Two simultaneous autoimmune processes in a patient presenting with respiratory insufficiency

Lauren Troy1,2, Paul Hamor1,2, Jane Bleasel2,3 & Tamera Corte1,2,4

1Department of Respiratory Medicine, Royal Prince Alfred Hospital, Sydney, New South Wales, Australia
2Sydney Medical School, University of Sydney, Sydney, New South Wales, Australia
3Department of Rheumatology, Royal Prince Alfred Hospital, Sydney, New South Wales, Australia
4Woolcock Institute of Medical Research, Sydney, New South Wales, Australia

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Abstract
The idiopathic inflammatory myopathies, including dermatomyositis, are uncommon acquired autoimmune diseases, sometimes associated with interstitial lung disease. Myasthenia gravis, a separate autoimmune disorder involving the neuromuscular junction, has some overlapping clinical features but has only rarely been reported to occur simultaneously within the same patient. Here we present the first reported case of concomitant dermatomyositis, myasthenia gravis, and interstitial lung disease.

Introduction
The idiopathic inflammatory myopathies, including dermatomyositis, are uncommon acquired autoimmune diseases with an annual incidence of 2–10 cases per million [1]. Characterized by symmetrical progressive muscle weakness with raised serum creatine kinase levels, these diseases sometimes manifest with other systemic features including skin changes, synovitis, and interstitial lung disease [2]. Myasthenia gravis, an autoimmune disorder involving the neuromuscular junction, has some overlapping clinical features with dermatomyositis, but has only rarely been reported to occur simultaneously within the same patient [3–5]. Here we present the first reported case of a patient with concomitant dermatomyositis, myasthenia gravis, and autoimmune interstitial lung disease.

Case Report
A 57-year-old male of Polish descent presented with a 6-week history of dyspnea, cough, painful small joint inflammatory arthritis, and diffuse erythematous rash. Progressive eyelid ptosis, dysphagia, and dysphonia prompted urgent hospital admission. His background history was remarkable for long-standing vitiligo and a first-degree relative with type 1 diabetes mellitus. He had no significant exposures including tobacco use.

The patient was in respiratory distress at rest, worse when lying supine. His oxyhemoglobin saturation was 90% with 2 L/min of supplemental oxygen. He had inspiratory crepitations at both lung bases. Dysarthria, diplopia, and bilateral ptosis were evident. There was weakness of facial muscles, neck flexors, and proximal limb muscles. Deep tendon reflexes were intact. Gottron’s papules, generalized erythematous rash, and synovitis of the metacarpophalangeal and proximal interphalangeal joints were also apparent.

Creatine kinase and troponin T were elevated (652 U/L, [normal < 250] and 218 ng/L, [normal < 14], respectively). He had a positive antinuclear antibody (ANA) at a titer of 1:640, (homogeneous pattern), acetylcholine receptor...
ACh-R antibody assay was strongly positive (>8 nmol/L) and erythrocyte sedimentation rate was high (53 mm/h). His extractable nuclear antibody (ENA) panel was negative, including Jo-1. Cerebrospinal fluid analysis was normal and echocardiography revealed no structural or functional cardiac abnormalities. Electromyography showed findings typical of both dermatomyositis and myasthenia with sparse fibrillation potentials and low amplitude polyphasic motor units in proximal limb muscles, along with decremental response to repetitive stimulation of extracellular muscles. Muscle biopsy of the left deltoid muscle revealed both neurogenic atrophy and inflammatory myopathy, supporting the clinical findings of concomitant myasthenia gravis and dermatomyositis.

A high-resolution computed tomographic scan of the chest showed bilateral inter- and intralobular reticular changes with diffuse ground glass, areas of peripheral consolidation, and traction bronchiectasis consistent with fibrosing organizing pneumonia (Fig. 1a). Pulmonary function testing demonstrated restrictive ventilation, with forced expiratory volume in 1 sec (FEV₁) 1.92 L, (59% predicted), forced vital capacity (FVC) 2.11 L, (52% predicted), FEV₁/FVC ratio 91%, diffusing capacity for carbon monoxide (DLco) 52% predicted, and total lung capacity 3.53 L, (53% predicted). Supine FVC was 1.39 L, 34% lower than the erect measurement, consistent with bilateral diaphragm weakness. Peak inspiratory and expiratory muscle strengths were 59% and 46% predicted, respectively. There was no evidence of thymoma or any other neoplastic process on positron emission tomography/computed tomography scanning.

Treatment initially comprised of oral prednisolone and broad-spectrum antibiotics with minimal improvement. This was followed by pulsed intravenous methylprednisolone (1000 mg/day). With little objective response, the patient was then given three doses of intravenous immunoglobulin (IVIG), and commenced on monthly intravenous cyclophosphamide 1000 mg (for 6 months). Pyridostigmine was also administered for myasthenia symptoms.

At 6-month follow-up, dyspnea, exercise limitation, and neuromuscular deficits had all resolved. Respiratory function was markedly better with FEV₁ 3.02 L (87% predicted), FVC 3.52 L (82% predicted), DLco 69.7% predicted and TLC 5.13 L (74% predicted). Respective peak inspiratory and expiratory muscle strengths were measured as 96% and 87% predicted. Radiological changes had also improved (Fig. 1b).

An aggressive treatment strategy with immunosuppressive therapy was successful in this patient, who continues to improve at 12 months on a regimen of prednisone 10 mg, mycophenolate 1000 mg bd, and pyridostigmine (Fig. 1c).

**Discussion**

The simultaneous occurrence of dermatomyositis and myasthenia gravis is extremely rare and has not previously been described in association with interstitial lung disease. Both conditions may arise as paraneoplastic syndromes with malignancy, but an extensive search did not yield any evidence for this. In particular, there was no sign of thymic pathology.

A number of different autoantibodies have been identified in thymoma-associated myasthenia gravis, including those targeting the ACh-R. In one series, skeletal muscle ryanodine receptor (RyR) antibodies were seen more frequently in patients with a concomitant myositis [5]. The authors of this paper proposed that a subgroup of myasthenia patients may have a tendency to produce autoantibodies targeting striated muscle proteins, as well as the neuromuscular junction. Without any evidence of thymoma, our case is particularly unusual, and the mechanism of autoimmunity remains unclear. RyR antibodies are not routinely tested for, and were not requested in this instance.

The respiratory compromise in our patient was likely the consequence of both respiratory muscle weakness and diffuse parenchymal lung involvement. Interstitial lung disease is well described in the inflammatory myopathies. The typical patterns of interstitial lung disease (ILD) include non-specific interstitial pneumonia (NSIP) and fibrotic organizing pneumonia [2]. In some cases, the ILD may pre-date the myositis symptoms, and thus detailed clinical and laboratory evaluation is paramount in all cases where disease progression is rapid. Aside from routine
autoimmune serology (including ANA and ENA), myositis-specific antibodies should also be considered when the clinico-radiological pattern is consistent.

In contrast, ILD is not commonly a feature of myasthenia gravis, and so prompted consideration of an additional process in this patient. In pure myasthenia gravis, respiratory failure arises from respiratory and bulbar muscle weakness, often complicated by aspiration pneumonitis.

Respiratory involvement in dermatomyositis is a poor prognostic indicator, and warrants a more aggressive treatment strategy from the outset. As there are no specific placebo-controlled trials in dermatomyositis-associated ILD, management strategies are based on experience and evidence from other forms of inflammatory ILD, such as NSIP. High-dose systemic corticosteroids as first-line therapy will often be beneficial. In cases where initial response is suboptimal or steroids cannot be weaned without deterioration in lung function, additional immunosuppressive therapy is indicated. In this case, the severity and rapidity of the disease at presentation warranted treatment with intravenous cyclophosphamide. In a small case series, cyclophosphamide, when given intravenously for a minimum six doses, was shown to reduce oxygen requirements and improve dyspnea and FVC [6]. IVIG is an additional therapeutic option, shown to be efficacious in muscle disease in a randomized controlled trial, although there is little evidence for its use in lung disease [7]. IVIG is widely used for its rapid action in the management of myasthenic exacerbations, making it an attractive therapy in this case. Rituximab, a monoclonal antibody directed against the CD20 antigen on B lymphocytes, could also have been considered.

Mycophenolate was used as maintenance therapy following the cyclophosphamide, based on the imperative to minimize steroid and cytotoxic exposure. There is some evidence to show benefit in ILD associated with inflammatory myositis, with more rigorous clinical trials currently underway [8].

In conclusion, this is a rare but interesting case of overlapping autoimmune diseases leading to respiratory failure. This highlights the importance of considering concomitant processes where the clinical presentation is not consistent with the presumed diagnosis. It is also essential to obtain an early and accurate diagnosis of autoimmune-associated fibrotic organizing pneumonia, so that the chances of treatment response are maximized.

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Disclosure Statements

No conflict of interest declared.

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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