Myositis-specific autoantibodies and their clinical associations in Idiopathic Inflammatory Myopathies

Victor Tak Lung Wong
Kwong Wah Hospital
Ho SO (h99097668@hotmail.com)
Kwong Wah Hospital https://orcid.org/0000-0001-7113-9390
Ronald Man Lung Yip
Kwong Wah Hospital

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Abstract

Background

The aims of the study were to investigate the prevalence of myositis specific autoantibodies (MSAs) and their associated complications in a cohort of patients with idiopathic inflammatory myopathies (IIMs).

Methods

A total of 201 consecutive patients with IIMs being followed up in the Rheumatology clinics of the participating regional hospitals in Hong Kong from July 2016 to January 2018 were recruited. Clinical characteristics, treatment history and disease complications were documented. Immunoblot assay was used to detect the MSAs.

Results

Out of the 201 patients, at least one MSA was found in 63.2% of patients. The most common MSAs were the anti-melanoma differentiation-associated gene 5 antibody (anti-MDA5 Ab) and the anti-transcriptional intermediary factor 1-gamma antibody (anti-TIF1-γ Ab) (both 13.9%), followed by anti-Jo-1 antibody (12.4%). Anti-MDA5 Ab was present exclusively in dermatomyositis (DM) and was strongly associated with digital ulcers, the clinically amyopathic phenotype and rapidly progressive interstitial lung disease (RP-ILD). Anti-TIF1γ Ab was strongly associated with refractory rash and malignancy. Multivariate analysis showed that the independent risk factors of RP-ILD included anti-MDA5 Ab (OR 14.5, p=0.001), clinically amyopathic DM (OR 13.9, p=0.015) and history of pulmonary tuberculosis (OR 12.2, p=0.026). Cox regression analysis showed that the independent predictors of malignancy included anti-TIF1γ Ab (HR 3.55, p=0.002), DM (HR 3.82, p=0.009) and family history of cancer (HR 3.40, p=0.038).

Conclusions

MSA testing enables dividing of patients with IIMs into phenotypically homogenous subgroups and prediction of potentially life-threatening complications.

Background

Myositis-specific autoantibodies (MSAs) are antibodies which 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 [1, 2]. 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 [3]. 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 were attributable to ILD [4]. 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 [5]. It has become one of the most important MSAs especially in Asia, which 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 [6]. 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 [7]. On the other hand, the anti-transcriptional intermediary factor 1-gamma antibody (anti-TIF1-γ Ab) was found to be significantly associated with malignancies [8, 9].

Despite the suggestion of association with potential life-threatening complications in IIMs, currently testing of MSA is not routinely performed. Up to this date, the MSAs profile and their clinical correlation have not been well established in large cohorts. Furthermore, apparently there are discrepancies in the prevalence and phenotypic presentation of MSAs in different populations [10].

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

Methods

Patient recruitment

A total of 201 consecutive Hong Kong Chinese patients with IIMs seen in the Rheumatology clinics and wards of the participating major regional hospitals were recruited in this multi-centre study. Diagnosis of idiopathic inflammatory myopathy was based on the Bohan and Peter's criteria with probable or definite IIMs being included [11]. Patients with CADM must have the typical Gottron's or heliotrope rash as determined by rheumatologists or dermatologists, and with no symptoms or signs of muscle involvement [12]. Patients under age of 18 or of non-Chinese ethnicity were excluded.

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, Raynauds' 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 [13]. Refractory skin rash and muscle weakness were defined as corresponding refractory diseases despite use of corticosteroids plus at least one immunosuppressants excluding hydroxychloroquine.

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) was used to detect the MSAs. After in-house calibration, antibodies with titres 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-Mi2 Ab, anti-Mi2αAb, anti-NXP2 Ab, anti-SAE1 Ab, anti-SRP Ab.

Statistical analysis

Version 23.0 of the SPSS statistical package was used. Descriptive statistics were presented as frequencies, means with standard deviation or medians with ranges as appropriate. Comparisons between clinical variables were done using chi-square test or Fisher's exact test for categorical variables, independent samples t-test for continuous variables for those with normal distribution or Mann-Whitney U test for nonparametric continuous variables. In each MSA subset, demographic features, clinical characteristics were studied, and antibody positive cases were compared to antibody negative cases. Logistic regression was used to determine the independent risk factors of RP-ILD, while cox regression was used to investigate the independent risk factors of malignancy. Results were considered statistically significant if the p value was less than 0.05.

Results

MSA prevalence

Out of the 201 patients with IIMs, 150 (74.6%) were female. Seven-nine patients (39.3%) had polymyositis (PM), 65 (32.3%) had DM and 57 patients (28.4%) had CADM. At least one MSA was found in 63.4% of patients. The most common MSAs were MDA5 (28, 13.9%) and TIF1γ (28, 13.9%), followed by Jo-1 (25, 12.4%) and SRP (17, 8.5%). Fourteen (7.0%) patients were tested positive for more than one MSA. Details of the prevalence of different antibodies and the clinical characteristics of the patients were listed in Table 1 and 2 respectively.

Association of MSAs with clinical features

For each MSA subset, antibody positive cases were compared to antibody negative cases for different clinical characteristics, as shown in Table 3.

Patients with anti-MDA5 Ab all had DM (100% vs 45.7%, p<0.001), and were predominantly male (78.0% vs 53.6%, p=0.006), 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<0.001) and the disease ran a shorter mean duration (21.8 ±19.4 months vs 77.0 ±80.0 months, p<0.001). Patients with the antibody had a significantly lower median peak CK level (152 vs 1441IU/L, p<0.001) and higher median ESR at onset (48 vs 37, p=0.014). Anti-MDA5 Ab was found to be associated with CADM (85.7% vs 19.1%, p<0.001), RP-ILD (57.1% vs 2.31%, p<0.001), refractory skin rash (21.4% vs 7.51%, p=0.032), cutaneous ulcers (50% vs 5.78%, p<0.001) and hoarseness (17.9% vs 3.50%, p=0.009). It was associated with lower risk of malignancy (3.57% vs 20.8%, p=0.029).

Patients with anti-TIF1γ Ab predominantly had DM (96.4% vs 54.9%, p<0.001). It was associated with lower median ESR at onset (31 vs 43, p=0.015), and was significantly associated with refractory skin rash (35.7% vs 5.20%, p<0.001) and malignancy (53.6% vs 12.7%, p<0.001) compared to those without the antibody. It was associated with lower risk of ILD (21.4% vs 64.2%, p<0.001).

Patients with anti-Jo-1 Ab more commonly had PM, compared to those without the antibody (80% vs 33.5%, p<0.001). Patients with the antibody had a significantly higher median peak CK level (5016 vs 697IU/L, p<0.001) and were more prone to develop ILD (88% vs 54.0%, p=0.001). It was negatively associated with cutaneous ulcer (0 vs 13.6%, p=0.049) and malignancy (0 vs 21.0%, p=0.006). Anti-PL-7 Ab was also found to be significantly associated with ILD (85.7% vs 56.1%, p=0.031). The patients had a higher median ESR level at disease onset (92 vs 39.5, p=0.001).

Anti-SRP Ab was found to be predominantly affecting PM patients (94.12% vs 34.2%, p<0.001). It was associated with a significantly higher median peak CK level (9710 vs 756IU/L, p<0.001) and refractory muscle weakness (23.5% vs 6.52%, p=0.034).

Two out of 5 anti-SAE1 Ab positive patients were found to have malignancy, which was not statistically significant compared to those without the antibody (40% vs 17.9%, p=0.229). Anti-SAE1 Ab was found to be associated with CADM (80% vs 27.0%, p=0.023). 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. One patient died 2 months after diagnosis because of infection. None of them was found to have malignancy. No statistically significant clinical difference was noted when comparing patients with and without the antibody.

For patients who did not have any positive MSA, they were found to have less RP-ILD (4.05% vs 13.4%, p=0.033), cutaneous ulcer (5.41% vs 15.7%, p=0.029) and refractory skin rash (4.05% vs 12.6%, p=0.046), compared to those who had at least one MSA.

Risk factors of 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, p<0.001), CADM (OR 13.5, p=0.007) and history of pulmonary TB (OR 12.4, p=0.019) were independent risk factors for the development of RP-ILD. Details of the results were shown in Table 4.

Risk factors of 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, p=0.003). Other independent risk factors included the DM subtype (HR 3.87, p=0.009) and family history of cancer (HR 3.67, p=0.029). History of immunosuppressant use was a negative predictor of malignancy (HR 0.355, p<0.027). Details were shown in Table 5.

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 [14]. In this local study it was found to be much more prevalent, with anti-MDA5 Ab identified in 23.0% of DM 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 [15]. 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 [16], while the combined allele frequencies of DRB1*0101 and DRB1*0405 were different between Japanese and Chinese [17, 18]. However the reason behind the even greater discrepancy between Hong Kong and Chinese patients was uncertain. 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 to immunoprecipitation for the detection of MSAs showed good concordance rates, justifying the use of the line blot testing in our study [19]. Another possible reason was that some patients who were supposed to be anti-MDA5 positive may have their antibodies become undetectable following treatment when disease remission achieved. Meanwhile the potential environmental influences on the frequency of MSAs should be further investigated.

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. 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-TIFγ Ab positive patients, 7 (46.7%) were NPC, followed by lung and gynaecological 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 [20]. 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 [21]. Further longitudinal studies would be needed to elucidate if 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 around 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 [10]. Again the lower prevalence could be explained 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 co-exist with each other [22]. However, there were reports of sporadic cases in which the MSAs coexist, and were associated with more complex disease expression [23, 24]. 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 [25]. 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 dermatomyositis, but it was less well-documented in anti-MDA5 Ab positive patients. Hoarseness in anti-MDA5 Ab positive patients was previously described in China in as well as in Japan [26, 27]. 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 to an increased awareness to the possible important anti-MDA5 Ab related complications.

The association of 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 [14]. More recently, a study involving 61 CADM and 61 classic DM patients also in the United States myositis patients showed that anti-MDA5 positivity was strongly associated with RP-ILD and significantly poorer survival [6]. 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.

Anti-MDA5 positivity and CADM have been well described as risk factors of RP-ILD at least in Asian countries, but history of TB infection as an independent risk factor was a new finding. Pulmonary TB is relatively common in Hong Kong and China. In 2016, there were 59.2 and 61.0 per 100 000 population new cases of TB in Hong Kong and China respectively. The incidence rate in USA was much lower, at only 2.9 per 100 000 population in 2016 [28]. The distribution of pulmonary TB infection and development of anti-MDA5 associated RP-ILD in the different regions 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 [29, 30]. 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 has been regarded as a key component in pathogenesis of anti-MDA5 Ab associated RP-ILD [31]. 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. It would be worthwhile to further look into the relationship between them by longitudinal and molecular studies.

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 [9]. The findings here were in agreement with the previously described characteristics in anti-TIF1γ Ab positive patients. 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 [32]. 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 is not yet fully validated. Secondly, there might be selection bias. Some IIM patients who had significant disability prohibiting their clinic visits or who died before the commencement of this study were not represented. Lastly, due to the retrospective nature of the study, some parameters, especially those which were not well-known before such as hoarseness, might be easily missed in the documentation. This might cause some of the data to be under-reported.

Conclusions

This study reports the profiling of MSAs and their clinical characteristics in Hong Kong Chinese patients with IIM. Anti-MDA5 and anti-TIF1γ Ab were found to be most prevalent, and significantly associated with

RP-ILD and malignancy respectively. It further confirms that MSA testing could enable earlier detection and hence better treatment of IIMs and their complications. 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 to the understanding of the pathogenesis of the deadly complications, and possibly improve management of the disease in future.

Declarations

Ethics approval and consent to participate

The Research Ethical Committee approval was granted by the Kowloon West Research Ethical Committee (KW/EX-17-044(109-09)). Patients' written consents to participate were obtained.

Consent for publication

Participants' written consents for publication were obtained.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

WV collected and analyzed the patient data, and was a major contributor in writing the manuscript. SH designed the study, collected and interpreted the patient data, and was a major contributor in writing the manuscript. YR designed the study and interpreted the patient data. All authors read and approved the final manuscript.

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Tables

Due to technical limitations, the tables are only available as a download in the supplemental files section.

Supplementary Files

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