Fatal Acute Interstitial Pneumonitis Complicating Polymyositis in a 41-Year-Old Man

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We report a case of a previously healthy 41-year-old man who was admitted for progressive dyspnea and cough, which culminated in respiratory failure, shock, and death. Lung and muscle biopsy results were consistent with interstitial lung disease secondary to polymyositis. Polymyositis and dermatomyositis are rare autoimmune diseases that primarily affect the muscles and skin, with frequent extramuscular and specifically pulmonary manifestations. Respiratory complications are in 2 categories: primary (the interstitial lung diseases, which can be acute or chronic) and secondary (aspiration pneumonia/pneumonitis, muscle weakness, infection, drug-induced disease, pulmonary congestion secondary to heart failure, pulmonary hypertension, and pneumomediastinum). Diagnosis of a specific interstitial lung disease relies mainly on high-resolution computed tomography of the chest and on tissue diagnosis. Prognosis depends on the histopathology findings and the specific form of interstitial lung disease and its response to therapy, which consists of high-dose steroids and immunomodulating agents. Unfortunately, patients with polymyositis/dermatomyositis associated with pulmonary complications have a worse prognosis than patients with isolated forms. *Key words: interstitial pneumonitis, polymyositis, dermatomyositis.* [Respir Care 2004;49(12):1515–1521. © 2004 Daedalus Enterprises]

Introduction

Polymyositis (PM) and dermatomyositis (DM) are autoimmune diseases, characterized by the presence of auto-antibodies and tissue inflammation involving mainly the muscles. Even though PM and DM are the largest group of acquired causes of muscle weakness, their occurrence is quite rare: 1–10 in 1,000,000,[1] with a female-to-male predominance of 2.5/1 and a bimodal age distribution, peaking in childhood and in the fourth to fifth decade of life. Despite the histological and immunological differences between the 2 diseases, the clinical presentation overlaps. For PM, finding the first 2 criteria listed

below makes the diagnosis probable, whereas finding all 4 makes it certain.[2]

1. Symmetric proximal muscle weakness
2. Muscle biopsy consistent with myositis
3. Elevation of the serum muscle enzymes
4. Myopathic changes on electromyogram

DM requires in addition to the above-mentioned findings the presence of the typical rash (heliotrope rash or Gottron's tubercles).

DM—but not PM—correlates with the presence of malignancy, especially cancers of the ovaries, breasts, and colon, and melanomas. Those malignancies can predate, appear concomitantly, or follow the clinical symptoms of DM.[3]

Treatment consists mainly of high doses of corticosteroids, but unfortunately 75% of patients require addition of an immunosuppressive agent (eg, cyclosporine, methotrexate). For refractory DM, intravenous immunoglobulin is beneficial.[4]

Extramuscular involvement in DM and PM is common and includes systemic and vascular symptoms (fever, Raynaud's phenomenon), gastrointestinal symptoms, dysphagia, cardiac disturbances, subcutaneous calcifications, and pulmonary dysfunction. Among all those complica-

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tions, pulmonary dysfunction appears to be the most common and a major cause of morbidity and mortality.

We report a case of a rapidly progressive and fatal pulmonary complication of PM in an otherwise healthy young man.

Case Summary

A 41-year-old man presented to another hospital with a 2-week history of progressive shortness of breath, nonproductive cough, upper-extremity muscle weakness, and generalized fatigue. Prior to admission, the patient received a 2-week course of antibiotics, with no relief of his symptoms. Past medical history was negative for chronic obstructive pulmonary disease, asthma, skin rashes, or muscular weakness. He was an ex-smoker (8 pack-years) who had stopped smoking 2 years prior to admission. He denied alcohol, illicit drug abuse, or risk factors for human immunodeficiency virus. He worked as an electrician. His father died from emphysema and his brother from liver disease. His admission chest radiograph showed bibasilar opacities. He was diagnosed with community-acquired pneumonia, admitted to the hospital, and treated with ceftriaxone and clarithromycin. Table 1 shows his laboratory results on admission and at day 8.

His condition worsened over the next few days. Sputum and blood cultures were repeatedly negative. A computed tomogram (CT) of the chest done at that time was consistent with bilateral air-space disease, with multilobar consolidations. A flexible bronchoscopy was performed; cultures of the bronchoalveolar lavage fluid were negative and the transbronchial biopsy was positive only for inflammatory cells. Pulmonary function tests (PFTs) were consistent with severe restrictive lung disease and reduced carbon monoxide diffusing capacity (D_{LCO}). Because of his progressively worsening condition without a clear source of infection, the patient was started on prednisone (1 mg/kg/d), intubated for hypoxic respiratory failure, and transferred to our medical center.

On admission to our center the patient was on mechanical ventilation and sedated. Vitals signs were stable, with oxygen saturation of 98% while breathing 50% oxygen. Respiratory examination showed bibasilar crackles. Otherwise, physical examination was unremarkable, and his skin had no rashes or lesions. Arterial blood gas values while on assist-control ventilation, positive end-expiratory pressure of 10 cm H_2O, 70% oxygen, and tidal volume of 650 mL were pH 7.45, P_{aO_2} 54 mm Hg, and P_{aCO_2} 48 mm Hg. An electromyogram was consistent with inflammatory myopathy. A transthoracic echocardiogram showed normal left-ventricular systolic function, with an ejection fraction of 60%. The right ventricle was markedly enlarged, with a reduced systolic function. The right atrium was also enlarged. His estimated pulmonary artery systolic pressure

Table 1. Blood Studies Results on Hospital Days 1 and 8

	Day 1	Day 8	Normal
WBC (#/mL)	13,100	19,200	4,000–11,000
Hematocrit (%)	32.4	31.5	42–50
Platelets (#/mL)	345,000	548,000	150,000–300,000
MCV (fL)	68	65.8	86–98
ESR (mm/hr)	51	48	1–15
BUN (mg/dL)	11	13	8–20
Creatinine (mg/dL)	0.9	0.7	0.7–1.5
AST (U/L)	373	383	10–40
ALT (U/L)	305	410	12–79 U/L
Alk Phos (U/L)	175	242	30–120
Total protein (g/dL)	NM	5.9	5.5–9.0
Albumin (g/dL)	NM	1.8	3.5–5.5
CK (U/L)	10,349	3,342	5–55
CK-MB (U/L)	31.9	34.8	< 5% of total
Troponin (U/L)	0.49	0.38	< 2.0 ng/mL
Anti-Jo1 antibody	Negative	NM	*
LDH (U/L)	NM	1,622	≤ 190 U/L
ANA†	Negative	NM	< 1:40†

WBC = white blood cells
MCV = mean corpuscular volume
fl = femtoliter
ESR = erythrocyte sedimentation rate
BUN = blood urea nitrogen
AST = aspartate aminotransferase
ALT = alanine aminotransferase
Alk Phos = alkaline phosphatase
NM = not measured
CK = creatinine kinase
CK-MB = creatinine kinase - myocardial band
*No reference range information available
LDH = lactate dehydrogenase
ANA = antinuclear antibody
†ANA is measured in serial dilutions.

was elevated, at 60 mm Hg. On day 3 the patient still required a high level of oxygen and positive end-expiratory pressure. An open lung biopsy and muscle biopsy were performed.

Lung biopsy (Fig. 1) showed usual interstitial pneumonitis with recent and old interstitial and intra-alveolar fibrosis. Patchy interstitial lymphatic infiltrate with organizing thrombosis of small pulmonary arteries was also seen, without any evidence of vasculitis, granuloma, or viral inclusions. Muscle biopsy (Fig. 2) was consistent with mild inflammatory myopathy. Treatment with methylprednisolone (1 g/d for 3 d) was initiated. The patient's oxygen requirements continued to increase, and he had hemodynamic instability, hypotension, and signs of organ failure. On the request of the family, life support was withdrawn.

An autopsy was done. Macroscopically the lungs showed diffuse consolidation and fibrosis, with areas of marked congestion and signs of hemorrhagic infarction.

Microscopic examination of the lung showed diffuse interstitial and intra-alveolar fibrosis, with patchy acute hemorrhage. Also noted was the acute alveolar damage
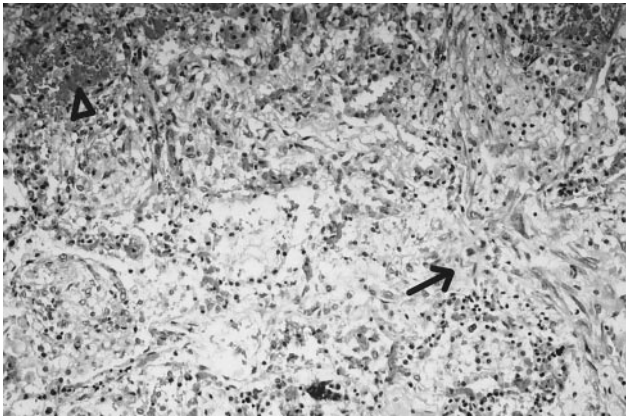
Fig. 1. Lung biopsy (hematoxylin and eosin stain, magnification 10) showing diffuse interstitial and intra-alveolar fibrosis (arrow) with patchy acute hemorrhage (arrowhead). There was focal thrombotic occlusion of the small pulmonary arteries (not shown). These findings are consistent with acute interstitial pneumonia (Hamman-Rich disease).
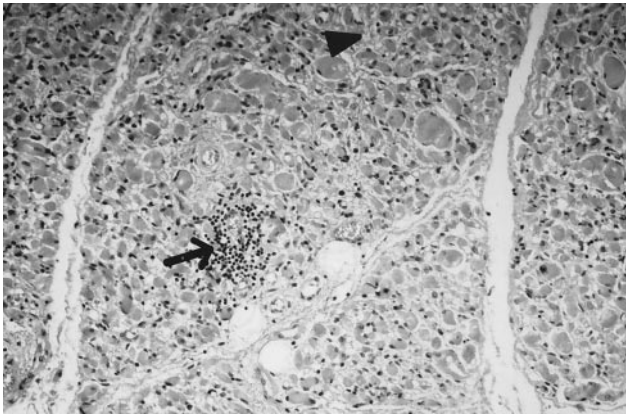

Fig. 2. Psoas muscle biopsy (hematoxylin and eosin stain, magnification 60) showing various degrees of muscle necrosis (arrowhead) in association with patchy lymphocytic infiltrates (arrow).

characterized by hyaline membrane formation. Multifocal thrombotic occlusion of small pulmonary arteries was found. Multiple foci of atypical squamous metaplasia were also noted. Overall findings were consistent with acute interstitial pneumonia (Hamman-Rich syndrome). Specimens taken from various muscle groups invariably showed muscle necrosis, with patchy lymphocytic infiltrate. The final diagnosis was acute interstitial pneumonitis secondary to a negative-serology PM.

Discussion

Pulmonary manifestations occur in 45% of patients with PM/DM.[5] Pulmonary complications of PM/DM are divided into primary complications (the interstitial lung disease [ILDs]) and secondary complications (aspiration pneumonia/pneumonitis, muscle weakness, infection, drug-induced disease, pulmonary congestion secondary to heart failure, pulmonary hypertension and pneumomediastinum).

Primary Pulmonary Complications of PM and DM

Interstitial Lung Disease. Initially described[6] in 1956, ILD complicates PM/DM in 5–30% of the cases. That variability in reports is due to different methods of diagnosis and referrals.[5,7,8] ILD is more common in women,[9] and the mean age at presentation is 50 years old. ILD occurs rarely if PM or DM is secondary to a malignancy.[10] Furthermore, the extent and severity of the myositis does not correlate with the occurrence of intrinsic lung disease. Pulmonary complications can appear prior to, concomitantly with, or after the diagnosis of the muscle or skin disease.[11]

The presentation of pulmonary involvement can be acute, chronic, or an incidental finding on chest imaging,[12] and it correlates with the underlying histopathologic disease. Six entities have been described in patients with PM/DM: bronchiolitis obliterans organizing pneumonia (BOOP); pulmonary capillaritis and alveolar hemorrhage; diffuse alveolar damage; nonspecific interstitial pneumonia; usual interstitial pneumonia; and acute interstitial pneumonia.

BOOP. BOOP can present acutely, with or without apparent muscle or skin manifestations, or can be found incidentally on radiograph, appearing as infiltrates in asymptomatic patients.[12] Pathologically, inflammatory polyps project into the terminal bronchioles and young connective tissue extends from the terminal bronchioles into the distal airways. A good response to corticosteroids and a good prognosis characterize BOOP, even though BOOP associated with collagen vascular disease tends to have a worse outcome than the isolated idiopathic form.[13] Some cases of BOOP may progress to usual interstitial pneumonia with honeycombing.[11,14]

Pulmonary Capillaritis and Alveolar Hemorrhage. Less commonly reported than BOOP, pulmonary capillaritis and alveolar hemorrhage presents acutely (< 2 wk), with or without hemoptysis. Typically, D_{LCO} is elevated and bronchoalveolar lavage fluid is hemorrhagic. The pathology findings consist of neutrophil infiltration of alveoli, intra-alveolar hemosiderin-laden macrophages, and pulmonary hemorrhage.[15] Pulmonary capillaritis and alveolar hemorrhage respond to steroids and thus carry a favorable prognosis.

Diffuse Alveolar Damage. Diffuse alveolar damage presents acutely, with or without skin or muscle manifestations. It results in acute respiratory distress syndrome and can be rapidly fatal.[16] Diffuse alveolar damage can com-

plicate a preexisting chronic ILD. The pathology findings consist of type II alveolar cell hyperplasia, alveolar edema with hemorrhage, hyaline membranes, and thickened, edematous interstitium.[12] Diffuse alveolar damage and the subsequent acute respiratory distress syndrome are resistant to steroids and immunosuppressive therapy and have a poor prognosis.[17]

Nonspecific Interstitial Pneumonia.   Katzenstein and Fiorelli[18] defined nonspecific interstitial pneumonia in 1994. Douglas et al[19] found nonspecific interstitial pneumonia the most common form of ILD complicating PM/DM (81.8% of 22 patients who underwent an open lung biopsy). Clinically, nonspecific interstitial pneumonia can present as chronic progressive symptoms of cough and dyspnea on exertion in a patient known to have PM/DM, as a radiographic infiltrate in an established case, or as an abnormal PFT or high-resolution CT, in a patient with normal chest radiograph.[16] Histologically, nonspecific interstitial pneumonia encompasses a broad spectrum of histologic features, with various degrees of alveolar wall inflammation or fibrosis. The "cellular" form consists of chronic interstitial inflammation with lymphocytes and plasma cells, with absent or little fibrosis, whereas the "fibrotic" form reveals on biopsy a temporally homogenous interstitial connective deposition, with loss of lung architecture. The latter form can be differentiated from usual interstitial pneumonia by the lack of temporal heterogeneity and fibroblasts foci. Radiographic findings consist of bilateral, predominantly lower lung fields parenchymal densities. CT features reflect the histological pattern. Bilateral, subpleural, and symmetrical ground-glass attenuation is the predominant finding in the cellular form, whereas reticular opacities and honeycombing are usually seen in the fibrotic form.[20] Treatment of nonspecific interstitial pneumonia consists of steroid therapy. Responsiveness to treatment depends on the histologic form: cellular nonspecific interstitial pneumonia is more responsive than the fibrotic form and thus carries a better prognosis.

Usual Interstitial Pneumonia.   The clinical presentation of usual interstitial pneumonia can be indistinguishable from nonspecific interstitial pneumonia. Usual interstitial pneumonia findings can precede the PM/DM symptoms by months to years. The pathology findings evolve from (1) a cellular pneumonia with extensive interstitial lymphoplasmocytic infiltrates and intra-alveolar macrophages, to (2) fibroblastic infiltrates and collagen deposition, to (3) the end stage of honeycombing and disruption of the anatomy.[12] However, honeycombing can also result from the progression of BOOP or nonspecific interstitial pneumonia. The prognosis is reserved, and usual interstitial pneumonia, as in idiopathic pulmonary fibrosis, responds poorly

to corticosteroids. Of note, the digital clubbing that is commonly seen with idiopathic pulmonary fibrosis/usual interstitial pneumonia is typically absent when usual interstitial pneumonia is associated with PM/DM.[21]

Acute Interstitial Pneumonia.   Similar to Hamman-Rich syndrome, acute interstitial pneumonia is another form of acute, fulminant ILD. As was the case with our patient, it can occur on top of a chronic form such as usual interstitial pneumonia or nonspecific interstitial pneumonia. The high-resolution CT findings (as reported by Akira et al) are bilateral, symmetrical areas of ground-glass opacity and consolidation.[14] Histologically, acute interstitial pneumonia is characterized by collagen deposition in the alveolar septum, type II alveolar lining cell hyperplasia, and minimal cellularity.[12] Acute interstitial pneumonia is poorly responsive to steroids, and mortality is high.

Diagnosis

The methods of choice for diagnosing ILD are high-resolution CT and PFT. It is highly recommended that those tests be part of the initial evaluation of a patient presenting with PM/DM, and during follow-up.[22] Furthermore, CT can have prognostic implications by suggesting one or the other of the histopathological forms. PFT will typically show a restrictive pattern, with reduced D_{LCO}. In early disease, exercise testing may be the only way to determine whether there is a gas exchange abnormality.

Bronchoalveolar lavage and transbronchial biopsy may be helpful in excluding other etiologies (eg, pneumonia or sarcoidosis), but are neither specific nor sensitive for the diagnosis of ILD. Open lung biopsy is the accepted standard for a final diagnosis.

Serological Markers

About 30% of patients with PM develop anti-Jo-1 antibodies. This anti-histidyl-tRNA synthetase, correlates strongly with the presence of ILD in PM.[17] In one report from 1985,[17] up to 66% of patients with PM and anti-Jo-1 developed radiographic evidence of pulmonary fibrosis. Its presence in a patient with PM warrants a close pulmonary follow-up for early detection of subclinical impairment.[22] A negative titer does not preclude the presence of IL; in one study 13% of anti-Jo-1-negative patients developed ILD, more recently Marie et al reported that 69% of their patients with ILD were seronegative for the anti-Jo-1 antibody.[23]

Of note is the antisynthetase syndrome, defined by arthritis "mechanic's hand," Raynaud's phenomenon, ILD, and a positive serologies for anti-synthetase (anti Jo-1, anti-EJ, PL-7, and PL-12).

Serum concentration of KL-6 (a mucinous glycoprotein expressed on type II pneumocytes), was found to be increased in patients with ILD associated with PM/DM and to correlate with the activity of the inflammatory process and its response to treatment.[24] It was demonstrated recently that KL-6 lacks specificity for ILD, since internal malignancies associated with PM/DM could increase the levels in patients free of lung involvement.[25]

In a small sample study, serum surfactant protein D was found to be increased in patients with PM/DM-associated ILD and to be inversely correlated with the vital capacity and the D_{LCO} in those patients.[26]

Course and Prognosis

Pulmonary disease can overshadow the primary muscle disorder, and patients with ILD have a higher mortality than patients with isolated PM/DM[27] (40% of patients with ILD die).[28] Prognosis depends on the histopathology findings, the specific form of ILD, and its response to therapy. Patients with interstitial pneumonia associated with collagen vascular diseases have a more favorable prognosis than those with idiopathic interstitial pneumonia. The larger proportion of nonspecific interstitial pneumonia than of usual interstitial pneumonia may explain that discrepancy.[29]

Progression of the ILD is more likely in patients with higher rates of skin and lung symptoms, milder muscle symptoms, lower levels of muscle enzymes, and negative anti-Jo-1 antibody.[30]

Other negative prognosticating factors for patients with DM include older age, dysphagia, concomitant aspiration pneumonitis, cardiac disease, and Raynaud's phenomenon.[12]

Treatment

The first-line treatment for PM/DM, with or without ILD, is steroids. The response to steroids depends on the underlying pathology feature. Corticosteroids therapy results in complete clinical, radiographic, and physiologic recovery in most patients with BOOP, for example, whereas usual interstitial pneumonia, diffuse alveolar damage, or acute interstitial pneumonia tend to be refractory to steroids. In a retrospective study, Nawata et al found that patients with lower levels of muscle enzymes are more likely to be resistant to steroids.[31]

Immunosupressive agents, cyclophosphamide, cyclosporine,[31] azathioprine, and tacrolimus should be used as second-line agents for patients who do not respond to corticosteroids. There have been no randomized, clinical trials comparing those different modalities, but the literature is abundant with case reports praising one or the other of those regimens or their combination.

Secondary Pulmonary Complications of PM and DM

Aspiration Pneumonia/Pneumonitis. Aspiration pneumonia/pneumonitis is one of the most common complications of PM/DM. It is secondary to pharyngeal or esophageal muscle involvement.[12] Aspiration can result in lung abscess formation or development of acute respiratory distress syndrome.

Infection. Aspiration and weak cough secondary to respiratory muscle inflammation and cytotoxic drugs explain the high prevalence of respiratory tract infections in PM/DM patients. Use of potent immunosuppressive drugs in patients with inflammatory diseases has been linked to opportunistic infections, including *Nocardia*[32] and *Pneumocystis carinii*.[33]

Respiratory Muscle Weakness. The respiratory muscles can be the targets of the autoantibodies, resulting in respiratory muscle inflammation and weakness. In that case the respiratory symptoms range from overt hypercapnic respiratory insufficiency that requires full ventilatory support to more subtle changes found on PFT or arterial blood gas analysis. Typically, the former will show a restrictive pattern with normal D_{LCO}, whereas the later will show a high P_{aCO_2} and some degree of hypoxemia. Measuring maximum inspiratory and expiratory pressures is a good tool to assess not only the lung involvement but also the severity of the generalized disease and its response to treatment.[34]

Cardiogenic Pulmonary Edema. Cardiac involvement in PM was described first in 1899.[35] Seventy percent of patients with PM are diagnosed with a cardiac abnormality during the course of the disease.[36] This can manifest as cardiac failure, myocarditis, myocardial ischemia, or conduction abnormalities.[37] Pulmonary edema can result from the above-mentioned cardiac complications and can present as interstitial infiltrates on chest radiograph, and/or hypoxia.[15]

Pulmonary Hypertension. Pulmonary hypertension is an uncommon but lethal complication of PM. It is most commonly secondary to the ILD-induced hypoxia, left ventricular failure, or hypercapnic respiratory insufficiency.[12] Pulmonary hypertension secondary to plexogenic pulmonary vascular disease is more common in scleroderma, the CREST syndrome (a variant of scleroderma characterized by *c*alcinosis, *R*aynaud's phenomenon, *e*sophageal motility disorders, *s*clerodactyly, and *t*elangiectasia), systemic lupus erythomatosis, and mixed connective tissue disease, than in PM,[38] but nonetheless was described with the latter and carries a poor prognosis.[39] Treatment is similar to primary pulmonary hypertension and includes calcium

channel blockers, prostacyclin infusion, endothelin-1 receptor blockers, and anticoagulation. Some experts recommend echocardiogram for patients with ILD as part of their ongoing assessment.[15]

Pneumomediastinum. Pneumomediastinum occurs in DM but not PM patients, usually DM patients who are on corticosteroids and with normal creatine kinase levels. Pneumomediastinum complicates 7.4% of cases among patients with ILD, but has been described in patients with no underlying lung pathology. The pathophysiology is unclear, but it is thought to be secondary to the vasculopathy associated with DM, which causes a disruption of the bronchial mucosal barrier,[40] or the ILD-induced cysts, which can rupture, especially when the interstitium is weakened by steroids.

Drug-Induced Lung Disease. Methotrexate causes lung disease in 3–5% of treated patients.[41] The presentation can mimic the myositis-induced interstitial pneumonitis and thus be indistinguishable from it. The presence of eosinophilia is suggestive of methotrexate lung injury, as is the presence of granulomas on lung biopsy.[10] Discontinuing methotrexate and adding steroids is the mainstay of the treatment. Usually this complication carries a favorable prognosis.[41]

Cyclophosphamide-induced pulmonary disease is similar in presentation, course, and treatment to methotrexate-induced pulmonary disease, but it occurs less frequently.

Conclusions

Pulmonary involvement in patients with PM/DM is frequent, and contributes substantially to the mortality and morbidity of the disease. The manifestations range from asymptomatic findings on chest radiograph to a more acute presentation that lead to death. This involvement is divided into primary and secondary manifestations. The primary manifestations include ILD, which can range from a chronic form (nonspecific interstitial pneumonia versus usual interstitial pneumonitis) to the more acute form (acute interstitial pneumonia). Secondary manifestations are, as the name implies, secondary to muscle weakness, aspiration, or to the treatment of PM/DM.

The most important prognostic factor is the histopathology findings from tissue provided by open lung biopsy. High-resolution CT and immunohistological studies may in the future allow us to predict with confidence the underlying interstitial disease and thus help with prognosis and treatment. High-dose steroids are the mainstay of the therapy; immunomodulating agents should be used as a second-line approach, as no randomized clinical trial has shown their definitive benefit. The case that we presented is a case of PM with negative anti-Jo1 antibodies, mild-

to-moderate increase of creatine kinase, and acute interstitial pneumonitis with fulminant course, complicating a more longstanding, insidious ILD (usual interstitial pneumonia), as evidenced by the lung biopsy. Unfortunately, the patient did not respond to steroids, and immunosuppressive treatment was not administered because of the high suspicion of secondary infectious processes.

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