CME CREDIT *EDUCATIONAL OBJECTIVE:* Readers will consider the diagnosis of antisynthetase syndrome in the appropriate clinical setting

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Antisynthetase syndrome: Not just an inflammatory myopathy

ABSTRACT

In recent years, antisynthetase syndrome has been recognized as an important cause of autoimmune inflammatory myopathy in a subset of patients with polymyositis and dermatomyositis. It is associated with serum antibodies to aminoacyl-transfer RNA synthetases and is characterized by a constellation of manifestations, including fever, myositis, interstitial lung disease, "mechanic's hands," Raynaud phenomenon, and polyarthritis. Physicians should be familiar with its variety of clinical presentations and should include it in the differential diagnosis in patients presenting with unexplained interstitial lung disease.

KEY POINTS

Antisynthetase syndrome can present with a wide variety of clinical manifestations, including myositis and interstitial lung disease.

The type and severity of interstitial lung disease usually determine the long-term outcome.

In the appropriate clinical setting, the diagnosis is usually confirmed by the detection of antibodies to various aminoacyl-transfer RNA synthetases, anti-Jo-1 antibody being the most common.

Although glucocorticoids are considered the mainstay of treatment, additional immunosuppressive agents such as azathioprine or methotrexate are often required as steroid-sparing agents and also to achieve disease control.

In the case of severe pulmonary involvement, cyclophosphamide is recommended.

A 66-year-old man was initially seen in clinic in March 2004 with a 5-month history of polyarthritis (affecting the finger joints, wrists, and knees) and several hours of morning stiffness. He also had significant proximal muscle weakness, progressive exertional dyspnea, and a nonproductive cough. There was no history of fever, chills, rash, dysphagia, or sicca symptoms. Findings on initial tests:

- His creatine kinase level was 700 U/L (reference range 30–220), which later rose to 1,664 U/L.
- He was positive for antinuclear antibody with a 5.7 optical density ratio (normal < 1.5) and for anti-Jo-1 antibody.
- An electromyogram was consistent with a necrotizing myopathy. Left rectus femoris biopsy revealed scattered degenerating and regenerating muscle fibers but no evidence of endomysial inflammation.
- On pulmonary function testing, his forced vital capacity was 80% of predicted, and his carbon monoxide diffusion capacity was 67% of predicted.
- High-resolution computed tomography revealed evidence of interstitial lung disease, characterized by bilateral patchy ground-glass opacities suggestive of active alveolitis, most extensive at the lung bases.
- Bronchoalveolar lavage indicated alveolitis, and transbronchial biopsy revealed pathologic changes consistent with cryptogenic organizing pneumonia. All cultures were negative.

This constellation of clinical manifestations, including myositis, interstitial lung disease, and polyarthritis, along with positive anti-Jo-1 antibody, confirmed the diagnosis of antisynthetase syndrome.

FIGURE 1. Thickened, hyperkeratotic, and fissured skin of the tips and margins of the fingers ("mechanic's hands").

In June 2004, for his interstitial lung disease, he was started on daily oral cyclophosphamide along with high-dose oral prednisone. Three months later the skin of the tips and radial margins of his fingers started thickening and cracking, the appearance of which is classically described as "mechanic's hands," a well-described manifestation of antisynthetase syndrome (**FIGURE 1**).

Cyclophosphamide was continued for about a year. Subsequently, along with prednisone, he sequentially received various other immunosuppressive medications (methotrexate, tacrolimus, mycophenolate mofetil, and rituximab) over the next few years in an attempt to control his progressive interstitial lung disease. All of these agents were only partially and temporarily effective. Ultimately, despite all of these therapies, as his interstitial lung disease progressed, he needed supplemental oxygen and enrollment in a pulmonary rehabilitation program.

In March 2010, he was admitted with worsening dyspnea and significant peripheral edema and was found to have severe pulmonary arterial hypertension. He was started on bosentan. Eight months later sildenafil was added for progressive pulmonary arterial hypertension. However, his oxygenation status continued to decline.

In July 2011, he presented with chills, increasing shortness of breath, and a mild productive cough. As he was severely hypoxic, he was admitted to the intensive care unit and started on mechanical ventilation and broad-spectrum antibiotics. Despite escalation of oxygen therapy, his respiratory status rapidly deteriorated, and he developed hypotension requiring vasopressors. He ultimately died of cardiac arrest secondary to respiratory failure.

◼ A CONSTELLATION OF MANIFESTATIONS

Antisynthetase syndrome, associated with anti-aminoacyl-transfer RNA (tRNA) synthetase antibodies, is characterized by a constellation of manifestations that include myositis, interstitial lung disease, mechanic's hands, fever, Raynaud phenomenon, and nonerosive symmetric polyarthritis of the small joints.[1]

Anti-Jo-1 antibody (anti-histidyl-tRNA synthetase) is the most common of the antibodies and also was the first one to be identified (**TABLE 1**). It was named after John P, a patient with polymyositis and interstitial lung disease, in whom it was first detected in 1980.[2] The onset of the syndrome associated with anti-Jo-1 antibody is often acute, and the myositis is usually steroid-responsive. However, not uncommonly, severe disease can develop over time, with a tendency to relapse and with a poor long-term prognosis.

◼ RARE BUT UNDERRECOGNIZED

The true population prevalence of antisynthetase syndrome is unknown. Because this syndrome is rare, comprehensive epidemiologic studies are difficult to perform.

In several retrospective studies, the annual incidence of idiopathic inflammatory myopathies has been reported to be 2 to 10 new cases per million adults per year.[3] Antisynthetase antibodies are detected in 20% to 40% of such cases.[4–6] The disease is two to three times more common in women than in men.[7]

Early diagnosis is difficult because the clinical presentation is varied and often nonspecific, clinically milder disease may escape detection, and many general practitioners lack familiarity with this syndrome and consequently do not recognize it. Moreover, tests for myositis-specific antibodies (including antisynthetase antibodies) are often not ordered in the evaluation of myositis, and hence the diagnosis of antisynthetase syndrome cannot be substantiated. Furthermore, interstitial

The true prevalence of antisynthetase syndrome is unknown, but it is rare

TABLE 1

Antisynthetase antibodies

Name	Antigen	Prevalence*	ILD	Myositis	Other manifestations
Jo-1	Histidyl-tRNA synthetase	25%–30%	++	++	Arthritis (75%) Raynaud phenomenon (50%) Mechanic's hands (20%)
PL-7	Threonyl-tRNA synthetase	2%–5%	++	+	Infrequent muscle involvement Severe arthritis
PL-12	Alanyl-tRNA synthetase	2%–5%	++	+	Pulmonary hypertension Esophageal involvement
OJ	Isoleucyl-tRNA synthetase	1%	++	+	ILD in all patients
EJ	Glycyl-tRNA synthetase	1%	+	+	Dermatomyositis
KS	Asparaginyl-tRNA synthetase	1%	++	–	Fever UIP in 40% of cases
Wa	Autoantibody to a 48-kDa transfer RNA-related protein	1%	+	+	
YRS	Tyrosyl-tRNA synthetase	NA	+	+	Rash Arthritis
Zo	Phenylalanyl-tRNA synthetase	NA	+	+	NSIP on biopsy Raynaud phenomenon Arthralgia

*In patients with dermatomyositis or polymyositis

ILD = interstitial lung disease; NA = not available; UIP = usual interstitial pneumonitis; NSIP = nonspecific interstitial pneumonitis

lung disease can predominate or can be the sole manifestation in the absence of clinically apparent myositis,[8–10] and patients can be misdiagnosed as having idiopathic pulmonary fibrosis when underlying antisynthetase syndrome is not suspected. This distinction may be important because these conditions differ in their pathology and treatment. Histologically, the predominant pattern of lung injury in idiopathic pulmonary fibrosis is "usual interstitial pneumonia" which does not respond to immunosuppressive therapy, and hence lung transplantation is the only therapeutic option. On the other hand, in antisynthetase syndrome, the usual pattern of lung injury is "nonspecific interstitial pneumonia," in which immunosuppressive therapy has a role.

Anti-Jo-1 antibody is detected in 15% to 25% of patients with polymyositis and in up to 70% of myositis patients with concomitant interstitial lung disease.[11] Autoantibodies to seven other, less frequently targeted, amino-acyl tRNA synthetases have also been described in patients with polymyositis and interstitial lung disease (**TABLE 1**).[11,12] In addition, an autoantibody to a 48-kDa transfer RNA-related protein (Wa) has been described.[13] These non-Jo-1 antisynthetase antibodies are detected in only about 3% of myositis patients.[14]

■ ROLE OF ANTISYNTHETASE ANTIBODIES

Synthetases play a central role in protein synthesis by catalyzing the acetylation of tRNAs. The propensity of organ involvement in antisynthetase syndrome suggests that tissue-specific changes in muscle or lung lead to the production of unique forms of target autoantigens, the aminoacyl-tRNA synthetases. There is evidence that these enzymes themselves may be

TABLE 2
Idiopathic inflammatory myopathy: Clinical features and investigations

Features	Investigations and main findings
Myositis	Clinical evaluation (manual muscle testing) – Proximal muscle weakness. Pelvic girdle muscles, especially iliopsoas and quadriceps, are predominantly affected, causing difficulty climbing stairs or getting up from a chair. Arm abductors (supraspinatus and deltoid) and neck muscles (sternocleidomastoid and splenius capitis) are also involved.
	Laboratory findings – Elevated muscle enzymes (creatine phosphokinase and aldolase) Positive antisynthetase antibody (see text); acute-phase reactants (erythrocyte sedimentation rate and C-reactive protein) may be elevated
	Electromyography – Fibrillation potentials, positive sharp waves, and myopathic motor unit potentials (ie, low-amplitude, short-duration polyphasic motor unit potentials on voluntary activation); early recruitment, in which the number of motor unit potentials is increased at low levels of muscle contraction due to loss of individual muscle fibers from the motor unit; complex repetitive discharges, which are indicative of a gradually progressive process
	Magnetic resonance imaging of affected muscles – May show increased signal intensity in the affected muscles and surrounding tissues (edema of the affected muscle groups)
	Upright and supine spirometry and fluoroscopy – May demonstrate evidence of diaphragmatic and intercostal muscle weakness
	Muscle biopsy – Characteristic features of inflammatory myopathy (see text)
Interstitial lung disease	Clinical evaluation – Bilateral end-inspiratory crackles on auscultation of lung bases
	Complete pulmonary function test (spirometry, static lung volumes, and transfer factor) – Restrictive lung disease (low forced vital capacity, total lung capacity, carbon monoxide diffusing capacity)
	Plain chest radiograph – Reduced lung volumes with bilateral reticular or reticulonodular opacities
	High-resolution computed tomography of lungs – Ground-glass opacification, reticulonodular shadows, traction bronchiectasis, or patchy air-space disease (organizing pneumonia)
	Lung biopsy – Different patterns of lung injury: cellular or fibrotic nonspecific interstitial pneumonitis, usual interstitial pneumonitis, organizing pneumonia or diffuse alveolar damage; some patients also develop pulmonary arteriopathy (intimal thickening and luminal narrowing) associated with pulmonary hypertension (see text)
Rash	Clinical evaluation – Mechanic's hands, Gottron papules, heliotrope rash
	Skin biopsy – Interface psoriasiform dermatitis
Inflammatory arthritis	Clinical evaluation – Tender, swollen joints (mostly small joints of hands, feet, wrists, and knees)
	Radiograph – Soft-tissue swelling, typically nonerosive; can sometimes be erosive and destructive, resembling rheumatoid arthritis
	Magnetic resonance imaging – Bone edema and evidence of synovitis or tenosynovitis
Dysphagia	Barium swallow – Differentiates from mechanical obstruction
	Videofluoroscopy – Dysmotility due to upper esophageal and oropharyngeal muscle (striated muscles) weakness
Cardiomyopathy	Electrocardiography – Sinus tachycardia, conduction abnormalities (sometimes)
	2D-echocardiography – Reduced ejection fraction, dilated cardiac chambers (global hypokinesia)
Pulmonary arterial hypertension	2D-echocardiography – Elevated estimated right ventricular systolic pressure (> 35 mm Hg), dilated right ventricle, right ventricular diastolic and systolic dysfunction
	Right heart catheterization – Elevated mean pulmonary artery pressure (> 25 mm Hg), normal pulmonary capillary wedge pressure (< 15 mm Hg)

involved in recruiting both antigen-presenting and inflammatory cells to the site of muscle or lung injury.[15] However, the molecular pathway that initiates and propagates this autoimmune response and the specific role of the antisynthetase antibodies in the pathogenesis of this syndrome are presently unknown.

■ SIX SALIENT CLINICAL FEATURES

There are six predominant clinical manifestations, which may be present at disease onset or appear later as the disease progresses:
- Fever
- Myositis
- Interstitial lung disease
- Mechanic's hands
- Raynaud phenomenon
- Inflammatory polyarthritis.

There is considerable clinical heterogeneity, and one or other manifestation can predominate or can be the only expression of the syndrome. Furthermore, in the same patient, the individual features can prevail at different times and may develop years after onset of the disease. Therefore, in addition to patients with myositis, it would be important to suspect antisynthetase syndrome in patients presenting with isolated lung involvement (amyopathic interstitial lung disease), as there are therapeutic implications. Studies have demonstrated the efficacy of immunosuppressive agents in interstitial lung disease associated with antisynthetase syndrome (where the predominant pattern of lung injury is "nonspecific interstitial pneumonitis"), whereas lung transplantation has so far been the only treatment option in idiopathic pulmonary fibrosis.

Fever
About 20% of patients have a fever at disease onset or associated with relapses. Sometimes the fever can persist until treatment of antisynthetase syndrome is started.

Myositis
Muscle disease is seen in more than 90% of patients with anti-Jo-1 antisynthetase syndrome. It can be subclinical (in the absence of proximal myopathy), manifested by transient creatine kinase elevation only, which may normalize after therapy is initiated.

However, more commonly, patients develop profound proximal muscle weakness and sometimes muscle pain (TABLE 2). Weakness of the striated muscles of the upper esophagus, cricopharyngeus, and hypopharynx may cause dysphagia and makes these patients susceptible to aspiration pneumonia. Diaphragmatic and intercostal muscle weakness can contribute to shortness of breath in some patients. Myocarditis has also been reported.

Pulmonary disease
Interstitial lung disease develops in most patients with anti-Jo-1 antisynthetase syndrome, with a reported prevalence of about 90% in one series.[16] Patients often present with acute, subacute, or insidious onset of exertional dyspnea. Sometimes there is an intractable nonproductive cough.

At the outset of antisynthetase syndrome, if the patient is profoundly weak because of myopathy or has inflammatory polyarthritis, mobility is significantly compromised, and exertional dyspnea may not be experienced. However, as the interstitial lung disease progresses, shortness of breath becomes overt, more so when the patient's level of activity improves with treatment of myositis.

Inspiratory crackles on auscultation of the lung bases or changes on chest radiography are relatively insensitive findings and can miss early interstitial lung disease. Therefore, if antisynthetase syndrome is suspected or diagnosed, a baseline pulmonary function test (spirometry and carbon monoxide diffusion capacity) is indicated. It will often detect occult interstitial lung disease, and the diagnosis can then be confirmed with thoracic high-resolution computed tomography (FIGURE 2).

Pulmonary hypertension. Recent studies indicate that, similar to patients with other autoimmune rheumatic diseases, pulmonary hypertension can develop in patients with antisynthetase syndrome, with or without concomitant interstitial lung disease.[17,18] This complication occurred in the case presented here. It has been found that when pulmonary hypertension coexists with interstitial lung disease, its degree may not correlate with the severity of the latter.[17] Additionally, pulmonary hypertension, when present, has been

Muscle disease is seen in > 90% of patients with anti-Jo-1 syndrome
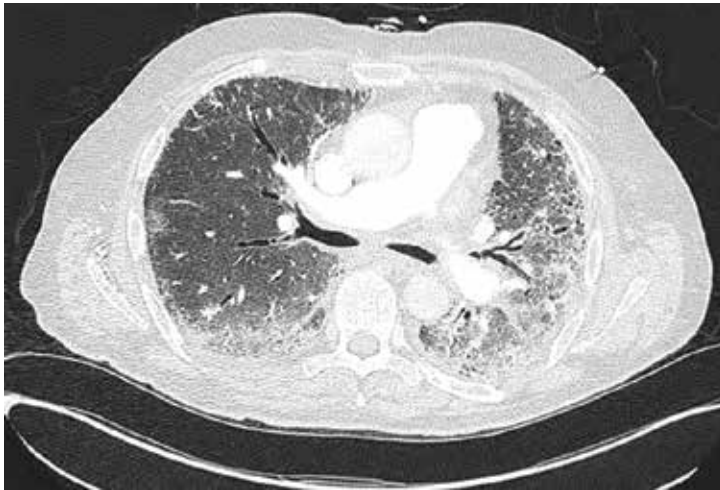
FIGURE 2. Thoracic high-resolution computed tomography in a 66-year-old man with interstitial lung disease and fibrosis associated with antisynthetase (anti-Jo-1) antibody syndrome. Note the bilateral patchy ground-glass opacities suggestive of active alveolitis, most extensive at the lung bases, along with bilateral subpleural reticular infiltrates and interlobular septal thickening.

found to contribute independently to prognosis and survival.

Injudicious testing for a long list of antibodies should be avoided

Mechanic's hands
In about 30% of patients, the skin of the tips and margins of the fingers becomes thickened, hyperkeratotic, and fissured, the appearance of which is classically described as mechanic's hands. It is a common manifestation of antisynthetase syndrome and is particularly prominent on the radial side of the index fingers (**FIGURE 1**). Biopsy of affected skin shows an interface psoriasiform dermatitis.[19] In addition, some dermatomyositis patients with Gottron papules and a heliotrope rash have antisynthetase antibodies.

Raynaud phenomenon
Raynaud phenomenon develops in about 40% of patients. Some have nailfold capillary abnormalities.[20] However, persistent or severe digital ischemia leading to digital ulceration or infarction is uncommon.[21]

Inflammatory arthritis
Arthralgias and arthritis are common (50%), the most common form being a symmetric polyarthritis of the small joints of the hands and feet. It is typically nonerosive but can

sometimes be erosive and destructive.[20]

Because inflammatory arthritis mimics rheumatoid arthritis, antisynthetase syndrome should be considered in rheumatoid factor-negative patients presenting with polyarthritis.

■ ASSOCIATION WITH MALIGNANCY

Traditional teaching has been that antisynthetase antibody is protective against an underlying malignancy.[22,23] However, several recently published case studies have reported various malignancies occurring within 6 to 12 months of the diagnosis of antisynthetase syndrome.[7,24] The debate as to whether these are chance associations or causal (a paraneoplastic phenomenon) has not been resolved at this time.[24]

It is now recommended that patients with antisynthetase syndrome be screened for malignancies as appropriate for the patient's age and sex. Screening should include a careful history and physical examination, complete blood cell count, comprehensive metabolic panel, chest radiography, mammography, and a gynecologic examination for women.[25] If abnormalities are found, a more thorough evaluation for cancer is appropriate.

■ DIAGNOSIS

Muscle enzyme levels are often elevated
Muscle enzymes (creatine kinase and aldolase) are often elevated. Serum creatine kinase levels can range between 5 to 50 times the upper limit of normal. In an established case, creatine kinase levels along with careful manual muscle strength testing may help evaluate myositis activity. However, in chronic and advanced disease, creatine kinase may be within the normal range despite active myositis, partly because of extensive loss of muscle mass. In myositis, it may be prudent to check both creatine kinase and aldolase; sometimes only serum aldolase level rises, when immune-mediated injury predominantly affects the early regenerative myocytes.[26]

Judicious use of autoantibody testing
The characteristic clinical presentation is the initial clue to the diagnosis of antisynthetase syndrome, which is then supported by serologic testing.

Injudicious testing for a long list of antibodies should be avoided, as the cost is considerable and it does not influence further management. However, ordering an anti-Jo-1 antibody test in the correct clinical setting is appropriate, as it has high specificity,[27,28] and thus can help establish or refute the clinical suspicion of antisynthetase syndrome.

Screening pulmonary function testing and thoracic high-resolution computed tomography for all patients with polymyositis or dermatomyositis is not considered "standard of care" and will likely not be reimbursed by third-party payers. However, in a patient with symptoms and signs of myositis, the presence of an antisynthetase antibody should prompt screening for occult interstitial lung disease, even in the absence of symptoms. As lung disease ultimately determines the prognosis in antisynthetase syndrome, early diagnosis and management is the key. Therefore, these tests would likely be approved to establish the diagnosis of interstitial lung disease and evaluate its severity.

If a myositis patient is also found to have interstitial lung disease or develops mechanic's hands, the likely diagnosis is antisynthetase syndrome, which can be confirmed by serologic testing for antisynthetase antibodies. Interstitial lung disease in antisynthetase syndrome is often from "nonspecific interstitial pneumonitis"; therefore, medications tested and proven effective for this condition should be approved and reimbursed by payers.[29–32]

The coexistence of myositis and interstitial lung disease increases the sensitivity of anti-Jo-1 antibody.[11] Thus, the clinician can have more confidence in early recognition and initiation of aggressive but targeted disease-modifying therapy.

Various methods can be used for detecting antisynthetase antibodies, with comparable results.[28] Anti-Jo-1 antibody testing costs about $140. If that test is negative and antisynthetase syndrome is still suspected, then testing for the non-Jo-1 antisynthetase antibodies may be justified (TABLE 1). Though the cost of this panel of autoantibodies is about $300, it helps to confirm the diagnosis, and it influences the choice of second-line immunosuppressive agents such as tacrolimus[29] and rituximab[32] in patients resistant to con-

ventional immunosuppressive agents such as azathioprine and methotrexate.

Often, anti-Ro52 SS-A antibodies are present concurrently in patients with anti-Jo-1 syndrome.[33] In observational studies in patients with anti-Jo-1 antibody-associated interstitial lung disease, coexistence of anti-Ro52 SS-A antibody tended to predict a worse pulmonary outcome than in those with anti-Jo-1 antibody alone.[34,35]

Electromyography
Electromyography not only helps differentiate between myopathic and neuropathic weakness, but it may also support the diagnosis of "inflammatory" myopathy as suggested by prominent muscle membrane irritability (fibrillations, positive sharp waves) and abnormal motor unit action potentials (spontaneous activity showing small, short, polyphasic potentials and early recruitment). However, the findings can be nonspecific, and may even be normal in 10% to 15% of patients.[36] Electromyographic abnormalities are most consistently observed in weak proximal muscles, and electromyography is also helpful in selecting a muscle for biopsy. Although no single electromyographic pattern is considered diagnostic for inflammatory myopathy, abnormalities are present in around 90% of patients (TABLE 2).[3]

Magnetic resonance imaging
Magnetic resonance imaging may show increased signal intensity in the affected muscles and surrounding tissues (FIGURE 3).[37] Because it lacks sensitivity and specificity, magnetic resonance imaging is not helpful in diagnosing the disease. However, in the correct clinical setting, it may be used to guide muscle biopsy, and it can help in monitoring the disease progress.[38]

Muscle histopathology
Muscle biopsy, though often helpful, is not always diagnostic, and antisynthetase syndrome should still be suspected in the right clinical context, even in the absence of characteristic pathologic changes.

Biopsy of sites recently studied by electromyography should be avoided, and if the patient has undergone electromyography recently, the contralateral side should be selected for biopsy.

In chronic and advanced cases, creatine kinase may be within the normal range despite active myositis, partly because of extensive loss of muscle mass
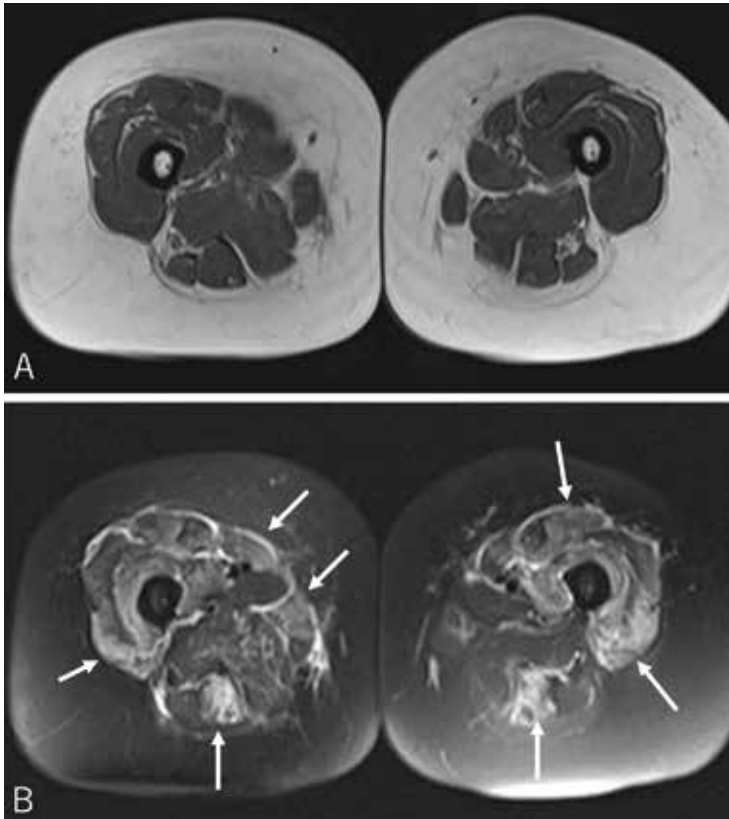
FIGURE 3. Magnetic resonance imaging of the thighs. **A,** axial T1-weighted image is essentially normal with no demonstration of intramuscular hemorrhage, muscle atrophy, or fatty replacement. **B,** axial fat-suppressed T2-weighted image shows extensive, symmetric increased signal intensity (arrows) involving muscles of the anterior and adductor compartments more so than the gluteals and posterior compartments. Imaging findings of muscle edema are consistent with an inflammatory myopathy but are nonspecific.

Reports of histopathologic findings in muscle biopsies in patients with antisynthetase syndrome document inflammatory myopathic features (**FIGURE 4**). In a series of patients with anti-Jo-1 syndrome, inflammation was noted in all cases, predominantly perimysial in location, with occasional endomysial and perivascular inflammation.[39] Many of the inflammatory cells seen were macrophages and lymphocytes, in contrast to the predominantly lymphocytic infiltrates described in classic polymyositis and dermatomyositis. Perifascicular atrophy, similar to what is seen in dermatomyositis, was encountered; however, vascular changes, typical of dermatomyositis, were absent. Occasional degenerating and regenerating muscle

fibers were also observed in most cases. Additionally, a characteristic perimysial connective tissue fragmentation was described, a feature less often seen in classic polymyositis and dermatomyositis.[39]

Pulmonary function testing
If antisynthetase syndrome is suspected or diagnosed, baseline pulmonary function testing (spirometry and carbon monoxide diffusion capacity) is indicated. It will often detect occult interstitial lung disease (reduced forced vital capacity and carbon monoxide diffusion capacity), and the diagnosis will be substantiated on thoracic high-resolution computed tomography. Respiratory muscle weakness can be detected with upright and supine spirometry.[40] Weakness of these muscles contributes to shortness of breath, and patients may need ventilatory support.

**Thoracic high-resolution
computed tomography**
Different patterns of lung injury can be seen in antisynthetase syndrome. Diffuse ground-glass opacification may suggest a nonspecific interstitial pneumonitis pattern, which is the most common form of interstitial lung disease (**FIGURE 2**), whereas coarse reticulation or honeycombing correlates with a usual interstitial pneumonitis pattern. Patchy consolidation or air-space disease can occur if cryptogenic organizing pneumonia is the predominant pattern of lung injury.

Swallowing evaluation
A comprehensive swallowing evaluation by a speech therapist may be necessary for evaluation of dysphagia (from oropharyngeal and striated esophageal muscle weakness) and determination of aspiration risk (**TABLE 2**).

Lung histopathology
If necessary, a surgical lung biopsy is needed to document the pathologic pattern of injury, including the amount of fibrosis in the lung. Historically, in idiopathic inflammatory myopathy patients in general, this has taken the form of usual interstitial pneumonia, organizing pneumonia, or diffuse alveolar damage.[41] With the emergence of the definition of nonspecific interstitial pneumonitis and fibrosis
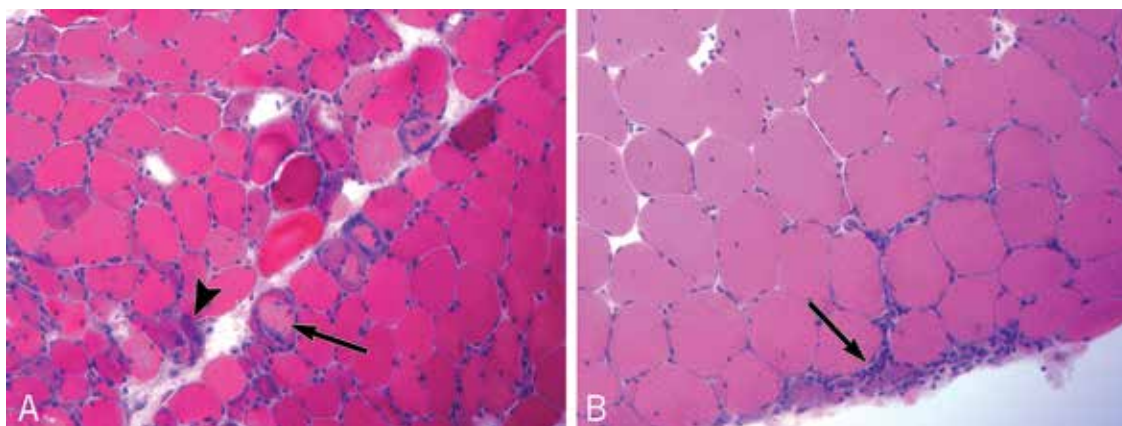
FIGURE 4. Muscle biopsy. **A,** scattered degenerating muscle fibers with pale staining cytoplasm (arrow) and several regenerating muscle fibers that show a purple staining with enlarged nuclei (arrowhead). Degenerating or necrotic muscle fibers and regenerating muscle fibers are common features of many inflammatory myopathic processes (hematoxylin and eosin, 200 X). **B,** a focus of chronic endomysial inflammation consisting primarily of benign appearing lymphocytes and macrophages (arrow) adjacent to a few regenerating muscle fibers (hematoxylin and eosin, 200 X).

as a documented and accepted pattern, more studies have found this to be the most common pattern of lung injury.[16] It is characterized by diffuse involvement of the lung by an interstitial chronic inflammatory infiltrate, a cellular type of nonspecific interstitial pneumonitis that progresses in a uniform pattern to a fibrotic type (**FIGURE 5**). This form of fibrosis rarely results in significant remodeling, so-called honeycomb changes. In addition, anti-Jo-1 antibody patients may also have an increased incidence of acute lung injury, including acute diffuse alveolar damage that is often superimposed on the underlying chronic lung disease.[42]

In patients with pulmonary hypertension, histopathologic studies of the muscular pulmonary arteries often show moderate intimal fibroplasia, suggesting that a pulmonary arteriopathy with intimal thickening and luminal narrowing develops in some of these patients (**FIGURE 5**), independent of chronic hypoxic pulmonary vasoconstriction or vascular obstruction due to its entrapment within fibrotic lung tissue.[17]

■ TREATMENT

Glucocorticoids are the mainstay

Glucocorticoids are considered the mainstay of treatment. Patients should be ad-

vised that long-term use of glucocorticoids is necessary, though the response is variable. It is also important to discuss possible side effects of long-term glucocorticoid use.

Standard practice is to initiate treatment with high doses for the first 4 to 6 weeks to achieve disease control, followed by a slow taper over the next 9 to 12 months to the lowest effective dose to maintain remission. If the patient is profoundly weak, especially with respiratory muscle weakness or significant dysphagia and aspiration risk, hospital admission for intravenous methylprednisolone 1,000 mg daily for 3 to 5 days may be necessary. Otherwise, oral prednisone 1 mg/kg/day would be the usual starting dose.

If the patient's muscle strength initially improves and then declines weeks to months later despite adequate therapy, glucocorticoid-induced myopathy should be suspected, especially if the muscle enzymes are within the reference range. This is more likely to occur if high-dose prednisone is continued for more than 6 to 8 weeks.

Improvement in muscle strength, which can take several weeks to several months, is a more reliable indicator of response to therapy than the serum creatine kinase level, which may take much longer to normalize.

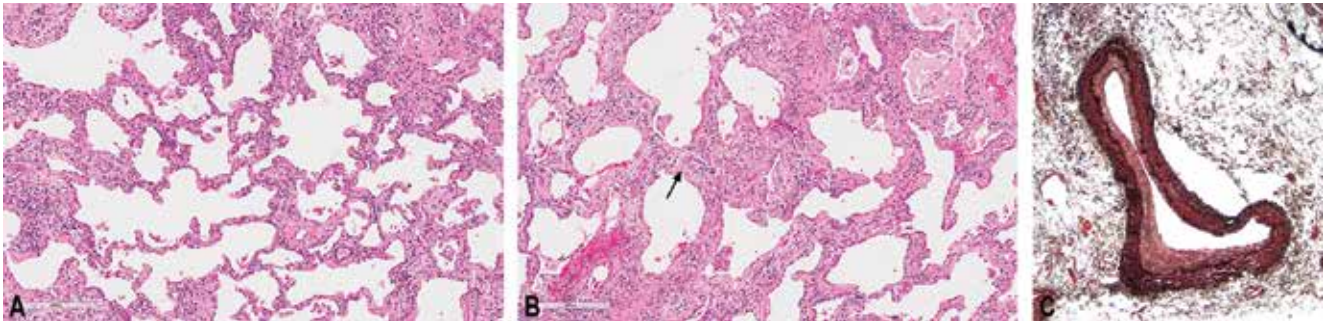**If antisynthetase syndrome is suspected or diagnosed, baseline pulmonary function testing is indicated**

FIGURE 5. Lung biopsy. **A,** nonspecific interstitial pneumonitis, cellular type. The lung parenchyma reveals a diffuse, homogeneous chronic inflammatory infiltrate involving the interstitium without evidence of fibrosis (hematoxylin and eosin, 130 X). **B,** nonspecific interstitial pneumonitis, fibrosing type. This pattern of injury shows a similar diffuse inflammatory infiltrate with evidence of collagenous-type fibrosis involving the interstitium (arrow) (hematoxylin and eosin, 130 X). **C,** pulmonary vasculopathy with intimal fibrosis. This image highlights the increased fibrosis present in the intima of the vessels with early collagenous-type fibrosis deposition narrowing the vessel lumen (Movat, 40 X).

Relying on normalization of the creatine kinase level alone may lead to unnecessary prolongation of high-dose glucocorticoid therapy. It may take several months for the muscle enzymes to normalize, and there is usually a time lag between normalization of muscle enzymes and complete recovery of muscle strength.

Long-term use of high-dose prednisone leads to glucocorticoid-induced osteoporosis. Therefore, patients should receive osteoporosis prophylaxis including antiresorptive therapy with a bisphosphonate. In addition, prophylaxis against *Pneumocystis jirovecii* is indicated for patients treated with high-dose glucocorticoids.

Additional immunosuppressive agents

Although glucocorticoids are considered the mainstay of treatment, additional immunosuppressive agents such as azathioprine and methotrexate are often required, both as glucocorticoid-sparing agents and to achieve adequate disease control.[10] Addition of such agents from the outset is particularly necessary in patients with profound muscle weakness or those who have concomitant symptomatic interstitial lung disease.

No randomized controlled trial comparing azathioprine and methotrexate has been conducted to date. Therefore, the choice is based on patient preference, presence of coexisting interstitial lung disease or liver disease, commitment to limit alcohol con-

sumption, and thiopurine methyltransferase status. Most patients need prolonged therapy.

In a randomized clinical trial, concomitant therapy with prednisone and azathioprine resulted in better functional outcomes and a significantly lower prednisone dose requirement for maintenance therapy at 3 years than with prednisone alone.[43,44] Although no such randomized study has been conducted using methotrexate, several retrospective studies have demonstrated 70% to 80% response rates, including those for whom monotherapy with glucocorticoids had failed.[45,46] The combination of methotrexate and azathioprine may be beneficial in patients who previously had inadequate responses to either of these agents alone.[47]

For severe pulmonary involvement associated with antisynthetase syndrome, monthly intravenous infusion of cyclophosphamide has been shown to be effective.[48,49]

Some recent studies established the role of tacrolimus in the treatment of both interstitial lung disease and myositis associated with antisynthetase syndrome.[29] Cyclosporine has also been successfully used in a case of interstitial lung disease associated with anti Jo-1 syndrome.[30]

Rituximab, a monoclonal antibody to B-lymphocyte antigen CD20, can also be used successfully in refractory disease,[31] including refractory interstitial lung disease.[32]

In an open-label prospective study, poly-

Physical therapy and rehabilitation should begin early if the patient is profoundly weak

myositis refractory to glucocorticoids and multiple conventional immunosuppressive agents responded well to high-dose intravenous immune globulin in the short term.[50] However, the antisynthetase antibody status in this cohort was unknown; therefore, no definite conclusion could be drawn about the efficacy of intravenous immune globulin specifically in antisynthetase syndrome.

General measures

In patients with profound muscle weakness, physical therapy and rehabilitation should begin early. The goal is to reduce further muscle wasting from disuse and prevent muscle contractures. Patients with oropharyngeal and esophageal dysmotility should be advised about aspiration precautions and may need a swallow evaluation by a speech therapist; some may need temporary parenteral hyperalimentation or J-tube insertion.

■ PROGNOSIS

If skeletal muscle involvement is the sole manifestation of antisynthetase syndrome, patients usually respond to glucocorticoids and immunosuppressive therapy and do fairly well. However, the outcome is not so promising when patients also develop interstitial lung disease, and the severity and type of lung injury usually determine the prognosis. As expected, patients with a progressive course of interstitial lung disease fare poorly, whereas those with a nonprogressive course tend to do relatively better. Older age at onset (> 60 years), presence of a malignancy, and a negative antinuclear antibody test are associated with a poor prognosis.[7] ■

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