INTRODUCTION

Myositis-specific autoantibodies (MSAs) are antibodies that direct against cytoplasmic or nuclear components involved in the regulation of protein synthesis in patients with idiopathic inflammatory myopathies (IIMs). They have been shown to be highly specific, be able to predict clinical features, and have prognostic implications in patients with IIMs. Over three decades ago, the anti-tRNA synthetase antibodies were recognized to be associated with a group of clinical characteristics, including Raynaud's phenomenon, Mechanic's
hands, arthritis, and fever. Examples of the anti-synthetase autoantibodies include anti-Jo-1, anti-PL-7, anti-PL-12, anti-OJ, and anti-EJ antibodies. Around 90% patients with anti-synthetase autoantibodies were found to have interstitial lung disease (ILD), and nearly 50% mortality in these patients was attributable to ILD. The anti-melanoma differentiation-associated gene 5 antibody (anti-MDA5 Ab), or formerly known as the anti-CADM-140 autoantibody, was first described in Japan in 2005. It has become one of the most important MSAs especially in Asia, and was found to be specifically expressed in patients with clinically amyopathic dermatomyositis (CADM). These patients may have a tendency to develop rapidly progressive interstitial lung disease (RP-ILD), which is associated with high mortality. A recent study in Hong Kong showed that anti-MDA5 Ab was present exclusively in 30% of patients with dermatomyositis (DM), which were all clinically amyopathic and was significantly associated with RP-ILD, suggesting the clinical usefulness of examination of this autoantibody. On the other hand, the anti-transcriptional intermediary factor 1-gamma antibody (anti-TIF1-γ Ab) was found to be significantly associated with malignancies.

Despite the suggestion of association with potential life-threatening complications in IIMs, currently testing of MSA is not universally performed. Up to this date, the MSA profile has not been well established in different populations, and apparently, there are discrepancies in the prevalence and phenotypic presentation of MSAs in different cohorts.

The primary objective of the study was to establish the prevalence of MSAs in existing adult Chinese patients with IIMs in Hong Kong. The secondary objective was to examine the association between different MSAs and the clinical features, as well as complications of these patients.

2 METHODS

2.1 Patient recruitment

Consecutive patients with IIMs seen in the rheumatology clinics and wards of the participating major regional hospitals were recruited in this multicentered prospective study. Diagnosis of IIMs was based on Bohan and Peter’s criteria with probable or definite cases included. Patients with CADM were also recruited, and they must have the typical Gottron’s or heliotrope rash as determined by rheumatologists or dermatologists, and with no symptoms or signs of muscle involvement. Patients under the age of 18 or of non-Chinese ethnicity were excluded. Enrolled patients were followed up regularly from July 2016 to January 2018.

Patient demographics and clinical features were recorded by a single investigator by reviewing the medical records. The clinical characteristics including age, sex, smoking status, type of myositis, and presence of concomitant connective tissue diseases and duration of disease were obtained. Cutaneous features including Gottron’s papules or sign, heliotropic rash, mechanic’s hands, Raynaud’s phenomenon, calcinosis, skin ulcers, and refractory rash were documented. Medical history such as history of pulmonary tuberculosis (TB) and family history of malignancy was recorded. Details of the treatment regime including the use of corticosteroid, use of high-dose corticosteroid, current corticosteroid dosage, and use of other immunosuppressants were recorded. High-dose corticosteroid use was defined as oral prednisolone more than 0.5 mg per kg body weight per day for more than 6 weeks. Blood parameters including creatine kinase (CK) level, lactate dehydrogenase (LDH) level, erythrocyte sedimentation rate (ESR), and C-reactive protein level (CRP) were recorded. Complications related to IIMs including ILD or RP-ILD, dysphagia, and malignancy were collected. Patients were considered as having ILD if defining features on computed tomography (CT) or high-resolution CT (HRCT) images of the chest were present. Defining features included radiologist-documented ground glass opacities, reticulation or honeycombing. RP-ILD was defined as an ILD showing progression within one month of onset of respiratory symptoms, as evidenced by all of three of the followings including worsening dyspnea symptoms, documented hypoxemia, and evidence of progression in imaging. Refractory skin rash and muscle weakness were defined as corresponding refractory diseases despite the use of corticosteroids plus at least one immunosuppressant excluding hydroxychloroquine.

The Research Ethical Committee approval was obtained in each of the participating centers. Patients’ written consents to participate were obtained. The study was conducted in accordance with the Declaration of Helsinki.

2.2 Identification of antibody

The line blot technique was used in this study. It is based on an immunoblotting procedure with highly purified antigens coated on protein-binding membrane without the need of gel electrophoresis. A commercial line blot immunoassay kit (Euroline Autoimmune Inflammatory Myopathies 15 Ag [IgG] Euroimmun) was used to detect the MSAs. After in-house calibration, antibodies with titers of 17 units or above in the assays were regarded as positive results. The MSAs tested included anti-MDA5 Ab, anti-TIF1γ Ab, anti-Jo-1 Ab, anti-PL-7 Ab, anti-PL12 Ab, anti-EJ Ab, anti-OJ Ab, anti-Mi2β Ab, anti-Mi2α Ab, anti-NXP2 Ab, anti-SAE1 Ab, and anti-SRP Ab.

2.3 Statistical analysis

The SPSS statistical package version 23.0 was used. Descriptive statistics were presented as frequencies, means with standard deviations or medians with ranges as appropriate. Comparisons between clinical variables were done using the chi-square test or Fisher’s exact test for categorical variables, independent-samples t test for continuous variables with normal distribution, or Mann-Whitney U test for nonparametric continuous variables. In each MSA subset, demographic features and clinical characteristics were studied, and antibody-positive cases were compared with antibody-negative
cases. Logistic regression was used to determine the independent risk factors for RP-ILD, while Cox regression was used to investigate the independent risk factors for malignancy. Potential explanatory variables of the outcomes were selected from the univariate analyses. They should have a $P$-value < .1 and were biologically plausible. Results were considered statistically significant if the $P$-value was < .05.

3 | RESULTS

3.1 | MSA prevalence

Out of the 201 recruited patients with IIMs, 150 (74.6%) were female. Fifty-four (26.9%) patients had CADM, 52 (52.9%) had DM, 44 (21.9%) had anti-synthetase syndrome (ASS), 34 (16.9%) had polymyositis (PM), and 17 (8.5%) had immune-mediated necrotizing myopathy (IMNM). At least one MSA was found in 63.4% of patients. The most prevalent MSAs were anti-MDA5 (28, 13.9%) and anti-TIF1γ (28, 13.9%), followed by anti-Jo-1 (25, 12.4%) and anti-SRP (17, 8.5%). Thirteen (6.5%) patients were tested positive for more than one MSA. Details of the prevalence of different antibodies and the clinical characteristics of the patients are listed in Tables 1 and 2, respectively.

### TABLE 1  Myositis-specific autoantibody (MSA) profile of the 201 patients with idiopathic inflammatory myopathies

| MSAs          | Number (%) |
|---------------|------------|
| MDA5          | 28 (13.9)  |
| TIF1γ         | 28 (13.9)  |
| Jo-1          | 25 (12.4)  |
| SRP           | 17 (8.5)   |
| PL-7          | 14 (7.0)   |
| Mi2           | 8 (4.0)    |
| PL-12         | 6 (3.0)    |
| SAE1          | 5 (2.5)    |
| NXP2          | 4 (2.0)    |
| EJ            | 4 (2.0)    |
| OJ            | 1 (0.5)    |

| Double-positive MSA combinations | Number (%) |
|---------------------------------|------------|
| TIF1γ + SAE1                    | 1 (0.5)    |
| TIF1γ + Jo-1 + TIF1γ + PL-12    | 1 (0.5)    |
| TIF1γ + Mi2                     | 2 (1)      |
| MDA5 + PL-7, MDA5 + Jo-1        | 2 (1)      |
| MDA5 + Mi2                      | 1 (0.5)    |
| SRP + Jo-1                      | 1 (0.5)    |
| SRP + Mi2                       | 1 (0.5)    |
| PL-7 + Jo-1                     | 1 (0.5)    |
| PL-7 + NXP2                     | 1 (0.5)    |

3.2 | Association of MSAs with clinical features

For the major MSA subsets, antibody-positive cases were compared with negative cases for different clinical characteristics, as shown in Table 3.

Patients with anti-MDA5 Ab all had DM rash (100% vs 45.7%, $P < .001$) and were predominantly male (78.0% vs 53.6%, $P = .006$), compared to those without the antibody. The mean age was lower in anti-MDA5-positive patients (50.5 ± 10.8 years vs 59.6 ± 12.4 years, $P < .001$), and the disease ran a shorter mean duration (21.8 ± 19.4 months vs 77.0 ± 80.0 months, $P < .001$). Patients with the antibody had a significantly lower median peak CK level (152 vs 1441 IU/L, $P < .001$) and higher median ESR at onset (48 vs 37, $P = .014$). Anti-MDA5 Ab was found to be associated with CADM (85.7% vs 19.1%, $P < .001$), RP-ILD (57.1% vs 2.31%, $P < .001$), refractory skin rash (21.4% vs 7.51%, $P = .032$), cutaneous ulcers (50% vs 5.78%, $P < .001$), and hoarseness (17.9% vs 3.50%, $P = .009$). It was associated with lower risk of malignancy (3.57% vs 20.8%, $P = .029$).

Patients with anti-TIF1γ Ab predominantly had DM (96.4% vs 54.9%, $P < .001$). It was associated with lower median ESR at onset (31 vs 43, $P = .015$) and was significantly associated with refractory skin rash (35.7% vs 5.20%, $P < .001$) and malignancy.

### TABLE 2  Clinical characteristics of the 201 patients with idiopathic inflammatory myopathies

| Clinical characteristics | Number (%) |
|--------------------------|------------|
| Female                   | 150 (74.6) |
| Clinically amyopathic dermatomyositis | 54 (26.9) |
| Dermatomyositis           | 52 (25.9)  |
| Anti-synthetase syndrome  | 44 (21.9)  |
| Polymyositis              | 34 (16.9)  |
| Immune-mediated necrotizing myopathy | 17 (8.5) |
| Gottron’s papules or sign | 72 (35.8) |
| Heliotrope rash           | 64 (31.8)  |
| Raynaud’s phenomenon      | 25 (12.4)  |
| Mechanic’s hands          | 14 (7.0)   |
| Calcinosis                | 4 (2.0)    |
| Cutaneous ulcers          | 24 (11.9)  |
| Refractory skin rash      | 19 (9.5)   |
| Arthritis                 | 72 (35.8)  |
| Fever                     | 13 (6.5)   |
| Interstitial lung disease | 117 (58.2) |
| Rapidly progressive interstitial lung disease | 20 (10.0) |
| Refractory muscle disease | 16 (8.0)   |
| Dysphagia                 | 43 (21.4)  |
| Malignancy                | 37 (18.4)  |
| Cardiac involvement       | 3 (1.5)    |
| Hoarseness                | 10 (5.0)   |
| Death                     | 17 (8.5)   |
(53.6% vs 12.7%, \( P < .001 \)) compared to those without the antibody. It was associated with lower risk of ILD (21.4% vs 64.2%, \( P < .001 \)).

Patients with anti-synthetase Ab had a significantly higher median peak CK level (2562 vs 560 IU/L, \( P < .001 \)) and ESR at disease onset (59 vs 39, \( P = .005 \)). They were more prone to develop ILD (86.4% vs 50.3%, \( P < .001 \)) but less likely to have malignancy (6.8% vs 19.7%, \( P = .043 \)).

Anti-SRP Ab was found to be associated with a significantly higher median peak CK level (9710 vs 756 IU/L, \( P < .001 \)). Patients with the antibody also had refractory muscle weakness (23.5% vs 6.52%, \( P = .034 \)).

Two out of 5 anti-SAE1 Ab-positive patients were found to have malignancy, and 4 of them had CADM. One of the patients died 5 months after the diagnosis of myositis of uncertain cause. One of the 4 patients with anti-NXP2 Ab had biopsy-proven calcinosis cutis, and one patient died 2 months after diagnosis because of infection. None of the anti-NXP2 Ab was found to have malignancy. No statistical tests were performed due to the small sample sizes.

For patients who did not have any positive MSA, they were found to have less RP-ILD (4.05% vs 13.4%, \( P = .033 \)), cutaneous ulcer (5.41% vs 15.7%, \( P = .029 \)), and refractory skin rash (4.05% vs 12.6%, \( P = .046 \)), compared with those who had at least one MSA.

### 3.3 Risk factors for RP-ILD

After adjusting for age, gender, smoking history, peak CK level, ESR, and CRP level at disease onset, digital ulcers, and hoarseness, logistic regression analysis suggested that the presence of anti-MDA5 Ab (OR 14.3), CADM (OR 13.5), and history of pulmonary TB (OR 12.4) were independent risk factors for the development of RP-ILD. Details of the results are shown in Table 4.
3.4 | Risk factors for malignancy

There were 34 malignancies diagnosed after and 3 before the onset of myositis. After adjusting for age, gender, smoking history, alcohol history, current use of immunosuppressants, and the presence of refractory rash, it was found that anti-TIF1γ Ab was an independent risk factor for malignancy (HR 3.42). Other independent risk factors included the DM subtype (HR 3.87) and family history of cancer (HR 3.67). History of immunosuppressant use was a negative predictor of malignancy (HR 0.355). Details are shown in Table 5.

3.5 | Survival of patients with different MSAs

The survival curves of patients with different MSAs are shown in Figure 1. Patients with anti-MDA5 and anti-TIF1γ were noted to have a poorer immediate outcome, while the long-term prognosis of patients with anti-synthetase antibodies was similarly bad. On the other hand, patients with anti-Mi2 and anti-SRP had good survival. Anti-NXP2 and anti-SAE were not included due to the small samples.
DISCUSSION

The prevalence of anti-MDA5 Ab was found to differ among different ethnicities. In a study performed in the United States in 2013, anti-MDA5 Ab was only found in 11 out of 160 (6.9%) DM patients. In this study, it was found to be much more prevalent, and was identified in 23.0% of DM/CADM patients. In one study comparing MSAs in 145 Chinese and 165 Japanese patients with IIMs, the prevalence of anti-MDA5 Ab was found to be 36.6% and 15.8%, respectively, in all IIM patients. The prevalence of anti-MDA5 Ab in all IIM patients in the current study was 13.9%, which was comparable to the Japanese cohort but significantly lower than that of the Chinese cohort. The discrepancies between the prevalence of anti-MDA5 Ab in Chinese and Japanese population may be explained by genetic and environmental factors. The association of anti-MDA5 Ab with DRB1*0101/*0405 was reported in Japanese patients, while the combined allele frequencies of DRB1*0101 and DRB1*0405 were different between Japanese and Chinese. However, the reason behind the even greater discrepancy between Hong Kong and Chinese patients was uncertain.

Another striking feature of the pattern of MSAs in our cohort was the prevalence of anti-TIF1γ (13.9%), which was much higher than that of the China (5.5%) and Japanese (8.5%) cohorts, as well as a large Caucasian (7%) cohort. Fifteen out of 28 (53.6%) anti-TIF1γ Ab-positive patients were found to have malignancy. A postulation of the reason behind this would be related to the high prevalence of nasopharyngeal carcinoma (NPC) in Hong Kong. Out of the 15 malignancies in anti-TIF1γ Ab-positive patients, 7 (46.7%) were NPC, followed by lung and gynecological malignancies (2 each). NPC was found to be most common in Southern China, with Hong Kong being one of the regions with the highest incidence. NPC is related to the chronic active infection of Epstein-Barr virus (EBV). In a Taiwanese study, it was suggested that EBV infection might induce generalized myositis and that the immune response to EBV contributed to the coexistence of IIM and NPC. Further longitudinal studies would be needed to elucidate whether there is any true relationship between anti-TIF1 Ab and NPC or EBV.

The prevalence of anti-Jo-1 Ab was 12.4% in this study, while all non-Jo-1 anti-synthetase antibodies combined were 12.5%, adding up to a total of 24.9% for all anti-synthetase antibodies. This figure was slightly lower than that in the Chinese and much lower than that in the Japanese population, which were 27.6% and 40.0%, respectively. This is also apparently lower than those reported in the Caucasian cohorts. Again, the lower prevalence could be explained by genetic and environmental factors. The association of anti-Jo-1 Ab with DRB1*0401/*0405 was reported in Japanese patients, while the combined allele frequencies of DRB1*0401 and DRB1*0405 were different between Japanese and Chinese. However, the reason behind the even greater discrepancy between Hong Kong and Chinese patients was uncertain.

### TABLE 5 Multivariate analysis of risk factors for malignancy after adjustment, by Cox proportional hazards regression

| Risk Factor                        | Hazard ratio (95% CI) | P-value * |
|------------------------------------|-----------------------|-----------|
| Anti-TIF1γ antibody                | 3.42 (1.55, 7.55)     | 0.003     |
| Dermatomyositis                    | 3.87 (1.31, 11.5)     | 0.009     |
| Family history of cancer           | 3.67 (1.31, 10.3)     | 0.029     |
| Ever use of immunosuppressants     | 0.355 (0.139, 0.907)  | 0.270     |
| Current use of immunosuppressants  | 0.419 (0.164, 1.07)   | 0.780     |

*P < .05 denotes clinical significance and is bolded.

One possibility could be the different MSA detection methods being used. In the Chinese and Japanese cohort, ELISA technique was used, while the current study employed the line blot assay. A study comparing the line blot technique with immunoprecipitation for the detection of MSAs showed good concordance rates, justifying the use of the line blot testing in our study. Meanwhile, the potential environmental influences on the frequency of MSAs should be further investigated.
by the difference in detection method, as well as genetic and environmental factors.

In this study, 7.0% of the patients were found to have more than one positive MSA. MSAs are supposed to be mutually exclusive, and previous studies have shown that MSAs rarely coexist with each other. However, there were reports of sporadic cases in which the MSAs coexist and were associated with more complex disease expression. MSA double positivity may also be a result of false positivity of the test. The clinical significance of this finding remains to be clarified.

Anti-MDA5 antibody was found to be more common in younger male DM patients and was associated with cutaneous ulcers, CADM, and RP-ILD. Similar associations have been found in previous studies of the Eastern Asian populations. There were some new findings from the univariate analyses of the current study that anti-MDA5 Ab was also associated with refractory skin rash and hoarseness. Refractory skin rash has been well known to be associated with cancer-related DM, but it was less well documented in anti-MDA5 Ab-positive patients. Hoarseness in anti-MDA5 Ab-positive patients was previously described in China and in Japan. The mechanism of hoarseness was believed to be linked to oropharyngeal dysfunction related to muscle weakness, but why it was predominantly affecting anti-MDA5 Ab-positive patients remained uncertain. It could be an important clinical feature to look for in DM patients, which could bring an increased awareness of the possible important anti-MDA5 Ab-related complications. The association between anti-MDA5 Ab and RP-ILD was not consistently shown in previous studies, especially in the Caucasian cohorts. In an earlier study in the United States, anti-MDA5 positivity was found to be not associated with RP-ILD. More recently, a study involving 61 CADM and 61 classic DM patients also in the United States showed that anti-MDA5 positivity was strongly associated with RP-ILD and significantly poorer survival. This shows that the presentation of the antibody may differ in different ethnicities and is possibly affected by genetic and environmental factors. In our current study, anti-MDA5 Ab was found to be the strongest independent risk factor for RP-ILD, followed by CADM and history of pulmonary tuberculosis. This reiterates that in patients with anti-MDA5 Ab, a strong vigilance for rapidly progressive ILD is necessary for early diagnosis and treatment. On the other hand, history of TB infection as an independent risk factor was a new finding in our study. Pulmonary TB is much more common in Hong Kong and China than the Western countries. The regions with increased prevalence of TB infection and anti-MDA5-associated RP-ILD apparently shared some similarities. Currently, there were no reports of pulmonary TB infection being associated with the development of RP-ILD in IIMs in the literature. However, preceding chest infection and inflammatory lung diseases have been shown to be more common in IIM patients than controls. A role for type I interferon in the lung during viral infection and in TB has been demonstrated. Enhanced type I interferon signaling and the subsequent self-perpetuating overwhelming autoimmune reaction have been regarded as a key component in pathogenesis of anti-MDA5 Ab-associated RP-ILD. One postulation is that the up-regulation of the type I IFN system and modification of host antigen after pulmonary TB infection could induce the dreadful disease in genetically predisposed individuals. Unfortunately, molecular analyses were not available in the current study.

Anti-TIF1γ Ab was found to be significantly associated with refractory skin rash and malignancy, and negatively associated with ILD. The association between anti-TIF1γ Ab and malignancy has been well established. The findings here were in agreement with the previously described characteristics in anti-TIF1γ Ab–positive patients. The use of immunosuppressants appeared to have a "protective" effect on malignancy in the regression analysis. It is likely because immunosuppressants were more used in patients who suffered from complications such as ILD, which were negatively associated with malignancy. Moreover, use of these agents might be avoided in patients at a high risk of malignancy, which further contributes to the possible confounding by indication. On the other hand, a recent Chinese study showed that apart from anti-TIF1γ Ab, anti-NXP2, and anti-SAE1 Ab were both associated with increased risk of malignancy in patients with IIMs. In our study, out of the 5 anti-SAE1 Ab–positive patients, 2 of them had malignancy (CA colon and NPC). However, the sample size was not large enough to give a statistically significant result. Larger studies will be necessary to confirm the association of malignancy with these antibodies. Meanwhile for anti-TIF1γ Ab–positive patients, vigilant malignant screening would be necessary.

There were a few limitations in this study. Firstly, despite the increasing popularity, the line blot immunoassay has not been fully validated. Some antibodies, for example anti-OJ antibody, could not be measured accurately by the line blot assay. The assay also did not test for anti-HMG-Coenzyme A reductase (HMGCRC) antibody, which was estimated to be present in around 5% of patients with IIMs. Secondly, Bohan and Peter’s criteria supplemented with Sontheimer's criteria for CADM were chosen when the study was designed in 2016. The new European League Against Rheumatism and American College of Rheumatology (EULAR/ACR) IIM classification criteria were only published in 2017. As a result, the classification and subgrouping suggested by the new criteria were not applied. Thirdly, some clinical characteristics that were not well known to be associated before, such as hoarseness, might be easily missed in the documentation. This might cause some of the features to be under-reported. Lastly, the prevalence of MSAs in IIMs may also depend on the subspecialty collecting the cohorts. For example, anti-MDA5 patients tend to be less in the cohorts where patients are recruited from neurology departments because weakness is not a main symptom. On the contrary, they tend to be more in the cohorts from rheumatology, pulmonology, and dermatology.

In conclusion, our study reports the profiling of MSAs and their clinical characteristics in adult Hong Kong Chinese patients with IIM. Anti-MDA5 and anti-TIF1γ Ab were found to be most prevalent among the identified MSAs, and significantly associated with RP-ILD.
and malignancy, respectively. It further confirms that MSA testing could assist in confirming the diagnosis of IIMs, and enable earlier detection and hence better treatment of their complications.\textsuperscript{38}

Given the difference in presentation of the disease in different regions, this offers further information for the global development in knowledge of the disease. Some new findings in this study, such as the association of pulmonary TB with the development of RP-ILD, might bring new insights into the understanding of the pathogenesis of the deadly complications, and possibly improve management of the disease in future.

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**CONFLICT OF INTEREST**

All authors report no disclosures relevant to the manuscript.

**DATA AVAILABILITY STATEMENT**

Data can be shared upon request.

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**REFERENCES**

1. Mimori T, Imura Y, Nakashima R, Yoshifuji H. Autoantibodies in idiopathic inflammatory myopathy: an update on clinical and pathophysiological significance. *Curr Opin Rheumatol*. 2007;19:523-529.

2. Tansley SL, Betteridge ZE, McHugh NJ. The diagnostic utility of autoantibodies in adult and juvenile myositis. *Curr Opin Rheumatol*. 2013;25:772-777.

3. Lega J-C, Fabien N, Reynaud Q, et al. The clinical phenotype associated with myositis-specific and associated autoantibodies: a meta-analysis revisiting the so-called antisynthetase syndrome. *Autoimmun Rev*. 2014;13:883-891.

4. Aggarwal R, Cassidy E, Fertig N, et al. Patients with non-Jo-1 anti-IRNA-synthetase autoantibodies have worse survival than Jo-1 positive patients. *Ann Rheum Dis*. 2014;73:227-232.

5. Sato S, Hirakata M, Kuwana M, et al. Autoantibodies to a 140-kd polypeptide, cadm-140, in Japanese patients with clinically amyopathic dermatomyositis. *Arthritis Rheum*. 2005;52:1571-1576.

6. Moghadam-Kia S, Oddis CV, Sato S, Kuwana M, Aggarwal R. Anti-melanoma differentiation-associated gene 5 is associated with rapidly progressive lung disease and poor survival in US patients with amyopathic and myopathic dermatomyositis. *Arthritis Care Res*. 2016;68:689-694.

7. So H, Ip WK, Wong TL, Yip ML. Analysis of anti-melanoma differentiation-associated gene 5 antibody in Hong Kong patients with idiopathic inflammatory myopathies: diagnostic utility and clinical correlations. *Int J Rheum Dis*. 2018;21:1076-1081.

8. Hoshino K, Muro Y, Sugihara K, Tomita Y, Nakashima R, Mimori T. Anti-MDA5 and anti-TIF1-γ antibodies have clinical significance for patients with dermatomyositis. *Rheumatology*. 2010;49:1726-1733.

9. Florentino D, Casiola-Rosen L. TIF1 autoantibodies in dermatomyositis shed insight into the cancer-miositis connection. *Arthritis Rheum*. 2012;64:346-349.

10. Fujimoto M, Watanabe R, Ishitsuka Y, Okiyama N. Recent advances in dermatomyositis-specific autoantibodies. *Curr Opin Rheumatol*. 2016;28:636-644.

11. Bohan A, Peter JB. Polymyositis and dermatomyositis. *N Engl J Med*. 1975;292:344-347.

12. Sontheimer RD. Clinically myopathic dermatomyositis: what can we now tell our patients? *Arch Dermatol*. 2010;146:76-80.

13. Fathi M, Lundberg IE. Interstitial lung disease in polymyositis and dermatomyositis. *Curr Opin Rheumatol*. 2005;17:701-706.

14. Hall JC, Casiola-Rosen L, Samedy LA, et al. Anti-MDA5-associated dermatomyositis: expanding the clinical spectrum. *Arthritis Care Res*. 2013;65:1307-1315.

15. Chen Z, Hu W, Wang Y, Guo Z, Sun L, Kuwana M. Distinct profiles of myositis-specific autoantibodies in Chinese and Japanese patients with polymyositis/dermatomyositis. *Clin Rheumatol*. 2015;34:1627-1631.

16. Gono T, Kawaguchi Y, Kuwana M, et al. Brief report: association of HLA-DRB1*0101/*0405 with susceptibility to anti-melanoma differentiation-associated gene 5 antibody-positive dermatomyositis in the Japanese population. *Arthritis Rheum*. 2012;64:3736-3740.

17. Nakajima F, Nakamura J, Yokota T. Analysis of HLA haplotypes in Japanese, using high resolution allele typing. *MHC*. 2001;8:1-32.

18. Qin Q, Su F, Xiao Yan W, et al. Distribution of human leucocyte antigen-A, B and -DR alleles and haplotypes at high resolution in the population from Jiangsu province of China. *Int J Immunogenet*. 2011;38:475-481.

19. Cavazzana I, Fredi M, Ceribelli A, et al. Testing for myositis specific autoantibodies: comparison between line blot and immunoprecipitation assays in 57 myositis sera. *J Immunol Methods*. 2016;433:1-5.

20. Betteridge Z, Tansley S, Shaddick G, et al. Frequency, mutual exclusivity and clinical associations of myositis autoantibodies in a combined European cohort of idiopathic inflammatory myopathy patients. *J Autoimmun*. 2019;101:48-55.

21. Cao SM, Simons MJ, Qian CN. The prevalence and prevention of nasopharyngeal carcinoma in China. *Chin J Cancer*. 2011;30:114-119.

22. Chen Y-J, Wu C-Y, Huang Y-L, et al. Cancer risks of dermatomyositis and polymyositis: a nationwide cohort study in Taiwan. *Arthritis Res Ther*. 2010;12:1-7.

23. Betteridge ZE, Chinroy H, Cooper RG, et al. Myositis-specific autoantibodies rarely coexist with each other: an analysis of the UKmyonet and Eumyonet Cohorts. *Rheumatology*. 2016;55(Suppl 1):133.

24. Vincze M, Molnár PA, Tumpek J, et al. An unusual association: anti-Jo-1 and anti-SRP antibodies in the serum of a patient with polymyositis. *Clin Rheumatol*. 2010;29:811-814.

25. Muro Y, Ishikawa A, Sugihara K, Akyama M. Clinical features of anti-TIF1-α antibody- positive dermatomyositis patients are closely associated with coexistent dermatomyositis-specific autoantibodies and anti-TIF1-γ or anti-Mi-2 autoantibodies. *Rheumatology*. 2012;51:1508-1513.

26. Hamaguchi Y, Kuwana M, Hoshino K, et al. Clinical correlations with dermatomyositis-specific autoantibodies in adult Japanese patients with dermatomyositis: a multicenter cross-sectional study. *Arch Dermatol*. 2011;147:291-298.

27. Cao H, Pan M, Kang YQ, et al. Clinical manifestations of dermatomyositis and clinically amyopathic dermatomyositis patients with positive expression of anti-MDA5 antibody. *Arthritis Res Ther*. 2012;14:1602-1610.

28. Sugimori Y, Yamashita H, Yorifuji H, et al. A case of clinically amyopathic dermatomyositis with hoarseness due to vocal cord necrosis. *J Clin Rheumatol*. 2018;24:50-51.

29. World Health Organization Tuberculosis Burden database. [Internet.] www.who.int/tb/country/data/download/en/. Accessed June 01, 2020.

30. Helmers SB, Jiang X, Pettersson D, et al. Inflammatory lung disease a potential risk factor for onset of idiopathic inflammatory myopathies: results from a pilot study. *RMD Open*. 2016;2:e000342.
31. Svensson J, Holmqvist M, Lundberg IE, Arkema EV. Infections and respiratory tract disease as risk factors for idiopathic inflammatory myopathies: a population-based case-control study. *Ann Rheum Dis*. 2017;76:1803-1808.

32. Moreira-Teixeira L, Mayer-Barber K, Sher A, O’Garra A. Type I interferons in tuberculosis: foe and occasionally friend. *J Exp Med*. 2018;215:1273-1285.

33. Walsh RJ, Kong SW, Yao Y, et al. Type I interferon-inducible gene expression in blood is present and reflects disease activity in dermatomyositis and polymyositis. *Arthritis Rheum*. 2007;56:3784-3792.

34. Yang H, Peng Q, Yin L, et al. Identification of multiple cancer-associated myositis specific autoantibodies in idiopathic inflammatory myopathies: a large longitudinal cohort study. *Arthritis Res Ther*. 2017;19:259.

35. Noguchi E, Uruha A, Suzuki S, et al. Skeletal muscle involvement in antisynthetase syndrome. *JAMA Neurol*. 2017;74:992-999.

36. Werner JL, Christopher-Stine L, Ghazarian SR, et al. Antibody levels correlate with creatine kinase levels and strength in anti-HMG-CoA reductase-associated autoimmune myopathy. *Arthritis Rheum*. 2012;64:4087-4093.

37. Lundberg IE, Tjarnlund A, Bottai M, et al. European League Against Rheumatism and American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their subgroups. *Ann Rheum Dis*. 2017;76:1955-1964.

38. Montagnese F, Babačić H, Peter Eichhorn P, Schoser B. Evaluating the diagnostic utility of new line immunoassays for myositis antibodies in clinical practice: a retrospective study. *J Neurol*. 2019;266:1358-1366.

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