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Anti Synthetase Syndrome: An Underdiagnosed Autoimmune Disease.

Sachin Gadiya*, Sunil Kumar, Deepali Lodha
Department of Medicine, Smt.B. K Shah Medical Institute and Research Centre, Sumandeep Vidyapeeth, Vadodara-391760

ABSTRACT

Antisynthetase syndrome (ASS) is a rare, chronic autoimmune disease and is a sub-group of idiopathic inflammatory myopathies. The hallmark of this disorder is the presence of autoantibodies against the aminoacyl-transfer ribonucleic acid (tRNA) synthetase. The patient presents with fever, exanthema on the hands (also referred to as mechanic's hands), myositis, and/or interstitial lung disease (ILD), and/or articular involvement. Nearly 70% of patients with ASS present with signs and symptoms of ILD. We are reporting a case of a patient who was having ILD, who turned out to have ASS on further workup. ASS as the causal diagnosis is missed many times. As an early and exact diagnosis has crucial therapeutic and prognostic implications, knowledge about this syndrome and a high level of suspicion is of utmost importance.

*Corresponding Author Email: sachinrgadiya@gmail.com
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INTRODUCTION

Antisynthetase syndrome (ASS) is a rare, chronic autoimmune disease of undetermined cause. The syndrome is considered a sub-group of idiopathic inflammatory myopathies (IIMs) [1.] IIMs are characterized by different degrees of skeletal muscle inflammation. They are further divided into three sub-groups: (a) sporadic inclusion-body myositis; (b) polymyositis (PM); and (c) dermatomyositis (DM) [2]. ASS is a subset of PM or DM. The hallmark of this disorder is the presence of autoantibodies against the aminoacyl-transfer ribonucleic acid (tRNA) synthetase, also known as antisynthetase antibodies, or anti-ARS [3]. Patients with this syndrome have a characteristic clinical picture consisting of fever, exanthema on the hands (also referred to as mechanic's hands), myositis, and/or interstitial lung disease (ILD), and/or articular involvement [4, 5]. Nearly 70% of patients with ASS present with signs and symptoms of ILD [6]. So, patients with ILD require a high level of suspicion for ASS based on other symptoms and signs described above. We are reporting a case of a patient who was having ILD but turned out to have ASS on further workup.

CASE REPORT:

60-year-old female, housewife, presented with complaints of multiple joint pain since 8 months, breathlessness and facial puffiness since 2 to 3 months. The patient was apparently alright 8 months back when she started developing joint pain initially involving bilateral hip joint then progressed to other large joints and then small joints followed by the development of swelling and stiffness. In about 2 weeks patient started having fever which was low grade, and intermittent for about 3-4 months. Patient visited local hospital where she underwent following investigations: Rheumatoid Factor (RA) (0-14 IU/ml) : <9.5, ANA titre <1:32-Negative, Anti CCP levels (0-5 IU/ml): 0.5, Hb Electrophoresis: Beta-thalassemia trait; and normal other routine biochemical investigation. So patient was diagnosed with seronegative Rheumatoid arthritis with thalassemia minor and was started on Tab. Prednisolone (60), Tab Methotrexate (7.5) once a week, and Tab. HCQ (200) (about 3 months back). After 15-20 days of treatment, the patient did not have any improvement in her symptoms and developed complaints of breathlessness, dry cough and facial puffiness. Breathlessness was initially only on walking about 500 meters which increased over 3 months and now came up even on walking 10 steps. Her HRCT Chest was done s/o Early features of interstitial lung disease; asymmetric in distribution and predominantly sub pleural basal segment region more on right- possibility of early features of CT pattern indeterminate for UIP. She was started on T. Azathioprine (50), and Tab Prednisolone (20mg). Patient's complains of joint pain and swelling improved. The patient after 15 days visited our hospital after with deterioration in her complaints of breathlessness, dry cough, ghabarman and facial puffiness. Patient now had breathlessness even on walking (MMRC Grade 4). There was no c/o fever, cough, chest pain,

or difficulty in swallowing. No pedal oedema, orthopnoea, paroxysmal nocturnal dyspnoea. The patient also complained of bluish discoloration of her fingertips when dipped in cold water while washing utensils. On examination, the patient was vitally stable with 98% saturation on room air. In the Respiratory system, the examination patient had bilateral basal Velcro crepitation. CVS, P/A and CNS examination was within normal limits. The patient had joint tenderness in PIP, MCP, wrist, elbow, shoulder, knee, and ankle, MTP joints with no swelling of joint or skin changes/joint deformity. She also had proximal muscle weakness with tenderness in both thigh muscles with no wasting. Following investigations were done: CBC (Hb/TLC/Plt): (13-17gm%, 4000-11000/cu mm, 1.5-4.5lacs/cu mm):9.3/1800/5.8, ESR (0-20 mm/hr):73, CRP (0-6 mg/dl):45.4, CPK Total (<171 u/l8i8):352. Her other biochemical investigations including LFT, RFT, and Serum Electrolyte were within normal range. 2D Echo: Normal. In view patient had multiple joint pain with proximal muscle pain/weakness and Interstitial Lung Disease, her ANA profile was sent. ANA Profile: RO-52:+++, Jo-1:+++, Anti Jo; 1 ELISA (<1.0: Negative, >1: Positive): 4.29. So, the patient was diagnosed to have Anti synthetase syndrome.

Treatment and follow up:

The patient was started on Tab Prednisolone (30mg) OD in tapering dose, Tab. Hydroxychloroquine (200mg) BD, Patient's Azathioprine was stopped i/v/o Leukopenia and was started on Tab. Methotrexate (15mg) once a week, Tab. Pirfenidone(200mg) BD, MDI with Foracort 2 puffs/day. The patient was followed after one month with this treatment. The patient had improvement in joint pain, stiffness and breathlessness and on the investigation was found to have decreased levels of ESR, CRP and CPK with improvement in PFT.

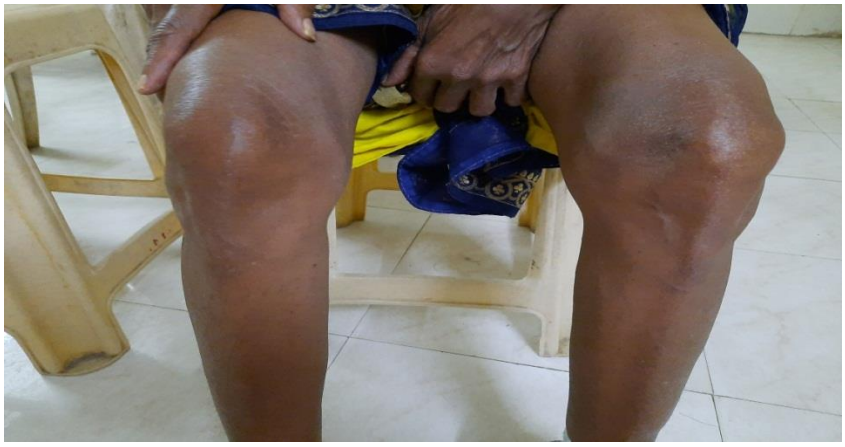

Figure 1: Showing swollen knees.

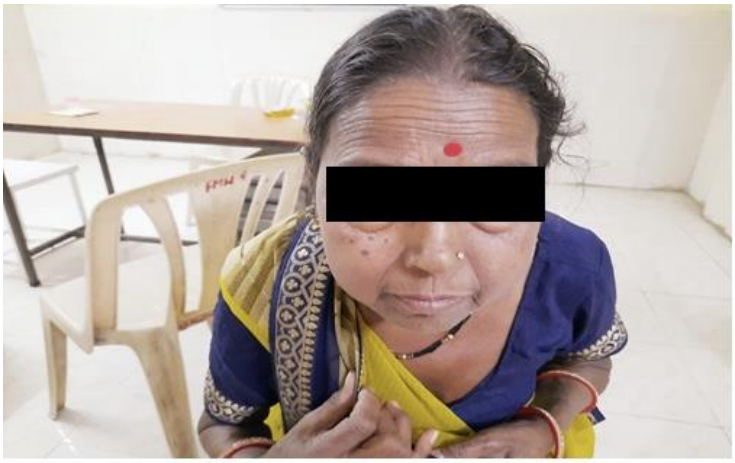

Figure 2: Showing facial puffiness.

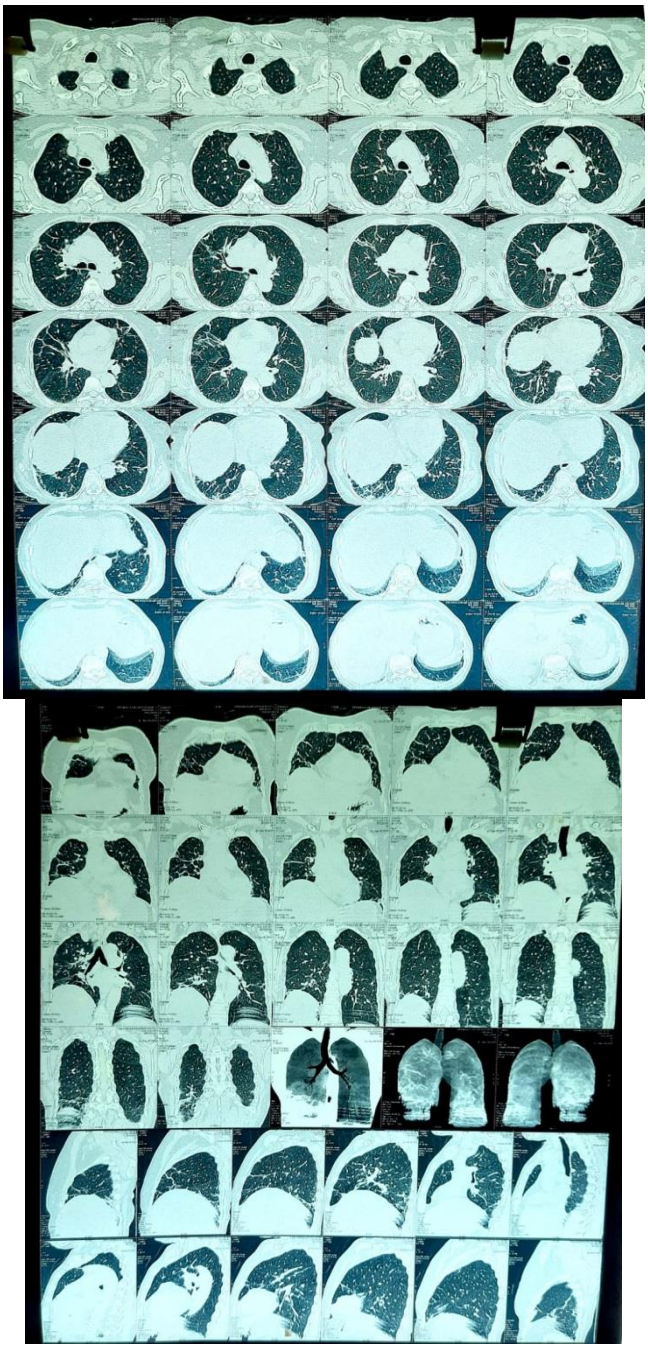

Figure 3: Shows HRCT s/o Early features of interstitial lung disease.

RESULTS AND DISCUSSION:

AS syndrome is a rare idiopathic inflammatory myopathy that involves a constellation of symptoms including interstitial lung disease (ILD), myositis, 'mechanic's hands', Raynaud's disease, fever and polyarthritis. In the presence of these clinical features, diagnosis can be confirmed based on the presence of specific autoantibodies against Aminoacyl-tRNA synthetase (ARS) [7, 8]. Human proteins are composed of 20 different amino acids, and a specific ARS enzyme catalyzes the formation of aminoacyl-tRNA from each amino acid and its cognate tRNA. Therefore, there are potentially 20 types of anti-ARS antibodies. Eight types of anti-ARS antibodies have been identified so far [9]. Most laboratories cannot test for known anti-ARS antibodies other than anti-Jo-1. So the diagnosis is missed many times. Anti-ARS antibodies are markers of disease. Disease activity may correlate with the level of antibodies [10].

Diagnostic criteria of antisynthetase syndrome:

The proposed diagnostic criteria of AS syndrome are the presence of anti-ARS antibodies plus two major criteria or one major and two minor criteria.

Major criteria	Minor criteria
1. ILD (not explained by environmental or occupational factors or drug exposure and not related to any other underlying disease) 2. Polymyositis or dermatomyositis in accordance with the Bohan and Peter criteria [11]	1. Arthritis 2. Raynaud's disease 3. Mechanic's hands.

Our patient had arthritis, Raynaud's disease and on further investigation i/v/o breathlessness was found to have ILD and ANA profile positive for Anti-ARS antibodies. Thus, fulfilling one major and two minor criteria with positive anti-Jo-1antibodies.

Fever - Present in 20% of patients. May occur at the onset of the disease. May persist or recur with relapses.

Myositis - Present in >90% of patients with antiJo1 AS syndrome. Most patients have polymyositis. A smaller proportion has dermatomyositis or overlap syndrome. Biochemical myositis precedes ILD in 12% of patients, whereas ILD precedes myositis in 37% and onset is concurrent in 50% of patients [12,13].

Inflammatory arthritis - Nearly 75% of patients experience joint pains or synovitis. Arthritis is non-erosive but can be deforming owing to joint subluxation. Symmetrical involvement of the metacarpal-phalangeal joints and wrists is very common[14,15] .

Lung disease - About 70%-100% of patients with AS syndrome develop lung disease, which is a cause of morbidity as well as mortality. ILD is the most common pulmonary manifestation [16] .Patients may present with sudden or gradual onset of dyspnea on exertion accompanied by dry cough. Patients may develop pulmonary hypertension with or without concomitant ILD[17] .NSIP is the most frequently reported histological pattern in ASS and the

presence of fibrosis (as opposed to cellular infiltrates) is an adverse predictor of response to immunosuppressive therapies[13, 14]. Indeed it has been suggested that ASS antibodies should be routinely tested in all patients with ILD, as the clinical presentation of ASS is frequently non-specific in the early stages.

Mechanic's hands -Affects ≈20% of patients. Thickened, hyperkeratotic, and fissured skin at the fingertips and radial margins of the fingers is the typical feature, as in our case.

Raynaud's disease - occurs in 40% of patients [14].

The diagnostic dilemma for Anti Synthetase syndrome:

It is not a known syndrome for most treating clinicians. ILD may be easily diagnosed using CT Thorax but ASS as the causal diagnosis is missed many times. Another problem/issue is a misdiagnosis of autoimmune diseases like seronegative RA, reactive arthritis, and non-specific arthritis in such cases. It is observed that ANA titers may be normal in many cases falsely ruling out this entity. A detailed ANA antibody profile with a good quality essay and a high level of suspicion is the key to the diagnosis of this rare autoimmune disease.

CONCLUSION:

There is considerable clinical heterogeneity and one or other manifestation can predominate or can be the only expression of the syndrome, leading to delayed diagnosis. As an early and exact diagnosis has crucial therapeutic and prognostic implications, knowledge about this syndrome and a high level of suspicion is of utmost importance.

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