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Clinical and pathologic differences in interstitial lung disease based on antisynthetase antibody type

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Summary
Background: Interstitial lung disease (ILD) is a common extramuscular manifestation of the idiopathic inflammatory myopathies (IIMs), dermatomyositis (DM) and polymyositis (PM). Patients with antisynthetase antibodies (ASA) demonstrate some or all of the features of the

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Antisynthetase syndrome

antisynthetase syndrome including IIM and ILD. It has been hypothesized that the clinical expression of antisynthetase syndrome varies between specific ASAs.
Objective: We sought to determine whether the myositis-associated ILD (MA-ILD) phenotype differs based on the presence of ASAs and by ASA subtype.
Methods: A cross-sectional and longitudinal analysis of consecutive patients enrolled at the Johns Hopkins Myositis Center with ILD in the setting of clinically diagnosed autoimmune myositis was conducted.
Results: Seventy-seven subjects were included; 36 were ASA negative, 28 were anti-Jo1 positive, and 13 were non-Jo1 ASA positive (5 anti-PL-12, 4 anti-PL-7, 2 anti-EJ, and 2 anti-OJ). Non-Jo1 ASA positive participants were more likely to be African-American than Caucasian as compared to both the anti-Jo1 positive ($p = 0.01$) and ASA negative groups ($p < 0.01$). ASA negative participants had better mean forced vital capacity percent predicted (FVC%) and total computed tomography scores over time compared to those with anti-Jo1 after controlling for potential confounders.
Conclusions: ASA status was significantly different by race. Those with anti-Jo1 antibodies had worse lung function and CT scores over time compared to those without detectable antisynthetase antibodies. Further prospective study in a larger cohort is needed to determine whether these apparent antibody-specific differences in demographics and manifestations of disease translate into meaningful disparities in clinical outcomes.

Introduction

Antisynthetase syndrome, the presence of idiopathic inflammatory myopathy in the setting of a positive antisynthetase antibody titer affects approximately 300,000 persons worldwide [1,2]. As initially described [3], the myositis of antisynthetase syndrome is variably accompanied by other non-myopathic manifestations [4], most notably, highly-morbid interstitial lung disease (ILD) in up to 75—86% of cases [5,6]. When present, ILD is estimated to confer an excess 5-year mortality upwards of 45%, making it the defining clinical feature of the disease with respect to both morbidity and mortality [7].

Antisynthetase antibodies (ASA) are autoantibodies directed against specific aminoacyl-tRNA synthetases, which serve as integral components in protein translation. Each of the 20 amino acids has a unique aminoacyl-tRNA synthetase. To date, antibodies have been identified against 8 unique aminoacyl-tRNA synthetases including Jo1 (histidyl), PL-7 (threonyl), PL-12 (alanyl), EJ (glycyl), OJ (isoleucyl), KS (asparginyl), Zo (phenylalanyl), and Tyr (tryosyl). Antisynthetase autoantibodies are very specific for myositis and are not seen at any frequency in the general population [8—10]. The most common antisynthetase antibody, anti-Jo1, is associated with 25—38% of cases of antisynthetase syndrome [11—13]. The remaining ASAs are less well characterized. Further, some patients with clinical manifestations consistent with antisynthetase syndrome are "antibody negative". This may represent a group of patients with myositis-associated interstitial lung disease (MA-ILD) and no autoantibody or possibly a heterogeneous group of patients with as-yet-unidentified ASAs. It is not known whether the pulmonary phenotype in antisynthetase syndrome varies as a function of the presence or absence of a specific antisynthetase antibody.

The Johns Hopkins Myositis Center, established in 2007, provides integrated multi-disciplinary care for patients with myositis. Over 750 patients with idiopathic inflammatory myopathies have been evaluated with records dating back to 1995, including approximately 20% who have concurrent pulmonary disease. Our aim in this retrospective analysis is to describe the clinical characteristics by antisynthetase antibody status, seen in this cohort.

Methods

Study population

This study was approved by the Institutional Review Board of the Johns Hopkins University School of Medicine. We queried the electronic medical records from January 1995 to December 2009 of patients evaluated at the Johns Hopkins Myositis Center. Eligibility criteria were as follows: possible, probable, or definite diagnosis of idiopathic inflammatory myopathy (specifically polymyositis [PM], dermatomyositis [DM], or myositis overlap syndrome based on Bohan and Peter criteria [14,15]), an established diagnosis of interstitial lung disease based on the American Thoracic Society (ATS) guidelines [16], and at least 6 months of clinical follow-up time at Johns Hopkins.

Clinical measures

Data obtained included demographic information (age, gender and race by self-identification), inflammatory myopathy subtype (DM, PM, or an inflammatory myositis presenting with clinical overlap with another autoimmune condition), antisynthetase antibody status, pulmonary function test and chest computed tomography (CT) data

both at the time of diagnosis with ILD as well as at the most recent follow up visit, and lung biopsy information when available.

All patients were tested for antisynthetase antibodies. ASAs were assayed by the RDL Reference Laboratory (10755 Venice Blvd. Los Angeles, CA 90034) or by the Johns Hopkins Rheumatic Disease Research Core Center using previously validated methods of immunoprecipitation. Participants with other known myositis specific autoantibodies, but without a clinically available antisynthetase antibody, were considered antisynthetase antibody negative. Of note, antibodies to melanoma differentiation-associated protein 5 (MDA5) were not included in this study since the assay was unavailable at the time.

Pulmonary function testing (PFT) included spirometry, lung volumes measured by helium dilution, and diffusing capacity by single breath carbon monoxide based on ATS criteria. [17]

All patients had baseline high resolution CT (HRCT) scans (1 mm slice thickness), which were performed at a number of centers. Follow-up HRCT scans were obtained only when clinically necessary. Scans performed at Johns Hopkins or with images uploaded into our system were scored for the cross-sectional and longitudinal analyses by a single blinded investigator using a previously-validated, standardized scoring system [18,19]. All scans were scored bilaterally by lung zone (upper, middle, lower) in each of four categories: honeycombing, interstitial thickening, interstitial fibrosis, and ground glass on a scale of 1–3. Results of the honeycombing, interstitial thickening, and interstitial fibrosis scores were combined into the category "fibrosis" for our purposes. A total CT score was also calculated by adding the fibrosis score (maximum possible score = 54) to the ground glass score (maximum possible score = 18). Grading of severity for fibrosis is as follows: 0 = no fibrosis, 1–18 = mild fibrosis, 19–36 = moderate fibrosis, $\geq$37 = severe fibrosis. Grading for severity of ground glass is as follows: 0 = no ground glass, 1–6 = mild ground glass, 7–12 = moderate ground glass, $\geq$ 13 = severe ground glass. The total CT scan score grading is as follows: 0 = no disease, 1–24 = mild disease, 25–48 = moderate disease, and $\geq$49 = severe disease.

Surgical lung biopsies where obtained only when deemed clinically warranted by the treating or referring clinician. The Johns Hopkins Surgical Pathology Department recommends targeting at least two lobes with areas of active ground glass on the most recent HRCT with specimens of at least 4 cm in greatest dimension when inflated. Some biopsy specimens were obtained outside from institutions where protocols may differ. To maximize the consistency of surgical lung biopsy results, only biopsy specimens that were interpreted by pathologists at our center were included in the analysis.

Statistical analysis

All statistical analyses were performed using Stata v.12.1 (Stata Corp., College Station Texas). Descriptive statistics were generated from baseline data. Fisher's exact test was used to compare categorical variable frequencies between antibody subtypes. Simple linear regression was used to compare unadjusted group means for continuous variables. For the longitudinal data analyses, we analyzed each outcome using a general linear model with correlated errors that considered time as a continuous variable. These models used weighted least-squares to generate estimates for the mean forced vital capacity percent predicted (FVC %), carbon monoxide diffusing capacity percent predicted (DLCO%), or total CT score as a function of time. We chose to model FVC% and DLCO% since these values are accepted measures of disease progression in patients with ILD. Restricted maximum likelihood estimation of the covariance parameters was used to provide robust inferences in the event of covariance structure misspecification. In each model exponential correlation was used to model the covariance structure among the repeat measures by subject. We chose this structure due to irregularly spaced follow-up measurements between subjects. All available data were used for the analyses; the data were assumed to be missing at random. A p value of <0.05 was used as the cutoff for statistical significance; estimates of uncertainty were presented as 95 percent confidence intervals (95% CI).

Results

Baseline characteristics

Demography and clinical features

Seventy-seven subjects met all inclusion criteria and were analyzed in our study; baseline participant characteristics are summarized in Table 1. Thirty-six were ASA negative, 28 had anti-Jo1 antisynthetase antibodies, and 13 were non-Jo1 ASA positive (5 anti-PL-12, 4 anti-PL-7, 2 anti-EJ, and 2 anti-OJ). Most participants were Caucasian women. There was no statistically significant difference in the mean age, gender, myopathy subtype, or presenting symptom among the different antibody subtypes. Although African-Americans made up only 36% of the cohort, participants who were non-Jo1 ASA positive were more likely to be African-American than Caucasian/Other as compared to both the anti-Jo1 positive (p = 0.01) and ASA negative groups ($p < 0.01$) (Fig. 1).

Pulmonary physiology

All subjects had baseline pulmonary function testing. Taken together, the cohort demonstrated moderate restrictive and gas transfer defects at the time of diagnosis (mean FVC% = 64%, mean TLC% = 67%, mean DLCO% = 58%). There was no significant difference in baseline mean FVC% or DLCO% based on ASA subtype. The cohort displayed significant heterogeneity in unadjusted lung function between the initial and follow-up visit with worsening disease (defined by $a \geq 5\%$ drop in FVC%) in 40% of the participants, no change in 16%, and improvement ($a \geq 5\%$ increase in FVC%) in 44% of participants. There was no significant difference in the proportion of those who worsened, improved, or remained the same based on ASA status (p = 0.72).

Chest CT findings

CT scan data was available for scoring in 65 (85%) subjects. The median length of time between CT scans was 18 months

Table 1 Baseline participant characteristics, by antisynthetase antibody.[a]

		ASA negative (n = 36)	Anti-Jo1 (n = 28)	Anti-PL-7 (n = 4)	Anti-PL-12 (n = 5)	Anti-EJ (n = 2)	Anti-OJ (n = 2)
Demographics	N/77						
Mean age		51	53	56	50	67	36
Women		22 (61)	22 (79)	4 (100)	4 (80)	1 (50)	1 (50)
Race							
Caucasian		25 (69)	19 (68)	1 (25)	—	2 (100)	—
African-American		9 (25)	9 (32)	3 (75)	5 (100)	—	2 (100)
Other		2 (6)	—	—	—	—	—
Clinical features	77						
Myopathy subtype							
Dermatomyositis		9 (25)	9 (32)	—	—	—	—
Polymyositis		12 (33)	10 (32)	4 (100)	3 (60)	2 (100)	1 (50)
Overlap syndrome		15 (42)	9 (32)	—	2 (40)	—	1 (50)
Presenting symptom							
Shortness of breath		14 (39)	12 (43)	4 (100)	4 (80)	1 (50)	—
Weakness		4 (11)	5 (18)	—	1 (20)	—	1 (50)
Fatigue		2 (6)	4 (14)	—	—	—	1 (50)
Pain		7 (19)	6 (21)	—	—	1 (50)	—
Dermatologic findings		9 (25)	1 (4)	—	—	—	—
Pulmonary physiology	77						
Mean FVC, % predicted		68.0	63.9	57.5	48.0	73.8	34.6
Mean DLCO, % predicted		62.8	57.6	54.4	43.6	56.0	35.7
Chest CT scores	49						
Mean Fibrosis Score		11	13	19	36	4	12
Mean ground glass score		8	7	10	12	8	10
Mean total CT Score		18	21	29	48	12	22
Biopsy findings	32						
OP		5 (36)	4 (50)	1 (33.3)	1 (20)	—	—
NSIP		4 (29)	4 (50)	1 (33.3)	1 (20)	—	—
UIP		4 (29)	—	1 (33.3)	3 (60)	—	2 (100)
Unclassifiable		1 (6)	—	—	—	—	—

ASA = antisynthetase autoantibody, FVC = forced vital capacity, DLCO = diffusing capacity for carbon monoxide, OP = organizing pneumonia, NSIP = nonspecific interstitial pneumonia, UIP = usual interstitial pneumonia.
[a] Data expressed as number (percent) unless otherwise specified.

(IQR 15—46 months). Fibrosis remained mild overall but was statistically significantly worse at follow-up compared to baseline (mean fibrosis score 16.1 vs. 13.9, respectively; p = 0.02). Ground glass was noted to be moderate initially (mean ground glass score 8.1) and stable over time (mean ground glass score 7.4, p = 0.24). The total CT scan score was mild overall, both on the initial scan (mean total CT score = 22.0) as well as on follow up study (mean follow up total CT score = 23.3, p = 0.26).

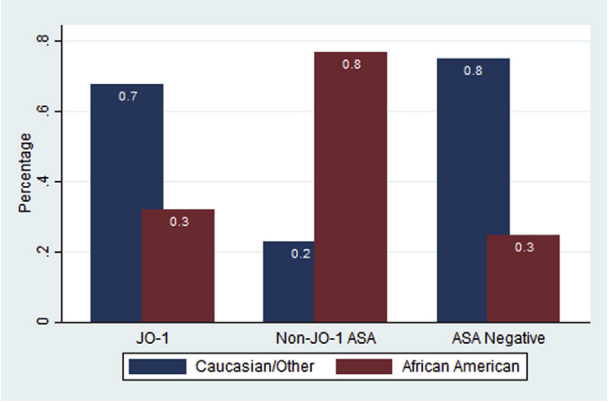

Figure 1 Racial breakdown by ASA status.

Surgical lung biopsy results

Lung biopsy data was available for 42% of all participants. The mean interval between the time of ILD diagnosis and biopsy acquisition was 15 months (range 1—51 months) and was not statistically different across all groups. The most common biopsy finding was organizing pneumonia (OP) (n = 11, 34.4%), followed by usual interstitial pneumonia (UIP) (n = 10, 31.3%) and nonspecific interstitial pneumonia (NSIP) (n = 10, 31.3%). There was 1 subject in whom the biopsy subtype could not be identified and was officially reported as "interstitial disease, non-specified", labeled "unclassifiable" in this paper. No significant difference was noted between the various antisynthetase antibody groups in regards to biopsy data. None of the eight anti-Jo1 positive participants who were biopsied demonstrated a UIP pattern.

Longitudinal analysis

Pulmonary Physiology

Seventy-six participants (99% of the entire cohort) had both initial and follow up pulmonary function test results available for analysis. The average follow up duration was 28 months (range 6–93 months). Participants with no demonstrable antisynthetase antibodies had better FVC% over time compared to those with anti-Jo1 and anti-OJ antibodies after controlling for potential confounders (Table 2). There was, however, no significant difference in the mean DLCO% over time based on ASA status (Table 3). The FVC% and DLCO% were significantly better over time for those who presented with non-pulmonary symptoms compared to those who presented with shortness of breath ($p < 0.01$, 95% CI 3.22 to 19.52 and $p < 0.01$, 95% CI 7.19 to 27.21, respectively). The diagnosis of overlap syndrome was associated with a worse FVC% and DLCO% over time compared to DM alone ($p = 0.02$, 95% CI −23.03 to −2.24 and $p = 0.02$, 95% CI −27.43 to −2.22, respectively).

Chest CT scores

Forty-nine subjects (64%) had both initial and follow-up chest CT results available for analysis. The average duration between scans was 31 months (range 6–134 months). Participants with no demonstrable antisynthetase antibodies had lower total CT scores over time compared to those with anti-Jo1 and anti-PL-12 antibodies after controlling for potential confounders (Table 4).

Discussion

We retrospectively investigated the association between specific antisynthetase antibody types and the clinical characteristics of patients with autoimmune myositis associated ILD. The power of this study is that it represents one of the largest cohorts of ASA positive patients with MA-ILD published to date.

Compared to previous population estimates, our cohort was similar with respect to mean age at disease onset and the ratio of men to women [20]. One unique feature of our

Table 3 Longitudinal regression model for carbon monoxide diffusing capacity percent predicted ($n = 76$).

Predictor	Estimate ± SE	p-value
Age	0.24 ± 0.23	0.29
Sex		
Male (Reference)		
Female	9.61 ± 5.13	0.06
Race		
African-American (Reference)		
Caucasian/other	10.28 ± 22.61	0.65
Antisynthetase antibody (ASA) status		
ASA negative (Reference)		
Anti-Jo1+	−13.79 ± 9.32	0.14
Anti-PL-7	−7.95 ± 13.13	0.55
Anti-PL-12	−12.29 ± 10.94	0.26
Anti-EJ	−6.15 ± 30.37	0.84
Anti-OJ	−22.66 ± 15.64	0.15
Clinical subtype		
Dermatomyositis (Reference)		
Polymyositis	−7.26 ± 6.85	0.29
Overlap syndrome	−14.82 ± 6.43	0.02
Presenting symptom		
Pulmonary (Reference)		
Non-pulmonary	17.20 ± 5.11	<0.01

Table 2 Longitudinal regression model for mean forced vital capacity percent predicted ($n = 77$).

Predictor	Estimate ± SE	p-value
Age	0.16 ± 0.18	0.37
Sex		
Male (Reference)		
Female	1.16 ± 4.18	0.78
Race		
African-American (Reference)		
Caucasian/other	−16.58 ± 18.68	0.38
Antisynthetase antibody (ASA) status		
ASA negative (Reference)		
Anti-Jo1+	−16.41 ± 7.67	0.03
Anti-PL-7	5.88 ± 10.85	0.59
Anti-PL-12	−8.45 ± 9.01	0.35
Anti-EJ	22.24 ± 22.21	0.32
Anti-OJ	−26.40 ± 12.94	0.04
Clinical subtype		
Dermatomyositis (Reference)		
Polymyositis	−10.91 ± 5.64	0.05
Overlap syndrome	−12.63 ± 5.30	0.02
Presenting Symptom		
Pulmonary (Reference)		
Non-pulmonary	11.37 ± 4.16	<0.01

Table 4 Longitudinal regression model for total CT score ($n = 65$).

Predictor	Estimate ± SE	p-value
Age	0.10 ± 0.15	0.49
Sex		
Male (Reference)		
Female	−3.92 ± 3.45	0.26
Race		
African-American (Reference)		
Caucasian/other	−13.29 ± 14.94	0.37
Antisynthetase antibody (ASA) status		
ASA negative (Reference)		
Anti-Jo1+	14.07 ± 6.88	0.04
Anti-PL-7	12.14 ± 9.28	0.19
Anti-PL-12	17.87 ± 6.63	<0.01
Anti-EJ	10.79 ± 19.35	0.58
Anti-OJ	10.13 ± 9.71	0.30
Clinical subtype		
Dermatomyositis (Reference)		
Polymyositis	6.80 ± 4.52	0.13
Overlap Syndrome	2.82 ± 4.20	0.50
Presenting symptom		
Pulmonary (Reference)		
Non-pulmonary	−6.50 ± 3.39	0.06

cohort was the racial composition related to the fact that our center cares for a larger number of African-American patients than other comparable centers worldwide. Despite a relative prevalence of autoantibodies similar to published cohorts [2], we found that non-Jo1 anti-synthetase autoantibodies were more prevalent in African-American patients than in Caucasian patients. A similar study of subjects with juvenile IIM also found statistically significant differences in the racial distributions of myositis associated and specific autoantibodies [21]. Additionally, there is mounting evidence that racial expression of auto-immunity varies resulting in important differences in clinical phenotypes and outcomes [22]. Whether the racial difference we found in antisynthetase autoantibody status confers better or worse clinical outcomes for African-Americans warrants further investigation.

The cohort as a whole demonstrated heterogeneity in lung function [23], with few differences in FVC% and DLCO% between antibody subtypes both at baseline and over time. ASA negative participants did have a higher FVC% over time compared to those with anti-Jo1 and anti-OJ antibodies but this difference was not seen in the DLCO%. The clinical significance of a better FVC% and DLCO% over time in those who presented with non-pulmonary symptoms compared to shortness of breath is unclear. Our study was not designed to measure symptoms, quality of life, or mortality over time. This finding, however, is consistent with previous reports that suggested inferior long-term prognosis when shortness of breath is the presenting symptom in anti-synthetase syndrome [24]. Similarly the fact that those who have an overlap syndrome had a worse FVC% and DLCO% over time compared to those with DM is interesting but has unknown clinical implications.

Expert radiologist CT scores reflected mild to moderate levels of fibrosis and ground glass with mild overall disease burden on imaging. The higher CT scores in those with anti-Jo1 compared to those who were antibody negative is internally consistent with the finding of worse lung function over time in those subjects.

Although a lung biopsy generally is not required to confirm ILD in patients with established myositis [25], over 40% of our subjects had lung biopsy specimens available for review. While not statistically significant, the surgical lung biopsy results of our patients suggest a potential difference in pathologic effect between the antibody subtypes. There were no instances of UIP by biopsy in our anti-Jo1 positive cohort, which has not been described in previous series. While a predominance of NSIP and OP on lung biopsy of anti-Jo1 positive patients [13] and antibody negative patients [26] has been reported previously, the high rate of UIP we found in non-Jo1 ASA patients is unique.

Our study was limited by the fact that it was a retrospective, observational, single-center study of small sample size. This could have an unforeseen impact on patient management or introduce a referral bias. All three of these are difficulties frequently encountered in the study of a rare condition. Further multicenter, collaborative efforts will likely be required to generate a cohort of myositis-associated ILD patients sufficiently large for adequately-powered, prospective trials to be performed. Patients were defined as ASA negative if they had ILD and clinically diagnosed IIM in the absence of clinically available ASAs. Therefore it may be possible that some patients in the ASA negative category have an ASA that is not yet easily detectable. Not all patients had an initial CT scan available for scoring, although all patients had a CT performed and reviewed by our treating pulmonologist to establish or confirm ILD. Given the high proportion of referrals not all scans were performed at our center and it is not routine practice to upload all images into our system. Follow-up CT imaging was only performed when clinically indicated. This could have introduced bias in the total CT scores over time. Another limitation is that all patients were enrolled through an outpatient treatment center, likely excluding the most ill and rapidly progressive patients. There are reports that a subset of patients, especially those with amyopathic dermatomyositis and ILD, commonly do not live past the initial phase of their illness [27—31]. The results of this study cannot be generalized to those patients. Finally, the patients studied came to our Myositis Center through referral, with many of them already started on corticosteroids or other immune-modulating therapy prior to their initial PFTs being performed. Thus "pre-treatment" and "post-treatment" analysis was not performed in this population, limiting the interpretation of the therapeutic response in PFTs over time.

Conclusion

Our data suggest several potential, clinically relevant, differences between the interstitial lung disease phenotype seen in patients with varying antisynthetase antibody subtypes. Further prospective study in a larger cohort is needed to determine whether these apparent antibody-specific differences in demographics and pathologic manifestations of disease will allow for the use of ASAs as biomarkers to inform prognosis and/or tailor therapeutic regimens for patients with myositis-associated interstitial lung disease.

Conflict of interest

All of the authors have no conflicts of interests to disclose.

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