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Transverse myelitis associated with chronic hepatitis C

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ABSTRACT

An infectious etiology is one of the postulated mechanisms for autoimmune diseases. An emergence of autoimmune phenomena associated with hepatitis C virus (HCV) infection has been reported. Transverse myelitis is an inflammatory disease of the spinal vasculature attributed to viral infections and to autoimmune diseases including systemic lupus erythematosus and the antiphospholipid syndrome.

A 34-year-old male was admitted for the rapid onset of numbness of the lower extremities and urinary retention. His past history included hepatitis C infection. The neurological examination and MRI of the thoracic spine confirmed the diagnosis of transverse myelitis. Abnormal laboratory results were hyperglobulinemia, abnormal liver function tests, and positive ANF, anti-dsDNA antibodies, and p and c-ANCA. The patient was treated with high dose prednisone, then tapered to a low dose, but regained only partial neurological function after 15 months of prednisone therapy. Persistent neurological deficits and elevated ANF and ANCA were present at a follow-up of 30 months. We describe the first reported case of a patient with chronic HCV who developed transverse myelitis.

Introduction

An infectious etiology is one of the postulated mechanisms for autoimmune diseases (1). Extra-hepatic autoimmune phenomena are reported with increasing incidence in HCV infection (2-5). Transverse myelitis (TM) is a sudden onset demyelinating disorder with loss of the fatty tissue around the nerves of the spinal cord. TM may occur alone or in combination with demyelination in other parts of the nervous system. Symptoms include low back pain, spinal cord dysfunction, muscle spasms, and numbness or tingling in the legs. TM may be caused by viral infections, spinal cord injuries, immune reactions, or insufficient blood flow through the blood vessels in the spinal cord, and may also occur as a complication of such disorders as optic neuromyelitis and multiple sclerosis. 20-40% of cases of acute transverse myelitis are attributed to viral infections, including hepatitis A, cytomegalovirus, and Ebstein-Barr virus (6-8). In addition, TM is reported in association with systemic lupus erythematosus (9) and the antiphospholipid syndrome (5). We describe a case of a patient with chronic hepatits C who developed transverse myelitis.

Case report

A 34-year-old male was admitted for the sudden onset of pain between the scapulas, followed by weakness and numbness in his legs and urinary retention. These symptoms progressed within a few hours to complete paraplegia. His past history included hepatitis C infection without evidence of chronic liver damage on biopsy. The liver function tests were within normal limits and no medication was required. The patient received a blood transfusion in the course of an urologic surgery 10 years prior to this admission. In addition, he had an intrapenile prosthesis implant.

The patient was initially admitted to another hospital. MRI of the thoracic spine showed swelling of the spinal cord and a second MRI examination revealed an increased intensity signal on T2 at the T4-5 level. Cervical spine MRI, brain MRI, nerve conduction and EMG studies were within normal limits. The lumbar puncture was normal, and there were no oligoclonal bands. He was diagnosed with transverse myelitis.

Physical examination upon transfer to the rehabilitation unit of our medical center two weeks later revealed BP 120/70 mmHg, heart rate 88/min. and regular, and body temperature 37°C. The general examination was without abnormal findings, except for a systolic heart murmur. The neurological examination revealed mild bilateral weakness of the interossei, bilateral positive Trommer's sign, spasticity of the lower limbs, and complete paraplegia, bilateral Babinsky sign, hypoesthesia below T 10, alteration of left lower limb deep sensation, and neuropathic bladder and bowel.

Laboratory results revealed WBC 10.150/dL, PMN 55%, Hg 13.0 g/dL, MCV 89.3 fl, MCHC 32.4 g/dl, PLT 233,000/μl, urea 15 mg/dL, creatinine

0.8 mg/dL, and glucose 82 mg/dL. There was an increase in globulins and liver function tests during the hospitalization. Serological tests included positive ANF, elevated anti-DNA antibody titers, c-ANCA, and p- ANCA (Table I).Serum immunoelectropheresis revealed hypergammaglobulinemia, IgG 2023 mg/dL. No oligoclonal bands in CSF were detected. EBNA and CMV IgG titers were detected, indicating previous infection. The anti-HCV titer was 33.9 IU and mRNA PCR was positive. Therapy with prednisone was initiated at 60 mg/day for one month, and then tapered by 10 mg/day every 2 weeks. The patient was treated with low-dose prednisone (10 mg/day) for a total of 15 months. During the follow-up period of 30 months, the neurological deficit improved gradually, but the patient remained paraparetic and required crutches for ambulation. Laboratory tests revealed normal liver function, but included persistently elevated ANF and c-ANCA levels.

Table I. Laboratory results during hospitalization and follow-up.

Laboratory test	On admission	Two weeks later	Follow-up (30 mos.)
Total protein	7.0 g/dL	9.3 g/dL	8.9 g/dL
Albumin	3.8 g/dL	4.2 g/dL	4.5 g/dL
Globulin	3.0 g/dL	5. 1 g/dL	4.4 g/dL
Alkaline phosphatase	56 IU/L	67 IU/L	61 IU/L
SGOT (AST)	84 IU	102 IU	36 M
SGPT (ALT)	98 IU	114 IU	39 IU
LDH	155 IU	200 IU	150 IU
ANF	Positive, speckled	NA	+++ homogenous
Anti-DNA Ab	17%	NA	15%
c-ANCA (PR3)	30 U	17.5 U	42 U
p-ANCA (MPO)	6U	22 U	negative
C3	151 mg/dL	NA	135 mg/dL
C4	29.1 mg/dL	NA	13.7 mg/dL
Cryoglobulins	±	NA	±

RF, ASLO, antibody titers (aCL IgG and IgM),VDRL, TPHA, circulating anticoagulants, protein C, protein S, anti-thrombin III, and homocysteine were negative.
Normal values: C3 [79-152 mg/dL]; C4 [16-38 mg/dL]; c and p-ANCA [0-15 U]; anti-DNA Ab [0-15%].
Cryoglobulins: types not determined; NA: not available.

Table II. The presence of autoantibodies in HCV.

Autoantibody study	Cacoub	Buskila	Calabrese	Lovy	Barrett ^	Cacoub#
Ref.	(3)	(5)	(13)	(2)	(14)	(15)
No. of patients	1,624	90	NA	Combined results	87	312
ANF*	10%	38%	27%	10-40%	5.1%	41%
RF	NA	44%	58%	60%	3.8%	38%
Cryoglobulin	40%**	NA	40%	40%	12.7%	56%
Anti-cardiolipin Ab	NA	IgM 28% IgG 22%	NA	20%	NA	27%
ANCA	NA		NA	10%***	NA	NA
Low C3	NA	12%	NA	NA	NA	NA
Low C4	NA	36%	NA	NA	NA	NA
Anti-smooth muscle antibodies	7%	NA	29%	7-20%	NA	9%
Anti-mitochondrial antibodies	NA	NA	NA	NA	3.8%	NA
Anti-Ro/anti-La	NA	NA	NA	NA	7.6%	NA
Anti-thyroid antibodies	NA	NA	NA	NA	13.9%	13%

*Speckled pattern most common; **65% type II, 35% type III; ***mixed c and p ANCA.
^From HCV PCR positive women; #at least one autoantibody was present in 70% of sera.

Discussion

We describe a patient with HCV who developed transverse myelitis. Extrahepatic rheurnatological manifestations of chronic HCV infection are considered to be of immunologic origin and include mixed cryoglobulinemia, arthralgias, myalgias, arthritis, vasculitis, sicca symptoms, and the presence of various autoantibodies (2-5, 10-11, 15). In one study, 90 anti-HCV positive patients were evaluated for the development of autoimmune phenomena (5). Rheumatic manifestations were found in 31% of subjects and included cryoglobulinemia (11%), arthralgias (9%), sicca symptoms (8%), and arthritis (4%). Less common manifestations included cutaneous vasculitis, polymyositis, and anti-phospholipid syndrome. Sixty-nine percent of patients had at least one autoantibody level detected in the serum (Table II). No association was observed between the presence of autoantibodies and the severity of liver disease. Rheumatic manifestations were not associated with the presence of autoantibodies (5).

Moder *et al.* (11) reported musculoskeletal complaints in 69% of 42 HCV infected individuals; most had myalgias and arthralgias. Three patients developed myasthenia gravis, inflammatory myopathy, and anti-phospholipid syndrome shortly after the establishment of HCV infection (5). A few cases of inflammatory myopathy have been described in patients with HCV. Neurological manifestations in HCV-infected patients are mostly associated with mixed cryoglobulinemia and include peripheral neuropathy (12, 15), cerebral vascular accident, seizures, and coma (12). Other described HCV-associated

neurologic disease were mononeuritis multiplex and central nervous system vasculitis (12). The prevalence of autoantibodies in HCV patients in 6 recent studies is depicted in Table II (2, 3, 5, 13-15). From these studies the most commonly found autoantibodies were ANF (10-41%), cryoglobulins (12.7 – 56%), RF (3.8 – 60%), anti-cardiolipin antibodies (20 – 28%), and anti-smooth muscle antibodies (7 – 29%). Other reported autoantibodies include anti-Ro/anti-La, anti-thyroid, and anti-mitochondrial antibodies (14). Specific autoantibodies such as anti-dsDNA, anti-RNP, and anti-Sm were rarely found (3). No association between any autoantibody positivity and clinical symptoms was found (3). Our patient had persistantly elevated titers of more than one autoantibody (ANCA and anti-dsDNA), reflecting the immunological autoimmune phenomenon in an HCV-infected individual. Viral infections may be a possible trigger for autoimmune disease. One postulated mechanism is molecular mimicry. The mechanism for extra-hepatic manifestations in HCV may be related to the replication of HCV outside of the liver, particularly in blood mononuclear cells (3).

In conclusion, we describe the first case of a patient with transverse myelitis associated with hepatitis C infection. Hepatitis C screening should be considered in patients who develop transverse myelitis. Treatment with steroids induced amelioration, without exacerbation of the hepatitis. Our patient was not treated with interferon because there was no evidence of active liver disease.

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