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Clinical Trial Paper

Clinical features and outcomes of interstitial lung disease in anti-Jo-1 positive antisynthetase syndrome

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ABSTRACT

Background: Interstitial lung disease (ILD) is a common extra-muscular manifestation of antisynthetase (AS) syndrome. ILD prevalence is higher with anti-Jo-1 antibody positivity. Data on long-term outcomes in these patients are lacking.
Methods: Over 15 years, we identified subjects with anti-Jo-1 positive AS syndrome and ILD. Demographics, pulmonary function testing (PFT), high-resolution computed tomography (HRCT), histopathology, and long-term survival were analyzed.
Results: We identified 103 subjects (mean age 49.2 years, female predominance [70%]). The predominant myopathy was polymyositis (64%) followed by dermatomyositis (24%). In approximately half of studied subjects, AS syndrome and ILD were diagnosed within 6 months of each other. The majority had restriction on PFTs (98%). Non-specific interstitial pneumonia (NSIP) was the most common HRCT pattern (52%), followed by NSIP overlapping with organizing pneumonia (OP) (22%). Thirty-nine subjects had biopsy data. Ten-year survival was 68%. Multivariable analysis adjusted for age at ILD diagnosis, gender, FVC and DLCO, revealed that male gender (HR = 2.60, p = 0.04) and DLCO at presentation (HR = 0.94, p = 0.05) significantly predicted mortality.
Conclusions: We present a large cohort of anti-Jo-1 positive AS syndrome with ILD and note good overall survival.

1. Introduction

Anti-synthetase syndrome (AS syndrome) is defined by the presence of autoimmune inflammatory myopathy [either polymyositis (PM), dermatomyositis (DM) or clinically amyopathic dermatomyositis (CADM)], interstitial lung disease (ILD), and positive serology for anti-aminoacyl-tRNA synthetase (antisynthetase ARS) antibodies [1–3]. Further, one or more of the following clinical features: arthritis, Raynaud's phenomenon and mechanic's hands, are also frequently observed in this syndrome [1–3].

ARS antibodies are directed against aminoacyl-transfer-RNA synthetases, a group of cytoplasmic enzymes that catalyze binding of amino acid groups to their cognate tRNA, a necessary step in the formation of polypeptides. To date, there are eight antibodies associated with AS syndrome. The first to be discovered and most commonly identified is anti-Jo-1, present in approximately 30% of cases [4]. Anti-Jo-1-antibody is directed against the cellular enzyme histidyl-tRNA synthetase [4,5].

ILD is the most common extra-muscular manifestation in AS syndrome with a prevalence ranging from 67% to 100% [3,6–10], higher than that reported in non-AS inflammatory myopathies which range from 20% to 75% [3,11–14]. In the presence of anti-Jo-1 positive serology, ILD appears more prevalent and carries with it a higher mortality. In a recent report by Aggarwal et al., ILD was the principal cause of death accounting for over 50% of observed mortality [15].

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While prior studies have reviewed the presenting clinical features of AS syndrome [10,16–18], little is known about anti-Jo-1 positive serology and severity of underlying ILD, response to treatment, and long-term survival. We reviewed all anti-Jo-1 antibody positive subjects with AS syndrome and associated ILD looking for predictors of disease progression and mortality.

2. Materials and methods

2.1. Study population and subject identification

Following approval by the Committee on Human Research at Mayo Clinic, Rochester, MN, we performed a retrospective cohort study reviewing the medical records of subjects with positive anti-Jo1-antibody and ILD seen at Mayo Clinic over a 15-year period (1995–2010). Criteria for AS syndrome in this study were: presence of positive Jo-1 anti-aminoacyl t-RNA (ARS) antibodies on serology, clinically diagnosed myopathic connective-tissue disease as determined by an expert rheumatologist (dermatomyositis, polymyositis, or overlap disease), and interstitial lung disease as defined by chest computed tomography (CT). Presence of associated clinical findings including arthritis, Raynaud's phenomenon, or mechanic's hands were collated but not used specifically to define the disease syndrome. Subjects with other identifiable causes for ILD, including other connective-tissue disease (CTD), medication related lung injury, environmental and occupational exposures, were excluded.

Demographics: Age, gender, underlying type of inflammatory myopathy, respiratory and rheumatologic symptoms, smoking history, gastroesophageal reflux disease, time since ILD diagnosis, characteristics of ILD findings, associated positive antibody serologies, and prior treatments and response to therapy were reviewed.

Pulmonary function tests (PFT): PFT data, including forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO) were abstracted at baseline and at serial follow-up. Disease progression on PFT was defined as decline in FVC by more than 10% of predicted, and/or decline in DLCO by more than 15% of predicted, similar to criteria established for idiopathic pulmonary fibrosis [19].

High Resolution CT chest: Chest CT images were reviewed at baseline and latest follow-up by two expert radiologists (DW and CWC) according to the 2013 American Thoracic Society classification of idiopathic interstitial pneumonias [20] as follows: usual interstitial pneumonia (UIP) pattern if the dominant abnormality was bilateral subpleural reticulation with lower lobe predominance and honeycombing with minimal or nonexistent ground glass opacities (GGO). Possible UIP was suggested by bibasilar and peripheral predominant reticular changes without specific honeycombing. Both UIP and possible UIP were grouped together for the purposes of this analysis. Nonspecific interstitial pneumonia (NSIP) pattern consisted of GGO and bilateral bibasilar reticulation with traction bronchiectasis and bronchiolectasis. An organizing pneumonia (OP) pattern consisted of patchy and/or migratory consolidation in a subpleural, peribronchial, or band-like pattern commonly associated with alternating ground-glass opacities. There was also an additional category of radiologic NSIP/OP overlap as previously described [21]. Those with radiologic features not fitting the above descriptions were labeled “atypical/unclassifiable.” ILD course assessed by CT was categorized as stable, improved, or progressing by serial CT assessment according to study radiologists’ interpretation [19]. If there were discrepancies between disease progression as measured by CT and PFT, we determined disease trend based on FVC findings. Progression of CTD was determined using rheumatology follow up assessment, and classified as improved, stable, or worsening in terms of extrapulmonary manifestations of AS syndrome.

Lung biopsy: When available, lung pathology was reviewed and categorized according to the 2013 American Thoracic Society/European Respiratory Society consensus statement in the following manner: UIP, NSIP, OP and diffuse alveolar damage [20]. An unclassified pattern was one that did not fit listed categories above. If a subject had discrepant findings on CT and biopsy, biopsy findings were taken to represent the underlying ILD pattern. Though transbronchial lung biopsies are not sufficient to diagnose or rule out a specific type of ILD, we included these biopsies when available. Our intention was to include all pathologic findings, recognizing that some transbronchial biopsies may have been performed to evaluate a superimposed acute infectious or inflammatory process.

2.2. Statistical analyses

Continuous data were expressed as mean (standard deviation) or median (interquartile range), as appropriate. Binary data were expressed as percentages. Predictors of disease progression or severity defined as worsening of radiologic and pulmonary function testing were evaluated using logistic and linear regression. A two-tailed p-value of <0.05 was considered statistically significant. Long-term all-cause mortality was assessed with Kaplan-Meier statistics using the Log rank method. Predictors of mortality were assessed using Cox proportional hazards analysis and a multivariate model was constructed with a priori adjustments for age, gender, FVC and DLCO. All statistical analysis was performed using JMP 10.1 (SAS Institute Inc., Cary, NC).

3. Results

Subject Characteristics: One hundred and three subjects with AS syndrome and positive anti-Jo-1 antibody over a 15-year period (1995–2010) were identified. There was noted female predominance (72/103, 70%) with a mean age of 49.5 (range 20.1–76.5) years at the time of ILD diagnosis. The most common underlying inflammatory myopathy was PM (66/103, 64%) followed by DM (25/103, 24%). Six subjects (6%) did not have myositis at presentation (Table 1).

In one-half of patients (52/103, 50%) CTD and ILD were diagnosed within 6 months of each other. In 16% of the cohort, ILD diagnosis preceded CTD diagnosis by over 6 months. Most subjects complained of dyspnea, cough, fatigue, and myalgia, with crackles noted on physical examination (Table 1). Raynaud's phenomenon and Mechanic's hands occurred in only 23% and 20% of subjects, respectively (Table 1). The majority of subjects were never smokers (60%).

Pulmonary function tests: Ninety-six subjects (93%) had available baseline PFT. The majority showed restriction (98%) with mean FVC at 65.7% and mean DLCO at 56.3% of predicted (Table 1). Follow-up PFT greater than 1 year after baseline was available in 56/96 (58%) subjects.

High Resolution CT chest: Eighty-five subjects (83%) had available baseline HRCT images that were reviewed by two independent radiologists. Seven additional subjects had radiological interpretations in the medical record, but no images available for review by the study radiologists. The most common pattern was NSIP ($n = 44$, 52%), followed by NSIP/OP ($n = 19$, 22%). Typical UIP pattern was not observed in any subject, with possible UIP pattern seen in 11 (13%) subjects. Fifty-five subjects had available follow-up HRCT chest images for review (Table 2).

Lung biopsy: Thirty-nine subjects (38%) had lung biopsy data, of which 30 (77%) were surgical and 9 (23%) were transbronchoscopic (Table 2). The most common histologic pattern was OP found in 10 subjects (26%) followed by NSIP in 9 (23%). UIP pattern was only