Novel case of anti-synthetase syndrome

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Abstract

Anti-synthetase syndrome (AS) is a heterogeneous group of systemic autoimmune diseases associated with anti-aminocarboxyl-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 myositis, non-erosive inflammatory arthritis, Raynaud’s phenomenon, interstitial lung disease, and cutaneous manifestations, including “mechanic’s hands.” Our patient presented with rhabdomyolysis, a rare but serious complication of this disorder, but without evidence of ILD, 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-Sjogren’s-syndrome-related antigen A (anti-SSA) (anti-SSA S2 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 rhabdomyolysis secondary to hydroxychloroquine was made, and she was treated with volume resuscitation. Hydroxychloroquine was withheld, and a muscle biopsy was done, but no immunosuppressive agents were started. Her symptoms improved, although never resolved. She was discharged home on hydrocortisone 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 symptoms. A repeat CK was greater than 14,000 U/L, and she was advised to return to the emergency department. On admission, her vitals were stable. The physical examination was significant for multiple excoriated, non-tender macules bilaterally on her anterior tibia and quadriceps. 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 bilaterally. Her cardiopulmonary exam was within normal limits. Lab findings were notable for a transaminitis 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 dermatomyositis (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), anti-SSA positive, and anti-SSB negative. The myositis panel revealed a positive anti-isoleucyl (OJ) (ARUP laboratories, which confirm this test by means of RNA immunoprecipitation), which manifest as an inflammatory myopathy. The AS has been associated with a high frequency of myositis, arthritis, Raynaud's phenomenon, 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 mechanic's hand (2). Of these criteria, our patient had clinical features consistent with PM/DM, Raynaud's phenomenon, and an anti-aminoacyl-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-EI), anti-asparagine (anti-ES), and anti-lysyl-tRNA (anti-VRS) (1, 3). Of these, anti-PL-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 prevalence than association with either PM or DM. Hence, pulmonary function tests are recommended 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 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 Japan. 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 involvement, 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 patients, 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 corticosteroids, 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 can be introduced. Although there is no official recommendation as to which adjunctive therapy should be used, frequently used agents include azathioprine, mycophenolate mofetil, rituximab, tacrolimus, cyclophosphamide, and IVIG. Our patient was started and maintained on azathioprine with complete resolution of her symptoms (10).

In addition to immunosuppressive therapy, a vigilant search for complications of AS including pulmonary hypertension and underlying malignancies must be thoroughly conducted. Thus, AS requires a multidisciplinary approach to optimally coordinate patient care across disciplines to achieve the best patient outcomes.

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