The antisynthetase syndrome

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ABSTRACT

Antisynthetase syndrome is an autoimmune disease affecting multiple organ systems that was first described as a triad of polymyositis, interstitial lung disease, and the presence of autoantibodies to aminoacyl-transfer ribonucleic acid synthetases. We describe a patient who developed respiratory symptoms following fume exposures. Following a prednisone taper for presumed hypersensitivity pneumonitis, he developed extrapulmonary symptoms suspicious for an autoimmune process discovered to be antisynthetase-associated interstitial lung disease and myositis. This case demonstrates the importance of avoiding anchoring to minimize morbidity and potentially mortality.

KEYWORDS Antisynthetase syndrome; hypersensitivity pneumonitis; interstitial lung disease

Antisynthetase syndrome (ASyS) is an autoimmune disease affecting multiple organ systems that was first described by Marguerie et al as a triad of polymyositis, interstitial lung disease (ILD), and the presence of myositis-specific autoantibodies to aminoacyl-transfer ribonucleic acid synthetases.^{1–4} The most specific autoantibody is anti-Jo-1, directed against histidyl-transfer ribonucleic acid-synthetase.¹ Other antibodies include anti-PL7, anti-PL12, anti-EJ, anti-OJ, anti-KS, anti-Zo, and anti-Tyr.⁵ Among idiopathic inflammatory myopathies, ASyS has a higher prevalence of ILD.^{2,5}

CASE PRESENTATION

A 22-year-old man with a past medical history of hypertension and morbid obesity (body mass index 43.05 kg/m²) presented to his primary care physician with complaints of 2 months of dyspnea on exertion, palpitations, and constant pleuritic chest tightness. Six months prior, he started working for a company producing ink for printers with several fume exposures. An echocardiogram was unremarkable except for mild diastolic dysfunction and global hypokinesis. He had a normal exercise treadmill study and 24-hour Holter monitoring. Computed tomography angiography of the chest showed multifocal patchy bilateral infiltrates and mediastinal lymphadenopathy (*Figure 1a*). His forced expiratory volume in 1 s (FEV₁) was 50% of predicted; forced vital

capacity (FVC), 47% of predicted; FEV₁/FVC ratio, 89; and diffusion capacity of the lung for carbon monoxide, 47% of predicted. Fiber-optic bronchoscopy with endobronchial ultrasound and transbronchial needle aspiration of a station 7 lymph node demonstrated normal lymphoid tissue with normal bilateral bronchial trees. Given the lack of infectious findings, he was started on prednisone 60 mg daily for presumed hypersensitivity pneumonitis related to a workplace exposure. He was tapered from 60 to 40 mg prednisone daily over the next few days.

Over the next 5 months, taking 5 mg of prednisone daily, he experienced partial improvement in dyspnea but developed brown urine, bilateral hamstring pain, bilateral knee pain associated with morning stiffness, and reduced range of motion at his bilateral hands, wrists, and shoulders. These symptoms worsened once he was completely off prednisone, prompting hospitalization. On examination, he had dry skin on bilateral elbows, mild erythema in the right second to fourth metacarpophalangeal joints, sclerodactyly, left second and right fourth digital tip pit, and no skin hyperkeratosis. Strength examination revealed proximal weakness. Repeat computed tomography scan of the chest showed some improvement in his bilateral pulmonary infiltrates with left lower lobe traction bronchiectasis (*Figure 1b*). Laboratory evaluation revealed elevations in C-reactive protein (52 mg/L; reference, 0.0–3.2), aspartate aminotransferase (694 IU/L; reference 0–40), alanine aminotransferase

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Figure 1. Computed tomography with a pulmonary embolism protocol at (a) initial presentation, showing multifocal patchy opacities primarily in a peribronchial distribution, and (b) 1 year later, showing improvement in the patchy bilateral opacities.

(481 IU/L; reference 0–68), creatine kinase (14,895 IU/L; reference 0–225), and aldolase (246.4 U/L; reference, 1.5–8.1). His white blood cell count was 15.0 with a lymphocytic predominance, and urinalysis showed 3+ blood, 1–2 red blood cells, and protein of 300 mg/dL. Infectious workup was negative, including antibody tests for HIV, *Coccidioides*, blastomycetes, serum and urinary *Histoplasma*, and an acute hepatitis panel. Anti-nuclear antibodies testing was positive, C-ANCA was positive at a titer of 1:20, and anti-Jo 1 antibody was positive at >8.0. Anti-SS-A, anti-SS-B, anti-Scl 70, rheumatoid factor screen, anti-double stranded deoxyribonucleic acid, anti-chromatin antibody, anti-Smith antibody, anti-RNP antibody, P-ANCA, myeloperoxidase antibody, and proteinase 3 antibody were all negative. Electromyography/nerve conduction studies were consistent with inflammatory myopathy and mild bilateral carpal tunnel syndrome. He was diagnosed with inflammatory myositis and ILD due to ASyS and discharged home on prednisone 40 mg daily. In rheumatology clinic follow-up, he was started on mycophenolate mofetil with tapering of his prednisone. Due to recurrence of symptoms once the prednisone dose was <20 mg, rituximab was added. Hydroxychloroquine was added for persistent cutaneous manifestations. He is now off prednisone and back to work with no dyspnea or joint weakness.

DISCUSSION

Clinical features of ASyS vary based on the presence of specific antibodies. In a meta-analysis of 27 studies involving 3487 patients, patients with non-anti-Jo1 antibodies had greater odds of presenting with fever and ILD. Patients with anti-Jo1 antibodies were more likely to present with myositis, mechanic's hands (hyperkeratotic skin changes along the lateral surfaces of the digits), and arthralgias compared to those with no anti-Jo1 antibodies.⁶ Disease presentation is heterogeneous, with patients presenting with organizing pneumonia, diffuse alveolar hemorrhage, pulmonary capillaritis without diffuse alveolar hemorrhage on biopsy, and even hypoxic respiratory failure leading to intubation.^{7–9}

ASyS pathogenesis remains poorly understood, highlighting the complexity of the disease. It is thought to result from environmental and/or infectious agents leading to pulmonary

injury.¹ There has been a high association of respiratory tract infections in the year preceding the onset of inflammatory myopathies based on a large population-based cohort study.¹⁰ In a genetically and immunologically susceptible individual, systemic immune activation leads to self-protein cleavage via the cytotoxic lymphocyte granule-induced death pathway.¹ Generation of these protein fragments has been linked to breakdown of tolerance.¹¹ The disease is believed to start in the lungs since >75% of patients have pulmonary involvement.¹

For diagnosis of ASyS, Connors et al proposed that patients must have the presence of a tRNA synthetase antibody plus one other clinical feature.¹² Solomon et al proposed stricter criteria to include the presence of an aminoacyl tRNA synthetase autoantibody plus two major or one major and two minor criteria.¹³ However, it is important to not exclude ASyS if there is high suspicion since antibody titers fluctuate during a disease course and some antibodies may have not yet been discovered.^{2,14}

Immunosuppressants are the mainstay of treatment. Corticosteroids are used in the initial treatment but carry a high risk of pulmonary symptom recurrence once tapered and have well-described side effects. Therefore, use of steroid-sparing agents is important for long-term therapy. Most commonly, agents include mycophenolate mofetil, tacrolimus, azathioprine, rituximab, and cyclophosphamide.¹ Most data supporting the use of these medications come from polymyositis, dermatomyositis, or other connective tissue disease-associated ILD. Unfortunately, there are no guidelines to aid prescribers in choice or duration of therapy.

In conclusion, we describe a patient with anti-Jo1-positive ASyS presenting with ILD symptoms. Due to occupational history with fume exposure, symptoms and imaging were interpreted as hypersensitivity pneumonitis. He was later found to have ASyS, which is easily missed if not considered early. To our knowledge, there are no other reports describing a patient misdiagnosed with hypersensitivity pneumonitis. Based on the proposed pathogenetic mechanism of ASyS, fume exposure may have been the environmental trigger. It is most likely that treatment for hypersensitivity pneumonitis blunted the rash, myopathy, and arthritis that manifested once steroids were tapered.

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Avocations

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