Intravenous immunoglobulin contributes to the control of antimelanoma differentiation-associated protein 5 antibody-associated dermatomyositis with palmar violaceous macules/papules

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Intravenous immunoglobulin contributes to control anti-melanoma differentiation-associated protein 5 (MDA5) antibody-associated dermatomyositis with palmar violaceous macules/papules: case reports

Short title: Anti-MDA5 antibody-associated dermatomyositis treated with IVIG

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Bulleted Statements:

What's already known about this topic? :

- Autoantibodies to melanoma differentiation-associated protein 5 (MDA5) are associated with a subset of patients with dermatomyositis (DM) accompanied by rapidly progressive interstitial lung disease with poor prognosis.
- In anti-MDA5 antibody-associated DM patients, serum levels of ferritin and anti-MDA5 antibodies correlate with the disease activity.

What does the study add? :

- This study reveals that intravenous immunoglobulin (IVIG) contributes to control of the disease activity of anti-MDA5 antibody-associated DM.
- Combined modality therapy including IVIG is recommended for treatment of anti-MDA5 antibody-associated DM.
- Palmar violaceous macules/papules around the interphalangeal joints might be a useful sign to suggest a diagnosis of anti-MDA5 antibody-associated DM.

ABSTRACT

Autoantibodies to melanoma differentiation-associated protein 5 (MDA5) are associated with a subset of dermatomyositis (DM) patients who have rapidly progressive interstitial lung disease (RP-ILD) with poor prognosis. Intensive immunosuppressive therapy is initiated before irreversible lung damage can occur; however, there are few lines of evidence for the treatment of RP-ILD. Here, we report 3 cases of anti-MDA5 antibody-associated DM with RP-ILD in which the patients were treated with combined modality therapy including high-dose prednisolone, tacrolimus, intravenous cyclophosphamide, and immunoglobulins (IVIG). In all 3 cases, the serum ferritin levels, which are known to represent the disease activity of RP-ILD, were decreased after IVIG administration. IVIG might contribute to control of the disease activity of anti-MDA5 antibody-positive DM. Moreover, palmar violaceous macules/papules around the interphalangeal joints, which was observed in all 3 cases in the incipient stage, might be a useful sign to suggest a diagnosis of anti-MDA5 antibody-associated DM.

Autoantibodies to melanoma differentiation-associated protein5 (MDA5) are associated with a subset of clinically amyopathic dermatomyositis (DM) patients with rapidly progressive interstitial lung disease (RP-ILD) with poor prognosis[1,2]. Moreover, levels of serum ferritin and anti-MDA5 antibody were associated with the status of ILD[2-4]. In anti-MDA5 antibody-positive patients, intensive immunosuppressive therapy is initiated before irreversible lung damage can occur; however, there are not many lines of evidence for the treatment of RP-ILD. Here, we report 3 cases of anti-MDA5 antibody-associated DM with RP-ILD in which the patients were treated with combined modality therapies including intravenous immunoglobulins (IVIG), which probably contributed to control of the disease activity.

Case report

Case 1

A 57-year-old woman presented with a 1-month history of periorbital edematous erythema (heliotrope rash), palmar violaceous macules/papules around the interphalangeal joints (Fig. 1a), scaly erythema over the dorsum of the metacarpophalangeal, interphalangeal, cubital, and knee joints and the auricles (Gottron's papules and Gottron's signs), and nail-fold telangiectasia. Biopsy from the Gottron's

papules around the interphalangeal joints showed basal cell vacuolar degeneration, mild perivascular lymphocytic infiltrate (interface dermatitis), and mucin deposition in the dermis. Manual muscle testing (MMT) revealed slight weakness of the flexor muscles of the neck. The laboratory data indicated slightly elevated serum levels of ferritin, lactate dehydrogenase (LDH), creatine kinase (CK), aldolase, aspartate amino-transferase (AST), and alanine transaminase (ALT), and normal serum levels of Krebs von den Lungen-6 (KL-6) and surfactant protein D (SP-D) (Table 1). Anti-MDA5 antibody was positive (197.6 index value, yielded by enzyme-linked immunosorbent assay [ELISA]). Computed tomography (CT) of the chest showed ground-glass opacities in the right inferior lobe of the lung (Fig. 2a). DM was diagnosed, and the patient was given oral prednisolone at 1.0 mg/kg/day with oral tacrolimus and biweekly intravenous cyclophosphamide (IVCY) at 500 mg/m^2. The eruptions were gradually disappeared. However, the serum ferritin level rapidly increased without any symptoms; thus, monthly IVIG (400 mg/kg/day for 5 days) was administered (Fig. 3a). Because both the serum ferritin level and the anti-MDA5 antibody index value rapidly decreased and because CT showed no further progression of ILD (Fig. 2a) with the slightly reduced serum KL-6 levels to 392 IU/mL, the oral prednisolone dose was gradually tapered and IVCY was stopped after 7 courses (Fig. 3a).

Case 2

A 57-year-old woman had been hospitalized in the neurology department of our hospital because of worsen paresthesia in the lower extremities from a month before. She developed edematous erythema over the left upper eyelid (heliotrope rash), Gottron's papules over the metacarpophalangeal and interphalangeal joints, palmar violaceous macules/papules around the interphalangeal joints (Fig. 1b), and scaly and itchy erythema on the precordium and the shoulders. As in case 1, biopsies from the Gottron's papules and palmar violaceous macules/papules showed interface dermatitis with mucin deposition in the dermis. MMT revealed slight weakness of the left hamstrings. The laboratory examinations indicated slightly elevated serum levels of ferritin, LDH, and AST and normal serum levels of KL-6, SP-D, CK, aldolase, and ALT (Table 1). Anti-MDA5 antibody was positive (200.3 index value, yielded by ELISA). CT showed ground-glass opacities in the right inferior lobe of the lung (Fig. 2b). DM was diagnosed, and the patient was given oral prednisolone 1.0 mg/kg/day with oral tacrolimus and biweekly intravenous cyclophosphamide (IVCY) at 500 mg/m^2. One week after administration of the combined therapy, the serum ferritin level increased rapidly, as did the anti-MDA5 antibody index value; thus, IVIG (400 mg/kg/day for 5 days) was added. In this case, after

only 1 course of IVIG, the serum ferritin level decreased (Fig. 3b). Accordingly, the ILD and eruptions gradually improved with the slightly reduced serum KL-6 levels to 191 IU/mL (Fig. 2b), the dose of oral prednisolone was tapered and IVCY was stopped after 4 courses (Fig. 3b).

Case 3

A 66-year-old man presented with edematous erythema over the right upper eyelid (heliotrope rash), scaly erythema on the metacarpophalangeal, interphalangeal, and cubital joints (Gottron's signs), palmar violaceous macules/papules around the interphalangeal joints (Fig. 1c), and nail-fold telangiectasia, with complaints about neck and shoulder pain gradually worsening from 1 month before. Biopsies from the heliotrope rash, Gottron's signs, and palmar violaceous macules/papules revealed interface dermatitis. MMT indicated slight weakness of the bilateral deltoid and biceps brachii muscles. The laboratory examinations indicated elevated serum levels of ferritin, LDH, CK, AST, and ALT, and normal serum levels of KL-6, SP-D, and aldolase (Table 1). Anti-MDA5 antibody was positive (213.5 index value, yielded by ELISA). CT showed ground-glass opacities and reticular shadows in the inferior lobes of both lungs (Fig. 2c). DM diagnosed, and the patient was given high-dose oral prednisolone (1 mg/kg),

tacrolimus at 5 mg/day, IVIG (400 mg/kg/day for 5 days), and IVCY at 750 mg/cm^2 (Fig. 3c). The eruptions gradually improved after the therapies. Because RP-ILD occurred (Fig. 2c) with a rapidly increased serum level of ferritin, we added methylprednisolone pulse therapy (1000 mg/day for 3 days). Although the serum ferritin level dramatically decreased (from over 8000 to less than 2000 ng/mL), as did the anti-MDA5-antibody index value, after the combined modality therapy (Fig. 3c), the patient died of respiratory failure with severe RP-ILD a month after we started treatment. In contrast to the reduced serum levels of ferritin and the anti-MDA5-antibody index value, the serum KL-6 level remained to be elevated (from 455 to 1640 U/mL) during the clinical course in this case.

Discussion

A meta-analysis study estimated that the pooled sensitivity and specificity of anti-MDA5 antibodies for RP-ILD were 77% and 86%, and the pooled diagnostic odds ratio was 20.41[5]. Gono *et al* reported that the cumulative 100-month survival rate for the entire anti-MDA5 antibody-positive DM patient group was 66% and a fatal outcome occurred remarkably often within the first 6 months[2]. A few previous reports suggested that intensive immunosuppressive therapies may improve the survival of RP-ILD in anti-MDA5 antibody-associated DM patients[6,7]. It was reported that treatment with IVCY

(combined immunosuppressive therapy including biweekly IVCY) more than 6 times was effectual for patients with DM accompanied by RP-ILD[7]. Unlike other therapies for DM, IVIG is not immunosuppressive and has been used in DM patients for more than 30 years[8]. In all of our 3 cases, treatment with IVIG was used in the incipient stage of the disease, which led to dramatically decreased serum ferritin levels and gradually decreased anti-MDA5 antibody titers. Especially in case 1, the serum ferritin level was decreased sensitively with usage of IVIG (Fig. 3a). In case 3, the serum ferritin level was dramatically decreased after administration of IVIG and additional steroid pulse therapy even though the outcome was fatal; thus, IVIG might also have contributed to temporary stabilization of the disease activity.

The results of the cases reported here suggest that combined modality therapy including IVIG in the incipient stage of the disease, before irreversible lung damage develops, might improve the survival of anti-MDA5 antibody-associated DM patients with RP-ILD. Fiorentino D *et al.* demonstrated that patients with DM presenting with cutaneous ulcerations and/or palmar papules may not have characteristic muscle inflammation of DM but are at increased risk of subacute or rapidly progressive interstitial lung disease[9]. Because palmar papules were present, we promptly confirmed the positivity of anti-MDA5 antibodies by ELISA, which has been established recently[6] and

is now available in Japan, and subsequently started a combined modality therapy in each of the cases. The patients presented with palmar macules/papules that looked violaceous uniquely compared to Gottron's papules/signs. The palmar violaceous macules/papules represented not only lichenoid reactions but also bleeding histologically, and were developing around the interphalangeal joints, which are protuberant and likely subject to pressure. Careful examination of the cutaneous manifestations and quick detection systems for the antibody are important to improve the survival rate of anti-MDA5 antibody-associated DM.

We have here reported 3 cases of anti-MDA5 antibody-associated DM accompanied by RP-ILD treated with combined modality therapy including IVIG started in the incipient stage of the disease. In all of the cases, the IVIG therapy probably contributed to decrease in the serum level of ferritin, which is known to represent the disease activity of anti-MDA5 antibody-associated RP-ILD. Although further evidence is needed to establish suitable therapies for anti-MDA5 antibody-associated DM, combined modality therapy including IVIG could be the best treatment measure at the present time.

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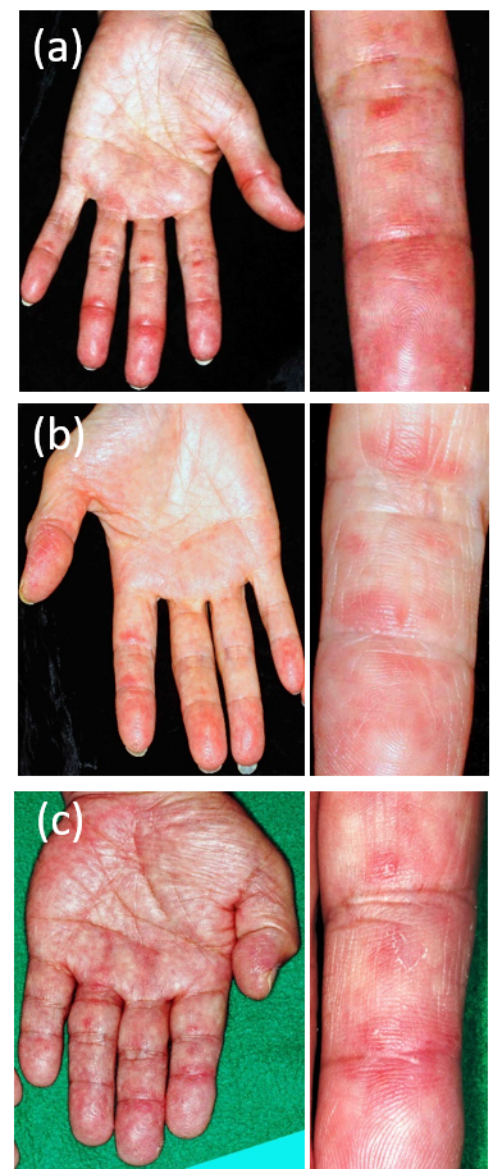
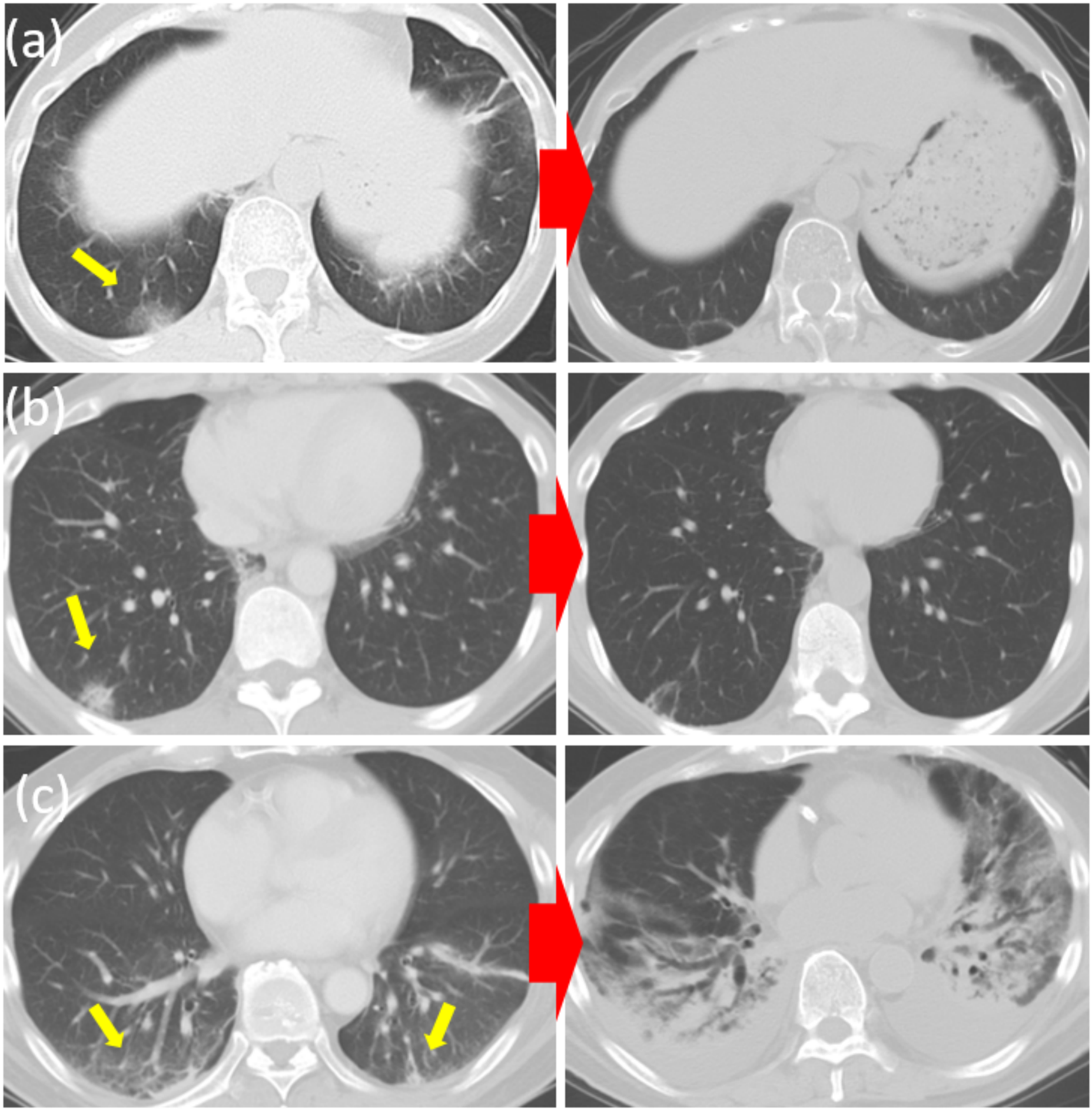
FIGURE LEGENDS

Figure 1. Palmar violaceous macules/papules around the interphalangeal joints of case 1 (a), case 2 (b) and case 3 (c).

Figure 2. Ground-glass opacities and reticular shadows detected by computed tomography (CT). (a) In case 1, ground-glass opacities in the right inferior lobe of the lung were detected at the first visit, and had disappeared 74 days after hospitalization. (b) In case 2, ground-glass opacities in the right inferior lobe of the lung were detected at the first visit, and had almost disappeared 43 days after hospitalization. (c) In case 3, ground-glass opacities and reticular shadows in the inferior lobes of both lungs were detected at the first visit, and had rapidly progressed 28 days after hospitalization.

Figure 3. Clinical courses of case 1 (a), case 2 (b) and case 3 (c). IVIG, intravenous immunoglobulin; IVCY, intravenous cyclophosphamide.


(a)
(b)
(c)


(a)
(b)
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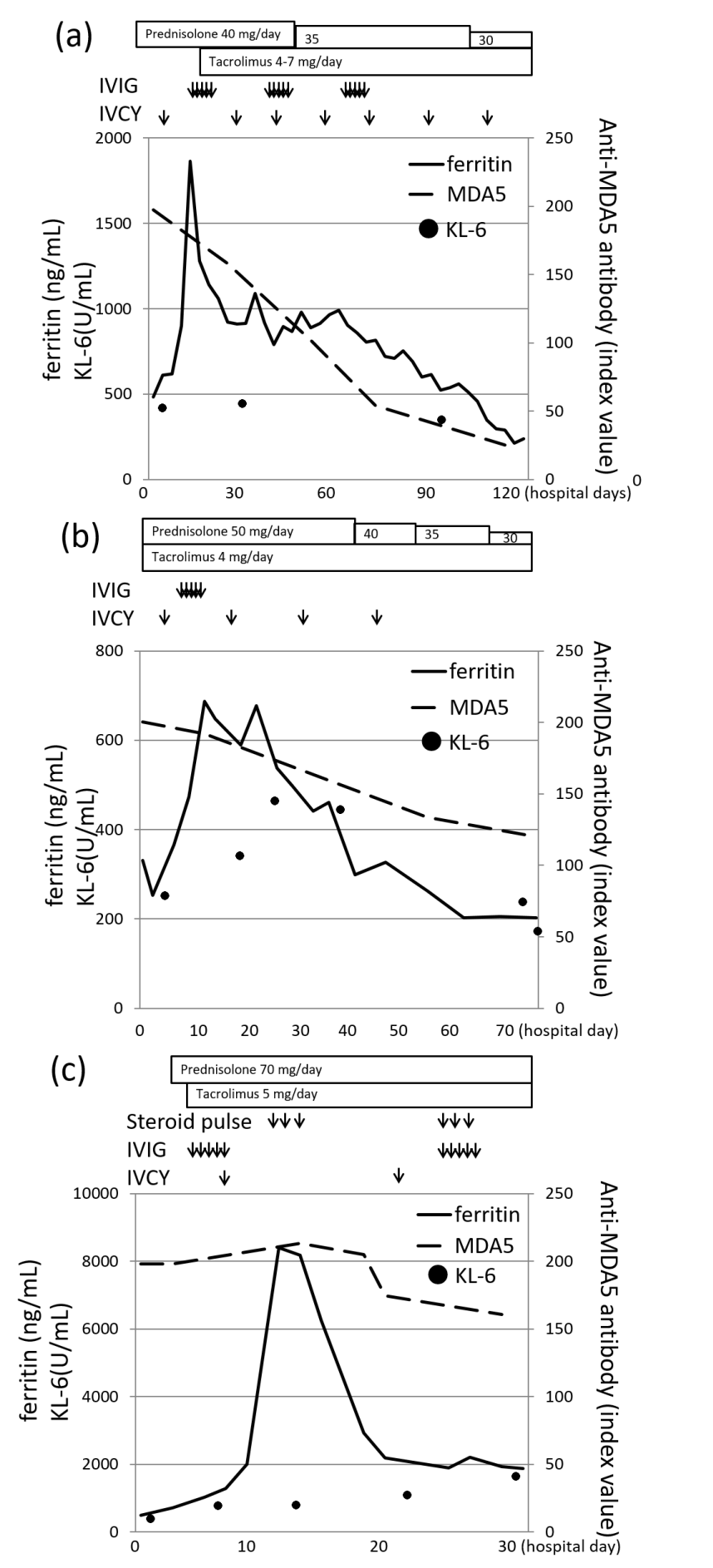
(a)
Prednisolone 40 mg/day
35
30
Tacrolimus 4-7 mg/day
IVIG
IVCY
ferritin
MDA5
KL-6
ferritin (ng/mL)
KL-6(U/mL)
Anti-MDA5 antibody (index value)
2000
1500
1000
500
0
250
200
150
100
50
0
0
30
60
90
120 (hospital days)
(b)
Prednisolone 50 mg/day
40
35
30
Tacrolimus 4 mg/day
IVIG
IVCY
ferritin
MDA5
KL-6
ferritin (ng/mL)
KL-6(U/mL)
Anti-MDA5 antibody (index value)
800
600
400
200
0
250
200
150
100
50
0
0
10
20
30
40
50
60
70 (hospital day)
(c)
Prednisolone 70 mg/day
Tacrolimus 5 mg/day
Steroid pulse
IVIG
IVCY
ferritin
MDA5
KL-6
ferritin (ng/mL)
KL-6(U/mL)
Anti-MDA5 antibody (index value)
10000
8000
6000
4000
2000
0
250
200
150
100
50
0
0
10
20
30 (hospital day)

Table 1. Laboratory examinations of the patients at the first visit

Investigation (normal range)	Case 1	Case 2	Case 3
Anti-MDA5 antibody (<32 index value)	197.6	200.3	213.5
ANA (negative)	1:40 (homogenous and speckled pattern)	Negative	Negative
Ferritin (3.6 - 114 ng/mL)	482.0	331.1	717.5
LDH (106 - 211 U/L)	327	337	682
KL-6 (0 - 499 U/mL)	430	254	455
SP-D (0-109 ng/mL)	27.1	17.9	36.3
CK (42 - 150 U/L)	308	124	1169
Aldolase (2.7 - 5.9 IU/L)	7.1	5.9	4.3
AST (8 - 38 U/L)	84	49	88
ALT (4 - 44 U/L)	57	35	159

MDA5, melanoma differentiation-associated protein 5; LDH, lactate dehydrogenase; KL-6, Krebs von den Lungen-6; SP-D, surfactant protein D; CK, creatine kinase; AST, aspartate amino-transferase; ALT, alanine transaminase; ANA, anti-nuclear antibody.