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Brief Report: Antisynthetase Syndrome–Associated Myocarditis

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Abstract

Background—The antisynthetase (AS) syndrome is characterized by autoimmune myopathy, interstitial lung disease, cutaneous involvement, arthritis, fever, and antibody specificity. We describe 2 patients with AS syndrome who also developed myocarditis, depressed biventricular function, and congestive heart failure.

Methods and Results—Both patients were diagnosed with AS syndrome based on clinical manifestations, detection of serum AS antibodies, and myositis confirmation with the use of skeletal muscle magnetic resonance imaging and skeletal muscle biopsy. In addition, myocarditis resulting in heart failure was confirmed with the use of cardiac magnetic resonance imaging and from endomyocardial biopsy findings. After treatment for presumed AS syndrome–associated myocarditis, one patient recovered and the other patient died.

Conclusions—AS syndrome is a rare entity with morbidity and mortality typically attributed to myositis and lung involvement. This is the first report of AS syndrome–associated myocarditis leading to congestive heart failure in 2 patients. Given the potentially fatal consequences, myocarditis should be considered in patients with AS syndrome presenting with heart failure.

Keywords

Antisynthetase syndrome; myocarditis; heart failure

Idiopathic inflammatory myopathies (IIMs) comprise a heterogeneous group of diseases including dermatomyositis (DM), polymyositis (PM), inclusion-body myositis, and immune-mediated necrotizing myopathies.^{1–4} DM and PM are the most common IIMs and share several clinical features, including proximal muscle weakness, elevation of serum skeletal muscle enzymes, irritability on electromyography, and histopathologic evidence of chronic inflammatory cell infiltrates in the skeletal muscle.¹ In 25%–30% of cases, DM and PM are

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Disclosures

None.

associated with antibodies against aminoacyl-tRNA synthetases, also known as anti-synthetase (AS) antibodies.^{4,5} Of these, the anti-histidyl (Jo-1) antibody is most common, with a prevalence of 15%–25% in patients with myositis.^{6–9} The presence of AS antibodies along with a distinctive clinical phenotype characterized by inflammatory myopathy, nonerosive arthritis, interstitial lung disease (ILD), fever, and scaly, fissured, hyperkeratotic skin changes on the lateral and palmar surface of the hands and fingers (“mechanic’s hands”) constitutes the AS syndrome.^{6–10} In patients with AS syndrome, significant morbidity and mortality is attributed to ILD, and the presence of AS antibodies is the strongest predictor for the development of ILD.^{10,11}

Cardiac involvement in DM and PM was first reported in 1899, has varying reported prevalence (6%–75%), and is associated with worse outcomes compared with cases without cardiac involvement.^{12–16} Abnormalities of nearly every component of the cardiac structure have been reported, including the pericardium (pericarditis), myocardium (conduction system abnormalities, myocarditis), and endocardium (mitral valve prolapse).^{13,14} Congestive heart failure occurs in 3%–25% of patients, leading to death in 10%–20% of patients with PM.^{14,17} Several reports have described myocarditis associated with IIM, identified with the use of cardiac magnetic resonance imaging (MRI).^{18–20} Cardiac involvement in AS syndrome is far less common, however, with only scant case reports, including a 63-year-old woman with severe congestive cardiomyopathy, a 26-year-old man with right heart failure, and a 47-year-old woman with severe aortic valve regurgitation.^{21–23} To our knowledge, the 2 patients with AS syndrome described in the present report are the first to have histologically proven myocarditis leading to congestive heart failure.

Case Descriptions

Patient 1

A previously healthy 44-year-old African-American man developed 3 months of unexpected weight loss, progressive leg and forearm edema, and hand “roughness.” His symptoms improved after 3 weeks of diuretic treatment; however, he declined a diagnostic work-up. He remained asymptomatic for 1 year but then developed progressive anasarca, orthopnea, paroxysmal nocturnal dyspnea, exertional dyspnea, muscle “tightness,” and a 9-kg weight increase. The patient’s familial history was rather unremarkable except for hypertension. He did not use alcohol, tobacco, illicit substances, or supplements. At presentation, he appeared fatigued and dyspneic after speaking a few sentences. Physical examination revealed signs consistent with acute decompensated congestive heart failure and marked bilateral proximal muscle weakness of the upper and lower extremities. In addition, he had “mechanic’s hands.”

Laboratory studies detailed in Table 1 were significant for elevations of serum creatine kinase (CK), lactate dehydrogenase (LDH), aldolase, CK-MB, and cardiac troponin I. Anti-Jo-1 antibody was positive. Electrocardiography (ECG) revealed a normal QRS axis at 92°, sinus tachycardia, first-degree atrioventricular block, and an age-indeterminate anteroseptal infarct pattern. Transthoracic echocardiography (TTE) showed severe enlargement of all 4 cardiac chambers, left ventricular end-diastolic diameter (LVEDD) of 6.2 cm, left

ventricular ejection fraction (LVEF) of 20%–25%, marked right ventricular (RV) dysfunction, and moderate tricuspid regurgitation, without evidence of pericardial effusion. Chest computerized tomography (CT) revealed signs consistent with congestive heart failure, and coronary CT angiography showed no coronary artery disease. MRI of the legs showed diffuse increased T2-signal intensity in the proximal thighs, leg muscles, and subcutaneous tissue, consistent with myositis. Electromyography (EMG) revealed features of irritable myopathy and sensory-motor axonal polyneuropathy. A biopsy obtained from the right rectus femoris muscle showed chronic perivascular inflammation, myofiber atrophy degeneration, and regeneration worse in perifascicular regions, along with moderate type 2 fiber atrophy with minimal neurogenic atrophy, consistent with DM.

He underwent pulmonary artery catheterization, which revealed elevated right- and left-sided filling pressures [right atrial (RA) mean 20 mm Hg, right ventricular (RV) 37/18 mm Hg, pulmonary artery (PA) 39/25 mm Hg, PA mean 31 mm Hg, pulmonary capillary wedge pressure (PCWP) mean 20 mm Hg, PA oxygen saturation 60%]. Cardiac MRI and endomyocardial biopsy of the RV intraventricular septum were performed, with findings consistent with myocarditis in the setting of AS syndrome.

He was initiated on 3 days of pulse-dose corticosteroid therapy, which resulted in improved muscle strength and exercise tolerance during his hospital admission. He was treated with diuretic therapy and initiated on guideline-based heart failure management, including angiotensin-converting enzyme inhibitor (ACE-I) and aldosterone antagonist therapies; beta-blocker therapy was initiated before discharge. From an immunosuppression standpoint, he was changed to an oral prednisone and methotrexate regimen. After his discharge, the patient declined further care. Further contact was limited to 1 telephone call 6 months later, when he reported continued improvement in his exercise tolerance, with mild leg edema as his only symptom. He remained on corticosteroid therapy, but declined further medication adjustments.

Patient 2

A 51-year-old white woman with inflammatory arthritis and hypothyroidism presented to another hospital with 6 months of increasing fatigue, bilateral proximal muscle weakness, leg edema, dyspnea, and orthopnea. She was transferred to our hospital with severe biventricular heart failure. Her family history was notable for esophageal cancer in her mother and coronary artery disease in several first-degree relatives. The patient smoked tobacco for 20 pack-years but had quit several years earlier and rarely consumed alcoholic beverages. Laboratory studies summarized in Table 1 were notable for elevated CK, aldolase, CK-MB, and cardiac troponin I levels. Anti-nuclear (ANA), anti-thyroid peroxidase, and anti-Jo-1 antibodies were all positive. ECG showed a QRS axis of 75, sinus rhythm, occasional premature atrial complexes, and low voltages in all leads. TTE showed mild to moderate LV dysfunction, mild RV dysfunction, and a moderate-sized circumferential pericardial effusion, measuring 1.4 cm inferiorly and 1.0 cm anteriorly, without signs of tamponade. MRI of the bilateral hips and thigh muscles demonstrated diffuse moderately increased T2 signal. EMG showed mildly irritable myopathy with evidence of right median neuropathy and ulnar neuropathy. Right triceps muscle biopsy

from another hospital revealed severe type II fiber atrophy, perifascicular atrophy, and chronic perivascular inflammation, histopathologically consistent with DM. Given the presence of anti-Jo-1 antibody, she was diagnosed with AS syndrome and treated with prednisone. In addition, her thyroid replacement therapy was increased, and she was started on guideline-based heart failure medications, including ACE-I and beta-blocker therapies.

Two months later, she presented with progressive heart failure but with improved muscle strength. Her ECG remained abnormal at that time. A repeated TTE showed severely depressed biventricular function, with an LVEF of 10%–15%, normal LV cavity size (LVEDD 4.5 cm), normal wall thickness, and apical dyskinesis. Mild mitral regurgitation was evident with a stable pericardial effusion. Coronary angiography demonstrated patent coronary arteries. Pulmonary artery catheterization revealed elevated LV and RV pressures (RA mean 33 mm Hg, RV 45/25 mm Hg, PA 43/31 mm Hg, PA mean 36 mm Hg, PCWP 30 mm Hg), with low cardiac output (cardiac index 1.18 liter/min/meter²; systemic vascular resistance index 3,817 dynes/sec/cm⁻⁵/m²). Cardiac MRI and endomyocardial biopsy of the RV intraventricular septum were then obtained, with findings consistent with myocarditis associated with AS syndrome.

She was treated with pulse-dose corticosteroid therapy, intravenous furosemide, inotrope therapy, and hemofiltration therapy. She was not considered for cardiac transplantation or other advanced mechanical therapies owing to progressive renal and hepatic failure, but did improve enough to be discharged with continuous intravenous dobutamine palliative therapy. Subsequent TTE studies showed no changes in cardiac function, with minimal improvement in her pericardial effusion. Two months later, she presented in cardiogenic shock, failed intensive medical therapy, and died after a cardiac arrest.

Methods

Each patient underwent cardiac MRI, skeletal muscle biopsy, and endomyocardial biopsy.

Cardiac MRI

Cardiac MRI images were obtained in short- and long-axis orientations. Cine sequences were acquired for assessing biventricular function. Delayed-enhancement T1-weighted images were obtained after injecting 0.2 mmol/kg gadopentetate dimeglumine (Magnevist; Schering).

Skeletal Muscle Biopsies

Skeletal muscle biopsies were obtained from patient 1, and a triceps muscle specimen was obtained from another hospital from patient 2. Both biopsy samples were frozen transverse muscle sections and were stained histochemically with hematoxylin and eosin (HE), modified Gomori trichrome, ATPase at pH 4.3, 4.6, and 9.4, NADH-tetrazolium reductase, acid phosphatase, SDH, cytochrome oxidase, esterase, alkaline phosphatase, periodic acid–Schiff (PAS), PAS-diastase control, Sudan black, fructose 1,6-bisphosphatase, fructose 6-phosphatase, myophosphorylase, and Congo red. In addition, paraffin embedment of formalin-fixed tissue and fascia was performed, and the sections were also stained with HE.

Endomyocardial Biopsies

Both patients had endomyocardial biopsies taken from the RV intraventricular septum. Histologic and immunohistologic preparations from the endomyocardial biopsies included HE, PAS, Congo red, Prussian blue, Masson trichrome, Movat pentachrome, CD3, and CD68.

Results

Cardiac MRI

The cardiac MRI of patient 1 showed severe biventricular global hypokinesis with mild dilation of the LV, mild to moderate dilatation of the RV, and severe dilatation of the right atrium. Delayed enhancement could not be assessed owing to motion artifact. The cardiac MRI of patient 2 (Fig. 1) showed severe biventricular global hypokinesis with diffuse biventricular myocardial and pericardial enhancement, consistent with severe inflammation and/or fibrosis, and a moderate pericardial effusion.

Skeletal Muscle Biopsy Specimens

Patient 1's skeletal muscle biopsy was from the right rectus femoris muscle and showed chronic perivascular inflammation, myofiber atrophy degeneration, and regeneration, which was worse in the perifascicular regions. There was also moderate type 2 fiber atrophy with minimal neurogenic atrophy. Patient 2's skeletal muscle biopsy specimen was obtained from the triceps muscle at another hospital and showed moderately severe type 2 fiber atrophy with scant endomysial chronic perivascular inflammation.

Endomyocardial Biopsy Specimens

The endomyocardial biopsies of both patients revealed active myocarditis (Fig. 2) with CD3⁺ lymphocytes clustered around injured myocytes. Also, CD68⁺ macrophages were diffusely increased throughout the biopsies with some clustering around the injured myocytes. No giant cells, eosinophils, or macrophages were seen.

Discussion

We present 2 cases of AS syndrome associated with histologically proven myocarditis and clinical heart failure. Although myocarditis has not been previously reported as a manifestation of AS syndrome, we postulate that there is a relationship between them. Both patients had typical signs of a chronic inflammatory state, with cellular infiltrates in their myocardium and skeletal muscle, similar to previous reports of cardiac involvement in patients with IIMs, particularly DM and PM.^{24,25} In addition, both patients' myocardial tissue displayed a similar histopathologic pattern previously described in patients with DM and PM, characterized by cardiac myocyte degeneration and mononuclear inflammatory cell infiltrate localized within the endomysium and perivascular areas.^{26,27}

Understanding the pathophysiologic mechanisms leading to AS syndrome would help with treatment; however, much remains speculative. There is probably a genetic component, as relationships between HLA types and racial subgroups can lead to different types of

autoimmune myopathies.^{28,29} In addition, environmental factors may play a role, such as exposure to ultraviolet radiation.³⁰ More likely, aberrant responses to infection due to “molecular mimicry” between autoantigen molecules and infectious agents may result in cross-reactive antibodies and myositis.^{31–34} As a result, B cells are activated, expressing immunoglobulin to the common epitope, and act as antigen-presenting cells for T cells after processing autoantigen molecules.³⁵

Disease-specific autoantibodies may play a direct role in the mechanisms of inflammation and myopathy as well, as clinical manifestations appear to depend on autoantibody conformation and AS antibody levels appear to correlate with disease severity.³⁵ However, there is no direct evidence demonstrating pathologic effects resulting in myositis. In fact, myositis autoantigen expression occurs in normal regenerating muscle cells, and high levels are also found in cultured myoblasts compared with differentiated mature myotubes.³⁶ Nevertheless, AS antibodies are likely to be associated with clinical disease. Intrinsically, AS antibody-associated fragments cause chemokine-like activities against inflammatory cells, such as CD4+ and CD8+ T cells, activated monocytes, and immature dendritic cells, in the setting of muscle cell injury.³⁷ In addition, AS antibodies act as signaling molecules, promoting tumor necrosis factor secretion from macrophages.³⁸ Finally, the Jo-1 antibody in particular up-regulates major histocompatibility complex I, inducing muscle and lung inflammation, and increasing lung endothelial cell intercellular adhesion molecule expression.^{39–41}

The effect of AS antibodies on the heart is unclear, and there are no earlier studies that have detected antibody expression levels in cardiac tissue. Proposed mechanisms of cardiac involvement in AS syndrome include coronary artery inflammation leading to vasculitis, intimal proliferation, microvascular disease, or coronary vasospasm, all of which may contribute to impaired LV function and conduction abnormalities.^{25,27} It is also probable that underlying autoimmune processes may contribute to myocarditis owing to AS effects on humoral and cellular immune mechanisms.^{7,42} Based on our limited experience in caring for these 2 patients, we suspect that intrinsic myocardial inflammation is more likely, although further investigation is warranted to better understand the mechanisms leading to AS syndrome-associated myocarditis.

As expected, there are no guidelines to aid in the diagnosis of cardiac manifestations associated with AS syndrome. ECG is a reasonable initial test to screen for cardiac involvement; up to 85% of IIM patients demonstrate ECG changes. However, ECG is neither sensitive nor specific for the detection of myocarditis.^{43,44} Other types of myocarditis have been associated with ECG findings of low voltage and acute myocardial ischemia which revert to normal with myocarditis improvement.⁴⁵ Reasonable initial screening laboratory tests include serum cardiac biomarkers (CK, troponins I and T), although CK and its isoform CK-MB are of limited utility owing to their low predictive value.⁴⁵ Cardiac troponin elevation is reported in 35% of IIM cases, with low sensitivity (34%, troponin I; 53%, troponin T) and high specificity (89%, troponin I; 94%, troponin T) for the detection of myocarditis.^{46,47} B-type natriuretic peptide may also be used in the setting of clinical heart failure. An early study of erythrocyte sedimentation rate (ESR) to characterize a population with “reactive” myocardial disease found the sensitivity and

specificity of ESR to be very low for myocarditis.⁴⁸ In IIM, ESR and C-reactive protein are associated with the presence of ILD; these markers are seldom elevated without lung involvement and are not associated with muscle injury.⁴⁹ Echocardiography is helpful for the detection of cardiomyopathy, and abnormalities are detected in up to 65% of IIMs; however, gadolinium-enhanced cardiac MRI is more useful for the diagnosis of myocarditis, because it can show areas of delayed enhancement, consistent with an inflammatory process.^{18,50–52} More definitively, endomyocardial biopsy may be performed, which confirmed myocarditis in the 2 patients in this report. However, the role for routine endomyocardial biopsy in patients suspected of having myocardial disease in the setting of AS syndrome is uncertain, because there are no guidelines addressing endomyocardial biopsy in autoimmune diseases, and biopsy findings may or may not alter disease management.⁵³

Corticosteroid therapy remains the first line of treatment for AS syndrome, although there are no controlled studies of this therapy.¹⁰ Steroid-sparing immunosuppressant agents, including azathioprine, mycophenolate mofetil, cyclosporine, and tacrolimus can be used; however, only case reports are available on the use of these treatments for AS syndrome, and their effects on AS syndrome-associated myocarditis are unknown.^{10,54–56} Rituximab may be useful, based on a randomized controlled study of patients with DM or PM showing an 83% rate of clinical improvement in those treated with rituximab.⁵⁷ The role for B-cell-depleting therapy is further supported in a recent case series of 6 patients with IIMs (3 with PM and 3 with AS syndrome), in which 5 out of 6 patients demonstrated significant improvement with 6 months of rituximab therapy.⁵⁸ In contrast, leukapheresis and plasma exchange should not be considered, based on studies in patients with corticosteroid-resistant DM or PM.⁵⁹ Medical therapy does not necessarily prevent cardiac complications, such as complete heart block or fatal arrhythmias, which have occurred in patients receiving treatment with steroids or steroid-sparing agents.^{52,60–62} Our own experience was instructive, with one patient clinically improving but the other developing rapidly progressive heart failure resulting in death, despite improvement in skeletal muscle symptoms.

In conclusion, to our knowledge these are the first reported cases of 2 patients with AS syndrome with histologically proven myocarditis and resultant congestive heart failure. Based on these observations, we suggest that myocarditis should be considered in patients with AS syndrome presenting with acute or subacute heart failure. Likewise, AS syndrome should be considered in patients presenting with an idiopathic cardiomyopathy and inflammatory myopathy. Finally, further investigation is needed to elucidate the pathophysiologic mechanisms of AS syndrome to improve diagnostic and therapeutic strategies.

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Fig. 1. Cardiac magnetic resonance images from patient 2. (A) Short-axis and (B) long-axis delayed-enhancement images show diffuse hyperintensity (bright signal) within the myocardium and pericardium (*arrows*), suggestive of an inflammatory process (normal myocardium is typically dark and unenhanced). Pericardial effusion is indicated with *asterisks*.

Fig. 2. Endomyocardial biopsy images from patient 1 (A and B). The biopsy images demonstrate myocyte loss with fibrosis and lymphocytic infiltration. No giant cells, granulomas, or eosinophils were seen. The histopathologic changes were present in multiple locations throughout the biopsy specimens and are consistent with the diagnosis of myocarditis (hematoxylin and eosin, scale 50 μ m, original magnification $\times 400$).

Table 1

Laboratory Values

Component	Reference Range	Patient 1		Patient 2	
		Initial	Discharge	Initial	3 Weeks Later
CK	24–170 U/L	1,640	424	2875	461
Aldolase	<8.1 U/L	21.3		47	16.9
BUN	7–22 mg/dL	19	31	21	32
Creatinine	0.5–1.2 mg/dL	0.8	0.9	0.7	1.1
Tropoin I	0–0.059 ng/mL	0.33	0.30 (day 3)	1.06	0.11
Total bilirubin	0.1–1.2 mg/dL	1.3	0.6	0.2	0.9
ALP	30–120 U/L	91	82	92	294
AST	<31 U/L	63	40	95	50
ALT	<31 U/L	117	58	65	59
ESR	4–30 mm/h	7	-	35	1
CRP	0–0.5 mg/dL	0.9	-	3	-
TSH	0.5–4.5 µIU/mL	8.05	-	9.55	5.09
Free T4	0.7–1.8 ng/dL	1.5	-	0.9	1.59
Serology	Reference Range	Result	Titer (Pattern)	Result	Titer (Pattern)
ANA		Negative		Positive	1:160 (speckled)
Anti-Jo-1	<0.9 U	Positive	6.4	Positive	6.9
Anti-dsDNA		Negative		Negative	
Anti-Ro		-		Negative	
Anti-La		-		Negative	
Anti-Smith		Negative		Negative	
Anti-RNP		Negative		Negative	
Rheumatoid factor	< 36 IU/mL; negative; 37–79 IU/mL: equivocal	Negative	27	Equivocal	60
Anti-CCP	<20 U	-		Negative	14
Anti-SCL-70		Negative		Negative	
Anti-thyroid peroxidase	>100 WHO U	-		Positive	111
Antithyroglobulin		-		Negative	

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CK, creatine kinase; BUN, blood urea nitrogen; ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; TSH, thyroid-stimulating hormone; ANA, antinuclear antibody.