CASE REPORT

Mononeuritis multiplex and painful ulcers as the initial manifestation of hepatitis B infection

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SUMMARY

Hepatitis B virus infection leads to multisystem manifestations owing to involvement of kidney, skin, vasculature, haematopoietic and nervous system. The hepatitis B infection can cause neuropathy either to vasculitis associated with polyarteritis nodosa or immune-mediated neural damage. In this submission, we report a young woman, who presented with mononeuritis multiplex and painful ulcerations as the first manifestation of chronic hepatitis B virus infection. The antiviral therapy along with steroids led to remarkable recovery. The clinical settings of hepatitis B virus infection should not be ignored in the presentation of mononeuritis multiplex with ulcers, although the commonest cause is leprosy in the Indian sub-continent.

BACKGROUND

The clinical manifestations of hepatitis B virus (HBV) are not just limited to liver disease. Extrahepatic manifestations like polyarteritis nodosa (PAN), glomerulonephritis, serum sickness, etc contribute to significant morbidity and mortality. Most of the extrahepatic manifestations are believed to be immune mediated.¹ In this case report we describe a young woman presenting with mononeuritis multiplex (MM) and painful ulcerations as the first manifestation of chronic HBV infection.

CASE PRESENTATION

A 24-year-old married woman presented with burning pain, tingling sensation and numbness in her left foot ascending up to the knee since 12 weeks. Within 20 days she developed similar tingling sensation and numbness in her right upper limb extending from elbow to hand. Over the period of next 1 month, she developed pinpricking sensation and numbness in her left foot extending up to the knee. She also had moderate-intensity burning pain in all her limbs which interfered with her sleep. Later on she developed painful ulcers over both feet (figure 1A,B). About a month later, she developed distal weakness in her left lower limb and right upper limb (difficulty in buttoning and unbuttoning, making morsels, besides slipping of footwear from her left foot without her knowledge). This was followed by similar weakness of right foot. However, there was no history of proximal weakness in any limb. No history of thickened nerve and hypoaesthetic patches. There was no history of bladder, bowel or cranial nerve involvement. She had a history of joint pain, stillbirth and photosensitive rash over cheeks. She had received blood transfusion 10 months back for anaemia. On

examination her higher mental functions and cranial nerves were found to be normal. On motor examination, hypotonia was noted in both her lower limbs. Power was Medical Research Council (MRC) grade 3/5 distally in both her upper limbs and MRC grade 2/5 power distally in her lower limbs. All deep tendon jerks were normal, except for the absence of bilateral ankle reflex. There was a sensory loss in the ulnar distribution of her left hand and in the lateral aspect of her left leg and in the dorsum and the sole of the foot. In her right lower limb sensory loss was on the lateral aspect of shin and dorsum of the foot. Joints, position and vibration sensations were impaired in both the upper and lower limbs. Other systemic examination was normal.

INVESTIGATIONS

Complete haemogram, fasting and postprandial blood sugars were normal. Liver, thyroid and renal function tests were normal. Vitamin B₁₂ level was 900 pg/ml (normal). Erythrocyte sedimentation rate was mildly elevated at 24 mm (Westergren method). C reactive protein was raised (18 mg/l). Virology screening showed surface antigen of the HBV ELISA positive, whereas HCV and HIV ELISA were negative. Further testing for HBV, hepatitis B e antigen was negative and HBV DNA titre was 1200 copies/ml. CT together with angiography of abdomen was normal. Nerve conduction studies showed absent bilateral sural, median and right ulnar sensory nerve action potentials and right median, bilateral common peroneal and tibial compound action potentials (CMAPs) are not recordable. Left median, bilateral ulnar CMAPs show reduced amplitude normal onset latencies and velocity suggestive of axonal sensorimotor polyneuropathy. Antinuclear antibodies were positive (1:100 titres). Double-stranded DNA was negative and perinuclear antineutrophil cytoplasmic antibodies (pANCA) were positive. Nerve biopsy was suggestive of vasculitic neuropathy (figure 2A–D).

DIFFERENTIAL DIAGNOSIS

TREATMENT

She was treated with pulse doses of 500 mg methylprednisolone (10 mg/kg) for consecutive 5 days followed by oral prednisolone 40 mg/day along with lamivudine 100 mg twice daily.

OUTCOME AND FOLLOW-UP

The pain and paraesthesia were the first symptoms to improve. This was followed by the recovery of power in the upper limbs within the next 4 weeks.

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Figure 1 (A) Photograph of foot showing ulcers on the both toes. (B) Photograph of feet on follow-up after 8 weeks showing healing of ulcer on the right toe.

On follow-up visit after 10 weeks she had partial recovery of bilateral foot drop and almost complete recovery of sensory loss. The ulcers have also started healing and no fresh lesions were seen.

DISCUSSION

MM is asymmetrical, asynchronous, usually painful involvement of at least two non-contiguous nerves leading to sensory and/or motor neuropathy. This type of neuropathy is seen in many conditions like leprosy, diabetes mellitus, connective tissue disorders (rheumatoid arthritis, systemic lupus erythematosus), sarcoidosis, primary systemic vasculitis, paraneoplastic syndromes, etc.^{1 2} Certain viruses like HBV and hepatitis C virus (HCV) have been found to be more often associated with conditions like PAN and cryoglobulinemia, respectively, which may clinically present as MM.

Vasculitis, that is, the inflammation of vasa nervosum or epineural arteries plays a central role in aetiopathogenesis of MM. The vascular damage leading to thrombosis and ischaemia along with the release of proinflammatory cytokines facilitates the neuropathy.³

Classical PAN is a rare systemic vasculitis that affects small- or medium-sized arteries of all organs and spares arterioles, capillaries or venules. Almost one-third cases are associated with HBV infection and approximately two-third cases develop neuropathy. The American College of Rheumatology recommends 3 out of 10 criteria to be present to diagnose PAN once the diagnosis of vasculitis is made (box 1).^{4 5} Our patient fulfilled 3 criteria out of 10 (HBV infection, MM, biopsy suggestive of vasculitis).

In HBV-related PAN, vasculitis is caused by direct vessel injury owing to replicating virus or immune complex deposition. The activation of complement cascade leads to inflammatory response and subsequent endothelial damage. Vasculitis usually occurs early in the disease course and may be the first presentation of HBV infection.⁶ The role of ANCA in the pathogenesis is still unclear.³ MM associated with chronic HBV infection has been reported in the absence of evidence of vasculitis both localised (on sural nerve biopsy) and systemic (no aneurysms on abdominal angiography). Sampling error, multifocal nature of disease and lack of visualisation of medium-sized vessels could be the causes for vasculitis negative biopsy. In this

Figure 2 (A, B) Microphotograph showing dense perineural and epineural chronic inflammation (H&E $\times 100$). (C, D) Microphotograph showing inflammatory exudate composed of chronic inflammatory cell infiltrate that comprises predominantly of lymphocytes (H&E $\times 400$).

Box 1 American College of Rheumatology criteria for classification of polyarteritis nodosa (PAN)

- ▶ Weight loss ≥ 4 kg
- ▶ Livedo reticularis
- ▶ Testicular pain or tenderness
- ▶ Myalgias, weakness or leg tenderness
- ▶ Mononeuropathy or polyneuropathy
- ▶ Diastolic blood pressure >90 mm Hg
- ▶ Elevated blood urea nitrogen or creatinine
- ▶ Hepatitis B virus
- ▶ Arteriographic abnormality
- ▶ Biopsy of small- or medium-sized artery containing polymorphonuclear neutrophils

report the authors have postulated high viral load as the probable cause of immune-mediated neuropathy which subsequently responded to steroids and oral lamivudine.⁷ However, sural nerve biopsy in our patient showed chronic inflammatory cell infiltrate comprising predominantly of lymphocytes.

Isolated cutaneous PAN (cPAN) is more commonly seen in women and has prolonged benign course. The skin histopathology is suggestive of leucocytoclastic vasculitis and is devoid of any systemic features of PAN. It is not associated with HBV or HCV infection and seldom have these patients developed systemic PAN. The ulcerative form of cPAN is often associated with neuropathy and has a prolonged clinical course. The intravenous steroids are used to achieve acute remissions.⁸ In one study, cPAN was retrospectively found to be associated with HCV infection and hence all patients of cPAN should be screened for hepatitis C infection.⁹

Owing to the high prevalence of leprosy in the Indian sub-continent, the possibility of leprosy neuritis cannot be overlooked in patients presenting with MM. The pure neuritic form of leprosy accounts for 4–8% of all cases of leprosy and presents nerve enlargement, tenderness, pain and sensory motor impairments. The diagnosis is aided by sensory nerve biopsy or fine needle aspiration.¹⁰

Most patients with HBV-associated PAN respond well to steroids plus antiviral plus plasmapheresis. This treatment is able to achieve remission in almost 81% patients and is even able to prevent further long-term complications arising from HBV infections.¹¹ The non-HBV-associated PAN can be treated with pulse doses of methylprednisolone 10 mg/kg or cyclophosphamide 15 mg/kg every 2 weeks for three times followed by 3–6 pulses every third week. This is followed by maintenance phase of 18–24 months with either prednisone (2 mg/kg) or azathioprine (7.5 mg/kg). The relapse rate in non-HBV PAN is higher than that of HBV-associated PAN.¹²

The prognosis of the patients with PAN can be assessed using a simple clinical score (five-factor score), assessed at diagnosis. It comprises of proteinuria (<1 g/day), elevated creatine (>1.58 mg/dl), gastrointestinal involvement, central nervous

system involvement and cardiomyopathy; the patients with higher score have lesser chances of survival.¹³ The five-factor score of this patient was zero indicating good prognosis and a survival chance of 86%.

Learning points

- ▶ The hepatitis B virus (HBV) infection can cause mononeuritis multiplex (MM) either due to systemic vasculitis associated with polyarteritis nodosa or immune-mediated neural damage.
- ▶ The HBV infection should be assessed in a presentation of MM with ulcerations.
- ▶ Leprosy is the commonest cause of MM in the Indian sub-continent, even though HBV infection should also be considered in investigative protocol.
- ▶ The early diagnosis of HBV infection-associated neuropathy is essential for good clinical outcome.

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Competing interests None.

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