Title: Antineutrophil Cytoplasmic Antibodies (ANCA)-Associated Vasculitis In Chronic Hepatitis B: Unraveling The Immune Puzzle" A Rare Case Report With Review Of Literature

Suresh Bhagoowani[1], Uooja Devi[2], Aqsa Munir[2], Ummulkiram Hasnain[2], and Javed Iqbal[3]

[1]Dr Ruth KM Pfau Civil Hospital Karachi
[2]Dow Medical College
[3]Hamad Medical Corporation

September 04, 2024

Title: Antineutrophil cytoplasmic antibodies (ANCA)-Associated Vasculitis in Chronic Hepatitis B: Unraveling the Immune Puzzle" A RARE CASE REPORT WITH REVIEW OF LITERATURE

Key clinical message:

Vasculitis, though rare, is a serious extrahepatic manifestation of HBV infection.Chronic HBV affects millions of people globally, causing significant morbidity and 600,000 deaths annually. HBV patients should be considered for evaluation of vasculitis, even if they lack liver symptoms. Steroid therapy has been found effective for vasculitis in HBV patients and is more beneficial when combined with antiviral treatment.

Keywords:

Hepatitis B, Small vessel vasculitis, C-ANCA, Chronic infection

1.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.

2.CASE PRESENTATION:

2.1 Case history/examination

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 discolouration of the tip of the nose, fingers and toes for eight days. The 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. The stools were watery and lacked any mucus, smell or blood. There was no complaint of tenesmus. The stools were easily flushable and had no association with food intake or abdominal pain. The patient's malaria test was positive, for which he was prescribed antimalarials, after which his fever subsided. He then developed blackish discolouration of the tip of the nose, fingers and toes. The onset of this discolouration was acute and painful. There was reddish discolouration initially, which later turned black and progressively involved the dorsum and soles of both feet. The patient denied any other 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 discolouration 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.

2.2 Method (Differential diagnosis, investigation, and treatment)

Baseline investigations revealed normocytic, normochromic anaemia with leukocytosis (Hb=10.4mg/dL, MCV=98.5fL, 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 8.3mg/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 titre 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 1g of Methylprednisolone for five days, followed by a low dose of 40 mg/day divided dose of prednisolone, which was tapered off gradually. The patient's lesions improved with this therapy. After tapering off steroids, 50 mg of azathioprine 2-4 mg/kg was added.

3.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 which remain unclear, particularly regarding its role in autoimmune-mediated vasculitis. Vasculitis is the most severe but uncommon extra-hepatic 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]

4.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-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.

REFERENCES:

1. WHO Hepatitis B. Available online: https://www.who.int/news-room/fact-sheets/detail/hepatitis-b
2. World Health Organization. Global hepatitis report 2017. World Health Organization; 2017.
3. Merkel PA, Polisson RP, Chang Y, Skates SJ, Niles JL. Prevalence of antineutrophil cytoplasmic antibodies in a large inception cohort of patients with connective tissue disease. Annals of Internal Medicine. 1997 Jun 1;126(11):866-73. DOI: 10.7326/0003-4819-126-11-199706010-00003
4. Ren Z, El Hasbani G, Jenkins CS, Chehab MR, Gummadi J. An Atypical Case of Hepatitis B-Associated Vasculitis. DOI/10.33590/emj/10300609
5. Singh H, Tanwar VS, Sukhija G, Kaur P, Govil N. Vasculitis as a presenting manifestation of chronic hepatitis B virus infection: a case report. Journal of Clinical and Diagnostic Research: JCDR. 2016 Feb;10(2):OD25. doi: 10.7860/JCDR/2016/17384.7304
6. Trépo C, Amiri M, Guillevin L. Extrahepatic manifestations of hepatitis B infection. Viral Hepatitis. 2013 Jul 26:154-62. PMCID: PMC3754772
7. Kappus MR, Sterling RK. Extrahepatic manifestations of acute hepatitis B virus infection. Gastroenterology & hepatology. 2013 Feb;9(2):123..PMID: 23983659

8. Zhang Q, Shi B, Zeng H. Antineutrophil cytoplasmic antibodies (ANCA)-positive patient with infective endocarditis and chronic hepatitis B virus: a case report and review of the literature. Journal of Medical Case Reports. 2020 Dec;14:1-8.. DOI: 10.1186/s13256-020-02373-1
9. Calhan T, Sahin A, Kahraman R, Altunoz ME, Ozbakır F, Ozdil K, Sokmen HM. Antineutrophil cytoplasmic antibody frequency in chronic hepatitis B patients. Disease Markers. 2014;2014(1):982150. DOI: 10.1155/2014/982150
10. Bonkovsky HL, Liang TJ, Hasegawa K, Banner B. Chronic leukocytoclastic vasculitis complicating HBV infection. Possible role of mutant forms of HBV in pathogenesis and persistence of disease. Journal of clinical gastroenterology. 1995 Jul 1;21(1):42-7. DOI: 10.1097/00004836-199507000-00011
11. Meng Z, Cui W, Arend L, Mikdashi J. Hepatitis B virus infection associated with polyarteritis nodosa and microscopic polyangiitis. BMJ Case Reports CP. 2021 May 1;14(5):e240015.DOI: 10.1136/bcr-2020-240015
12. Joshi U, Subedi R, Gajurel BP. Hepatitis B virus induced cytoplasmic antineutrophil cytoplasmic antibody-mediated vasculitis causing subarachnoid hemorrhage, acute transverse myelitis, and nephropathy: a case report. Journal of Medical Case Reports. 2017 Dec;11:1-5. DOI: 10.1186/s13256-017-1255-x

TABLE 1 (SUMMARY OF CASES REPORTED):

S.No	STUDY	YEAR	AGE/SEX	CLINICAL FEATURES	INVESTIGATIONS	MANAGEMENT	PROGNOSIS
1	Meng et al.	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 gram was given over the course of 3 days, proceeded with oral steroids, cyclophosphamide, and entecavir.	Good, no relapse till 6 months.

S.No	STUDY	YEAR	AGE/SEX	CLINICAL FEATURES	INVESTIGATIONS	MANAGEMENT	PROGNOSIS
2	**Joshi et al.**	2017	33-year-old male	Headache,body swelling, weakness in legs,and back pain.	HBsAg: Positive Anti-HBe: Positive 24-hour urinary total protein: 3.9 g/day C-ANCA: positive CT suggested SAH MRI suggested Transverse myelitis	Oral entecavir, 1g IV methyl-prednisolone 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.**	2016	60-year-old male	Dark discoloration of the hands and both lower limbs	HBsAg: Positive Anti HBc antibody: Raised Biopsy from skin lesions: leucocyto-clastic vasculitis	0.5mg/day oral Entacavir with 30 mg/day oral Prednisolone	Good, no symptoms after 6 months

Keywords:

Hepatitis B, Small vessel vasculitis, C-ANCA, Chronic infection

Author Contribution:

Dr. Suresh Bhagoowani : Conceptualization; supervision; writing—original draft; writing—review and editing.

Dr. Uooja Devi : Writing—original draft; writing—review and editing. Aqsa Munir: Writing—original draft; writing—review and editing.

Ummulkiram Hasnain : Writing—original draft; writing—review and editing.

Javed Iqbal : writing—review and editing.

Acknowledgement: Open Access funding provided by the Qatar National Library.

Funding sources : This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

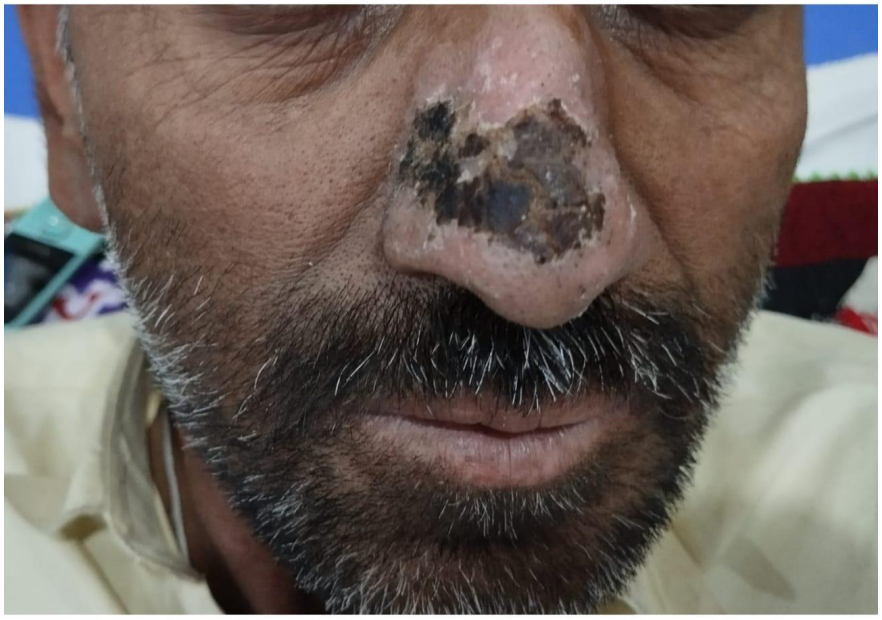
Ethics statement:

Ethical approval does not imply to case reports from institutional IRB.

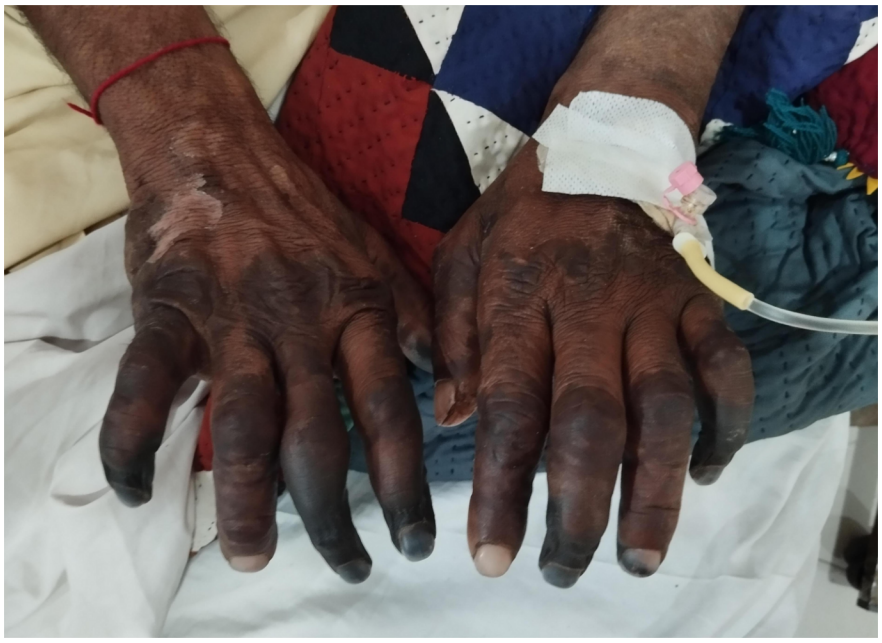
Informed consent: Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

Disclaimer : None

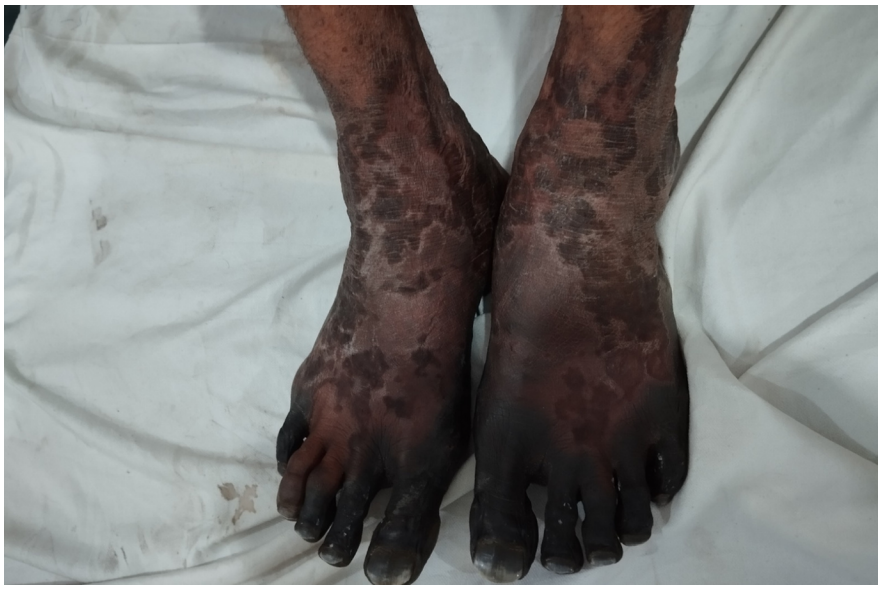
Conflicts of interest : None



A



B



C

Figure 1: discolouration of nose(A), discolouration of fingers (B), discolouration of feet (C)