Antisynthetase syndrome: An under-recognized cause of interstitial lung disease

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Abstract

Background: Antisynthetase syndrome (AS) is an uncommon and under-recognised connective tissue disease characterized by the presence of antibodies to anti-aminoacyl t-RNA synthetase along with features of interstitial lung disease (ILD), myositis and arthritis. The aim of the current study is to describe our experience with management of AS. Materials and Methods: This was a 2-year (2013-2014) retrospective analysis of patients diagnosed with anti-Jo-1-related AS. The presence of anti-Jo-1 antibody was tested by the immunoblot assay. All patients underwent high-resolution computed tomography of the chest, transthoracic echocardiography and evaluation for inflammatory myositis. Transbronchial lung biopsies and muscle biopsies were obtained when clinically indicated. Results: Nine patients (mean age: 43.8 years) were diagnosed with anti-Jo-1-related AS. The median duration of symptoms before diagnosis of AS was 6 months. All patients were negative for antinuclear antibodies by indirect immunofluorescence. The prevalence of ILD, myositis and arthritis at presentation was 100%, 77.8% and 55.6%, respectively. The most common ILD pattern was non-specific interstitial pneumonia (n = 6) followed by organizing pneumonia (n = 2) and usual interstitial pneumonia (n = 1). ILD was the sole manifestation in two patients and was subclinical in two patients. Six patients had pleuroperticardial effusions, three patients had pulmonary artery hypertension and two patients had venous thromboembolism. Eight of the nine patients improved after treatment with steroids and other immunosuppressants. Conclusion: Antisynthetase syndrome is an important and a treatable cause of ILD. Strong clinical suspicion is needed to achieve an early diagnosis.

Key Words: Antisynthetase syndrome, anti-Jo-1 antibody, diffuse parenchymal lung disease, inflammatory myositis, interstitial lung disease, non-specific interstitial pneumonia

Introduction

Antisynthetase syndrome (AS) is an uncommon multisystem connective tissue disease (CTD) characterized by the presence of circulating anti-aminoacyl t-RNA synthetase (ARS) antibodies and clinical features of interstitial lung disease (ILD), inflammatory myositis and polyarthritis. Other clinical features include fever, mechanic’s hand and Raynaud’s phenomenon (RP).[¹]

Though anti-ARS antibodies were initially considered to be myositis specific, subsequent studies have shown that they characterize their own clinical phenotype.[¹]

The clinical presentation of AS is variable and partly depends on the type of anti-ARS antibody.[²] Though typical
Most cases of AS are either misdiagnosed as idiopathic ILD or inflammatory myopathy not only due to the lack of awareness of the disease entity but also due to the lack of facilities for detection of anti-ARS antibodies.

Till date, nine different anti-ARS antibodies have been described, the commonest being anti-Jo-1 antibody directed against histidyl t-RNA synthetase. Others include anti-PL-7 (threonyl t-RNA synthetase), anti-PL-12 (alanyl t-RNA synthetase), anti-OJ (isoleucyl t-RNA synthetase), anti-EJ (glycyl t-RNA synthetase), anti-KS (asparaginyl t-RNA synthetase), anti-YRS (tyrosyl t-RNA synthetase), anti-Zo (phenylalanyl t-RNA synthetase) and anti-Wa (directed against NEFA, a t-RNA-related protein) antibodies. These antibodies are mutually exclusive of one another and can be detected by several methods including immunoprecipitation, counter current immunoelectrophoresis, chemiluminescent immunooassay, immunoblot or enzyme-linked immunosorbent assay (ELISA). The gold standard for detection of anti-ARS antibodies is the immunoprecipitation assay as this allows complete enumeration of all anti-ARS antibodies. Though tests for five of the anti-ARS antibodies are commercially available, only Jo-1 can be detected by ELISA. Others require specialized testing in reference laboratories and most centers in the developing world do not have facilities to detect anti-ARS antibodies other than anti-Jo-1 antibody.

In the current study, we present the clinical details of nine patients diagnosed with anti-Jo-1-related AS over a 2-year period at our institute. We also describe the clinical course and treatment outcomes of these patients.

**MATERIALS AND METHODS**

This was a 2-year (2013-2014) single-center retrospective study conducted at the Departments of Pulmonary Medicine and Internal Medicine of our institute, a tertiary care referral center in North India. All patients with a diagnosis of anti-Jo-1 antibody-related AS were included. A diagnosis of AS was made if the patient satisfied the following criteria: (a) Presence of anti-Jo-1 antibodies in the serum on any one occasion; and, (b) presence of either ILD, myositis or arthritis.

**Data extraction**

The case records of the included patients were retrieved from the medical records department of our institute and data was entered into a standard data extraction sheet. The following clinical details were noted: (a) Demographic details (age, sex of the patient); (b) basis for the diagnosis of AS; (c) clinical symptoms and signs at presentation; (d) comorbid conditions; (e) investigations (immunology, radiology, histopathology and others) performed during the hospital stay; and, (f) treatment details and hospital outcomes. We also evaluated the response to treatment, treatment-related complications and functional outcomes of the patients. Data are presented in a descriptive fashion.

**Investigations and definitions**

Serum anti-nuclear antibodies (ANA) and anti-neutrophil cytoplasmic antibodies (ANCA) were assessed by indirect immunofluorescence assay using NOVA Lite HEp-2 kit (INOVA Diagnostics, Inc. CA, USA) and in-house blood group O neutrophil spots, respectively. All patients were tested for the presence of anti Jo-1 antibodies in the serum by the immunoblot assay using Euroimmun ANA profile 3 EUROLINE kits (EUROIMMUN Medizinische Labordiagnostika, Deutschland). Other immunologic investigations were performed when considered clinically essential.

High-resolution computed tomography (HRCT) scan of the chest was performed in all patients. Patients were considered to have ILD if there were suggestive features (inter/intra-lobular septal thickening, honey combing, ground glass opacities or traction bronchiectasis) on HRCT chest with or without clinical symptoms. The pattern of ILD was classified according to the ATS/ERS classification of idiopathic interstitial pneumonias. Chest CT scans were independently reported by three authors (two pulmonary physicians and one pulmonary radiologist) and any difference in opinion was resolved by consensus. Spirometry was performed in all patients according to the standards set by the ATS/ERS task force. A restrictive physiology was defined as an FEV1/FVC ratio greater than the lower limit of normal and FVC < 80% predicted. Severity of restrictive physiology was classified as mild (predicted FVC%: 60-79%), moderate (predicted FVC%: 40-59%) and severe (predicted FVC%: <40%). Transbronchial lung biopsies (TBLB) were performed when clinically warranted in a subset of patients. All patients also underwent a baseline transthoracic echocardiography (TTE). Presence of left ventricular systolic dysfunction, pulmonary arterial hypertension (PAH) and presence of pericardial effusion were noted.

All patients with clinical evidence of proximal muscle weakness had an electromyography (EMG) evaluation, serum creatine kinase (CK) assessment and/or muscle biopsy performed. Diagnosis of polymyositis (PM) or dermatomyositis (DM) was made as per the Bohan and Peter classification criteria. The diagnosis of inflammatory arthritis was considered if the patient had inflammatory arthralgia (early morning stiffness lasting > 30 minutes) and synovitis of at least one joint. Mechanic’s hands were defined by the presence of characteristic hyperkeratotic lesions on the radial and palmar aspects of the hands and fingers with fissuring and scaling of the skin. A diagnosis of Raynaud’s phenomenon (RP) was made according to the 2014 international consensus criteria using the three step approach.
RESULTS

A total of nine patients fulfilled the criteria for anti-Jo-1-related antisynthetase syndrome during the study period [Table 1]. The mean age of the patients was 43.8 years (standard deviation, 11.4 years). The clinical presentation was with pulmonary symptoms, pyrexia of unknown origin, and arthritis/muscle weakness, in four, two and three patients, respectively. The most common symptom at presentation was fever (n = 9) followed by dyspnea (n = 7), arthralgia (n = 7) and proximal muscle weakness (n = 7). The median duration of symptoms before the diagnosis of AS was 6 months.

At the time of diagnosis of AS, all nine patients had radiologic evidence of ILD, whereas inflammatory myositis and arthritis were present in seven and five patients, respectively. Raynaud’s phenomenon was present in four patients and mechanic’s hands were seen in two patients. All patients were positive for anti-Jo-1 antibodies, and serum ANA and ANCA were not detectable in any patient. Investigations revealed the presence of normocytic normochromic anemia (hemoglobin < 12 gm/dL) in six patients, thrombocytosis (platelet count > 450,000/µL) and leucocytosis (total white blood cell count > 11,000/µL) in two patients each, and hypoalbuminemia (serum albumin < 3 gm/dL) in four patients. Serum electrolytes, liver and renal function tests were normal in all patients.

Cardiopulmonary manifestations

The most common pattern of ILD on HRCT chest was non-specific interstitial pneumonia (NSIP) (n = 6), followed by organizing pneumonia (OP) (n = 2) and usual interstitial pneumonia (UIP) (n = 1) [Table 2 and Figure 1]. Spirometry was performed in all except one patient (who was intubated). All patients had a restrictive abnormality on spirometry with a mean FVC of 50.6% predicted (standard deviation, 13.8). The restrictive physiology was mild in three patients, moderate in three patients and severe in two patients. Five patients had pleural effusion visualized on CT chest (bilateral in two patients and unilateral in three patients). The effusion was minimal (seen on CT chest but not on chest radiograph) in all patients and a diagnostic thoracentesis could be performed in only one patient in whom the pleural fluid analysis revealed an exudative lymphocytic effusion with low adenosine deaminase level (27 U/L). There was presence of pericardial effusion (without features of pericarditis or cardiac tamponade) in four patients [Figure 2]. The median thickness of the pericardial fluid was 7.5 mm (range, 4-17 mm). Echocardiography revealed the presence of PAH in three patients and dilated cardiomyopathy (left ventricular ejection fraction of 22%) in one patient. Two patients also had evidence of venous thromboembolism (case 4: Pulmonary thromboembolism and case 5: upper limb deep venous thrombosis). Both these patients were investigated for the presence of anti-phospholipid (aPL) antibodies, which were negative.

Table 1: Clinical characteristics of patients with anti-Jo-1-related antisynthetase syndrome

| Age (years) | 43.8±11.4 |
| Male sex | 3/9 (33.3) |
| Symptoms at diagnosis |  |
| Fever | 9/9 (100) |
| Weight loss | 2/9 (22.2) |
| Anorexia | 2/9 (22.2) |
| Dyspnea | 7/9 (77.8) |
| Dry cough | 6/9 (66.7) |
| Arthralgia | 7/9 (77.8) |
| Joint swelling | 5/9 (55.5) |
| Proximal muscle weakness | 7/9 (88.9) |
| Myalgia | 4/9 (44.4) |
| Raynaud’s phenomenon | 4/9 (44.4) |

Clinical findings on examination

- Polyarthritides: 6/9 (66.7)
- Mechanics hands: 2/9 (22.2)
- Calcinosis cutis: 1/9 (11.1)
- Gottron’s papules: 1/9 (11.1)
- Malar rash: 1/9 (11.1)
- Cutaneous ulcers: 1/9 (11.1)
- Cracksles on chest auscultation: 8/9 (88.9)

Investigations

- Anti-Jo antibody: 9/9 (100)
- Rheumatoid factor: 2/9 (22.2)
- ANA (IIF): 0/9
- ANCA: 0/9

Values are expressed as mean±S.D. or n/N (%). ANA=Anti-nuclear antibody, ANCA=Anti-neutrophil cytoplasmic antibody, IIF=Indirect immunofluorescence

Table 2: Cardiopulmonary manifestations in patients with antisynthetase syndrome

| Case | Pattern of ILD | Pleural effusion | Spirometric abnormality (% predicted FVC) | HPE findings (TBLB) | Echocardiographic findings | Thromboembolic manifestations |
|------|----------------|-----------------|------------------------------------------|---------------------|---------------------------|-------------------------------|
| 1    | NSIP           | None            | Restriction (55)                         | NA                  | Normal                    | None                          |
| 2    | UIP            | Right           | Restriction (45)                         | NA                  | PE                        | None                          |
| 3    | NSIP           | None            | Restriction (64)                         | DIP                 | PE                        | None                          |
| 4    | OP             | Bilateral       | Restriction (65)                         | OP                  | PE                        | Sub-segmental PTE             |
| 5    | OP             | Right           | Restriction (37)                         | OP                  | DCM, PAH                  | Left BCV thrombosis           |
| 6    | NSIP           | None            | NA*                                      | LNM                 | PAH                       | None                          |
| 7    | NSIP           | Left            | Restriction (43)                         | NA                  | Normal                    | None                          |
| 8    | NSIP           | None            | Restriction (66)                         | NA                  | Normal                    | None                          |
| 9    | NSIP           | Bilateral       | Restriction (30)                         | NA                  | PE                        | None                          |

BCV=Brachiocephalic vein, DCM= Dilated cardiomyopathy, DIP=Desquamative interstitial pneumonia, FVC=Forced vital capacity, HRCT=High resolution computed tomography, ILD=Interstitial lung disease, LMN=Lymphomononuclear infiltrate, NA=Not available, NSIP=Non-specific interstitial pneumonitis, OP=Organizing pneumonia, PAH=Pulmonary artery hypertension, PE=Pericardial effusion, PTE=Pulmonary thromboembolism, TBLB=Transbronchial lung biopsy, UIP=Usual interstitial pneumonitis
Musculoskeletal manifestations

Seven patients had proximal muscle weakness on clinical examination [Table 3]. EMG showed the presence of myopathic pattern in six patients, and serum CK (total) levels and serum transaminases were elevated in six patients. Of the nine patients, four patients fulfilled the diagnostic criteria for definite polymyositis (PM), two fulfilled the criteria for probable PM and one had possible PM. The most common articular manifestation was the presence of small and large joint non-erosive polyarthritis (n = 5) followed by polyarthritis (n = 2). The commonly involved joints were the small joints of the hand (n = 5), ankle (n = 5), knee (n = 5), wrist (n = 4), shoulder (n = 3) and elbow (n = 2). The arthritis spared the distal inter phalangeal joints in all except one patient (case 9). Inflammatory arthritis was the initial manifestation of the disease in three patients.

Treatment and clinical outcomes

All patients were treated with a combination of steroids and other immunosuppressant medications [Table 4]. The treatment induction was with high dose oral corticosteroids (1 mg/kg/day) in all patients. Six patients were also given cyclophosphamide pulses (4-6 pulses of 500 mg/m² at four weekly intervals). Steroids were gradually tapered over a 3-month duration and the treatment was maintained with low-dose steroids and azathioprine (1.5-2 mg/kg/day). Eight of the nine patients had clinical improvement and were discharged. Patients were followed up for a median duration of 1 year (range, 3 months-1.25 years). During the follow-up, one patient (case 1) had disease relapse while on steroid taper and one patient (case 5) developed sputum-positive pulmonary tuberculosis. One patient (case 5) expired after 1 year of treatment. The functional status at last follow-up was good in six patients.

DISCUSSION

To the best of our knowledge, this is the first series of patients with antisynthetase syndrome from India. Of the nine patients diagnosed with anti-Jo-1-related AS, ILD was present in all patients; inflammatory myositis and arthritis were present in seven and five patients, respectively. Majority of the patients improved with therapy.

Anti-Jo-1 antibodies were first described and characterized in the year 1980,[11] and their association with ILD and myositis established in 1983.[12] However, there is still no consensus on the diagnostic criteria for AS. The obligatory criterion for the diagnosis of AS remains the demonstration of anti-ARS antibodies in the serum. There are several assays for detection of these anti-ARS antibodies. Some consider the diagnosis of AS only when two consecutive tests for anti-ARS antibody are positive, whereas others diagnose AS even when a single test is positive.[9,13] The three major clinical criteria for the diagnosis of AS include ILD, myositis and arthritis. Presence of any one major
criterions is sufficient to make the diagnosis of AS although inclusion of inflammatory arthritis as a major criterion is debatable, and some consider it as a minor criterion.[14]

Minor criteria for the diagnosis of AS include the presence of mechanic’s hands, RP and fever. Whether the diagnosis of AS can be made solely on the basis of minor criteria is not clear.

Anti-ARS antibodies can be detected in 30-40% of patients with inflammatory myositis,[15] and in 7-10% of patients with idiopathic interstitial pneumonia.[14] The most common anti-ARS antibody is the anti-Jo-1 antibody (60% cases of AS), followed by anti-PL-7 and anti-PL-12 antibodies (10-15% cases of AS). Other antibodies are less common and are seen in less than 5% of AS patients.[14]

There is significant clinical heterogeneity among patients with AS. Those with anti-Jo-1 antibodies more often present with arthritis, myositis and mechanics hands, whereas those with non-anti-Jo-1 antibodies present with fever and ILD.[16]

Pulmonary involvement in encountered in 70-100% of the patients with AS and is a cause of morbidity as well as mortality.[17] The most common pulmonary manifestation of AS is the presence of ILD. The prevalence of ILD in patients with AS varies from 40 to 100%, and depends on the type of anti-ARS antibody (anti-Jo-1 vs. non-anti-Jo-1), the criteria used for diagnosis of ILD (clinicoradiological vs. radiological; chest radiograph vs. HRCT chest), and the duration of follow-up.[18] ILD in AS can be the initial as well as the only manifestation of the disease. In fact,

The patterns of ILD in patients with AS include the NSIP pattern, UIP pattern, OP pattern [Figure 3] and the acute interstitial pneumonia (AIP) pattern.[19,20] As compared to patients with idiopathic interstitial pneumonias (IIP), patients with AS-related ILD present at a younger age, more often have NSIP pattern, have raised serum inflammatory markers, features suggestive of a CTD and have a better survival.[4] However, ILD in AS may be indistinguishable from that of IIP in patients with subclinical or sine myositis. Similar to earlier reports,[4,23] NSIP pattern was the most common pattern of ILD in our patients with AS.
Also, the mean age of our patients was 43.8 years, which is less than that in IIPs.

Two of the nine patients in the current study presented with ILD as the initial manifestation and did not have associated arthritis or myositis (case 6 and case 7). It is important to recognize this subset of individuals who are often mislabelled as having IIP or an undifferentiated CTD (UCTD). Also, all our patients had a negative serum ANA. Anti-ARS antibodies cause cytoplasmic staining instead of nuclear staining on indirect immunofluorescence. In resource constrained settings, when patients with ILD and features suggestive of a CTD are evaluated, serum ANA levels are used as the screening test and if negative, other auto-antibodies are not looked for. As a result, the diagnosis of AS is missed and such patients are often labeled as IIP or UCTD. The clinical presentation of ILD in patients with AS is also variable. The interstitial involvement may be subclinical, detectable only on imaging/pulmonary function tests or may lead to acute respiratory failure. Two patients (case 1 and case 8) in our study did not have any respiratory symptom at presentation (subclinical ILD). Interstitial involvement was suspected because of the presence of fine end inspiratory crackles on chest auscultation and ILD was subsequently confirmed by HRCT imaging. Patients with myositis or arthritis often have significant functional limitation because of the disease per se, and this may result in poor perception of respiratory symptoms, especially dyspnea. Hence, it is important to perform a thorough respiratory system examination for detection of ILD in such patients.

Other less common pulmonary manifestations of AS include PAH, pleuro-pericardial effusions and venous thromboembolism. In a recent study of 203 patients with AS, PAH was suspected on echocardiography in 47 patients (23%) and was associated with lower survival. Pulmonary hypertension is most often of the pre-capillary type, usually secondary to ILD and can be severe. Similar to this study, the prevalence of PAH in our study was 33.3% and it was severe in one patient. Six patients had pleuro-pericardial effusions (five with pleural effusion, four with pericardial effusion and three with both pericardial and pleural effusions). These effusions were subclinical in all patients. Presence of pericarditis and pericardial effusions have been reported in earlier studies as well.

CONCLUSIONS

In conclusion, antisynthetase syndrome is a treatable cause of ILD and its true prevalence remains unknown. A younger age at presentation and the presence of NSIP pattern on imaging should raise a clinical suspicion of AS. Such patients need to be evaluated for AS even in the absence of other features of the disease.

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Conflicts of interest
There are no conflicts of interest.

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