Gurpreet Dhaliwal, MD^{1,3}


¹Department of Medicine, University of California, San Francisco, San Francisco, California; ²Division of Hospital Medicine, Providence Regional Medical Center, Everett, Washington; ³Medical Service, San Francisco VA Medical Center, San Francisco, California.


 A 43-year-old woman presented to an outside hospital with painful plaques and patches on her bilateral lower extremities. Two weeks prior to presentation, she had noticed a single red lesion on her left ankle. Over the next two weeks, the lesion enlarged to involve the lower half of her posterior calf and subsequently turned purple and became exquisitely tender. Similar but smaller purple, tender lesions simultaneously appeared, first over her right shin and then on her bilateral thighs and hips. She also reported fatigue as well as diffuse joint pains in her hands and wrists bilaterally for the past month. She denied any swelling of these joints or functional impairment. She denied fevers, weight loss, headache, sinus symptoms, difficulty breathing, or abdominal pain.

Although we do not yet have a physical exam, the tempo, pattern of spread, and accompanying features allow some early hypotheses to be considered. Distal lower extremity lesions which darkened and spread could be erythema nodosum or erythema induratum. Malignancies rarely have such prominent skin manifestations, although leukemia cutis or an aggressive cutaneous T cell lymphoma might present with disseminated and darkened plaques, and Kaposi's sarcoma is characteristically purple and multifocal. Autoimmune disorders such as sarcoidosis, cutaneous lupus, and psoriasis may similarly present with widespread plaques. Most disseminated infections that start with patches evolve to pustules, ulcers, bullae, or other forms that reflect the invasive nature of the infection; syphilis warrants consideration for any widespread eruption of unknown etiology. Antecedent arthralgias with fatigue suggest an autoimmune condition, although infections such as hepatitis or parvovirus can do the same. Systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA) would be favored initially on account of her demographics and the hand and wrist involvement, and each can be associated with vasculitis.


The significant pain as described is not compatible with most of the aforementioned diagnoses. Its presence, coupled with potential autoimmune symptoms, suggests a vasculitis such as polyarteritis nodosa (which can have prominent diffuse skin

involvement), Henoch Schonlein purpura (with its predilection for the lower extremities, including extension to the hips and buttocks), cryoglobulinemia, or SLE- or RA-associated vasculitis. Calciphylaxis is another ischemic vascular disorder that can cause diffuse dark painful lesions, but this only warrants consideration if advanced renal disease is present.

 A skin biopsy of her right hip was taken at the outside hospital. She was discharged on a two-week course of prednisone for suspected vasculitis while biopsy results were pending. Over the next two weeks, none of the skin lesions improved, despite compliance with this treatment, and the skin over her left posterior calf and right shin lesions began to erode and bleed. In addition, small purple, tender lesions appeared over the pinnae of both ears. Three weeks after her initial evaluation, she presented to another emergency department for ulcerating skin lesions and worsening pain. At that point, the initial skin biopsy result was available and revealed "vasculopathy of the small vessels with thrombi but no vasculitis."

 The patient had no children, and denied a history of miscarriages. Her past medical history was unremarkable. She did not report any history of thrombotic events. She started a new job as a software engineer one month ago and was feeling stressed about her new responsibilities. She denied any high-risk sexual behavior and any history of intravenous drug use. She had not traveled recently and did not own any pets. There was no family history of rheumatologic disorders, hypercoagulable states, or thrombotic events.

This picture of occluded but noninflamed vessels shifts the diagnosis away from vasculitis and focuses attention on hypercoagulable states with prominent dermal manifestations, including antiphospholipid antibody syndrome (APLS) and livedoid vasculopathy. In this young woman with arthralgias, consideration of SLE and APLS is warranted. Her recent increase in stress and widespread purpuric and ulcerative lesions could bring to mind a factitious disorder, but the histology results eliminate this possibility.

 The patient's temperature was 36.5°C, her blood pressure was 110/70 mmHg, respiratory rate was 16 breaths per minute, and her heart rate was 65 beats per minute. She was well-appearing but in moderate pain. She did not have any oral lesions. Her cardiac, respiratory, and abdominal exams were normal. Skin exam revealed a 10-cm by 4-cm area of bloody

*Address for correspondence and reprint requests: Jennie Wei, University of California, San Francisco, 505 Parnassus Avenue, Room M987, San Francisco, CA 94143-0296; Tel.: 617-308 2085; E-mail: jennie.wei@ucsf.edu

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granulation tissue draining serosanguinous fluid, surrounded by stellate palpable netlike purpura on her left posterior calf. There was a similar 4-cm by 2-cm ulcerated lesion on her right shin. Both lesions were exquisitely tender to palpation. On her bilateral thighs and hips, there were multiple stellate purpuric patches, all 4 cm in diameter or less, and only minimally tender to palpation. She also had 1-cm purpuric bullae on the helices of both ears (Figure 1) which were slightly tender to palpation. Splinter hemorrhages were also noted on multiple nail beds bilaterally. Musculoskeletal exam did not reveal any synovitis.

The original purpura on her calf and ear demonstrate a clear demarcation corresponding to cutaneous vascular insufficiency. The development of bullae (ear) and ulceration (calf) are compatible with ischemia. Despite the presence of multiple splinter hemorrhages, the distribution of lesions is very unusual for an embolic phenomenon (eg, endocarditis, cholesterol emboli, or atrial myxoma). The multifocal nature of the skin lesions with progression to well-demarcated cutaneous necrosis is reminiscent of calciphylaxis or warfarin-induced skin necrosis, although she lacks the relevant risk factors. A toxin such as cocaine or methamphetamine mediating multifocal vasoconstriction or hypercoagulability should be excluded.

The bilateral ear involvement remains decidedly unusual and makes me wonder if there is something about the ear, such as the nature of its circulation or its potentially lower temperature (as an acral organ) that might render it particularly susceptible, for instance, to cryoglobulinemia or cryofibrinogenemia-mediated ischemia.

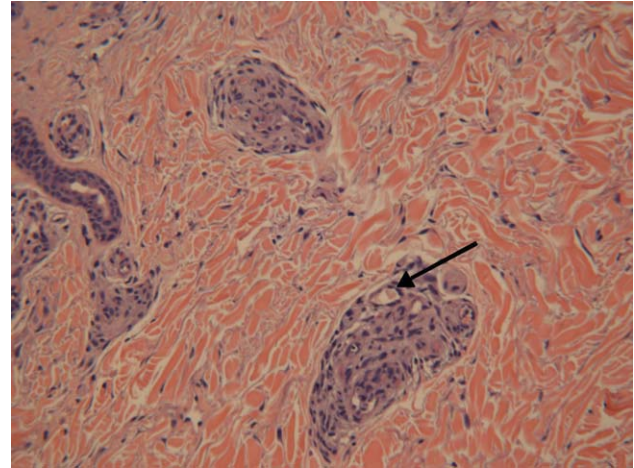


FIG. 2. Punch biopsy of left calf lesion revealing blood vessel occluded by fibrin thrombi (arrow). [Color figure can be viewed in the online issue, which


Laboratory studies demonstrated: white blood cell count of $1500/\text{mm}^3$ (37.3% neutrophils, 5.1% lymphocytes, 6.7% monocytes, and 1.3% eosinophils); hemoglobin 9.3 g/dl (mean corpuscular volume 91 fL); platelet count $212/\text{mm}^3$; erythrocyte sedimentation rate 62 mm/hr; C-reactive protein 14.6 mg/L. Serum electrolytes, liver tests, coagulation studies, and urinalysis were normal. Fecal occult blood test was negative.

Her neutropenia and anemia suggest decreased production in the marrow by infection, malignancy, or toxin, or increased destruction, perhaps from an autoimmune process. The associated infections are usually viral, such as human immunodeficiency virus (HIV) and Epstein-Barr virus (EBV), although their linkage with her cutaneous disease is tenuous. It is possible that malignancy could be present in the marrow with resultant dermal hypercoagulability and ischemia, but this seems unlikely. We do not know about any toxins that she has been exposed to, but these hematologic findings would mandate directed inquiry along those lines. In this young woman with cutaneous ulcers secondary to thrombotic vasculopathy, bicytopenia, antecedent arthralgias without synovitis, and elevated inflammatory markers, I favor an autoimmune process such as SLE, which I would evaluate with an antinuclear antibody (ANA) and antiphospholipid antibody studies.


She was admitted to the hospital and received hydromorphone for pain control. Corticosteroids were not administered. Peripheral blood morphology was normal. Antibodies against HIV1 and 2 were negative, as were antibodies against cytomegalovirus, EBV, parvovirus B19, mycoplasma pneumoniae, and hepatitis C virus. Bilateral lower extremity ultrasound was negative for deep vein thrombosis. Transthoracic echocardiogram was normal. Repeat skin biopsy confirmed small vessel vasculopathy without vasculitis (Figure 2). The results of the following investigations were also negative: ANA, rheumatoid factor, double-stranded DNA (dsDNA), cyclic citrullinated peptide, ribonucleoprotein (RNP), and anti-Smith antibodies. C3 and C4 complement levels were normal.

Given how much the histology is driving the clinical reasoning and focusing the differential diagnosis in this case, I agree with the decision to repeat the biopsy. In complex or

undiagnosed cases, repeat histology samples allow for confirmation of the original interpretation (often with the perspective of new clinicians and pathologists) and sometimes reveal pathognomonic or additional findings that only appear after the disease has evolved over time. HIV seronegativity helps constrain the differential diagnosis, and parvovirus is another excellent consideration for arthralgias and cytopenias (with the predilection to involve cells lines other than RBCs particularly seen in HIV), although ulcers are not seen with this condition. Herpes simplex virus (HSV) is another viral infection that can cause painful skin ulcerations and cytopenias, although the duration and distribution are highly atypical. The negative ANA and dsDNA and normal complement levels make SLE unlikely. The negative lower extremity ultrasound helps frame the thromboses as a local cutaneous process rather than a systemic hypercoagulable state. Although the peripheral blood smear is normal, a bone marrow biopsy will be necessary to exclude a marrow invasive process, such as leukemia or lymphoma. A bone marrow biopsy would also provide another opportunity to examine tissue for mycobacteria or fungi which can cause ulcerations and cytopenias, although there is little reason to suspect she is susceptible to those pathogens. As this clinical picture fails to fit clearly with an infectious, autoimmune, or neoplastic disorder, I would revisit the possibility of toxins—prescription, complementary, over-the-counter, or illegal (eg, cocaine) at this time.

 In further discussion with the patient, she reported using cocaine intranasally for the past three months. Her urine toxicology was positive for cocaine. She was found to have positive perinuclear antineutrophil cytoplasmic antibodies (p-ANCA), antimyeloperoxidase (MPO) antibodies, anticardiolipin (ACL) antibodies, and lupus anticoagulant (LAC). By hospital day 3, her lesions had significantly improved without any intervention, and her absolute neutrophil count increased to 1080/mm³.

The presence of widespread cutaneous ischemia (with bland thrombosis) and detectable ACL and LAC antibodies is compatible with APLS; the APLS could be deemed primary, because there is no clear associated rheumatologic or other systemic disease. However, neutropenia is not a characteristic of APLS, which has thrombocytopenia as its more frequently associated hematologic abnormality. Livedoid vasculopathy, a related disorder, is also supported by the ACL and LAC results, but also does not feature neutropenia. While the presence of diffuse thrombosis could be attributed to a widespread secondary effect of cocaine vasoconstriction, the appearance of ANCA (which can be drug-induced, eg, propylthiouracil [PTU]) and the slowly resolving neutropenia during hospitalization without specific treatment is very suggestive of a toxin. The demographic, diffuse skin ulcers, and hematologic and serologic profile is compatible with the recently described toxidrome related to levamisole adulteration of cocaine.

 A send-out study of a urine sample returned positive for levamisole. Based on purpuric skin lesions with a predilection for the ears, agranulocytosis, and skin biopsy revealing thrombotic vasculopathy, she was diagnosed with levamisole-adulterated cocaine exposure. One week after discharge, her lower extremity pain and ulcerations were significantly improved. Her absolute neutrophil count increased to 2820/mm³. Her urine toxicology screen was negative for cocaine.

DISCUSSION

Levamisole was initially developed in 1964 as an antihelminthic agent. Its incidentally discovered immunomodulatory effects led to trials for the treatment of chronic infections, inflammatory bowel disease, rheumatic diseases,¹ and nephrotic syndrome in children.² By 1990, 3 major studies supported levamisole as an adjunctive therapy in melanoma³ and colon cancer.⁴

Although levamisole appeared to be nontoxic at single or low doses, long-term use in clinical trials demonstrated that 2.5%-13% of patients developed life-threatening agranulocytosis, and up to 10% of those instances resulted in death.⁵ A distinctive cutaneous pseudovasculitis was noted in children on therapeutic levamisole. They presented with purpura that had a predilection for the ears, cheeks, and thighs,⁶ and positive serologic markers for ANCA and antiphospholipid antibodies. Skin biopsies of the purpuric lesions revealed leukocytoclastic vasculitis, thrombotic vasculitis, and/or vascular occlusions.

Levamisole was withdrawn from the market in 2000 in the United States due to its side effects,⁷ but quickly found its way onto the black market. It was first detected in cocaine in 2002, and the percentage of cocaine containing levamisole has steadily been increasing since then. In July 2009, over 70% of cocaine seized by the Drug Enforcement Administration was found to contain levamisole.⁸ It is unclear exactly why this drug is used as an adulterant in cocaine. Theories include potentiation of the euphoric effects of cocaine, serving as a bulking agent, or functioning as a chemical signature to track distribution.⁹

The resurgence of levamisole has brought a new face to a problem seen over a decade ago. Current reports of levamisole toxicity describe adults presenting with purpura preferentially involving the ears, neutropenia, positive ANCA, and positive antiphospholipid antibodies.¹⁰⁻¹² Since 2002, there have been at least 20 confirmed cases of agranulocytosis and two deaths associated with levamisole-adulterated cocaine.^{8,13,14} In September 2009, the Department of Health and Human Services issued a public health alert warning of an impending increase in levamisole-related illness.

Levamisole is not detected on routine toxicology screens, but can be tested for using gas chromatography and mass spectrometry. Most laboratories do not offer testing for levamisole and send-out testing is required. Given its half-life of 5.6 hours, levamisole can only be detected in the blood within 24 hours, and in the urine within 48-72 hours of exposure.^{15,16} Urine samples are preferred over blood samples, since blood levels decline more rapidly and have lower sensitivity. Cocaine can also be sent out to local or state forensics laboratories to be tested for levamisole. The only definitive treatment for levamisole-induced cutaneous pseudovasculitis and neutropenia is cessation of toxin exposure.

Although the discussant had familiarity with this toxidrome from local and published cases, he was only able to settle on levamisole toxicity after a series of competing hypotheses were ruled out on the basis of irreconcilable features (vasculitis and histology results; APLS and neutropenia; SLE and negative ANA with no visceral involvement) and by using analogical reasoning (eg, to infer the presence of a toxin on the basis of neutropenia [as seen with chemotherapy and other drugs] and ANCA induction [as seen

with PTU]). It was a laborious process of hypothesis testing, but one that ultimately allowed him to crack the case.

Key Teaching Points

1. In patients presenting with neutropenia and purpuric skin lesions—particularly with a predilection for the ears—consider levamisole-adulterated cocaine exposure.
2. Tests supporting this diagnosis include positive serologies for ANCA and antiphospholipid antibodies, and skin biopsies that show leukocytoclastic vasculitis, thrombotic vasculitis, or vascular occlusion. Urine studies for levamisole are definitive if sent within 48 to 72 hours of exposure.

This case was presented by the authors (J.W., P.P.K.) at the Society of Hospital Medicine Annual Meeting in April 2010. This case was also described briefly (two paragraphs with images) in a research letter in the March 2010 issue of the *Journal of the American Academy of Dermatology* (reference 12).

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