



Case report

Antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis in chronic Hepatitis B: Unraveling the immune puzzle - a rare case report with review of literature

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ABSTRACT

Background: Hepatitis B virus (HBV) infection affects millions worldwide, predominantly targeting the liver, leading to conditions like cirrhosis and hepatocellular cancer. However, HBV can also cause extrahepatic complications, including autoimmune-mediated vasculitis. Small vessel vasculitis, often associated with antineutrophil cytoplasmic antibodies (ANCA), can occur in chronic infections like HBV.

Case presentation: A 46-year-old man with chronic hepatitis B presented with high fever, diarrhoea, and painful black discoloration on his nose, fingers, and toes. Lab results revealed anaemia, leukocytosis, elevated inflammatory markers, positive c-ANCA, and HBV PCR positivity. He was diagnosed with c-ANCA-associated small vessel vasculitis secondary to chronic hepatitis B. Treatment with methylprednisolone followed by tapering prednisolone and azathioprine led to significant improvement in his condition.

Conclusion: This case highlights the rare occurrence of c-ANCA-associated vasculitis in chronic HBV without typical liver symptoms. ANCA testing may aid in early diagnosis and management of such cases. Further research is needed to explore the underlying immunological mechanisms and refine therapeutic approaches.

Introduction

Globally, the most common cause of viral hepatitis and a significant factor in end-stage liver disease is the hepatitis B virus (HBV) [1]. Approximately thirty million people are newly infected with HBV each year globally, and a total of 296 million people are currently living with chronic HBV [2]. Autoantibodies, usually of the IgG subtype, known as antineutrophil cytoplasmic antibodies (ANCAs), are directed against lysosomal components and azurophilic granules found in the cytoplasm of neutrophils and monocytes. The incidence of ANCAs in the general population is thought to be minimal (less than 5%), making them sensitive and specific indicators of ANCA-associated vasculitis [3]. Here, We provide a case of a male patient in his middle age who was diagnosed with c-ANCA-associated small vessel vasculitis secondary to Hepatitis B. Our case involves a rare occurrence of chronic hepatitis associated with c-ANCA-associated vasculitis. It helps us better understand this rare occurrence and enables us to manage it timely.

Case presentation

A 46-year-old married man without any known medical conditions was admitted to Civil Hospital, Karachi, via emergency due to complaints of fever for nine days, loose stools, and blackish discoloration of the tip of the nose, fingers, and toes for eight days. Patient presented with a high-grade, abruptly onset fever that was recorded up to 104°F, intermittent and relieved by antipyretics, associated with rigours, chills, and loose stools. The loose stools had an acute onset eight days back. There were five or six episodes per day. Stools were watery and lacked any mucus, smell, or blood. There was no complaint of tenesmus. They were easily flushable and had no association with food intake or abdominal pain. Patient's malaria test was positive, for which he was prescribed antimalarials, after which his fever subsided. He then developed blackish discoloration of the tip of the nose, fingers, and toes. The onset of this discoloration was acute and painful. There was reddish discoloration initially, which later turned black and progressively involved the dorsum and soles of both feet. Patient denied any other

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symptoms. His past medical history was significant for hepatitis B, which was discovered upon routine testing ten years ago. He never consulted any doctor for this. Past surgical, transfusion, drug, and personal histories are insignificant.

The physical examination revealed a man with average build and height, a BP of 135/80 mmHg, a pulse rate of 90 bpm, a regular and average volume, a temperature of 98.6°F, and a respiratory rate of 18 breaths/min. He had anaemia, and blackish discoloration was visible on the tip of the nose, hands, and feet (Fig. 1. A, B, C). The peripheries were cold to the touch. His pulses were palpable except for the dorsalis pedis on both feet, which were feeble. The rest of the examination was insignificant. Baseline investigations revealed normocytic, normochromic anaemia with leukocytosis (Hb=10.4 mg/dL, MCV=98.5 fL, TLC=17). His ESR and CRP levels were elevated at 80 mm/hr and 23 mg/L (normal ESR= <20 mm/hr, CRP= <10 mg/L), respectively. His serum calcium levels were slightly decreased at 8.3 mg/dL (8.5–10.3 mg/dL). The rest of the biochemistry analyses were normal. His LFTs revealed an elevated SGPT value of 106 U/L (7–56 U/L), decreased albumin of 3.0 g/dL (3.4–5.4 g/dL), and elevated globulin level of 4.2 g/dL (2.0–3.5 g/dL). His coagulation profile is normal. His Lipid profile showed a decreased HDL level of 16 mg/dL (40–60 mg/dL). His urine D/R was normal. His blood and urine cultures were negative for any growth. His abdominal ultrasound revealed no abnormalities. Doppler ultrasound of both upper limbs was normal. Doppler ultrasound of the left posterior tibial artery showed biphasic spectrum, normal peak systolic velocity, and bilateral dorsal pedis, and the right posterior tibial arteries showed monophasic spectrum and normal peak systolic velocities. His transthoracic echocardiography didn't reveal any abnormalities. He tested positive for ANA with an antibody titer of 1:240. His ENA profile was negative, and his anti-dsDNA was normal. His serum c-ANCA came out to be positive at 9.56. His serum ACE and IgE levels were not elevated. His LDH levels were 397 U/L (140–280 U/L), and uric acid levels were 2.0 mg/dL (3.5–7.2 mg/dL). His HbA1c was normal at 5.3 %, TSH was at 2.58 mIU/L (0.5–5.0 mIU/L), and anti-CCP was negative (6.6 EU/mL, negative at <20 EU/mL). All the viral markers were negative except for hepatitis B PCR, which was positive and revealed a quantity of 3040 IU/mL. Hepatitis D PCR was negative. His endoscopy revealed diffuse candidiasis and mild pancreatitis. Fibroscan showed normal-mild fibrosis (F1) with a mean metavir score of 7.0 kPa.

After extensive testing and multiple opinions from different

departments (dermatology, nephrology), a diagnosis of C-ANCA-associated small vessel vasculitis secondary to Hepatitis B was made.

Treatment started with 1 g of Methylprednisolone for five days, followed by a low dose of 40 mg/day divided dose of prednisolone, which was tapered off gradually. Patient's lesions improved with this therapy. After tapering off steroids, 50 mg of azathioprine 2–4 mg/kg was added.

Discussion

Hepatitis B virus (HBV) infection exhibits varied clinical manifestations, influenced by factors such as the patient's age, immune response during infection, and the timing of disease detection. Chronic HBV infection is notably prevalent worldwide, with an estimated 360 million individuals persistently infected. Tragically, HBV-related liver diseases, including hepatocellular carcinoma, claim approximately 600,000 lives annually [4]. hepatitis B virus (HBV) infection has complex clinical implications that remain unclear, particularly regarding its role in autoimmune-mediated vasculitis. Vasculitis is the most severe but uncommon extrahepatic manifestation of HBV infection. Vasculitis associated with HBV infection are Polyarteritis nodosa, Cryoglobulinemic Vasculitis, and Leukocytoclastic Vasculitis [5]. Polyarteritis nodosa (PAN) is the most dramatic manifestation of primary HBV infection [6]. General symptoms of PAN include fever, weakness, fatigue, reduced appetite, and weight loss. Skin manifestations can vary from palpable purpura to nodules and red rashes. Multiple studies have reported that patients treated with interferon have experienced clinical improvement and remission of PAN [7].

However, our case presented cANCA associated with vasculitis secondary to hepatitis B as the initial manifestation of chronic HBV infection. The presence of the cANCA is a significant diagnostic marker for many small-vessel vasculitis, including granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis. These conditions are commonly grouped under "antineutrophil cytoplasmic antibody-associated vasculitis" (AAV) [8]. HBV is notably linked with PAN and, to a lesser extent, cryoglobulinemic vasculitis. There are cases where HBV triggers antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), affecting blood vessel health in diverse ways. Still, the exact pathophysiological mechanisms underlying these associations remain a subject of ongoing research [5]. Only three cases have been reported in the literature to date. (Table 1).

According to Turan et al., there is a notable prevalence of ANCA in Patients diagnosed with Chronic hepatitis B(CHB). Therefore, Patients diagnosed with CHB should undergo evaluation, focusing on C-ANCA and PR3-ANCA, especially when presenting with vasculitis symptoms and lesions. The relationship between ANCA and vasculitis or other immune-related conditions in CHB patients remains controversial. Additionally, it's crucial to ascertain whether HBV induces ANCA production independently or if some underlying immune-related symptoms mimicking vasculitis are present [9].

Management of patients these patients presents a unique challenge; however, these patients have shown positive responses to steroid therapy; however, for patients with coexisting conditions, steroids should be administered alongside antiviral therapy to decrease immune complex reaction and viral load, respectively [10].

Conclusion

In conclusion, the case presents the unusual relationship between HBV infection and autoimmune-mediated C-ANCA-associated small vessels as an initial presentation of chronic HBV infection. This rare association highlights the importance of considering vasculitis in the differential diagnosis of patients with HBV, even in the absence of liver-related symptoms. The presence of cANCA in such cases prompts further investigation into the immunological mechanisms underlying HBV-



Fig. 1. discolouration of nose(A), discolouration of fingers (B), discolouration of feet (C).

Table 1
Summary of cases reported.

S. No	STUDY	YEAR	AGE/SEX	CLINICAL FEATURES	INVESTIGATIONS	MANAGEMENT	PROGNOSIS
1	Meng et al. [11]	2021	77-year-old male	Weakness in both extremities accompanied by numbness and weight loss, examination revealed foot drop and a dull, purplish, lacy pigmentation the legs and hands	Serum creatinine (mg/dL): 2.1 ESR: 75 Hepatitis B core IgG: Positive P-ANCA: Positive	Solumedrol 1 g was given over the course of 3 days, proceeded with oral steroids, cyclophosphamide, and entecavir.	Good, no relapse till 6 months.
2	Joshi et al. [12]	2017	33-year-old male	Headache, body swelling, weakness in legs, and back pain.	HBsAg: Positive Anti-HBc: Positive 24-h urinary total protein: 3.9 g/day C-ANCA: positive CT suggested SAH MRI suggested Transverse myelitis	Oral entecavir, 1 g IV methylprednisolone was administered for the duration of 3 days, continued with brief course of oral prednisolone	At the 3-month follow-up, sensory symptoms had improved, but there was no change in motor function
3	Singh et al. [13]	2016	60-year-old male	Dark discoloration of the hands and both lower limbs	HBsAg: Positive Anti Hbc antibody: Raised Biopsy from skin lesions: leucocytoclastic vasculitis	0.5 mg/day oral Entacavir with 30 mg/day oral Prednisolone	Good, no symptoms after 6 months

associated vasculitis, suggesting a potential role for ANCA testing in CHB patients presenting with vasculitis symptoms. Continued research is essential for better understanding this complex association's mechanisms and management strategies.

CRedit authorship contribution statement

Javed Iqbal: Resources, Funding acquisition. **Dr. Suresh Bhagoowani:** Supervision, Investigation, Conceptualization. **Aqsa Munir:** Writing – review & editing, Writing – original draft, Conceptualization. **Dr. Uooja Devi:** Supervision, Investigation, Conceptualization. **Ummulkiram Hasnain:** Writing – review & editing, Writing – original draft.

Ethical approval

Not applicable because we have hid patient's identity.

Informed consent

Informed consent was taken from patient for the publication of this case.

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Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used Grammarly and Quilbot in order to improve language. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Declaration of Competing Interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

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