CLINICAL VIGNETTE

Blue Fingers: A Rare Cause of Vasculitis

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A 67-year-old female with previously treated Hepatitis C (HCV) and chronic lymphocytic leukemia (CLL), presented for rheumatologic evaluation of digital ischemia. She reported significant pain and ulceration of her fingertips and symptoms of triphasic color changes (white, blue and red) concerning for Raynaud's phenomenon and mild fixed ischemia affecting distal tips of her digits. She was previously admitted to a community hospital and treated with heparin and discharged on ribaroxaban, pentoxyfylline and pain medications. Her fingers continued to show signs of digital ischemia which worsened in cold temperature and was referred to rheumatology for evaluation.

She was diagnosed with CLL several years ago after routine labs showed leukocytosis with subsequent confirmation on bone marrow biopsy. She was asymptomatic under watchful monitoring for her CLL. She was successfully treated for Hepatitis C with ledipasvir/sofosbuvir in the past. She currently smokes two packs per day for many years and denied any family history of blood clots or connective tissue disease.

Initial presentation revealed a tearful patient in acute distress due to her digital pain. Vital signs were normal except for mild tachycardia. Cardiopulmonary and abdominal examinations were unremarkable. She was wearing latex gloves as she had covered her fingers in a zinc ointment to help soothe the pain. Her fingers were tender and noticeably violaceous with digital ulcers. Her radial pulses were intact. There was no edema of her lower extremities and her neurological examination was normal.

The patient was started on a calcium channel blocker, amlodipine. Given her presentation, Thromboangiitis Obliterans (Buerger's disease) was suspected and smoking cessation was strongly encouraged. On her return visit, the patient reported tolerating amlodipine, but no improvement in symptoms. She had developed multiple palpable, purpuric lesions and lower extremity edema. She also had new onset of difficulty walking and was dragging her right foot consistent with foot drop.

Her initial laboratory workup included normal comprehensive metabolic panel, complete blood counts and urinalysis. Her inflammation markers were only mildly elevated. Rheumatologic testing included negative ANA, dsDNA, centromere, SM, RNP, SSA/SSB, scleroderma- 70, anti -CCP, ANCA antibodies and negative antiphospholipid antibodies (Anti-Cardiolipin and Beta-2- Glycoprotein). Her lupus anticoagulant was positive but this was checked while on anticoagulation. Other significant findings included a positive Rheumatoid Factor at 234 (normal <25), low complements (C3, C4) and a positive cryocrit at 13%. Infectious testing included reactive Hepatitis C antibodies, Hepatitis B core antibody and Hepatitis B e antibody but negative Hepatitis B e antigen. Hepatitis B and C PCR were both negative. MTB Quantiferon gold and Cocci serologies were also negative.

Echocardiogram revealed normal ejection fraction, no valvular abnormalities and no patent foramen ovale. Arterial duplex ultrasound of the upper extremities did not reveal any occlusions or hemodynamically significant stenoses. Digit plethysmography of the fingers revealed dampened flow signals in the 2^{nd}, 3^{rd}, and 4^{th} fingers on the left hand with normal signals on the right. These results were suggestive of a vasospastic disorder. MR angiogram with contrast of the chest, abdomen, pelvis and lower extremities showed no evidence of vasculitis or stenosis.

The elevated cryocrit, hypocomplementemia, and elevated rheumatoid factor raised suspicion for Cryoglobulinemic Vasculitis. This was further supported by a skin biopsy which showed perivascular and interstitial dermatitis, lymphocyte-predominant with neutrophils and rare eosinophils. The foot drop was most likely related to mononeuritis multiplex but this was not further evaluated as there was enough evidence to diagnose a vasculitic process.

Though rare, it was felt that the patient had developed CLL-associated vasculitis. Her cryoglobulinemic vasculitis was thought to be less likely related to Hepatitis B or C as the viral loads were undetectable. The digital ischemia was further compounded by Raynaud's phenomenon which is also a complication of cryoglobulinemic vasculitis. Raynaud's phenomenon improved with lifestyle changes such as keeping core body temperature warm, smoking cessation and medical treatment with calcium channel blockers and phosphodiesterase inhibitors. The patient was treated with daily ibrutinib 420mg and weekly rituximab 375mg/m^2 4 weeks, followed by monthly treatment for 6 months according to CLL dosing guidelines. She was also started on daily tenofovir 300mg to prevent reactivation of HBV.

Discussion

Cryoglobulins are serum immunoglobulins that precipitate at temperatures less than 37°C and dissolve when rewarmed.[1] There are three different subtypes. Type 1 cryoglobulinemia is characterized by monoclonal immunoglobulins, IgM or IgG, and is associated with lymphoproliferative disorders.[1] Type 2 cryoglobulinemia is composed of immune complexes and results from the production of a monoclonal RF and is most commonly seen in HCV infection though is also seen in B- cell CLL, Non-Hodgkins lymphoma, and connective tissue disease.[1] Type 3 is also composed of immune complexes and consists of a polyclonal RF which is detectable at low levels in healthy individuals.[1] Cryoglobulinemic vasculitis results when these cryoglobulins precipitate in the small blood vessels of different tissues leading to inflammation, vascular occlusion and activation of the complement cascade.[1,2] Histologically, leukocytoclastic vasculitis with immune complex deposition is seen on immunofluorescence.[1]

Though the clinical course of cryoglobulinemic vasculitis is not severe in more than 50% of patients, life threatening disease may occur and must be treated promptly.[3] These cryoglobulins can cause ischemia, purpura and infarction and can affect many different organs such as the skin, joints, kidneys, and peripheral nervous system.[1] Cardiac and gastrointestinal manifestations, though rare, are associated with poor outcomes.[1,4] Cardiovascular involvement usually occurs along with severe involvement of other organ systems. Cardiac dysfunction with pulmonary edema is the main manifestation and may present with mild troponin elevation or subtle T wave or ST segment changes.[3] Cryoglobulinemic vasculitis may cause ischemic bowel disease, gastrointestinal hemorrhage, peritonitis, and acute lesions in the gallbladder.[3] Among the skin manifestations, cryoglobulinemia can lead to purpuric lesions, skin necrosis, ulcers, livedo reticularis, Raynaud's phenomenon, acrocyanosis and digital gangrene.[1]

CLL can trigger autoimmune phenomena. A rare complication of CLL is the production of cryoglobulins.[5] Due to the vast possible causes of cryoglobulinemia, there are no uniform treatment guidelines. Identifying the cause is very important, as treatment options primarily focus on treating the underlying disease or to provide immunosuppression if no underlying cause is identified. In patients with HCV associated cryoglobulinemic vasculitis treatment includes antiviral therapy. Unfortunately, for some patients this treatment may be contraindicated or may not allow for rapid control of the condition. Other treatment suppresses the viral-induced immune response with glucocorticoids, plasmapheresis, or immunosuppressant agents such as rituximab, cyclophosphamide or azathioprine.[6] Recent studies have shown that rituximab monotherapy to be a good option for patients with severe cryoglobulinemia vasculitis due to HCV.[6] In general, plasmapheresis is utilized for organ threatening disease or for patients who do not respond to immunosuppressant treatment.

Our patient underwent treatment for CLL which lead to complete resolution of her weakness, palpable purpura and her digital ischemia. She remains in remission on Ibrutinib. This case highlights the importance of considering cryoglobulinemic vasculitis as the cause of digital ischemia and understanding the etiology of the vasculitis. Targeting the underlying cause resulted in successful response.

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