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RESEARCH ARTICLE

AN UNUSUAL CASE OF SMALL VESSEL VASCULITIC ULCER ASSOCIATED WITH CHRONIC INACTIVE HEPATITIS B INFECTION

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ABSTRACT

PAN is a systemic disease which can have different skin manifestations including tender erythematous nodules, purpura, livedo reticularis, ulcers, and bullous or vesicular eruption. Here we present a case of rapidly progressing skin ulcers in a 67 year old male with a past medical history significant for seizure disorder, hypothyroidism, and chronic inactive hepatitis B. He was admitted for right lower extremity cellulitis with necrotic ulceration. Surgical excisional debridement was performed at the bedside on the left leg. Post-debridement the patient started having fever spikes and was treated with intravenous ciprofloxacin. Cultures revealed growth of pseudomonas aeruginosa and beta hemolytic streptococcus group B from the right lower extremity. Venous studies revealed an old deep vein thrombosis in bilateral common femoral, femoral and popliteal veins. Rheumatological work up revealed elevated ESR levels of 104 mm/hr, high sensitivity CRP of >160.0 and positive ANA titers of 1:80 with speckled pattern. The probability of PAN became high in our differential given his history of chronic hepatitis B infection. A skin biopsy of the left ankle revealed acute and chronic inflammation along with perivascular neutrophilic inflammation, suggestive of leukocytoclastic vasculitis confirming the diagnosis of PAN. The patient was then started on prophylactic Tenofovir and steroids which led to significant improvement as evidenced by declining inflammatory parameters, rapidly healing ulcers and no further fever spikes. Antibiotics were slowly tapered off and the patient was discharged home on oral prednisone and Tenofovir. Hepatitis B infection regardless of activity status should prompt physicians to include PAN in the differential diagnosis of patients presenting with similar skin lesions along with signs of systemic inflammation. Timely initiation of steroids remains the gold standard therapy after prophylactic antiviral therapy is initiated in patient with chronic inactive status.

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INTRODUCTION

Polyarteritis nodosa (PAN) also known as pan-arteritis nodosa/periarteritis nodosa (Rapini, Ronald, 2007), is a systemic necrotizing vasculitis of small or medium-sized arteries, typically involving renal and visceral vessels but sparing the pulmonary circulation. It is shown to be associated with hepatitis B virus (HBV) Infection, hepatitis C virus infection, and hairy cell leukemia. With treatment, five-year survival isup to 80%; without treatment, five-year survival prognosis is very poor i.e. 13%. Death is often a consequence of kidney failure, myocardial infarction, or stroke (Volume, 2014). This disease can present with different skin manifestations such as tender erythematous nodules, purpura, livedo reticularis, ulcersand bullous or vesicular eruption.

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About 30% of people with PAN have chronic hepatitis B infection with vascular deposits containing Hepatitis B surface Antigen-antibody complexes, indicating an immune complex–mediated cause where as in the rest of the cases cause remains unknown. There is significant clinical and causal distinctions between classic idiopathic PAN, cutaneous forms of PAN and the PAN associated with chronic hepatitis (Kumar, 2015). Here we present a case of rapidly progressing skin ulcers in a patient with chronic inactive hepatitis B virus infection.

Case presentation

A 67 year old male with past medical history of chronic renal failure, hypothyroidism, seizures and chronic inactive Hepatitis B virus infection was admitted to Queens Hospital Center for right lower extremity cellulitis and necrotic ulcerations. He was started on ciprofloxacin and underwent wide surgical

excisional debridement. On the fourth day of hospitalization, his left leg which was initially found to have small superficial skin erosions over lateral malleolus, were noted to become very erythematous. This progressed to necrotic ulcers with purulent/serosanguinous drainage. Later the patient developed weakness of the distal left leg with a foot drop.Debridement was then performed andcultures revealed growth of pseudomonas aeruginosa and beta hemolytic streptococcus group B from the right lower extremity. Antibiotic treatment was continued in view of positive culture results. Rheumatologic workup revealed high levels of erythrocyte sedimentation rate (ESR) of 104 mm/hr (reference range < 15-20 mm/hr), high sensitivity C-reactive protein (CRP) of >160.0mg/L (reference range 5-10 mg/L) and positive anti-nuclear antibody (ANA) titers of 1:80 with speckled pattern.Anti-double stranded DNA (anti-dsDNA) test, Cryoglobulins levels, cytoplasmic anti-neutrophilic cytoplasmic antibody (c-ANCA) and perinuclear anti-neutrophilic cytoplasmic antibody (p-ANCA) levels were all negative. C3, C4 complement levels remained normal throughout course of the disease.

Table 1. Hepatitis B viral serology and interpretation

DISEASE PHASE	HBs Ag	Anti-HBs	HBeAg	Anti-HBe Ab*	Anti-HBc Ab*
Acute HBV	positive		positive		IgM*
Window				positive	IgM
Chronic HBV (high infectivity)	positive		positive		IgG*
Chronic HBV (low infectivity)	positive			positive	IgG
Recovery		positive		positive	IgG
Immunized		positive			

*IgM: Immunoglobulin M, IgG: Immunoglobulin G, Anti-HBe Ab: Anti Hepatitis B e-antigen antibody, Anti-HBc Ab: Anti Hepatitis B core antibody.

The liver enzymes were within normal limits. The patient was hypoalbuminemic with levels of 2.6 mg/dl (reference range 3.5-5.5 mg/dl). Hepatitis B serology revealed a positive hepatitis B surface antigen (HBsAg), negative hepatitis B surface antibody (HBsAb), negative hepatitis B e antigen (HBeAg), viral PCR of 41 IU/ml and a PCR log of 1.62 IU/ml.PAN became high on our differentialdue to his positive history of chronic hepatitis B virus infection. A CT angiogram could not be performed because of compromised renal function, and hence a skin biopsy of the left ankle was performed which revealed acute and chronic inflammation with perivascular neutrophilic inflammation, suggestive of leukocytoclastic vasculitis confirming a diagnosis of PAN. The patient was then started on prophylactic Tenofovir and steroids which led to significant improvement as evidenced by declining inflammatory parameters, rapidly healing ulcers and no further fever spikes. Antibiotics were slowly tapered off and the patient was discharged home on oral prednisone and Tenofovir which led to the complete resolution of the ulcers and resulted in undetectable viral loads.

DISCUSSION

Hepatitis is an inflammatory disease of hepatocytes resulting due to hepatitis virus infection. There are 5 different types for hepatitis viruses which are categorized as Hepatitis A-E viruses. The course of disease, presenting signs and symptoms, nuclear composition, routes of transmission, carrier status, incubation period, risk of developing malignancies and superinfections are specific for each type of Hepatitis virus. Hepatitis B virus (HBV) is DNA virus belonging to Hepadnavirus family of viruses. It can be transmitted via parenteral, sexual, maternal-fetal routes. HBV can be detected in all body fluids with the exception of stool. The incubation period ranges in months and can remain in latent phase as well. Hepatitis virus serology is very important in making the diagnosis about the status of hepatitis B virus infection as shown in the table below. Replication of Hepatitis B virus is very vital factor resulting in progression of the disease. The HBV replication results due to DNA polymerase enzyme in the nuclear material which has both DNA- and RNA- dependent activities. Upon entry into the nucleus, the polymerase functions to complete the partial dsDNA. The host RNA polymerase transcribes mRNA fromviral DNA to make viral proteins. The DNA polymerase then reverse transcribes viral RNA to DNA, which helps form new viral particles. HBVcan result in subacute, acute and chronic infections, though the prevalence of chronicity is much lower as compared to Hepatitis C virus (HCV).About one percent of HBV and HCV infected patients may develop PAN as an extrahepatic manifestation of liver disease (Mahr, 2004 and van Timmeren, 2014). PAN is a vasculitic disorder involving visceral and systemic blood vesselspresenting in subacute or chronic phase. These patients can develop features of PAN as early as six months post infection (Ebert, 2008). Thirty percent patients of PAN have HBV infection as their etiological factor whereas the rest are idiopathic (Mahr, 2004). In subacute (prodromal) phase HBV is also associated with serum sickness like syndrome presenting with signs and symptoms of fever, malaise, myalgia, joint pains, urticaria like rash, fatigue, lymphadenopathy and pruritus. Presenting features of PAN include fatigue, weight loss, weakness, fever, arthralgia, skin lesions, hypertension, renal insufficiency, neurologic dysfunction and abdominal pain (Lhote, 1998). The onset is gradual over weeks to months, and the initial symptoms are often nonspecific. The earliest clues that the patient has vasculitis come usually from the skin (where vasculitis may appear as palpable purpura, livedo reticularis, digital gangrene, or tender nodules), or the peripheral nervous system (where infarction of one mixed motor and sensory nerve after another results in mononeuritis multiplex, one of the most specific clues that a patient has vasculitis). Renal involvement eventually develops in most and is accompanied by hypertension in half of patients, whereas Wegener's granulomatosis rarely elevates the blood pressure. PAN also commonly involves the gut (abdominal angina, hemorrhage, perforation), heart (myocarditis, myocardial infarction), or eye (scleritis). Rupture of renal or mesenteric micoaneurysms can simulate an acute abdomen (https://www.hopkinsvasculitis.org/types-vasculitis/polyarteritis-nodosa/). Confirming the diagnosis requires either biopsy specimens showing small– or medium–sized arteries, or mesenteric arteriography showing microaneurysms or alternating areas of stenosis and dilation. Biopsy of a symptomatic nerve or a symptomatic muscle is 65% sensitive, whereas biopsy of an asymptomatic site is less than 30% sensitive. Because mesenteric angiography is 60%

sensitive, it should be done when there is not a symptomatic site to biopsy. Renal biopsy should be avoided unless angiography rules out microaneurysms susceptible to rupture (https://www.hopkinsvasculitis.org/types-vasculitis/ polyarteritis-nodosa/). Circulating immune complexes containing viral proteins deposit in vessel walls of visceral arteries and induce focal inflammation resulting in stenosis and microaneurysms (https://www.hopkinsvasculitis.org/types-vasculitis/ polyarteritis-nodosa/) Adequate biopsy specimens demonstrate necrotizing vasculitis within the walls of arteries, usually in the deep dermis or in the subcutaneous fat. In the absence of an obvious site for biopsy, angiography may reveal micro aneurysms of blood vessels in the renal, hepatic, or mesenteric circulation.

The American College of Rheumatology (ACR) has established criteria that should be fulfilled before diagnosis a case of PAN and a patient should have at least 3 of the 10 ACR criteria [8].

- Weight loss of > 4 kg since beginning of illness
- Livedo reticularis
- Testicular pain or tenderness
- Myalgias, weakness, or leg tenderness
- Mononeuropathy or polyneuropathy
- Development of hypertension
- Elevated BUN or creatinine unrelated to dehydration or obstruction
- Presence of hepatitis B surface antigen or antibody in serum
- Arteriogram demonstrating aneurysms or occlusions of the visceral arteries
- Biopsy of small or medium-sized artery containing granulocytes.

Our patient had more than 3 ACR (American College of Rheumatology) criteria for PAN: weight loss >4 kg, myalgia, weakness, leg tenderness, foot drop, diastolic pressure >90, hepatitis B virus, biopsy of the small vessel containing leukocytes. Without treatment, almost all affected patients die within 2 to 5 years. Treatment with prednisone (starting at 1 mg/kg daily) and cyclophosphamide (2 mg/kg daily) appeared to revolutionize the outcome of polyarteritis nodosa by achieving 70% 10–year survivals and established this combination of agents as the standard therapy. However, newer studies suggest that prednisone alone may achieve the same high survival as prednisone and cyclophosphamide, although flares were less frequent in patients taking cyclophosphamide. Other studies indicate that the traditional therapy with prednisone and cyclophosphamide should be abandoned in patients with polyarteritis nodosa associated with hepatitis B. Patients treated with the traditional combination respond, but almost all survivors become chronic carriers of hepatitis B and may die later of cirrhosis or variceal bleeding. The newly proposed regimen consists of 2 weeks of prednisone to control the vasculitis, followed by plasmapheresis to remove immune complexes, and accompanied by antiviral therapy with lamivudine to rid the patient of the hepatitis B infection. The long–term value of anti–viral therapy for polyarteritis nodosa associated with hepatitis C is not established.

Conclusion

PAN should always be considered as a possible cause of skin ulcerations in chronic hepatitis-B infections. PAN as an independent entity may be missed in specialized clinics evaluating liver pathologies, due to its insidious onset, atypical clinical symptoms and multi-systemic manifestations. The knowledge of extrahepatic, renal and vascular manifestations of hepatitis B unrelated to liver disease should be considered by physicians at the time of diagnosis and management of patients with HBV. It is prudent for diagnosticians and physicians to be aware of this entity and its imaging features, which may help as pointers to its diagnosis (Shalini Thapar Laroia, 2016). Hepatitis B infection regardless of activity status should prompt physicians to include PAN in differential diagnosis of patients presenting with skin lesions along with signs of systemic inflammation. Timely initiation of steroids remains the gold standard therapy after prophylactic antiviral therapy initiated in patient with chronic inactive status.

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World J Clin Cases. 2016 Mar 16; 4(3): 94–98. Published online 2016 Mar 16. doi: 10.12998/wjcc.v4.i3.94PMCID: PMC479217Hypertension in the liver clinic - polyarteritis nodosa in a patient with hepatitis BShalini Thapar Laroia and Suman Lata

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