Clinical characteristics of Vietnamese patients with idiopathic inflammatory myopathies and autoantibodies to aminoacyl-transfer RNA synthetases

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Abstract

Objective: To assess clinical phenotypes of anti-aminoacyl-transfer RNA synthetases (aaRS) autoantibodies in Vietnamese patients of Kinh ethnicity with idiopathic inflammatory myopathies (IIM).

Methods: In a cross-sectional study 23 patients with anti-aaRS autoantibodies were compared to 36 patients with other myositis-specific antibodies and to 69 seronegative patients with IIM. Assessments included muscle performance, extra-muscular involvement, and disease activity according to the International Myositis Assessment and Clinical Studies (IMACS). Sera were tested by a line immunoassay (Euroline Myositis Profile 4).

Results: The frequency of anti-Jo-1 antibodies was 56.5%, anti-EJ antibodies 26.1%, and anti-PL-7 antibodies 17.4%, while anti-PL-12 and anti-OJ antibodies were not present in any case. All patients with anti-aaRS autoantibodies had signs of myositis. At time of investigation 22/23 patients had muscle weakness, 52.2% arthritis, 34.8% Raynaud’s phenomenon, 73.9% fever, 14.3% mechanic’s hands and 56.5% dysphagia. Interstitial lung disease was present in 52.2%, and pulmonary hypertension in 56.5%. The anti-aaRS autoantibody positive group had higher disease activity in the domains of skin and pulmonary disease compared to the seronegative group and had lower disease activity in skeletal disease compared to the anti-melanoma differentiation-associated protein 5-positive patients. The clinical presentation of antisynthetase syndrome was similar between the aaRS autoantibody specificities with the exception of more frequent pulmonary hypertension in anti-Jo-1 positive patients.

Conclusions: Different aaRS autoantibody specificities may vary between different ethnic populations for reasons that still need to be clarified. Furthermore, the high frequency of pulmonary hypertension is noteworthy but otherwise clinical manifestations associated with aaRS autoantibodies did not differ from other ethnic populations.

KEYWORDS
antisynthetase autoantibodies, dermatomyositis, Kinh ethnicity, myositis, polymyositis
1 | INTRODUCTION

Idiopathic inflammatory myopathies (IIM) collectively named myositis, represent a group of rare disorders characterized by dysfunction of skeletal muscle and inflammatory infiltrates in muscle tissue and frequent involvement of extra-muscular organs such as skin, joints, lung, heart, and the gastrointestinal tract. Based on different clinical and histopathologic manifestations, patients with myositis are often subclassified into dermatomyositis (DM), polymyositis (PM), inclusion body myositis (IBM) and more recently also into the subset named immune-mediated necrotizing myopathy (IMNM).1-4

Autoantibodies are common in IIM, present in up to 80% of patients with PM and DM, and less frequently in IBM.5,6 Recently a number of new autoantibody specificities have been identified in patients with IIM. They can be classified as myositis associated auto-antibodies (MAAs) including anti-Ro52, anti-La, anti-Ku, anti-PM-Scl and anti-U1RNP that can also be found in other autoimmune diseases, and in myositis-specific autoantibodies (MSAs).7 The MSAs are not only specific for myositis but are also strongly associated with distinct clinical phenotypes. The most frequent MSA, the anti-Jo1 autoantibody, present in up to 30% of Caucasian patients with IIM, is associated with a clinical entity known as antisynthetase syndrome (myositis, interstitial lung disease [ILD], non-erosive arthropathy, mechanic’s hands, fever, and Raynaud’s phenomenon).8 ILD is especially prevalent in antisynthetase syndrome, occurring in about 75% of patients with anti-Jo1 autoantibodies compared to about 30% of patients with IIM in the absence of antisynthetase autoantibodies.8 There are 7 other less frequently occurring aminoacyl-transfer RNA synthetase (aaRS) autoantibodies (anti-EJ, anti-OJ, anti-PL-12, anti-PL-7, anti-Ha, anti-Zo and anti-KS) all associated with features of antisynthetase syndrome.9

The different anti-aaRS autoantibodies have been reported with different clinical phenotypes in patients with different ethnicities. Thus in Caucasian patients myositis is more frequent in anti-Jo1 positive compared to anti-PL-7 or anti-PL-12 positive patients who have a higher frequency of ILD, whereas in Japanese patients anti-PL-7 was more often associated with myositis compared to anti-PL-12. Patient survival was also conditioned by the anti-aminocyl-transfer RNA synthetases (anti-ARS) specificity, and was significantly lower in patients with anti-PL-7/12 autoantibodies than in anti-Jo1 positive patients.10-12 Thus different anti-aaRS autoantibodies may be associated with different clinical phenotypes in different ethnic populations. In this study we aimed to assess the clinical phenotype of anti-aaRS autoantibodies in Vietnamese patients of Kinh ethnicity with IIM.

2 | PATIENTS AND METHODS

2.1 | Patients

This is a descriptive study including all patients who were seen at the Rheumatology Department at Bach Mai Hospital, Hanoi, Vietnam, between March 2011 and December 2013. From a cohort of 151 patients of Kinh ethnicity with IIM who were subject to a cross-sectional study previously published, we selected the aaRS autoantibody positive (n = 23) patients for a thorough review regarding clinical and laboratory data.13 The aaRS antibody positive patients were compared to 69 patients seronegative for MSAs and MAAs and to patients from the 3 largest groups with other MSAs namely anti-signal recognition particle (anti-SRP) (n = 17), anti-melanoma differentiation-associated protein 5 (anti-MDA5) (n = 11) or anti-Mi-2 (n = 8) autoantibodies. IIM was defined by experienced rheumatologists as probable or definite PM/DM according to the Bohan and Peter criteria.14,15 In the cohort of 151 patients with IIM, 74 patients fulfilled the criteria for definite and 14 for probable PM and 55 for definite DM and 8 probable DM; information for the respective subgroups is presented in Table 1. The patients who did not have classical skin manifestations of DM according to the Bohan and Peter criteria were excluded from the analysis. Patients with clinical overlap syndromes were also excluded. Information on age, gender, disease duration, initial symptoms, accumulated clinical manifestations and treatment was recorded. At time of study all patients had detailed clinical and laboratory examination including computed tomography (CT) scan of thorax, abdomen and pelvis, and echocardiogram. Gastroscopy was performed when clinically indicated. Women had a gynaecological examination. The assessment also included disease activity using the myositis disease activity assessment tool (MDAAT) proposed by the International Myositis Assessment and Clinical Studies group (IMACS).16

Patients were treated with immunosuppressive agents according to the treating physician’s choice. All patients were treated with glucocorticoids. Methotrexate and azathioprine were the most often used immunosuppressive drugs. Patients with steroid refractory disease received intravenous pulse cyclophosphamide. All patients with ILD received combination therapy including methylprednisolone pulse therapy, plus methotrexate, azathioprine or cyclophosphamide.

Antisynthetase syndrome (ASS) was defined as a positive aaRS autoantibody together with at least 1 of the following clinical manifestations: myositis, ILD, fever, Raynaud’s phenomenon, arthritis, or mechanic’s hands.17 Pulmonary involvement was systematically investigated at time of study and in some cases at time of diagnosis. Pulmonary function was tested according to the American Thoracic Society guidelines, using standard equipment.18 High resolution computed tomography (HRCT) of the lungs without intravenous contrast during end inspiration was performed in all patients. A radiologist who is a specialist of respiratory disease evaluated the HRCT findings in a blinded fashion. ILD was defined as presence of either: (a) chest radiograph abnormalities indicative of fibrosis, and pulmonary function tests: forced expiratory volume in 1 second (FEV1) < 80%, and forced vital capacity (FVC) < 80% (predicted), and total lung capacity (TLC) < 80% and/or >80% predicted FEV1/FVC; or (b) abnormal findings on HRCT scan, showing at least 1 of the following features: reticulation and fibrosis, traction bronchiectasis, honeycombing, ground-glass opacification.19
In patients with symptoms indicating an infection, bronchoscopy and bronchoalveolar lavage was performed to rule out tuberculosis or other infections. In addition, skin test of tuberculosis and extended history for exposure to tuberculosis was performed.

Cardiac involvement was defined by abnormalities on electrocardiogram or echocardiogram, performed in all patients at time of this study.

Pulmonary hypertension was defined as a systolic pulmonary arterial pressure >30 mm Hg as estimated by Doppler echocardiography.

### TABLE 1  Clinical features and laboratory characteristics at time of investigation of 23 patients with anti- aminoacyl-transfer RNA synthetase (aaRS) autoantibodies compared to patients with anti-SRP, anti-Mi2 or anti-MDA5 autoantibodies and to autoantibody negative patients with idiopathic inflammatory myopathy (IIM)

| Feature                        | Antisynthetase n = 23 | Anti-SRP n = 17 | Anti-Mi2 n = 8 | Anti-MDA5 n = 11 | No antibody n = 69 |
|--------------------------------|----------------------|-----------------|---------------|-----------------|-------------------|
| Age, mean ± SD, y              | 45.8 ± 13.9          | 42.2 ± 13.8     | 48 ± 16.5     | 39.1 ± 10.8     | 43.3 ± 16.6       |
| Disease duration, mean, mo ± SD| 16.0 ± 22.3          | 31.7 ± 37.2     | 19 ± 28.7     | 18.1 ± 9.9      | 21.9 ± 30.3       |
| Female, n (%)                  | 16 (70)              | 15 (88)         | 7 (88)        | 9 (82)          | 49 (71)           |
| Diagnosis, PM/DM               | 9/14                 | 9/8             | 5/3           | 5/6             | 44/25             |
| Definite PM/DM                 | 7/12                 | 8/8             | 5/2           | 3/4             | 36/22             |
| Probable PM/DM                 | 2/2                  | 1/0             | 0/1           | 2/2             | 8/3               |

**Constitutional manifestations, n (%)**
- Fever: 17 (74) *P < .05 compared to antibody negative group (negative against all investigated antibodies).*
- Heliotrope rash: 10 (71) *P < .01 compared to antibody negative group.
- Gottron’s papules: 9 (64.3) *P < .01 compared to anti-aaRS antibody positive group. *
- Mechanic’s hands: 2 (14.3)

**Cutaneous involvement, n (%)**
- Myositis: 23 (100)
- Severe proximal muscle weakness, n (%): 7 (30)
- Arthritis, n (%): 12 (52) *P < .01 compared to antibody negative group.
- Raynaud’s phenomenon: 8 (35)
- Pericarditis: 7 (30) *P < .01 compared to antibody negative group.

**Skeletal manifestations, n (%)**
- Myositis: 23 (100)
- Severe proximal muscle weakness, n (%): 7 (30)
- Arthritis, n (%): 12 (52) *P < .01 compared to antibody negative group.

**Pulmonary involvement, n (%)**
- Interstitial lung disease: 12 (52) *P < .01 compared to antibody negative group.
- Pulmonary hypertension: 13 (56.5) *P < .0005 compared to antibody negative group.

**Gastrointestinal involvement, n (%)**
- Dysphagia: 13 (56.5)

**Laboratory investigations**
- Raised CRP, n (%): 17 (74) *P < .05 compared to antibody negative group.
- CK, IU/L, mean ± SD: 3019 ± 5716.2

**Treatment**
- Prednisolone mean daily dosage, mg ± SD: 27.2 ± 12.2 (min = 5, max = 40)
- Number of patients with methotrexate/azathioprine/cyclophosphamide/mycophenolate mofetil: 4/4/9/0
Muscle involvement was defined as abnormalities on electromyography, or in muscle biopsy. Muscle strength was tested by manual muscle test (MMT)-8, with a maximal score of 80. Muscle weakness was defined as MMT-8 score below 80. Active muscle inflammation was defined as creatine kinase (CK) level above at least twice the upper limit of normal level (>280 IU/L) and muscle disease activity on visual analog scale (VAS) ≥ 5 in the MDAAT.

Laboratory tests at the time of clinical examination included blood tests for erythrocyte sedimentation rate (ESR), hemoglobin, leukocytes, platelets, C-reactive protein (CRP), CK, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), creatinine, protein and albumin.

Sera from all individuals who gave consent were stored at −80°C until analyses were performed.

2.2 | Autoantibodies

Sera were tested by a myositis antibody line immunoassay (LIA) in the Department of Clinical Immunology, Uppsala University Hospital, Sweden, according to the manufacturer’s instructions (Myositis Profile 4 Euroimmun) including: anti-Jo1 (histidyl), anti-PL-7 (threonyl), anti-PL-12 (alanyl), anti-EJ (glycyl), anti-OJ (isoleucyl-tRNA synthetase), anti-SRP, anti-Mi-2 (alpha and beta chains investigated separately), anti-MDA5, anti-transcriptional intermediary factor-1 gamma, anti-nuclear matrix protein 2 (anti-NXP2), anti-small activating enzyme, anti-PM-Scl (100 kD), 75 kD units tested separately) and anti-Ku. Scanned densitometry data were calculated using the Euroline Scan software (Euroimmun). The autoantibody profile of this group has previously been reported. A validation of the used LIA was recently published. The cut off for each autoantibody was ≥11 densitometry units for all autoantibodies. When investigating 60 healthy Swedish blood donors with the myositis LIA, 2 individuals showed weak reactivity for anti-NXP2 and anti-Mi-2 alpha, respectively, whereas all other reactions were negative.

2.3 | Human leukocyte antigen cell surface receptor (HLA-DR) typing

HLA-DR typing was performed by sequence-specific primer polymerase chain reaction assay (SSP-PCR; DR low-resolution kit; Olerup SSP AB).

2.4 | Ethics

This study complies with the Declaration of Helsinki, (as revised in Brazil 2013), and was approved by the local ethics committee at Hanoi Medical University (1720/IRB-HMU) and informed consent has been obtained from the subjects in this study.

2.5 | Statistical analyses

Data analyses were performed using Statistical Package for the Social Sciences (SPSS) version 10.0. Student’s t test and the Mann-Whitney U test were used for comparison of continuous variables (age). We used either the Chi-square test (for sample sizes of >5) or Fisher’s exact test (for sample sizes of ≤5) for discrete variables (gender, prevalence of laboratory tests and symptoms). P values <0.05 were considered to be statistically significant. The antisynthetase group was compared to the anti-Mi-2, the anti-SRP, the anti-MDA5 autoantibody positive groups and the seronegative groups respectively. Although correction for multiple testing would be appropriate for our study, we present raw P values, but consider possible type I errors when making the conclusions.

3 | RESULTS

Twenty-two of the 23 aaRS autoantibody positive patients had 1 single MSA and one patient had 2 MSAs, anti-EJ and anti-Mi-2. The most commonly detected anti-aaRS antibody was anti-Jo-1 (n = 13), followed by anti-EJ (n = 6) and anti-PL-7 (n = 4). Anti-PL-12 and anti-OJ were not present in any case. Demographic and clinical data are summarized in Table 1. A higher prevalence of anti-aaRS autoantibodies was observed in patients with DM (n = 14) than in PM (n = 9) whereas in the seronegative group PM (n = 44) was more common than DM (n = 25). Clinical features and laboratory characteristics in patients with anti-aaRS autoantibodies (Jo1, PL-7 and EJ) are presented in Table 1. All 23 anti-aaRS autoantibody positive patients fulfilled the criteria for ASS.

The anti-aaRS positive group did not differ from the seronegative patients with IIM or from the patients with 1 of the other myositis-specific antibodies concerning age, gender or mean disease duration at time of investigation. At time of investigation anti-aaRS-positive patients had higher frequencies of fever, arthritis, ILD, pericarditis and raised CRP compared to the seronegative patients. The anti-aaRS-positive patients also had higher frequency of arthritis compared to the anti-SRP-positive patients and higher frequency of ILD compared to the anti-Mi-2 positive patients (Table 1). A higher frequency of arthritis compared to the seronegative group was also recorded in the anti-MDA5 positive patients (Table 1).

Next, we compared disease activity applying the MDAAT score of patients with anti-aaRS autoantibodies to the seronegative comparator group and to the patients with each of the other myositis-specific antibodies. The anti-aaRS autoantibody positive group had a higher disease activity in the domains skin and pulmonary disease compared to the seronegative group but had lower disease activity in skeletal disease compared to the anti-MDA5-positive patients (Table 2). The anti-MDA5-positive patients also had a higher disease activity in the cutaneous disease compared to the seronegative group (Table 2). At time of investigation the mean CK level of patients with anti-aaRS autoantibodies was 3019 U/L and for the seronegative group 1565 U/L, but the difference was not statistically significant. Additionally the patients with anti-SRP autoantibodies
or anti-Mi-2 had significantly higher serum levels of muscle enzymes compared to the seronegative patients (Table 1). Seventy-four percent of patients with anti-aaRS autoantibodies had raised CRP compared to 42% in the seronegative group.

Finally, we compared the cumulative presence of clinical manifestations between the 3 aaRS autoantibody positive groups, anti-Jo1, anti-EJ and anti-PL7 (Table 3). Pulmonary hypertension was present in 69%, 25% and 50% of the anti-Jo1, anti-PL7 and anti-EJ positive patients respectively and ILD in 46%, 75%, and 50% of the anti-Jo1, anti-PL7, and anti-EJ positive patients respectively. These differences were not statistically significant.

No association between anti-aaRS-positivity or the other autoantibody defined subgroups and HLA-DRB1 haplotypes was detected in our study. The frequencies of HLA-DRB1 haplotypes are presented in Table 4.

Two patients with anti-aaRS autoantibodies (anti-Jo1 and anti-EJ antibodies), 1 anti-MDA5 positive patient, 1 anti-Mi-2 positive patient and 3 seronegative patients died during the follow-up. Cause of death was rapidly progressive ILD (RPILD) in the 2 anti-aaRS positive patients and in the seronegative group RPILD in 1, infectious pneumonia in 1 and vasculitis and infection in a 3rd case. The patient with anti-MDA5 autoantibodies died due to infectious pneumonia and the patient with anti-Mi-2 autoantibodies died due to myocarditis, pulmonary hypertension and RPILD.

### TABLE 2 Disease activity assessment at time of investigation of 23 patients with anti-aminocyl-transfer RNA synthetase (aaRS) autoantibodies compared to patients with anti-SRP, anti-Mi2 or anti-MDA5 autoantibodies and autoantibody negative patients with idiopathic inflammatory myopathies (IIM)

| Feature, mean ± SD | Antisynthetase n = 23 | Anti-SRP n = 17 | Anti-Mi-2 n = 8 | Anti-MDA5 n = 11 | No antibody n = 69 |
|-------------------|-----------------------|----------------|----------------|----------------|------------------|
| Constitutional disease activity, VAS (max score = 10) | 5.6 ± 2.6 | 5 ± 2.4 | 5.9 ± 2.9 | 5.6 ± 2.5 | 4.8 ± 2.8 |
| Cutaneous disease activity, VAS, mean ± SD (max score = 10) | 4.0 ± 3.5 | 2.9 ± 3.2 | 4 ± 4.0 | 5.8 ± 3.2 | 2.3 ± 2.9 |
| Muscle disease activity, VAS, mean ± SD (max score = 10) | 5.5 ± 2.6 | 5.5 ± 2.5 | 6.9 ± 3.0 | 5.6 ± 2.5 | 5.1 ± 2.6 |
| Skeletal disease activity, VAS (max score = 10) | 1.9 ± 2.9 | 1 ± 2.2 | 1.9 ± 2.3 | 4.4 ± 3.9* | 1.8 ± 3.1 |
| Gastrointestinal disease activity, VAS (max score = 10) | 2.6 ± 3.0 | 2.3 ± 2.7 | 2.9 ± 3.9 | 2.9 ± 2.4 | 2.3 ± 2.8 |
| Pulmonary disease activity, VAS, mean ± SD (max score = 10) | 3.7 ± 3.5 | 2.0 ± 1.8 | 3.5 ± 3.2 | 2.5 ± 1.8 | 2.4 ± 2.7 |
| Cardiovascular disease activity, VAS (max score = 10) | 1.3 ± 2.2 | 0.5 ± 1.1 | 1.4 ± 1.6 | 0.9 ± 1.6 | 0.48 ± 1.2 |

Abbreviations: IIM, idiopathic inflammatory myopathy; NS, not significant; SD, standard deviation; VAS, visual analog scale.

1P < .05 compared to antibody negative group (negative against all investigated antibodies).

P < .01 compared to antibody negative group. *P < .05 compared to anti-aaRS antibody positive group. †P < .0005 compared to antibody negative group.

4 | DISCUSSION

In our cohort of Vietnamese patients of Kinh ethnicity with anti-aaRS autoantibodies, anti-Jo1 was the most frequent autoantibody, followed by anti-EJ and anti-PL7 autoantibodies. Furthermore, aaRS autoantibodies were more common in patients within the subgroup DM compared to the PM subgroup. The aaRS autoantibody positive patients had a high frequency of extra-muscular manifestations and all fulfilled the proposed criteria for ASS. That anti-Jo1 autoantibodies were the most common of anti-aaRS autoantibodies in our cohort is similar to what has been reported from other cohorts with different ethnicities. However, anti-EJ antibodies being the second most common anti-aaRS autoantibodies is different from reports in Caucasian and Japanese cohorts, although our data need to be interpreted with caution due to the low number of patients. Antisynthetase autoantibodies constitute an important risk factor for ILD in patients with IIM. ILD frequently predominates at presentation and contributes to the high morbidity and mortality in patients with ASS and was one of the most common extra-muscular manifestations in our patients with ASS found in 51%, a frequency comparable to what has previously been reported in other ethnic groups.22-24 Similar to other ethnic groups, the frequency of ILD was in particular high in patients with anti-PL7 autoantibodies where 3 of our 4 cases had ILD.12,25 All of our patients with anti-aaRS autoantibodies had signs of myositis, thus there was no difference between anti-aaRS antibody specificities, which was unexpected and different from previous reports.26,27 Our data on clinical associations with different antisynthetase autoantibodies in Asian patients of Kinh ethnicity differ from a previous report from Japan with 165 patients having anti-aaRS autoantibodies.28 Myositis was found in less than 60% of Japanese patients during follow-up and the frequency of myositis varied among anti-aaRS subgroups. The patients with anti-Jo1, anti-EJ and anti-PL7 autoantibodies had a higher frequency...
of myositis compared to anti-PL12, anti-KS and anti-OJ. In addition, ILD was found in nearly all Japanese patients with anti-aaRS autoantibodies, a strikingly higher frequency in comparison with our cohort.

Notably, pulmonary arterial hypertension (PAH) was equally frequent as ILD in our patients with anti-aaRS autoantibodies and was more often recorded in patients with anti-Jo-1 autoantibodies compared to patients with other aaRS autoantibodies although the difference was not statistically significant. The frequency of PAH in our cohort is higher compared to other populations where PAH was reported in 7.9%-14.8% of patients with anti-aaRS autoantibodies.\(^{29,30}\)

An explanation for the high frequency observed in our cohort may be because all patients were screened with echocardiography. Moreover, both anti-aaRS-positive and anti-MDA5-positive patients had a high prevalence of arthritis and in the anti-aaRS-positive patients the frequency of arthritis was higher compared to the anti-SRP-positive patients (52% vs 12%).

The high frequency of DM skin rash in our patients with anti-aaRS autoantibodies is in agreement with previous reports from Japan,\(^{28,31}\) but different compared to a Chinese population in which the frequency of DM was lower.\(^{32}\) This difference may indicate that other factors than the autoantibodies may influence the clinical effects.

### TABLE 3: Clinical manifestations at time of investigation in patients subgrouped by the 3 different aminoacyl-transfer RNA synthetase autoantibodies

| Characteristic                                      | Anti-Jo-1 (n = 13) | Anti-PL-7 (n = 4) | Anti-EJ (n = 6) | P value |
|-----------------------------------------------------|--------------------|-------------------|-----------------|---------|
| Age, mean ± SD y                                    | 42.7 ± 14.6        | 39 ± 8.3          | 57 ± 9.4        | NS      |
| Diagnosis, PM/DM                                    | 7/6                | 1/3               | 1/5             | NS      |
| Constitutional manifestations n (%)                 |                    |                   |                 |         |
| Fever                                               | 8 (61.5)           | 4 (100)           | 5 (83.3)        | NS      |
| Skin lesions n (%)                                  |                    |                   |                 |         |
| Heliotrope rash                                     | 4 (66.7)           | 3 (100)           | 3 (60)          | NS      |
| Gottron’s papules                                   | 5 (83.3)           | 1 (33.3)          | 3 (60)          | NS      |
| Mechanic’s hands                                    | 1 (16.7)           | 0 (0)             | 1 (20)          | NS      |
| Skeletal manifestations n (%)                       |                    |                   |                 |         |
| Arthritis                                           | 7 (53.8)           | 2 (50)            | 3 (50)          | NS      |
| Myositis                                            | 13 (100)           | 4 (100)           | 6 (100)         | NS      |
| Muscle weakness                                     | 12 (92.3)          | 4 (100)           | 6 (100)         | NS      |
| Manual muscle test-8, mean ± SD                     | 61 ± 16            | 52 ± 20           | 54 ± 27         | NS      |
| Dysphagia                                           | 7 (53.8)           | 2 (50)            | 4 (66.7)        | NS      |
| Raised SGOT                                         | 7 (53.8)           | 3 (75)            | 2 (33.3)        | NS      |
| Raised SGPT                                         | 6 (46.2)           | 3 (75)            | 3 (50)          | NS      |
| Raised lactic dehydrogenase                         | 5 (38.5)           | 2 (50)            | 1 (16.7)        | NS      |
| CK, IU/L, mean ± SD, (ref; 26-140 IU/L)              | 3364 ± 6947.1      | 4966 ± 5230.7     | 972 ± 1777.1    | NS      |
| Cardiovascular manifestations n (%)                 |                    |                   |                 |         |
| Raynaud’s phenomenon                                 | 5 (38.5)           | 2 (50)            | 1 (16.7)        | NS      |
| Pericarditis                                         | 4 (30.8)           | 2 (50)            | 1 (16.7)        | NS      |
| Pulmonary involvement n (%)                          |                    |                   |                 |         |
| Interstitial lung disease, PM/DM                    | 6 (46) (4/2)       | 3 (75)            | 3 (50)          | NS      |
| Pulmonary hypertension                              | 9 (69)             | 1 (25)            | 3 (50)          | NS      |
| Laboratory investigations                            |                    |                   |                 |         |
| Raised CRP, n (%)                                   | 10 (76.9)          | 3 (75)            | 4 (66.7)        | NS      |
| Disease activity assessment, mean ± SD              |                    |                   |                 |         |
| Cutaneous disease activity, VAS (max score = 10)    | 3.2 ± 3.4          | 4.3 ± 3.1         | 5.7 ± 4.1       | NS      |
| Muscle disease activity, VAS (max score = 10)       | 5.1 ± 2.4          | 6.8 ± 2.2         | 5.5 ± 3.5       | NS      |
| Joint disease activity, VAS (max score = 10)        | 2.9 ± 3.1          | 0                 | 1.2 ± 2.9       | NS      |
| Pulmonary disease activity, VAS (max score = 10)    | 3.4 ± 3.5          | 5.3 ± 2.5         | 3.2 ± 4.0       | NS      |

Abbreviations: CK, creatine kinase; CRP, C-reactive protein; DM, dermatomyositis; SGOT, serum glutamic oxalo-acetic transaminase; SGPT, serum glutamate pyruvate transaminase; NS, not significant, reference values for CK = 26-140 IU/L; PM, polymyositis; SD, standard deviation; VAS, visual analog scale.
phenotypes in anti-aaRS positive patients, where both environmental and genetic factors may contribute. However, this question could not be addressed in our study with only 1 ethnic group.

The disease activity score in the pulmonary domain of the MDAAT score was higher at time of investigation in patients with ASS compared to patients without autoantibodies in our study. The patients with anti-PL-7 antibodies had the highest pulmonary activity score of the 3 anti-aaRS autoantibody positive subgroups. When we compared disease activity at time of investigation, the DM patients with anti-aaRS autoantibodies had more active disease in the skin domain compared to DM patients without autoantibodies. The patients with anti-aaRS autoantibodies have been reported to have higher disease activity compared to patients without autoantibodies. In addition, patients with aaRS autoantibodies have poor prognosis with a high mortality rate due to ILD and severe myositis. However, patients with anti-Jo-1 antibodies often have a more favorable prognosis and lower mortality rate than patients with other aaRS autoantibodies. In our cohort the occurrence of fever and CRP levels was also significantly higher in patients with anti-aaRS antibodies compared to previous reports were observed such as a high frequency of pulmonary hypertension supporting the need for careful surveillance of extra-muscular organ manifestations including pulmonary hypertension in patients with anti-aaRS autoantibody positive IIM, at least in patients of the Kinh ethnicity.

**TABLE 4** Human leukocyte antigen cell surface receptor (HLA-DR)B1 alleles in Vietnamese patients with anti-aaRS autoantibodies, patients with anti-SRP, anti-Mi2 or anti-MDA5 autoantibodies and seronegative IIM

| HLA-DRB1* | Antisynthetase (n = 22) | Anti-SRP (n = 17) | Anti-Mi2 (n = 8) | Anti-MDA5 (n = 11) | Seronegative IIM (n = 68) |
|-----------|------------------------|------------------|-----------------|-------------------|------------------------|
|           | n (%)                  | n (%)            | n (%)           | n (%)             | n (%)                  |
| *01       | 0 (0)                  | 0 (0)            | 0 (0)           | 0 (0)             | 1 (1.5)                |
| *03       | 5 (22.7)               | 2 (11.8)         | 0 (0)           | 0 (0)             | 6 (8.8)                |
| *04       | 5 (22.7)               | 1 (5.9)          | 2 (25)          | 3 (27.3)          | 11 (16.2)              |
| *07       | 1 (4.5)                | 0 (0)            | 1 (12.5)        | 0 (0)             | 4 (5.9)                |
| *08       | 4 (18.2)               | 2 (11.8)         | 2 (25)          | 1 (9.1)           | 9 (13.2)               |
| *09       | 2 (9.1)                | 4 (23.5)         | 0 (0)           | 2 (18.2)          | 14 (20.6)              |
| *10       | 3 (13.6)               | 0 (0)            | 2 (25)          | 0 (0)             | 12 (17.6)              |
| *11       | 0 (0)                  | 2 (11.8)         | 0 (0)           | 0 (0)             | 4 (5.9)                |
| *12       | 13 (59.1)              | 3 (17.6)         | 3 (37.5)        | 9 (81.8)          | 30 (44.1)              |
| *13       | 2 (9.1)                | 2 (11.8)         | 2 (25)          | 1 (9.1)           | 7 (10.3)               |
| *14       | 2 (9.1)                | 6 (35.3)         | 2 (25)          | 1 (9.1)           | 1 (1.5)                |
| *15       | 4 (18.2)               | 7 (41.2)         | 1 (12.5)        | 0 (0)             | 20 (29.4)              |
| *16       | 1 (4.5)                | 0 (0)            | 0 (0)           | 0 (0)             | 5 (7.4)                |

Abbreviations: IIM, idiopathic inflammatory myopathy.

*No significant differences were found between the groups.

may also affect the autoantibody pattern that we found. A clear limitation of our study is the low number of patients, making comparisons of the small subgroups with different aaRS autoantibodies unreliable.

In conclusion, Vietnamese myositis patients of Kinh ethnicity with anti-aaRS autoantibodies had a high frequency of extra-muscular manifestations. Some differences in clinical phenotypes associated with anti-aaRS autoantibodies compared to previous reports were observed such as a high frequency of pulmonary hypertension supporting the need for careful surveillance of extra-muscular organ manifestations including pulmonary hypertension in patients with anti-aaRS autoantibody positive IIM, at least in patients of the Kinh ethnicity.

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**CONFLICT OF INTEREST**

Dr Ingrid Lundberg has received research grants from Astra-Zeneca and Bristol-Myers Squibb and has served on the advisory board of Corbus Pharmaceuticals, Inc. The other authors have no conflict of interest to declare.

**AUTHOR CONTRIBUTIONS**

Authors’ contributions to the paper: Dr Thuy Nguyen Thi Phuong designed the study, collected data, wrote the first draft of the manuscript, performed 50% of the work; Dr Lan Nguyen Thi Ngoc was involved in study design 5%-10%; Dr Johan Rönnelid performed the autoantibody assay, 5%-10%; Dr Leonid Padyukov performed the
genetic analyses, 5%-10%; Ingrid E. Lundberg was involved in study design, discussing the results and writing the manuscript, 10%-20%.

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