CLINICAL VIGNETTE

Neuropathy and Digital Ischemia in a Patient with Hepatitis C

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Case

A 57-year-old female was admitted from the emergency department for severe pain and burning in her bilateral hands and feet. She had presented to several hospitals over the past month with similar bilateral burning and tingling leg pain which began 8 months prior. More recently her symptoms escalated and she began to experience left foot weakness requiring her to have a high-stepping gait to avoid tripping. She also reported intermittent discoloration, pain, and stiffness of her right index finger and left thumb that improved with use. Past medical history notable for HIV on antiretroviral therapy (abacavir-dolutegravir-lamivudine), treatment-naïve HCV, alcohol use disorder, and heart failure with recovered ejection fraction.

Further questioning revealed new bilateral lower extremity swelling that had developed over the past month, as well as generalized upper and lower extremity weakness. The patient also acknowledged poor compliance with her HIV medications over the previous 6 months. Extended review of systems was otherwise negative. She denied chest pain, shortness of breath, dyspnea on exertion, orthopnea, photophobia, vision changes, rash, fever, chills, nausea, vomiting, or changes in weight. Family history was negative for arthritis, cancer, or autoimmune disease.

On admission, the patient was hemodynamically stable normal vital signs. She appeared chronically ill and her physical exam was notable for a left sided foot drop and an inability to extend her left great toe. In her upper extremities, there was duskiness of the right index finger and left thumb without ulcerations, as well as swelling of her right wrist and 2nd and 3rd metacarpophalangeal joints. No additional rashes or skin lesions were noted. Laboratory testing on admission included a white blood cell count of 12.3/µL, hemoglobin 9.4 g/dL, platelets 1,181,000/µL, and sodium 129 mmol/L. Inflammatory markers were elevated with ESR > 130 and CRP 7. Viral studies were notable for Hepatitis C RNA quantitative PCR of 478,306 IU/mL and HIV RNA quantitative PCR of 62 copies/mL. Her CK, hepatic panel, and urine studies were negative, and SPEP was without any monoclonal proteins. Chest X-ray and X-rays of her bilateral wrists and hands showed no significant osseus abnormalities.

The patient's constellation of symptoms was consistent with a peripheral neuropathy, and an extensive evaluation was performed for neurologic, autoimmune, hematologic, and nutritional etiologies including consultations from rheumatology, hematology-oncology, and neurology. MRI of the brain, cervical spine, and lumbar spine was normal. Testing for myeloproliferative neoplasm was negative, and her thrombocytosis was felt to be reactive. SPEP, UPEP, and serum and urine free light chains were within normal limits. Broad autoimmune testing, including ANA with subserologies, rheumatoid factor, CCP, ANCA, complements, cryocrit, and antiphospholipid antibodies was notable for a rheumatoid factor of 14 IU/mL, elevated cryocrit of 3%, and low C4 at 6 mg/dL.

Due to her ongoing neuropathic symptoms, left foot drop, progressive digital ischemic skin findings, and elevated cryocrit with low complements, the diagnosis of cryoglobulinemic vasculitis secondary to her underlying HCV infection was confirmed. She was started on sofosbuvir/velpatasvir for her HCV in addition to pulse dose steroids. However, despite antiviral and steroid therapy, her digital ulceration rapidly worsened leading to necrosis of her affected digits. She also developed proteinuria, raising concern for renal vasculitis. Five days of plasmapheresis was started, followed by rituximab infusion. Her symptoms improved and she was discharged to continue with outpatient rituximab infusions.

Discussion

Cryoglobulinemic vasculitis, or cryoglobulinemia syndrome, is an inflammatory syndrome precipitated by cryoglobulin-containing immune complexes leading to inflammation of small and medium-sized vessels. Cryoglobulinemia syndrome typically occurs secondary to an underlying infectious, autoimmune, or lymphoproliferative disorder. It is most commonly associated with hepatitis C virus (HCV) infection, however can also be due to chronic infections including hepatitis B, HIV, Cytomegalovirus, and Epstein Barr virus, autoimmune conditions (systemic lupus erythematosus and Sjogren syndrome), as well lymphoproliferative disorders such as monoclonal gammopathies, chronic lymphocytic leukemia, and Non-Hodgkin lymphoma.[1] Cryoglobulinemic vasculitis should be considered in patients who present with peripheral neuropathy, arthralgias, and skin manifestations such as purpura or skin ulcers. The Brouet classification is based on the type of immunoglobulin that leads to cryoprecipitation. Type I cryoglobulins are monoclonal immunoglobulins, whereas Type II and III are mixed cryoglobulins.[2] These classifications aid in diagnosis and often correlate with clinical manifestations and pathogenicity.

Type I cryoglobulins result in hyperviscosity due to an underlying lymphoproliferative disorder and may produce symptoms related to vascular occlusion within small vessels. These include cutaneous symptoms such as Raynaud's phenomenon, digital ischemia, and skin necrosis.[3] These manifestations most often occur at temperatures below 37°C. Additional less common extracutaneous manifestations, include renal involvement, neuropathy, and arthralgias. Type II and III cryoglobulins, or mixed cryoglobulinemia, generally result from chronic viral infections or connective tissue diseases.[4,5] The manifestations are often nonspecific, and include cutaneous findings in addition to arthralgias, weakness, fatigue, and neurologic symptoms such as sensory or sensorimotor polyneuropathy.[6] Renal involvement with membranoproliferative glomerulonephritis is also commonly observed and portends a poorer prognosis.[1]

Given the broad range of clinical presentations associated with cryoglobulinemic vasculitis, diagnosis requires a high index of suspicion and consideration of clinical, laboratory, and pathologic data. While there are no formal diagnostic criteria, presence of cryocrit with low C4 is the most prominent finding suggestive of cryoglobulinemia.[7] Some labs will further delineate cryoglobulin concentration and components, which can assist in distinguishing between subtypes. For example, the monoclonal component in type II cryoglobulinemia is most commonly IgM kappa, and frequently has positive rheumatoid factor activity. Cryocrit over 0.5-1% is considered clinically significant. Individuals without cryoglobulinemia have undetectable levels.[7] The cryocrit in affected patients can approach 50% in type I disease, whereas it is generally 2-7% in type II and 1-3% in type III disease. These percentages do not always correlate with symptoms and severity of disease.[8] Additional testing should include urinalysis and metabolic panels to assess for renal involvement, viral serologies, acute phase reactants, complement levels, and autoantibody serologies. Diminished serum complement levels, may reflect ongoing consumption by cryoglobulin immune complexes, and in conjunction with an elevated rheumatoid factor, is particularly prevalent in type II cryoglobulinemia.[9] Biopsies of affected organs can provide histologic evidence of disease but are not required for diagnostic purposes. Similarly, bone marrow biopsy, electromyography, and imaging may be indicated depending on the clinical context.

Initial treatment of cryoglobulinemia is directed against the underlying etiology to reduce circulating immune complex-mediated damage.[1] For patients with underlying lymphoproliferative or autoimmune disorders, disease-specific therapy should be initiated. Similarly, patients with chronic HCV should receive antiviral therapy. Further treatment is typically guided by severity of disease. For mild disease, with manifestations such as rash without necrotizing lesions, mild neuropathy, or arthralgias, treatment is primarily symptomatic and immunosuppression is typically not required. In moderate to severe disease, including glomerulonephritis, digital ischemia, progressive neuropathy, or life-threatening manifestations such as pulmonary hemorrhage or neurocognitive involvement, immunosuppression therapy is initiated. Immunosuppressive regimens include high-dose steroids and plasmapheresis in combination with rituximab or cyclophosphamide.[10]

This patient demonstrates many of the classic epidemiologic, clinical, and laboratory findings of severe cryoglobulinemic vasculitis. In addition, it exemplifies the importance of a thorough history and physical exam to obtain an accurate diagnosis and initiate appropriate treatment promptly.

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