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REVIEW ARTICLE

Dermatomyositis: Myositis-specific autoantibodies and skin manifestations

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Abstract

Idiopathic inflammatory myopathies including dermatomyositis (DM) and polymyositis (PM) are a heterogeneous group of disorders with varying degrees of muscle disease, cutaneous manifestations and internal organ involvement. Myositis-specific autoantibodies (MSA) are useful tools, as they further define more homogeneous subsets. Anti-Mi-2 antibodies have been shown to represent a distinct DM phenotype with a low risk of interstitial lung disease (ILD) or cancer. Anti-aminoacyl tRNA synthetase antibodies, such as anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ, anti-OJ and anti-KS antibodies, identify patients who share similar clinical features including ILD and myositis, which are referred to as "anti-synthetase syndrome". Anti-155/140 antibodies and anti-CADM140 antibodies have recently been described, and are considered as serological markers for cancer-associated DM and clinically amyopathic DM with rapidly progressive ILD, respectively. In addition, recent studies have revealed anti-NXP-2 autoantibodies that are one of the predominant MSA in juvenile-onset DM and anti-small ubiquitin-like modifier activating enzyme (SAE) antibodies that are also associated with a distinct phenotype. These autoantibodies are also associated with the distinct phenotype of skin manifestations. Thus, identification of the autoantibody profile in an individual patient is beneficial for management and therapy. Despite the clinical utility of MSA, these autoantibodies are unlikely to have direct pathogenic roles in the development of the disease. Findings suggest that the production of these antibodies reflects changes in autoantigen expression within the tissue targeted by the immune response. Furthermore, the nature of several autoantigens suggests their potential roles in tumor immunity and infection. (Clin Exp Neuroimmunol doi: 10.1111/j.1759-1961.2012.00028.x, May 2012)

Introduction

Dermatomyositis (DM) is an inflammatory disorder of skeletal muscle and skin with presumed autoimmune etiology.[1,2] DM affects both adults and children. DM patients present pathognomic skin lesions including heliotrope rash and Gottron's papules/signs. Furthermore, a variety of skin symptoms characteristic or suggestive of DM have been known, such as V sign, shawl sign, holster sign, periungual erythema, nailfold punctate hemorrhage, seborrheic dermatitis-like rash and flagellate erythema (Fig. 1). Although muscle weakness is observed in a majority of patients, some show prototypic skin manifestations of DM without overt muscle disease. Furthermore, DM is associated with a variety of clinically critical symptoms including interstitial lung disease (ILD) and cancer. Thus, DM contains a heterogeneous population of patients in a wide age range with varying degrees of muscle disease, cutaneous manifestations and internal organ involvement.

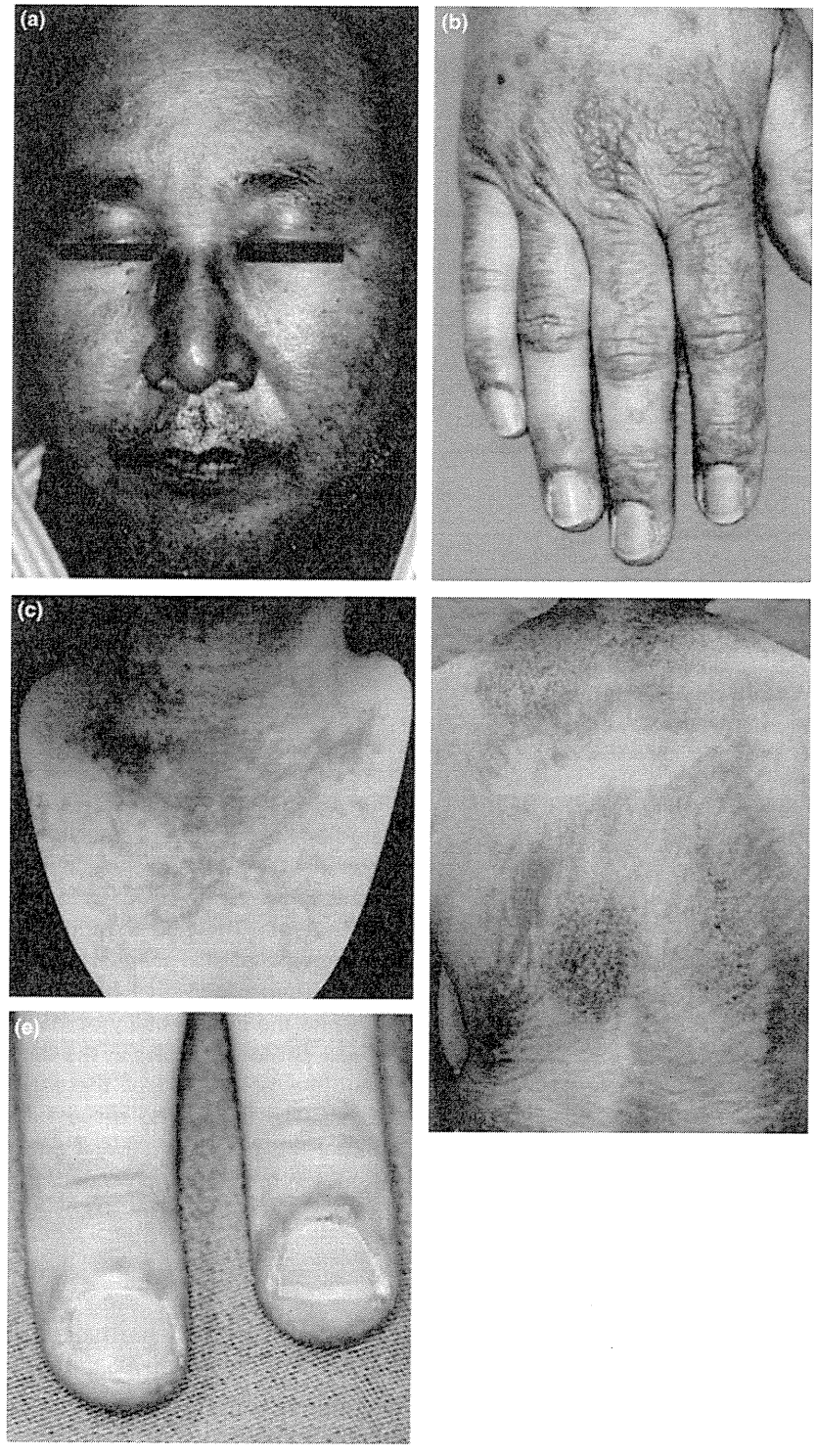

Figure 1 Cutaneous manifestations of dermatomyositis. (a) Heliotrope rash. (b) Gottron's papules. (c) V sign. (d) Shawl sign and flagellate erythema. (e) Periungual erythema and nailfold punctate hemorrhage.

Dermatomyositis is classified into adult and juvenile onsets. Although juvenile-onset DM (JDM) is not associated with malignancy, there is a significantly increased risk of malignancy in adult-onset DM. In addition, ILD is a critical complication both in JDM and adult-onset DM. Of note, malignancy and ILD are almost mutually exclusive. Thus, JDM can be classified into DM alone and DM with ILD, whereas adult-onset DM can be classified into DM alone, DM with malignancy and DM with ILD

Table 1 Provisional classification for dermatomyositis

Juvenile-onset DM
Classic DM alone
Classic DM with ILD
CADM alone
CADM with ILD
Adult-onset DM
Classic DM alone
Classic DM with cancer
Classic DM with ILD
CADM alone
CADM with cancer
CADM with ILD

CADM, clinically-amyopathic dermatomyositis; DM, dermatomyositis; ILD, interstitial lung disease.

(Table 1). Patients with typical cutaneous manifestations, but with no muscle symptoms, form a subset of amyopathic DM. In addition, some cases have subclinical muscle involvement, and the term, hypomyopathic DM, is used for such cases. Hypomyopathic DM is defined as follows: patients with cutaneous DM and no clinical evidence of muscle disease (i.e. weakness) who during evaluation are found to have subclinical evidence of myositis on laboratory (e.g. muscle enzymes), electrophysiological and/or radiological evaluation.[3] Amyopathic DM and hypomyopathic DM are referred to as clinically-amyopathic DM (CADM).[3] The definition of CADM is complicated, because some cases develop muscle symptoms later, whereas others do not. For classification, the criteria of clinical skin symptoms typical of DM, but minimal or no clinical features of myositis for more than 6 months (or 2 years) after the onset of skin manifestation, have been proposed.[3] Both juvenile DM and adult DM are comprised of classic DM and CADM. Furthermore, patients with CADM are also at risk of systemic disease and cancer.

Myositis-specific autoantibodies (MSA) are useful tools to determine which subset each patient is likely to belong to, as MSA are associated with clinical phenotype.[4–7] Anti-Mi-2 and anti-Jo-1 antibodies (Ab) are among the first described MSA. Anti-Mi-2 Ab are highly specific for DM and represent a distinct phenotype. By contrast, anti-Jo-1 Ab are detected both in DM and polymyositis (PM). As mentioned later, patients with anti-Jo-1 Ab or other subsequently identified anti-aminoacyl tRNA synthetase (ARS) Ab share similar clinical features, and thus are often referred to as having "anti-synthetase syndrome (ASS)".[8] In recent years, furthermore, studies have shown several novel autoantibodies that have close associations with disease manifestations. Anti-155/140 Ab and anti-CADM140 Ab have been recently described, and are considered as serological markers for cancer-associated DM and CADM with rapidly progressive and severe ILD, respectively.[9–11] Autoantibodies to nuclear matrix protein 2 (NXP-2) and small ubiquitin-like modifier activating enzymes (SAE) have also been reported.[12,13] Thus, a substantial percentage of IIM patients are positive for some MSA. Considering that each autoantibody represents a distinct clinical group, identification of the autoantibody profile in an individual patient is beneficial for management and therapy. Importantly, these serologically determined subsets are also related with characteristic skin manifestations, which are also helpful for definition of more homogeneous subsets within the disease. The present review highlights the clinical significance of MSA detected in DM and their associations with skin manifestations. These evaluations are among the least invasive examinations and are useful not only for the diagnosis, but for prediction of forthcoming organ involvement and prognosis.

Anti-Mi-2 Ab

Anti-Mi-2 autoantibodies were first described in a 60-year-old woman with DM (patient Mi) by Reichlin and Mattioli in 1976.[14] Anti-Mi-2 Ab are directed to a nuclear complex of eight proteins ranging from 240 to 34 kDa (240, 200, 150, 72, 65, 63, 50 and 34 kDa).[15,16] Its components (Mi-2 α and β) exert helicase and acetylase–deacetylase activities that regulate transcription-factor binding to DNA. Mi-2β is also known as nucleosome remodeling deacetylase (NuRD). Anti-Mi-2 Ab have strong specificity for DM, and are detected in both adult and JDM patients. Anti-Mi-2 Ab are identified in 10–20% of adult DM patients, whereas the frequency in JDM patients is lower, ranging between 4 and 10%.[17–21] The majority of patients positive for anti-Mi-2 Ab show a classic DM phenotype with typical cutaneous manifestations. In our survey of Japanese DM patients with anti-Mi-2 Ab (n = 9), heliotrope rash, Gottron's papules, Gottron signs, periungual erythema, and truncal erythema including V sign and shawl sign were observed in 67%, 89%, 56%, 89% and 89% of patients, respectively.[22] Cutaneous calcification is also occasionally observed, whereas skin ulcers are rare. Patients have a lower risk of ILD and typically respond well to therapy,[17–21] which results in better overall prognosis than for other subsets. However, the recurrence of skin and/or muscle symptoms is sometimes observed.[22]

Genetic studies have shown a strong correlation between anti-Mi-2 Ab and HLA-DR7, and there is evidence for the crucial role of a tryptophan residue at position 9 of the HLA-DRβ chain as a common epitope essential for Mi-2 antibody production.[23] This strong association with HLA-DR4 might explain a lower frequency of anti-Mi-2 Ab in Japanese DM patients compared with Caucasian patients. A geographic study has shown that the relative prevalence of female DM patients with anti-Mi-2 Ab is associated with ultraviolet (UV) radiation intensity.[24] In addition, another study reported that the production of anti-Mi-2 Ab occurs more frequently at lower latitudes; in Guatemala City, 60% of DM patients are Mi-2 positive, but in Glasgow, a mere 6.7% of DM patients produce anti-Mi-2 Ab.[25]

Like HisRS, Mi-2 protein levels have been found to be relatively low in normal muscle, whereas muscle biopsy specimens from patients with DM had significantly increased expression of Mi-2.[26] Notably, Mi-2 protein is highly expressed in DM muscle, but not in PM muscle. Expression of Mi-2 was also found to be markedly upregulated during muscle regeneration in a mouse model of muscle injury and repair.[27] In the skin, Mi-2 has been shown to be essential for proper development and repair of the basal epidermis using conditional gene targeting in a mouse model.[28] Burd et al. showed that UV radiation induces higher expression levels of the Mi-2 protein in keratinocytes than the other members of the NuRD complex.[29] As UV radiation has a significant role in the initiation of diseases in this subset, the immune response against Mi-2 protein might be related to the development of a skin rash in DM patients with anti-Mi-2 Ab.

Anti-ARS Ab

Anti-Jo-1 Ab was the identified first MSA, which was described in 1980.[30] The targeted autoantigen was subsequently identified as histidyl tRNA-synthetase (HisRS), one of the ARS.[31,32] The ARS are ubiquitously expressed cytoplasmic enzymes that catalyze the binding of specific amino acids to their cognate tRNA to form aminoacyl-tRNA. There is a unique ARS for each of the 20 amino acids. Among these ARS, autoantibodies to eight members have been described so far: anti-PL-7 (threonyl), PL-12 (alanyl), EJ (glycyl), OJ (isoleucyl), KS (asparaginyl), Ha (tyrosyl) and Zo (phenylalanyl) Ab, in addition to anti-Jo-1 Ab.[33–37] Anti-Jo-1 Ab are the most common anti-ARS Ab found in approximately 20% of IIM patients, whereas the other anti-ARS Ab are detected in approximately 1–5% of myositis patients.[38] The most recently found are anti-Zo and anti-Ha Ab, both of which have been described in a single case.

The presence of anti-ARS Ab is associated with distinct clinical manifestations including myositis, ILD, non-erosive arthritis, fever, Raynaud's phenomenon and "mechanic's hands".[8] ILD, usually in chronic form, is a hallmark, as it is highly prevalent, with some studies reporting the incidence to be as high as 95%.[39–41] It should be noted that some patients with anti-ARS Ab have ILD without overt muscle disease. In addition, patients can show skin lesions pathognomonic for DM with or without muscle disease.[42] Thus, patients with anti-ARS Ab can be diagnosed as having PM, DM or interstitial pneumonia, depending on the individual's symptoms, and also the diagnosis might change later if other symptoms appear. Therefore, it is beneficial to integrate them into a diagnosis of ASS,[8] which defines relatively homogeneous patients. Recently, criteria for ASS have been proposed.[43] These criteria suggest that a diagnosis of ASS can be made in the presence of positive serological testing of one of the anti-ARS Ab plus one of the following: myositis, ILD, arthritis, Raynaud's phenomenon or "mechanic's hands".

While "mechanics hands", hyperkeratotic lesions along the radial aspects of the fingers, are characteristic for ASS (Fig. 2), patients with ASS might also exhibit other skin manifestations. Nonetheless, their skin eruptions tend to be modest or atypical, and the frequency is relatively low. Heliotrope rash and Gottron's papules are seen in 7–38% and 9–69% of patients, respectively.[42,44,45] In addition, some patients show swollen fingers, periungual erythema and nailfold capillary changes. Although anti-ARS Ab roughly represent clinically homogeneous patients, certain differences between patients with different anti-ARS Ab have been recognized. We have an impression that anti-EJ Ab are found relatively often in DM patients among anti-ARS Ab.

Mozaffar and Pestronk examined histopathological features of myositis in patients with anti-Jo-1 Ab, and showed prominent perimysial inflammation with fragmentation and perifascicular myopathic changes, whereas endomysial inflammation was uncommon and capillary density was normal.[46] These findings are consistent with the DM pattern. By contrast, other studies have shown that patients with anti-ARS Ab show muscle histopathology with the PM pattern rather than the DM pattern, and there are also reports suggesting that both patterns can be observed.

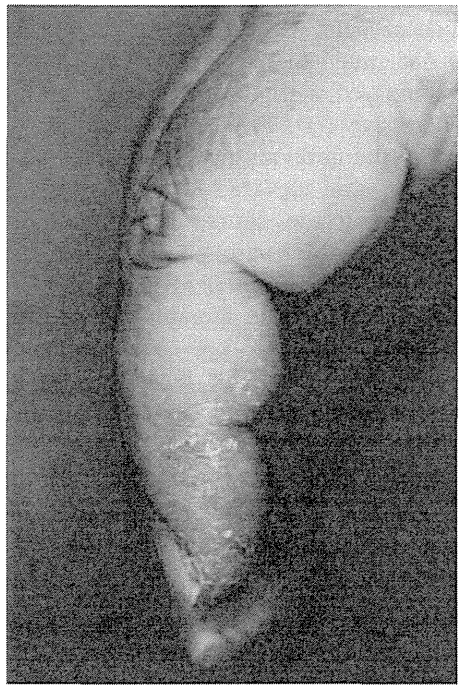

Figure 2 "Mechanic's hands" in a patient with anti-synthetase syndrome.

The frequency of anti-ARS autoantibodies in juvenile myositis is much lower than that in adult myositis. Rider et al.[20] reported that anti-ARS Ab were detected in just 2.6% of cases in 77 children with myositis and overlapping connective tissue diseases. In a study by Feldman et al.,[19] none of the 42 children, 35 with JDM and 7 with other forms of IIM, had anti-ARS autoantibodies. Wedderburn et al.[47] examined sera from 99 children with JDM in the UK and Ireland, and found that no children with JDM were positive for anti-ARS Ab, and two of the 24 children with JDM–scleroderma overlap were positive for anti-Jo-1 Ab. Notably, both the anti-Jo-1-positive children had myositis, DM rash, arthritis and Raynaud's phenomenon, and one of them also had ILD and "mechanic's hands". Thus, juvenile myositis positive for anti-ARS autoantibodies is uncommon, whereas the clinical manifestations resemble ASS in adults.

The Jo-1 antigen, HisRS, has been shown to be expressed at very low levels in normal muscle, but at high levels in myositis muscle.[26] Furthermore, HisRS, with a novel conformation after cleavage by granzyme B, is enriched in the alveolar–epithelial layer of the lung in comparison with that in other tissues, including muscle,[48] suggesting that the autoimmune response to HisRS is initiated and propagated in the lung with a secondary attack of muscle.

These autoantigens might not just be bystanders. Howard et al. showed that HisRS and asparaginyl-tRNA synthetase (KS antigen) can induce leukocyte migration, but that non-antigenic ARS, such as aspartyl-tRNA and lysyl-tRNA synthetases, are not chemotactic.[26] Therefore, autoantigenic ARS are not only overexpressed in damaged muscles, but can also promote an immune response, which might have a role in the development of myositis.

Anti-CADM-140 Ab (anti-MDA5 Ab)

The absence of muscle disease does not mean that patients with CADM are free from the risk of systemic disease. Rather, rapidly progressive ILD has been reported in association with CADM, especially in a high incidence in Asian patients.[49–51]

In 2006, Sato et al.[11] reported novel autoantibodies that reacted with a 140-kD cytoplasmic protein, termed anti-CADM-140 Ab. These autoantibodies are detected mainly in CADM patients, but also in some patients with classic DM, whereas they are not detected in patients with PM or other connective tissue diseases. They further reported that anti-CADM140 Ab were associated with CADM and rapidly-progressive ILD in a Japanese cohort. Anti-CADM140 Ab were detected in 53% of CADM patients, among whom 50% developed rapidly progressive ILD. The antigen for anti-CADM-140 Ab has been identified as a RIG-I-like receptor encoded by melanoma differentiation-associated gene 5 (MDA-5).[52,53] MDA5 is a member of the RIG-I-like receptor family that is characterized by two *N*-terminal caspase recruitment domains (CARD), a central DEAD box helicase/ATPase domain and a *C*-terminal regulatory domain.

Besides reports from Japan,[22,53–55] a study from Korea recently reported that anti-CADM140 Ab were detected in 23.7% of DM patients, and that 44% of them developed rapidly-progressive ILD.[56] Rapidly-progressive ILD associated with CADM is considered to be less frequent in non-Asian patients.[33] In the USA, Fiolentino et al. reported that anti-MDA5 Ab were found in 13% of DM patients.[57] Among them, 50% had CADM. Although 67% had ILD, just 22% developed rapidly-progressive ILD. Furthermore, they had a characteristic cutaneous phenotype consisting of skin ulceration and tender palmar papules (Fig. 3). Typical areas of skin ulceration included the lateral nailfolds, Gottron papules and elbows. Gangrene does not occur frequently,

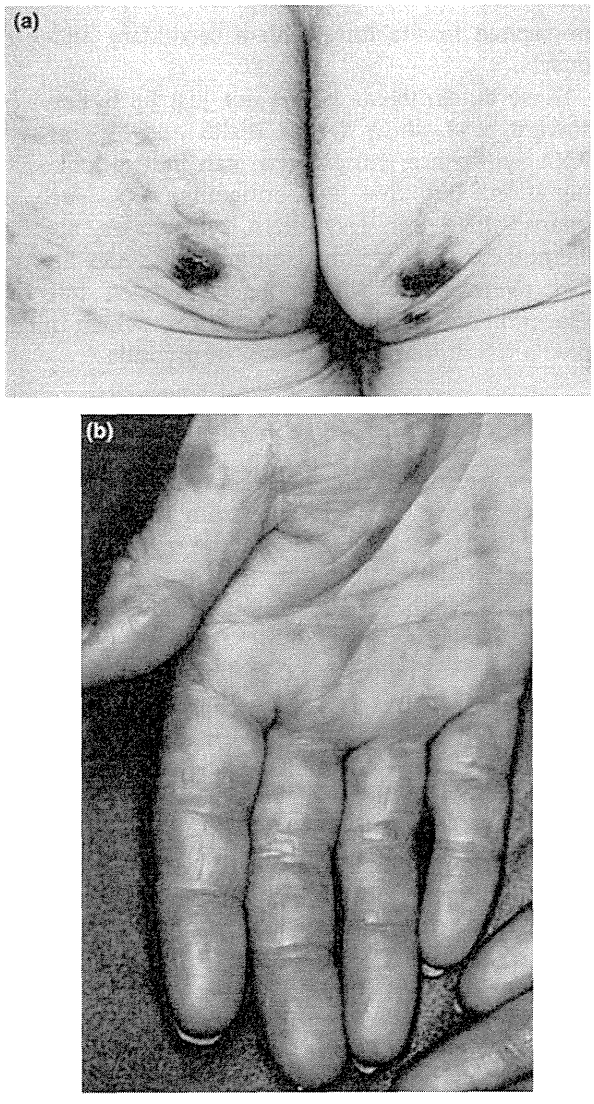

Figure 3 (a) Skin ulcer in a dermatomyositis patient with anti-CADM140 antibodies. (b) Palmar papules in a dermatomyositis patient with anti-CADM140 antibodies.

but is occasionally present. Biopsy specimens of the palmar papules showed a vasculopathy characterized by vascular fibrin deposition with variable perivascular inflammation. Collectively, representative skin manifestations associated with anti-CADM140 Ab are likely to reflect vascular injury. These cutaneous features are likely to help to further identify CADM patients with a higher risk of developing severe ILD.

Although rapidly-progressive ILD is relatively uncommon in juvenile DM, Kobayashi et al. reported that anti-CADM140 Ab can certainly be positive in children.[58] They evaluated anti-CADM140 Ab in 13 JDM patients, and found five of the six patients with JDM-associated ILD, but not in the seven patients without ILD. Three patients with RP-ILD had much higher titers of anti-CADM Ab in ELISA compared with the other three without rapidly progressive ILD. However, in contrast to adult cases, all of the antibody-positive cases showed muscle weakness and elevated levels of muscle-derived enzymes during the course of the disease. Thus, anti-CADM140 Ab serves as a serological marker for rapidly-progressive ILD in JDM.

MDA5 is involved in innate immune responses against viral infections.[59] RIG-I-like proteins serve as intracellular receptors that recognize the genomic RNA of dsRNA viruses and dsRNA generated as the replication intermediate of ssRNA virus.[60] Therefore, an intriguing hypothesis is that the disease is initiated by a specific environmental factor (i.e. virus) in genetically susceptible individuals (i.e. Asians).

Anti-155/140 Ab (anti-p155 Ab, anti-TIF1 Ab)

The association between cancer and IIM has been well appreciated since the first two cases were reported in 1916.[61,62] In the largest population-based study utilizing the national databases of Sweden, Denmark and Finland, cancer was detected in 32% and 15% of 618 DM and 914 PM patients, respectively.[63] This represented an increased risk of both groups compared with the general population, with standardized incidence ratios (SIR) of 3.0 for DM and 1.3 for PM. The majority of cancers were diagnosed within 1 year of the development of myositis. Adenocarcinomas were the most common and accounted for 70% of all the associated malignancies.

Recently-described anti-155/140 autoantibodies have a strong association with cancer-associated DM.[64–66] These autoantibodies were described independently by Targoff et al., and by us as anti-p155 Ab and anti-155/140 Ab, respectively.[9,10] These two reports showed that anti-155/140 autoantibodies were detected in 21% and 13% of adult DM patients, and were highly specific for DM. Targoff et al.[67] showed that the 155-kD protein is transcriptional intermediary factor 1-γ (TIF1-γ also known as TRIM33). Recently, we have revealed that the 140-kD protein is TIF1-α (also known as TRIM24).[64] Additionally, some patients with anti-155/140 Ab also have Ab to TIF1-β (also known as TRIM28).[64]

A cross-sectional study of UK Caucasian adult myositis patients showed that anti-155/140 Ab were exclusively found in DM patients at an overall frequency of 18%.[65] Another study from Spain reported that anti-155/140 Ab were found in 23% (15/65) of

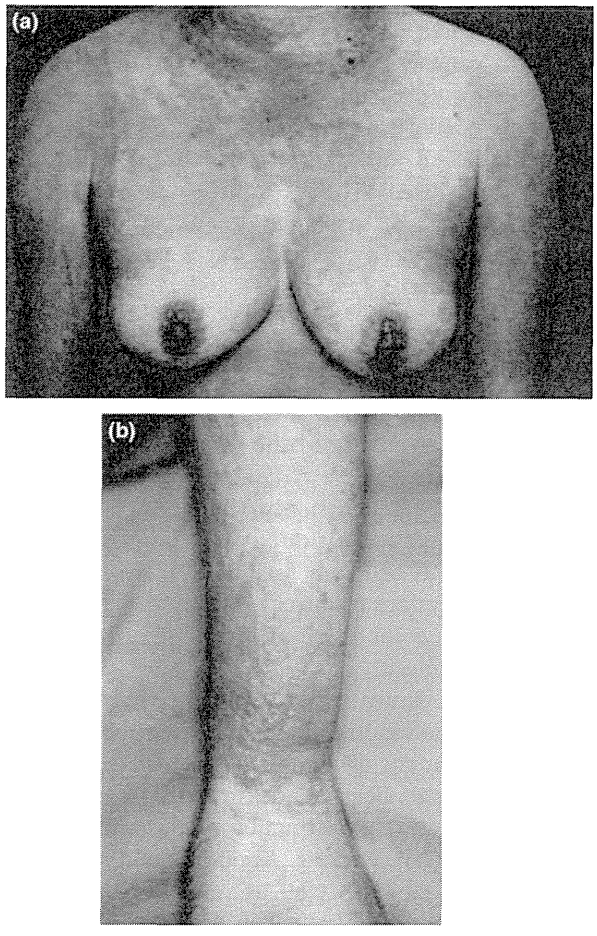

Figure 4 (a) An erythodermic dermatomyositis patient with anti-155/140 antibodies. (b) Bullous formation in a patient with anti-155/140 antibodies.

patients with adult DM, and also in a patient with PM.[68] Patients positive for anti-155/140 Ab had a markedly higher rate of malignancy. The rate of malignancy in anti-155/140-positive adult patients is 50–75%.[9,10,22,55,64,65,68] A recent systemic review and meta-analysis[66] showed that the pooled sensitivity and specificity of anti-p155 for diagnosing cancer-associated DM was 78% (95% confidence interval [CI] 45–94%) and 89% (95% CI 82–93%), respectively. The diagnostic odds ratio was 27.26 (95% CI 6.59–112.82%). Anti-155/140-positive DM patients have a wide distribution of skin disease often accompanied by edema and bulla formation, sometimes showing erythroderma (Fig. 4). By contrast, ulceration on the joints and digital gangrene suggestive of vasculopathy are uncommon and modest, if any, in anti-155/1340-positive patients. Collectively, cutaneous lesions associated with anti-155/140 Ab are likely to be characterized by widespread edematous erythema.

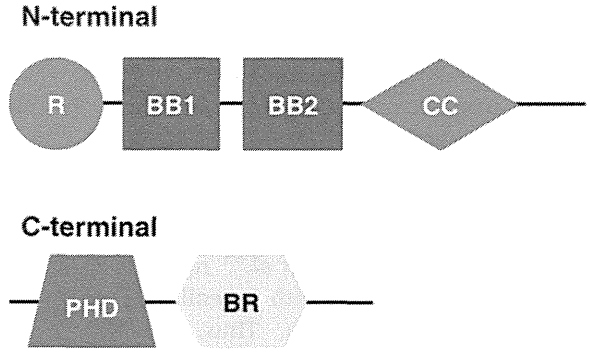

Figure 5 The TIF1 family is the TRIM subgroup (C-VI), which expresses the Ring domain (R), two B-boxes (BB1 and BB2) and a coiled-coil domain (CC) on the *N*-terminal region, and the plant homeodomain (PHD) and bromodomain (BR) on the *C*-terminal region.

Anti-155/140 Ab are also detected in JDM patients. Targoff et al. and Gunawardena et al. have shown that anti-155/140 Ab are present at 29% and 23%, respectively, in JDM patients.[9,69] In JDM, there is no association with malignancy. In addition to an increased risk of malignancy in adult patients, clinical characteristics of anti-155/140-positive DM include severe cutaneous involvement,[69] which is similar in adults and children. Collectively, anti-155/140 Ab are one of the most frequently detected MSA in DM, and form two distinct subsets: adult cancer-associated DM and JDM, with severe cutaneous involvement and a low frequency of ILD.

The TIF1 family is a subgroup (C-VI family) of the tripartite motif-containing (TRIM) proteins that are involved in a broad range of biological processes.[70,71] TRIM proteins are characterized by the TRIM motif of a really interesting new gene domain, one or two B-box domains and a coiled-coil domain in the *N*-terminal region (Fig. 5). The TIF1 family consists of at least four members: TIF1-α (TRIM24), TIF1-β (TRIM28, KAP1), TIF1-γ (TRIM33) and TIF1-δ (TRIM66). TIF1 family members have a plant homeodomain finger-bromodomain unit in the *C*-terminal domain. TIF1 proteins have been implicated in transcription regulation involving histone modifiers and heterochromatin-binding proteins.[72,73] Related to these functions, the critical roles of TIF1 proteins in carcinogenesis have been shown.[64,74–79] Thus, anti-TIF1 Ab might be associated with anti-tumor immune responses.

Anti-NXP-2 Ab (anti-MJ Ab, anti-p140 Ab)

Oddis et al.[80] first reported autoantibodies to a 140-kD protein, termed anti-MJ Ab, in a USA cohort

of juvenile myositis. Subsequently, Targoff et al.[81] identified the MJ autoantigen as nuclear matrix protein (NXP-2, also known as MORC3), which is involved in nuclear transcription, and the activation and localization of a tumor suppressor gene, p53.[82] Gunawardena et al. and Espada et al. showed that anti-NXP-2 Ab were detected in 23% and 25% of JDM patients in the UK and Argentina, respectively.[12,83] In addition to JDM, Espada et al.[83] reported that two (28%) of seven patients with juvenile PM were also positive for anti-NXP2 Ab. Thus, anti-NXP-2 Ab are among the most common MSA in juvenile myositis, especially JDM, along with anti-155/140 Ab.

Anti-NXP-2 Ab appear to define a different clinical phenotype to the anti-p155/140 JDM subset. Gunawardena et al. reported that patients with anti-NXP-2 Ab have a high frequency of calcinosis. Anti-p155/140 Ab and anti-MJ Ab occur collectively in >40% of JDM patients, and represent two serological subsets in JDM.

In adult-onset myositis, anti-NXP-2 Ab are less frequent than in children. In our study of a Japanese cohort of adult myositis,[84] eight adult patients positive for anti-NXP-2 Ab were identified; the frequencies were 1.6% in both adult DM and adult PM, although the total number of PM patients (n = 62) was much smaller than that of DM patients (n = 445) in this cohort. Of note, 37.5% of adult IIM patients positive for anti-NXP-2 Ab had malignancy in our study. Furthermore, all of these carcinomas were at an advanced stage. By contrast, Betteridge et al. reported that anti-NXP-2 Ab were detected in 5% of DM patients, but not in PM patients in a UK cohort.[85] In their study, anti-NXP-2 Ab were not associated with malignancy, but with ILD.[85]

Anti-SAE Ab

Autoantibodies to SAE were recently described by Betteridge et al.[13] The target autoantigen has been identified as the SUMO-1 activating enzyme heterodimer, SAE1 and SAE2, of 40 and 90 kD, respectively. It localizes in the nucleus and facilitates protein sumoylation.

Anti-SAE Ab are detected in 8% of patients with adult DM, and are highly specific for DM. Anti-SAE-positive patients present with severe skin involvement and mild myopathic features at disease onset. During follow up, clinical evidence of myositis and systemic features frequently appeared in the majority of patients. More than 75% of patients had dysphagia and more than 80% had systemic features as defined by fever, weight loss and increases in inflammatory markers. Among 11 patients positive for anti-SAE Ab, 18% were associated with cancer. Mild ILD was also found in 18%. Anti-SAE Ab are strongly related to a peculiar HLA haplotype (DRB1*04-DQA1*03-DQB1*03).[13] Collectively, anti-SAE Ab might occur in patients who present with CADM first, and then progress to develop myositis with a high frequency of systemic features including dysphagia, but a low frequency of ILD and cancer.

Conclusion

In the past several years, the discovery of novel MSA in DM has advanced the knowledge of how to evaluate and treat these patients. However, most of these autoantibodies can only be identified by radioactive immunoprecipitation assays, and thus they are restricted to research facilities. Therefore, more accessible assays are required. Enzyme-linked immunosorbent assays for these autoantibodies have been under development.

Despite the clinical utility of MSA, it is unlikely that these autoantibodies have direct pathogenic roles in the development of the disease. Nonetheless, great progress has also been made in understanding the molecular structure and function of autoantigens and their role in pathogenesis. Their overexpression in the affected tissues, as well as neoplasms and their proinflammatory properties, appear to be key features.[4,26,74] Further precise understanding of the molecular mechanisms of how these autoantigens are recognized and how they are involved in the development of idiopathic inflammatory myopathies will provide new strategies to overcome these disorders.

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Interstitial Lung Disease in Myositis: Clinical Subsets, Biomarkers, and Treatment

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Abstract Interstitial lung disease (ILD) is the most frequent organ involvement (found in nearly half) of myositis patients, but it reveals various clinical courses and therapeutic responsiveness according to clinical and serological subsets. Autoantibodies, as well as imaging and histopathological studies, are useful for the classification of ILD in myositis and provide useful information for predicting prognosis and determining treatment. Antisynthetase antibodies are correlated with chronic and recurrent ILD, whereas anti-CADM-140 (MDA5/IFIH1) antibodies are a marker of acute progressive ILD in clinically amyopathic dermatomyositis. Serum KL-6, SP-D, and ferritin are useful biomarkers for monitoring the activity and severity of ILD. Regarding treatment, glucocorticoids are the first-line drug, but additional immunomodulating drugs are also used in refractory patients. Cyclophosphamide and calcineurin inhibitors (cyclosporine and tacrolimus) appear to be the key drugs in the treatment of refractory myositis–ILD. Rituximab may become another candidate if these drugs are not effective.

Keywords Idiopathic inflammatory myopathy · Myositis · Biomarkers · Polymyositis · Dermatomyositis · Clinically amyopathic dermatomyositis · Interstitial lung disease · Interstitial pneumonia · NSIP · Antisynthetase antibody · Anti-CADM-140 antibody · Aminoacyl-transfer RNA synthetase · MDA5 · IFIH1 · HRCT · KL-6 · SP-D · Ferritin · Glucocorticoids · Cyclophosphamide · Cyclosporine · Tacrolimus · Rituximab · Treatment

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Introduction

Idiopathic inflammatory myositis (IIM), including polymyositis (PM)/dermatomyositis (DM), refers to a group of systemic inflammatory disorders that involve not only the muscle and skin but also many organs, such as joints, the heart, and the lungs. Several autoantibodies can be detected in sera from PM/DM patients, some of which are specific to PM/DM (known as myositis-specific autoantibodies [MSAs]) or myositis overlap syndrome (known as myositis-associated autoantibodies [MAAs]). These autoantibodies are closely associated with subsets, complications, reactivity to therapy, and prognosis of PM/DM [1].

Interstitial lung disease (ILD), or interstitial pneumonia (IP) is the most common internal organ manifestation that affects the prognosis of PM/DM patients. Therefore, diagnosis and evaluation of ILD is also very important to determine the treatment strategy when PM/DM is diagnosed [2•, 3•, 4•].

Recently, two types of MSAs, namely anti-aminoacyl transfer RNA synthetases and anti-CADM-140 (MDA5/IFIH1) antibodies, have been elucidated to be closely associated with ILD in myositis. Moreover, ILD associated with these two antibodies represents completely different clinical subsets, providing us with useful information for predicting the clinical course and prognosis of ILD and for administering the optimal treatment. In this article, we review recent advances and update on the clinical subsets, biomarkers, and treatment of ILD associated with PM and DM.

Epidemiologic Aspect of Interstitial Lung Disease in Myositis

The prevalence of ILD in myositis has been reviewed in many myositis cohorts. In an earlier era, lung involvement in PM/DM had been considered to be rather rare, as only 5% was reported in a review by Frazier and Miller [5] in 1974. However, the development and routine use of CT scan enables to detect early interstitial changes in the lung, and as a result, the prevalence of ILD has become increased. In the recent cohort studies (single and multicenter), the prevalence of ILD in myositis has reached close to 50%, ranging from 21% to 78% [6–13].

PM/DM patients with accompanying ILD have poorer prognosis than those without ILD [9–11]. Prevalence of ILD seems to be similar in both PM and DM, but DM-ILD has an obviously more severe course, is more refractory to treatment, and carries a poorer prognosis than PM-ILD [14, 15, 16•]. This may be attributed to the presence of anti-CADM-140 antibody, a poor prognostic marker of DM and amyopathic DM, which may be included in cohorts of DM-ILD (as discussed later).

Autoantibodies Associated with Interstitial Lung Disease in Myositis: Association Between Clinical and Serological Subsets of Myositis–Interstitial Lung Disease

Several autoantibodies can be detected in sera from IIM patients and are closely associated with clinical subsets of IIM. In these MSAs, anti-aminoacyl transfer RNA synthetases and anti-CADM-140 (MDA5/IFIH1) antibodies have been known to be closely associated with ILD in myositis. However, ILD associated with these two antibodies represents different clinical subsets with different clinical courses, prognoses and responses to therapy (Table 1).

Anti-Aminoacyl-Transfer RNA Synthetase Antibodies and Interstitial Lung Disease

Aminoacyl-transfer RNA synthetases (ARS or synthetase) are the enzymes that catalyze the binding of amino acids to their corresponding transfer RNAs, and so there are 20 kinds of synthetases. Among MSAs, antisynthetase antibodies are found most frequently in PM/DM patients, and eight different autoantibodies reacting with different synthetases have been identified thus far: anti-Jo-1 (histidyl) [17, 18], anti-PL-7 (threonyl) [19], anti-PL-12 (alanyl) [20], anti-EJ (glycyl) [21], anti-OJ (isoleucyl) [22], anti-KS (asparaginyl) [23], anti-Zo (phenylalanyl) [24], and anti-tyrosyl-tRNA synthetase antibodies [25]. With a few exceptions, each patient has only one of these autoantibodies, but patients show similar clinical manifestations, including ILD, myositis, arthritis, fever, Raynaud's phenomenon, and mechanic's hand, called *antisynthetase syndrome* [26]. ILD is the most frequent extramuscular manifestation and is found in 79% to 95% of patients with antisynthetase antibodies [27–30, 31•].

Although antisynthetase-positive patients show similar clinical manifestations of antisynthetase syndrome, some detailed clinical studies suggest that there are some differences in clinical manifestations among patients with different antisynthetase antibodies. Anti-Jo-1 is closely associated with high prevalence of both myositis and ILD, whereas anti-OJ, anti-PL-12, and anti-KS have stronger associations with ILD than myositis [32, 33, 34•, 35]. Anti-PL-7 antibody may be associated with PM-scleroderma overlap syndrome as well as ILD [36].

Detailed clinical features of ILD in patients with antisynthetase antibodies have been described in several reports.

Table 1 Two subsets of ILD in myositis defined by autoantibodies

	Antisynthetase-related ILD	Anti-CADM-140-related ILD
Target antigen	Aminoacyl-tRNA synthetases (8 types)	*MDA5/IFIH1*
Frequency in myositis	~30% in whole PM/DM	~10–20% in DM
		~50–70% in C-ADM
Frequency of ILD	70–95%	50–90%
Type of ILD	Chronic or subacute	Acute progressive
Histopathology	Mostly NSIP	NSIP? (early stage)
	Sometimes UIP and OP	DAD (end stage)
HRCT pattern	Basilar GGO Reticular or linear opacity	Lower and random GGO/consolidation
	Rare honeycombing	
Prognosis	Fair but recurrent	Poor
Response to treatment	Fair	Poor
Recommended therapy	GC+CSP or TAC	GC+IVCYC+CSP

CSP cyclosporine; *DAD* diffuse alveolar damage; *DM* dermatomyositis; *GC* glucocorticoids; *GGO* ground glass opacity; *HRCT* high-resolution CT; *ILD* interstitial lung disease; *IVCYC* intravenous pulse cyclophosphamide; *NSIP* nonspecific interstitial pneumonia; *OP* organizing pneumonia; *PM* polymyositis; *TAC* tacrolimus; *UIP* usual interstitial pneumonia

The characteristics of ILD in antisynthetase-positive patients show mostly chronic clinical course, but subacute course is also found [37•]. In one third to one half of patients with antisynthetases, ILD precedes the development of myositis [29, 30]. Yoshifuji et al. [29] reported the usefulness of antisynthetase in clinical course prediction of ILD with IIM patients. This retrospective study analyzed 74 patients with myositis, 41 of whom had ILD. Any of the antisynthetases were detected in 28% (21 of 74) of whole IIM patients. ILD was accompanied in 41 (55%) of 74 IIM patients, and antisynthetases were found in 49% (21 of 41) of IIM–ILD patients. Antisynthetase-positive patients had a significantly higher frequency of ILD (95%) than negative patients (40%), and ILD among the most positive patients was diagnosed at the same time or before development of myositis. ILD of patients with antisynthetases showed a better response to initial glucocorticoid therapy but revealed a significantly higher recurrence than those without antisynthetases. As a result, the 2-year prognosis of pulmonary function was not different between the two groups of antisynthetase status. The detection of antisynthetases may be useful to predict late-onset myopathy in ILD-preceding patients and to predict the clinical course of ILD in myositis patients.

Anti-SS-A/Ro antibody is detected in various connective tissue diseases, but anti-Ro52 antibody is categorized in one MAA. Isolated anti-Ro52 in myositis patients is often correlated with anti-Jo-1 antibody [38–40]. Anti-SS-A/Ro antibody in patients with antisynthetase syndrome seems to be associated with the development of a more severe form of ILD [39], a more frequent association with fibrosis of lung, and lesser efficacy of immunosuppressive therapy [40].

The production of disease-specific autoantibodies may closely correlate with pathogenic mechanisms of inflammatory myopathy. Patients with antibodies to different synthetases show the same clinical syndrome. This strongly suggests that the immune response to molecules with analogous functions leads to a similar clinical syndrome. However, the pathophysiologic role of antisynthetase antibodies in myositis and/or ILD remains to be clarified. Several reports suggest a possible pathogenic role of antisynthetases.

In an animal model, immunized mice with murine Jo-1 antigen generated specific B and T cells targeting species-specific epitopes of murine Jo-1 and developed a phenotype consistent with muscle and lung inflammation resembling features of human antisynthetase syndrome [41]. Sera from anti-Jo-1-positive PM-ILD patients induced a significant effect on the expression of ICAM-1 from human lung endothelial cells [42•], although autoantibodies themselves might not be the endothelial cell-activating factor, as purified IgG did not induce ICAM-1 expression.

Recent reports demonstrate that certain synthetase molecules (histidyl-, asparaginyl-, and seryl-tRNA synthetases) and their proteolytic fragments have chemokine-like activities against inflammatory cells such as $CD4^+$ and $CD8^+$ T cells and activated monocytes and immature dendritic cells [43]. Mononuclear cells expressing chemokine receptors such as CCR3 and CCR5 infiltrate muscle tissues of myositis patients, but not healthy muscle, supporting the results that histidyl- and asparaginyl-tRNA synthetases activate $CCR5^+$ and $CCR3^+$ cells, respectively [43]. These findings indicate that the liberation of autoantigenic synthetases from damaged tissues may recruit inflammatory mononuclear cells and perpetuate the inflammation process of myositis and ILD, and also induce autoimmune responses to autoantigens.

Anti-CADM-140 (*MDA5/IFIH1*) Antibody and Interstitial Lung Disease

Amyopathic DM (ADM) and clinical ADM (C-ADM) are defined as disorders that show the typical skin manifestations of DM but no or little evidence of clinical myositis [44, 45]. It is known that C-ADM patients, mostly in Asian countries, frequently develop life-threatening acute, progressive ILD [46–50].

Until recently, it was thought that MSAs could not be detected in patients with C-ADM, and this appeared to be a characteristic feature. In 2005, however, Sato et al. [51] reported the identification of a specific autoantibody in C-ADM patients. They screened the sera of 314 patients and controls by ^{35}S-methionine-labeled protein immunoprecipitation and immunoblotting techniques using K562 cells, and 8 of 15 patients with C-ADM immunoprecipitated a 140-kD protein. This newly identified autoantibody was named *anti-CADM-140 antibody*. In 15 patients with C-ADM, 13 developed ILD, 5 with acute ILD. Among the five patients with acute ILD, four had anti-CADM-140 antibody. Later, the presence of anti-CADM-140 and the association with C-ADM–ILD were confirmed worldwide. The antibody can be detected exclusively in DM (11–26%) or C-ADM (50–73%) [52••, 53•, 54–56].

Nakashima et al. [52••] reported the characteristics of anti-CADM-140-positive patients. In the screening of 192 patients with various connective tissue diseases, 13 were revealed to be positive with anti-CADM-140 antibody. All anti-CADM-140-positive patients with DM had either typical DM (2 cases) or C-ADM (11 cases), and 9 (69%) patients had fever higher than 38°C, while 12 patients (92%) had ILD and 7 (54%) developed acute, progressive ILD. Prognosis was significantly poorer in anti-CADM-140-positive patients than in anti-CADM-140-negative DM patients, and 6 (46%) died of respiratory failure within 6 months of the onset of disease. Interestingly, the serum ferritin concentrations in 11 of the anti-CADM-140-positive patients were already elevated within 1 month of their

admission, with significantly high frequency in comparison with anti-CADM-negative DM patients (85% vs 33%; $P=0.005$). Moreover, the serum ferritin level correlated with the activity of ILD in anti-CADM-140-positive patients.

ILD in anti-CADM-140-positive patients was correlated with abnormalities in serum hepatobiliary enzymes and interleukin-18, which worsened in accordance with ILD and ferritin levels [57••, 58]. Thus, the anti-CADM-140 antibody appeared to be associated with macrophage activation syndrome developed in C-ADM and intractable acute ILD.

The target autoantigen of anti-CADM-140 antibody was identified as melanoma differentiation-associated gene 5 (*MDA5*), also known as interferon induced with helicase C domain protein 1 (*IFIH1*) [52••, 59••]. *MDA5/IFIH1* is one of the retinoic acid–inducible gene-I (*RIG-I*)-like receptors that are involved in the recognition of viral RNAs and play an important role in innate immune responses. *RIG-I* and *MDA5/IFIH1* are able to interact with viral RNA and mediate signaling pathways, leading to the expression of type 1 interferon and inflammatory cytokines.

Finding *MDA5/IFIH1* as the autoantigen specifically recognized by one of the DM-specific autoantibodies is strikingly interesting because many reports have suggested the possible association between myositis and viral infections [60–62], in particular Coxsackie B virus belonging to the picornaviruses that are targeted by *MDA5/IFIH1*. To increase our understanding of the pathophysiology of acute ILD accompanied by C-ADM and to develop more effective therapy, whether anti-CADM-140 antibody and its target antigen, *MDA5/IFIH1*, have pathogenic roles in ILD and C-ADM should be elucidated.

Radiological and Histopathological Findings of Interstitial Lung Disease in Myositis

In histopathological analysis by VATS or TBLB, nonspecific interstitial pneumonia (NSIP) is the most frequent histologic pattern of ILD in myositis, but usual interstitial pneumonia (UIP), organizing pneumonia (OP), and diffuse alveolar damage (DAD) can also be found, though less frequently [14, 63–65]. These histologic findings are partially, but not always, associated with the underlying disease (PM or DM), clinical course (acute or chronic), and autoantibody profiles. While NSIP is widely found in both PM and DM, UIP is associated with chronic ILD (both PM and DM), and DAD is characteristically found in acute refractory ILD in DM and C-ADM. OP shows a good response to glucocorticoid therapy. High-resolution CT (HRCT) scanning of the chest is a most sensitive technique to detect ILD and provide information for prognosis and response of treatment.

Typical HRCT findings in myositis-associated ILD include ground glass opacities (GGO), micronodules, linear and reticular opacities, peribronchovascular or subpleural consolidation, irregularity of interface, and traction bronchiectasis (Fig. 1) [15, 46, 65, 66]. These findings are compatible with NSIP. Honeycombing pattern suggesting UIP is also found in ILD-myositis, but with lower frequency.

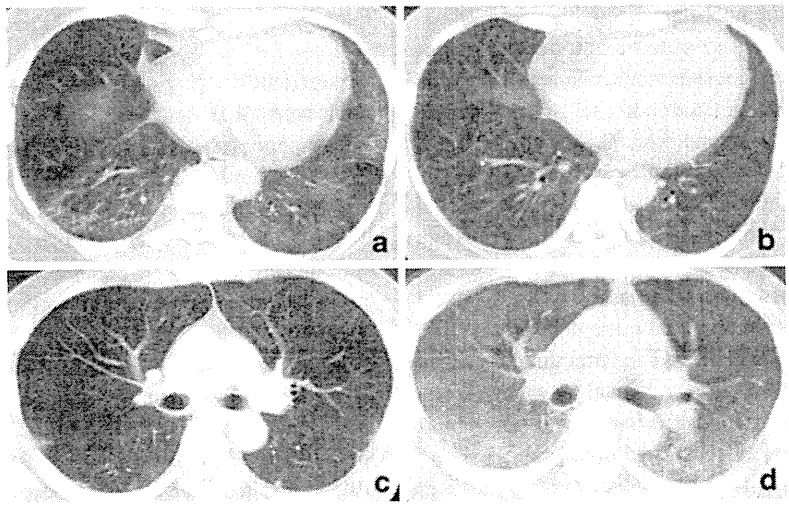

Fig. 1 Radiographic imaging of CT in patients with myositis–interstitial lung disease having antisynthetase (**a** and **b**) and anti-CADM-140 antibody (**c** and **d**). A typical CT image shows basilar ground glass opacities (GGOs), reticular opacities, and traction bronchiectasis in a 47-year-old woman with dermatomyositis (DM) and anti-PL-7 antibody (**a**). A CT image of the same patient 1 year later shows significant improvement achieved by treatment with high-dose corticosteroids (**b**). CT image shows random consolidation/GGOs in subpleural region in a 44-year-old man with DM and anti-CADM-140 antibody at diagnosis (**c**). One month later, the patient developed severe respiratory failure and died despite treatment. Diffuse GGOs and consolidation were extended in the whole lung (**d**)

Recent studies suggest characteristics of HRCT findings in two myositis/ILD-associated autoantibodies. Watanabe et al. [67•] reported the HRCT and pathological findings in 13 ILD cases with antisynthetase syndrome but without clinical myositis. Pleural irregularities and/or prominent interlobular septa, GGO, reticulation, and traction bronchiectasis were the major findings, while honeycombing was not found in any cases. Although most of these cases showed histologic NSIP if lung biopsies were applied, even in cases with pathological diagnosis of UIP, HRCT findings were not compatible with a typical UIP pattern showing honeycombing.

Tanizawa et al. [68••] described HRCT findings of ILD in DM/C-ADM with anti-CADM-140 antibody. GGO, nonseptal linear or plate-like opacity, and consolidation were the common findings in ILD of both antibody-positive and negative DM. However, intralobular reticular opacities (abnormal thickening of intralobular interstitial tissues) found in the antibody-negative ILD was significantly less in the positive ILD patients. Moreover, lower consolidation/GGO pattern (lower peripheral or peribronchovascular consolidation or GGO) and random GGO pattern (random peripheral GGO) were mainly found in anti-CADM-140-positive patients, whereas lower reticulation pattern (lower peripheral or peribronchovascular reticulation) was the main finding among anti-CADM-140-negative patients. The latter HRCT pattern is compatible with NSIP and likely with that of anti-synthetase-positive ILD patients, while three patients who were negative for both anti-CADM-140 and antisynthetases showed lower reticulation pattern as well. Thus, HRCT of anti-CADM-140-positive DM/C-ADM-ILD is characterized by lower consolidation/GGO and random GGO patterns and the absence of intralobular reticular opacities, which are different from typical NSIP patterns (Fig. 1).

A lower reticulation pattern is consistent with NSIP and likely with that of antisynthetase-positive ILD patients. On the other hand, lower consolidation/GGO and random GGO patterns in anti-CADM-140-positive ILD are hard to interpret because the pathological approach is usually difficult in the early stage of the disease. Lower consolidation/GGO may represent OP or localized DAD [68••]. These findings and the absence of lower reticulation and intralobular reticular opacities in anti-CADM-140-positive ILD may suggest a lower prevalence of pathological NSIP.

Biomarkers of Interstitial Lung Disease in Myositis

There are no specific serum biomarkers for myositis-associated ILD. Nevertheless, certain serum markers predicting activity of ILD should be necessary, as a correlation is often not recognized between activities of myositis and ILD. HRCT of the lung is the most valuable and sensitive method to detect and predict the activity of ILD, but frequent examination should be avoided because of the risk of high-radiation exposure by CT. Several biomarkers that may reflect inflammatory activity of lung have been utilized.

KL-6 and SP-D

KL-6 (Krebs von den Lungen-6) is a mucin-like glycoprotein expressed in type II alveolar epithelial cells. Because serum level of KL-6 increases by reflecting hyper-expression of KL-6-producing cells and alveolar injury in ILD, its detection is useful as a serologic biomarker for diagnosis and monitoring ILD. Several studies suggested the usefulness of KL-6 in disease activity, therapeutic response, and prognosis for myositis-ILD [69–74]. Satoh et al. [72] demonstrated that a high serum level (>1,000 U/mL) of KL-6 was a poor prognostic factor in 152 idiopathic IP- and 67 connective tissue disease-associated ILD patients, including 16 PM/DM patients, before treatment [72].

SP-D (surfactant protein-D) is a lung-specific surfactant lipoprotein secreted from type II alveolar epithelial cells. Serum level of SP-D reflects the activity of certain lung diseases such as ILD and pulmonary alveolar proteinosis [71, 73]. Compared with KL-6, SP-D appears to have the same specificity but lower sensitivity [71].

Ferritin

Recent studies suggest serum ferritin level as a marker for severity of acute progressive ILD in DM and C-ADM patients [52••, 57••, 75•, 76]. The serum ferritin concentrations in anti-CADM-140-positive patients are already elevated from the early stage of the disease, with significantly high frequency in comparison with antibody-negative DM patients, even if ILD is not worsened [52••]. Moreover, the serum ferritin concentration correlates with the activity of ILD in anti-CADM-140-positive patients.

Gono et al. [75•] showed that the serum ferritin level before initial treatment in acute or subacute ILD in DM patients was significantly higher (mean, 790 ng/mL) than in chronic ILD (188 ng/mL) and non-ILD patients (160 ng/mL). Patients with a ferritin level more than 1,500 ng/mL showed significantly poorer prognosis than those with less than 1,500 ng/mL. They also reported that serum ferritin was significantly elevated in patients with anti-CADM-140 (MDA5)-positive acute ILD and correlated with prognosis and disease activity [57••, 76].

Titers of Autoantibodies

It is not clear whether myositis-specific autoantibodies are directly involved in pathophysiologic mechanisms of myositis and ILD. Correlation between titers of such autoantibodies and activity of myositis or ILD is controversial. There are several reports that anti-Jo-1 antibody titers are correlated with activity of myositis as well as lung [77], and anti-CADM-140 titer disappeared after intensive treatment of ILD in ADM patients [78]. However, these changes of antibody titers are modest, and further studies will be necessary before we can draw conclusions.

Treatment

Regarding the therapy of ILD in myositis, glucocorticoids are the empiric first-line drug, and additional immunosuppressive agents are often used as the second-line drugs in cases of refractory disease. However, these therapies are not based on high levels of evidence (ie, randomized controlled trials), but rather based on long-term experiences, retrospective studies, and small-scale case series or case reports. Because ILD is a progressive and fatal disease and glucocorticoids have been established as the standard therapy, it is difficult to conduct placebo-controlled, prospective trials.

Glucocorticoids

Oral high-dose glucocorticoids (>1 mg/kg per day of prednisone) or pulse therapy of methylprednisolone (1,000 mg intravenously for 3 days) are the first-line therapy for ILD in myositis. Roughly half of ILD patients with myositis respond well to the initial glucocorticoid therapy [14, 29, 37•, 79]. However, acute ILD, especially rapid, progressive ILD in anti-CADM-140-positive DM/C-ADM, is usually not responsive to glucocorticoids alone [51, 52••, 53•, 54–56].

Fujisawa et al. [14] reported 28 ILD patients with myositis (16 PM and 12 DM) and their difference in efficacy of treatment. Glucocorticoids alone achieved a favorable response in six patients (37.5%) with PM-ILD, but in only one (8.3%) with DM-ILD. Overall 2.5-year survival in DM-ILD was 58%, and 5-year survival in PM-ILD was 81%. In a similar study by Nawata et al. [79], when ILD was classified into two groups according to serum creatine kinase (CK) levels (high CK or normal CK), the normal CK group showed significantly more resistance to glucocorticoid therapy and poorer prognosis than those with high CK (1-year survival, 31% vs 89%) [79].

Although these studies have not reported the autoantibody status, glucocorticoid-refractory ILD with DM (not PM) or normal CK patients may represent the characteristic features of patients with anti-CADM-140 antibody who have reported to have treatment resistance and poor prognosis. It has been obvious that the prognosis of initial glucocorticoid-resistant ILD patients is not improved even if immunosuppressive drugs are added after exacerbation of respiratory symptoms. The efficacy of glucocorticoids as the initial therapy of ILD is limited; nevertheless, glucocorticoids remain the mainstay of therapy.

Cyclophosphamide

Cyclophosphamide (CYC), oral or intravenous pulse (IVCYC), is commonly used in acute or refractory ILD and has demonstrated its efficacy in several case series and small-scale open-label trials [7, 80–82]. Yamasaki et al. [82] reported 17 cases of refractory ILD in myositis who were treated with IVCYC (300–800 mg/m^2 at least 6 times every 4 weeks) and who showed significant improvement in dyspnea, pulmonary function, and HRCT findings.

CYC is also used in combination with other immunosuppressive drugs in refractory ILD [83, 84]. Kameda et al. [84] reported the efficacy of IVCYC in combination with glucocorticoids and cyclosporine (CSP) in 10 DM patients with acute ILD. Although five patients who received the combination therapy died of respiratory failure within 3 months, the mortality rate tended to become lower than in the historical control, in which 9 of 12 patients died despite high-dose glucocorticoid therapy with or without a choice of CYC, CSP, or azathioprine (AZT).

Calcineurin Inhibitors

Calcineurin inhibitors such as CSP and tacrolimus (TAC) targeting activated T cells by inhibiting calcineurin and nuclear translocation of NF-AT may become the cornerstone of the treatment of ILD in myositis.

Cyclosporine

Several retrospective or open-label studies have analyzed the efficacy of CSP in PM/DM-ILD [14, 37•, 79, 85, 86]. Takada et al. [86] reported a multicenter retrospective analysis of 38 cases with acute ILD in PM/DM. In this study, ILD in PM (9 cases) and chronic ILD in DM (5 cases) showed good efficacy of CSP and good prognosis, whereas patients with acute IP in DM showed poor response and poor prognosis (7 of 17 died). Moreover, in a further analysis of 32 cases with acute DM-ILD, 9 of 13 starting CSP within 2 weeks from initial glucocorticoid treatment survived (survival rate, 69%), whereas all 17 cases receiving only glucocorticoids more than 2 weeks as the initial therapy died within 9 months from the onset of therapy. In the retrospective study by Kotani et al. [87] analyzing the efficacy of CSP in 16 DM cases with acute or subacute ILD, 9

cases treated initially with glucocorticoids and CSP (mean interval, 3.8 days) appeared to show good prognosis (only 1 died), whereas 4 of 7 cases (57%) in whom CSP was added when initial glucocorticoid treatment was not effective (mean interval, 20.0 days) died of respiratory failure related to ILD [87].

Monitoring of serum CSP concentration is important for achieving maximal efficacy and for reducing toxicity. Trough level (C0) and 2-hour postdose blood concentration (C2) are correlated with the therapeutic effects [88•, 89•]. Authors also suggest that once-daily preprandial administration of CSP, rather than twice daily, may be beneficial in DM patients with progressive ILD [89•]. These studies, although they were small-scale retrospective analyses, suggest the effectiveness of early intervention and tight control by CSP in combination with glucocorticoids in the treatment of refractory myositis–ILD.

Tacrolimus

TAC is another calcineurin inhibitor that is 100-fold more potent in inhibiting T-cell activity compared with CSP. TAC recently has been utilized in refractory ILD in myositis patients, as well as CSP. Several case series and retrospective studies have shown the efficacy and tolerability of TAC in patients with PM/DM-ILD refractory to CSP [86, 90–92]. TAC appears to be more effective in ILD of antisynthetase syndrome [91, 92]. Wilkes et al. [92] retrospectively analyzed 13 antisynthetase-positive patients treated with TAC and showed its efficacy (and that it was well-tolerated) for refractory ILD and myositis.

Rituximab

Rituximab is a biologic agent of chimeric monoclonal anti-CD20 antibody that targets B cells. Recently, its potential usefulness has been demonstrated in various autoimmune diseases, and several case reports and case series of rituximab have also been reported in myositis–ILD [93•, 94, 95]. Sem et al. [93•] reported 11 refractory ILD in antisynthetase syndrome patients treated with rituximab and showed that rituximab stabilized and/or improved the ILD in 7 of 11. Rituximab reduced the serum titer of anti-Jo-1 antibody, but the effect was modest.

Other Immunomodulating Therapies

Methotrexate

Although methotrexate (MTX), inhibitor of folic acid and purine metabolisms, is widely used in treatment of refractory PM/DM, there is no obvious evidence in myositis–ILD. The use of MTX in ILD is controversial because there are patients who respond favorably to this treatment, but the risk of idiosyncratic drug-induced ILD has also been reported. Particular care should be taken if using MTX for ILD in myositis.

Azathioprine

AZT has been widely used in myositis and ILD as the second-line immunomodulating drug, but its efficacy is modest. AZT may be useful as a maintenance therapy for the control of ILD after CYC.

Mycophenolate Mofetil

In a few case series, the potential efficacy of mycophenolate mofetil has been shown in stabilization of progressive ILD and reducing glucocorticoid dose in ILD patients with connective tissue diseases, including PM/DM [96•, 97•].

Intravenous Immunoglobulin

The efficacy of intravenous immunoglobulin has been demonstrated in muscular symptoms of refractory DM and PM, but the usefulness in ILD associated with myositis is uncertain. One case series of five patients with severe ILD reported its potential usefulness as a salvage therapy [98].

Anticytokine Biologics

The use of anti-tumor necrosis factor [99, 100] and other biologics (including tocilizumab [101] and anakinra [102]) has been reported in some case reports and case series and in a randomized pilot trial [100]. However, all of them focused on severe or refractory myopathy and not on ILD. They appear to be effective in myositis occasionally, but some reports suggest no effect or even worsening muscle symptoms [99]. Their efficacy in ILD has not been discussed. Experience with ant-cytokine therapies on myositis–ILD should be collected and investigated carefully.

Conclusions

ILD is the most frequent extramuscular organ involvement and the most important prognostic factor of IIM, but it reveals various clinical courses and therapeutic responsiveness according to the clinical and serological subsets. Autoantibodies as well as imaging and histopathological studies are useful for the classification of ILD in myositis and provide us with useful information for predicting the prognosis and determining therapeutic strategy. Routine examination of anti-CADM-140 antibody and antisynthetase antibodies, except for anti-Jo-1, is not available thus far, as

these antibodies can only be detected using complicated immunoprecipitation techniques. Quantitative methods to detect these MSAs are now being developing and will be available in the near future.

As treatment of ILD in myositis, glucocorticoids remain the first-line drug, and various immunomodulating drugs are also frequently used in refractory patients. Among these drugs, CYC (especially IVCYC) and calcineurin inhibitors (CSP and TAC) appear to be the key drugs for the treatment of refractory ILD in myositis. Rituximab may be another candidate if these drugs are not effective. However, there are no large-scale, randomized clinical trials to guarantee the efficacy and safety of these drugs. Although it may be difficult to conduct placebo-controlled trials in such a progressive and fatal condition, the construction of evidence is necessary to achieve the best management of an intractable disease such as ILD.

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