CLINICAL VIGNETTE

Peripheral Neuropathy, Digit Gangrene and a Rash

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Case Report

A 60-year-old woman with idiopathic peripheral neuropathy presented with painful discoloration of her upper extremity digits and left great toe for one month (Figures 1 and 2). She described the pain as a sharp and throbbing sensation, which was new and differed from her baseline painful peripheral neuropathy. Additionally, she reported cold-induced pruritic rashes on her legs, trunk and buttocks (Figure 3) as well as cold-induced whitish discoloration of her hands. She also noted weight loss and hair loss over the past 6 months.

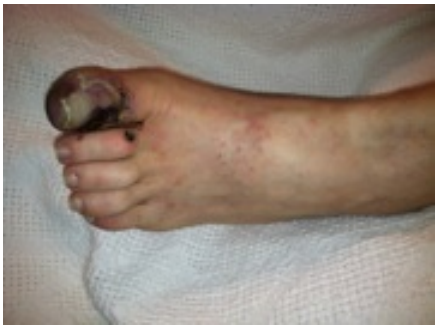

Figure 1. Areas of erythematous maculopapular blanching rash over dorsum of foot with dry gangrene of the left great toe.

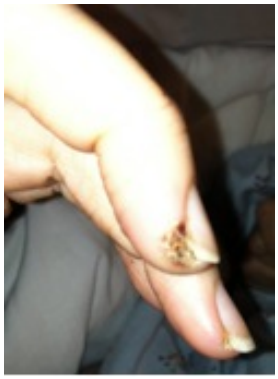

Figure 2. Dry gangrene of the left middle finger.

She was taking no regular medications and doesn't use tobacco or drink alcohol. She does extensively use herbal supplements. Physical examination was remarkable for blanching reticular erythema over the dorsal aspect of both feet extending to mid calf. Erythematous, non-blanching, confluent papules also covered her inner thighs, back and buttocks. In addition, the distal phalange of her left first toe was necrotic. The distal tips of her left third finger and right second fingers were also necrotic, consistent with dry gangrene. Neurological exam revealed a lower extremity distal sensory neuropathy.

Significant laboratory findings included elevated inflammatory markers: C-reactive protein 2.1 mg/dL; erythrocytes sedimentation rate 51 mm/hr; ferritin 230 ng/mL. Antinuclear antibody (ANA), double-stranded DNA, SM, RNP, SSA/SSB and rheumatoid factor were negative, as well as Antineutrophil cytoplasmic antibody (ANCA), proteinase 3 and myeloperoxidase. Complement levels were within normal limits and Cryoglobulins and serology for human immunodeficiency virus and hepatitis A-E were negative. Renal function was normal except for persistent mild proteinuria. Abdominal and lower extremity computed tomography revealed numerous non-enhancing hypodensities throughout the liver (Figure 4) and occlusion of the left anterior tibial artery at the level of the mid calf. Ultrasound guided liver biopsy reveals necrotizing granulomatous inflammation. Dermal punch biopsy of the confluent papules reveals leukocytoclastic vasculitis. Nerve conduction studies reveals a sensorimotor polyneuropathy affecting her left peroneal and sural nerves.

Final Diagnosis: Polyarteritis nodosa (PAN) versus ANCA-negative vasculitis.

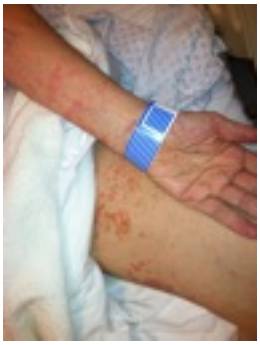

Figure 3. Areas of erythematous non-blanching, confluent papules overlying inner thighs and forearms.

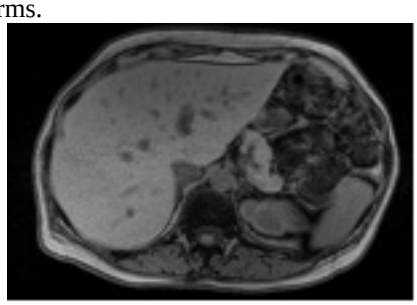

Figure 4. Ill-defined subcentimeter foci of hypoenhance-ment in posterior lobe of liver

Discussion

PAN is a systemic necrotizing vasculitis that typically affects medium-sized muscular arteries, which may lead to diffuse organ involvement. However, variants of PAN include single-organ disease and cutaneous-only PAN[1]. This patient has systemic PAN given her diffuse liver, nerve and skin involvement. Most cases are idiopathic, however secondary PAN can result from hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, and hairy cell leukemia[1].

Our patient presented with systemic symptoms of weight loss and signs of neurologic dysfunction, skin and vascular involvement. She was diagnosed with a sensorimotor neuropathy of unknown etiology two years prior to presentation, which is common in PAN and occurs in up to 70 percent of patients[1].

Skin findings of PAN are multiple and may include tender erythematous nodules, purpura, livedo reticularis, ulcers, and bullous or vesicular eruptions[2]. Our patient had recurrent, cold-induced, palpable and purpuric lesions overlying her bilateral lower extremities, buttocks and back which were biopsied, revealing leukocytoclastic vasculitis of her postcapillary venules. Vascular involvement of her cutaneous lesions became progressively worsened resulting in infarction and gangrene of her fingers and toe. Digital and limb ischemia are possible manifestations of PAN and typically reflect involvement of larger than "medium-sized" vessels[2].

The kidneys are the most commonly involved organ in PAN causing glomerular ischemia with sub-nephrotic or minimal proteinuria[3], as with this patient.

Gastrointestinal involvement is also common in PAN and can produce intestinal angina. Segmental pancreatic infarction and necrotizing pancreatitis have rarely reported[4]. This patient developed necrotizing granulomatous hepatitis, which has not been reported in association with PAN.

The diagnosis of granulomatosis polyangiitis (GPA) was also considered given the association with necrotizing hepatic granulomas and the similar presentation to PAN with constitutional symptoms, cutaneous and nervous system manifestations[5]. ANCA negative vasculitidies also typically manifest with ear, nose, throat and pulmonary symptoms, which are atypical of PAN[5]. Our patient denied these symptoms. At least 10% of patients with GPA are ANCA negative[6]. All other routine laboratory and imaging tests are generally nonspecific in GPA as in PAN and are performed in order to exclude other potential etiologies or to ascertain the extent of the disease process in other organs. As in PAN, the diagnosis of GPA is confirmed by tissue biopsy, most commonly of the skin, kidney, or nares. Our patient did not have overt kidney disease or involvement of her nares. Open or thoracoscopic lung biopsy would have been the next step, however, the absence of granulomatous vasculitis on transbronchial speci-mens does not exclude the diagnosis.

Biopsy of her sural and peroneal nerves may have provided more conclusive evidence for a diagnosis of PAN vs. ANCA-negative vasculitis given active involvement at the site, however the patient declined. Because there is no difference in management between the two diagnoses, she was started on prednisone and discharged with rheumatology follow-up.

Conclusion

The case illustrates the difficulty in distinguishing between various vasculitidies. Tissue biopsies are the gold standard method, however, they do not always provide clarifying answers. Confirmatory biopsy may not be needed if the information would not change management. Because treatment for PAN and ANCA-negative GPA is identical, further invasive testing was not pursued.

The prognosis for treated PAN and treated GPA is similar with a five-year survival rate ranging between 80-90% of patients with either disease[7]. Clinical manifestations of both diseases are similar and in either disease survival is heavily influenced by the extent of organ involvement, which varies greatly from individual to individual. Despite overlap in

multiple organ systems, PAN generally has a predilection for the kidneys, GI tract and CNS whereas the major causes of death in GPA are secondary to renal and pulmonary failure[7]. Therefore, continued follow-up and assessment of organ system involvement may lead to future clarification. Furthermore, patients with ANCA negative vasculitides may eventually become ANCA positive later on the disease course, therefore repeated ANCA testing may also provide some insight. Unfortunately this patient has not returned for follow-up.

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Submitted on June 25, 2012