Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.4498-20
Intern Med 59: 3075-3078, 2020
http://internmed.jp

【 CASE REPORT 】

Hepatitis B Virus-related Vasculitic Neuropathy in an Inactive Virus Carrier Treated with Intravenous Immunoglobulin

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Abstract:
We herein report a 33-year-old woman who was an asymptomatic hepatitis B virus (HBV) carrier and presented with distal muscle weakness in the legs and asymmetrical paresthesia in the distal extremities. A nerve biopsy specimen revealed fibrinoid necrosis associated with inflammatory infiltration in the perineural space, and deposition of hepatitis B core antigen and C4d complement was detected in the vascular endothelial cells as well as around the vessels. She was diagnosed with HBV-related vasculitic neuropathy and treated with intravenous immunoglobulin (IVIG). Her symptoms completely subsided after eight weeks. Vasculitic neuropathy rarely develops in the chronic inactive stages of HBV infection. This is the first report of an HBV-inactive carrier with vasculitic neuropathy successfully treated with IVIG.

Key words: hepatitis B virus (HBV), vasculitic neuropathy, intravenous immunoglobulin (IVIG)

(Intern Med 59: 3075-3078, 2020)
(DOI: 10.2169/internalmedicine.4498-20)

Introduction

Hepatitis B virus (HBV) infection affects more than 400 million people worldwide and is an important cause of infectious liver disease (1). The risk rate of chronicity is about 90% among those who acquire HBV infection under 1 year old (1). Extrahepatic manifestations are also sometimes observed, including serum sickness-like syndrome, glomerulonephritis, polyarthritis, polyarteritis nodosa (PAN), cryoglobulinemia, and various neurological, psychiatric, and dermatological disorders (2).

We herein report a rare case of HBV-related vasculitic neuropathy in an HBV-inactive carrier, which was successfully treated with intravenous immunoglobulin (IVIG).

Case Report

A 33-year-old woman initially noticed numbness in the lower legs. As the numbness worsened, she became unable to walk in high-heeled shoes. Eighteen days after the onset, she also felt numbness in her right hand. By 27 days after onset, the leg numbness had ascended to her knees, and she was hospitalized on day 31. She had a history of appendicitis, an ovarian tumor, and an ectopic pregnancy but no diabetes mellitus. Her mother had also been diagnosed with HBV infection. A physical examination was unremarkable, and a neurological examination revealed distal muscle weakness in the legs (a Medical Research Council score of 3/5). Asymmetric paresthesia was present in the distal extremities.

Laboratory findings revealed normal counts of platelets and red and white blood cells. A lipid panel, liver function tests, glucose level, and renal profile were all normal. The

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Received: January 17, 2020; Accepted: June 11, 2020; Advance Publication by J-STAGE: August 4, 2020
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Table. **Nerve Conduction Study on Admission.**

	Normal value	Right	Left
Median nerve			
MCV (m/s)	>48	58.2	57.4
Distal CMAP (mV)	>4.9	10.39	9.21
DML (ms)	<3.7	3.39	3.18
SCV (m/s)	>47	60.7	54.5
SNAP (μV)	>29.4	44.40	49.00
Ulnar nerve			
MCV (m/s)	>49	62.1	56.0
Distal CMAP (mV)	>5.5	8.10	7.82
DML (ms)	<2.9	2.58	2.49
SCV (m/s)	>44	52.9	51.5
SNAP (μV)	>35.6	18.1	35.7
Tibial nerve			
MCV (m/s)	>41	42.9	40.2
Distal CMAP (mV)	>3	1.8	1.03
DML (ms)	<4	3.63	3.54
Peroneal nerve			
MCV (m/s)	>40	57.1	46.2
Distal CMAP (mV)	>0.6	ND	ND
Sural nerve			
SCV (m/s)	>46.9	46.4	46.4
SNAP (μV)	>5	4.3	3.00

Abnormal values are expressed in underlined. Amplitude was measured from baseline to peak. MCV: motor conduction velocity, CMAP: compound muscle action potential, DML: distal motor latency, SCV: sensory conduction velocity, SNAP: sensory nerve action potential. ND: not detected

patient's erythrocyte sedimentation rate was elevated at 19 mm/h. Anti-DNA, anti-nuclear, anti-SSA/Ro, anti-SSB/La, and anti-neutrophil cytoplasmic antibodies (ANCAs), including myeloperoxidase (MPO)-ANCA and proteinase 3 (PR3)-ANCA, were undetectable, as were serum cryoglobulins. The results of immunoelectrophoresis were negative. Serum HBV antigens and anti-HBV antibodies were examined by an enzyme immunoassay. Hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), and hepatitis B envelope antibody (HBeAb) tests were positive, but hepatitis B surface antibody (HBsAb) and hepatitis B envelope antigen (HBeAg) tests were negative. HBV DNA titers were below 2.1 IU/mL. These findings indicated that the patient was an asymptomatic HBV carrier after HBeAg seroconversion.

A cerebrospinal fluid analysis revealed a normal cell count and protein level. The results of brain and spinal cord magnetic resonance imaging and fluorodeoxyglucose positron emission tomography/computed tomography were unremarkable.

A nerve conduction study revealed severe and generalized neuropathic involvement, mainly in the lower limbs (Table). The compound muscle action potentials in the lower limbs showed decreased amplitude or were undetectable. Although the sensory nerve conduction velocity was normal, the sensory nerve action potential (SNAP) amplitudes were decreased in the right ulnar nerve and in the bilateral sural nerves in a left-dominant manner, suggesting the existence of motor and sensory axonal neuropathy (Table). Furthermore, discrepant SNAP results in the right median and ulnar nerves and asymmetrical nerve involvement, such as in the ulnar nerves, suggested a form of mononeuropathy multiplex that was compatible with the clinical existence of asymmetric paresthesia.

A biopsy specimen of the right sural nerve revealed fibrinoid necrosis and lymphocyte-predominant inflammatory infiltration in the perineural space (Figure A). The endoneurium of the patient's nerves appeared to be edematous, but no thinning, demyelination, or onion-bulb appearance was observed. (Figure B). A teased-fiber analysis revealed that 64.2% of the fibers were type E according to Dyck's classification (3), indicating the presence of axonal neuropathy (Figure C). Immunostaining with anti-HBcAg antibody showed immunoreactivity around the epineural vessels (Figure D) and in endothelial cells (Figure E). In addition, positive staining of the whole vessels, including vascular endothelial cells, was observed by immunostaining with an antibody against C4d, indicating an immune response (Figure F). Based on these findings, subacute HBV-related vasculitic neuropathy was diagnosed.

Because treatment with corticosteroids may promote viral persistence and replication, IVIG was administered at a dose of 400 mg/kg for 5 days. The patient's bilateral leg weakness and the numbness in her right arm and both legs improved three weeks after treatment. She became able to walk unaided eight weeks after treatment.

Discussion

Approximately 20% of HBV-infected patients exhibit extrahepatic manifestations, and 5% have neurological disorders, including peripheral neuropathy and myopathy (4). Various types of HBV-related peripheral neuropathy have been reported, including Guillain-Barré syndrome, PAN, non-PAN vasculitic neuropathy, and chronic neuropathy syndromes, such as chronic polyneuropathy/polyradiculoneuropathy, mononeuritis multiplex, and chronic relapsing demyelinating polyneuropathy (4). Vasculitis is the major pathology in HBV-related neuropathy as well as in neuropathies due to other viral infections, such as hepatitis C virus, human immunodeficiency virus, cytomegalovirus, and parvovirus B19 (5, 6). The vasculitic neuropathy caused by HBV is characterized by the deposition of immune complexes containing HBV-related antigen in nerves or blood vessel walls, as well as by perivascular lymphocytic infiltrates (7). In the present case, immunostaining was positive for HBcAg in vascular endothelial cells as well as around the vessels in the epineurium, confirming the diagnosis of HBV-related vasculitic neuropathy. In addition, complement immunostaining revealed positive staining of whole vessels, including vascular endothelial cells, suggesting the presence of an immune response. However, whether or not HBV had directly

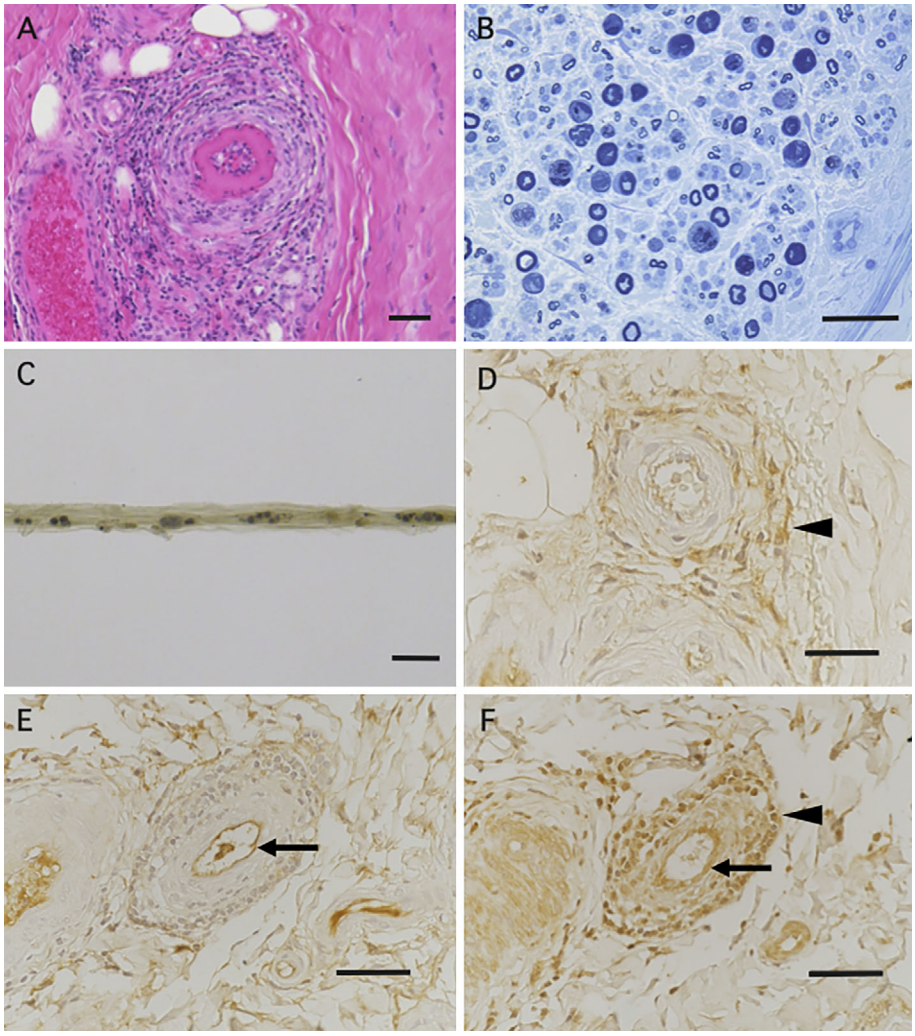

Figure. **Pathological findings in a sural nerve biopsy specimen. A: Right sural nerve biopsy sample stained with Hematoxylin and Eosin staining. An intense lymphocyte-predominant inflammatory infiltrate with fibrinoid necrosis is observed within a transverse section of the epineurium (×100, scale bar=50 μm). B: Right sural nerve biopsy specimen stained with toluidine blue. The endoneurium is edematous, but there is no thinning, demyelination, or onion-bulb appearance (×400, scale bar=50 μm). C: A teased-fiber analysis revealed axonal neuropathy: 64.2% of fibers were type E according to Dyck's classification (×100, scale bar=50 μm). D: Right sural nerve biopsy specimen immunostained with anti-hepatitis B core antigen (HBcAg) (anti-HBcAg antibody: rabbit polyclonal, 1: 200, # ab115992; Abcam, Cambridge, UK). The arrowhead indicates HBcAg deposition around the small vessel (×40, scale bar=50 μm). E: The arrow indicates the deposition of HBcAg in vascular endothelial cells (×40, scale bar=50 μm). F: Right sural nerve biopsy specimen immunostained with C4d complement (anti-human C4d antibody: rabbit polyclonal, 1: 30, #BI-RC4D; Biomedica, Vienna, Austria). C4d immunoreactivity is observed in the whole vessel (arrowhead), including the vascular endothelial cells (arrow) (×40, scale bar=50 μm).**

infiltrated the peripheral nerves was unclear. According to the Chapel Hill Consensus Conference (CHCC2012) definitions for the aetiopathogenesis of vasculitis, our case was considered to be consistent with "Vasculitis associated with possible etiology, Hepatitis B virus-associated vasculitis" (8).

In acute HBV infections, the emergence of HBsAg is rapidly followed by the appearance of HBeAg, leading to increased rates of HBV replication and enhanced infectiousness. Accordingly, in most cases HBV-related vasculitis has been reported to develop in the acute stage of HBV infection (9). In contrast, individuals who remain HBsAg-positive for at least six months are considered to be hepatitis B carriers, and those with chronic HBV infection may also develop neuropathy during viral relapse. However, carriers who have seroconverted to HBeAg-negative status with positivity for HBeAb, as in our case, have very little viral multiplication and rarely develop HBV-related neuropathy. Several cases of vasculitic neuropathy in HBV-inactive carriers have been reported, but only in the 1980s, and those patients were

mainly treated with corticosteroids (7, 10) since the use of IVIG in autoimmune neuropathy was not common at that time.

It would be interesting to learn the differences in the clinical and pathological phenotypes of HBV-related neuropathy between HBV-inactive carriers and patients with acute HBV infection. HBV-related PAN usually occurs within six months of virus infection but is very rare in chronic HBV-infected patients (4, 10). Characteristics of PAN include systemic necrotizing vasculitis targeting medium-sized arteries along with neutrophil-predominant infiltration. Unlike PAN, most previous cases of HBV-inactive carriers were pathologically characterized by necrotizing vasculitis associated with lymphocyte-predominant infiltration in small blood vessels in the epineurium (7), as in our case. In addition, patients with HBV-related neuropathy in the acute stage of infection were reported to show a protracted course (3-24 months) (11), which contrasts with the fact that complete recovery was achieved after 2 months in our case, although IVIG treatment might have modified the disease duration.

The main limitation of this report is the lack of evidence for HBsAg deposition in the sural nerve specimen despite several trials of orcein staining and immunostaining using anti-HBsAg antibody (data not shown). This might be due to poor sensitivity of these staining techniques or to an actual lack of HBsAg deposition. In fact, a discrepant deposition pattern has been reported between HBsAg and HBcAg in the glomeruli of patients with HBV-related renal disease (12). Although existing studies have not applied HBcAg staining to HBV-related neuropathy, the presence of this HBV-related antigen in vascular endothelial cells and around the nerve vessels in our case seems to be strong evidence for the role of HBV in neuropathy.

Future analyses of the relationships between the clinical or pathological phenotypes and different expression patterns of HBV antigens (HBs, HBc, and HBe) on nerve biopsy specimens may reveal new aspects of the pathogenesis of HBV-related neuropathy.

Conclusion

The present case provides the first evidence of the effectiveness of IVIG in an HBV-inactive carrier with vasculitic neuropathy. IVIG may be a more effective option for preventing HBV activation than corticosteroids.

The authors state that they have no Conflict of Interest (COI).

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