Rheumatology International (2019) 39:901–909
https://doi.org/10.1007/s00296-019-04255-2

Rheumatology
INTERNATIONAL

GENES AND DISEASE

Liver dysfunction in anti-melanoma differentiation-associated gene 5 antibody-positive patients with dermatomyositis

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Received: 14 January 2019 / Accepted: 14 February 2019 / Published online: 21 February 2019

Abstract

The objective was to investigate the clinical and histological features of liver dysfunction in patients with polymyositis (PM) or dermatomyositis (DM).A total of 115 patients (38 with PM and 77 with DM), who were admitted to our hospital between 2001 and 2012, were retrospectively reviewed. Liver dysfunction was defined as an alanine transaminase (ALT) level ≥ 60 U/l and a disproportionate ALT elevation relative to the creatine kinase level. The histological findings from liver biopsies were also assessed.The frequencies of liver dysfunction were 3% and 17% in the patients with PM and DM, respectively. Liver dysfunction was not observed in the patients who had malignancies. Among the patients with DM with no malignancies ($n = 50$), 20% had liver dysfunction, and all of the patients with liver dysfunction were positive for the anti-melanoma differentiation-associated gene 5 (MDA5) antibody. Compared with those in the patients who did not have liver dysfunction, the ALT, alkaline phosphatase, γ-glutamyl transferase, and KL-6 levels were significantly elevated in the patients who had liver dysfunction. Six patients, comprising four with DM and two with PM, underwent liver biopsies, and the common histological findings associated with DM were steatosis, hepatocyte ballooning, increases in the pigmented macrophage numbers, and glycogenated nuclei. Hemophagocytosis was detected in two of three patients with DM who underwent liver biopsies and bone marrow aspirations. In conclusion, Liver dysfunction might be an extramuscular manifestation in patients with DM who are anti-MDA5 antibody-positive. Steatosis and hepatocyte ballooning could be common histological features.

Keywords Fatty liver · Macrophage activation syndrome · Non-alcoholic fatty liver disease · Skin ulcer

Introduction

Polymyositis (PM) and dermatomyositis (DM) are immune-mediated disorders characterized by the inflammation of the skeletal muscles. Extramuscular manifestations often occur in patients with PM or DM that involve the skin, lungs, and joints. Muscle injuries often cause liver enzyme elevations in patients with PM or DM [1, 2], because the skeletal muscles contain liver enzymes, namely, aspartate transaminase (AST) and alanine transaminase (ALT). The serum transaminase levels correlate with the serum creatine kinase (CK) levels in patients with myositis [1, 3, 4]. The frequency of liver dysfunction in patients with PM or DM ranges from 30 to 72%, depending on the criteria used for its diagnosis [5–7].

Liver involvement that is demonstrated histologically is uncommon in patients with PM or DM, and it includes primary biliary cholangitis (PBC), autoimmune hepatitis (AIH), hepatitis virus infections, fatty liver, hepatic arteritis,

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hepatic congestion, and nonspecific or regenerative changes [5, 7–11]. Although liver enzyme elevations often indicate muscle inflammation in these patients, some studies' findings suggest that actual liver damage occurs [6, 12]. Disproportionate ALT level elevations have been described in patients with PM or DM compared with those in patients whose CK levels rose following extreme exercise [6]; however, liver biopsies were not undertaken during these studies.

Anti-melanoma differentiation-associated gene 5 (MDA5) antibody is a specific antibody for DM that is often positive in patients with clinically amyopathic DM (CADM) [13]. In these patients, liver enzymes, including γ-glutamyl transferase (γGT), are elevated, despite relatively low CK levels [12]. Liver function tests may be minimally affected in patients with CADM. Patients who are anti-MDA5 antibody-positive may present with actual liver dysfunction. In this retrospective study, we examined the frequency of liver dysfunction in patients with PM or DM, and elucidated the clinical and histological characteristics of the patients with liver abnormalities.

Patients and methods

All the patients with PM or DM who were admitted to the Rheumatology Division at Jichi Medical University Hospital, Tochigi, Japan, from 2001 to 2012, were reviewed retrospectively. Diagnoses of PM or DM were based on the criteria proposed by Bohan and Peter [14]. CADM was diagnosed according to the definition proposed by Sontheimer et al. [15]. Cancer-associated myositis was diagnosed if a malignant tumor was detected within 3 years of a myositis diagnosis. All the patients were comprehensively examined to detect any underlying malignancies using contrast-enhanced computed tomography (CT) of the chest and abdomen, upper gastroduodenoscopy, abdominal ultrasonography, fecal occult blood tests or colonoscopy, serum prostate-specific antigen assays, mammography, and cervical smears.

The medical records were reviewed retrospectively to evaluate the patients' clinical features and laboratory data. The laboratory test results were obtained on the day of admission. Anti-aminoacyl-transfer RNA synthetase antibodies were detected using immunoblotting kits (Euroline Myositis Profile 3; Euroimmun AG, Luebeck, Germany), and the presence of the anti-MDA5 antibody was evaluated using an anti-MDA5 assay (MESACUP™; Medical & Biological Laboratories Co., Ltd., Nagoya, Japan). The anti-mitochondrial antibody and anti-mitochondrial M_2 antibody levels were measured by SRL, Inc. (Tokyo, Japan).

Interstitial lung disease (ILD) was diagnosed by radiologists based on the presence of interstitial changes using chest CT. Fatty liver was diagnosed using abdominal ultrasonography, and a diagnosis was based on the presence of echogenic contrast between the liver and kidney (bright liver). Chronic liver damage included other nonspecific findings detected by abdominal ultrasonography, namely, heterogeneous changes in the parenchyma, dull edges, and an irregular surface.

At our hospital, the normal ranges for both AST and ALT are ≤ 30 U/l, and the normal range for CK is ≤ 188 U/l. We defined liver dysfunction as an ALT level ≥ 60 U/l, that is, more than double the upper limit of the normal range, and the disproportionate elevation of the ALT level relative to the CK level, which was defined as an ALT level divided by its upper limit of normal that was greater than the CK level divided by its upper limit of normal, or ALT/30 ≥ CK/188. A drinker of alcohol was defined as a patient who consumed the equivalent of > 20 g of ethanol per day. Hepatitis B virus and hepatitis C virus (HCV) infections were defined as the presence of hepatitis B virus surface antigens (HBsAg) and anti-HCV antibodies, respectively.

The liver histology findings were classified according to the histological scoring system established by Kleiner et al. for nonalcoholic fatty liver disease (NAFLD) with modifications [16]. Steatosis, fibrosis, inflammation, liver cell injury, and other findings, namely, Mallory–Denk bodies, pigmented macrophages, and glycogenated nuclei, were scored semi-quantitatively.

Statistical analyses

The Chi-squared test or Fisher's exact test was used to compare two groups in relation to the categorical data, and the Mann–Whitney test was used for the continuous variables. Since this was an exploratory study, probability (P) values < 0.05 were considered significant for these analyses, with no corrections for multiple comparisons. All the analyses were performed using JMP software, version 11 for Windows (SAS Institute Inc., Cary, NC, USA).

Results

During the period studied, 44 patients were diagnosed with PM and 79 patients were diagnosed with DM. Six patients, comprising five with PM and one with DM, whose diagnoses overlapped with systemic sclerosis, and one patient with DM whose diagnosis overlapped with systemic lupus erythematosus, were excluded. One patient with PM who was aged < 15 years was also excluded. A total of 115 patients were included in this study (Table 1), comprising 90 with definite myositis, 14 with probable myositis, and 11 with possible myositis. Their median age was 55 years, and 66 patients (57%) were women. Of the 115 patients, 13 (11%)

Table 1 Comparisons of the clinical and laboratory characteristics between patients with dermatomyositis or polymyositis

	DM ($n=77$)	PM ($n=38$)	P
Age (years)	56 (47–68)	54 (44–65)	0.42
Women	42 (55)	24 (63)	0.43
BMI (kg/m^2)	22.0 (19.6–25.2)	22.2 (20.0–23.5)	0.46
Alcohol > 20 g/day	11 (14)	6 (16)	1.00
HBV or HCV-positive	3 (4)	2 (5)	1.00
Glucocorticoid naive	69 (90)	33 (87)	0.76
Cancer-associated myositis	20 (26)	9 (24)	0.79
ILD	54 (70)	22 (58)	0.20
Fatty liver	21/66 (32)	7/33 (21)	0.27
CRP (mg/dl)	0.57 (0.14–2.14)	0.33 (0.88–1.22)	0.13
ANA ≥ 160 ×	26 (34)	6 (16)	0.04*
Anti-ARS antibodies	17 (22)	15 (39)	0.05
Anti-MDA5 antibody	30 (39)	0 (0)	< 0.001**
AMA	0/19 (0)	2/11 (18)	0.17
Other autoantibodies[a]	23 (30)	10 (26)	0.83
CK (U/l)	566 (125–2410)	2472 (1250–7305)	< 0.001**
Aldolase (U/l)[b]	9.9 (6.8–25.1)	51.6 (27.7–88.7)	< 0.001**
AST (U/l)	85 (49–137)	104 (57–204)	0.21
ALT (U/l)	51 (29–100)	91 (48–212)	< 0.005**
ALT ≥ 60 U/1	32 (42)	24 (63)	0.03*
Liver dysfunction	13 (17)	1 (3)	0.03*
Ferritin (ng/m1)[b]	375 (171–763)	119 (52–219)	0.001**
LDH (U/l)	423 (342–614)	580 (427–1033)	< 0.005**
ALP (U/l)	205 (175–249)	200 (160–275)	0.93
γGT (U/l)	28 (19–47)	17 (13–39)	0.03*
WBC (/μl)	6600 (5050–9550)	7600 (5675–9325)	0.39
Lymphocytes (/μl)	800 (600–1100)	1350 (909–2597)	< 0.001**
Hb (g/dl)	12.4 (11.4–13.6)	13.0 (11.7–14.0)	0.33
Platelets (× 10^4/μl)	23.0 (19.0–30.0)	29.4 (21.0–36.3)	0.02*

The data presented are the medians (interquartile ranges) or the numbers (%)

ALP alkaline phosphatase (reference range: < 337 U/l), *ALT* alanine transaminase; AMA, anti-mitochondrial antibody or anti-mitochondrial M_2 antibody; ANA, antinuclear antibodies, *ARS*, anti-aminoacyl transfer RNA synthetase, including Jo-1, PL-7, PL-12, and EJ, *AST* aspartate transaminase, *BMI* body mass index, *CK* creatine kinase, *CRP* C-reactive protein, *DM* dermatomyositis, *γGT* γ-glutamyl transferase (reference ranges: men < 70 U/l, women < 30 U/l), *Hb* hemoglobin, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *ILD* interstitial lung disease, *LDH* lactate dehydrogenase (reference range: < 216 U/l), *MDA5* melanoma differentiation-associated gene 5, *PM* polymyositis, *WBC* white blood cell

*$P < 0.05$

**$P < 0.01$

[a]Other autoantibodies detected included anti-Ro-52, anti-Mi-2, anti-signal recognition particle, and anti-PM-Scl75

[b]The aldolase and serum ferritin levels were measured in 84 and 72 patients, respectively

had been treated with glucocorticoids to control ILD, myositis, or arthritis before they were referred to our hospital. Twenty-nine patients (25%) had cancer-associated myositis. CADM was diagnosed in 11 out of 77 patients (14%) with DM.

There were no differences between the patients with DM and those with PM in relation to the body mass index, alcohol consumption, and the frequency of fatty liver. Of the 30 patients (26%) who were evaluated for the presence of anti-mitochondrial or anti-mitochondrial-M_2 antibodies, 2 patients with PM were positive for these antibodies. Two patients with DM were positive for the anti-HCV antibody, but both of these patients' serum viral loads were undetectable. One patient with DM and two patients with PM were positive for the HBsAg. HBV-DNA was undetectable

in two patients with PM, and it was detected in the patient with DM.

The liver dysfunction frequencies were 17% (13 out of 77 patients) and 3% (1 out of 38 patients) in the patients with DM and PM, respectively. The levels of all muscle enzymes (except AST) and lymphocyte count were higher in the patients with PM than in those with DM. The serum ferritin and γGT levels, and the anti-MDA5 antibody positivity were higher in the patients with DM than in those with PM. None of the patients who were positive for the HBsAg, anti-HCV antibodies, or anti-mitochondrial antibodies fulfilled the study's definition of liver dysfunction, and none of the patients with cancer-associated myositis had liver dysfunction. One patient with PM who had liver dysfunction had been treated with moderate doses of prednisolone (PSL) for concomitant neurological disease before referral to our hospital.

Since most of the patients with liver dysfunction were diagnosed with DM (13 out of 14 patients), we compared the patients with DM who did and did not have liver dysfunction (Table 2), which involved excluding the patients with cancer-associated myositis and those who had been treated with high-dose glucocorticoids before referral. Among the patients with DM who did not have malignancies ($n=50$), 10 (20%) had liver dysfunction. All of the patients with liver dysfunction were positive for the anti-MDA5 antibody. Compared with the patients who did not have liver dysfunction, the CK level was lower ($P=0.01$), and the transaminase, alkaline phosphatase (ALP), and γGT levels were higher in the patients with liver dysfunction. The aldolase and lactate dehydrogenase levels did not differ between the patients who did and did not have liver dysfunction ($P=0.71$ and $P=0.59$, respectively).

Figure 1 shows the serial changes in the ALT and CK levels in the patients with DM and liver dysfunction. After treatment with moderate-to-high-dose glucocorticoids, the ALT levels increased transiently in all of the patients, except one, and the γGT levels increased transiently in all of the patients (data not shown). The CK levels decreased steadily in most of the patients. Additional treatment with methylprednisolone pulse therapy and/or the immunosuppressive agent, cyclosporine, was required by 70% of the patients for ILD, myalgia, and general malaise, because their responses to PSL were insufficient. Three out of 10 patients died as a consequence of rapidly progressive ILD ($n=2$) or pneumocystis pneumonia ($n=1$).

Six patients, comprising four with DM and two with PM, underwent liver biopsies (Table 3), and all of the patients, except one, underwent these biopsies before glucocorticoid treatment. Two of the patients (patient numbers 1 and 2) with DM fulfilled the criteria for liver dysfunction on admission. One patient with PM was positive for anti-mitochondrial antibodies, and was suspected of having PBC. The

Table 2 Comparison of the patients with dermatomyositis who had and did not have liver dysfunction

	Liver dysfunction present ($n=10$)	Liver dysfunction absent ($n=40$)	*P*
Age (years)	51.5 (36.0–62.5)	55.0 (47.0–68.8)	0.23
Women	5 (50)	27 (68)	0.46
BMI (kg/m^2)	22.3 (20.2–24.7)	21.4 (18.9–23.8)	0.46
Alcohol > 20 g/day	1 (10)	3 (8)	1.00
CADM	2 (20)	7 (18)	1.00
ILD	10 (100)	30 (75)	0.18
Death caused by ILD	2 (20)	5 (13)	0.61
Fatty liver	4/9 (44)	8/33 (24)	0.28
CRP (mg/dl)	0.42 (0.10–2.97)	0.47 (0.11–1.26)	0.98
ANA ≥ 160 ×	1 (10)	10 (25)	0.42
Anti-ARS antibodies	0 (0)	10 (25)	0.18
Anti-MDA5 antibody	10 (100)	17 (43)	< 0.001**
CK (U/l)	116 (68–255)	303 (111–1910)	0.01*
CK < 300 U/l	10 (100)	20 (50)	< 0.005**
Aldolase (U/l)[a]	10.2 (8.1–12.8)	8.8 (5.8–37.2)	0.71
AST (U/l)	133 (97–149)	60 (39–127)	0.01*
ALT (U/l)	115 (85–173)	31 (23–67)	< 0.001**
ALT ≥ 60 U/l	10 (100)	11 (28)	< 0.001**
LDH (U/l)	420 (362–660)	414 (321–608)	0.59
ALP (U/l)	312 (188–391)	202 (169–230)	0.01*
γGT (U/l)	210 (70–240)	23 (16–33)	< 0.001**
Ferritin (ng/ml)[a]	896 (312–3127)	286 (145–666)	0.10
KL-6 (U/ml)[a]	751 (455–1260)	467 (319–649)	0.04*
IgG (mg/dl)[a]	1543 (1162–1795)	1483 (1228–1654)	0.74
WBC (/μl)	5450 (3075–7675)	5950 (4600–8400)	0.37
Lymphocytes (/μl)	770 (578–853)	715 (600–1200)	0.91
Hb (g/dl)	12.3 (10.2–13.2)	12.5 (10.8–13.6)	0.55
Platelets (×10^4/μl)	19.2 (17.0–27.6)	24.9 (19.4–30.0)	0.11

The data presented are the medians (interquartile ranges) or numbers (%)

ALT alanine transaminase, *ALP* alkaline phosphatase, *ANA* antinuclear antibodies, *ARS* anti-aminoacyl transfer RNA synthetases, including Jo-1, PL-7, PL-12, and EJ, *AST* aspartate transaminase, *BMI* body mass index, *CADM* clinically amyopathic dermatomyositis, *CRP* C-reactive protein, *CK* creatine kinase, *γGT* γ-glutamyl transferase, *Hb* hemoglobin; *IgG* immunoglobulin G, *ILD* interstitial lung disease, *LDH* lactate dehydrogenase, *MDA5* melanoma differentiation-associated gene 5, *WBC* white blood cell

*$P<0.05$

**$P<0.01$

[a]The aldolase, serum ferritin, KL-6, and IgG levels were measured in 41, 32, 42, and 43 patients, respectively

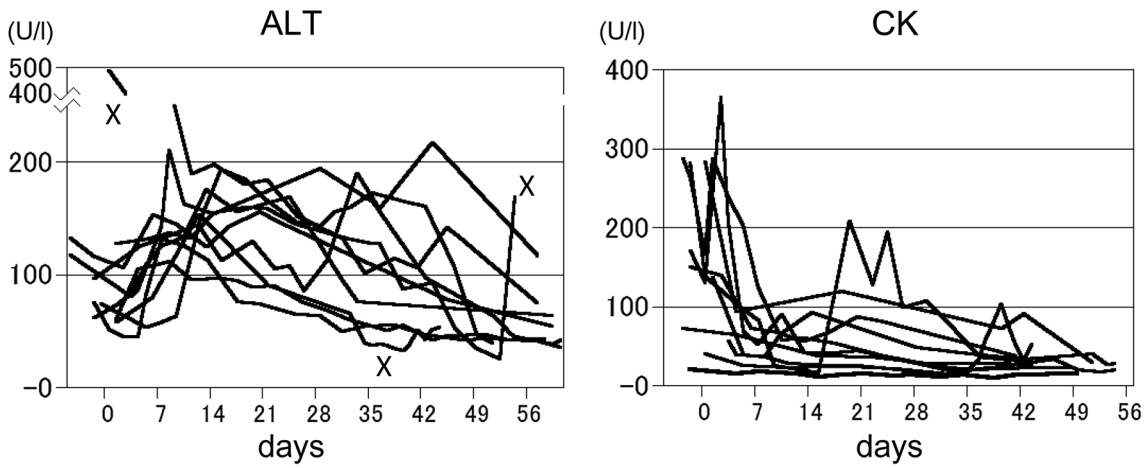

Fig. 1 Serial changes in the alanine transaminase and creatine kinase levels in ten patients with dermatomyositis and liver dysfunction. Prednisolone treatment began on day 0, and the enzyme levels from day − 5 to 60 were plotted. *X* indicates the patients who died. *ALT* alanine transaminase, *CK* creatine kinase

remaining patient with PM had a high antinuclear antibody titer (640×), and was suspected of having AIH. Abdominal ultrasonography detected fatty liver in four patients, but rather than being obese, three of these patients were emaciated as a consequence of fever, arthralgia, and general malaise. The four patients with DM were anti-MDA5 antibody-positive, and they had ILD and skin ulcers. The ILD did not progress rapidly in these patients. Patient number 3 was treated with low-dose PSL (10–20 mg/day) for 7 weeks. Thereafter, a liver biopsy was performed, because the patient showed general fatigue, lost 10 kg in 4 months, and showed progressive liver dysfunction.

The original diagnoses from the pathology reports were suspected drug-induced liver injury in patient number 1, suspected nonalcoholic steatohepatitis (NASH) in patient number 3, acute liver injury in patient numbers 2 and 4, suspected PBC in patient number 5, and AIH in patient number 6. After the cessation of nonsteroidal anti-inflammatory drugs (NSAIDs), the liver dysfunction did not improve in patient number 1 who was suspected of having drug-induced liver injury.

Since four patients had fatty changes at biopsy, we tried to apply the histological scoring system for NAFLD with some modifications. The common histological findings in the four patients with DM were hepatocyte ballooning, pigmented macrophages, and glycogenated nuclei (Figs. 2, 3). Mild steatosis was present in three out of four patients. The distributions of steatosis and hepatocyte ballooning were not necessarily confined to the portal area or central vein, rather, they extended across wide areas. The remaining patient with DM who did not have steatosis (patient number 4), underwent a liver biopsy, because the liver enzyme levels that had been nearly normal on admission, had increased sharply by > 5 times within 2 weeks, and a mild lymphocytic infiltration was seen only in this patient. None of the patients had Mallory–Denk bodies within their hepatocytes.

Three out of four patients with DM (patient numbers 1, 2, and 3) underwent bone marrow aspirations as well as liver biopsies, because of suspected macrophage activation syndrome. Hemophagocytosis was found in patient numbers 1 and 3.

Discussion

The findings from this study showed that liver dysfunction was seen in one-fifth of the patients with DM who did not have malignant tumors. Liver dysfunction as defined by our criteria, was rare, and occurred in 3% of the patients with PM. All of the patients with DM and liver dysfunction were anti-MDA5 antibody-positive. The serum KL-6 level was higher in the patients with liver dysfunction, but the frequency of ILD and the mortality as a consequence of ILD did not differ between the patients who had and did not have liver dysfunction. After glucocorticoid treatment, the ALT levels increased transiently in most of the patients with DM and liver dysfunction, and they required intensive treatment. Steatosis and hepatocyte ballooning were the main histological findings from the liver biopsies.

Liver dysfunction is an extramuscular manifestation in patients with CADM who are anti-MDA5 antibody-positive. Liver dysfunction was obvious in the patients with CADM, because the CK levels were almost normal. The transaminase, ALP, and γGT levels were high, which clearly indicated that the abnormal liver enzyme levels were caused by liver injury alone, rather than muscle inflammation. High serum AST, ALT, γGT, and ferritin levels have been described in Japanese patients with DM who had ILD and

Table 3 Clinical and laboratory characteristics of, and the histological findings from the patients who underwent liver biopsies

	Patient number					
	1	2	3	4	5	6
Diagnosis	DM	DM	DM	DM	PM	PM
Age (years)/sex	64/W	37/M	55/M	47/W	54/W	37/W
Duration from onset to biopsy (months)	1.5	6	5	1	12	3
Medication	NSAID (on demand)	None	S/T PSL 20 mg Ranitidine Pitavastatin	None	None	UDCA
BMI (kg/m^2)	20.0	21.0	18.3	17.5	19.6	24.4
Weight loss	NA	− 6 kg in 4 months	− 10 kg in 4 months	NA	− 6 kg in 12 months	NA
Skin ulcer	(+)	(+)	(+)	(+)	(−)	(−)
ILD	(+)	(+)	(+)	(+)	(−)	(−)
US findings	Chronic liver damage	Fatty liver	Fatty liver	Normal	Fatty liver chronic liver damage	Fatty liver
HPS/BMA	(+/+)	(–/+)	(+/+)	(/–)	(/–)	(/–)
Laboratory findings						
ANA	160 ×	(–)	(–)	(–)	(–)	640 ×
AMA	(–)	(–)	(–)	(–)	(+)	(–)
Anti-MDA5 antibody	(+)	(+)	(+)	(+)	(–)	(–)
AST (U/l)	95	99	91	212	37	222
ALT (U/l)	100	76	105	158	31	231
LDH (U/l)	629	319	384	390	274	405
ALP (U/l)	237	338	254	312	423	292
γGT (U/l)	71	178	112	57	125	59
CK (U/l)	72[a]	72	19	84	579	1703
Ferritin (ng/ml)	6662[b]	452	1368	425	102	NA
Histological findings						
Original pathological diagnosis	Drug-induced injury s/o	Acute liver injury	NASH s/o	Acute hepatitis like	PBC s/o	AIH compatible
Steatosis (0−3)	1	1	1	0	1	0
Fibrosis (0−4)	0	0	1	0	1	2
Lobular inflammation (0−3)	0	0	0	1	1	2
Portal inflammation (0−1)	0	0	0	0	0	1
Ballooning (0−2)	2	2	1	2	1	0
Acidophil bodies (0−1)	0	1	1	1	0	1
Pigmented macrophages (0−1)	1	1	1	1	0	0
Glycogenated nuclei (0−1)	1	1	1	1	1	0

The laboratory values were obtained just before liver biopsy

AIH autoimmune hepatitis, *ALP* alkaline phosphatase, *ALT* alanine transaminase, *AMA* anti-mitochondrial antibodies, *ANA* antinuclear antibodies, *AST* aspartate transaminase, *BMA* bone marrow aspiration, *BMI* body mass index, *CK* creatine kinase, *DM* dermatomyositis, *γGT* γ-glutamyl transferase, *HPS* hemophagocytosis, *ILD* interstitial lung disease, *LDH* lactate dehydrogenase, *M* man, *MDA5* melanoma differentiation-associated gene 5, *NA* not available, *NASH* nonalcoholic steatohepatitis, *NSAID* nonsteroidal anti-inflammatory drug, *PBC* primary biliary cholangitis, *PM* polymyositis, *PSL* prednisolone, *s/o* suspected, *S/T* sulfamethoxazole/trimethoprim, *UDCA* ursodeoxycholic acid, *US* ultrasound, *W* woman

[a]2 weeks before liver biopsy

[b]1.5 months after liver biopsy

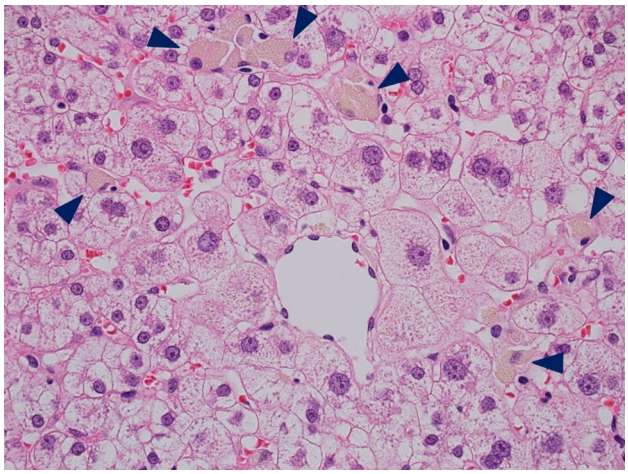

Fig. 2 Histopathology of the liver showing round and enlarged hepatocytes with clear cytoplasms. The arrowheads indicate the pigmented macrophages that are stained yellow–orange. (Hematoxylin and eosin, × 400)

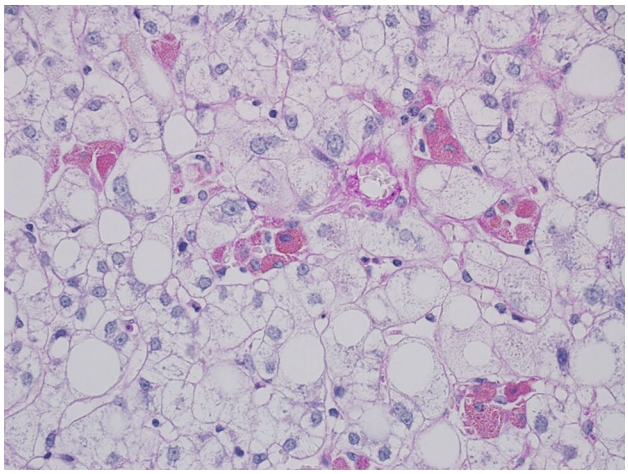

Fig. 3 The activated macrophages are conspicuous (pink) within the background of the pale ballooned hepatocytes. (Periodic acid-Schiff, × 400)

were anti-MDA5 antibody-positive [12]. Disproportionate ALT level elevations have also been described in Japanese patients with PM or DM [6]. Since few patients with PM fulfilled the study's criteria for liver dysfunction, we were unable to determine whether the patients with PM had genuine liver dysfunction.

The patients with DM who did and did not have liver dysfunction did not differ in relation to mortality. Although the serum KL-6 level was high in the patients with liver dysfunction, the frequency of ILD and the mortality caused by rapidly progressive ILD did not differ between the patients who did and did not have liver dysfunction. In contrast to the findings from a previous study [12], liver dysfunction did not indicate a poor prognosis for the patients with DM. There were no differences between the patients who did and did not have liver dysfunction in relation to the serum ferritin level and anti-MDA5 antibody positivity, both of which are markers of a poor prognosis for ILD in patients with DM [12, 17–19]. This may explain why the patients with DM who did and did not have liver dysfunction did not differ in relation to their prognoses.

In most of the patients with DM and liver dysfunction, the transaminase levels increased transiently after treatment with glucocorticoids, which may reflect general disease activity. Most of the patients (70%) with liver dysfunction did not respond adequately to the glucocorticoids and required additional immunosuppressive therapy. Three out of ten patients had rapidly progressive ILD. After treatment intensification, the transaminase levels decreased gradually in all of the patients. In one patient who underwent a liver biopsy (patient number 4), the AST and ALT levels increased sharply by > 5 times within 2 weeks before treatment was administered. Hence, if treatment had been delayed in the patients with liver dysfunction, it might have progressed further.

Fatty liver occurs in 22–67% of patients with PM or DM [5, 11]. In contrast, another study's findings did not indicate that fatty liver was the cause of liver dysfunction in patients with PM or DM, but liver biopsies were not undertaken in this study [7]. In the present study, the liver biopsies showed that three out of four patients with DM had mild steatosis. Although the frequency of fatty liver detected using ultrasonography did not differ, the γGT levels were high in the patients with liver dysfunction. γGT is a marker of NAFLD in patients with metabolic syndrome [20]; hence, elevated γGT levels may indicate fatty changes in patients with DM.

Hepatocyte ballooning is considered a histological feature of DM; it is characterized by swollen hepatocytes that contain rarefied cytoplasm and it indicates hepatocellular injury [21]. However, hepatocyte ballooning is not specific to a particular disease, and it can be present in a variety of conditions, including acute viral hepatitis, AIH, alcoholic steatohepatitis, NASH, and toxic liver damage [22]. Drug-induced fatty liver can also show the histologic features associated with NASH [23], which could explain why the original diagnoses from the pathology reports varied. Patient number 3 might have been diagnosed with NASH, because glucocorticoid treatment had preceded the liver biopsy, and the patient had diabetes; however, the patient was treated for 7 weeks only, and was diagnosed with diabetes for the first time during this admission. Increased numbers of pigmented macrophages and glycogenated nuclei were found in all of the patients. Glycogenated nuclei are also commonly seen in patients with NAFLD and diabetes [21]. Hence, although hepatocyte ballooning, fatty changes, glycogenated nuclei, and Kupffer cell hyperplasia are commonly seen in the livers

of patients with DM, they are nonspecific findings [24]. We postulate that the constellation of these nonspecific findings is a histological feature of the liver in DM.

It is unclear why fatty liver and hepatocyte ballooning occur in patients with DM who are anti-MDA5 antibody-positive. Pigmented macrophages were common in all of the patients with DM. We speculate that the pathogenic mechanism, which is similar to that underlying NASH, also occurs in patients with DM. Activated macrophages (Kupffer cells) play an important role in the pathogenesis of NASH [25]. Activated Kupffer cells secrete many cytokines and chemokines, and they can promote fat accumulation in hepatocytes through the expression of tumor necrosis factor (TNF)-α and interleukin-1β, which alter hepatocyte fatty acid oxidation and triglyceride accumulation. Depleting the Kupffer cells or administering anti-TNF agents attenuate fat accumulation in the liver in animal studies [26, 27]. Inflammation precedes steatosis in NASH, and hepatic steatosis may be a "bystander phenomenon" [28]. This view may be supported by the histological findings from patient number 4 whose early liver biopsy revealed a mild lymphocytic infiltration despite the absence of steatosis. Activated Kupffer cells and hepatocyte ballooning were already present in the absence of steatosis, and the γGT level, which is a marker of NAFLD, was within the normal range on admission.

Macrophage activation underlies the pathophysiology of DM in patients who are anti-MDA5 antibody-positive [12, 13]. If the alveolar macrophages are activated in the lung, patients could present with rapidly progressive ILD. Likewise, excessive Kupffer cell activation may cause severe hepatic injury. In the bone marrow, macrophage activation presents as cytopenia caused by hemophagocytosis. Although there were no differences between the patients who had and did not have liver dysfunction in relation to the white blood cell count, hemoglobin level, and platelet count, hemophagocytosis was detected in two of three patients with DM who underwent bone marrow aspirations and liver biopsies. Thus, as well as macrophage activation in the lung and liver, systemic macrophage activation within the bone marrow may underlie the pathophysiology of DM in patients who are anti-MDA5 antibody-positive [29].

This study's limitations are described next. Given that this study was retrospective, the collection of the data was not comprehensive, and associated conditions, including dyslipidemia and diabetes, which may influence the development of fatty liver, were not evaluated. The method used to detect the anti-MDA5 antibody was not based on immunoprecipitation, and the definition of liver dysfunction used in the present study is not generally recognized. Moreover, drug-induced liver injury could not be excluded, because patients who are positive for the anti-MDA5 antibody often have fever, arthralgia, and ILD, and these patients might have been administered antibiotics or NSAIDs before they were referred to our hospital. Furthermore, the number of patients was small, and the classification and grading of the liver histology were not blinded; however, the purpose of classifying the liver histology was to clarify the characteristic histopathological findings from patients with myositis, not to distinguish between NAFLD and NASH. Fatty changes, namely, steatosis, and hepatocyte ballooning, were common among the patients with DM, and they were easily identified, even without classification.

In conclusion, liver dysfunction is an extramuscular manifestation in patients with DM, especially among those who have CADM and are anti-MDA5 antibody-positive. The histological findings from the liver biopsies, namely, fatty changes, hepatocyte ballooning, increased numbers of pigmented macrophages, and glycogenated nuclei, were nonspecific, but similar to the findings from the liver biopsies of patients with NASH, except for fibrosis, which is always present in NASH. If the transaminase levels are disproportionately higher than the CK levels, the anti-MDA5 antibody should be examined in patients with DM. If patients are positive for the anti-MDA5 antibody, intensive treatment with immunosuppressive drugs should not be delayed for fear of drug-induced liver dysfunction, because it is more likely to reflect DM disease activity.

Acknowledgements We thank all of the staff at our institution who treated the patients. We would like to thank Editage (http://www.editage.jp) for English language editing support.

Author contributions Study concept and design: TN and SM; data acquisition: TN, YK, and MI; data analysis and interpretation: TN, YK, MI, HO, NF, and SM; and approval of the final manuscript: TN, YK, MI, HO, NF, and SM.

Funding None.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study complied with the guidelines of the Declaration of Helsinki and was approved by Jichi Medical University's Institutional Review Board (No. 17–062, May 29, 2017). The requirement for the need to obtain written informed consent from the patients was waived in accordance with the relevant Japanese regulations.

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