

## A Link between Lung Injury and Inflammatory Myopathies: Making the Diagnosis

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### Abstract

Pulmonary fibrosis associated with various connective tissue diseases often presents insidiously but can progress to rapid deterioration. Previous studies have shown that, in the patients with connective tissue diseases, the presence of pulmonary fibrosis has prognostic implications and therefore early detection may be essential in the management of these patients. Our case outlines the close association between pulmonary fibrosis and idiopathic polymyositis. We report the findings of a patient who presented with slow onset progressive exercise dyspnea followed by proximal muscle weakness and joint and skin changes.

**Keywords:** Muscle inflammation; Interstitial lung disease; Treatment options; Skin changes

### Case Report

A 68-year-old Caucasian man presented to the emergency room with a 6-week history of progressive dyspnea associated with dry cough and diffuse pleuritic chest pain. He also complained of muscle weakness and diffuse myalgias which predated his respiratory symptoms, which now impacting on his daily activities. He denied hemoptysis and constitutional symptoms. His General Practitioner (GP) had treated him for a respiratory tract infection with clarithromycin, inhaled albuterol, budesonide and formoterol daily without improvement. A computed tomography (CT) scan of the chest arranged by his GP showed extensive lung fibrosis with honeycombing. He was awaiting a respirology referral when he developed worsening dyspnea and bilateral leg swelling, at which point he presented to Toronto General Hospital. His past medical history consisted of hypercholesterolemia controlled on rosuvastatin and benign prostatic hypertrophy. He was a lifetime nonsmoker and a nonalcohol user. Currently retired but had worked in the printing business for 40 years.

On physical examination he was alert and oriented with no signs of respiratory distress. His vitals were: blood pressure 100/62 mmHg, heart rate of 85 beats per minute, axillary temperature 36.5°C. At rest he required 2 litres of oxygen but easily desaturated with activity. He had clubbing bilaterally but no palpable lymphadenopathy, no signs of cyanosis, no classical skin lesions of dermatomyositis. Fine inspiratory crackles audible in mid to lower lung zones bilaterally. He had no signs of volume overload and a normal cardiovascular examination. His abdomen was soft, no palpable organomegaly or masses. He had bilateral pitting pedal edema to the ankles. His proximal and distal interphalangeal joints were erythematous, swollen and tender bilaterally. He had a maculopapular rash on the dorsal surface of his hands and periungual erythema, (Figure 1). He had good handgrip but bilateral proximal muscle weakness in both the upper and lower extremities (Table 1).

A repeat contrast CT scan of the chest showed (Figure 2) moderate and severe opacity in the right middle lobe and lower lobe respectively, with some traction bronchiectasis. Mild subpleural reticulation in the left upper lung, moderately severe opacity in the lingula and left lower lobe. Normal airway anatomy was observed on fiberoptic bronchoscopy. Bronchoalveolar lavage (BAL) fluid examination ruled out infection. The BAL differential cell count revealed: 39% neutrophils, 1% lymphocytes and 60% bronchial lining cells. Pulmonary function testing (Table 2) was consistent with severe restrictive lung disease. A structurally normal heart, ejection fraction >55% and estimated



**Figure 1:** Metacarpal phalangeal joints, proximal interphalangeal joints and distal interphalangeal joints were erythematous, swollen and tender bilaterally. He had a maculopapular rash on the dorsal surface of his hands bilaterally and periungual erythema.

### Blood Work

WBC		16.2 × 10 <sup>9</sup> /L
• Neutrophils		• 13 × 10 <sup>9</sup> /L
• Lymphocytes		• 1.56 × 10 <sup>9</sup> /L
• Monocytes		• 1.04 × 10 <sup>9</sup> /L
• Eosinophils		• 0.53 × 10 <sup>9</sup> /L
• Basophils		• 0.03 × 10 <sup>9</sup> /L
Hemoglobin		127 g/L
Platelets		314 × 10 <sup>9</sup> /L
Creatinine		72 mmol/L
Electrolytes:		
• Sodium		• 130 mmol/L
• Potassium		• 4.1 mmol/L
• Chloride		• 99 mmol/L
• Calcium		• 2.14 mmol/L
• Magnesium		• 0.85 mmol/L
• Phosphate		• 1.06 mmol/L

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Transaminases:	
• Aspartate Aminotransferase (AST)	• 38 U/L (8-20 U/L)
• Alanine Aminotransferase (ALT)	• 36 U/L (8-20 U/L)
• Alkaline Phosphatase	• 57 U/L (35-100 U/L)
• Lactate Dehydrogenase (LDH)	• 336 U/L (100-250 U/L)
• Erythrocyte Sedimentation Rate	• 70 mm/hr
• Creatine Phosphokinase (CPK)	• 351 U/L (52-336 U/L)
• Bilirubin	• 12 (< 26µmol/L)
• Anti-nuclear Antibodies (ANA)	• 1:64
• Anti-Sjogren's Syndrome-related Antigen A (SSA also termed anti-Ro)	• Negative

Table 1: Patient's blood work.



Figure 2: CT chest with Contrast. Demonstrates in the right lung mild apical fibrosis, mild subpleural reticulation in the right upper lobe, moderate opacity in the right middle lobe with some traction bronchiectasis representing interstitial thickening. Severe opacity in the right lower lobe consisting of reticulation, traction bronchiectasis, likely some subpleural honeycombing. The left lung showed mild subpleural reticulation in the left upper lobe, moderately severe opacity in the lingula consisting of reticulation, and severe opacity in the left lower lobe similar to the right lower lobe.

Pulmonary Function Testing	Absolute value	Compared to Predicted Value
Pre-bronchodilator forced expiratory volume (FEV1)	1.2 litres	37%
Pre-bronchodilator forced vital capacity (FVC)	1.7 litres	39%
FEV1/FVC ratio	93%	
Total Lung Capacity (TLC)	3.1 litres	46%
Diffusing capacity of the lung for carbon monoxide (DLCO)		52%

Table 2: Pulmonary function testing.

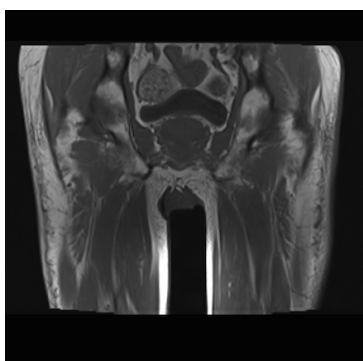


Figure 3: Magnetic resonance imaging (MRI) of the lower extremities demonstrates scattered bilateral areas of edema in the gluteus minimus and lower quadriceps muscles primarily, more evident on the right side which are nonspecific but suggested inflammatory changes as seen in polymyositis or dermatomyositis. There was no muscle atrophy or fatty infiltration observed.

systolic pulmonary artery pressure of 27 mmHg on transthoracic echocardiogram. Magnetic resonance imaging (MRI) of the lower extremities (Figure 3) showed scattered bilateral edema, suggestive of inflammatory changes as seen in inflammatory myopathy. No muscle atrophy was observed. Muscle biopsy of gluteus minimus showed large variation in fiber size with many atrophic fibers of the skeletal muscles, extensive fiber splitting with increased internal nuclei, foci of lymphocytic inflammation, moderate fibrosis and fatty infiltration. Frozen sections showed no inclusions or 'ragged red' fibers. These findings were more consistent with polymyositis. Malignancy workup was all negative. HIV risk factor screening was negative.

## Discussion

### Polymyositis with interstitial lung disease (ILD)

Polymyositis (PM) is a multi-systemic connective tissue disorder which typically affects skeletal muscles but can also affect the lungs. Its prevalence ranges from 0.5 to 8 cases per million with the prevalence of lung involvement ranging from 5% to as high as 64% in some studies [1]. Early diagnosis of ILD in PM has prognostic implications and therefore it is essential to screen for ILD in these patients. The exact nature of the autoimmune destruction of skeletal muscle and lung parenchyma is not entirely clear but experimental studies have shown it is likely a targeted cell mediated immunity in response to an exogenous antigen or autoantigen [2].

### The clinical picture of polymyositis with ILD

The typical clinical presentation of PM is that of proximal muscle weakness with progressive worsening over weeks to months. Patients present with symptoms such as difficulty climbing stairs, combing their hair and getting up from a sitting position. Interstitial lung disease can present either acutely which can be rapidly progressive, subacutely or as a subclinical disease with no respiratory symptoms [3]. Commonly it presents with an insidious onset of dyspnea and non-productive cough. ILD has been reported to occur before myositis in 20% of cases and if diagnosed at the same time or after the diagnosis of myositis, the duration between the two diagnoses is typically less than 12 months [3]. In this case, our patient's initial symptoms were respiratory and within weeks he developed proximal muscle weakness. His first CT scan of the chest showed a pattern of severe lung fibrosis this suggests that his lung injury started months prior to him experiencing symptoms.

### Diagnosis of polymyositis

Idiopathic polymyositis and dermatomyositis are subgroups of a heterogeneous group of inflammatory muscle diseases. Table 3 provides a differential diagnosis. The main diagnostic criteria of idiopathic PM requires symmetric proximal muscle weakness, generally subacute onset, elevated serum muscle enzymes (creatine kinase is the most sensitive muscle enzyme and always increases in active disease states to as much as 50 times in some cases), and inflammatory infiltrates on muscle biopsy [4-6]. Typical cutaneous eruptions are seen dermatomyositis (DM) but not in PM (the only feature distinguishing DM from PM). Electromyography (EMG) showing myopathic changes and muscle biopsy is essential for showing characteristic findings namely multifocal lymphocytic infiltrates surrounding and invading healthy muscle fibers. Our patient met four of the required criteria for a definitive diagnosis of PM, these included: (1) symmetric proximal muscle weakness; (2) elevated CK; (3) EMG showing myopathic changes and (4) muscle biopsy showing features in keeping with PM in the absence of any classic skin lesions of DM. Of note his MRI findings showed significant muscle inflammation yet

Myopathies	Skin lesions	Muscle weakness Onset	Histopathological features in the muscle biopsy	Serum autoantibodies	Other features	Creatine kinase
Dermatomyositis (DM) DM with severe skin symptoms and rapidly progressive ILD	Cutaneous eruption? (specify) -shawl sign/Gottron's papules/arthritis/V sign	Subacute/ Acute	Inflammatory infiltrates	Anti-MI2 Anti-SAE	Investigate for malignancy	Increased
Polymyositis	"mechanic's hands"	Subacute	Inflammatory infiltrates	Anti-Jo1 typically in patients who develop ILD	Investigate for ILD and malignancy	Increased
Inclusion-Body Myositis	Not reported	Subacute	inclusions or 'ragged red' fibers		Investigate for malignancy	Increased
Overlap Myositis	Cutaneous eruption similar to dermatomyositis	Subacute	Perifascicular, interfascicular and perimysial regions	Antisynthase		Increased
Drug-Induced (Statins/ Antiretroviral drugs)	Not reported	Usually acute	Necrotizing associated with statins	Anti-HMG-CoA teductase		Increased
Dystrophic Myopathies	Not reported	Chronic/ subclinical	Atrophy and fatty infiltration			Normal
Hypothyroidism	Not reported	Subacute	Fibre atrophy and muscle loss			Increased
Paraneoplastic related myositis	Not reported	Subacute/ acute	?	Anti-155/140		Normal

**Table 3:** Differential diagnosis.

muscle biopsy showing more chronic changes suggesting a subacute presentation of our patient's myositis. In the presence of a patients with idiopathic PM, it is essential to investigate for a concomitant ILD. Typical radiological changes include increased interstitial markings (reticular and nodular opacities) more prominently in the lower lung fields and typically non-specific interstitial pneumonia (NSIP), which is the most common pattern (56.3%). A lung biopsy is needed to confirm the histopathological diagnosis of the ILD when the chest imaging is inconclusive and may also help in determining the prognosis but it is associated with morbidity and mortality and for this reason it is usually reserved to few selected patients [5,7-9]. Our patient's radiological findings were consistent with NSIP. A lung biopsy to confirm the diagnosis was not performed.

## Management

The main therapeutic objectives are to improve muscle strength and treat extramuscular manifestations (rash, dysphagia, dyspnea, arthralgia, fever). In general, clinical practice has shown that DM responds better to treatment than does PM [6,10]. Despite a lack of high quality randomized controlled trials, the mainstay of treatment for idiopathic inflammatory myositis with and without ILD are systemic glucocorticoids that usually improve respiratory symptoms, improve muscle strength and normalize serum muscle enzymes (despite a decrease in serum CK alone is not a sign of clinical response). In patients with rapidly worsening disease, it is preferable to administer intravenous methylprednisolone before starting treatment with oral glucocorticoids [9,10]. The exact mechanism of action of glucocorticoids in these diseases has not been fully understood; it is thought they likely dampen the host's immune response. Patients who do not improve with systemic glucocorticoids alone, other immunosuppressive drugs are used, selected empirically on the basis of personal experience and the relative efficacy/safety ratio. Improved outcomes have been shown with a number of agents including azathioprine, methotrexate, rituximab, intravenous immunoglobulin, mycophenolate mofetil, tacrolimus or cyclosporine. Plasmapheresis and leukapheresis have shown no apparent benefit. More high-quality randomized controlled trials are underway in order to establish the role of immunosuppressive agents in the treatment of these conditions and the clinical context in which they are most likely to be beneficial [7,8,11,12]. In common

practice, azathioprine in combination with methotrexate has been shown to be superior to intravenous methotrexate alone in refractory inflammatory myositis, although there has been a trend favouring combination therapy [10-12]. In fact clinical experience suggests that glucocorticoids in combination with other immunosuppressive drugs in PM/DM-related ILDs of benefit a significant proportion of patients, particularly those with certain histological patterns of disease, such as cellular NSIP, in controlling disease progression [10-12]. In addition to pharmacologic therapy for ILD patients, long term home oxygen treatment and pulmonary rehabilitation can improve functional daily performance levels especially in those with chronic progressive ILD [12]. Our patient was started on high dose prednisone (1 mg/kg/ daily) and mycophenolate mofetil (500 mg twice daily) and gradually increased to a maximum dose of 1 g twice daily. After starting therapy his respiratory status, proximal muscle weakness improved and his rash disappeared. He continued to require oxygen to maintain normal saturations especially when ambulating and was discharged on home oxygen therapy.

## Conclusion

PM/DM with ILD has significant prognostic implications and therefore early diagnosis can affect long term outcome. Given the lack of definitive evidence on therapy, the management of these patients remains challenging. More research on the pathophysiology of this entity may provide further insights and thereby better treatment options which will further impact in patient prognosis, quality of life and long term outcomes.

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