We describe a case of polymyositis (PM) with liver injury that occurred in a patient with rheumatoid arthritis (RA). A 74-year-old woman who had a 12-year history of RA was admitted to our hospital because of muscle weakness and liver dysfunction. CD8-positive T cell infiltration was found in the interstitium of both the liver and muscle. In addition to the administration of a large amount of prednisolone (PSL), high-dose intravenous immunoglobulin (IVIG) successfully improved myositis and hepatitis. Our case indicates the pathogenic potential of CD8-positive T cells in PM-associated liver injury.

**Key words:** polymyositis, liver disturbance, CD8-positive T cell, IVIG

*(DOI: 10.2169/internalmedicine.45.1710)*

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**Case Report**

A 74-year-old woman suffered from dysphagia, general malaise and muscle weakness in the extremities in the end of November 2002. The patient had no fever or flu-like symptoms. The patient was admitted to a regional hospital on December 25, 2002. Blood chemistry of the patient showed elevated level of aspirate aminotransferase (AST), 378 IU/l (normal levels, 5-35), alanine aminotransferase (AST), 258 IU/l (normal levels, 5-40), and creatine phosphokinase (CK), 2800 IU/L (normal levels, 40-150). Under the diagnosis of hepatitis and myositis, the patient was treated with prednisolone (PSL) at oral doses of 30 mg/day and intravenous injection of stronger neo-minophagen C (40 ml/day). However, muscle weakness and elevated levels of AST, ALT, and CK did not improve. The patient, therefore, was transferred and admitted to our hospital on January 14, 2003, for further management. The patient has been suffering from rheumatoid arthritis for 12 years and has been treated with D-penicillamine at doses of 100 mg/day for 6 months from May 2002 to November 2002, just before admission to the regional hospital. Physical examination revealed muscle weakness in the bilateral upper and lower extremities, especially in the proximal parts of the extremities. The manual muscle test showed grade III of V in four extremities. Myalgia was not a complaint anywhere in the body. Articular deformity due to rheumatoid arthritis was

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1 Divisions of Rheumatology, Ohta Nishinouchi Hospital, Koriyama, 2 Divisions of Neurology, Ohta Nishinouchi Hospital, Koriyama and 3 Divisions of Pathology, Ohta Nishinouchi Hospital, Koriyama

Received for publication December 26, 2005; Accepted for publication June 5, 2006

Correspondence to Dr. Atsushi Takahashi, Second Department of Internal Medicine, Fukushima Medical University, School of Medicine, 1 Hikarigaoka, Fukushima 960-1295
Figure 1. T2-weighted magnetic resonance images revealed high intensity changes in bilateral femoral rectus muscle (arrows).

noted in the bilateral wrists and proximal interphalangeal joints. Skin rash was not noted anywhere in the body.

Laboratory examination on admission (January 15, 2003) revealed the following values: AST 347 IU/L, ALT 498 IU/L, lactate dehydrogenase (LDH), 1706 IU/L (normal levels, 110-220), alkaline phosphatase (ALP), 283 IU/L (normal levels, 85-339), gamma-glutamyl transeptide (γ-GTP), 100 IU/L (normal levels, <55), leucine aminopeptidase (LAP), 175 IU/L (normal levels, 70-170), CK, 4374 IU/L, aldolase 95.0 IU/L (normal levels, 2.7-5.9), myoglobin 4930 ng/ml (normal levels, <60), rheumatoid factor (RF), 81 IU/ml (normal levels, <20). Anti-nuclear antibody (ANA) was positive at a titer of 1:160, with a centromere pattern. Anti-Jo-1 antibody, anti-smooth muscle antibody, hepatitis C virus (HCV) antibody and hepatitis B virus (HBV) antigen were negative. Moreover drug-induced lymphocyte stimulation test (DLST) for D-penicillamine was negative. There were no abnormal findings in abdominal computed tomography (CT) and ultrasonography (US). Magnetic resonance images (MRI) of lower limb which were taken on January 28, 2003 showed abnormal signal intensity in bilateral femoral rectus muscle by T2-weighted images (Fig. 1). An electromyogram showed short duration and low amplitude in the bilateral biceps and femoral rectus muscle. The biopsied liver specimen revealed a mild fibrosis and slight perivascular lymphocyte infiltration in Glisson’s area. However, no degeneration or necrosis of liver cells were noted in the acinar region. No cholestasis was noted in the acinar region and Glisson’s area (Fig. 2A). Immunofluorescent staining showed a predominant presence of CD8 T cells over CD4 T cells (Fig. 2B, C). Muscle biopsy was undertaken from the left femoral rectus muscle on February 21, 2003. The biopsied muscle tissue revealed a small number of lymphocyte infiltration areas in the interstitial area and degeneration of muscle fibers (Fig. 3A, B). Immunofluorescent staining of these lymphocytes using monoclonal antibodies revealed positive staining for CD8 T cells but not for CD4 T cells (Fig. 3C).

Considering the all findings mentioned above, the present patient had a diagnosis of PM according to the PM criteria of both Bohan and Peter (3) and Tanimoto et al (4) in Japan. The patient was treated from January 15, 2003 with PSL at a dose of 60 mg/day. However, the muscle weakness did not improve and the serum CK still remained at a high level (4300 IU/L). Therefore, the patient was treated by high-dose intravenous injection with immunoglobulin (IVIG)
Figure 3. A, B, Micrograph of biopsy material from the right femoral rectus muscle (HE stain, ×400). Myogenic muscle fiber atrophy and degeneration is visible, with the infiltration of mononuclear cells into the space between muscle fibers. C, Immunohistological staining of the same specimens. The infiltrated mononuclear cells were stained with anti CD8 monoclonal antibodies (×400).

at a dose of 20 g/day for 5 consecutive days (January 22-26). After IVIG administration, along with decreasing levels of CK and transaminase, muscle weakness and general malaise improved gradually (Fig. 4). The serum levels of CK, AST and ALT on April 4, 2003, were 57 IU/L, 25 IU/L, and 23 IU/L, respectively.

Discussion

Collagen diseases are autoimmune disorders affecting multiple organs. Liver disturbance is a relatively common phenomenon in collagen diseases. However, liver disturbance is not always caused by collagen diseases themselves but by many factors, such as drug toxicity, fatty infiltration, and viral infection. It is sometimes very difficult to identify the reason for liver injury in patients with collagen diseases. Hyper-globulinemia and high titers of serum ANA, which are the diagnosis markers for collagen disease, are often found in patients with autoimmune hepatitis (AIH). Therefore, it is difficult to diagnose as AIH without liver histology. Liver histology of AIH shows piecemeal necrosis, bridging necrosis, marked infiltration of lymphocytes, and rosette formation of hepatocytes (5). Further subdivision of infiltrating T-cells in liver show a predominance of CD4 over CD8 (6). On the other hand, a variety of histological findings of liver including non-specific reactive hepatitis are found in patients with collagen disease (2, 7). In the present case, liver histology showed mild perivascular infiltration by CD8 T cells, which were uncommon in AIH. In addition, according to the criteria of AIH, our patient’s score was 9, indicating a low possibility that this case was an AIH.

The most common liver damage in collagen disease patients is considered to be non-specific reactive hepatitis. Therefore, we cannot totally rule out the possibility that the liver injury in this patient was closely related to RA. However, previous reports pointed out liver disturbance in rheumatic diseases usually occurs at the onset of the underlying diseases and the severity of liver disturbance is positively correlated with the activity of underlying diseases (1). In the present case, the patient had 12-year history of RA and her arthritis was well controlled when she was referred to our hospital. Moreover, clinical symptoms and abnormal laboratory findings of myositis improved in parallel with the recovery of liver disturbance. Further, the levels of transaminase and CK improved together by the administration of prednisolone and IVIG. These clinical findings indicate

Figure 4. Summary of the patient’s clinical course.
that liver disturbance in this case was associated with polymyositis, rather than RA.

It has been reported that autoreactive CD8-positive T cells introduce necrosis into myocytes by means of perforin and granzyme (8-10). Histological findings of muscle in the present case support previous reports. Interestingly, immunohistochemical staining showed that infiltrated lymphocytes in the liver are CD8-positive T cells, too. Some lines of evidence suggest that IVIG is effective treatment in PM (11-14). In our case, liver disturbance also improved in accordance with myositis after the administration of IVIG. These findings indicate some common mechanisms induced myositis and liver injury in the present case. There are several possible mechanisms by which these two organ’s injury occurred simultaneously in the present case. First, CD8-positive T cells recognized an unknown antigen, which was commonly expressed both on hepatocytes and myocytes. For example, MHC-class I is always expressed on hepatocytes and is overexpressed on muscle fibers in PM patients (15, 16). Second, CD8-positive T cells specific for myositis cross-reacted with an antigen on hepatocytes. Third, oligoclonal CD8-positive T cells were activated by unknown triggers and injured the muscle and liver. In fact, certain CD8-positive T cells are clonally expanded both in the circulation and in muscle (17-19). Further examinations will be necessary to clarify the mechanism of myositis and liver injury in patients with PM.

D-penicillamine is used for the treatment of Wilson’s disease, scleroderma, and RA. Some autoimmune diseases have been induced by D-penicillamine including lupus erythematosus, Goodpasture’s syndrome, myasthenia gravis, and polymyositis/dermatomyositis (20-24). The frequency of D-penicillamine-induced polymyositis/dermatomyositis has varied between 0.2-1.2% in previous reports (23, 24). Our patient was treated by D-penicillamine at 100 mg/day for 6 months before admission. Therefore, it may be possible to speculate that polymyositis was induced by D-penicillamine in the present case. However, the drug did not seem to be related to liver injury directly, because this patient did not satisfy the criteria of drug-induced liver injury (25) and the histological findings were different from the ones of hepatic injury due to drugs.

In summary, this case report demonstrates the pathogenic potential of CD8-positive T cells in liver injury in patients with PM. Further investigations are necessary to define the exact pathogenesis of liver disturbance in collagen diseases.

References

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