Interstitial Lung Disease in Classic and Skin-Predominant Dermatomyositis

A Retrospective Study With Screening Recommendations

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Objectives: (1) To determine the prevalence of interstitial lung disease (ILD) and isolated low diffusing capacity for carbon monoxide (DLCO) in a large cohort of outpatients with dermatomyositis. (2) To compare the pulmonary abnormalities of patients with classic dermatomyositis and those with skin-predominant dermatomyositis.

Design: Retrospective cohort study.

Setting: University hospital outpatient dermatology referral center.

Patients: Medical records of 91 outpatients with adult-onset dermatomyositis seen between May 26, 2006, and May 25, 2009, were reviewed.

Main Outcome Measures: Presence of ILD on thin-slice chest computed tomographic (CT) scans and DLCO.

Results: Of the 71 patients with dermatomyositis who had CT or DLCO data, 16 (23%; 95% confidence interval [CI], 13%-33%) had ILD as defined by CT results. All patients with ILD had a reduced DLCO, and the ILD prevalence was not different between patients with skin-predominant dermatomyositis (10 of 35 [29%]) and those with classic dermatomyositis (6 of 36 [17%]) (P = .27). Eighteen of 71 patients with dermatomyositis (25%; 95% CI, 15%-36%) (7 of 35 [20%] with skin-predominant dermatomyositis; 11 of 36 [31%] with classic dermatomyositis; P = .41) had a low DLCO in the absence of CT findings showing ILD. The prevalence of malignant disease was higher in patients with classic dermatomyositis than in those with skin-predominant dermatomyositis (P = .02), and no patients with skin-predominant dermatomyositis had internal malignant disease.

Conclusions: Radiologic ILD and isolated DLCO reductions, which may signify early ILD or pulmonary hypertension, are common in dermatology outpatients with both classic and skin-predominant dermatomyositis. Because DLCO testing is both inexpensive and sensitive for pulmonary disease, it may be appropriate to screen all patients with dermatomyositis with serial DLCO measurements and base further testing on DLCO results.

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Interstitial lung disease (ILD) is commonly associated with dermatomyositis (DM) in adults. Although the definitive diagnosis of ILD is made with radiography, ILD is associated with a characteristic profile on pulmonary function testing. Patients typically have a low diffusing capacity for carbon monoxide (DLCO) and often also have restrictive impairment (low total lung capacity). Like other patients with ILD, patients with DM and ILD have an extremely variable clinical presentation, ranging from asymptomatic disease to rapidly fatal respiratory failure.

Interstitial lung disease associated with DM and other connective tissue diseases may be responsive to immunosuppressive therapies such as corticosteroids, cyclophosphamide, azathioprine, and mycophenolate mofetil, and early diagnosis may enable treatment before irreversible fibrosis occurs. Although screening patients with DM for ILD may improve outcome, screening practices are highly variable. Among those physicians who screen, pulmonary function tests (PFTs) are often the first-line modality. However, physicians may be uncertain about how to interpret or when to repeat PFTs, when to obtain a chest computed tomographic (CT) scan, and when to refer patients to pulmonary specialists.

Developing screening guidelines based on the available literature is problematic for several reasons. Most existing studies fail to address the patients with DM who, despite normal findings
on radiologic imaging, have PFT abnormalities that may be indicative of early ILD or pulmonary hypertension, such as a low DLCO. Many prior studies also do not enable us to ascertain whether patients with DM who have a normal DLCO on initial testing are at risk for developing ILD or low DLCO in the future. In addition, patients with DM without clinically significant muscle disease have been excluded from numerous studies because many investigators use a definition of DM developed by Bohan and Peter that requires the presence of symptomatic muscle disease.

The primary purpose of this retrospective study was to examine the prevalence of radiologic ILD and low DLCO in a large cohort of outpatient patients with DM and to propose preliminary pulmonary screening and initial management guidelines for these patients. A secondary goal was to compare the pulmonary abnormalities of patients with DM with and without clinically significant muscle disease, because previous reports have suggested that ILD may be more common and more severe in those with skin-predominant disease.

Table 1. Definitions of Dermatomyositis (DM) Categories

<table>
<thead>
<tr>
<th>DM Category</th>
<th>Criteria</th>
</tr>
</thead>
</table>
| Classic DM (CDM) | Hallmark cutaneous manifestations of DM  
Clinically significant muscle weakness  
Objective evidence of myositis (elevated serum muscle enzyme levels or abnormal electromyography or magnetic resonance imaging of muscles) |
| Amyopathic DM (ADM) | Hallmark cutaneous manifestations of DM  
Lasting >6 mo  
No objective evidence of myositis  
Not treated with systemic immunosuppressants for >2 consecutive months during the first 6 mo after rash onset |
| Hypomyopathic DM (HDM) | Hallmark cutaneous manifestations of DM  
Lasting >6 mo  
No clinically significant muscle weakness  
Objective evidence of myositis (elevated serum muscle enzyme levels or abnormal electromyography or magnetic resonance imaging of muscles) |
| Early-treated ADM | Treated with systemic immunosuppressants for >2 consecutive months during the first 6 mo after rash onset  
Otherwise meets ADM criteria |
| Early-treated HDM | Treated with systemic immunosuppressants for >2 consecutive months during the first 6 mo after rash onset  
Otherwise meets HDM criteria |
| Premyopathic DM (PRMDM) | Preliminary category for patients with DM  
Duration of <6 mo who have the hallmark cutaneous manifestations and no clinically significant muscle weakness |
| Clinically ADM (CADM) | An umbrella designation for patients with ADM and HDM |
| Skin-predominant DM | Designation created for this article to include all patients with DM with no history of clinically significant muscle disease. This includes CADM (ADM, HDM), PRMDM, early-treated ADM, and early-treated HDM |

We performed a retrospective medical chart review at our outpatient dermatology clinic, a tertiary university referral center. All patients in this study were seen in the referral practice of the primary investigator (V.P.W.). Our institutional review board approved the study protocol and waived the requirement for consent of subjects.

Patients seen in our clinic between May 26, 2006, and May 25, 2009, and with a primary diagnosis of DM were identified by the International Classification of Diseases, Ninth Revision (ICD-9) code 710.3, and their clinic charts were retrospectively reviewed. New prospective data that became available during the course of data collection were also included in the review. Exclusion criteria were the following: juvenile DM (defined as symptom onset before age 18 years), the diagnosis of DM was clinically uncertain, the patient had chronic lung disease that would complicate the diagnosis of ILD, or the patient was miscoded as having DM.

DM CLASSIFICATIONS

Patients were categorized either as classic DM (CDM) or skin-predominant DM (SDM). Patients with SDM were subclassified as having hypomyopathic DM (HDM), amyopathic DM (ADM), premyopathic DM (PRMDM), early-treated ADM, or early-treated HDM. See Table 1 for full definitions of the DM categories. The categories ADM, HDM, and PRMDM were derived from the previous literature. The early-treated ADM and early-treated HDM classifications were created to encompass patients who were treated with systemic immunosuppressants for more than 2 consecutive months in the first 6 months after disease onset and never developed muscle symptoms. Such patients are excluded from ADM and HDM diagnoses owing to the possibility that the immunosuppression prevented the development of muscle disease. However, patients presenting with lung disease (or recalcitrant skin disease) early in their disease course often receive long-term systemic immunosuppressants, and excluding these patients or automatically classifying them as having CDM may prevent accurate characterization of the DM population without muscle symptoms.

PULMONARY FUNCTION TESTING

Results of all available PFTs with DLCO were recorded. The DLCO values were not corrected for hemoglobin levels. Restrictive impairment was defined as total lung capacity (TLC) less than 80% predicted. If TLC was not available, forced vital capacity (FVC) of less than 80% predicted and forced expiratory volume in 1 second to FVC ratio of 70% or greater was classified as restrictive impairment (only 2 patients were classified as having restrictive impairment using this criterion). When comparing serial DLCO and TLC values, improvement was defined as a 15% increase in DLCO and 10% increase in TLC, as suggested in the American Thoracic Society’s international consensus statement on idiopathic pulmonary fibrosis.

CHEST CT SCANS

Radiologist or pulmonologist reports of all thin-slice (≤3-mm slices or specified as high-resolution or pulmonary embolism protocol) CT scans of the chest were recorded. Chest CT scans obtained for evaluation of malignant disease that used slices greater than 3 mm were not considered sufficient to rule out the presence of early ILD and were not included in the data analysis.
ILD CATEGORIES

Patients were categorized into one of the following groups based on chest CT and DLCO data: (1) ILD, defined by compatible chest CT findings (all patients also had reduced DLCO); (2) low DLCO of uncertain significance, defined by lowest DLCO below 80% predicted in the absence of chest CT findings compatible with ILD (including patients who never got a CT scan); and (3) no evidence of ILD, defined as at least 1 normal lung test (DLCO, CT, or both) and no abnormal test findings.

STATISTICAL ANALYSIS

Statistics were calculated using SAS software (version 9.1; SAS Institute Inc, Cary, North Carolina). P < .05 was considered significant, and Fisher exact tests were 2-tailed. To compare the patient characteristics of the CDM and SDM groups, Fisher exact test was used for categorical variables, and t tests were used for continuous variables. Ninety-five percent confidence intervals (CIs) were calculated for the prevalence of each lung disease category, and Fisher exact test was used to compare the prevalence of the lung disease categories in the CDM and SDM groups. Fisher exact test was also used to compare (1) the prevalence of ILD in each initial DLO group, (2) the percentage of patients of male sex and the percentage of patients with overlap connective tissue disease in the ILD category vs the other lung disease categories, and (3) the percentage of patients with individual skin findings in each lung disease category. Analysis of variance (general linear models) was used to compare the mean number of skin findings per patient in each lung disease category.

RESULTS

PATIENT POPULATION

Of the 123 patients identified by the ICD-9 code 710.3, 32 were excluded for the following reasons: a patient had juvenile DM (8 patients), the diagnosis of DM was uncertain (8 patients), medical records could not be located (7 patients), the diagnosis was miscoded (6 patients), or a patient had sarcoidosis (2 patients) or pulmonary Langerhans cell histiocytosis (1 patient). The remaining 91 patients were included in this study.

Seven patients (3 with SDM, 4 with CDM) had overlap with other connective tissue diseases, including diffuse scleroderma, limited scleroderma, rheumatoid arthritis, and systemic lupus erythematosus. Antinuclear antibodies (considered positive if the titer was >1:160 or the report specified a positive finding but gave no titer) were common, occurring in 21 of 41 patients (51%), with no difference between CDM and SDM (P = .12). Tests for anti-histidyl–transfer RNA synthetase (Jo-1) antibodies were negative in all 50 patients (51%), with no difference between CDM and SDM (26 with SDM, 24 with CDM) who were tested.

Table 2 details the other clinical and laboratory characteristics of the patient population. Aside from data pertaining to the assessment and treatment of muscle disease, the only significant difference between patients with SDM and those with CDM was a higher rate of malignant disease in the CDM group (P = .02). The patients with CDM had a 6% prevalence rate of nonmelanoma skin cancer (3 of 47 patients) and a 13% prevalence rate of internal malignant diseases (6 of 47 patients), whereas only 2% of patients with SDM (1 of 44) had a nonmelanoma skin cancer, and no patients with SDM had internal malignant diseases.
ILD AND PULMONARY DIFFUSION ABNORMALITIES

Of the 91 patients reviewed, 71 had DLCO results, thin-section chest CT results, or both. These patients were classified according to lung disease categories as shown in Figure 1. Sixteen of these 71 patients (23%) (95% CI, 13%-33%) were considered to have ILD based on thin-section CT results (14 were definitely compatible with ILD, and 2 were possibly compatible with ILD per the radiologist’s or pulmonologist’s reading). There was no statistically significant difference (P = .27) between the prevalence of ILD in patients with SDM (10 of 35 [29%]) (95% CI, 13%-44%) vs those with CDM (6 of 36 [17%]) (95% CI, 4%-30%). All of the patients with CT scans compatible with ILD had a reduced lowest DLCO (mean [SD], 47% [12%] predicted; range, 24%-66%), and 11 of 16 (69%) had restrictive impairment on PFTs at the time of their lowest DLCO value.

Patients with at least 1 normal lung test (DLCO, thin-section CT, or both) and no abnormal test results were considered to have no evidence of ILD. Thirty-seven of 71 patients (52%) (95% CI, 40%-64%) fell into this category, with no difference between the SDM group (18 of 35 [51%]) (95% CI, 34%-69%) and the CDM group (19 of 36 [53%]) (95% CI, 36%-70%) (P > .99). Only 1 patient in this category had restrictive impairment on PFTs, and the restriction in this patient was likely extrinsic given the patient’s morbid obesity (a body mass index [calculated as weight in kilograms divided by height in meters squared] of 53.2). This patient also had CDM, and because maximal inspiratory and expiratory pressures were not performed, respiratory muscle weakness could not be ruled out as a contributing factor to the restrictive impairment.

Eighteen of 71 patients (25%) (95% CI, 15%-36%) fit into a middle category of patients with lung diffusion abnormality of uncertain clinical significance. There was no statistically significant difference between the percentage of patients with SDM (7 of 35 [20%]) (95% CI, 6%-34%) and those with CDM (11 of 36 [31%]) (95% CI, 15%-46%) falling into this category (P = .41). These patients had reduced DLCO (mean [SD], 66% [11%] predicted; range, 40%-79%) in the absence of any findings of ILD on CT, which may represent an early stage of ILD or pulmonary hypertension. Only 3 of these 18 patients (17%) had restrictive impairment on PFTs at the time of their lowest DLCO. See Table 3 for detailed categorizations of ILD and pulmonary function abnormalities.

SKIN FINDINGS AND LUNG FUNCTION ABNORMALITIES

To assess for an association between the severity of skin disease and the presence of ILD, we compared the mean number of unique skin findings (heliotrope rash, Gottron papules or sign, V-sign, shawl sign, periorbital edema, calcinosis cutis, periungual erythema or telangiectasia, cuticular changes, mechanic’s hands, facial erythema, livedo reticularis, and scalp disease) of the patients in each lung disease category. This analysis was limited to the 37 patients who had both DLCO testing and thin-section CT performed. Although the mean number of skin findings was lower in patients with lung disease (mean [SD] for the ILD group: 3.8 [2.2]; range, 1-8; for the group with lung diffusion abnormality of uncertain significance: 4.9 [1.6]; range, 2-7; for the group with no evidence of ILD: 5.3 [1.7]; range, 3-8), this finding was not statistically significant (P = .13). The V-sign (erythema in a V-neck distribution) was less common in patients with ILD than those without ILD (P = .047), but no other individual skin finding had a statistically significant association with lung disease category.
When patients were classified according to their initial DLCO values (categories shown in Figure 2), the prevalence of ILD was higher in patients with lower initial DLCO values (P < .001). However, ILD did occur in 2 of 38 patients (5%) with an initial DLCO measurement in the reference range (both developed a low DLCO within 1.5 years of ILD diagnosis on CT) and in 5 of 12 patients (42%) with a mild initial reduction in DLCO.

Table 4 shows the prevalence of ILD, the timing of ILD diagnosis on CT relative to the initial DLCO measurement, and the percentage of patients who had a thin-section CT performed in each initial DLCO category. Figure 2 shows the results of serial DLCO testing. Some patients with initial DLCO values in the normal range, borderline low, and mild reduction categories dropped into the moderate or severe reduction categories on repeated testing. Among those with an initial DLCO value in the reference range that subsequently dropped below normal, the...
mean time from the initial DLCO test to dropping below 80% predicted was 482 days (range, 155-974 days).

CHARACTERISTICS OF PATIENTS WITH ILD CONFIRMED BY CT SCAN

Sixteen patients had thin-slice CT chest findings that were consistent with ILD (14 were definitely consistent with ILD, and 2 were possibly consistent with ILD per radiologist or pulmonologist interpretation). In comparison with the other lung disease groups, the ILD group had more males (3 of 16 [19%], ILD group; 3 of 55 [5%], not ILD group; *P* = .12) and more patients who had overlap with other connective tissue diseases (3 of 16 [19%], ILD group; 3 of 55 [5%], not ILD group; *P* = .12), but neither of these differences were statistically significant. The 3 overlap connective tissue diseases were diffuse scleroderma, rheumatoid arthritis, and systemic lupus erythematosus. Four patients had lung biopsies; 3 showed nonspecific interstitial pneumonia, and 1 showed bronchiolitis obliterans with organizing pneumonia. A diagnosis of ILD on CT occurred more than 1 year before rash onset in 1 patient, more than 1 year after rash onset in 5 patients, and within 1 year before to 1 year after rash onset in 10 patients. See Table 5 for more clinical characteristics of the ILD group.

OUTCOME OF PATIENTS WITH ILD CONFIRMED BY CT SCAN

The mean duration of ILD follow-up, defined as the date of ILD diagnosis on CT scan to the last PFT follow-up, was 25 months (range, 0-83 months). For varying durations during this time, 11 of 12 patients (92%) with definite ILD on CT scan for whom treatment data were available were treated with high-dose glucocorticoids, and 10 of 12 (83%) were also treated with other immunosuppressants. The 2 patients with possible ILD on CT were treated only with mycophenolate mofetil. All immunosuppressants and antifibrotic used for at least 1 month between ILD diagnosis and the final ILD follow-up (by PFTs) are listed in Table 5, with the caveat that some were administered for treatment of connective tissue disease manifestations in organs other than the lung.

Of the patients with at least 6 months of ILD follow-up, 8 of 11 (73%) experienced improvement (≥15% increase from baseline) from the lowest DLCO (percentage predicted) as assessed at the last date of PFT follow-up (mean increase, 33%; range, 21%-111%). Two patients were excluded from this DLCO comparison, 1 because DLCO was measured only once during serial PFTs, and 1 because DLCO was not measured at the final PFT follow-up. Table 5 lists the lowest and final DLCO values for each patient, along with the timing of these measurements relative to ILD diagnosis and individual medications.

The TLC values from the corresponding dates were also compared for patients with at least 6 months of ILD follow-up. Five of 10 patients (50%) had an improvement in TLC (defined as ≥10% increase from baseline; mean increase, 31%; range, 11%-47%), whereas 1 of 10 (10%) had a deterioration in TLC (a 13% decrease from baseline), and 4 of 10 (40%) had a stable TLC percentage predicted (<10% change from baseline). Three patients were excluded from TLC analysis owing to missing values. Only 1 of 16 patients (6%) had complete normalization of TLC and DLCO (both >79%) at the date of latest follow-up.

Among the patients who had repeated thin-section CT scans of the chest, 4 showed complete resolution of ILD, 2 were improved but still showed interstitial disease, 3 showed stable ILD, and 1 showed worsening of ILD. Five patients had no repeated scans available, and 1 repeated scan showed ILD but was not compared with prior imaging.

This retrospective review of a large cohort of patients with DM seen in the outpatient dermatology setting demonstrates several important findings. First, the prevalence of ILD in outpatients with CDM and those with SDM was high. Twenty-three percent (95% CI, 13%-33%) of patients with DM with at least 1 thin-slice chest CT or DLCO measurement had ILD as defined by CT imaging. This ILD prevalence estimate is at the lower end of the wide prevalence range (approximately 20%-70%) that has been reported in recent studies of patients with DM and those with polymyositis performed mostly by rheumatology departments.2,7,9,12,33 Although patients with SDM seemed to have a higher prevalence of ILD than those with CDM, this difference was not statistically significant (*P* = .27).

It should be noted that 2 patients with ILD in this study had a recent history of methotrexate (a drug that can cause

### Table 4. Prevalence of ILD Based on Initial DLCO Measurement, Limited to Patients With a DLCO Measured at Least Once

<table>
<thead>
<tr>
<th>DLCO Category at Initial Measurement</th>
<th>Had a Thin-Section CT Performed</th>
<th>ILD Prevalence as Defined by Thin-Section CT*</th>
<th>Time After Initial DLCO That ILD Diagnosis Was Made by CT, Range, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal, &gt;79% predicted</td>
<td>12/38 (32)</td>
<td>2/38 (5)</td>
<td>≥7 to 0</td>
</tr>
<tr>
<td>Borderline low, 76%-79% predicted</td>
<td>4/5 (80)</td>
<td>0/5 (0)</td>
<td>NA</td>
</tr>
<tr>
<td>Mild reduction, 61%-75% predicted</td>
<td>10/12 (83)</td>
<td>5/12 (42)</td>
<td>-1 to 56</td>
</tr>
<tr>
<td>Moderate reduction, 40%-60% predicted</td>
<td>8/9 (89)</td>
<td>6/9 (67)</td>
<td>≤2 to 7</td>
</tr>
<tr>
<td>Severe reduction, &lt;40% predicted</td>
<td>3/3 (100)</td>
<td>3/3 (100)</td>
<td>0 to 1</td>
</tr>
</tbody>
</table>

Abbreviations: CT, computed tomography; DLCO, diffusing capacity for carbon monoxide; ILD, interstitial lung disease.

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It should be noted that 2 patients with ILD in this study had a recent history of methotrexate (a drug that can cause
One patient stopped the methotrexate treatment (after 2 months of use) owing to alopecia and elevated liver function test results several weeks before her CT showed ILD. She had already been dyspneic for at least 6 months before starting the methotrexate treatment. The other patient discontinued methotrexate treatment within a few weeks after her ILD diagnosis (after 1 year of use). Given the rarity of methotrexate-induced ILD (especially chronic ILD) and the time course of these patients’ ILD (chronic symptom onset with no response to methotrexate regimen discontinuation), DM was thought to be a much more likely cause of the ILD than the methotrexate. However, because ILD secondary to DM and methotrexate-induced ILD can be clinically indistinguishable and are both diagnoses of exclusion, we cannot rule out the possibility that methotrexate was at fault in these 2 patients.

We found no significant difference between the mean number of skin manifestations seen in patients with and without lung abnormalities ($P = .13$). In addition, we did not observe an increased prevalence of mechanic’s hands in patients with ILD ($P = .34$). The mechanic’s hands finding was of particular interest because this cutaneous finding has been previously associated with the antisynthetase syndrome (manifestations include antisynthetase antibodies [most commonly Jo-1 antibody], ILD, and myositis]. Given that all 50 of the 91 patients who were tested for Jo-1 antibodies had negative test results, we are not surprised that we did not observe an increased prevalence of mechanic’s hands in the patients with ILD. However, a prospective study using a reliable and validated measure of skin disease, such as the Cutaneous Dermatomyositis Disease Area and Severity Index, could more accurately discern correlations between skin and lung disease.

## Table 5. Clinical Characteristics of Patients With Interstitial Lung Disease (ILD) on Chest CT Scan

<table>
<thead>
<tr>
<th>Sex/Age, y</th>
<th>DM Type</th>
<th>Timing of Medications, months Post-ILD Diagnosis</th>
<th>Timing of Lowest DLCO, months Post-ILD Diagnosis</th>
<th>Timing of Final PFT Follow-up, months Post-ILD Diagnosis</th>
<th>DLCO at Final PFT, % Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>F/61 Early-treated ADM</td>
<td>GC: 3-37</td>
<td>3</td>
<td>46</td>
<td>40</td>
<td>65</td>
</tr>
<tr>
<td>F/68 HDM</td>
<td>mycophenolate mofetil: 9-present</td>
<td>5</td>
<td>24</td>
<td>49</td>
<td>33</td>
</tr>
<tr>
<td>F/62 CDM</td>
<td>GC: &lt;0.5-present</td>
<td>0</td>
<td>60</td>
<td>9</td>
<td>65</td>
</tr>
<tr>
<td>F/54 Early-treated ADM</td>
<td>Unknown</td>
<td>11</td>
<td>39</td>
<td>40</td>
<td>44</td>
</tr>
<tr>
<td>F/64 ADM</td>
<td>GC: 0-present</td>
<td>0</td>
<td>37</td>
<td>9</td>
<td>79</td>
</tr>
<tr>
<td>F/48 Early-treated ADM</td>
<td>GC: 27-44 (off and on)</td>
<td>49</td>
<td>35</td>
<td>49</td>
<td>35</td>
</tr>
</tbody>
</table>

Abbreviations: ADM, amyopathic dermatomyositis [DM]; CDM, classic DM; CT, computed tomography; CYC, cyclophosphamide; DLCO, diffusing capacity for carbon monoxide; GC, high-dose glucocorticoids; HDM, hypomyopathic DM; ILD, interstitial lung disease; PFT, pulmonary function test. See Table 1 for definitions of DM categories.

*The CT scans of the last 2 patients were possibly consistent with ILD (radiologist/pulmonologist read).

*All antifibrotics and immunosuppressives taken for at least 1 month between ILD diagnosis on CT and final ILD follow-up by PFT are listed.

*The patient was already taking this medication before the ILD diagnosis.

*After the ILD diagnosis, DLCO could not be measured owing to very low forced vital capacity during all PFTs except the final PFT. The lowest and only DLCO occurred at this final PFT.

*Lowest DLCO occurred before the ILD diagnosis.

ILD) use at the time that ILD was first diagnosed by CT. One patient stopped the methotrexate treatment (after 2 months of use) owing to alopecia and elevated liver function test results several weeks before her CT showed ILD. She had already been dyspneic for at least 6 months before starting the methotrexate treatment. The other patient discontinued methotrexate treatment within a few weeks after her ILD diagnosis (after 1 year of use). Given the rarity of methotrexate-induced ILD (especially chronic ILD) and the time course of these patients’ ILD (chronic symptom onset with no response to methotrexate regimen discontinuation), DM was thought to be a much more likely cause of the ILD than the methotrexate. However, because ILD secondary to DM and methotrexate-induced ILD can be clinically indistinguishable and are both diagnoses of exclusion, we cannot rule out the possibility that methotrexate was at fault in these 2 patients.
Another interesting finding in this study was that our patients with SDM had a very low prevalence of malignant disease. Although a recent literature review found a 14% prevalence of malignant disease in patients with clinically amyopathic dermatomyositis, only 1 of the 44 patients with SDM in this study (2%) had a malignant disease, which was a nonmelanoma skin cancer. Additional studies are needed to determine the necessity of screening for malignant disease in patients with DM without muscle symptoms.

A substantial percentage of patients with DM had a low DLCO of uncertain significance in the absence of CT findings consistent with ILD. Twenty-five percent of patients (95% CI, 15%-36%) fell into this category, with no prevalence differences between patients with SDM and those with CDM. Patients in the group with low DLCO of uncertain significance had a higher mean (SD) lowest DLCO (66% [11%] predicted) than the patients with CDM. Patients in the group with low DLCO of uncertain significance had a higher mean (SD) lowest DLCO than the patients with CDM (47% [12%] predicted; range, 24%-66%). Among patients with a low DLCO of uncertain significance, restrictive impairment on PFTs was uncommon (17%), whereas in the group of patients with ILD on CT, most (69%) had restrictive impairment on PFTs. Notably, 5 patients in the group with low DLCO of uncertain significance did not have a thin-section CT to rule out ILD, possibly because their DLCO values were not severely reduced (range, 60%-79% predicted).

Etiologies of a substantial reduction in DLCO in the absence of CT findings of ILD include early ILD and pulmonary hypertension. Pulmonary hypertension has a strong association with scleroderma, whereas there is not a well-recognized association with DM. However, measurement of pulmonary artery systolic pressure is needed to more definitively rule out pulmonary hypertension as an etiology for the isolated DLCO reductions observed in this study. Anemia and active cigarette smoking can also decrease DLCO, although the reduction is typically very small. While DM has no known association with anemia, and only 9% of patients in this study were current smokers, these variables may have contributed to DLCO reductions seen in individual patients. Although most studies of patients with DM do not address the population with a DLCO reduction in the absence of radiographic ILD, the authors of a recent prospective study of 9 patients with CDM and 14 with polymyositis reported that 33% of patients had an isolated reduction in DLCO. The authors noted that an isolated reduction of DLCO did not predict progression to restrictive lung disease but acknowledged that a larger study with longer follow-up is needed to assess the clinical significance of this finding. Such a study would ideally include patients with DM without clinically significant muscle disease.

Although this study is limited by the retrospective design and the small sample size, the findings of a high prevalence of both definite ILD and a low DLCO of uncertain significance are a cause for concern. These findings may justify screening all patients with DM with PFTs. Patients should be routinely questioned about dyspnea, but systematic screening of all patients is also important because using symptoms to diagnose ILD is notoriously unreliable in patients with connective tissue disease.

If a patient has a moderately or severely reduced DLCO (<61% predicted) on initial testing, we recommend obtaining a high-resolution CT scan of the chest and referring the patient to pulmonary specialists for further management. Based on our data, it seems reasonable that those with a mild reduction of DLCO (61%-75% predicted) should also have a high-resolution CT scan to assess for ILD, but if the findings are negative, following these patients closely with serial PFTs and monitoring for clinical symptoms of ILD (cough, dyspnea) would be appropriate. Such patients should also be evaluated for pulmonary hypertension (via echocardiography and/or right heart catheterization) and anemia. In addition, it may be beneficial to obtain serial DLCO measurements for all patients with DM because this study demonstrates that DLCO values may drop over time, even in patients with normal or borderline low DLCO at initial measurement. However, many patients in this study did not have multiple measurements of DLCO, and a prospective study is needed to better establish the need for serial PFTs in patients with a normal DLCO at baseline.

Figure 3 summarizes our preliminary suggestions for initial screening and management of ILD and low DLCO in patients with DM.

Our recommendations for patients with DM are similar to the strategies generally used to manage those...
with scleroderma. Pulmonary function tests with DLCO are the most common method for screening patients with scleroderma and no pulmonary symptoms for ILD and pulmonary hypertension.21 Diffusing capacity for carbon monoxide, which is a predictor of mortality in patients with scleroderma, is also commonly used to monitor disease progression in patients with known pulmonary abnormalities and to serially screen patients without pulmonary symptoms or known pulmonary abnormalities.22-24 A combination of high-resolution CT and PFTs with DLCO is typically used for diagnosis of suspected ILD.25

Treatment of patients with established ILD will be predominantly managed by pulmonary specialists. However, the question of whether to treat patients with isolated reductions in DLCO is controversial and may be decided by dermatologists or rheumatologists. In our experience, some patients with isolated low DLCO (in the absence of radiologic ILD) who are given immunosuppressants such as mycophenolate mofetil or azathioprine for their skin and/or muscle disease experience improvement on repeated testing of DLCO. Given the uncertain clinical significance and natural history of an isolated reduction in DLCO, we cannot make recommendations regarding treatment. However, if a low DLCO is indicative of early ILD and can be reversed before clinically significant fibrosis occurs by immunosuppressants with relatively few adverse effects, intervention at an early stage could be crucial.

This retrospective study was limited by missing data. Because many patients did not have serial DLCO measurements, it is difficult to make definitive recommendations for serial DLCO screening. In addition, few patients with low DLCO values had echocardiography with estimation of pulmonary artery systolic pressure to evaluate for pulmonary hypertension, and 5 of the 42 patients with low DLCO values did not have thin-section CT scans to assess for ILD. Furthermore, we had to rely on reports of chest CT scans because the images were not available, and PFTs lacked standardization because they were performed in a variety of laboratories. We also had to use DLCO values that were not corrected for hemoglobin because few PFT laboratories performed this correction. In addition, although to our knowledge this is one of the largest studies of patients with SDM in the literature, our sample size was limited by the rarity of this disease, and our statistical power may have been inadequate to show differences between the lung disease seen in patients with CDM and those with SDM. Larger studies would also help discern whether male patients or patients with overlap connective tissue diseases are at a higher risk for ILD. Although these groups seemed to have a high prevalence of ILD in this study, this observation was not statistically significant (P = .12, overlap connective tissue disease; P = .12, males). Our results may also reflect selection bias because all of our patients were seen at a single university hospital referral center.

Multicenter prospective studies of patients with DM are needed to more accurately characterize the prevalence and course of ILD, the natural history of an isolated reduction in DLCO, and the effect of immunosuppressants on this history. Our retrospective study does not enable us to determine whether early detection and treatment of ILD or a low DLCO affects the clinical outcome. An ideal observational study would include serial PFTs with DLCO and high-resolution CT of the chest, functional pulmonary studies (eg, the 6-minute walk), systematic assessment of skin disease activity and pulmonary symptoms, and documentation of pulmonary artery systolic pressure and hemoglobin level. Randomized controlled interventional studies assessing the effect of immunosuppressants on ILD and isolated DLCO reductions will be complicated to perform because the same medications are used to treat skin, muscle, and lung disease in patients with DM, but such trials are needed to determine optimal management.

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Author Contributions: Dr Werth had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Morganroth, Kreider, and Werth. Acquisition of data: Morganroth, Okawa, and Werth. Analysis and interpretation of data: Morganroth, Kreider, Taylor, and Werth. Drafting of the manuscript: Morganroth, and Werth. Critical revision of the manuscript for important intellectual content: Morganroth, Kreider, Okawa, Taylor, and Werth. Statistical analysis: Morganroth, Taylor, and Werth. Administrative, technical, and material support: Morganroth, Kreider, Okawa, and Werth. Study supervision: Morganroth, Kreider, Okawa, and Werth.

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REFERENCES


However, all anogenital dysplasias (anal, cervical, vaginal, and vulvar) remained unchanged.

Comment. Previous evidence has indicated that prophylactic HPV vaccination does not accelerate HPV clearance and therefore is not recommended to treat prevalent infections. In line with this, we did not observe any relevant changes in the patient’s HPV spectrum 6 months after the last vaccine dose. Moreover, using a previously published multiplex HPV serologic assay based on HPV-L1 glutathione-s-transferase fusion proteins, we did not find any substantial increases of type-specific antibodies before or after HPV vaccination (no antibodies against HPV-16, -18, or -57 before or after vaccination; and no increase in median fluorescence intensities for HPV-6, -11, or -52). Although the mechanism by which a prophylactic HPV vaccine against HPV-6, -11, -16, and -18 induced regression of HPV-57–positive warts remains unclear, alterations of the local cytokine microenvironment and/or induction of interferon-γ-producing CD4+ T cells or CD8+ cytotoxic T lymphocytes could be involved, as observed in therapeutic HPV vaccination with synthetic long peptides. Since HPV-57 (belonging to HPV genus alpha-4) is not closely related to HPV-6 and HPV-11 (both HPV genus alpha-10), HPV-16 (genus alpha-9), or HPV-18 (genus alpha-7), the non-HPV constituents of the vaccine may play a role.

Future investigations are warranted to elucidate the mechanisms that lead to wart clearance following quadrivalent HPV vaccination in the 2 reported patients. We agree with Venugopal and Murrell that this interesting observation should encourage the initiation of prospective, placebo-controlled studies on the efficacy of quadrivalent HPV vaccination to treat cutaneous warts, especially in immunosuppressed people who are particularly susceptible to recalcitrant and persistent disease. Such studies could also rule out accidental temporal association of 2 unrelated events.

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