

CASE REPORT

Multiplex neuritis in a patient with autoimmune hepatitis: A case report

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Abstract

A 37-year old woman presented with a 9-year history of hepatitis of unknown origin and aminotransferases within a 3-fold upper limit of normal. Autoimmune hepatitis (AIH) was diagnosed on the basis of elevated aminotransferases, soluble liver antigen/liver pancreas (SLA/LP) autoantibodies and characteristic histology. Immunosuppressive therapy led to rapid normalization of aminotransferases. Two years later, the patient developed left sided hemisensory deficits under maintenance therapy of prednisolone and azathioprine (AZT). Later she developed right foot drop and paraesthesia in the ulnar innervation territory on both sides. Magnetic resonance imaging (MRI) and cerebral panangiography suggested cerebral vasculitis. Neurological investigation and electromyography disclosed multiplex neuritis (MN) probably due to vasculitis. Consistent with this diagnosis, autoantibodies to extractable nuclear antigens were detectable in serum. Immunosuppression was changed to oral 150 mg cyclophosphamide (CPM) per day. Prednisolone was increased to 40 mg/d and then gradually tapered to 5 mg. Oral CPM was administered up to a total dose of 40 g and then substituted by 6 times of an interval infusion therapy of CPM (600 mg/m²). Almost complete motoric remission was achieved after 3 mo of CPM. Sensibility remained reduced in the right peroneal innervation territory. Follow-up of cranial MRI provided stable findings without any new or progressive lesions. This is the first report of multiplex neuritis in a patient with autoimmune hepatitis.

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Key words: Multifocal peripheral neuropathy; Immu-

INTRODUCTION

Autoimmune hepatitis (AIH) is a chronic autoimmune disease of the liver of unexplained aetiology associated with autoantibodies^[1]. Overlapping syndromes with other autoimmune liver diseases, such as primary biliary cirrhosis or primary sclerosing cholangitis are increasingly reported. AIH can also be associated with extra-hepatic autoimmune diseases such as Graves' disease, Hashimoto thyroiditis, mixed connective tissue disease^[2], membranous glomerulonephritis^[3], Sjogren's syndrome^[4] and more often with systemic lupus erythematosus (SLE)^[5]. While SLE is often associated with neuropathic symptoms, only four cases of neuropathy in AIH are published to date.

Multiplex neuritis (MN) results from multifocal injury of the peripheral nerves. Causative processes include vasculitis (frequently related to diabetes or polyarteritis nodosa), sarcoidosis, lymphoma and peripheral nerve tumours^[6].

We observed a patient with AIH who developed MN due to vasculitis during combined immunosuppressive treatment with corticosteroids and azathioprine two years after AIH diagnosis. Treatment with cyclophosphamide led to remission of both conditions.

CASE REPORT

A 37-year old woman presented in June 2000 with a 9-year history of hepatitis of unknown origin and aminotransferases ranging from 70 U/L to 100 U/L (2-3 × ULN). Two years before presentation, antibodies to TPO were found, but the patient since then was still euthyretic. Except for that, she had no previous medical history and was asymptomatic. Physical examination showed no pathological findings. She had no history of alcohol abuse and did not commonly use any medications. She had no neurological symptoms. At presentation, aspartate aminotransferase (AST; 37 U/L, normal value < 32 U/L) and alanine aminotransferase (ALT; 54 U/L,

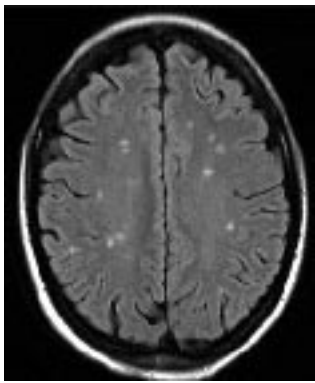


Figure 1 MRI (T2w/FLAIR) of the centrum semiovale showing multiple foci of subcortical signal enhancements which are characteristic but not specific for vasculitis.

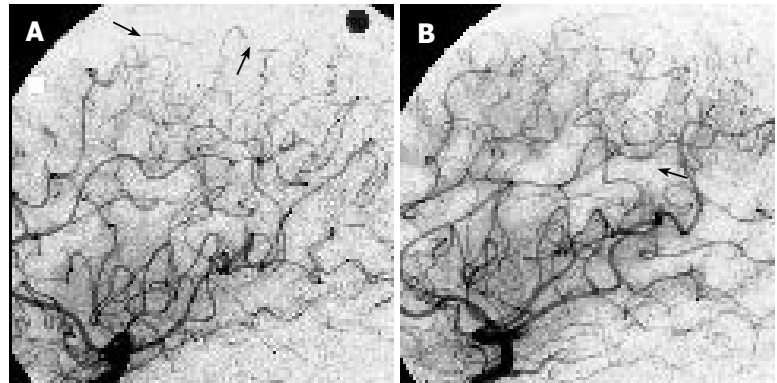


Figure 2 Left internal carotid artery (ACI) demonstrating irregularities of the distal parts of branches of the callosomarginal artery (arrows) (A) and right ACI demonstrating the break of a central branch of the middle cerebral artery (arrow) (B).

normal value < 31 U/L) were slightly elevated. In contrast, gamma-glutamyltransferase (gamma-GT; 19 U/L, normal value ranging 5-36 U/L), alkaline phosphatase (AP; 123 U/L, normal value ranging 70-180 U/L), total bilirubin (0.24 mg/dL, normal value < 1.2 mg/dL), total serum protein (79 g/L, normal value ranging 60-80 g/L), albumin (65.5%), gamma-globulin (16.4%) and serum IgG (13.4 g/L) were normal. Complete peripheral blood count, blood urea nitrogen and creatinine levels were normal. Testing for hepatitis B surface antigen (HBsAg) and antibodies to hepatitis B core antigen (HBcAb) was negative, testing for antibody to hepatitis C virus (HCV) by ELISA and HCV-RNA by polymerase chain reaction was also negative. Serum levels of copper and ceruloplasmin were normal. Autoantibodies to soluble liver antigen/liver pancreas (SLA/LP) were found at a titre of > 200 U/mL by ELISA. The presence of SLA/LP autoantibodies was confirmed by immunoblot. At that time no other autoantibody was found. Liver biopsy showed mild periportal hepatitis, some areas showed dissection of the liver parenchyma by inflammatory cells with hepatocyte ballooning and rosetting.

Based on these findings, the diagnosis of SLA/LP positive AIH was made. Treatment with prednisolone at a daily dose of 20 mg was initiated and due to a quick and complete normalization of aminotransferases, prednisolone could be gradually tapered to a maintenance dose of 5 mg per day. Six months later, treatment was tapered out, but the disease slowly relapsed with a mild elevation of liver enzymes and progressive fatigue. Therefore, immunosuppressive treatment was readjusted to a daily dose of 40 mg prednisolone, which was then reduced weekly down to a maintenance dose of 10 mg per day. Serum aminotransferase levels rapidly normalized and clinical symptoms disappeared. Azathioprine was added at a dose of 75 mg per day and increased to 100 mg per day after two weeks.

In the following months, complete remission of AIH was maintained by medication with 7.5 mg/d prednisolone and 100 mg/d azathioprine. At this stage, the patient developed acute neurological disturbances, initially with a left sided hemisensory deficit. A few weeks

later, the patient developed paraesthesia in both ulnar innervation territories and subsequently a right sided peroneal paresis and mild weakness of hip flexion. She never had any lumbar pain. An infection with *Borrelia burgdorferi* and *Treponema pallidum* was ruled out by the absence of antibodies. MRI of the brain showed multiple paraventricular lesions, which were assumed to be of vasculitic character (Figure 1). Angiography of the brain showed irregularities of intracerebral arteries (Figure 2) consistent with vasculitis. Cerebrospinal fluid examination and electrophysiological examination (evoked potentials) were normal. Electromyography showed acute denervation in the anterior tibialis muscle and to a lesser degree in the medial proportion of the thigh muscle. To exclude radicular lesions, MRI of the spinal cord was performed, which showed distant degenerative changes, but no pathology on the right-sided L4 and L5 nerve roots. Accordingly, neurological examination revealed no loss of deep tendon reflexes or radicular pain. History, clinical and neurophysiological examination, cerebral angiography and MRI together with the emergence of autoantibodies to Ro/SSA supported the clinical diagnosis of MN, due to vasculitis of the nervous system.

For the treatment of vasculitis, azathioprine was replaced by cyclophosphamide (CPM) at an initial dose of 150 mg/d given orally. CPM is also effective in the treatment of AIH^[7]. Prednisolone was increased to 40 mg/d and then gradually tapered to 5 mg/d. According to the guidelines for the treatment of isolated vasculitis of the nervous system, oral CPM was administered at a total dose of 40 g. Thereafter, CPM was given 6 times by infusion therapy (600 mg/m²) at an 8-wk interval. Total recovery of the motoric deficits and almost complete recovery of the sensory deficits were achieved after 3 mo. Sensibility was only diminished in the peroneal nerve segment of the right leg. Cranial follow-up MRI, performed 6 mo after the initiation of CPM provided stable findings. The patient was in the fifth year of follow-up after AIH diagnosis and was receiving maintenance therapy consisting of 5 mg prednisolone and 100 mg azathioprine, AIH was still in remission and the patient remained free of further neurologic symptoms at the time she reported.

DISCUSSION

Multiplex neuritis (MN) occurs as a complication of vasculitis but can also develop in toxic or metabolic processes. Small vessel vasculitis typically affects the 50-400 micron vessels of the vasa nervorum, leading to randomly distributed ischemia along the nerve^[8]. This, in turn, may lead to a distinctive clinical picture of scattered neurological symptoms, which can be attributed to multiple complete or incomplete peripheral nerve or nerve root lesions. It is reported that more than half of vasculitis patients present with MN^[9]. The most frequent single nerve lesion is the peroneal nerve paresis^[10].

To date multiplex neuritis in hepatic diseases has been reported as a rare complication in patients with chronic hepatitis B^[11-13], in one patient with acute hepatitis A infection^[14] and in patients with hepatitis C and associated cryoglobulins^[15]. This latter manifestation is likely due to the cryoglobulinemic vasculitis seen in hepatitis C. The pathogenesis of this neuropathy in viral hepatitis without cryoglobulins has not yet been fully elucidated. It has been suggested that nerve lesions result from viral factors directly or from deposits of immune complexes in the vasa nervorum, which then may cause vasculitis and ischemia of the nervous fibers, as it has been shown for cryoglobulinemic neuropathies^[11,12,16].

Neuropathies in AIH patients are an extremely uncommon finding. Four patients have been described in the literature suffering from AIH and peripheral neuropathy^[17,18] and one patient suffering from AIH and cranial neuropathy, but this patient also had positive HCV serology and polymyositis^[19]. The patient described here suffered from clearly defined SLA/LP-positive AIH without any evidence for viral infection. Her asymmetric sensory and motor symptoms of both central and peripheral nervous system origin, with a clear stepwise onset developing over months, suggested vasculitis of the nervous system, which was compatible with the multifocal peripheral nerve involvement and ischemic brain lesions on MRI. Cerebral angiography provided objective evidence for nervous system vasculitis, and neurophysiological studies confirmed multiple peripheral nerve involvement.

To our knowledge, this is the first reported patient with AIH associated with vasculitic MN. Our report indicates that MN can develop in non-viral hepatitis. Both AIH and vasculitic MN are autoimmune systemic disorders of unknown origin, which occurred sequentially in our patient, suggesting that MN seems to develop independently of AIH. In our patient, the disease activity of AIH was not associated with that of MN, and MN developed despite immunosuppressive therapy with 7.5 mg prednisolone and 100 mg azathioprine per day, suggesting that MN may need higher levels of immunosuppression for remission than AIH.

In conclusion, medication with cyclophosphamide in combination with intensified prednisolone therapy can rapidly improve neurological symptoms and offer an

option for the prevention of further nerve injury.

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