The Imitation Game: Drug Reaction Presenting as Autoimmunity Presenting as Syphilis

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Introduction

Syphilis is a very common disease in the US and abroad, with a prevalence of 207,255 cases in the US alone in 2022, the highest rate since 1950, and an increase of 17.3% over the year before(1). 3,761 infants were born with congenital syphilis in 2022, with 231 related stillbirths and 51 deaths during infancy(2). Syphilis can cause a range of symptoms, including aortic aneurysms, coronary stenosis, movement disorders, dementia, paralysis, and fetal malformation or loss(3). As a result, both the Centers for Disease Control and the United States Preventive Services Taskforce recommend broad screening of both women and men. Although little data is available regarding the number of tests administered annually, in just 81 public health laboratories, over 1.2 million *Treponema* tests were processed, typically a mix of Rapid Plasma Reagin (RPR), Venereal Disease Research Laboratory (VDRL), particle agglutination, or enzyme immunoassay(5). Of these, the RPR and VDRL are most frequently used in screening and target patient antibodies to a combination of cardiolipin, lecithin, and cholesterol; the particle agglutination assay uses a different mechanism, but also responds to these antigens, which also comprise portions of human mitochondrial and cell membranes(6) and typically these false positives are seen at low dilutions(7).

Systemic lupus erythematous (SLE) is an autoimmune disease that can cause widespread dysfunction in affected individuals. Like other autoimmune diseases, there can be considerable variation in clinical manifestations. Common symptoms include arthritis/arthralgia, constitutional symptoms (fever, fatigue, and/or weight loss), and skin lesions. Additionally, SLE can lead to hematologic, renal, pulmonary, neurological, and cardiac complications. (8). Current estimates place the incidence of SLE in North America at approximately 23.2 cases per 100,000 people (9), more common in those of African, Hispanic, or Asian backgrounds (10). Diagnosis of SLE depends upon a combination of clinical findings and laboratory testing. Specific laboratory testing should begin with antinuclear antibody (ANA) as a negative ANA is incompatible with the diagnosis of SLE. If positive the patient should subsequently be tested for anti-double stranded DNA (anti-dsDNA), anti-SSA/SSB, anti-Smith, anti-ribonucleoprotein (anti-RNP), and antiphospholipid (8).

Antiphospholipid syndrome is an autoimmune disease characterized by the formation of antiphospholipid antibodies, such as lupus anticoagulant and anticardiolipin. This disease commonly manifests in patients who have SLE, with up to approximately one third of SLE patients also having antiphospholipid syndrome (11,12). Patients with antiphospholipid syndrome are at high risk for clotting and are at increased risk for spontaneous abortions. False positives on syphilis testing attributable to anticardiolipin antibodies have been characterized for over 80 years (13). A less common manifestation of antiphospholipid syndrome is livedo reticularis, which is a net-like pattern of reddish-blue discoloration, mostly in the extremities (14).

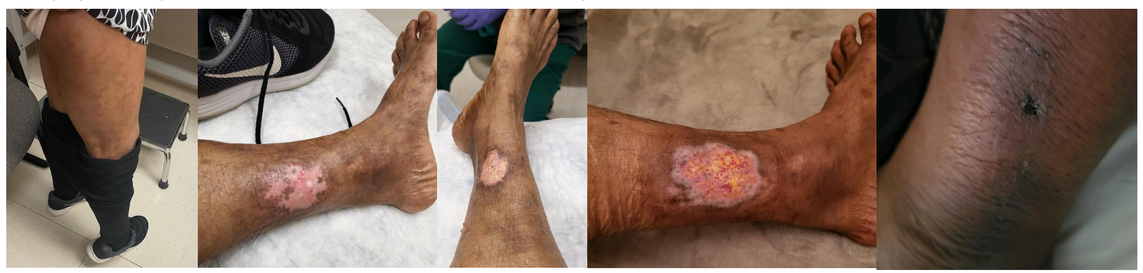
Leukocytoclastic vasculitis (LCV) is a term to describe the histopathologic findings in several small vessel vasculitides. Histopathologic evaluation of individuals with LCV demonstrates fragmentation of the neutrophil nucleus, fibrinoid necrosis, and an inflammatory infiltrate composed of neutrophils (15). In the United States the incidence of LCV has been estimated to be 4.5 per 100,000 person years (16). The known causes of LCV include infections, medications, malignancies, and systemic diseases (17). Examples of medications known to cause LCV include rituximab, tocilizumab, statins, tumor necrosis factor (TNF) inhibitors, immune checkpoint inhibitors (ICI), selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, antipsychotics, anticonvulsants, and anxiolytics (15-18). Systemic diseases associated with LCV include granulomatosis with polyangiitis, cryoglobulinemic vasculitis, Henoch-Schonlein purpura, systemic lupus erythematous, and rheumatoid arthritis (15).

Case Presentation

A 52-year-old woman was referred to the Rowan Infectious Disease service with a chief complaint of lower extremity biopsy-proven leukocytoclastic vasculitis with joint pain particularly in the ankles, swelling, and new ulcers accompanied by a syphilis titer of 1:8 on RPR. She denied sexual activity or use of antimicrobials within the last year and had no exposure to yaws, Lyme disease, malaria, or tuberculosis. Her comorbidities included obsessive-compulsive disorder and antiphospholipid syndrome. She was a prior smoker but has been a nonsmoker for over 10 years.

Her medication history included a short, subtherapeutic dose of 100mg of minocycline; and prednisone taper, naproxen 220 mg twice daily, famotidine 20 mg at night, ibuprofen 800 mg twice daily, Olmesartan-amlodipine-hydrochlorothiazide 40-5-25 mg daily, pentoxifylline 400mg twice daily, fluvoxamine maleate 100 mg twice daily, and albuterol HFA 108 as needed. Physical exam demonstrated a lace-like rash and narrowing on upper and lower extremities with ulceration and substantial edema. Further physical examination revealed the presence of oral candidiasis. Subsequent laboratory testing revealed the results in Table 1. Specific testing for syphilis was negative, despite the initially positive RPR screening. Testing for other sexually transmitted infections, including HIV and gonorrhea, was negative. Rheumatologic investigation was negative as all values, other than c-reactive protein (CRP) was negative. The dermatopathology report for the left pretibial region demonstrated a superficial and deep perivascular and interstitial infiltrate comprised mainly of neutrophils and neutrophilic nuclear “dust”. All vessels in the dermis and subcutaneous fat contain fibrin and plugs of erythrocytes. There is also epidermal necrosis and separation of the epidermis from the dermis. They further noted that the combination of patterns would lead them towards a differential of septic vasculitis, mixed cryoglobinemia, ANCA vasculitis, and a peculiar drug reaction. In the left thigh, the increased number of dilated venules in the upper part of the dermis was thought to represent livedo reticularis and post-inflammatory focal hyperpigmentation.

Her symptoms improved after discontinuation of fluvoxamine and prednisone initiation.



Laboratory Testing

Test	Patient	Normal
C-Reactive Protein (CRP)	3	<10
Erythrocyte Sedimentation Rate (ESR)	34	0-40
Antinuclear Antibody (ANA)	Negative	Negative
Rapid Plasma Reagin (RPR) Quantitative	1:8 titer	Nonreactive <1:1 titer
Treponema pallidum antibodies	Negative	Negative
Red Blood Cell (RBC) Count	3.80x10e6/uL	3.77-5.28x10e6/uL
White Blood Cell (WBC) Count	6.3x10e3/uL	3.4-10.8x10e3/uL
Hemoglobin (Hgb)	12.0 g/dL	11.1-15.9 g/dL
Hematocrit (Hct)	35.4%	34.0-46.6%
Anticardiolipin Ab, IgG	<10	<15
Anticardiolipin Ab, IgM	48	<13
Anticardiolipin Ab, IgA	<10	<12
Atypical pANCA	<1:20	<1:20
CCP IgG and IgA	<1 U	0-19U
Parvovirus B19 IgG	0.3	0.0-0.8 index
Parvovirus B19 IgM	0.2	0.0-0.8 index
Lyme IgG P93, P66, P58, P45, P41, P39, P30, P28, P23, P18, antibody	absent	absent
Lyme IgM P41, P39, P23 antibody	absent	absent

Discussion

Leukocytoclastic vasculitis has previously been reported in association with fluvoxamine as well as other SSRIs and may have incited a broader immune response to self antigens(8). It is possible that her antiphospholipid syndrome and leukocytoclastic vasculitis may have predisposed her to form autoantibodies against mitochondrial or cell membrane proteins such as cardiolipin, cholesterol, and lecithin. Little is known about the baseline prevalence of antiphospholipid syndrome, with various studies reporting widely different numbers, and patients are not routinely screened for this in the absence of symptomatic disease. In patients with no known exposure history to syphilis and an unexpected positive test result by non-treponemal screening tests, consider potential false positives from medications, adverse effects of medications, or underlying conditions. Future directions for research may include correlating the level of antiphospholipid syndrome-associated antibody anticardiolipin to the risk of falsely positive nontreponemal testing.

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