

A case of polymyositis associated with hepatitis B infection

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ABSTRACT

This report describes the case of a 47-year old man who developed myositis in association with hepatitis B surface antigen-positive hepatitis. Interestingly, the myositis repeatedly worsened 2 months after the exacerbation of hepatitis in this case, suggesting a close association between hepatitis B infection and myositis. The dose of prednisolone was increased twice in order to treat the exacerbating myositis, resulting in improvement of the muscle symptoms, but the patient eventually died of liver failure. Only 5 other myositis patients with hepatitis B antigenemia have been reported in the literature. We review these cases of the association between hepatitis B infection and myositis.

Introduction

Polymyositis (PM) is an inflammatory muscle disease characterized clinically by proximal muscle weakness and histologically by chronic inflammation of the affected muscles. The etiology of this disorder is unknown, but a variety of causes have been implicated. Among them, some infectious agents have been reported to be associated with myositis. We now describe the case of a 47-year-old man who developed myositis in as-

sociation with hepatitis B surface antigen (HBsAg)-positive hepatitis.

Case report

A 43-year-old man was found to have an elevated serum aminotransferase level and to have developed HBsAg-positive hepatitis in September 1987 (obscurity in detail). In September 1991, he was hospitalized for one month at another institution with a complaint of severe myalgia. Corticosteroid therapy was initiated with prednisolone 15 mg daily, which was followed by the gradual disappearance of the myalgia (Fig. 1). In February 1992 the patient was referred to Keio University Hospital (KUH) due to an elevation of his serum aminotransferases [aspartate aminotransferase (AST) 172 IU/L (14-32) and alanine aminotransferase (ALT) 333 IU/L (8-41)]. There was no past history of blood transfusions, smoking, or abuse of alcohol. The diagnosis of chronic HBsAg-positive hepatitis was confirmed based on the clinical course and serological examinations (HBsAg (+) and HBs antibody (-) by enzyme immunoassay; hepatitis C virus antibody (HCVAb) (-) by the passive hemagglutination assay). The patient then developed myalgia and weakness of the larger muscles, includ-

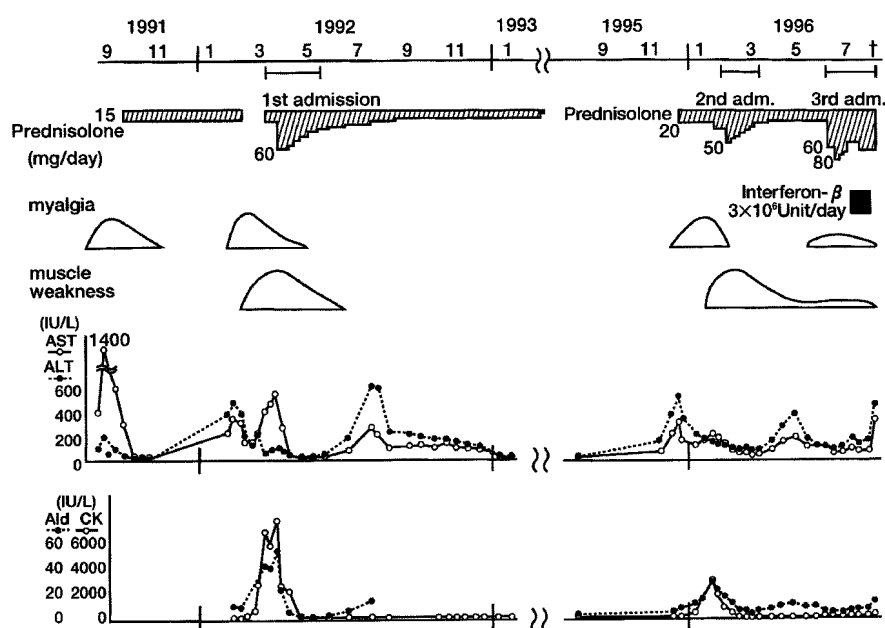


Fig. 1. Clinical course of the patient. Elevated serum aminotransferase levels (such as creatine kinase and aldolase) were regularly observed preceding exacerbation of the myogenic enzyme. AST: aspartate aminotransferase; ALT: alanine aminotransferase; Ald: aldolase; CK: creatine kinase.

ing the deltoid, biceps, quadriceps and hamstrings. In March 1992 he was admitted to our hospital because his muscle symptoms had become severe and his creatine kinase (CK) level was 6,447 IU/L (67-210) (1st admission, 47 years old). On examination, the patient's vital signs were normal. There was no detectable thyroidmegaly or lymphadenopathy. Chest and cardiovascular examination revealed no remarkable findings. Abdominal examination revealed that the liver was not tender, but extended 2 cm below the right costal margin. Musculoskeletal evaluation showed weakness in the proximal muscle groups on resistive testing. Palmar erythema was noted, but he did not have any arthritis, Raynaud's phenomenon, Heliotrope rash, or Gottron sign.

Results of complete blood cell counts were normal, and the Westergreen erythrocyte sedimentation rate (ESR) was 35 mm/hr. AST (416 IU/L) and ALT (132 IU/L) were elevated. Total bilirubin (TB) and alkaline phosphatase (ALP) were normal, but total protein (TP, 6.2 g/dl) and serum albumin (ALB, 2.4 g/dl) were low. CK was increased at 7,221 IU/L (MM 100%). Rheumatoid factor was positive (1:80), but fluorescent antinuclear antibody (FANA) was negative. C3 and CH50 were normal. C4 was 18 mg/dl (20-35).

Prednisolone was restarted at 15 mg daily. A left biceps muscle biopsy was done on April 7th. A diagnosis of PM was then made on the basis of an electromyogram (EMG) (myopathic change) and the muscle biopsy [necrotic and degenerating findings of muscle fiber (with no lined vacuoles) and endomysial infiltration of a few inflammatory mononuclear cells]. Prednisolone was increased to 60 mg daily, resulting in dramatic improvement in the muscle symptoms and normalization of the CK level. Throughout his first hospital stay at KUH, serum aminotransferases (AST 172 IU/L and ALT 333 IU/L) remained high. However, interferon therapy was not adopted because tests for hepatitis B envelope antigen (HBeAg) and HBV DNA polymerase were negative and the histological findings for the liver were compatible with the pre-cirrhotic stage of chronic

hepatitis (mild-moderate activity: mild-moderate piecemeal necrosis, mild intralobular necrosis, mild portal inflammation and expanding portal tract).

In 1994 the corticosteroid dose was tapered and finally discontinued, because the myositis activity had stabilized. In November 1995 general fatigue was noted and liver dysfunction (AST 89 IU/L, ALT 158 IU/L) was demonstrated. The patient developed myalgia and prednisolone therapy was restarted at a dose of 20 mg daily in December 1995. However, muscle symptoms became severe and the CK level rose to 3,066 IU/L. The prednisolone dose was then increased to 30 mg daily at the end of January.

In February 1996 the patient was re-admitted to KUH (2nd admission). Results of complete blood cell counts and ESR were normal. AST (156 IU/L) and ALT (132 IU/L) were elevated. TB and ALP were normal, but TP (6.2 g/dl) and ALB (3.1 g/dl) were low. CK was elevated at 1,859 IU/L. Antibodies to hepatitis B envelope and core and to HBsAg were positive, while HBeAg and HBsAb were negative. HBV DNA polymerase was 2,205 cpm (0-30), while HCVAb was negative. Rheumatoid factor was positive (50 IU/ml), but FANA, anti-Jo-1 antibody, anti-U1-RNP antibody, anti-Sm antibody, and anti-smooth-muscle antibody were negative. C4 was 15 mg/dl. Immune complex (anti-C3d antibody) was negative. Thyroid-stimulating hormone and free T4 were normal. EMG again showed mild myopathic changes in the proximal muscles. Abdominal ultrasonography showed some parenchymal changes in the liver.

The prednisolone dose was then increased to 50 mg daily against the progressive myositis, resulting in an improvement in the muscle symptoms. The patient was admitted for a third time to KUH in June 1996 due to exacerbated liver dysfunction (AST 186 IU/L, ALT 366 IU/L). The prothrombin time was prolonged (45%). TP (5.3 g/dl) and ALB (2.0 g/dl) were low. Both direct bilirubin (1.3 mg/dl) and indirect bilirubin (1.6 mg/dl) in serum and the blood ammonia level were elevated (76 micro mol/l; normal < 50). Abdominal ultrasonography showed progressed parenchymal chan-

ges in the liver suggestive of liver cirrhosis. HBV DNA polymerase was high (2,938 cpm). Despite high-dose corticosteroid therapy (prednisolone 80 mg daily) and interferon-beta therapy (3 x 10⁶ unit daily), the patient died in August due to liver failure.

Discussion

Polymyositis is an inflammatory muscle disease that may be closely related to immune-mediated processes triggered by exposure to environmental factors in genetically susceptible individuals. The triggering event of myositis is unknown, but infectious agents including bacteria, viruses, and parasites have been implicated (1-2). Among these agents, a variety of viral infections associated with myositis have been reported. Influenza virus, echovirus, and adenovirus have been cultured in some patients with myositis (3-5). Electron microscopy analysis has also identified enterovirus (coxsackievirus) in some patients with PM (6). Retroviruses, including HIV and human T-cell leukemia-lymphoma virus type I, have been associated with the inflammatory myopathies on the basis of clinical and histopathologic findings (7).

Various mechanisms have been proposed for virus-induced myositis, such as direct injury to muscle, alteration of muscle function from nearby infection, and an autoimmune response to viral antigens bound to intracellular enzymes (8-10). The present patient clearly had viral hepatitis, as evidenced by the presence of liver dysfunction with HBs antigen and by liver biopsy. In acute viral hepatitis, some patients develop myalgia and arthralgia, but muscle weakness rarely occurs. The coexistence of polymyositis was confirmed by proximal muscle weakness, elevated muscle enzymes, EMG, and muscle biopsy.

Five myositis patients with hepatitis B antigenemia have been described in the literature, and we summarize the clinical features of these patients as well as the present case in Table I. Four of 6 cases were characterised by the simultaneous occurrence of hepatitis and PM, while 2 cases had chronic hepatitis B virus infection for years prior to the emergence of myositis. It should be

Table I. Reports in the literature of polymyositis/dermatomyositis and hepatitis B.

Cases	Patten <i>et al.</i> 1977	Mihás <i>et al.</i> 1978	Pittsley <i>et al.</i> 1978	Koike <i>et al.</i> 1980	Reginster <i>et al.</i> 1984	Nojima <i>et al.</i> 1996
Sex	Female	Male	Female	Female	Female	Male
PM/DM (age at onset)	PM (23)	PM (51)	DM (17)	PM (39)	PM (54)	PM (47)
Hepatitis B	23	51	17	39	50	43
Muscle weakness	+	++	+++	+	+	++
Myalgia	++	++	++	+	++	++
Electromyogram#	Not tested	Not tested	+	+	+	+
Muscle biopsy	+	+	Not tested	+	+	+
Interstitial lung disease	-	-	-	-	-	-
Heart disease	-	-	-	AV block	-	-
Autoantibody	Not tested	ANA	a-DNA Ab	-	-	RF
Therapy	PSL 40 mg/d	PSL 100 mg/d	PSL 40 mg/d	Steroid	PSL 5 mg/d	PSL 60 mg/d
Steroid response	Good	Good	Good	Good	Good	Good
Outcome	In remission	Deceased (pneumonia)	In remission	In remission	In remission	Deceased (liver failure)

PM/DM: Polymyositis/dermatomyositis; ANA: antinuclear antibody; a-DNA Ab: anti-dsDNA antibody; RF: rheumatoid factor; PSL: prednisolone.

presence or absence of myopathic change.

noted that all of the patients had myalgia that could have been part of a flu-like prodrome to hepatitis B, and none of them had interstitial lung disease. With respect to the autoantibodies, antinuclear antibody, anti-DNA antibody, and rheumatoid factor were found in 3 cases (nos. 2, 3, and 6). Corticosteroid therapy was performed and was effective against myositis in all cases. However, case 2 died of aspiration pneumonia and case 6 died of liver failure (11-15).

In the previous reports, the clinical course of the patients was not described in detail. Interestingly, myositis continually worsened 3 months after the exacerbation of hepatitis in our case, suggesting a close association between hepatitis B infection and myositis. However, it will be necessary to elucidate the existence of hepatitis B virus in muscle specimens using immunochemistry, *in situ* hybridization, or the polymerase chain reaction assay.

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