Antisynthetase syndrome-An underdiagnosed entity

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Abstract

Anti-synthetase syndrome is an autoimmune disease, characterized by aminoacyl transfer RNA synthetase antibodies with clinical features that can include interstitial lung disease, myositis, Raynaud’s phenomenon, and arthritis. There is a higher prevalence and increased severity of interstitial lung disease in patients with the anti-synthetase syndrome as compared to other inflammatory myopathies. Diagnosis is made by serological, radiographic, and muscle and/or lung biopsy results. Patients frequently require multi-modality immunosuppressive therapy to manage muscular and pulmonary manifestations of the disease. Careful attention is required to the adverse effects and complications of chronic immunosuppressive therapy, as well as to the disease complications which include progressive interstitial lung disease, pulmonary hypertension, and malignancy. Increased awareness of this syndrome will allow for early diagnosis and treatment improving outcomes in patients.

Keywords: Antisynthetase syndrome, myositis, interstitial lung disease

1. Introduction

“It is said that no one truly knows a nation until one has been inside its jails. A nation should not be judged by how it treats its highest citizens, but its lowest ones.” - Nelson Mandela

More than 10.2 million people worldwide are held in prisons. As per the World Prison Population List-2013, there is a general trend of growth in prison population in majority of nations, including in India. As of 2017, the latest figures available for India, there are and belong to marginalized or socially disadvantaged groups and have limited knowledge about health and practice unhealthy lifestyles. Thus, they represent a distinct and vulnerable health group needing priority attention [1].

International Law

Antisynthetase syndrome (ASS) was first described by Marguerite and coworkers in 1990 [1]. It is a rare idopathic autoimmune connective tissue disorder characterized by the presence of autoantibodies against the aminoacyl-tRNA synthetase (anti ARS) complex with variable clinical presentation. Typically cases present with a triad of interstitial lung disease (ILD), arthritis, and myositis whereas Raynaud’s phenomenon, mechanic’s hands, and fever are less prevalent. ASS affects women and men in an approximate ratio of 2:1 and ages from 22-74 years [2]. Solomon et al (2011) diagnostic criteria is used to confirm the diagnosis.

Solomon et al (2011) diagnostic criteria [3]

Required Criteria: Presence of anti-aminoacyl tRNA synthetase antibody Plus 2 major or 1 major and 2 minor criteria

Major
1) Interstitial lung disease (not attributable to another cause)
2) Polymyositis or dermatomyositis by Bohan and Peter criteria

Minor
1) Arthritis
2) Raynaud’s phenomenon
3) Mechanic’s hands
2. Case Report
A 35-year-old male presented with gradually progressive grade 2 exertional dyspnea and dry cough since 3 years. History of joint pain over bilateral knees, elbows, and wrists with Raynaud’s phenomenon affecting fingertips was present since 1.5 years. There was no history of fever, weakness in thighs or shoulder girdle, photosensitivity, oral ulcers or difficulty in swallowing. General physical examination was normal. Cutaneous examination revealed hyperkeratotic, scaly plaques with fissuring over palmar and radial aspect of hands, akin to mechanic’s hand (Fig 1 A and B) mild tapering of the left index finger was seen (Fig 2). Respiratory system examination revealed decreased chest expansion to 3 cm on palpation and fine bibasilar Velcro crepitations (inspiratory) on auscultation. Musculoskeletal system examination was normal with normal muscle power and a normal range of movements was present. Cardiovascular system examination was normal. His complete blood count, liver function test, renal function test, random Blood Sugar, thyroid-stimulating hormone, T3, T4, anti-cyclic citrullinated peptide, phosphokinase values were within normal limits. Serum VDRL, HIV, HBsAg, and HCV was nonreactive. Electrocardiography, 2D echocardiography, ultrasonography of abdomen and pelvis, X-ray hand (AP view), X-ray pelvis (AP view) X-ray bilateral knee joint (AP view) were normal. Chest X-Ray showed patchy consolidation in bilateral lower lobes (fig 3). High-resolution computed tomography (HRCT) showed intra and interlobar septal thickening, mild tubular traction bronchiectasis, and diffuse ground-glass opacity in both lower lobes, suggestive of non-specific interstitial pneumonia (fig 4). Serum anti-nuclear antibodies (ANA) profile was positive for anti-JO-1 (+++) and antiRO-52(+++). Diagnosis of ASS was confirmed on basis of presence of required criteria (Anti-JO1 antibody) along with one major criteria (ILD) and three minor criteria (Raynauds phenomenon, mechanics hand, arthritis). The patient was prescribed azathioprine 50 mg orally once a day and supportive therapy for 6 months. As there was little clinical improvement, he was given intravenous cyclophosphamide pulse therapy, 500 mg every 4 weeks with regular monitoring. He was maintained on oral prednisolone 0.5 mg/kg daily, multivitamins, calcium 500mg+ vitamin D3, 250 IU, metered dose inhaler levosalbutamol/levalbuterol 50mcg+ ipratropium 40mcg, emollients and topical clobetasol (0.05%)+ salicylic acid cream(3%). Significant improvement was observed in cutaneous lesions and joint pain however there was no improvement in dyspnea.

3. Discussion
ASS is an idiopathic inflammatory myopathy (IIM). Associated signs and symptoms include ILD, myositis, arthritis, Raynaud’s phenomenon, fever and mechanic’s hand (Fig 5). A higher prevalence of ILD is seen in ASS relative to other inflammatory myopathies 3. Incomplete forms, especially initial symptoms may not suggest ASS. ASS can also present with isolated manifestations of either ILD, arthritis, or myositis4. Our patient presented with ILD without myositis and fever. In atypical cases inflammatory arthritis may mimic RA. In cases of oesophageal involvement or pulmonary hypertension, overlapping systemic sclerosis should be considered. Several antinuclear antibodies such as anti JO-1, anti-PL-7, anti-PL-12, anti-OJ, anti-EJ, anti-ZO, anti-YRS/Ha and anti-KS are seen. Presence of one or more of the above antibodies is a “required criteria for diagnosis of ASS” (Table-1). Other myositis specific autoantibodies may also be seen in ASS (Fig. 6).

Management of ASS includes systemic corticosteroids 1mg/kg/day as the first-line therapy. Some ASS patients may have corticosteroid resistant myositis or ILD. Azathioprine 1mg/kg/day is a second-line agent. IVIG or MMF (mycophenolate mofetil) can also be used as add on therapy. In acute exacerbations cyclophosphamide 500 mg IV every 4 weeks or Rituximab 1g with an interval of 2 weeks can be used as rescue therapy5.

The ILD in ASS cases is often severe and rapidly progressive, causing increased morbidity and mortality as compared with other IIMs. Patients with pulmonary hypertension and age greater the 60 years have poor prognostic factors. The most common causes of death are pulmonary fibrosis and pulmonary hypertension. Hence severe and aggressive ILD require multi-modality therapy and lung transplantation is to be considered when the disease is progressive and fails to respond to treatment6.

4. Conclusion
Antisynthetase syndrome is a lesser known but important and treatable cause of ILD. Unexplained acute respiratory distress syndrome, Raynaud’s phenomenon, and mechanic’s hands should raise the suspicion of anti-synthetase syndrome for appropriate management to reduce morbidity and mortality of patient.

Table 1: Presence of one or more of the above antibodies is a “required criteria for diagnosis of ASS”

| Myositis-specific antibodies related to ASS | Target antigen | Significance |
|------------------------------------------|----------------|-------------|
| Anti-JO-1                                 | histidyl t- RNA synthetase | The most common antisynthetase antibody, Develops as the classical form. Strong predictor for ILD (70-90%), but also a strong predictor of clinical response to immunobiological drug |
| Anti-PL-7                                 | threonyl t- RNA synthetase | Increased involvement of the gastrointestinal tract, Raynaud’s phenomenon, and ILD. Isolated ILD is typical, but milder compared to anti-PL-12. This happens in myositis as well |
| Anti-PL-12                                | alanyl t- RNA synthetase | Increased involvement of the gastrointestinal tract, Raynaud’s phenomenon, and ILD. ILD isolated is typical but has a greater burden of ILD and esophageal involvement and a lower chance of developing arthritis and myositis compared to anti-PL-7 |
| Anti-OJ                                   | isoleucyl t- RNA synthetase | ILD is common but responds very well to glucocorticosteroids. Strong association with neoplasia, but without statistical evidence |
| Anti-EJ                                   | glycyl t- RNA synthetase | It develops the classic form with myopathy and ILD and is possibly the one with the lowest association with malignancy |
| Anti-KS                                   | asparaginyl t- RNA synthetase | Myositis was not evidenced |
| Anti-ZO                                   | phenylalanyl t- RNA synthetase | <1% in ASS, Develops as the classical form. |
| Anti-YRS or Anti-TyR or anti-Ha           | tyrosyl t- RNA synthetase | <1% in ASS, Develops as the classical form. |
5. References
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