

## Rapidly progressive fatal interstitial lung disease in a patient with systemic sclerosis

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**Background.** A 36-year-old woman developed new-onset Raynaud phenomenon and rapidly progressive dyspnea over a 2-week period. A lung biopsy demonstrated pauci-inflammatory nonspecific pneumonitis, which proved refractory to systemic corticosteroid and intravenous cyclophosphamide therapy. Her preterminal course in an intensive care unit was typified by sequential organ failure. Postmortem examination showed extensive organ fibrosis, including severe diffuse alveolar damage and parenchymal fibrosis, and a notable lack of potentially treatable tissue inflammation.

**Investigations.** Chest radiography, physical examination, screening for autoantibodies, measurement of serum creatinine, creatine phosphokinase, and brain natriuretic peptide levels, cardiac examination, pulmonary function tests, electrocardiography, transthoracic Doppler echocardiography, right heart catheterization, high-resolution thoracic CT, pulmonary ventilation/perfusion scan, lung biopsy.

**Diagnosis.** Interstitial lung disease associated with diffuse systemic sclerosis.

**Management.** Treatment with oxygen, oral and intravenous corticosteroids, mycophenolate mofetil and intravenous cyclophosphamide.

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### The case

A previously healthy 36-year-old woman developed single digit ischemia followed by Raynaud phenomenon involving all digits and progressively worsening dyspnea over a 2-week period. Chest radiography demonstrated bilateral lower lobe infiltrates. The patient was diagnosed with community acquired pneumonia and commenced treatment with antibiotics. The dyspnea worsened, however, and the patient was admitted to a local hospital. Physical examination revealed the presence of bibasilar crackles, but no skin changes. High-resolution CT (HRCT) confirmed the presence of bilateral infiltrates in the lower lobes consistent with typical nonspecific interstitial pneumonia (NSIP). Pulmonary function testing revealed a severe restrictive ventilatory defect with a reduction in the diffusing capacity in the lung for carbon monoxide (DLCO). A lung biopsy confirmed the presence of NSIP. Hyaline membranes were focally present, and there was focal intra-alveolar organization of fibrinous exudate. The patient was placed on oxygen and 60 mg daily of oral prednisone.

Two months later, the patient was evaluated at a university referral center for worsening symptoms of dyspnea. Physical examination was notable for sclerodactyly and dilated nailfold capillaries but no capillary loop drop-out. Cardiac examination revealed a loud pulmonic component

of the second heart sound, which can indicate the presence of elevated pulmonary pressures, a grade 2/6 systolic ejection murmur at the left upper sternal border, and a grade 3/6 holosystolic murmur of tricuspid regurgitation at the left lower sternal border. Immunostaining for serum antinuclear antibodies using a Hep-2 substrate was negative, as were specific tests for anti-Ro/SSA, anti-La/SSB, anti-Smith, anti-RNA-binding protein and anti-scl-70 (also known as antitopoisomerase I) antibodies. Serum creatinine levels and measures of creatine phosphokinase and brain natriuretic peptide were normal. Transthoracic Doppler echocardiography revealed an elevated, estimated right ventricular systolic pressure of 58 mmHg (normal <35 mmHg). A pulmonary ventilation/perfusion scan indicated an intermediate probability of pulmonary embolism, and subsequent HRCT showed worsening NSIP, but no evidence of pulmonary embolism or right to left cardiac shunt. Right heart catheterization revealed normal hemodynamic parameters, including a resting mean pulmonary arterial pressure of 20 mmHg, a pulmonary wedge pressure of 6 mmHg, pulmonary vascular resistance of 156 dyn·s/cm<sup>5</sup>, and a cardiac index of 4.08 l/min/m<sup>2</sup>. The patient was treated with 1 g oral mycophenolate mofetil twice-daily and 750 mg/m<sup>2</sup> intravenous cyclophosphamide each month. In addition, prednisone was continued but the dose was subsequently tapered to 10 mg/day.

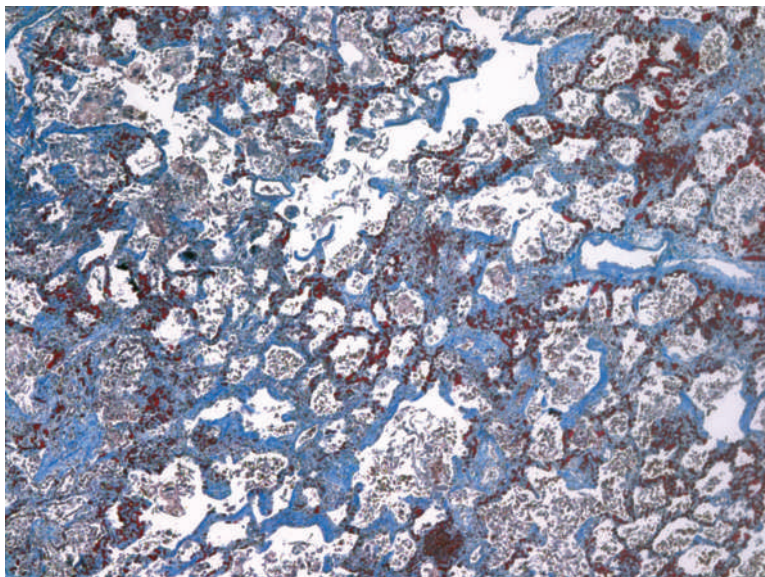
Over the following month, the dyspnea worsened and the patient was again admitted to the referral center with severe hypoxic hypercapnic respiratory failure and

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### Competing interests

The authors declared no competing interests.



**Figure 1** | Histological sample taken at autopsy from a patient with interstitial lung disease associated with systemic sclerosis, showing severe diffuse alveolar damage and interstitial fibrosis, with a notable lack of parenchymal inflammation.

witnessed aspiration events. A further physical examination revealed worsening skin changes, involving the forearms, upper arms and anterior chest. Electrocardiography showed a new right bundle branch block, and transthoracic Doppler echocardiography showed a small pericardial effusion and increasing right ventricular dilation. Immunosuppression was suspended and the patient was treated with broad-spectrum antibiotics. Hypotension ensued, which required treatment with multiple vasopressors. After further decline, and in keeping with the patient's wishes, the family made the decision to pursue comfort measures only and the patient expired the following day.

Postmortem evaluation demonstrated small serosanguinous pleural effusions, pulmonary edema and severe pulmonary fibrosis. No thromboembolic disease was seen. Fibrinous pericarditis and cardiomegaly with hypertrophy of the right ventricle and dilation of the right atrium and ventricle were demonstrated. Coronary arteries were normal, and the myocardium showed no inflammatory infiltrate. Cardiac biopsy revealed a reduction in the number of nuclei, with loss of striation and occasional lipofuscin deposits, which is consistent with a diagnosis of diffuse ischemia. Histopathology of the lung showed severe diffuse alveolar damage and interstitial fibrosis with areas of hyaline membrane disease (Figure 1).

### Discussion of diagnosis

This case highlights challenges in the diagnosis and treatment of rapidly progressive interstitial lung disease (ILD) associated with diffuse systemic sclerosis (SSc), as well as the complexities involved in the pathogenesis

of ILD. Pulmonary involvement has emerged as the primary cause of mortality in SSc, currently accounting for 60% of SSc-related deaths, with pulmonary hypertension and ILD being near-equal contributors.<sup>1</sup> Although ILD is seen in patients with both diffuse and limited SSc,<sup>2</sup> the pathogenesis of this manifestation is not well understood. The current consensus suggests that immune activation causes microvascular injury and luminal inflammation of the alveoli leading to fibrosis.<sup>3</sup> This theory has been questioned, however, owing to the relatively small changes observed in the lung function of patients with SSc who undergo immunosuppressive treatment.<sup>4</sup>

Similar to other pulmonary manifestations of SSc, ILD presents with dyspnea. In a patient with SSc, the differential diagnosis of dyspnea includes pulmonary hypertension, myocardial involvement, deconditioning, aspiration pneumonitis and interstitial pulmonary fibrosis. Awareness of these manifestations is essential when caring for patients with SSc, as the presence of just one of these processes can contribute to a decline in pulmonary status. For example, aspiration caused by impaired esophageal motility and gastroesophageal reflux is a frequent finding in patients with SSc, and can lead to a significant worsening of fibrosis and pulmonary function.<sup>5</sup> A patient's medical history, physical examinations, and pulmonary, radiographic, laboratory, and cardiac studies can aid in establishing the relative contribution of each of these processes.

Early diagnosis of ILD in patients with SSc is enhanced by a high index of clinical suspicion and awareness of the clinical effect of ILD. HRCT is the current, noninvasive gold standard for the diagnosis of ILD, and can be used early in the assessment of patients with suspected pulmonary involvement. The technique is more sensitive than chest radiography and has been shown to correlate with both total lung capacity and DLCO (gas transfer).<sup>6</sup> Goh and colleagues have shown that 'disease extent' quantified by HRCT is a powerful predictor of mortality, and can help predict the progressivity of pulmonary fibrosis.<sup>7</sup> Furthermore, both pulmonary function testing and HRCT are important diagnostic tools for determining the severity of ILD and monitoring future progression of the disease in patients with SSc. In addition, a decreased forced vital capacity (FVC) (<80% predicted) and decreased baseline gas transfer (<60% predicted) can be predictive of pulmonary decline.<sup>8,9</sup> An FVC of less than 70% of the predicted value and the extent of involvement by HRCT can help to predict further decline in FVC, DLCO and survival.<sup>7</sup>

Bronchoalveolar lavage (BAL) is another test that is commonly used in patients with ILD to diagnose the presence of lung inflammation (also known as 'alveolitis'). The usefulness of BAL has been called into question, however, as it is less sensitive than HRCT in identifying active lung inflammation, and no clear correlations have been found between the results of cellular analysis and clinical outcomes in patients with SSc.<sup>10</sup>

In the present case, the finding of digital ischemia with new-onset Raynaud phenomenon and dyspnea supports the diagnosis of SSc with lung involvement. The absence of antinuclear and anti-scl-70 antibodies, however, was considered an unusual finding. Antibodies against Th/To and U3RNP (fibrillarin) were not tested, and would not have been demonstrated on indirect immunofluorescence assay. Furthermore, although severe restrictive ventilatory defects and reduced gas transfer are both predictive of pulmonary hypertension and ILD manifestations, right heart catheterization in this patient did not demonstrate pulmonary hypertension. False positive tests for pulmonary artery hypertension, however, are common in the setting of ILD.<sup>11</sup> The diagnosis was established in this case by characteristic HRCT and by lung biopsy demonstrating NSIP.

### Treatment and management

In the present case, oxygen, corticosteroids, mycophenolate mofetil and cyclophosphamide therapies were all used, albeit unsuccessfully, as treatments for severe, rapidly progressive ILD in the setting of diffuse SSc. There is currently no proven available therapy to abrogate widespread fibrosis associated with SSc. The treatment strategies, therefore, involve targeting the inflammatory pathway through the use of corticosteroids and immunosuppressants, although limited efficacy has been demonstrated in slowing disease progression with these treatments.

The most widely used and studied treatment for early and severe SSc with lung involvement is cyclophosphamide. The adverse effects associated with this agent, however, have raised considerable debate as to whether the benefits of cyclophosphamide outweigh the costs to patient quality of life.<sup>12,13</sup> The Scleroderma Lung Study investigated the effects of 12 months of oral cyclophosphamide in a double-blind, placebo-controlled, randomized trial of 158 patients with SSc and mild to moderate ILD, as indicated by abnormal BAL and/or ground glass opacities on HRCT.<sup>14</sup> The results demonstrated a slightly greater loss of FVC in the placebo group compared with cyclophosphamide-treated patients ( $P < 0.03$ ). Evaluation of lung function at 24-month follow-up, however, showed that the treatment effects of cyclophosphamide were not durable.<sup>14,15</sup> Furthermore, a risk-benefit analysis using a Markov decision model showed that patients treated with cyclophosphamide fared slightly worse than their non-treated counterparts, with a loss of 0.21 quality-adjusted life years.<sup>13</sup>

Another multicenter, prospective, double-blind, placebo-controlled trial evaluated the effect of corticosteroids and intravenous cyclophosphamide followed by azathioprine for the treatment of ILD in SSc.<sup>4</sup> The study included 45 patients with diffuse or limited SSc who were randomly assigned to receive low-dose corticosteroids and intravenous cyclophosphamide once every 4 weeks

for 6 months, followed by oral azathioprine, or placebo. At 6 months, no significant changes in FVC were detected in the treatment group, although there was a trend, albeit minimal, towards increased FVC in the treatment group ( $P = 0.08$ ). Changes in HRCT pattern and extent of disease were not significant.

The results of these two trials suggest limited benefits of cyclophosphamide therapy in patients with SSc-associated ILD. A meta-analysis of randomized, controlled trials and open-label, prospective case-series concluded that cyclophosphamide treatment did not seem to result in clinically significant improvements in pulmonary function in this setting.<sup>16</sup> Further research is needed to better define those patients who might be more likely to benefit from cyclophosphamide therapy.<sup>12,17</sup> It is clear that the response to immunosuppression with cyclophosphamide in some patients is dramatic, and that the selection of appropriate, enriched populations for future studies will lead to clearer results.<sup>12,17</sup> There is a simple, humbling facet to this tragic case. Premortem lung biopsy and postmortem study of all organs failed to demonstrate evidence of inflammation—a process that might be considered treatable with corticosteroids and immunosuppressants. The possibility remains that pulmonary inflammation, although uncommon, is epiphenomenal to the basic processes leading to SSc myofibroblast proliferation and differentiation, and that treatment breakthroughs will be those that focus on specific signals that govern this feature of pathobiology.

### Conclusions

We present the unusual case of a patient with aggressive, diffuse SSc and rapidly progressive ILD, which did not respond to treatment with intravenous cyclophosphamide. ILD is a common manifestation of SSc and often the cause of death in these patients. Thus, patients with SSc and dyspnea should be evaluated early on in the course of disease for all pulmonary manifestations. Pulmonary function testing and HRCT are important diagnostic tools and can help physicians identify those patients who are at highest risk for rapid decline. Effective therapies for this devastating disease remain elusive. Cyclophosphamide is currently the most widely used and studied treatment for ILD in SSc, although it is associated with many adverse effects and is thought to offer limited benefit. A classification system for identifying those patients who would benefit most from treatment with immunosuppression or antifibrotic agents should be developed. In addition, research efforts should be aimed at identifying a tissue process that is a predictable target of treatment in SSc. When treatment with immunosuppressants shows such limited improvements in lung function and disease process, researchers must be urged to reconsider the current model. It is important to investigate the underlying mechanisms in the pathogenesis of lung fibrosis in SSc so that more effective treatments can be developed.

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