Myositis-related interstitial lung disease and antisynthetase syndrome*, ,**

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Abstract

In patients with myositis, the lung is commonly involved, and the presence of anti-aminoacyl-tRNA synthetase (anti-ARS) antibodies marks the presence or predicts the development of interstitial lung disease (ILD). A distinct clinical entity—antisynthetase syndrome—is characterized by the presence of anti-ARS antibodies, myositis, ILD, fever, arthritis, Raynaud's phenomenon, and mechanic's hands. The most common anti-ARS antibody is anti-Jo-1. More recently described anti-ARS antibodies might confer a phenotype that is distinct from that of anti-Jo-1-positive patients and is characterized by a lower incidence of myositis and a higher incidence of ILD. Among patients with antisynthetase syndrome-related ILD, the response to immunosuppressive medications is generally, but not universally, favorable.

Keywords

Lung diseases; interstitial; Pneumonia; Infection

Introduction

The idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of acquired muscle diseases characterized by varying types and degrees of skeletal muscle inflammation. Three major subtypes are recognized: sporadic inclusion-body myositis; polymyositis (PM); and dermatomyositis (DM). However, aside from the skin involvement, PM and DM are similar enough that authors often use the term "PM/DM" when making reference to them.

Although PM and DM both typically manifest as progressive skeletal muscle weakness that spares the face and eyes, manifestations not involving the skeletal muscles are common and can be more clinically significant than the myositis. For example, abnormalities of the

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swallowing mechanism, cardiac involvement, and pulmonary disease are all frequently found in patients with PM/DM. In fact, the direct or indirect pulmonary manifestations of PM/DM are a major cause of morbidity and mortality. In 5% of PM/DM patients, respiratory muscle weakness leads to hypoventilation, resulting in atelectasis and complicating pneumonia. [1] A potentially fatal condition, aspiration pneumonia secondary to pharyngeal muscle dysfunction, occurs in 17% of patients with PM/DM.[2] Interstitial lung disease (ILD) is a long recognized complication, having first been described in the 1950s.[3] Mainly due to the sensitivity of chest CT, ILD is now recognized as the most common non-musculoskeletal manifestation of the disease; from one half to three quarters of PM/DM patients have evidence of ILD on HRCT scans of the chest.[4,5]

Autoantibodies are detectable in the sera of 50% of PM/DM patients and consist of myositis-associated and myositis-specific antibodies (MAAs and MSAs, respectively).[6] The MAAs are not specific to PM/DM and are found in a variety of autoimmune diseases. The MSAs are divided into those directed at the following: components of a nucleosome remodeling complex (anti-Mi-2)[7]; a macromolecular complex involved in RNA degradation and processing (anti-PM/Scl)[8]; ribonucleoproteins involved in translational transport (anti-signal recognition particle, or anti-SRP); and ribonucleoproteins involved in protein synthesis (anti-aminoacyl-tRNA synthetase antibodies, also known as antisynthetase antibodies, or anti-ARS).[9]

A specific subset of PM/DM patients have a clinical syndrome consisting of the presence of anti-ARS antibodies, ILD, and some of the following clinical features: fever, arthralgias, Raynaud's phenomenon, and exanthema on the hands (also referred to as mechanic's hands). This combination of findings is designated antisynthetase (AS) syndrome. In this paper, we review the data on PM/DM-related ILD, with a particular focus on AS syndrome.

AS syndrome

History

The association of PM/DM and extraskeletal manifestations has been recognized since the 1950s,[3] although it was not until the 1990s that AS syndrome was defined as a unique clinical entity. In 1990, Marguerie et al. described a series of 29 subjects with PM/DM and additional clinical features, including Raynaud's phenomenon, inflammatory arthritis, ILD, and a handful of anti-ARS antibodies (e.g., anti-Jo-1, PL-7, or PL-12).[10] In a subsequent study, Love et al. built on these findings by analyzing a cohort of PM/DM patients stratified by autoantibody profile.[11] The authors recognized significant differences in signs, symptoms, immunogenetics, and prognosis among the subgroups. In particular, PM/DM patients with anti-ARS antibodies were more likely to have fever, dyspnea, mechanic's hands, arthritis, and ILD than were those without such antibodies.

Autoantibodies

Although MAAs are common, they are not universally seen in PM/DM patients; antinuclear antibodies (ANAs), anti-SSA/Ro antibodies, and anti-U1 ribonucleoprotein (anti-U1-RNP) antibodies are found in 52%, 12%, and 11%, respectively.[11] In contrast, MSAs appear to define specific clinical phenotypes. Anti-Mi-2 antibodies are found in 4–14% of PM/DM patients and are associated with diffuse, cutaneous, steroid-sensitive skin involvement. [7,9,12] Anti-PM/Scl antibodies are found in approximately 8% of the patients who have the PM/systemic sclerosis overlap phenotype, which typically consists of skin manifestations of systemic sclerosis, together with clinical features similar to those seen in patients with anti-ARS antibodies.[13,14] Anti-SRP autoantibodies are present in 4% of the patients with myositis and might portend a poor prognosis, given their apparent association

with severe muscle disease and with cardiac involvement that is poorly responsive to treatment.[9,15,16]

Anti-ARS antibodies are directed against cytoplasmic enzymes that catalyze the formation of the aminoacyl-tRNA complex from an amino acid and its cognate tRNA. To date, eight different anti-ARS antibodies have been described: anti-PL-7 (anti-threonyl)[17]; anti-PL-12 (anti-alanyl) [18]; anti-OJ (anti-isoleucyl)[19]; anti-EJ (anti-glycyl)[19]; anti-KS (anti-asparaginyl)[20]; anti-ZO (anti-phenylalanyl)[21]; anti-tyrosyl[22]; and anti-Jo-1 (anti-histidyl).[23] All of these antibodies are directed at functionally related enzymes and are mutually exclusive in a given patient. Although initially believed to represent the general presence of an autoimmune myositis, it has subsequently become clear that they are in fact markers of AS syndrome clinical phenotypes.[10]

Anti-Jo-1 was the first anti-ARS to be discovered and characterized.[23] Perhaps because the other anti-ARS antibodies have only more recently been identified and few laboratories have the ability to test for them, anti-Jo-1 is the most commonly identified anti-ARS antibody, and most of the clinical data about AS syndrome is based on patients who are anti-Jo-1-positive. It is found in 20–30% of PM patients, in 5–10% of those with DM,[11] and in 75% of all reported cases in which an anti-ARS is present. The strongest predictor of ILD in PM/DM is the presence of anti-Jo-1—over 70% of anti-Jo-1-positive patients have ILD[4,24]—and disease activity might correlate with the levels of the antibody.[25] The significance of a positive result for anti-Jo-1 in the setting of ILD without any other criterion for AS syndrome remains unclear. Other anti-ARS antibodies are far less common: anti-PL-7 or anti-PL-12 are detected in 2–5% of the patients; and the rest (anti-OJ, anti-EJ, anti-KS, anti-ZO, and anti-tyrosyl) are identified in < 2% of the patients.[26]

Epidemiology

Although the overall incidence of inflammatory myopathies ranges from 6 to 10 per 1,000,000 population,[1,27] the incidence of anti-Jo-1 positivity ranges from 1.2 to 2.5 per million, with a reported prevalence of 1.5 per 100,000 population.[28,29] The average age at diagnosis of patients with anti-Jo-1-positive AS syndrome is 50 years (range, 22–74 years). [10,30] A predominantly female condition, the mean female/male ratio of AS syndrome is 2:1 (in some studies, this ratio is as great as 13:1). [31] In Japan and in the USA, patients with anti-Jo-1-positive AS syndrome appear to have similar phenotypes.[32] In one study of anti-Jo-1-positive patients, ILD was found to be more severe in African-Americans than in Whites.[30] There is an association between certain HLAs and PM: among anti-Jo-1-positive patients, 91% are positive for HLA-DR3, and 80% are positive for HLA-DQ2.[11,33]

Clinical characteristics of AS syndrome

The population of patients with AS syndrome present with a constellation of clinical and biochemical features. Key features for diagnosis include the presence of an anti-ARS antibody, accompanied by myositis, ILD, or both. Although arthritis, mechanic's hands, and Raynaud's phenomenon support the diagnosis, their presence is not necessary. In Chart 1, we propose diagnostic criteria for AS syndrome.

Myositis

Most anti-Jo-1-positive patients have PM, a smaller proportion having DM or overlap syndromes (57% vs. 28% in one study).[31] Muscle histopathology in anti-Jo-1-positive patients differs from that observed in antibody-negative patients. In contrast to antibody-negative patients, in whom there is predominately endomysial and perivascular inflammation, anti-Jo-1-positive patients have fragmentation of the perimysial connective

tissue with macrophage predominant inflammation and, in rare cases, vascular involvement.[34]

Myositis is not universal and can develop subsequent to the diagnosis of AS syndrome. Biochemical myositis is recognized to precede ILD in 12% of the patients with AS syndrome, whereas ILD precedes myositis in 37% of these, and their onset is simultaneous in 50%.[35] In one recent study, 31% of the patients who presented with ILD and anti-Jo-1 antibodies met the criteria for a diagnosis of myositis at the outset, and 56% of the patients eventually developed myositis over a median follow-up period of 62 months.[36] Because the diagnosis of AS syndrome can occur in the absence of myositis (termed "amyopathic" AS syndrome), the true incidence of clinically significant myositis in anti-Jo-1-positive patients with AS syndrome is unknown—most case series have required an a priori diagnosis of myositis.

Arthritis and other features

In anti-Jo-1-positive AS syndrome, arthritis, which is observed in up to 75% of the patients,[24,31,37] is symmetrical, involving the wrists and metacarpal/phalangeal joints, whereas the proximal interphalangeal joints, shoulders, knees, and elbows are less affected. The majority of articular symptoms occur early in the disease, are usually mild, and resolve with the treatment of myositis. In the majority of the patients with AS syndrome, such symptoms are non-deforming; however, up to a third of the patients will have joint subluxation without erosion and occasional periarticular calcinosis. [38] Joint effusions with inflammatory synovial fluid can occur.[39] Raynaud's phenomenon is often associated with the presence of anti-Jo-1 antibodies,[24,31,37] but mechanic's hands are a rare finding.[31,37] Fever is reported to occur in up to 35% of patients at some point during the course of disease.[31,35]

Associated diseases

The association between inflammatory myopathies (DM in particular) and malignancy is well recognized. Oddly, anti-ARS antibodies seem to be somewhat protective—subjects with anti-ARS antibodies are less likely to have malignancy.[40,41] However, two cases of malignancy (one of poorly differentiated lung adenocarcinoma and one of colon cancer) have been reported in patients with DM, positivity for anti-Jo-1 antibodies, and features of AS syndrome.[42,43] There have been multiple case reports of patients with AS syndrome developing other clinical disorders, including sarcoidosis,[44] myasthenia gravis,[45] ankylosing spondylitis,[46] Klinefelter syndrome,[47] and Kennedy's disease (an X-linked neuromuscular disease).[48] One case of suspected drug-induced AS syndrome has also been described.[49]

ILD

Depending upon the inclusion criteria, the method of investigation, and the length of the follow-up period, up to 75% of PM/DM patients will have some evidence of ILD at the time of diagnosis of the connective tissue disease. Therefore, in patients with PM/DM and respiratory symptoms, ILD should always be included in the differential diagnosis.

Clinical presentation—In many patients with AS syndrome-related ILD, the onset of dyspnea is gradual (occurring over a matter of months). However, in a subset of patients, the onset of ILD, fever, and respiratory insufficiency is abrupt (occurring over a few days or weeks).[36,50,51] Among a recently described group of 32 subjects with AS syndrome, equal numbers presented with acute respiratory insufficiency and a more insidious onset of dyspnea.[36]

Physiological, chest imaging, BAL fluid, and histological findings—Patients with AS syndrome-related ILD present with a restrictive pulmonary pattern and impaired gas exchange (mean TLC   60% of predicted; mean FVC   60% of predicted, and mean DLCO   50% of predicted).[10,30,36] An obstructive pattern is rare.

A pattern of nonspecific interstitial pneumonia (NSIP), with or without areas of consolidation (suggestive of organizing pneumonia), is usually revealed on HRCT scans. A usual interstitial pneumonia (UIP) pattern can also be seen. [30,36] In our experience, many patients present with a distinct pattern that is highly suggestive of AS syndrome-related ILD. In this pattern, there are (predominantly basilar) reticular and ground-glass opacities, accompanied by a loss of lung volume, traction bronchiectasis, and scattered (usually peribronchovascular) areas of consolidation (Figure 1).[52]

In BAL fluid, the few data available suggest that lymphocytes (primarily CD8-positive cells) predominate.[10,35,36,53] On surgical lung biopsy, an NSIP pattern is the most common; a UIP pattern, organizing pneumonia, or diffuse alveolar damage are observed in less than 20% of the patients (Figure 2).[10,35,36,53] In our experience, the combination of an NSIP pattern and organizing pneumonia is more common than is either in isolation.

Prognosis—Recognizing the limitations imposed by the variability in design, the retrospective format, and the limited number of the studies available, we can nevertheless surmise that the usual course of ILD in patients with AS syndrome is stabilization or improvement. Among patients who have ILD in the setting of PM/DM, the presence or absence of an anti-ARS antibody does not seem to affect the long-term outcome, although the antibodies might be markers of the patients who are more likely to have "flares" of ILD that require courses of high-dose corticosteroids or of other immunosuppressants.[54]

Anti-Jo-1-negative AS syndrome

Recent data suggest that there are subtypes of AS syndrome whose clinical characteristics (myositis, skin disease, severe ILD, or other clinical features, such as esophageal involvement or pulmonary hypertension) depend on which specific anti-ARS antibody is present (Chart 2). [5,10,30–32,35–38,53,55–60] For example, among patients with amyopathic AS syndrome, anti-Jo-1 is detected far less frequently than are other anti-ARS antibodies.[61]

Anti-PL-12

There have been six case series comprising 69 subjects that have reported the clinical syndrome associated with anti-PL-12 antibodies. [10,18,52,62–64] Similarly to patients with anti-Jo-1 antibodies, the average age of those patients at the time of diagnosis was 52 years (range, 22–87 years). Over 75% of the subjects with anti-PL-12 antibodies were women, and there was a high incidence of MAAs (over 80% of the subjects in one study), including anti-U1-RNP and anti-Sm antibodies, which are rarely seen in patients with anti-Jo-1-positive AS syndrome. [37,64] Compared with anti-Jo-1-positive AS syndrome patients, those testing positive for anti-PL-12 antibodies have a higher incidence of ILD (70–100%) and a lower incidence of biochemical myositis. Although early studies reported an incidence of myositis of 60–100%,[10,18,64] more recent reports have identified myositis in a smaller proportion of subjects (0–50%).[52,62,63] In a case series of subjects with amyopathic AS syndrome and ILD, anti-PL-12 antibodies were identified in 60% of the subjects.[65,66]

Among anti-PL-12-positive patients, Raynaud's phenomenon occurs in 40–100% but mechanic's hands are rare. Data from some studies suggest a higher incidence of pulmonary hypertension and esophageal involvement.[62,63,67] A UIP pattern of lung injury might be more common in patients with anti-PL-12-positive AS syndrome than in those with the anti-

Jo-1-positive form, which was present in over half of the subjects for whom histological data were available.[63] Prognosis seems to depend on the severity of ILD, and the response to immunosuppressive therapy is variable.[52]

Anti-PL-7

In six published studies, a combined total of 21 anti-PL-7-positive subjects were evaluated, and 63% were women.[10,17,52,68,69] The average age at diagnosis was in the fourth decade of life (range, 15–68 years). Compared with anti-Jo-1-positive AS syndrome patients, those testing positive for anti-PL-7 antibodies appear to have a higher incidence of ILD and a lower incidence of myositis. In a study of ANA-negative and anti-Jo-1-negative AS syndrome subjects with ILD, anti-PL-7 antibodies were identified in 77%, 42% of whom had muscle involvement. [10,52] Raynaud's phenomenon and arthritis have been reported.

Other anti-ARS antibodies

There have been isolated case reports of AS syndrome in subjects testing positive for anti-ARS antibodies that were discovered more recently. A study conducted in Japan evaluated 7 subjects with anti-OJ antibodies[70]: 4 were women; 4 had myositis; and all had ILD. In other studies, a total of 6 subjects with anti-KS antibodies have been described: all were women; none had myositis; but all had ILD.[20,35,71] Among 4 such subjects who underwent surgical lung biopsy, a UIP-pattern was identified in 2, and a NSIP-pattern was identified in 2. There has been only one reported case of anti-ZO-positive AS syndrome: a 49-year-old woman with myositis, arthritis, Raynaud's phenomenon, and an HRCT pattern consistent with NSIP.[21]

Therapy and prognosis

Early reports looking at IIM-associated ILD suggested a favorable response to therapy with prednisone[72,73]: 30–40% of the subjects improved; and 20–40% stabilized based on symptoms and pulmonary function. A subset of patients are resistant to corticosteroids, and there are reports of remission induced by the addition of azathioprine, methotrexate, cyclophosphamide, cyclosporine, tacrolimus, or mycophenolate mofetil.[74–80] In early studies, deaths from ILD were rare: the death rate from respiratory failure was reported to be approximately 10% at a median follow-up period of 4 years. Among all comers (i.e., with or without AS syndrome), the five-year survival rate for individuals with PM/DM-related ILD appears to be similar to that reported for those with idiopathic NSIP—60% for both.[74]

In a comprehensive evaluation of patients with IIM and ILD followed for a median duration of 53 months, one group of authors observed that among the subjects treated with immunosuppressive drugs, ILD resolved in 19% and improved in 55%.[24] The authors reported one-, three-, and five-year survival rates of 94.4%, 90.4%, and 86.5%, respectively. In 25%, ILD progressed, and, in that group, there was a higher incidence of neutrophilia in BAL fluid and a UIP pattern on biopsy. As observed by other investigators, the presence of anti-Jo-1 was not associated with the outcome.[54,57] One group of investigators prospectively followed 20 consecutive patients with ILD and PM/DM, the majority of whom had AS syndrome: 10 had a stable, nonprogressive course, and 10 had rapidly progressive ILD. All of those with progressive disease stabilized or improved with the addition of cyclophosphamide (to the background therapy with prednisolone), although relapses occurred.[76] In one study focusing on patients with AS syndrome, the majority of the subjects improved with immunosuppression: 72% of the patients stabilized with the treatment. However, 28% developed progressive respiratory failure and died. Relapse was more common in those treated with corticosteroids alone. There were no differences in the response to therapy or in the outcome at one year among those presenting with acute

respiratory failure or gradual onset of dyspnea.[36] Another group of authors studied 14 anti-ARS-positive ILD patients and observed that ILD improved with corticosteroids (with or without cyclosporine) in 64%; only 1 patient died from respiratory failure.[35] One group of investigators observed that, at a mean disease duration of 5 years, the subjects with anti-ARS antibodies had a mortality rate of 21% compared with that of 7% in the subjects with no MSA.[11] The poorer outcome in these subjects has been attributed to the presence of ILD.[81,82]

Our usual approach to therapy for PM/DM-related ILD (including patients with AS syndrome) is to use a combination of glucocorticoids and a steroid-sparing agent (usually mycophenolate mofetil or azathioprine). We use cyclophosphamide for cases with clinically severe or rapidly progressive ILD. For patients in whom ILD worsens despite aggressive conventional therapy, rituximab has been used with moderate success,[83,84] with the stabilization or improvement of 7 of the 11 patients evaluated in one case series (Chart 3).[85]

Acknowledgments

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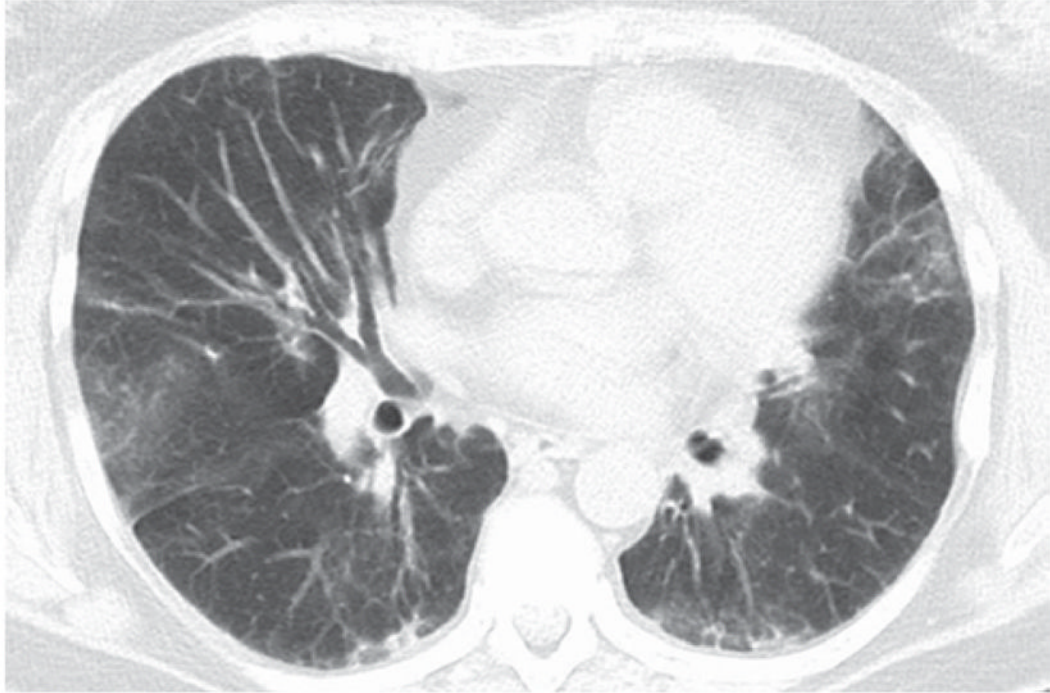
Figure 1.
Slice through the lower lung zones from an HRCT scan of a patient with antisynthetase syndrome and interstitial lung disease showing reticular and patchy ground-glass opacities in the lung bases.
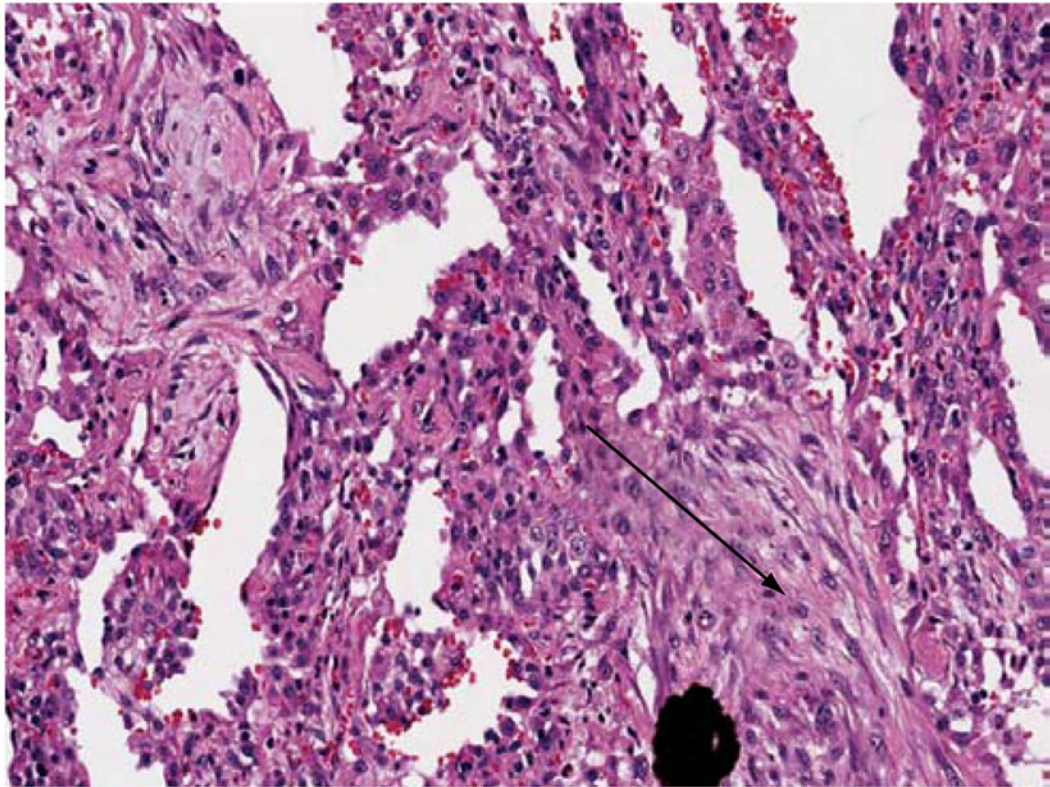
Figure 2.
Lung biopsy from a patient with antisynthetase syndrome and interstitial lung disease showing cellular interstitial infiltrate and organizing pneumonia (arrow).

Presence of an anti-aminoacyl-tRNA synthetase antibody plus two major criteria or one major and two minor criteria.

Major Criteria

    1. ILD (not explained by environmental, occupational, or drug exposures and not related to any other underlying disease)

    2. Polymyositis or dermatomyositis in accordance with the Bohan & Peter criteria

Minor Criteria

    1. Arthritis

    2. Raynaud's phenomenon

    3. Mechanic's hands

ILD: interstitial lung disease.

Chart 1.

Proposed criteria for the diagnosis of antisynthetase syndrome.

Anti-ARS antibody	Amino acid tRNA synthetase target	Patients	Age, years	Female	Lung involvement	Myositis	Other
		n	Median	%	%	%	
Anti-Jo-1	Histidine	308[5,30,31,35-37]	50	66	84	78-100	Arthritis in up to 75%; Raynaud's phenomenon in 50%; mechanic's hands in up to 20%
Anti-PL-12	Alanine	69[10,18,52,62-64]	52	75	95	60	Reports of higher pulmonary hypertension and esophageal involvement
Anti-PL-7	Threonine	21[10,17,52,68,69]	47	63	84	84	Infrequent muscle involvement in recent studies
Anti-OJ	Isoleucine	9[35,70,86]	53	67	55	100	All described patients with ILD
Anti-KS	Asparagine	6[20,35,71]	51	100	100	0	UIP in 40% of biopsies
Anti-EJ	Glycine	1[35]	57	100	100	100	Dermatomyositis
Anti-ZO	Phenylalanine	1[21]	49	100	100	100	NSIP on biopsy

Anti-ARS: anti-aminoacyl-tRNA synthetase; ILD: interstitial lung disease. UIP: usual interstitial pneumonia; and NSIP: nonspecific interstitial pneumonia.

Chart 2.
Anti-aminoacyl-tRNA synthetase antibodies and associated clinical phenotypes.

Treatment (for)	Medications
Mild and moderate disease	Systemic corticosteroids plus a steroid-sparing agent[a]
Severe disease	Cyclophosphamide[76,78]
Rescue	Rituximab[83-85]

[a]Studies with azathioprine, methotrexate, cyclosporine, tacrolimus, and mycophenolate mofetil.[24,35,36,74,75,79,80]

Chart 3.
Treatment of patients with antisynthetase syndrome and interstitial lung disease.