Pulmonary Manifestations of the Idiopathic Inflammatory Myopathies

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KEYWORDS

- Myositis • Pulmonary complications
- Interstitial lung disease

The idiopathic inflammatory myopathies (IIMs) are chronic, acquired, autoimmune disorders causing muscle weakness due to skeletal muscle inflammation. Based on clinical, histopathologic, and immunologic features, IIMs have been classified into 3 general subtypes including polymyositis (PM), adult and juvenile dermatomyositis (DM), and inclusion body myositis (IBM). However, overlap syndromes of myositis with other connective tissue diseases (CTD) and malignancy-associated myositis also occur under the rubric of IIM. These subsets of IIM are characterized by proximal muscle weakness, elevation of serum muscle enzymes (most commonly creatine kinase [CK]), electromyographic features of myopathy, and inflammatory cell infiltrates in muscle tissue. Patients manifesting any of several characteristic rashes are classified as having DM (**Fig. 1**); and various organs may be involved in PM or DM including the lungs, heart, gastrointestinal tract and joints. Many investigators include amyopathic dermatomyositis (ADM) with the IIM as a potentially distinct category; these patients have skin findings consistent with DM but no muscle involvement. This review focuses on the pulmonary manifestations seen in the inflammatory myopathies, and here the term myositis or PM-DM is used interchangeably with IIM.

CLASSIFICATION AND EPIDEMIOLOGY

Many classification systems have been suggested in IIM. Bohan and Peter[1,2] proposed the 5 criteria already mentioned for the diagnosis of PM and DM, which are still used today; Dalakas and Hohlfeld[3] suggested new criteria based on immunohistochemical and pathologic features. The subsequent discovery of autoantibodies associated with the myositis syndromes led to a different classification scheme incorporating serologic features.[4] The Bohan and Peter criteria have come under considerable scrutiny,[1,2] and myositis investigators are currently pursuing efforts to update IIM classification criteria.[5] **Table 1** compares the 2 classification systems, the original Bohan and Peter classification and the later proposal relying on immunohistochemistry.

IIM is a rare disease, with an overall incidence ranging from 2 to 10 new cases per million persons at risk per year in various populations.[6–10] The prevalence and incidence may be increasing as a result of better physician awareness and the availability of laboratory tests. Although inflammatory myopathy can occur at any age, there are childhood and adult peaks with a 3:1 to 4:1 Afro-American to Caucasian ratio of incidence.

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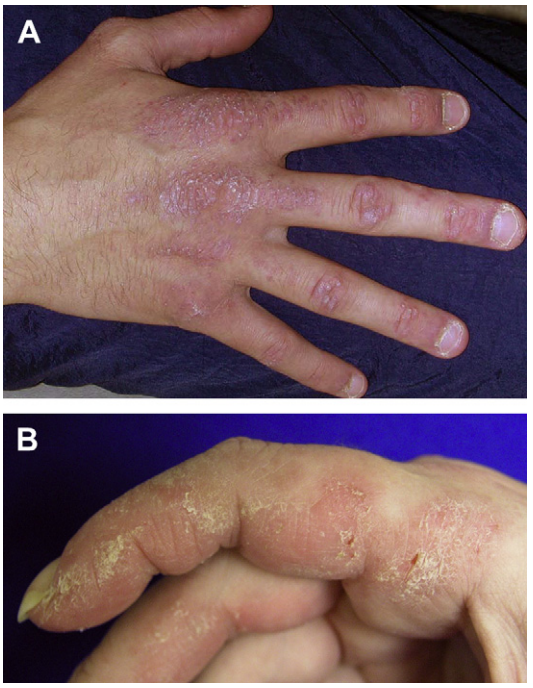

Fig. 1. (*A*) DM-associated rashes. Extensor erythema over the knuckles and interphalangeal joints of a patient with DM consistent with Gottron papules. (*B*) DM-associated cutaneous features. "Mechanic's hands" in a patient with the anti–Jo-1 autoantibody. Erythema, hyperkeratosis, and cracking of the lateral aspects of the fingers is noted.

IMMUNOPATHOGENESIS OF THE MYOSITIS SYNDROMES

The pathogenesis of myositis is incompletely understood. The presence of T cells and B cells in muscle tissue, the finding of serum autoantibodies in many patients, and the coexistence of myositis with other autoimmune diseases certainly support an immune-mediated cause. The spectrum of myositis is thought to be triggered by environmental (eg, infectious agents such as viruses) factors in individuals with a genetic predisposition to autoimmunity. Many recent reports strongly support this genetic component in the immunopathogenesis of myositis, as there are significant correlations of HLA class II haplotypes with clinical and serologic profiles in large cohorts of primarily Caucasian patients with myositis.[11–13] Histopathologic changes in muscle provide strong evidence for autoimmunity in PM and DM. In PM, the myofiber appears to be the target of immunologic attack because non-necrotic fibers are surrounded and invaded by mononuclear $CD8^+$ T cells (**Fig. 2**). These fibers demonstrate major histocompatibility complex (MHC) class I expression suggesting that the pathology of PM is mediated by the recognition of a surface antigen on the muscle fiber by antigen-specific T cells (**Fig. 3**). On the contrary, DM is thought to be more humorally mediated, with the blood vessel being the

Table 1
Diagnosis of PM-DM

Criteria	Features	Diagnosis
Bohan and Peter (1975)[1,2]	1. Symmetric proximal muscle weakness 2. Elevated serum muscle enzymes 3. EMG consistent with myopathy 4. Muscle biopsy with characteristic features 5. Typical rash	1–4 criteria present: definite PM Any 3 of 1–4 present: probable PM Any 2 of 1–4 present: possible PM Rash + any 3 of 1–4: definite DM
Dalakas and Hohlfeld[3]: emphasis on histology and immunopathology	1. Subacute proximal muscle weakness 2. Elevated serum muscle enzymes 3. Muscle biopsy 4. Typical rash	Criteria 1,2 with muscle biopsy showing inflammation with CD8/MHC-I complex and no vacuoles: definite PM Criteria 1 and 2 with muscle biopsy showing MHC-I expression without T cells or vacuoles: probable PM Rash + muscle biopsy: definite DM No rash + typical biopsy: probable DM Rash without muscle weakness: ADM

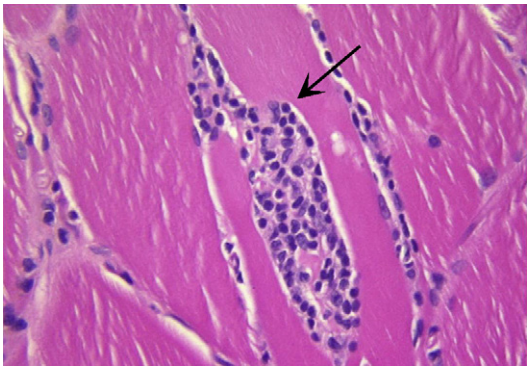

Fig. 2. Muscle biopsy (H&E stain) in PM. Invasion of a non-necrotic muscle fiber by lymphocytes in a patient with PM.

immunologic target. $CD4^+$ T cells and B cells are more common with complement activation, leading to C5-9 membrane attack complex deposition in muscle capillaries. Antinuclear or anticytoplasmic autoantibodies are found in up to 90% of patients with PM or DM and are useful in defining clinically homogeneous subsets of patients.[14] Myositis-specific autoantibodies (MSAs) have been previously reported to occur exclusively in IIM but have been detected in patients without evidence of myositis (**Table 2**).[15] A negative antinuclear antibody test does not exclude an MSA because the antigens targeted by these autoantibodies may be cytoplasmic in location. Autoantibodies seen in other CTD may also be found in patients with myositis and are termed myositis-associated autoantibodies (MAA). Of relevance to the pulmonary problems seen with myositis is anti–Jo-1, which is directed against histidyl-tRNA synthetase, one of a group of antiaminoacyl-tRNA synthetases. The clinical associations of the various antisynthetase antibodies are similar

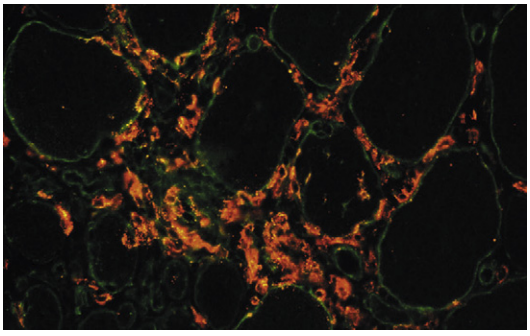

Fig. 3. MHC-I/CD8 complexes in PM. MHC-I is upregulated on all muscle fibers (*green*). $CD8^+$ T cells that also express MHC-I invade muscle fibers. (*From* Dalakas MC, Hohlfeld R. Seminars: polymyositis and dermatomyositis. Lancet 2003;362:974; with permission.)

and comprise the ''antisynthetase syndrome'' that includes myositis, fever, Raynaud phenomenon, ''mechanic's hands'' (cracking and hyperkeratosis of the lateral surfaces of the fingers), polyarthritis, and interstitial lung disease (ILD).[4]

LUNG AND MYOSITIS

The lung is the most common extramuscular organ involved in PM-DM. Pulmonary complications occur in more than 40% of patients, causing significant morbidity and mortality.[16] Complications include ILD, aspiration, pneumonia, drug-induced lung diseases, and nonparenchymal problems such as ventilatory (diaphragmatic and intercostal) muscle weakness. However, ventilatory muscle weakness leading to respiratory failure or significant dyspnea is uncommon, occurring in less than 5% of patients.[4,17] Pulmonary disease may be observed in patients without overt muscle involvement.[18] Beyond these issues, parenchymal lung involvement may include pulmonary arterial hypertension and diffuse alveolar hemorrhage with pulmonary capillaritis, the latter being uncommon but frequently fatal.[19] On the other hand, pneumomediastinum and pneumothorax are being increasingly reported, and may be associated with rapidly progressive ILD even in the setting of ADM (see **Table 2**).[20,21]

NONPULMONARY CAUSES OF DYSPNEA

Muscle Weakness

Respiratory failure due to respiratory muscle weakness is a rare complication in adult PM, the prevalence of which is unknown.[22,23] Chronic respiratory failure has been described in patients with advanced myositis and a history of dysphagia. Only 4 cases with acute respiratory failure due to respiratory muscle weakness have been reported.[22] Patients without obvious parenchymal lung involvement or respiratory complaints may show a higher than expected proportion of diaphragmatic abnormalities. The standard pulmonary function tests (PFTs) may be unremarkable, with only reduced inspiratory or expiratory pressures.[24] With progressive disease restrictive physiology is seen, showing low total lung capacity and vital capacity, and low maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP),[25] with normal forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC), diffusion, and alveolar-arterial oxygen tension difference. Supine respiratory function tests are useful for clinical diagnosis and respiratory risk stratification. The critical predictive parameters include respiratory muscle strength

Table 2
Lung in myositis

Lung Disease in Myositis	Diagnosis	Prevalence (40–65%)
Parenchymal disease	Aspiration pneumonia	17%
	Infectious pneumonia	
	ILD	5%–65%
	Drug-induced ILD	
	PAH	
	Diffuse alveolar hemorrhage	
	Pneumomediastinum	
	Pneumothorax	
Nonparenchymal disease	Ventilatory failure	<5%

(MIP and MEP) less than 30% of predicted and vital capacity less than 55% predicted.[26] In one study, the most severe degree of diaphragmatic dysfunction was found in DM.[24] The presence of diaphragmatic weakness may also be an independent risk factor for sleep-disordered breathing and for respiratory failure.

Cardiac Causes

Serious cardiac involvement in IIM is unusual, but dyspnea is a common symptom from any of the several cardiac issues. Congestive heart failure,[27] left ventricular diastolic dysfunction, coronary artery disease, and arrhythmias may contribute to dyspnea. Pulmonary edema due to myocarditis and/or cardiomyopathy usually occurs together with active muscle disease; subclinical cardiac manifestations of myositis include various conduction blocks and occasionally atrial or ventricular arrhythmias.[28]

PULMONARY CAUSES OF DYSPNEA

Infections Including Aspiration Pneumonia

Infectious complications have been reported in up to 26% of patients resulting in an increased mortality rate.[29] Immunosuppressive medications have been implicated, with most patients developing lung infections in the first year following diagnosis. In a study of 156 patients with PM-DM, 33% of the cohort developed infectious complications led by aspiration pneumonia (17%), opportunistic infections (11.5%), septicemia, and pneumonia (2% each). *Pneumocystis jiroveci* and *Candida albicans* were responsible for 50% of all infections while *Pseudomonas* and *Staphylococcus* were common organisms in patients with pneumonia. Predisposing factors include dysphagia, lymphopenia, low serum total protein, thoracic muscle myopathy,[30] and concurrent immunosuppressive therapy.[29]

Interstitial Lung Diseases

ILD is a common manifestation in IIM with a prevalence of 5% to 65%, varying depending on the means of detection.[31] In an enriched population of 90 Jo-1 antibody positive patients with clinical, radiographic, and pulmonary function data, 77 (86%) met criteria for ILD.[32] ILD is an important prognostic factor and may cause life-threatening complications. Myositis-associated ILD (MA-ILD) can precede, occur concomitantly with, or present after the diagnosis of IIM.[31] The clinical presentation is variable because patients may be asymptomatic, present acutely, develop rapidly progressive respiratory failure, or follow a subacute or chronic course.

In a study of 36 patients with ILD, most (58%) had a chronic course, 25% were asymptomatic at diagnosis, and 17% presented with acute respiratory failure. ILD was diagnosed concomitantly with skin and muscle disease in 42% of the patients and preceded IIM in 19% of the patients.[33] The most common symptom was dyspnea, followed by cough. Acute ILD is more frequently seen in DM, particularly the ADM subset. A prospective study from Sweden identified 11 of 17 (65%) new PM and DM patients over a 2.5-year period with lung disease, 18% of whom had subclinical ILD.[34] Of note, DM-associated ILD (DM-ILD) may be more commonly associated with diffuse alveolar damage (DAD) and be more resistant to treatment and progressive,[35] reflecting pulmonary histologic differences and high-resolution computed tomography (HRCT) findings that may further distinguish PM from DM.[36,37] Joint symptoms, anti–Jo-1 positivity, and older age at onset predict ILD in patients with myositis.[38] In a retrospective Korean study of 72 patients with myositis, a Hamman-rich like presentation, features of ADM, and an initial FVC less than or equal to 60% were predictive of poor prognosis.[39] In addition, the concomitant finding of

anti-Ro/SSA autoantibodies in patients with an antisynthetase antibody may be associated with more severe and progressive ILD.[40,41] Another study demonstrated that poor survival rate corresponds to an initial bronchoalveolar lavage (BAL) showing neutrophilic alveolitis.[42]

The most common histologic subtype reported in myositis is nonspecific interstitial pneumonia (NSIP).[42,43] Other histologic subtypes in MA-ILD include usual interstitial pneumonia (UIP), DAD, and organizing pneumonia (OP)[31,33,44] (**Fig. 4**). Lymphocytic interstitial pneumonitis is uncommon,[43,45] and only 1 of 17 biopsies was positive for this histology.[43] A new histologic pattern, acute fibrinous and organizing pneumonia, has been described in 17 reported cases, of which one had PM. This subgroup should also be taken into consideration.[46]

Pulmonary Hypertension

Pulmonary hypertension (PH) is poorly defined and is limited to case reports in IIM.[45,47] Patients typically present with exertional dyspnea, restriction on PFTs, or an isolated reduction in the diffusion capacity. PH seems to be predominant in the female population, and in one autopsy series, 4 of 20 patients with myositis had medial hypertrophy in the pulmonary artery.[48] Progressive pulmonary fibrosis may lead to severe PH that is poorly responsive to vasodilator therapy. Mortality is high despite treatment with immunosuppressive agents and vasodilators. Although a decreased diffusion on PFTs warrants an echocardiogram, the diagnosis should be confirmed by documentation of elevated pulmonary pressures by cardiac catheterization. Early referral for lung transplantation should be considered, given the grim prognosis.

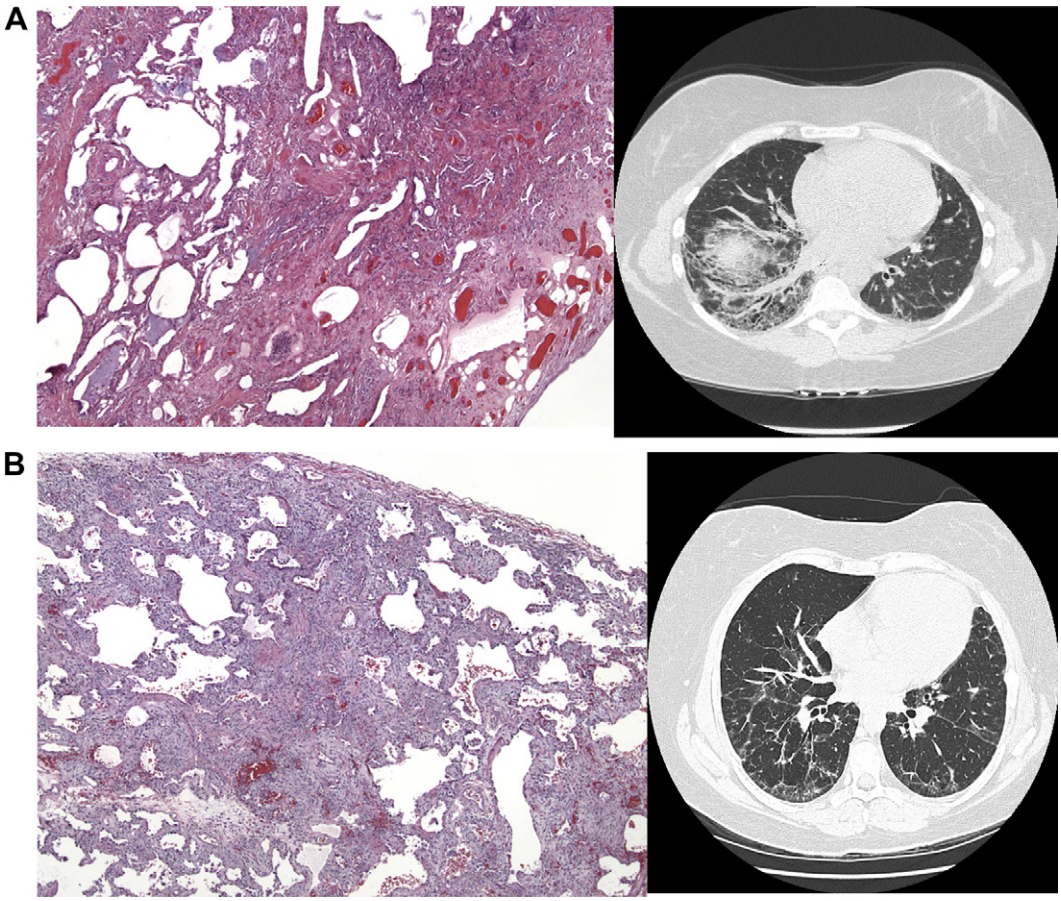

Fig. 4. Lung biopsy and CT images of MA-ILD. (*A*) H&E stained open lung biopsy (*left*) shows features of usual interstitial pneumonia (fibroblastic foci, mild inflammatory infiltrate, fibrosis and cystic changes); chest CT shows basal, peripheral honeycombing along with septal thickening. (*B*) H&E stained open lung biopsy (*left*) shows features of diffuse alveolar damage (edema, protein exudate, and inflammatory cell infiltrate in the alveolar spaces and interstitium). Chest CT shows patchy, peripheral ground-glass opacities in the lower lobes.

Pneumomediastinum and Pneumothorax

Considered rare in other CTDs, pneumomediastinum and pneumothorax may occur early in myositis (including ADM) resulting from rupture of alveoli or pericardiac blebs. In one report, the investigators identified 62 patients with CTD-associated pneumomediastinum, of whom 80% had DM and nearly half had ADM.[21] Thus, ADM should be considered in the setting of ILD and pneumothorax/pneumomediastinum. Pneumomediastinum was treated symptomatically in all cases, but pneumothorax, seen in 4 patients, was treated with thoracic drainage followed by pleurectomy. Although 3 patients died, 7 patients had a favorable outcome with relatively mild impairment of their PFTs. Lung histology varied and the overall mortality was 34%, with a cumulative estimated survival of 55% at 2 years.

Drug-Induced Lung Diseases

Several immunosuppressive agents used to treat myositis have specific pulmonary toxicities. Cyclophosphamide can cause an early, acute interstitial pneumonitis that is generally reversible with discontinuation.[49] Chronic, low-dose therapy can cause irreversible fibrosis that presents after years of therapy.[49] Methotrexate-induced pneumonitis, accompanied by dyspnea, cough, and constitutional symptoms, has been reported in 2% to 7% of rheumatoid patients and is idiosyncratic, and often occurs within the first year of treatment.[50] The reported mortality rate is 17% with a recurrence rate of 50%.[51]

DIAGNOSIS OF LUNG DISEASE IN MYOSITIS

Pulmonary Function Tests

PFTs are necessary for diagnosis, long-term follow-up, and monitoring the response to therapy. Restrictive impairment is characterized by a decrease in total lung capacity (TLC), functional residual capacity (FRC), FVC, FEV_1, diffusion lung capacity for carbon monoxide (DLCO) and a normal or increased FEV_1/FVC. Respiratory muscle weakness can also cause a reduction in TLC and FVC, but measurement of the MIP and MEP distinguishes it from restriction due to ILD.

Radiography

HRCT scanning correlates well with the open lung biopsy findings.[31] The most common HRCT pattern in PM or DM involves reticular and/or ground-glass opacities with or without consolidation and without honeycombing, correlating best with underlying NSIP histology.[17] The ground-glass opacities are potentially treatment-responsive inflammatory conditions with a more favorable prognosis.[52] With treatment, serial computed tomography (CT) scans show improvement in opacities and limited fibrotic progression.[53] ''Honeycombing,'' which corresponds to fibrosis, is less amenable to anti-inflammatory or immunosuppressive therapy.[52] Of the 32 retrospectively studied anti–Jo-1 positive patients who had HRCT, 15 (47%) presented acutely with respiratory insufficiency, whereas 17 (53%) had a more gradual onset of ILD symptoms.[54] Fever and HRCT findings of diffuse ground-glass opacities were common in the acute-onset group, contrasting with the gradual-onset patients in whom neutrophil-predominant BAL fluid and non–Jo-1 autoantibodies were characteristic along with traction bronchiectasis and honeycombing on CT. Although patients in the acute-onset group had a better initial treatment response at 3 months, they ultimately had more long-term ILD progression requiring combined therapy. Chest radiographs are less sensitive than HRCT; **Fig. 5** shows basal predominant alveolar infiltrate in a Jo-1–positive patient with acute dyspnea.

However, outcomes may not always correlate with the varied HRCT patterns that may be seen in PM and DM, as evidenced by a retrospective study showing a fatal outcome in DM-associated ILD characterized by ground-glass attenuation and reticular opacities without significant fibrosis.[36] When changes on HRCT are seen in the setting of normal PFTs, their clinical significance and outcome is not known.

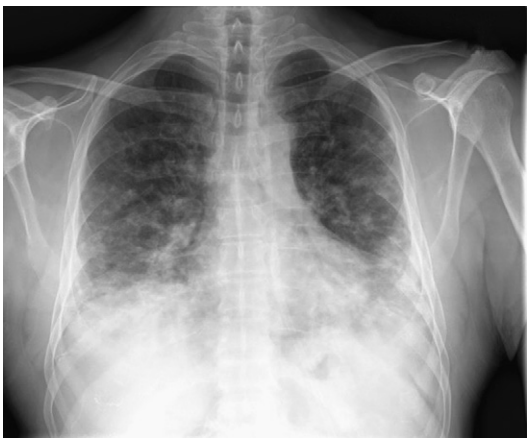

Fig. 5. Chest radiograph in IIM-ILD. Radiograph shows bilateral, basal, predominant alveolar opacities in a Jo-1–positive PM patient with acute-onset dyspnea and subsequent ARDS. (*Courtesy of* Chester V. Oddis, MD, Pittsburgh, PA.)

Bronchoalveolar Lavage

BAL, mostly done to rule out infection in the setting of MA-ILD, primarily reveals $CD8^+$ T cells and a minor B-cell component.[17] One report notes increased $CD8^+$ and CD 25^+ T cells in a corticosteroid-resistant group, while the CD4/CD8 ratio was not significantly different between steroid-sensitive and steroid-resistant patients.[55] Protein expression in BAL fluid was significantly different in the 3 subgroups of 11 patients with myositis and overlap syndrome, suggesting that a proteomic approach may provide pathogenic clues to MA-ILD.[56]

Lung Biopsy

Tissue biopsy may not be necessary if there are classic findings on HRCT.[57] When performed, surgical lung biopsies are preferred to transbronchial specimens because of the patchy nature of the disease. The histopathology was discussed earlier,[38,42,44] but different patterns may coexist, as reported retrospectively in a review of 13 patients.[44]

Biomarkers for ILD

The strongest predictor of ILD is the presence of anti–Jo-1, directed against histidyl-tRNA synthetase, one of a group of antiaminoacyl tRNA synthetases (**Table 3**). The prevalence of ILD in this group approximates 70% in synthetase-positive patients.[4,34] The clinical associations of the various antisynthetase antibodies are similar and have been described as comprising the ''antisynthetase syndrome,'' but the reason for such patients having such a high frequency of lung involvement is poorly understood. One thought-provoking observation is that a proteolytically sensitive conformation of histidyl-tRNA synthetase exists in the lung, suggesting that an immune response to this antigen may be initiated and propagated in this tissue.[58] Similarly, the occurrence of shared T-cell receptor gene segment usage in the muscle and lungs of a small group of IIM patients (some with the Jo-1 autoantibody) could indicate a common target antigen in these organs.[59] Multiplex enzyme-linked immunosorbent assays (ELISAs) have demonstrated disease-specific associations between anti–Jo-1 antibody positive ILD and serum levels of interferon-γ–inducible chemokines.[32]

Other peripheral blood markers indicating lung involvement include antiendothelial antibodies, found in 20 of 56 patients with myositis and 10 of 15 with ILD.[60] The concentration of KL-6, a mucinous glycoprotein expressed on type II pneumocytes and bronchiolar epithelial cells, decreases with treatment in adults with myositis and children with JDM.[61] Cytokeratin 19 fragment, a cytoskeletal structural protein of bronchial epithelial cells, was significantly increased in the serum of patients with myositis who have ILD; it correlated with DAD and fluctuated with ILD progression or improvement.[62] Serum surfactant protein D, a phospholipid and protein moiety that

Table 3
Clinical profile of myositis-specific antibodies

Antisynthetase	Antigen	Clinical Profile	Prevalence
Anti–Jo-1	Histidyl-tRNA synthetase	Antisynthetase syndrome (AS)	20%
Anti-PL 7	Threonyl-tRNA synthetase	AS; milder myositis	5%–10%
Anti–PL-12	Alanyl-tRNA synthetase	AS; ILD > myositis	1%–5%
Anti-EJ	Glycyl-tRNA synthetase	AS: ILD > myositis	<5%
Anti-OJ	Isoleucyl-tRNA synthetase	AS; ILD > myositis	1%–5%
Anti-KS	Asparaginyl-tRNA synthetase	AS; ILD > myositis	1%–5%
Anti-YRS	Tyrosyl-tRNA synthetase	AS	<1%
Anti-Zo	Phenylalanyl-tRNA synthetase	AS; relapsing ILD	1%
Other MSA Anti-SRP Anti–Mi-2	SRP–intracytoplasmic protein translocation Helicase protein	Acute necrotizing myositis; cardiomyopathy DM with hallmark cutaneous features, mild muscle disease, low risk of ILD, good response to treatment	<1% <10%
Anti–CADM-140		Associated with cancer	Unknown

Data from Kalluri M, Sahn SA, Oddis CV, et al. Clinical profile of anti-PL-12 autoantibody: cohort study and review of the literature. Chest 2009;135(6):1550–6; and Gunawardena H, Betteridge ZE, McHugh NJ. Myositis-specific autoantibodies: their clinical and pathogenic significance in disease expression. Rheumatology (Oxford) 2009;48(6):607–12.

covers the alveolar surface, was found to be a useful marker for ILD when assayed in patients with PM and DM.[63]

The antisynthetase antibodies, in particular anti–Jo-1 anti–PL-12, have been strongly associated with ILD. Two recently published studies on anti–PL-12 confirmed this association, as the presence of anti–PL-12 was associated with ILD more than myositis.[64,65] In a Japanese study of 64 PM-DM and 28 IPF patients, the prevalence of antisynthetase autoantibodies was 51%, and 96% of antibody-positive patients had ILD, again suggesting that presence of antibody is a stronger marker of ILD than myositis in PM-DM.[66] In addition, the antibody-positive subset required immunosuppressive agents in addition to prednisone.

TREATMENT

The optimal treatment for MA-ILD remains to be determined. There are no controlled trials of any agents for ILD, but the standard therapeutic approach includes corticosteroids to which 50% of patients may respond favorably.[67] Patients with DM and normal CK levels tend to be resistant to corticosteroid therapy and have a poor survival compared with MA-ILD patients with an elevated CK.[68] Other immunosuppressive or immunomodulatory agents used to treat ILD include cyclophosphamide,[69–71] azathioprine,[72,73] methotrexate,[42] cyclosporine,[68,74] intravenous immune globulin (IVIg), and plasma exchange (**Table 4**).[75,76] IVIg was used in a small number of patients with refractory ILD and an acute presentation.[76] Calcineurin inhibitors have also demonstrated consistent efficacy. Cyclosporine inhibits interleukin-2 production and T-cell proliferation, and may be an appropriate choice for early, slowly progressive, nondiffuse ILD. Tacrolimus, which is 100 fold more potent than cyclosporine in inhibiting T-cell activation, was efficacious in several case series of patients, including those refractory to cyclosporine and in patients with ILD associated with antisynthetase autoantibodies.[35,77,78] Tacrolimus may have a more favorable safety profile than cyclosporine. Mycophenolate mofetil (MMF), an antimetabolite, not only disrupts T-cell activation via inactivation of inosine monophosphate dehydrogenase but also interferes with fibroblast activity, proliferation, and release of profibrotic cytokines such as transforming growth factor-β.[79,80] MMF has potential efficacy in reversing progression or stabilization of disease activity in CTD-ILD including MA-ILD.[80,81]

Early administration of aggressive therapy may be beneficial in a select subgroup of patients. There is increasing evidence that cyclosporine may induce a response and prolong survival, but most of these studies are retrospective case series or open-label trials.[68] Combination therapy is often used. One study of chronic ILD compared 23% of the patients treated with prednisone with 77% of the patients who were given combination immunosuppressive therapy; after 6 months, the improvement in FVC in the latter group was statistically better and was maintained for up to 3 years.[82]

PROGNOSIS

In a study by Marie and colleagues,[33] the survival of IIM-associated ILD was reported to be 94%, 90%, and 87% at 1, 3, and 5 years, respectively. This rate is similar to that reported for idiopathic NSIP. The presence or absence of anti-Jo-1 did not influence survival in this group of 36 patients with PM or DM-ILD. The predictors of poor outcome include: acute presentations; neutrophilic alveolitis[33]; initial DLCO lesser than 45%; FVC lesser than or equal to 60%[39]; DM, microangiopathy and digital infarcts in DM, ADM[39,83]; and histologic UIP.[31,33]

Table 4
Treatment of IIM-ILD

Drug/Dose	Outcome
Methotrexate (15–25 mg/wk by mouth or by injection)	Generally favorable results with myositis; rarely used for ILD
Azathioprine (2–3 mg/kg/d)	Used for myositis and ILD
Cyclosporine (2–5 mg/kg/d)	Efficacy reported in ILD
Tacrolimus—dose depends on trough level	Check drug levels; effective in refractory Jo-1 patients with ILD
Mycophenolate mofetil (1g twice a day)	Used for refractory DM rash; ILD
Cyclophosphamide (1–2 mg/kg/d by mouth or monthly intravenous pulse	Conflicting results; effective in ILD

In a study of 17 patients with biopsy-proven ILD and a median follow-up of 3.4 years, 5 died, 1 received lung transplant, and the survival rate at 5 years was 50%. The cause of death was progressive respiratory failure in all cases. The remaining 11 patients improved with combination immunosuppressive therapy. NSIP was seen in 65% of the cases.[35] Histopathology of ILD has prognostic value. NSIP and organizing pneumonia tend to have the best prognosis and respond to therapy, whereas UIP has intermediate prognosis and the worst outcomes are seen in DAD.[33,84]

SUMMARY

ILD is common in myositis and may precede the onset of CTD-related symptoms, so an early or occult rheumatologic disease should be considered in this setting. The relatively low incidence and prevalence of many forms of ILD has hampered attempts at performing adequately powered and soundly designed clinical trials to evaluate pharmacologic treatments for these disorders. More insight into the etiopathogenesis from ongoing clinical trials is likely, and additional well-designed prospective studies are necessary to answer the questions of optimal treatment strategies for all forms of autoimmune ILD.

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