Novel case of anti-synthetase syndrome

Aniruddh Kapoor, Philip Vaidyan, Basmah Jalil, Chitra Upaluri

Abstract

Anti-synthetase syndrome (AS) is a heterogeneous group of systemic autoimmune diseases associated with anti-aminoacyl-transfer RNA synthetases. These inflammatory myopathies present with a constellation of symptoms including myositis, arthritis, Raynaud’s phenomenon, and interstitial lung disease (ILD). We present a novel case of a 44-year-old female, who presented with Anti-OJ AS with severe myopathy and rhabdomyolysis without evidence of ILD, which, in our literature review and to the best of our knowledge, has not been previously reported. Furthermore, our patient was initially misdiagnosed, highlighting the paucity of cases and physicians’ unfamiliarity with this disease. After her diagnosis was confirmed, the patient was successfully treated with high-dose steroids and transitioned to azathioprine, and she continues to do well. This case report emphasizes a novel presentation of the rarely diagnosed AS. We also discuss the significant overlap between the inflammatory myopathies and consolidate relevant pathophysiology and current trends in the management of this disease.

Keywords: Anti-synthetase syndrome, myopathy, dermatomyositis, polymyositis, rhabdomyolysis

Introduction

We present a case of anti-synthetase syndrome (AS) associated with the amino acyl-transfer antibody, the anti-OJ antibody. This rare disorder is on the spectrum of anti-inflammatory myopathies, and it presents with a constellation of symptoms including myopathy, non-erosive inflammatory arthritis, Raynaud’s phenomenon, interstitial lung disease (ILS), and cutaneous manifestations, including “mechanic’s hands.” Our patient presented with rhabdomyolysis, a rare but serious complication of this disorder, but without evidence of ILS, which is usually seen in the AS spectrum, especially in conjunction with the anti-OJ antibody subtype.

Case Presentation

A 46-year-old female with a past medical history of autoimmune disease, initially suspected to be on the spectrum of systemic lupus erythematosus (SLE), presented to our hospital with a subacute onset of progressive muscle pain and an elevated creatinine kinase (CK). She complained of a constant pain exacerbated by activity and worse in the evenings, such that it precluded her from performing routine activities, including combing her hair and standing up from a seated position. Difficulty standing for extended periods of time prompted her to take a leave of absence from her work as a dental assistant. Associated symptoms included dark, non-blanching, macular rashes on her shins and thighs, as well as diffuse arthralgias in the small joints of her upper and lower extremities.

Past medical history included a recent diagnosis of a mixed connective tissue disease with the SLE features, Sjögren’s disease, and Raynaud’s phenomenon. In particular, symptoms of polyarthritis and finger, knee, and hip pain were consistent with SLE; dry eyes and dry mouth were consistent with Sjögren’s; and the patient exhibited classic features of Raynaud’s. Previous immune work up revealed a negative antinuclear antibody (ANA) (Titer <1:40, previously 1:160) and anti-Sjögren’s-syndrome-related antigen A (anti-SSA) (anti-SSA 52 75 and anti-SSA 60 149), with a negative anti-Sjögren’s-syndrome-related antigen B (anti-SSB). She also had a diagnosis of dyslipidemia but had never been initiated on a statin. Her only medication was hydroxychloroquine.

One week prior to this presentation, the patient was admitted to our hospital with similar complaints. At this time, she was noted to have diffuse muscle tenderness in her proximal limbs and 4/5 strength in her upper extremities, with a new increase in CK to more than 14,000 Units per liter (U/L). Labs were also notable at this time for an increased aspartate aminotransferase (AST) (530 U/L), alanine aminotransferase (ALT)
of 472 U/L, the erythrocyte sediment rate of 31
millimeter per hour, and a C-reactive protein of
0.40 milligrams per deciliter. Creatinine was 0.8
milligrams per deciliter.

A presumptive diagnosis of non-traumatic rhab-
domyolysis secondary to hydroxychloroquine
was made, and she was treated with volume
resuscitation. Hydroxychloroquine was with-
held, and a muscle biopsy was done, but no
immunosuppressive agents were started. Her
symptoms improved, although never resolved.
She was discharged home on hydrocodone to
be taken as needed and with close outpatient
follow-up after her CK decreased to 9,800 U/L.

Three days after discharge she was seen by her
primary care physician for continued symp-
toms. A repeat CK was greater than 14,000 U/L,
and she was advised to return to the emergen-
cy department. On admission, her vitals were
stable. The physical examination was signifi-
cant for multiple excoriated, non-tender mac-
ules bilaterally on her anterior tibia and quad-
riceps. Her motor exam revealed no obvious
muscle wasting, fasciculations, or abnormal
movements with intact and symmetric reflexes.
Strength was 3/5 in both her shoulders and
hips, which was evidenced by flexion of her
shoulder and hip against resistance. She had
diffuse tenderness of her proximal muscles bi-
laterally. Her cardiopulmonary exam was with-
in normal limits. Lab findings were notable for
a transaminis with an ALT of 308 U/L and an
AST of 340 U/L. CK had increased to 12,021 U/L.

Based on her clinical picture, an inflammatory
myopathy, most likely polymyositis (PM) was
suspected. Other considerations included der-
matomyositis (DM), inclusion body myositis,
or possibly a viral myopathy. The possibility of
hydroxychloroquine-induced myopathy was still
in the differential. Initial work up confirmed
that the patient was ANA negative (Titer <1:40),
antii-SSA positive, and anti-SSB negative. The
myositis panel revealed a positive anti-isoleu-
cyl (OJ) (ARUP laboratories, which confirm this
test by means of RNA immunoprecipitation),
raising a concern for AS.

Methylprednisolone 1,000 mg/day was started for
3 days, after which the patient was transitioned
to prednisone and azathioprine for the
AS treatment. She continued to improve and
was discharged on Day 5 with a CK of 3,198
U/L. At her 3-month follow-up, the patient dis-
played complete resolution of her symptoms.
At her 6-month follow-up, after a slow taper,
the patient was taken of prednisone and is
now managed only with azathioprine. Given
the association of AS and ILD, pulmonary func-
tion tests were done as an outpatient, but were
within normal limits. A high-resolution com-
puted tomography (CT) was discussed and
was to be performed by her rheumatologist as
an outpatient. Her muscle biopsy, which was
received shortly after her discharge, revealed
scattered muscle fibers in varying stages of
necrosis and regeneration on hematoxylin and
eosin stain. Further, the Gomori trichrome
showed scattered necrotic and regenerating
muscle fibers. Also, alkaline phosphatase stain-
ing of the perimysium was suggestive of an
immune disorder. A mildly active myopathy with
scattered muscle fibers in varying stages of
necrosis and regeneration or immaturity was
noted in the interpretation. Given the improve-
ment with steroids, the anti-OJ antibody, and
muscle biopsy, the diagnosis of AS is thought
to be most likely.

This case highlights the challenges in accurate-
ly diagnosing inflammatory myopathy in the
context of significant overlap between system-
ic autoimmune rheumatological disorders. Our
aim is to consolidate the literature on the less
known AS.

Discussion

Anti-synthetase syndrome is a heterogenous,
rare group of systemic autoimmune diseases
which manifest as an inflammatory myop-
athy. The AS has been associated with a high
frequency of myositis, arthritis, Raynaud’s phe-
nenomenon, ILD, fevers, and other diseases (1).
A proposed criterion includes the presence of
anti-aminoacyl-transfer RNA synthetases plus
either unexplained ILD or PM/DM, or one of
the major criteria and two minor criteria that
include arthritis, Raynaud’s phenomenon or me-
chanic’s hand (2). Of these criteria, our patient
had clinical features consistent with PM/DM,
Raynaud’s phenomenon, and an anti-aminoa-
cyl-transfer RNA synthetase, anti-OJ antibody.

The anti-aminoacyl-transfer RNA synthetases,
which characterize AS include, anti-histidyl
(JO), or in our case, anti-isoleucyl (OJ). Other
antibodies which are part of the syndrome
include anti-threonyl (anti-PL-7), anti-alanyl
(anti-PL-12), anti-glycyl (anti-EJ), anti-aspar-
ginyl (anti-KS), anti-phenylalanyl (anti-Z0), and
anti-tyrosyl-RNA (anti-VRS) (1, 3). Of these, an-
ti-JO-1 was the first antibody to be recognized
and has been detected in 20%–30% of PM or
DM patients (4, 5). By contrast, anti-OJ antibodies
are rare and are seen in less than 2%–3% of
patients with PM or DM (6).

Prior case reports suggest that up to 70%–75% of
AS are associated with ILD, a higher preva-
ience than association with either PM or DM.
Hence, pulmonary function tests are recom-
ended in patients positive for OJ, where a
restrictive pattern is most consistently seen
with ILD, although obstructive patterns can
also be seen. Non-specific ILD with or without
signs of organizing pneumonia are seen most
often by CT though interstitial pneumonia has
also been seen on high-resolution computed
computed tomography (HRCT) (2).

A paucity of knowledge exists for Anti-OJ AS.
An extensive literature search revealed a total
of only 10 case reports from America and Ja-
pan. These have all reported ILD in the context
of AS. Although the presence of ILD cannot
be completely excluded without a HRCT, our
patient is unique as she has anti-OJ positive
AS, currently, without evidence of ILD, which,
to the best of our knowledge, has never been
reported.

Disease progression and the AS prognosis
are predominantly affected by the lung in-
volvelement, while myositis may remain on a
subclinical level (8). In one study, it appeared
that patients with anti-JO negative AS have
decreased survival compared to anti-JO-1 pa-
tients, although further research is required
to confirm this as other case reports suggest a
robust response to glucocorticoids (9).

Our patient was initially treated with cortico-
steroids, which remains the first line treatment
for symptomatic disease. Usually, when muscle
and lung disease stabilize, a steroid taper can
be initiated, after which a steroid sparing agent

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In addition to immunosuppressive therapy, a
vigilant search for complications of AS includ-
ing pulmonary hypertension and underlying
malignancies must be thoroughly conducted.
Thus, AS requires a multidisciplinary approach
resulting in optimal coordinated care across
disciplines to achieve the best patient out-
comes.

Informed Consent: Informed consent was not required as all patient information has been de-identified.

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