Liver damage in patients with polymyositis and dermatomyositis

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Objective: To clarify the prevalence of liver damage associated with polymyositis (PM) and dermatomyositis (DM)

Methods: Forty-two patients with PM/DM were exhaustively studied. Six patients showed liver diseases of known etiology, including drug-induced hepatitis, fatty liver, metastatic liver tumor, primary biliary cirrhosis and autoimmune hepatitis. As a control, 8 patients with miscellaneous diseases who showed elevation of the creatine kinase (CK) due to extreme exercise were studied. Serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and CK, as well as the ratios of AST/CK, ALT/CK and AST/ALT were evaluated.

Results: ALT levels were significantly elevated in PM/DM compared with control group. The ratios of AST/CK and ALT/CK were significantly elevated in PM/DM compared with the control group. AST/ALT ratios in PM/DM were significantly lower than those in control group (P < 0.0001). Twenty-six of 36 patients (72.2%) with PM/DM showed AST/ALT ratios below the minimum value of AST/ALT ratios in the control patients. Additionally, 10 of 26 patients (38.5%) showed hepatocellular liver damage. There were no significant differences in the levels of AST, ALT or CK, or in the ratios of AST/CK, ALT/CK or AST/ALT between PM and DM.

Conclusions: The results indicate that a disproportionate elevation of ALT takes places in patients with PM/DM. These data, therefore, strongly suggest that PM/DM might cause liver damage.

Key words: Liver damage, polymyositis, dermatomyositis

Introduction

Polymyositis (PM) is an inflammatory muscle disease of unknown etiology, characterized by the presence of proximal muscle weakness as a prominent symptom, muscle enzyme elevation including creatine kinase (CK) and lymphocytic infiltration into muscular tissues. In addition to these muscular manifestations, dermatomyositis (DM) frequently presents with specific cutaneous symptoms such as Gottron's sign and heliotrope rash. The prevalence and incidence of PM/DM are 10−13 per 100,000 populations and 10−13 per 1,000,000 person-years, respectively, in Japan. Therefore, PM/DM are rather common.

Elevation of liver enzyme aspartate aminotransferase (AST) is often seen along with elevation of CK in a variety of muscle diseases, including PM/DM. Because alanine aminotransferase (ALT) is contained in skeletal muscles at much lower quantities than is AST, it is marginally elevated in myopathies. By contrast, several case reports revealed that disproportionate elevations of ALT were observed in patients with PM or DM. These cases suggest the possible presence of liver damage caused by PM/DM.

Noteworthy, liver damage has been known to sometimes reflect the activity of connective tissue diseases (CTDs) itself other than various causes, including drug-induced hepatitis, fatty liver, and viral hepatitis. In a previous histopathological investigation of 160 patients with CTDs, including 18 patients with PM/DM, hepatic arteritis was observed in 27 patients with the incidence of 100% in polyarteritis nodosa and 8.3%−25% in other CTDs. Furthermore, CD8-positive T cell infiltration was found to infiltrate in the interstitium of both liver and muscle tissues, indicating the pathogenic potential roles of CD8-positive T cell in liver injuries. The present study was designed to explore whether or not liver damage, not related with drug-induced liver dysfunction,
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Fatty liver, viral hepatitis, or malignancy is prevalent in patients with PM and DM.

Methods

Patients
Forty-two patients with PM/DM, who had been admitted to the Department of Rheumatology and Infectious Diseases, Kitasato University Hospital, between January 2006 and October 2011, were included in the present study. These patients were diagnosed with PM/DM or amyopathic DM based on Bohan and Peter’s or Sontheimer’s criteria. Among the 42 patients, 6 patients showed liver diseases of known etiology, including drug-induced hepatitis (1 patient), fatty liver (1 patient), metastatic liver tumor (1 patient), primary biliary cirrhosis (PBC) (1 patient) and autoimmune hepatitis (AIH) (2 patients). The diagnosis of fatty liver was evaluated by abdominal ultrasonography (US) and computed tomography (CT). Metastatic liver tumor was diagnosed by US and CT findings and histopathological manifestation. The diagnoses of PBC and AIH were based on the criteria provided by Sasaki et al. and by the International Autoimmune Hepatitis Group, respectively. These 6 patients were excluded from the analyses. None of the other 36 patients were positive for HBs antigen, HBs antibody, HBc antibody, or hepatitis C antibody. As a control, 8 patients with various diseases who showed elevation of CK due to extreme exercises were studied (2 HIV patients, 1 fibromyalgia patient, 2 polymyalgia rheumatica patients, 1 rheumatoid arthritis patient, 1 systemic sclerosis patient, and 1 Beçhet’s disease patient).

Data recording and the definition of liver damage
Serum levels of AST, ALT, alkaline phosphatase (ALP) and CK were measured before treatment. The normal ranges of AST, ALT, ALP, and CK were 10—35 U/l, 5—40 U/l, 115—359 U/l and 60—247 U/l, respectively. In the present study, a liver biopsy was not performed in patients with PM/DM and control. Therefore, we defined liver damage as an increase of more than twice that of the upper normal range of ALT. We compared the AST/ALT ratio between PM/DM and the control group. The patients with PM/DM, who showed AST/ALT ratio below the minimum value of the AST/ALT ratio in the control patients, were defined as patients with liver damage. Furthermore, the prevalence of hepatocellular liver damage for these patients was examined. This study was carried out in compliance with the Declaration of Helsinki, and the ethical guideline for epidemiological research issued by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare of the Japanese Government.

Statistical analyses
Comparison of various parameters between PM/DM and the control group and between PM and DM was carried out by the Mann-Whitney U-test, and comparison of the AST/ALT ratio of the patients with PM/DM between before and after 4 weeks of treatment with immunosuppressive agents was carried out by the Wilcoxon matched-pairs signed rank test, using GraphPad Prism 6 for Microsoft Windows, GraphPad Software, San Diego, CA, USA.

Results

Demographic data of the patients
Clinical characteristics of 36 patients with PM/DM and 8 control patients are shown in Table 1. Control patients showed elevation of CK due to extreme exercise, which subsided spontaneously without any immunosuppressive therapy. Although there were no significant differences in clinical and demographic features between 10 patients with PM and 26 patients with DM, a larger number of patients with DM received cyclosporin A, intravenous cyclophosphamide pulse therapy and tacrolimus.

Liver enzymes and CK in sera from patients with PM/DM
We initially compared the serum levels of AST, ALT and CK in PM/DM with those in the control group. ALT levels were significantly elevated in PM/DM compared with the control group (P=0.0132), whereas there were no significant differences in the levels of AST and CK (Figure 1). As shown in Figure 2, the ratios of AST/CK and ALT/CK were significantly elevated in PM/DM compared with those in the control group, indicating that the levels of AST and ALT were disproportionately higher than expected by the values of CK in PM/DM. Furthermore, AST/ALT ratios in PM/DM were significantly lower than those in the control group. The results indicate that ALT was disproportionately elevated in patients with PM/DM. Because ALT is present at much lower levels than AST in muscle tissues, the data strongly suggest that the damage in liver tissue occurs in PM/DM. Twenty-six of 36 patients (72.2%) with PM/DM showed AST/ALT ratios below the minimum value of AST/ALT ratios in the control patients. Additionally, among those 26 patients, 10 patients (38.5%) had liver damage, which was considered hepatocellular, and 1
Table 1. Clinical characteristics of the patients

<table>
<thead>
<tr>
<th></th>
<th>Control n = 8</th>
<th>Polymyositis n = 10</th>
<th>Dermatomyositis* n = 26</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>55.6 ± 21.8</td>
<td>51.8 ± 10.7</td>
<td>52.9 ± 12.8</td>
</tr>
<tr>
<td>Female : Male</td>
<td>1 : 7</td>
<td>7 : 3</td>
<td>21 : 5</td>
</tr>
<tr>
<td>Interstitial pneumonia</td>
<td>0</td>
<td>7 (70.0%)</td>
<td>19 (73.0%)</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hepatic cirrhosis with ascites</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Laboratory findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>0.6 ± 0.2</td>
<td>0.4 ± 0.1</td>
<td>0.4 ± 0.2</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.1 ± 0.5</td>
<td>3.4 ± 0.6</td>
<td>3.4 ± 0.5</td>
</tr>
<tr>
<td>Prothrombin time (%)</td>
<td>-</td>
<td>87.5 ± 9.2</td>
<td>96.6 ± 12.6</td>
</tr>
<tr>
<td>Activated partial thromboplastin time (sec)</td>
<td>-</td>
<td>34.7 ± 5.9</td>
<td>38.5 ± 9.9</td>
</tr>
<tr>
<td>Therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predonisolone, initial dose (mg/day)</td>
<td>-</td>
<td>47.7 ± 9.0</td>
<td>52.1 ± 14.3</td>
</tr>
<tr>
<td>Methyl-predonisolone pulse (case)</td>
<td>-</td>
<td>4 (40.0%)</td>
<td>9 (34.6%)</td>
</tr>
<tr>
<td>Other immunosuppressant agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporin A</td>
<td>-</td>
<td>3 (30.0%)</td>
<td>12 (46.2%)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>-</td>
<td>3 (30.0%)</td>
<td>5 (19.2%)</td>
</tr>
<tr>
<td>IVCY</td>
<td>-</td>
<td>0</td>
<td>6 (23.1%)</td>
</tr>
<tr>
<td>IVIG</td>
<td>-</td>
<td>1 (10.0%)</td>
<td>0</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>-</td>
<td>0</td>
<td>3 (11.5%)</td>
</tr>
</tbody>
</table>

*Three of 26 patients with dermatomyositis were diagnosed as clinically amyopathic dermatomyositis.
IVCY: intravenous cyclophosphamide, IVIG: intravenous immunoglobulin

![Figure 1](image_url)

Figure 1. Serum levels of AST, ALT, and CK in PM/DM

Each symbol represents 1 subject. The shaded area represents the normal range of AST, ALT, and CK. Horizontal lines show the mean, and error bars show the SEM. Statistical analysis was carried out by the Mann-Whitney U-test. The mean ± SD for AST, ALT, and CK were 85 ± 81.2, 40.5 ± 42.3, and 4,396.4 ± 5,387.5 in the 8 control subjects. These in 36 patients with PM/DM were 146.1 ± 173.6, 108.4 ± 105, and 2,425.2 ± 3,155.4, respectively. ALT, alanine aminotransferase: AST, aspartate aminotransferase: CK, creatine kinase
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Figure 2. The ratios of AST/CK, ALT/CK and AST/ALT ratios in PM/DM

The mean ± SD for AST/CK, ALT/CK, and AST/ALT were 0.029 ± 0.016, 0.012 ± 0.006, and 2.41 ± 0.99 in the 8 control subjects. These in 36 patients with PM/DM were 0.33 ± 0.64, 0.23 ± 0.4, and 1.37 ± 0.46, respectively. Each symbol represents 1 subject. Horizontal lines show the mean, and error bars show the SEM. Statistical analysis was carried out by the Mann-Whitney U-test.

Figure 3. Comparison of the levels of AST, ALT and CK between PM and DM

The mean ± SD for AST, ALT, and CK were 147.7 ± 136.8, 125.4 ± 89.1, and 3,608.9 ± 3,450.4 in 10 patients with PM. These in 26 patients with DM were 145.5 ± 188.3, 101.9 ± 111.4, and 1,970 ± 2,979.5, respectively. The shaded area represents the normal range of AST, ALT, and CK. Horizontal lines show the mean; error bars show the SEM. Statistical analysis was carried out by the Mann-Whitney U-test.

Figure 4. Comparison of the AST/CK, ALT/CK and AST/ALT between PM and DM

The mean ± SD for AST/CK, ALT/CK, and AST/ALT were 0.075 ± 0.06, 0.06 ± 0.037, and 1.31 ± 0.73 in 10 patients with PM. These in 26 patients with DM were 0.43 ± 0.73, 0.3 ± 0.45, and 1.39 ± 0.32, respectively. Horizontal lines show the mean, and error bars show the SEM. Statistical analysis was carried out by the Mann-Whitney U-test.
patient (12.5%) showed liver damage in the control group.

We then examined whether or not there was any difference in liver damage between PM and DM, because some studies suggest differences in their pathogenesis.1,16 There were no significant differences in the levels of AST, ALT and CK nor in the ratios of AST/CK, ALT/CK and AST/ALT between PM and DM (Figures 3, 4), although the ratios of AST/CK and ALT/CK appeared to be higher in DM than those in PM. Altogether, these data indicate that serum ALT disproportionately elevated liver damage is prevalent in PM as well as in DM.

Furthermore, comparison of the AST/ALT ratio in 26 patients with PM/DM between before and after 4 weeks of treatment with immunosuppressive agents is shown in Figure 5. Immunosuppressive therapy significantly improved the AST/ALT ratio in patients with PM/DM.

Discussion

In the present study, we examined the prevalence of liver damage in PM and DM. It should be noted that PBC and AIH were complicated in 1 and 2 patients, respectively, among the 42 patients in the study. Therefore, the prevalence of PBC and AIH in this series of patients was comparable to a previous studies.7 More importantly, the data in the present study have disclosed that approximately 72.2% of patients with PM/DM have liver damage, as evidenced by the disproportionate elevation of ALT as well as by the decrease in AST/ALT ratios. In Japanese healthy-young subjects, AST/ALT ratios after 96 hours post-exercise have been found to rise above 2 − 3, although the elevation of ALT levels was delayed in comparison with AST levels.17 Accordingly, in the present study, AST/ALT ratios in the control group were above 2. By contrast, the average of AST/ALT ratios in PM/DM was 1.38, which was significantly lower than that in control. These findings indicate that serum levels of ALT in PM/DM were elevated disproportionately against serum AST levels. It should be noted that the amount of ALT contained in muscle was much lower than AST,15 and that ALT is mainly present in liver.18,19 It is, therefore, most likely that the disproportionate elevation of ALT along with the decreased AST/ALT ratios might be a result of liver damage in PM/DM patients. Because the decrease in AST/ALT ratios returned to normal after treatment with immunosuppressive agents (Figure 5), the liver damage was likely caused by PM/DM.

Takahashi et al.7 previously reported that 9 of 27 patients presented with hepatitis associated directly with PM/DM. However, the prevalence of liver damage with PM/DM was higher in the present cohort of patients. This might be due to differences in the assessment of liver damage. Thus, Takahashi et al.7 defined liver damage as an elevation of at least 2 of ALT, alkaline phosphatases (ALP), and γ-glutamyl transpeptidase. It should be noted that ALT levels in PM/DM in their study7 were comparable to those in the present study. Moreover, ALP levels were the lowest among various CTDs in their study.7 Therefore, it is possible that liver damage might be underestimated in their study.

Major histocompatibility complex (MHC) class 1 is known to be overexpressed within the inflammatory myofasia and muscle fibers in patients with myositis.20-22 It is, therefore, suggested that CD8-positive T cells invading the muscle tissues might recognize some antigens presented by MHC class 1, leading to muscle injuries, although the nature of such antigens that trigger immune responses remains unknown. Notably, Takahashi et al.5 reported a case of PM with liver injury without secondary hepatitis, in which CD8-positive T cell infiltration was found simultaneously both in the liver and in the muscle.5 It is, therefore, possible that such CD8-positive T cells might recognize the antigens that were expressed commonly in the liver as well as in the muscle in the patient. Further studies are warranted to identify such antigens.

On the other hand, a number of reports have revealed that patients with viral hepatitis, including HAV, HBV, and HCV hepatitis developed PM/DM.23-26 It is possible that infection of these hepatitis viruses induce some unknown antigens or viral antigens in the context of MHC.
class I in hepatocytes as well as in muscle tissues, against which CD8-positive T cells might respond and cause tissue damage.

The major limitation of this study is that we did not perform liver biopsies for control and PM/DM patients. A liver biopsy may facilitate the pathological and immunological assessment. Other limitations of this study are the relatively small size of the control population of patients, especially more women, would support our conclusions more convincingly.

In summary, these data demonstrate that liver damage was much more prevalent than expected in patients with PM/DM. Further studies designed to investigate such antigens that are commonly expressed in liver and muscle would be important for a more complete understanding of the mechanisms of liver damage in PM/DM.

Conflict of interest
All authors declare that they have no conflicts of interest.

This study was carried out in compliance with the Declaration of Helsinki, and the ethical guideline for epidemiological research issued by the Ministry of Health, Labour and Welfare of the Japanese Government. Informed consent was obtained from all patients included in the study.

References


