Antti Synthetase Syndrome – A Case Report

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Abstract – Anti-synthetase syndrome (ASS) has been recognized as an important cause of autoimmune inflammatory myopathy in a subset of patients with polymyositis and dermatomyositis. Its hallmark is the presence of serum antibodies to aminoacyl-transfer RNA synthetases and is characterized by a constellation of manifestations. Clinicians should be familiar with this entity. There is favorable response to steroids and immunosuppressants. We describe here a case of ASS presenting with myositis, interstitial lung disease (ILD), fever, deforming arthritis and Raynaud’s phenomenon who had high titre of anti Jo-I antibodies. The patient responded well to steroids and cyclophosphamide pulse.

Keywords- autoimmune, myopathy, aminoacyl-transfer RNA synthetases, myositis, interstitial lung disease

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I. Introduction

Anti-synthetase syndrome is a rare, chronic, autoimmune disorder of unknown etiology, which is described classically by the triad of interstitial lung disease (ILD), inflammatory myositis and presence of aminoacyl-tRNA synthetase (anti-Synthetase) antibodies[1,2]. Raynaud’s phenomenon, fever, “mechanic’s hand” and inflammatory polyarthritis are also observed[3]. It was first described by Marguerie et al in 1990.[4] It has been recently recognized as a major subgroup of inflammatory myopathies.[5] Out of the antibodies detected anti Jo-1 is the most commonly detected; around 60-80% cases.[3,6,7] Other anti-Synthetase antibodies are far less common: anti-PL-7 or anti-PL-12 are detected in around 10% of the patients; and the rest (anti-OJ, anti-EJ, anti-KS, anti-ZO, anti-Ha-YRS, and anti-SRP) are identified in < 5% of the patients.[7,8,9]

Pulmonary involvement is the main determinant of morbidity and mortality in these patients.[10] Patients with progressive interstitial lung disease have a poorer prognosis.[11] However, in contrast to other inflammatory myopathies, cardiac involvement is far less common.

Prevalence in general population is still unknown. But it is seen in 20-40% of polymyositis/dermatomyositis cases.[1,12,13] It affects mainly adults with mean age of 42-60 years and female:male ratio of 2:3:1.[14,15] Studies have found the incidence to be higher in Caucasian women.[11] Early diagnosis is difficult because the clinical presentation is varied and often nonspecific. And many times lung manifestations predominate in absence of clinically apparent myositis.[16,17]

Most treatment regimens include glucocorticoids alone or in combination with other immunosuppressants.

Here we report a case of young female with Anti-Synthetase syndrome presenting with chest symptoms, myositis and fever who develops heart block.

II. Case Report

A 25 year old female presented to the Department of Internal Medicine in our hospital with chief complaints of fever, non-productive cough, dyspnoea on exertion and weakness of limbs for 1 month. She gave a history of joint pain for last 3 years involving bilateral interphalangeal and metacarpophalangeal joints, elbow and knee joints and history suggestive of Raynaud’s phenomenon. On presentation she had pallor and pedal edema and swollen deformity of her fingers. BP was 90/70 mmHg with pulse rate of 108/min. Auscultation of chest revealed basal end inspiratory crepitations. On neurological examination her proximal muscles were weak. She had no other significant past history apart from joint pain. Menstrual history was normal. She had no known allergies and family history was not significant. She was started on broad spectrum antibiotic, antipyretic and other supportive.

Routine investigations showed anemia (Hb 9.4 gm/dl), ESR of 77 mm AEH, CRP of 43.6 mg/dl, serum albumin of 1.7 gm/dl, serum globulin of 5 gm/dl and raised SGOT (605 U/L), SGPT (387U/L), ALKP (548 U/L), GGT (283 U/L), CPK (490 U/L). RA factor was 16 IU/ml while anti-CCP was <7 U/ml. As TSH was 10.66 IU/L, Thyroxine 25 mcg was started. In ANA reflex panel, ANA was 3+ with titre of 1:1000 and cytoplasmic granular fluorescence pattern; anti Ro-52 was 2+, anti Jo-1 was 3+, centromere B antibodies was 3+ and nucleosome

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antibodies 1+. CT scan of thorax revealed subpleural patchy consolidations and infiltrates with septal thickenings. Electromyography (EMG) of all 4 limbs revealed a generalized myopathic pattern (proximal>distal). Nerve conduction velocity (NCV) study was normal. Muscle biopsy from biceps showed inflammatory myopathy consistent with polymyositis.

IV methylprednisolone 1g pulse was started from 3rd day of admission. On 5th day of admission, patient had worsening of chest symptoms with left sided lower chest pain. She had BP of 100/70mmHg and pulse was 50/min, regularly irregular and she became hypoxic. Chest X-ray showed haziness in lower zones bilaterally and apparent cardiomegaly. ECG showed 2:1 AV block Mobitz type 1. She was empirically started on higher generation antibiotics and put on non-invasive ventilation (NIV) support. After excluding infective pathology she was started on Cyclophosphamide pulse. She responded well, her NIV support was removed after 5 days, her ECG changed to sinus rhythm.

Patient was discharged on 20th day with no chest symptoms and improved muscle power and was advised to continue monthly cyclophosphamide and oral prednisolone. She was on regular follow-up with gradual tapering of the steroid. Now, at 21 months of follow-up, she is off steroids for more than 6 months and is asymptomatic.

III. Figures

Figure 1: joint deformity of the hand

Figure 2: muscle biopsy showing features consistent with polymyositis
IV. Discussion

ASS is a serological subtype of idiopathic inflammatory myositis characterized by the production of anti-1RNASynthetaseantibodies and the development of dermatomyositis(DM)or polymyositis(PM)[90%], interstitial lung disease[60-90%], symmetrical non-erosive arthritis or arthralgia[50%],Raynaud’s phenomenon[40%], mechanic’s hand[30%]and fever[20%][11]; accompanied by some less frequentmanifestations, such as photosensitivity, cutaneous vasculitis, calcinosiscutis, periungual telangiectasia, sclerodactyly, mesangial proliferative glomerulonephritis,pulmonary hypertension, carditis and cardiomyopathy.[3,18,19,20,21,22][The disease course is usually chronic and prognosis of this entity is found to be worse than other myopathies.[23,24]Lung involvement is considered to be the most importantprognostic indicator[25]. The clinical presentation of ASS is frequentlynon-specific in the early stages; so diagnosis may be missed in many cases, especially those presenting with ILD only.[26]Approximately 5-8% of ASS casesmanifest as overlap syndromes with anotherconnective tissue disease such as Systemic lupuserythematosus, Systemic sclerosis and Sjögren’s syndrome.[27][Etiopathogenesis remains incompletelyunderstood.[9] All the published studies confirm that the HLADR B1*0301, DQA1*0501 and DQB1*0201 genes are risk factors for development of ASS with anti-Jo-1 positives.[28]

Onset of myositis is usually acute and presents with proximal muscle weakness,muscle tenderness, pain and eventually muscle atrophy. EMG may showsmall amplitude, short polyphasic potentials, spontaneous fibrillations, positive spike at rest, irritability and high frequency repetitive discharges. Muscle inflammation triggers release of creatinine kinase, aldolase, ALT, AST and LDH. Muscle biopsy helps to confirm diagnosis and to exclude other disorders which present with similar picture.[5,29] Most anti-Jo-1-positive patients have PM, a smaller proportion having DM or overlap syndromes (57% vs. 28% in one study).[26] Our case also had PM features in biopsy. Muscle histopathology in anti-Jo-1-positive patients differs from that observed in antibody-negative patients. In contrast to antibody negative patients, in whom there is predominately endomyisal and perivascular inflammation, anti-Jo-1-positive patients have fragmentation of the perimysialconnective tissue with macrophage predominant inflammation and, in rare cases, vascular involvement.[30] Myositis is not universal(amyopathic AS syndrome) and can develop subsequent to the diagnosis of AS syndrome. ILD precedes myositis in 37% of cases, and their onset is simultaneous in 50%.[31]

ILD can have a slow onset or lead to acute respiratory failure, sometimes highly refractoryto treatment.[32]Adult respiratory distress syndrome, bronchiolitis obliterans organizing pneumonia (BOOP), and fibrosingalveolitis areassociated with ILD.[33]Lung manifestations include dyspnea,cough, chest pain, exercise intolerance and respiratory failure.Chest X-ray can reveal an interstitial pattern. Ground glass lesions, linear opacities, pulmonary parenchyma consolidations, honeycombing and micronodules can also beseen on computed tomography. The pulmonary function test shows a restrictive pattern. The patients with BOOP in lung biopsy usually have a more favorable prognosis compared with those with either diffuse alveolar lesions or
interstitial pneumonia. Anti-Ro antibodies presence has been associated with pulmonary fibrosis in the ASSyndrome[23,34]

Cases with joint involvement have arthralgia or arthritis with or without bone erosions. Almost all patients have joint symptoms early in the disease.[32] Typically, the arthritis is mild, non-deforming, and non-erosive,[35] although a subgroup of patients might develop an erosive and/or subluxing joint disease. The joints commonly affected are: distal and proximal interphalangeal joints, metacarpophalangeal joints, wrists, elbows, and knees.[36] In this patient joint symptoms were present for 3 years and she had bilateral deforming arthritis. Joint effusions within inflammatory synovial fluid can occur in some.[37] Because inflammatory arthritis mimics RA, ASS should be considered in atypical cases.[26,38]

“Mechanic’s hands” mean hyperkeratosis, scaling, and fissure in fingertips and lateral aspects of the fingers; being more frequently found in the Antisynthetase Syndrome and interstitial lung disease.

Raynaud’s phenomenon is early in 2/3rd of patients and can precede the myositis in years. It is more frequently found in anti-Jo-1 positive patients.[26,38] Our patient also had this sign.

A skin vasculitis has also been described. A mesangial proliferative glomerulonephritis has been observed, but it is rare and has a good prognosis.[39]

Cardiac involvement is much less reported than in other myopathies. These include cases of cardiomyopathy, right heart failure, severe AR and myocarditis leading to CCF.[40-43] Pericardial effusion also reported in one.[44]

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) have been reported in PM/DM cases, but exact prevalence in ASS is unknown.[45,46] And unlike this case, heart blocks have not been reported yet in ASS. Proposed mechanisms of cardiac involvement in ASS 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.[47,48] It is also probable that underlying autoimmune processes may contribute to myocarditis owing to its effects on humoral and cellular immune mechanisms.[49] Echocardiography and Cardiac MRI may help to detect cardiac involvement.[43]

Out of the myositis specific antibodies anti-Jo-1 is the most commonly detected.[3,6,7] Other antibodies are less commonly detected as mentioned earlier[7,8,9]. Muscle disease is seen in >90% anti-Jo-1 positive cases. In one study, patients who had ILD without apparent myositis, anti-PL-12 was the most commonly found antibody (60%), followed by anti-Jo-1 and anti-OJ antibodies (20% each).[16]

The most commonly detected type of myositis-associated antibodies in ASS is the anti-Ro/SSA antibody.[20,50]

As this is a rare condition, no controlled clinical trials have been performed for assessment of the different treatment options. Currently, the first-line therapy of the ASS includes methylprednisolone at a starting daily dose of 1 mg per kg body weight for 4-6 weeks followed by slow taper over next 9-12 months. IV steroids are recommended for 3-5 days in severe disease. As second-line treatment, the administration of cyclophosphamide as pulse therapy, cyclosporin, azathioprine, tacrolimus, methotrexate, mycophenolate mofetil, intravenous immunoglobulin, anakinra and leflunomide can be considered.[3,11,18,19,20,21] These are helpful in steroid resistant cases. Studies suggest that CD20 depletion therapy (rituximab) might be valuable in refractory cases.[51]

For severe pulmonary involvement associated with ASS, monthly intravenous infusion of cyclophosphamide has been shown to be effective.[52,53] This has been seen in our case also. Some recent studies established the role of tacrolimus in the treatment of both interstitial lung disease and myositis associated with ASS.[54] Cyclosporine has also been successfully used in a case of ILD associated with anti Jo-1 syndrome.[55] Few reports have shown favorable response to prednisone: 30–40% of the patients had an improvement and 20–40% became stable for symptoms and pulmonary function.[18,51] A late relapse following an initial remission is more common in ASS. Anti-Jo-1 positive myopathies have a worse prognosis than other inflammatory myopathies.[56]

Thus, early clinical diagnosis and timely aggressive immunosuppressive therapy is essential to prevent the development of severe respiratory failure and pulmonary hypertension in these patients.[19,23,34]. Older age at onset (> 60 years), presence of a malignancy, and a negative antinuclear antibody test are associated with a poor prognosis.[57]

V. Conclusion

Antisynthetase Syndrome is a rare autoimmune disorder with myositis and ILD being the core manifestations and the latter being the main determinant of mortality. The disease can have a fulminant course and can end fatally if not treated rapidly. Immunosuppressants are the mainstay of treatment and glucocorticoids are the commonly used first line agents. Timely diagnosis and early institution of treatment will help prevent morbidity and mortality of the patients.
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References


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