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Clinical signs associated with an increased risk of interstitial lung disease: a retrospective study of 101 patients with dermatomyositis

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Pulmonary complications are common in dermatomyositis (DM) and contribute to significant morbidity and mortality^{1–3}. Patients with dermatomyositis and anti-synthetase⁴, anti-PM/ScI⁵ or anti-MDA5⁶ antibodies have specific signs (mechanic's hands in anti-synthetase phenotype; skin and oral ulcers, arthritis and arthralgia, and alopecia in anti-MDA5 phenotype and sclerodermatous changes in anti-PM/ScI phenotype) and an increased risk of interstitial lung disease (ILD). Screening dermatomyositis patients for these myositis specific antibodies (MSA) can help to predict ILD and allow targeted intervention. However, antibody testing at this juncture is neither routinely available nor standardized, although this is likely to change in the near future. Identifying cutaneous features associated with ILD will be an ideal and cost effective way to target its screening. The aim of our study is to determine which of the above clinical signs are associated with an increased risk of ILD in our cohort of adult onset dermatomyositis patients. The second aim is to look for any significant association between the presence of MSA at enrollment, clinical signs and ILD in our patient cohort.

The University of Pennsylvania Dermatomyositis database prospectively enrolls DM patients who agree to participate at the Department of Dermatology. These patients are examined and their clinical data recorded by the principal author (VPW) and her research team at baseline and during study visits. We performed a retrospective analysis of patients enrolled in this database from May 2008 to September 2013. We included patients with adult

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onset DM defined by a cutaneous histology consistent with DM and typical clinical features. We excluded patients with juvenile DM, overlap connective tissue disease or those with missing data. Assignment to classic or clinically amyopathic DM was based on established criteria⁷⁻¹⁰. We recorded the presence of six signs (Gottron's papules, mechanic's hands, arthralgia or arthritis, skin ulceration over existing inflamed papules and plaques, oral ulceration and diffuse alopecia), demographic data, disease information, CDASI score and the results of pulmonary investigations. Our patients underwent pulmonary function testing (PFTs) and high resolution chest computer tomography (HRCT) per published protocol¹. Serum samples were collected at enrollment if the patients consented to a blood draw. The presence of myositis specific antibodies (anti-MDA5, anti-TIF1- γ , anti synthetases, anti-NXP-2, anti-SAE, anti-SRP and anti-Mi-2) were identified with immunoprecipitation (IP) assays using extracts of the leukemia cell line K562^{4,11}. The patients were divided into 2 outcome groups for analysis: the first group had ILD (diagnosed on HRCT and/or lung biopsy) or an isolated reduced lung diffusion capacity (DLCO less than 80% predicted) on PFTs in the absence of significant findings on HRCT (indicating possible subclinical ILD¹). The other group had either normal screening PFTs or non-ILD pulmonary pathology. The study was approved by the University of Pennsylvania IRB and was performed in accordance with the Helsinki Declaration. Prism 5.0 software (GraphPad Software Inc, San Diego, CA) was used for data analysis. We had 2 null hypotheses: there was no difference in the demographic variables between the 2 comparison groups, and there was no association between the clinical signs described above and ILD. Fisher's exact test was used to compare the proportions of patients with different clinical variables and ILD status and to calculate the odds of having ILD or an isolated reduced DLCO in relation to each clinical sign. Comparison of median variables in table 1 was performed with Mann Whitney test. The level of statistical significance was set at 0.05.

One hundred and one patients from our database of 126 patients were included in the analysis. Fifty three patients (52.48%) had classic DM while 48 patients (47.52%) had clinically amyopathic DM. Thirty eight patients (37.62%) had an isolated low DLCO (19 patients) or ILD on HRCT and/or lung biopsy (19 patients). Sixty three patients (62.38%) had either normal screening PFTs (42 patients) or other pulmonary pathologies (21 patients). There was no statistically significant difference detected for the different demographic data between those with isolated low DLCO or ILD versus the non-ILD group, except for race. There was a higher proportion of Caucasians in the non-ILD group compared to the ILD and isolated low DLCO group (98.41% vs. 86.84%, $p=0.03$) (Table 1).

Twenty-eight out of 38 (73.68%) patients with all subtypes of DM and an isolated low DLCO or ILD had mechanic's hands, compared to 29 out of 63 (46.03%) patients in the non-ILD group. The presence of mechanic's hands conferred a statistically significant odds ratio of 3.28 (95% CI, 1.37–7.88) of having an isolated low DLCO or ILD ($p=0.01$) compared to those without mechanic's hands. Conversely, the presence of Gottron's papules conferred a protective effect with a statistically significant odds ratio of 0.36 (95% CI, 0.14–0.94) of having an isolated low DLCO or ILD ($p=0.05$) compared to those without Gottron's papules. All the other clinical signs were not statistically associated with having an isolated low DLCO or ILD (Table 2). When we recomputed the statistics looking at 19 patients with established ILD vs. 82 patients in the non-ILD group (normal screening PFT, other lung

pathology, isolated low DLCO), the odds of having ILD in those with mechanic's hands was 2.54 (95% CI= 0.84–7.70, $p=0.13$) and with Gottron's papules was 0.42 (95% CI=0.14–1.22, $p=0.13$).

Serum samples from 43 patients who consented to the blood draw were analysed. We found no detectable myositis specific antibodies in 21 patients, anti-TIF1- γ antibody in 17 patients, anti-MDA5 antibody in 3 patients, anti-Jo-1 antibody in 1 patient, and anti-OJ antibody in 1 patient.. All of the subjects with anti-MDA5, -Jo-1 and -OJ antibodies had frank ILD. Three out of 17 subjects (17.65%) with anti-TIF1- γ antibodies had ever had a malignancy. Both patients with anti-synthetase (anti-Jo-1 and anti-OJ) antibodies had arthritis and arthralgias. These associations were as expected for the respective MSA-associated phenotypes, although the prevalence of malignancy in patients with anti TIF1- γ antibodies seemed lower than expected. Twenty six of the 43 subjects had mechanics hands at enrollment. Of these, all of the patients with detectable anti-MDA5 antibodies had mechanics hands, while 12/17 (70.59%) and 11/21 (52.38%) of subjects with anti-TIF1- γ antibodies or no detectable antibodies had mechanics hands respectively. The 2 patients with anti-Jo-1 and anti-OJ antibodies did not have mechanic's hands. In the large study of 166 Japanese patients with anti-synthetase antibodies⁴, mechanic's hands were present in a varying proportion of patients in the antibody subgroups and was seen in up to 56% of their cohort with anti-Jo-1 antibodies. In our cohort of patients, mechanic's hands were also seen in patients with anti-TIF1- γ and anti-MDA5 as well as in those with no detectable antibodies. This suggests that mechanic's hands are a risk factor for ILD, regardless of the type of myositis specific antibodies present. Thirteen of the 43 patients had both mechanic's hands and lung involvement (isolated low DLCO or ILD). There were no statistically significant association between the presence of anti-TIF1- γ antibodies and cancer, mechanics hands, or the presence of isolated low DLCO/frank ILD (data not shown) in the 43 patients, although this was not generalizable to the entire cohort due to the low numbers analysed.

There are several limitations to our study. We have a greater proportion of Caucasian patients in the non-ILD group compared with the isolated low DLCO/ILD group which may influence the results. Our results are not representative of non-Caucasian patients. There is a potential for selection bias as we only included patients who agreed to be in the database instead of all dermatomyositis patients seen in the clinic, although fewer than 10% of patients refused to participate. Allocation bias may be introduced by placing the patients with isolated low DLCO (indicating possible subclinical ILD) into the ILD group for further analysis. When only frank ILD was compared with the rest of the study population, the association found between gotton's papules or mechanic's hands and frank ILD became statistically insignificant, probably from lack of statistical power. We attempted to reduce the potential for information bias by using a validated scoring system (CDASI) and having 2 assessors (VPW and another study author) during each study visit.

Defining dermatomyositis subsets using MSAs is appealing but is limited by the variable association between serotype and phenotype, differing sensitivity and specificity, limited access, and cost of the assays. We look forward to scientific advances that will address the

above limitations. Until then, we recommend screening dermatomyositis patients for ILD, especially if mechanic's hands are present.

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What's already known about this topic

- Dermatomyositis confers an increased risk of interstitial lung disease (ILD), especially in subsets of patients with anti-synthetase, anti-PM/Scl and anti-MDA5 antibodies.
- These phenotypes have specific skin and extracutaneous findings which may be useful predictors of risk for ILD

What does this study add

- Patients with mechanic's hands have an odds of 3.28 (95% CI, 1.368 – 7.88) for ILD when compared to those without mechanic's hands (p=0.01).
- Patients with Gottron's papules have an odds of 0.363 (95% CI, 0.14 – 0.94) for ILD when compared to those without Gottron's papules (p=0.05).

Table 1

Demographic data of patients with isolated low DLCO and ILD compared to those with PFT and HRCT not diagnostic of ILD.

	Isolated low DLCO and ILD (n=38)	Pulmonary screening not suggestive of ILD (n=63)	P value
Proportion of patients with classic DM (%)	19/38 (50.00%)	34/63 (53.97%)	0.84
Proportion of males (%)	7/38 (18.42%)	6/63 (9.52%)	0.23
Proportion of Caucasians (%)	33/38 (86.84%)	62/63 (98.41%)	0.03
Proportion of Smokers (%)	16/38 (42.11%)	24/63 (38.10%)	0.83
Proportion of patients who had treatment for their DM prior to or during enrollment (%)	35/38 (92.11%)	55/63 (87.30%)	0.53
Proportion of patients with other connective tissue diseases (%)	3/38 (7.89%)	3/63 (4.76%)	0.67
Proportion of patients with malignancies within 5 years of diagnosis (%)	6/38 (15.79%)	8/63 (12.70%)	0.77
Median CDASI activity score (range)	11.5 (0 to 47)	17.0 (0 to 43)	0.12
Median age at enrollment (range)	55.80 (23.71 to 73.34)	54.07 (20.79 to 82.39)	0.60
Median age at onset of DM (range)	50.45 (22.29 to 68.56)	48.58 (20.07 to 77.15)	0.50
Median duration of DM (range)	4.22 (1.30 to 33.78)	6.18 (0.34 to 20.55)	0.27
Median duration of follow-up (range)	2.51 (0 to 9.81)	2.68 (0 to 14.46)	0.56

Table 2

Comparison of the association between the different clinical signs of dermatomyositis and ILD status in dermatomyositis patients.

Number of DM patients (n=101) with:	Isolated low DLCO and ILD (n=38)	Pulmonary screening not suggestive of ILD (n=63)	odds ratio (95% confidence interval)	P value
Gottron's papules (%)	25 (65.79%)	53 (84.13%)	0.36 (0.14 – 0.94)	p=0.05
Arthritis and arthralgia (%)	18 (47.37%)	26 (41.27%)	1.28 (0.57 – 2.88)	p=0.68
Mechanic's hands (%)	28 (73.68%)	29 (46.03%)	3.28 (1.37 – 7.88)	p=0.01
Skin ulceration (%)	2 (5.26%)	5 (7.94%)	0.64 (0.12 – 3.50)	p=0.71
Oral ulceration (%)	1 (2.63%)	4 (6.35%)	0.39 (0.04 – 3.64)	p=0.65
Hair loss (%)	8 (21.05%)	15 (23.81%)	0.85 (0.32 – 2.26)	p=0.75