Rheumatol Int (2017) 37:1335–1340
DOI 10.1007/s00296-017-3729-y

Rheumatology INTERNATIONAL

BIOMARKERS

Comparison of long-term prognosis and relapse of dermatomyositis complicated with interstitial pneumonia according to autoantibodies: anti-aminoacyl tRNA synthetase antibodies versus anti-melanoma differentiation-associated gene 5 antibody

Kentaro Isoda[1,4] · Takuya Kotani[2] · Tohru Takeuchi[2] · Takao Kiboshi[1] · Kenichiro Hata[2] · Takaaki Ishida[2] · Kenichiro Otani[3] · Takao Kamimori[3] · Hiroshi Fujiwara[3] · Takeshi Shoda[1] · Shigeki Makino[2]

Received: 16 December 2016 / Accepted: 21 April 2017 / Published online: 27 April 2017

Abstract The aim of this study was to investigate long-term prognosis and relapse of dermatomyositis complicated with interstitial pneumonia (DMIP) according to anti-aminoacyl tRNA synthetase (ARS) antibodies and anti-melanoma differentiation-associated gene 5 (MDA5) antibody. This retrospective study comprised 36 patients with DMIP who were divided into the anti-ARS antibody-positive group (ARS+) ($n = 12$), anti MDA5 antibody-positive group (MDA5+) ($n = 11$), double-negative group (ARS−/MDA5−) ($n = 11$), and double-positive group (ARS+/MDA5+) ($n = 1$). Clinical features, treatment, prognoses, and relapses during the 2 years after initiation of treatment were compared between three groups excluding ARS+/MDA5+ group. Although short-term (24-week) mortality in MDA+ was higher than that in ARS+ or ARS−/MDA5− ($P = 0.004$), there was no difference in long-term (2-year) mortality between the three groups. Relapse rate in ARS+ was higher than that in MDA5+ and ARS−/MDA5− during the 2 years after initiation of treatment ($P = 0.044$). There was no difference in serum KL-6 levels at the initiation of treatment between ARS+ and MDA5+, but serum ferritin levels in MDA5+ were significantly higher than those in ARS+ ($P = 0.406$, 0.042, respectively). Serum KL-6 and ferritin levels at 2 years after initiation of treatment in ARS+ were significantly higher than those in MDA5+ ($P = 0.008$, 0.034, respectively). We found that in MDA5+ DMIP, acute alveolar inflammation caused a poor prognosis early in the disease course, and in ARS+ DMIP, chronic injury to the alveolar epithelial cells or basement membrane caused long-term recurrence.

Keywords Dermatomyositis · Interstitial pneumonia · Anti-aminoacyl tRNA synthetase antibodies · Anti-melanoma differentiation-associated gene 5 antibody · Prognosis · Relapse

Introduction

Dermatomyositis (DM) is an autoimmune inflammatory muscle disorder that is accompanied by a characteristic rash such as Gottron's papules and heliotrope eyelids, and includes a subtype of clinical amyopathic DM (CADM) with few muscular symptoms. CADM is frequently positive for anti-melanoma differentiation-associated gene 5 (MDA5) antibody (Ab), and is a pathological condition with poor prognosis that is highly complicated by acute/subacute interstitial pneumonia (A/SIP) that is resistant to glucocorticosteroids (GC) [1, 2]. Anti-aminoacyl tRNA synthetase (ARS) Ab-positive DM is often complicated by interstitial pneumonia (DMIP) along with Raynaud's phenomenon or arthritis, but the response of IP to GC is good [3]. A variety of myositis-specific Ab besides anti-ARS Ab and anti-MDA5 Ab exist in DM, and clinical manifestations, clinical course, responsiveness to therapy, and

✉ Kentaro Isoda
in1317@osaka-med.ac.jp

[1] Department of Rheumatology, Yodogawa Christian Hospital, Osaka, Japan

[2] Department of Internal Medicine IV, Osaka Medical College, Osaka, Japan

[3] Department of Respiratory Medicine, Yodogawa Christian Hospital, Osaka, Japan

[4] 1-7-50 Kunijima, Higashiyodogawa-ku, Osaka 533-0024, Japan

prognosis differ depending on the presence of these autoantibodies [4, 5]. There are several reports of clinical manifestations or prognoses related to each autoantibody, but no report has investigated the relationship between these autoantibodies and long-term prognosis or relapse in DMIP [2, 3].

We retrospectively investigated clinical findings, laboratory findings and treatments of DMIP with anti-ARS Ab or anti-MDA5 Ab, in addition to long-term prognosis and relapse for 2 years from the initiation of treatment (IOT). This is the first report to show long-term relapses and prognoses of patients with DMIP with anti-ARS Ab and anti-MDA5 Ab.

Materials and methods

Study design

Participants in this retrospective study comprised Japanese patients with DMIP admitted to Yodogawa Christian Hospital or Osaka Medical College Hospital during the period October 2011–September 2014. After excluding patients with other connective tissue diseases or malignant tumors and those receiving high-dose GC therapy, steroid pulse therapy or immunosuppressant therapy before admission to our hospitals, 35 patients were analyzed. DM and CADM were diagnosed according to the criteria of Bohan and Peter, and Sontheimer and Gerami, respectively [6–9]. IP was evaluated by chest radiography or high-resolution computed tomography (HRCT). A/SIP was defined as in a previous report [10]. Anti-ARS Ab and anti-MDA5 Ab were determined as described previously [11, 12]. Patients were divided into the anti-ARS Ab-positive (ARS+) group, anti-MDA5 Ab-positive (MDA5+) group, double-positive (ARS+/MDA5+) group, and double-negative (ARS−/MDA5−) group. ARS+/MDA5+ patients were excluded from this study. We compared the clinical and laboratory findings, contents of treatment, short-term (24 weeks from IOT) and long-term (2 years from IOT) prognosis, and relapse during the 2 years from IOT between the three groups.

Clinical findings, laboratory parameters, and contents of treatment

Patient background, clinical findings, and contents of treatment were evaluated. The laboratory test items evaluated were creatine kinase, aldolase, lactic acid dehydrogenase, creatinine, C-reactive protein, ferritin, KL-6, PaO_2, $PaCO_2$, PaO_2/FiO_2 ratio, and the alveolar–arterial oxygen gradient ($P[A\text{-}a]O_2$). Serum levels of ferritin and KL-6 were compared between baseline, 1 and 2 years after IOT.

As contents of treatment, dosages of GC, cyclosporin A (CSA), tacrolimus (TAC), steroid pulse therapy, and intravenous cyclophosphamide were compared. Dosages of GC, CSA, and TAC were also compared between 1 and 2 years after IOT.

Prognosis and relapses

We evaluated short- and long-term prognoses from IOT and relapses occurring during the 2 years from IOT. Relapse was defined when all of the following conditions were fulfilled: aggravated respiratory status, deterioration in IP based on HRCT findings and the necessity to intensify treatment with GC or immunosuppressants.

Statistical analysis

Data are presented with median and interquartile range for continuous variables and frequencies, and percentages for dichotomous variables, and were analyzed with the statistical program JMP for the Windows, version Pro 12.0.1 (SAS Institute Inc., Cary, NC, USA). Statistical analyses were performed with the chi-square test or Fisher's exact test for binary data and with the Mann–Whitney *U* test between two groups or the Kruskal–Wallis tests between three groups for continuous data. A P value of < 0.05 was considered to indicate significance.

Results

Anti-ARS and -MDA5 antibodies, baseline characteristics and contents of treatment

Results of the measurement of the antibodies and comparisons of patient backgrounds, clinical manifestations, laboratory findings, and contents of treatment between the ARS+, MDA5+, and ARS−/MDA5− groups are shown in Table 1. Among the 35 patients, 12 patients (34.3%) were ARS+, 10 were anti-Jo-1 Ab+, one was anti-PL-7 Ab+, one was anti EJ Ab+, and 11 (31.4%) were MDA5+. One patient (0.3%) was ARS+/MDA5+, and 11 (34.3%) were ARS−/MDA5−.

There were no differences in age, sex, CADM, A/SIP, and muscle enzymes between the three groups. Serum levels of KL-6 and ferritin before IOT in ARS−/MDA5− were lower than those in the other two groups. Arterial blood gas analysis showed no difference in the PaO_2, $PaCO_2$, and PaO_2/FiO_2 ratio, but the $P[A\text{-}a]O_2$ in MDA5+ was greater than that in ARS+.

There were no differences in prednisone dosage at initiation and at 1 and 2 years after IOT between the three groups. Calcineurin inhibitors such as CSA and TAC were

Table 1 Patient backgrounds, clinical manifestations, laboratory finding, contents of treatment, prognosis, and relapse

	ARS+	MDA5+	ARS−/MDA5−	*P* value
Nunber of patients	12	11	11	–
Age	61 (56.3–75.8)	61 (50–70)	65 (48–73)	0.825
Female, *n* (%)	4 (33.3)	5 (45.5)	2 (18.2)	0.435
CADM, *n* (%)	7 (63.6)	6 (50.0)	9 (81.8)	0.365
A/SIP, *n* (%)	8 (66.7)	11 (100)	6 (54.6)	0.034*
Arthritis, *n* (%)	3 (25.0)	6 (54.6)	4 (36.4)	0.374
Gottron sign, *n* (%)	8 (66.7)	10 (90.9)	8 (72.7)	0.467
Heliotrope eyelids, *n* (%)	1 (8.3)	8 (72.7)	2 (18.2)	0.003*
Mechanic's hands, *n* (%)	4 (33.3)	4 (36.4)	1 (9.1)	0.380
Periungual erythema, *n* (%)	6 (50.0)	9 (81.8)	2 (18.2)	0.011*
Skin ulcers, *n* (%)	0 (0.0)	5 (45.5)	0 (0.0)	0.003*
Creatine kinase, U/L	565 (94–1426)	287 (43–301)	181 (47–1252)	0.459
Aldolase, U/L	16.8 (5.8–48.8)	10.1 (5.2–11.5)	7.0 (4.5–30.0)	0.357
Lactate dehydrogenase, U/L	378 (202.8–656.8)	386 (325–485)	247 (219–502)	0.555
Creatinine, mg/dL	0.56 (0.51–0.90)	0.65 (0.50–0.78)	0.49 (0.48–0.61)	0.118
C-reactive protein, mg/dL	1.66 (0.11–6.92)	0.95 (0.61–2.10)	0.15 (0.03–12.14)	0.287
KL-6, U/mL	2062.5 (872–2580)	1182 (794–2284)	542 (299–984)	0.008*
Ferritin, ng/mL	322.0 (147.3–619.4)	1108.0 (477.7–1890.0)	103.0 (49.4–126.0)	0.002*
PaO_2, Torr	82.1 (62.0–94.8)	75.2 (66.7–95.3)	84.5 (75.5–88.0)	0.851
$PaCO_2$, Torr	35.0 (32.5–40.0)	34.4 (29.7–39.1)	39.7 (37.7–40.0)	0.079
PaO_2/FiO_2 ratio	307.5 (263.5–336.8)	285.5 (225.5–323.8)	306 (222.0–381.0)	0.641
P[A-a]O_2, Torr	24.5 (5.1–45.7)	47.6 (31.8–92.8)	18.6 (10.5–22.0)	0.003*
From onset to treatment, months	3 (1–5)	1 (0.6–3)	2.05 (1.25–2.58)	0.145
Steroids, *n* (%)	12 (100)	11 (100)	11 (100)	1.000
PSL at start, mg/kg/day	1.00 (0.96–1.00)	1.00 (0.94–1.00)	0.96 (0.65–1.00)	0.142
PSL 1 year later/start ratio	0.18 (0.13–0.23)	0.20 (0.15–0.22)	0.28 (0.19–0.31)	0.053*
PSL 2 years later/start ratio	0.15 (0.10–0.24)	0.14 (0.12–0.23)	0.23 (0.15–0.34)	0.196
CSA, *n* (%)	8 (66.7)	7 (63.6)	4 (36.4)	0.678
At start, mg/day	212.5 (181.3–243.8)	225.0 (200.0–300.0)	200.0 (175.0–275.0)	0.403
1 year later, mg/day	175.0 (97.5–225.0)	250.0 (150.0–300.0)	225.0 (150.0–275.0)	0.370
2 years later, mg/day	150.0 (137.5–200.0)	250.0 (150.0–325.0)	150.0 (125.0–225.0)	0.269
TAC, *n* (%)	4 (33.3)	3 (27.2)	7 (63.6)	0.455
At start, mg/day	3.0 (2.0–6.3)	6.0 (3.0–12.0)	4.5 (2.4–8.0)	0.440
1 year later, mg/day	3.0 (1.8–5.3)	3.3 (2.5–4.0)	5.0 (3.0–8.0)	0.300
2 years later, mg/day	2.5 (1.8–4.0)	2.0 (2.0–2.0)	4.0 (3.0–6.0)	0.193
Steroid pulse, *n* (%)	1 (8.3)	5 (45.8)	1 (9.1)	0.046
IVCY, *n* (%)	6 (50.0)	11 (100)	3 (27.3)	0.001*
Dead at 24 weeks, *n* (%)	1 (8.3)	6 (54.6)	0 (0.0)	0.004*
Dead during 25 week ~ 2 years, *n* (%)	0/11 (0.0)	0/5 (0.0)	1/10 (9.1)	1.000
Dead at 2 years, *n* (%)	1 (8.3)	6 (54.6)	1 (9.1)	0.020*
Relapse at 2 years, *n* (%)	4/11 (36.3)	1/5 (20.0)	0/10 (0.0%)	0.044*

* *P* value <0.05

Data are presented as the mean value ± standard deviation (S.D.) or the median value (interquartile range)

ARS+ anti-aminoacyl tRNA synthetase antibodies-positive, *MDA5+* anti-melanoma differentiation-associated gene 5 antibody-positive, *CADM* clinical amyopathic dermatomyositis, *A/SIP* acute and subacute interstitial pneumonia, *KL-6* Krebs von den Lungen-6, *P[A-a]O_2* alveolar-arterial oxygen gradient, *PSL* prednisolone, *CNI* calcineurin inhibitor, *CSA* cyclosporine A, *TAC* tacrolimus, *IVCY* intravenous pulse cyclophosphamide therapy

used except in one MDA5+ patient, and there was no difference in the dosages of CSA and TAC at IOT, 1 and 2 years after IOT between the three groups. Steroid pulse therapy and intravenous cyclophosphamide therapy were used more often in MDA5+ than in the other two groups.

Changes in serum levels of KL-6 and ferritin

Figure 1 shows changes in serum levels of KL-6 and ferritin in ARS+ and MDA5+ from IOT to 1 and 2 years later. There was no significant difference in the serum KL-6 levels at IOT between ARS+ (2062.5, IQR 872.0–2580.5) and MDA5+ (1182.0, IQR 794.0–2287.0), but serum ferritin levels in MDA5+ (1108.0, IQR 477.7–1890.0) were significantly higher than those in ARS+ (332.0, IQR 147.3–619.4) ($P = 0.406$, 0.042, respectively). Serum KL-6 levels at 1 year after IOT in ARS+ (505.0, IQR 469.0–1111.0) were significantly higher than those in MDA5+ (290.0, IQR 265.0–425.0), and those at 2 years after IOT in ARS+ (661.0, IQR 464.0–1472.0) were significantly higher than those in MDA5+ (271.0, IQR 238.5–318.5) ($P = 0.002$, 0.008, respectively). There was a non-significant difference in serum ferritin levels at 1 year after IOT between ARS+ (72.1, IQR 33.3–191.3) and MDA5+ (42.4, IQR 16.7–54.1), but the levels at 2 years after IOT in ARS+ (97.7, IQR 41.5–233.9) were higher than those in MDA5+ (19.0, IQR 12.5–49.1) ($P = 0.157$, 0.034, respectively). Especially, serum ferritin levels at 2 years after IOT had normalized in all cases of MDA5+.

Outcomes and relapses

Short- and long-term prognoses of ARS+, MDA5+ and ARS−/MDA5− DMIP are shown in Table 1. Mortality at 24 weeks and 2 years after IOT in MDA+ (54.6 and 54.6%) was higher than that in ARS+ (8.3 and 8.3%) or in ARS−/MDA5− (0.0 and 9.1%) ($P = 0.004$ and 0.020, respectively). Only one patient in ARS−/MDA5− died during the period from 25 weeks to 2 years after IOT, and there was no significant difference between the three groups ($P = 1.000$). The relapse rate in ARS+ (36.3%) was higher than that in MDA5+ (20.0%) and ARS−/MDA5− (0.0%) during the 2 years after IOT ($P = 0.044$).

Discussion

We investigated clinical features, contents of treatment, short- and long-term prognoses and relapse during the 2 years from IOT according to anti-ARS Ab and anti-MDA5 Ab. Such poor prognostic factors as ferritin level and P[A-a]O_2 before treatment, frequency of steroid pulse therapy and intravenous cyclophosphamide therapy were significantly

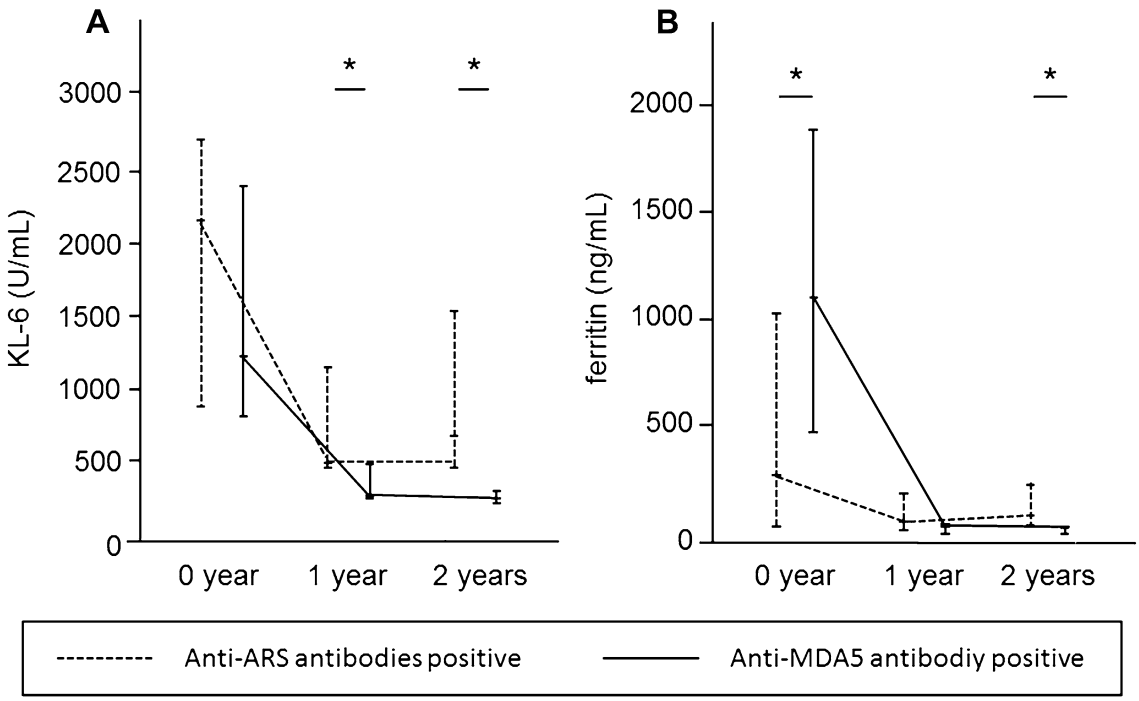

Fig. 1 Changes in serum KL-6 level (**a**) and serum ferritin level (**b**) in patients with anti-ARS antibodies DMIP and anti-MDA5 antibody-positive DMIP from the initiation of treatment to 1 and 2 years later. *P value < 0.05

higher in MDA5+ than in ARS+, indicating that MDA5+ DMIP is refractory to treatment and has a poor prognosis [11, 13]. In fact, mortality at 24 weeks after IOT had significantly increased in MDA5+. In contrast, over the long term, the ferritin level at 2 years after IOT and the KL-6 levels at 1 and 2 years after IOT had increased in ARS+ more than in MDA5+. The relapse rate at 2 years after IOT was significantly higher in ARS+ than in the other two groups, which indicated the possibility that the disease activity had continued for long periods in ARS+. This is the first report, to our knowledge, to investigate the relationship between serum biomarkers of anti-ARS Ab and anti-MDA5 Ab, and long-term prognosis and relapse in DMIP.

Clinical manifestations and prognosis in DMIP vary depending on the presence of myositis-specific antibodies [4, 5]. Although both ARS+ and MDA5+ DM have high rates of complication with IP, MDA5+ patients have a poor short-term prognosis [1–3]. It was previously reported that DM-A/SIP patients with increased levels of serum ferritin and P[A-a]O_2 before treatment had poor short-term prognosis [11]. In this study, as in previous reports, serum ferritin levels and P[A-a]O_2 were higher, and the short-term mortality after IOT was higher in MDA5+ than in ARS+ and ARS−/MDA5−. Meanwhile, there was no difference in mortality during the period from 25 weeks to 2 years after IOT between the three groups, but the relapse rate in ARS+ was higher than that in the other groups. Furthermore, the ferritin level 2 years after IOT in ARS+ was significantly higher than that in MDA5+, indicating that the ferritin level had normalized in all cases of MDA5+. In DMIP, ferritin activates alveolar macrophages, which are thought to reflect inflammation of the pulmonary alveolus [13, 14]. The present results show that MDA5+ DMIP caused severe inflammation of the pulmonary alveoli in the acute stage, but once it subsided with treatment, the inflammation disappeared. In contrast, the results also showed that even though inflammation of the pulmonary alveoli in ARS+ DMIP was less severe than in MDA5+ in the acute stage, it was likely to recur because of chronic inflammation.

This study also showed differences in the KL-6 level between MDA5+ and ARS+ before treatment and at 1 and 2 years after IOT. In IP, regeneration and proliferation of type II alveolar epithelial cells increase the expression of KL-6, which is liberated into the alveolar space and enters the blood due to damage to the alveolar epithelium or the basement membrane, thus leading to an increase of the serum KL-6 level [15, 16]. That is, unlike the serum ferritin level, an increased serum KL-6 level does not reflect alveolar inflammation but rather the injury to alveolar epithelial cells or to the basement membrane in the alveolar area and the extent of vascular permeability. It is reported that in IP complicating DM/polymyositis, KL-6 varies depending on the disease activity, and in diffuse alveolar damage in particular, KL-6 is often expressed on the glassy membrane, proliferating type II alveolar epithelial cells, bronchial epithelial cells, and pulmonary vein endothelial cells [17]. Also, there were no significant differences in KL-6 levels at IOT between ARS+ and MDA5+. However, KL-6 at 1 and 2 years after IOT had maintained higher levels in ARS+ than in MDA5+. This shows that in MDA5+ DMIP, alveolar epithelial cells are severely injured in the acute stage, but over the long term, the activity subsides, whereas in ARS+ DMIP, the activity persists for a long time, and chronic injury of the alveolar epithelial cells continues.

This study was carried out retrospectively in a small number of patients. In addition, differences in treatment regimens in the initial stage might have led to differences in the relapse rates. To confirm these results, a long-term prospective observation comprising many more patients is needed.

We suggested that in MDA5+ DMIP, alveolopathy was caused by intense alveolar inflammation in the acute stage, but once the inflammation subsided with treatment, IP was unlikely to relapse. However, in ARS+ DMIP, although it is not as severe as MDA5+ in the acute stage, chronic alveolar inflammation and injury to the alveolar epithelial cells or basement membrane persist and are likely to recur in the long term. These results show the need for early-stage intensive treatment for MDA5+ and long-term careful observation along with assiduous treatment on a continuing basis for ARS+. This study showed not only short-term but also long-term pathologies and treatment strategies for DMIP, and should be very helpful to clinicians who are involved in clinical immunology.

Compliance with ethical standards

Conflict of interest All Authors declare that they have no conflict of interest.

Ethical approval This study was conducted in accordance with the 1964 Helsinki declaration and its amendments, and was approved by the Yodogawa Christian Hospital and Faculty of Medicine Ethics Committee and the Osaka Medical College and Faculty of Medicine Ethics Committee.

Informed consent Informed consent was obtained from all individual participants included in this study.

References

1. Sato S, Hirakata M, Kuwana M, Suwa A, Inada S, Mimori T, Nishikawa T, Oddis CV, Ikeda Y (2005) Autoantibodies to a 140-kd polypeptide, CADM-140, in Japanese patients with clinically amyopathic dermatomyositis. Arthritis Rheumatol 52:1571–1576

2. Gono T, Kawaguchi Y, Satoh T, Kuwana M, Katsumata Y, Takagi K, Masuda I, Tochimoto A, Baba S, Okamoto Y, Ota Y, Yamanaka H (2010) Clinical manifestation and prognostic factor in anti-melanoma differentiation-associated gene 5 antibody-associated interstitial lung disease as a complication of dermatomyositis. Rheumatology (Oxford) 49:1713–1719
3. Yoshifuji H, Fujii T, Kobayashi S, Imura Y, Fujita Y, Kawabata D, Usui T, Tanaka M, Nagai S, Umehara H, Mimori T (2006) Anti-aminoacyl-tRNA synthetase antibodies in clinical course prediction of interstitial lung disease complicated with idiopathic inflammatory myopathies. Autoimmunity 39:233–241
4. Gunawardena H, Betteridge ZE, McHugh NJ (2009) Myositis-specific autoantibodies: their clinical and pathogenic significance in disease expression. Rheumatology (Oxford) 48:607–612
5. Casciola-Rosen L, Mammen AL (2012) Myositis autoantibodies. Curr Opin Rheumatol 24:602–608
6. Bohan A, Peter JB (1975) Polymyositis and dermatomyositis (first of two parts). N Engl J Med 292:344–347
7. Bohan A, Peter JB (1975) Polymyositis and dermatomyositis (second of two parts). N Engl J Med 292:403–407
8. Sontheimer RD (2002) Dermatomyositis: an overview of recent progress with emphasis on dermatologic aspects. Dermatol Clin 20:387–408
9. Gerami P, Schope JM, McDonald L, Walling HW, Sontheimer RD (2006) A systematic review of adult-onset clinically amyopathic dermatomyositis (dermatomyositis sine´ myositis): a missing link within the spectrum of the idiopathic inflammatory myopathies. J Am Acad Dermatol 54:597–613
10. American Thoracic Society (2000) Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). Am J Respir Crit Care Med 161:646–664
11. Isoda K, Takeuchi T, Kotani T, Hata K, Shoda T, Ishida T, Yoshida S, Kimura Y, Makino S, Hanafusa T (2014) Pre-treatment ferritin level and alveolar-arterial oxygen gradient can predict mortality rate due to acute/subacute interstitial pneumonia in dermatomyositis treated by cyclosporine a/glucocorticosteroid combination therapy: a case control study. PLoS One 9:e89610
12. Chen F, Wang D, Shu X, Nakashima R, Wang G (2012) Anti-MDA5 antibody is associated with A/SIP and decreased T cells in peripheral blood and predicts poor prognosis of ILD in Chinese patients with dermatomyositis. Rheumatology Int 32:3909–3915
13. Gono T, Kawaguchi Y, Hara M, Masuda I, Katsumata Y, Shinozaki M, Ota Y, Ozeki E, Yamanaka H (2010) Increased ferritin predicts development and severity of acute interstitial lung disease as a complication of dermatomyositis. Rheumatology (Oxford) 49:1354–1360
14. Gono T, Sato S, Kawaguchi Y, Kuwana M, Hanaoka M, Katsumata Y, Takagi K, Baba S, Okamoto Y, Ota Y, Yamanaka H (2012) Anti-MDA5 antibody, ferritin and IL-18 are useful for the evaluation of response to treatment in interstitial lung disease with anti-MDA5 antibody-positive dermatomyositis. Rheumatology (Oxford) 51:1563–1570
15. Kohno N, Kyoizumi S, Awaya Y, Fukuhara H, Yamakido M, Akiyama M (1989) New serum indicator of interstitial pneumonitis activity. Sialylated carbohydrate antigen KL-6. Chest 96:68–73
16. Nakajima H, Harigai M, Hara M, Hakoda M, Tokuda H, Sakai F, Kamatani N, Kashiwazaki S (2000) KL-6 as a novel serum marker for interstitial pneumonia associated with collagen diseases. J Rheumatol 27:1164–1170
17. Bandoh S, Fujita J, Ohtsuki Y, Ueda Y, Hojo S, Tokuda M, Dobashi H, Kurata N, Yoshinouchi T, Kohno N, Takahara J (2000) Sequential changes of KL-6 in sera of patients with interstitial pneumonia associated with polymyositis/dermatomyositis. Ann Rheum Dis 59:257–262