Pulmonary involvement in polymyositis and dermatomyositis

Pulmonary complications play an important role in causing morbidity and mortality in myositis, and interstitial lung disease (ILD) has been reported in up to 65% of myositis patients. Clinical symptoms including cough and dyspnoea are common, but they are not reliable for ILD detection. The diagnosis should be based on pulmonary function tests, chest radiographs and high resolution computed tomography, which should all be regarded as standard procedures for the initial evaluation of all myositis patients. Biomarkers, in particular anti-aminoacyl tRNA synthetase antibodies, have been demonstrated to be useful in predicting the risk of ILD in patients with myositis. Glucocorticoids remain the mainstay of therapy in adult polymyositis and dermatomyositis patients with ILD, but most patients fail to fully respond to this treatment and require additional immunosuppressives such as methotrexate, cyclophosphamide, azathioprine and ciclosporin A. Other treatment options include intravenous γ-globulins, tacrolimus and CD20 monoclonal antibodies. Myositis is closely related to the antisynthetase syndrome, which also includes manifestations such as ILDs, arthritis, Raynaud's phenomenon, fever and mechanic's hands. In this syndrome, ILD is often the first manifestation of a chronic inflammatory disease. There is now also accumulating data to support a role of a T-cell- and B-cell-mediated immune response in the development of ILD in patients with anti-tRNA synthetase autoantibodies.

KEYWORDS: autoantibodies, dermatomyositis, HRCT, interstitial lung disease, lung function tests, polymyositis

Göran Tornling[1], Maryam Fathi[1] & Ingrid E Lundberg[2†]

[†]Author for correspondence
[1]Unit of Respiratory Medicine and Allergy, Karolinska University, Sweden
[2]Rheumatology Unit, Karolinska University Hospital, SE-171 76 Stockholm, Sweden
Tel.: +46 851 776 087
Fax: +46 851 773 080
Ingrid.Lundberg@ki.se

The idiopathic inflammatory myopathies, collectively named myositis, are inflammatory connective tissue diseases that primarily affect skeletal muscle, with symmetrical muscle weakness in the proximal muscles of the arms and legs being characteristic clinical symptoms. Another typical finding is inflammatory cell infiltrates in muscle tissue. Based on some differences in clinical and histopathological features, three major subgroups have been identified: polymyositis (PM), dermatomyositis (DM) and inclusion body myositis. In addition, more recently a subset of DM has been described, clinically amyopathic dermatomyositis (CADM), where patients have the typical skin rash of DM but do not exhibit clinically manifested muscle symptoms [1]. Other organs are frequently involved, such as the lungs, joints, GI tract and heart, particularly in PM and DM, but less often in inclusion body myositis. One of the most common extramuscular manifestations in PM and DM is pulmonary involvement, which is the topic of this review.

Another way to subclassify patients with myositis is to use autoantibody profiles, as the presence of certain autoantibodies is associated with distinct clinical phenotypes [2]. Autoantibodies are frequently found in PM and DM, but less often in inclusion body myositis [3]. Positive antinuclear autoantibodies may be found in up to 80% of patients with PM or DM [4]. Autoantibodies in myositis patients are often subgrouped according to those that are also found in other inflammatory connective tissue diseases, so called myositis-associated autoantibodies such as Scl70, anti-Ro, anti-La and anti-U1RNP, and the so-called myositis-specific autoantibodies (MSAs) [2]. The MSAs are not totally specific for myositis, as some of them may also be found in patients with idiopathic interstitial lung disease (ILD), but they are rarely present in other rheumatic disorders. There are three categories of MSAs, and the most frequent are the anti-tRNA synthetase autoantibodies of which antihistidyl tRNA-synthetase antibody (anti-Jo-1) is the most common. Anti-Jo-1 is found in approximately 20–30% of PM or DM patients [3]. Other less frequently found antisynthetase autoantibodies are anti-PL-7 (antithreonyl synthetase), anti-PL-12 (anti-alanyl synthetase), anti-EJ (antiglycyl synthetase), anti-OJ (anti-isoleucyl-tRNA synthetase), anti-KS (anti-asparaginyl-synthetase), anti-Ha (antityrosylsynthetase) and the recently detected

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anti-Zo (antiphenylalanyl synthetase) [5]. Anti-Jo-1 autoantibodies are strongly associated with a clinical phenotype characterized by ILD, myositis, nonerosive arthritis, Raynaud's phenomenon and skin changes on the hands (so called mechanic's hands) [2]. This clinical phenotype has also been associated with other antisynthetase autoantibodies and was thus named antisynthetase syndrome. However, the full clinical syndrome is not found in all patients with anti-tRNA synthetase autoantibodies, but these autoantibodies rather seem to be markers of ILD as emphasized by the detection of the new anti-tRNA synthetase autoantibodies: anti-OJ, anti-ZO, anti-KS and anti-PL-12, which are primarily found in patients with ILD [5–8].

Anti-Mi-2 is another MSA, which is predominantly found in patients with DM and typical skin rash, and may reflect a good prognosis [2]. A third MSA is anti-SRP, which is a rare autoantibody and is associated with a subtype of myositis referred to as necrotizing myopathy based on histopathological changes with pronounced muscle fibre necrosis but sparse inflammation [9]. This subset seems to have a less favorable prognosis. These latter two autoantibodies have not been associated with pulmonary complications of myositis.

Pulmonary involvement in myositis

Pulmonary complications play an important role in causing morbidity and mortality in patients with PM and DM [10–12]. ILD is the most common direct pulmonary feature in myositis, and will be addressed below.

Pneumothorax, pneumomediastinum & subcutaneous emphysema

Pneumothorax, pneumomediastinum and subcutaneous emphysema are rare complications of primarily DM, and two different clinical pictures have been described in case reports. One is associated with severe ILD either with or without vasculopathy carrying high mortality, while the other shows signs of vasculopathy such as skin ulcers and bronchial wall necrosis with mild or no ILD, and has a favorable prognosis [13,14]. Thus, active pulmonary vasculitis should be suspected in myositis patients with these complications, and appropriate investigations and treatment should be undertaken. A review of published cases with DM and pneumomediastinum indicates that the best outcome was obtained when immunosuppressive agents were used, whereas the use of high-dose glucocorticoids alone was associated with poorer prognosis, and it was suggested that controlling disease activity with an immunosuppressive agent and progressive tapering of glucocorticoids was the most reasonable approach in these cases [14].

Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a life-threatening and debilitating complication of several connective tissue diseases, and has occasionally been reported in association with myositis. There are no studies systematically addressing the treatment of PAH in myositis, but long-term treatment with bosentan, an oral dual endothelin receptor antagonist, ET(A)/ET(B), has been reported to be effective in improving exercise capacity and pulmonary hemodynamics in patients with PAH related to connective tissue diseases [15]. Whether this is also applicable for myositis patients with PAH still needs to be determined.

Aspiration pneumonia

Aspiration pneumonia is not uncommon in patients with myositis, and was reported in 17.3% of the patients in a recent study [11]. The aspiration is caused by dysfunction of striated muscle of the pharynx and upper esophagus, resulting in loss of normal swallowing and regurgitation, and the majority of the affected individuals also complain of dysphagia. Patients with more extensive muscle and skin disease are reported to be at increased risk of developing this complication [16].

Respiratory failure caused by hypoventilation

Respiratory failure caused by hypoventilation due to severe weakness of the inspiratory and expiratory respiratory muscles has been regarded as an uncommon complication in myositis, but the prevalence of respiratory failure was reported to be as high as 21.8% in a large retrospective study of patients with PM and DM [11]. Lung function tests demonstrate reduced maximum inspiratory and expiratory pressures and restrictive lung function impairment – that is, reduced total lung capacity (TLC), increased residual volume, and the ratio of normal forced expiratory volume in 1 s versus forced vital capacity (FEV_1/FVC). Changes seen on chest radiographs are small lung volumes and basal atelectasis with elevation of the diaphragm. Since the cough reflex is reduced in patients with respiratory muscle weakness, atelectasis and pneumonia

may develop due to mucus plugging. In rare cases when muscle weakness does not respond to immunosuppressive treatment, home mechanical ventilation can improve the quality of life and even be life-saving in some cases [17].

Lung cancer

Lung cancer may, like other forms of malignancies, be associated with DM as a paramalignant phenomenon [18]. Although out of the scope of this review, it should be noted that after lung-cancer-targeted drug therapy, nearly complete disappearance of the myositis symptoms may occur [19].

Interstitial lung disease in myositis

ILD is the most frequent primary pulmonary lung complication in patients with adult PM and DM, and it contributes substantially to morbidity and mortality. Several reviews have recently been published on this topic [20–23].

Incidence of interstitial lung disease associated with myositis

The reported incidence of ILD in patients with myositis varies considerably based on which diagnostic tools have been used to detect the pulmonary involvement. As in other connective tissue diseases, systematic use of high-resolution computed tomography (HRCT) and bronchoalveolar lavage (BAL) for screening would certainly increase the reported incidence of ILD in myositis [24,25]. Furthermore, cross-sectional studies will tend to underestimate the risk of ILD, since the presence of pulmonary involvement can vary over time.

Earlier cross-sectional studies, using different criteria for patient selection and diagnostic methods, have reported an incidence between 5 and 46% [11,26–29]. In a recent retrospective investigation on 145 patients with myositis, it was concluded that the presence of clinical ILD, which was present in over 40% of the patients, was a significant risk factor for poor outcome [30]. In two recent studies of newly diagnosed patients with PM and DM, 65 and 78% of patients, respectively, were diagnosed with ILD defined as the occurrence of radiographic signs of ILD on chest radiographs and/or HRCT and/or restrictive ventilatory defects [31,32]. The high incidence of ILD in this study could be a result of the investigation examining all newly diagnosed patients with myositis, regardless of clinical lung symptoms, and some asymptomatic patients were detected with signs of ILD.

Although there are conflicting data on the prevalence rate of pulmonary involvement in patients with DM compared with PM [10,31–35], several recent studies have demonstrated that the incidence of ILD depends on the myositis phenotype, with higher incidence in DM than in PM [30,36,37].

Diagnosis of interstitial lung disease associated with myositis

Clinical symptoms

Coughing and dyspnoea are commonly reported and should alert further investigations. However, symptoms from the respiratory tract are not reliable for ILD detection in patients with myositis. In a recent study, 27% of the patients without any signs of ILD were asymptomatic, but of the patients without any signs of ILD on radiographs/HRCT, or reduction of lung volumes two-thirds had either coughs or dyspnoea [31].

Pulmonary function tests

Pulmonary function tests are essential not only for objective assessment of respiratory symptom, but also for estimation of disease severity and response to therapy. Typically, the patients demonstrate a restrictive ventilatory impairment, reduced functional residual capacity, residual volume, FEV_1, FVC and diffusing capacity for carbon monoxide (DLco), but with a normal or elevated FEV_1/FVC ratio. Not all of these abnormalities are reported in every patient, and normal pulmonary function tests do not exclude ILD.

It should be noted that decreased DLco is not specific for ILD in patients with myositis, but can also be seen in pulmonary hypertension, which can occur in patients with myositis as well as in other connective tissue diseases. Furthermore, myositis-associated respiratory muscle weakness can cause a similar reduction in lung volumes (TLC and FVC) to ILD. Reduction of maximal inspiratory pressure, maximal expiratory pressure and maximal voluntary ventilation indicate that respiratory muscle weakness is a contributing factor to the reduction in lung volume. Since the patients may have several different categories of pulmonary involvement, a careful evaluation should always be performed.

Chest radiographs

Chest radiographs are useful in screening for significant ILD, but have low sensitivity for detection of early disease. However, the easy access and low radiation dose provides the opportunity

for serial examinations to follow the course of the disease, and for the diagnosis of other pulmonary complications such as infections.

High-resolution computed tomography

HRCT of the lungs should be regarded as a standard procedure for the initial evaluation of all patients with suspected ILD. HRCT has higher sensitivity than chest radiographs for ILD detection, and is also of value for identifying the extent and severity of the disease. The most common pattern is irregular linear opacities with areas of consolidation and ground-glass attenuation. Honeycombing, an indication of 'end-stage lung', is not a common finding in patients with myositis [38–41]. Some studies have suggested that ground-glass opacities are more suggestive of active inflammation than of fibrotic disease. Although it is not always possible to ascertain the severity of fibrosis versus the severity of inflammation, HRCT may have implications for the choice of therapy. However, HRCT abnormalities are indistinguishable between patients with myositis and those with ILD of other etiology. It is thus important to consider other differential diagnoses such as drug-induced lung disease, infection and bronchoalveolar cell carcinoma, especially when results from HRCT are not typical for the disease.

Bronchoalveolar lavage

BAL has a limited role in the routine investigation of patients with myositis and suspected ILD, since the BAL cell profile is not specific for the diagnosis of parenchymal involvement in myositis. Although subclinical alveolitis assessed by BAL is reported in myositis as well as in other connective tissue diseases, the clinical significance is unclear [24]. It has been suggested that the BAL cell profile may give supportive information in the assessment of disease activity and prognosis, and similarly to the case in idiopathic pulmonary fibrosis, neutrophil-dominated alveolitis and increased eosinophil cell count may indicate progressive disease with poor prognosis, but this still needs to be confirmed [10,34]. However, BAL is a useful tool to identify other causes of ILD such as infections, drug-induced reactions and malignancy.

Histopathology

Histophathology by lung biopsy is not routinely performed in patients with myositis with signs of ILD, since open-lung biopsy is associated with morbidity [42]. Transbronchial lung biopsies are not helpful in distinguishing between histopathological patterns of ILD due to the patchy pattern of the disease and the small size of biopsies. Furthermore, it has been demonstrated that the pattern of abnormalities on HRCT is valid in predicting the histopathological appearance [43–46]. However, in some instances, transbronchial biopsies can be helpful, for example in the case of demonstrating granulomas or carcinoma. Moreover, transbronchial lung biopsies could also be of value for diagnosing opportunistic infections during immunosuppressive treatment.

Several different histopathological patterns of ILD, such as usual interstitial pneumonia, nonspecific interstitial pneumonia (NSIP), organizing pneumonia and diffuse alveolar damage (DAD) have been reported in patients with myositis and ILD [10,41,42,47]. Furthermore, patients with myositis-associated ILD tend to exhibit a mixture of histopathological patterns, and in a retrospective review of lung biopsies in patients with a diagnosis of PM and DM, more than one histopathological pattern of ILD was found in several patients [47]. A lung biopsy could potentially be helpful to determine the prognosis of ILD, since patients with organizing pneumonia and cellular NSIP tend to have a good response to glucocorticoid treatment, while patients with DAD have the worst prognosis with a high mortality rate, and patients with usual interstitial pneumonia have an intermediate course [10,42]. To date, it is not clear if, or how, the histological appearance should influence the choice of therapy in patients with myositis-associated ILD.

Biomarkers

Biomarkers, in particular anti-aminoacyl tRNA synthetase antibodies, have been demonstrated to be useful in predicting a risk for ILD in patients with myositis, and are found in many patients with myositis and ILD [2]. Anti-Jo-1 is detected in approximately 20–30% of patients with myositis, and the reported prevalence of ILD in patients with these antibodies is more than 70% [2,10,31]. There are also reports on patients with ILD and antisynthetase antibodies but without overt myositis, strengthening the association between these autoantibodies and ILD [48,49].

Other potential biomarkers for ILD in patients with myositis include Krebs Von den Lungen-6 (KL-6), a glycoprotein expressed on Type II alveolar pneumocytes and bronchiolar epithelial cells, and serum surfactant protein D [50–52]. Serum

levels of KL-6 and surfactant protein D have been found to be increased in patients with ILD associated with myositis, and the levels have shown an inverse correlation with pulmonary function tests such as FVC and DLco [52]. Furthermore, serum cytokeratin 19 fragment (CK-19), a structural component of bronchial epithelial cells, is associated with the presence of ILD and is correlated with disease activity in patients with myositis. In addition, patients with histopathological evidence of DAD had a higher level of CK-19 than patients with NSIP [53]. Furthermore, in patients with CADM, the presence of anti-CADM-140 autoantibodies has been associated with rapidly progressive ILD [54]. However, both the lack of routine analyses and insufficient validation against clinical outcome suggest that further investigations are needed before KL-6, surfactant protein D, CK-19 or anti-CADM-140 autoantibody analyses can be used in clinical practice as diagnostic or prognostic biomarkers for myositis-associated ILD.

Treatment of interstitial lung disease associated with myositis

Although glucocorticoids remain the mainstay of therapy in adult PM and DM patients with ILD, most patients fail to fully respond to this treatment and require additional immunosuppressive agents. Combinations of glucocorticoids and immunosuppressive agents such as methotrexate, cyclophosphamide, azathiopine and ciclosprorin A have often been reported as successful in case reports or case series [32,55–61]. However, evidence of efficacy from large prospective, randomized and controlled trials is lacking. In a recent retrospective study, a primary intensive approach of starting immunosuppressive agents simultaneously with glucocorticoids in the initial treatment for active ILD was associated with better survival than a step-up approach, where therapy was started with glucocorticoids and other immunosuppressive agents were later added in those who failed to respond to treatment with glucocorticoids [35]. However, the efficacy and safety of this approach needs to be confirmed in larger prospective, randomized, controlled trials.

Intravenous immunoglobulin (IVIG) has been reported to be useful in the treatment of patients with DM-associated ILD. In a recent case report concerning a woman with DM and progressive interstitial pneumonia, adding IVIG to a combination therapy with prednisolone and ciclosporin A resulted in full remission without side effects such as exacerbation of opportunistic infections or mental disturbance [62]. This report confirms the results of an earlier study in which adding IVIG resulted in a significantly higher probability of maintaining complete remission in the cases with refractory or relapsing disease [63]. None of these studies could demonstrate any further benefit by plasmapheresis. In an open-label study on patients with refractory myositis without ILD, high-dose IVIG had limited clinical effect on muscle performance, and inflammatory signs in muscle biopsies persisted in muscle tissue after treatment for 3 months, arguing against the rationale to use high-dose IVIG to treat refractory muscle impairment [64].

Another new drug that seems promising in treatment of ILD in myositis is tacrolimus. A few studies in the past couple of years suggest that tacrolimus is effective in the treatment of PM-associated ILD, resulting in improvement of computed tomography findings and pulmonary function tests [65–67].

There are a few case reports using biological agents in myositis patients with ILD. The CD20 monoclonal antibody, rituximab, has been used successfully in other autoimmune diseases such as rheumatoid arthritis [68]. In an open-label pilot study of six patients with DM, rituximab resulted in improved FVC in three patients [69]. Rituximab was well tolerated, and the administration was not associated with any serious adverse events. In a patient with antisynthetase syndrome, treatment with rituximab resulted in regression of abnormalities on HRCT [70].

Information on the efficacy of TNF inhibitors in myositis patients refractory to glucocorticoids or as induction therapy is conflicting [71–73]. In an open-label trial of combination therapy with anti-TNF treatment and methotrexate, one of six patients dropped out because of progression of pulmonary fibrosis [72], and in another study no effect from anti-TNF therapy was noted in a DM patient who had prior radiographic evidence of mild interstitial fibrosis [71]. Further studies are needed to illuminate if certain subgroups of myositis patients respond to this therapy, and if it is effective in the treatment of myositis-associated ILD. It should be mentioned that ILD has also been reported as a possible complication in association with the use of different TNF inhibitors in other autoimmune diseases. In an analysis of clinical characteristics, outcome and patterns of reported autoimmune disease associated with the use of anti-TNF agents, 24 cases of ILD were reported. Of the 19 cases in whom the outcome

was detailed, 53% showed no resolution of pulmonary involvement after withdrawal of anti-TNF therapy and initiation of glucocorticoids and other immunosuppressive agents. Fatal outcome was reported in 32%. Notably, most of the reported cases had a pre-existing pulmonary disease [74].

Prognosis of interstitial lung disease associated with myositis

Since treatment of myositis is usually started as soon as the diagnosis has been established, little is known about the natural course of the ILD in myositis. Furthermore, it is hard to deduce solid conclusions about prognostic factors in myositis-associated ILD from the available studies due to retrospective designs of the studies, small numbers of included patients, differences in diagnostic criteria for ILD and the influence of different treatment regimes. In a recent longitudinal study, with a mean follow-up time of 35 months, 23 patients with newly diagnosed myositis were included. At the initial investigation, 78% demonstrated findings on radiographic examination and/or pulmonary function tests compatible with ILD. All were treated with high-dose glucocorticoids and other immunosuppressive agents. Two patients died due to ILD, both with active myositis. During the follow-up, TLC improved in 33%, remained stable in 39% and deteriorated in 28%. However, changes in TLC correlated only partially with findings on HRCT, and pathological changes remained even after normalizing of lung function [32]. Although most patients with ILD associated with collagen vascular diseases have a chronic indolent course with a relatively favorable prognosis, the development of ILD has been shown to increase morbidity and mortality in patients with myositis [30,75,76].

ILD has been reported to have a more severe prognosis and to be more resistant to glucocorticoid therapy when associated with DM compared with PM [30,36,77]. Rapidly progressive ILD with fatal outcome has been reported in a distinct subgroup of mainly Asian patients with typical skin rash but without muscle involvement – CADM [1,30,56,57,78–80].

Myositis-associated ILD may proceed, appear concomitantly with, or develop after the onset of skin or muscle manifestations. Two different clinical presentations of ILD have been described, one with acute progressive disease and unfavorable outcome, and one chronic progressive disease with a relatively favorable prognosis. According to a recent study, the 3-year survival rate was 23.9% for patients with acute ILD (dyspnoea within 1 month before diagnosis), compared with 78.8% for those with chronic ILD [76]. Patients with an acute presentation had ground-glass opacity and consolidation on HRCT, in contrast to reticulation and honeycombing in the chronic type. However, as stated previously, honeycombing is not common in patients with ILD due to myositis, in contrast to patients with idiopathic pulmonary fibrosis. The acute form of ILD has primarily been reported in patients with DM, and in particular for those with CADM.

In a recent retrospective study, it was demonstrated that HRCT gave prognostic information for patients with ILD-associated myositis. The occurrences of fatal disease were 0, 20 and 83% in patients with a consolidation dominant pattern, ground-glass attenuation/reticular opacity dominant with chronic fibrosing process and ground-glass attenuation/reticular opacity dominant without chronic fibrosing process, respectively [36].

Other manifestations, such as characteristic nail fold capillaroscopic microangiopathy [81], low serum levels of creatine kinase (CK) [36], lack of antinuclear antibody in CADM [30], low DLco [10], increased neutrophils in BAL fluid [34] and histopathological pattern compatible with DAD [10] have all been considered as predictors of poor prognosis in patients with myositis-associated ILD. In contrast, ILD associated with antisynthetase antibodies appears to respond well to glucocorticoids in combination with other immunosuppressive agents [32,55,82,83]. However, population-based longitudinal studies are needed to obtain more valid data on prognostic markers for myositis-associated ILD.

Possible pathogenic mechanisms of interstitial lung disease in myositis

The differences in clinical features and histopathology of myositis patients suggest that there are different disease mechanisms driving these subsets of myositis. This is probably also true for ILD in myositis, as two clinically different phenotypes have been described, one acute with poor prognosis and one chronic with a more favorable prognosis [56,57,76,80]. Furthermore, the histopathological features of ILD in myositis are also heterogeneous, similar to what has been seen in idiopathic ILD. In myositis-associated ILD there is a predominance of NSIP, but other forms have also been reported in myositis, suggesting that different disease mechanisms may be the cause of ILD in myositis.

Although little information is available on the molecular mechanisms of ILD in association with myositis, in the specific subset of ILD in patients with myositis and anti-tRNA antibodies, novel information has been discovered that suggests a role of specific immune reactions of the ILD, and that these autoantibodies could serve as a link between ILD and muscle inflammation. Most available information is related to ILD and anti-Jo-1 autoantibodies, and accumulating data suggest a role of anti-Jo-1 antibodies in the disease mechanisms of myositis based on both clinical and experimental observations.

There are a few case reports in which anti-Jo-1 autoantibodies preceded clinical symptoms of myositis by a few years, which is similar to what has been reported for rheumatoid factor and anticitrullinated antibodies in rheumatoid arthritis [84,85]. Further clinical support for a role of anti-Jo-1 antibodies is the correlation between anti-Jo-1 autoantibody titres and clinical indicators of disease activity in myositis [86]. Moreover, the antibody response to histidyl-tRNA synthetase undergoes class switching, spectrotype broadening and affinity maturation, all of which are indicators of a T-cell-dependent antigen-driven process [85,87–89]. This indicates that a T-cell response directed against histidyl-tRNA synthetase might drive autoantibody formation and tissue damage.

There are now several reports to suggest that the immune reaction in the lungs is a primary event in myositis with ILD and anti-tRNA synthetase autoantibodies. In this syndrome, ILD is most often the first manifestation of a chronic inflammatory disease that in many patients leads to myositis and sometimes also to arthritis and Raynaud's phenomenon [32,83,90]. Interestingly, a restricted accumulation of T lymphocytes expressing selected T-cell receptor V (TCR V) gene segments were detected in BAL fluid, and a corresponding selective TCR V usage was found in muscle tissue in a small series of PM and DM patients, suggesting a common antigen in the muscles and the lungs [91]. Notably, the largest expansions in BAL fluid were recorded in two PM patients with anti-Jo-1 antibodies and the *HLA-DRB1*03* allele. They both had BAL fluid with $BV3^+$ T-cell expansions in the CD4 population, and BV3 was also a prominent TCR V segment in muscle tissue.

In another study, single-strand conformation polymorphism analysis demonstrated an increased number of accumulated T-cell clones in BAL fluid of three PM/DM patients, but not in the healthy subjects. Furthermore, the junctional sequence analysis showed the presence of conserved amino acid motifs in the TCR-CDR3 region of BAL fluid lymphocytes from PM/DM patients, which were not detected in the controls. Although there are limitations by the low number of patients, still, this study supports our previous findings that T cells in BAL fluid may recognize a restricted antigen and accumulate via antigen-driven stimulation, suggesting that T cells may play a crucial role in the development of ILD in patients with PM and DM [92]. A T-cell-dependent immune response is also supported by the association between ILD and the *HLA-DRB1*03-DQA1*05-DQB1*02* haplotype in a large study in UK Caucasians [92]. This association was irrespective of myositis subtype or presence of anti-aminoacyl tRNA synthetase antibodies.

Why the lungs?

Interestingly, the autoantigen of anti-Jo-1 antibodies, the ubiquitously expressed histidyl-tRNA synthetase, has different levels of expression in different tissues. Moreover, the antihistidyl-tRNA synthetase antibodies seem to recognize epitopes of the histidyl-tRNA synthetase that are exposed after cleavage by granzyme B, and the granzyme B-cleavable form is enriched in the lung and localized to the alveolar epithelium [93]. A proteolytically sensitive conformation of histidyl-tRNA synthetase exists in the lung, the target tissue associated with this autoantibody response. Thus, the autoimmunity to histidyl-tRNA synthetase could be initiated and propagated in the lung [93] (**Figure 1**). Notably, there is also an overexpression of histidyl-tRNA in regenerating muscle fibers compared with differentiated fibers, indicating that regenerating fibers, for example, after a trauma, may become targets of the immune reaction in patients who have already developed antihistidyl-tRNA autoantibodies [94]. In addition, mice immunized with murine histidyl-tRNA synthetase (Jo-1 antigen) developed a striking combination of muscle and lung inflammation that replicates features of the human antisynthetase syndrome [95].

The presence of autoantibodies in myositis with ILD naturally supports a role of B cells in the pathogenesis of this clinical phenotype. A role of B cells is also supported by the higher serum levels of B-cell-activating factor in myositis patients with ILD compared with those

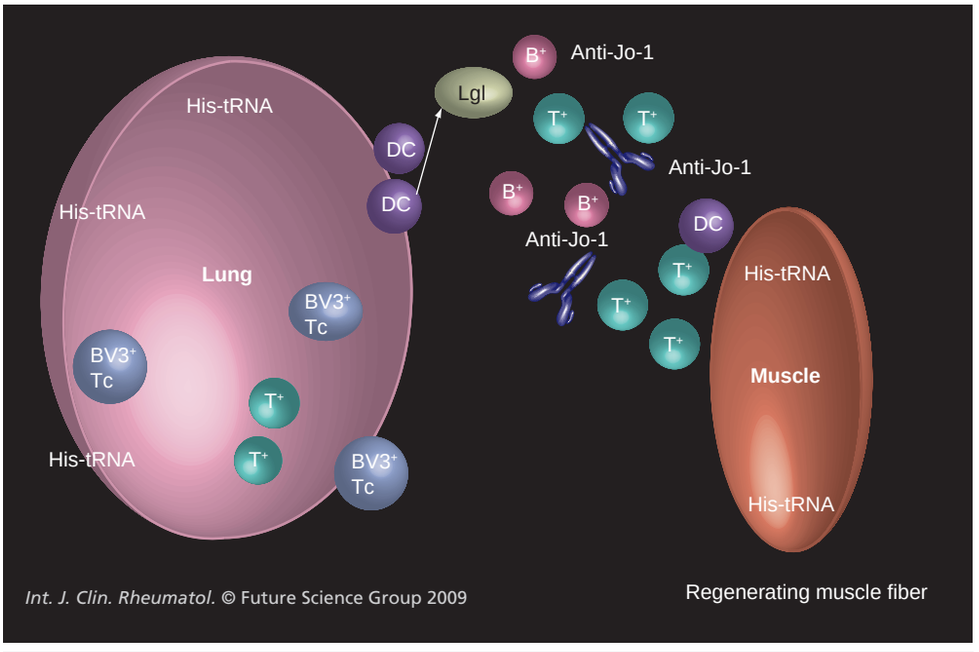

Figure 1. A schematic presentation of a possible association between interstitial lung disease and muscle inflammation in patients with antihistidyl-tRNA synthetase autoantibodies (anti-Jo-1).
B: B cells; DC: Dendritic cells; his-tRNA: Histidy-tRNA; Lgl: Lymph node; T: T cells.

without ILD or controls [96]. In this study, this association could be explained by presence of anti-Jo-1 autoantibodies.

Taken together, there is now accumulating data to support a role of a T-cell- and B-cell-mediated immune response in the development of ILD in patients with anti-tRNA synthetase autoantibodies. This hypothesis still needs to be further tested, and the initial events that lead to the autoantibody formation still need to be explored. This is likely to be done through more detailed molecular studies on the lungs in patients with these autoantibodies in combination with models of these disorders. Concerning the molecular mechanisms leading to ILD in patients without these autoantibodies, we have a lot more to learn. The acute form in particular, with a rapid development and poor prognosis which is often associated with DM, is a particular challenge.

Future perspective

With the rapid advances in immunology and molecular biology research, as well as in imaging technology, within 10 years we can anticipate an increased knowledge of molecular pathways that are important for the development of ILD in patients with inflammatory myopathies. Based on such novel information, we are likely to develop accessible new and targeted therapies for many of the patients with these conditions. We can also anticipate having access to biomarkers that could be used not only to predict the development of ILD in patients with myositis, but also to predict responses to different therapies and the outcome for individual patients.

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Executive summary

- Myositis-associated pulmonary involvement, in particular interstitial lung disease, confers a significant complication and is an important cause of morbidity and mortality among myositis patients.
- In the evaluation of myositis-associated pulmonary complications, careful clinical follow-up, repeated pulmonary function tests and high-resolution computed tomography are pivotal.
- Decisions concerning the need for immunosuppressive therapy should be based upon disease activity, laboratory tests such as autoantibody status and results of pulmonary function tests and high-resolution computed tomography. Current immunosuppressive treatments have beneficial effects in most cases, and may stabilize and even lead to improved pulmonary function. Further studies are needed to establish more effective therapeutic regimes.
- The role of new biologic agents in the treatment of myositis-associated interstitial lung disease is unclear.
- Recent studies have highlighted the importance of genetic predispositions and autoimmune reactions, which together may contribute to interstitial lung disease with pulmonary dysfunction in patients with inflammatory myopathies.

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▪▪ **A comprehensive review on a rare and often overlooked disease entity where pulmonary complications could be severe.**

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