Clinical Profile of Anti-PL-12 Autoantibody*

Cohort Study and Review of the Literature

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Background: **The antisynthetase syndrome consists of interstitial lung disease (ILD), arthritis, myositis, fever, mechanic's hands, and Raynaud phenomenon in the presence of an antisynthetase autoantibody, most commonly anti-Jo-1. It is believed that all the antisynthetases are associated with a similar clinical profile, but definitive data in this diverse group are lacking. The purpose of this study was to examine the clinical profile of anti-PL-12, an antisynthetase autoantibody directed against alanyl-transfer RNA synthetase.**

Methods: **Thirty-one subjects with anti-PL-12 autoantibody were identified from the databases at the Medical University of South Carolina, the University of Pittsburgh Medical Center, Johns Hopkins Medical Center, and Brigham and Women's Hospital. The medical charts were reviewed and the following data were recorded: demographic information; pulmonary and rheumatologic symptoms; connective tissue disease (CTD) diagnoses; serologic autoantibody findings; CT scan results; BAL findings; pulmonary function test results; lung histopathology; and treatment interventions.**

Results: **The median age at symptom onset was 51 years; 81% were women and 52% were African American. Ninety percent of anti-PL-12-positive patients had ILD, 65% of whom presented initially to a pulmonologist. Ninety percent of anti-PL-12-positive patients had an underlying CTD. Polymyositis and dermatomyositis were the most common underlying diagnoses. Raynaud phenomenon occurred in 65% of patients, fever in 45% of patients, and mechanic's hands in 16% of patients. Test results for the presence of antinuclear antibody were positive in 48% of cases.**

Conclusions: **Anti-PL-12 is strongly associated with the presence of ILD, but less so with myositis and arthritis. Idiopathic ILD diagnosed as idiopathic pulmonary fibrosis may, in fact, be associated with anti-PL-12 and be a "forme fruste" of an underlying autoimmune disorder.**

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Abbreviations: ANA = antinuclear antibody; BWH = Brigham and Women's Hospital; CTD = connective tissue disease; DM = dermatomyositis; HRCT = high-resolution CT; IIM = idiopathic inflammatory myopathy; ILD = interstitial lung disease; IP = immunoprecipitation; IPF = idiopathic pulmonary fibrosis; JHMC = Johns Hopkins Medical Center; MSA = myositis-specific antibody; MUSC = Medical University of South Carolina; NSIP = nonspecific interstitial pneumonitis; OP = organizing pneumonia; PM = polymyositis; tRNA = transfer RNA; UIP = usual interstitial pneumonitis; UPMC = University of Pittsburgh Medical Center

Polymyositis (PM) and dermatomyositis (DM) are part of the spectrum of the idiopathic inflammatory myopathies (IIMs). They are acquired, chronic myopathies of unknown cause presenting with symmetric proximal muscle weakness; DM is associated with characteristic skin rashes. Like other autoimmune diseases, PM and DM are associated with several autoantibodies. These antibodies are classified as myositis-associated antibodies and myositis-specific antibodies (MSAs). A myositis-associated antibody may be found in patients with other connective tissue diseases (CTDs), whereas MSAs are thought to be exclusively associated with PM and DM. MSAs are a heterogeneous group of autoantibodies directed against specific antigens that include aminoacyl-transfer RNA (tRNA) synthetases (Table 1) Each autoantibody may be associated with distinctive phenotypic features and prognosis.[1]

Table 1—*Prevalence of Antisynthetase Antibodies in PM/DM**

MSAs (Anti-tRNA Synthetases)	Antigen	Prevalence
Jo-1	Histidyl-tRNA synthetase	15–20%
PL-7	Threonyl-tRNA synthetase	5–10%
PL-12	Alanyl-tRNA synthetase	< 5%
EJ	Glycyl-tRNA synthetase	5–10%
OJ	Isoleucyl-tRNA synthetase	5%
KS	Asparaginyl-tRNA synthetase	< 5%
Zo	Phenylalanyl-tRNA synthetase	< 1%
YRS	Tyrosyl-tRNA synthetase	< 1%

*Adapted from Table 1 in the article by Mimori et al.[1]

Patients with the anti-Jo-1 autoantibody, which was first described and characterized in 1980,[2] often present with one or more of the following features: myositis; interstitial lung disease (ILD); polyarthritis; Raynaud phenomenon; mechanic's hands; and fever. This constellation of symptoms and signs has been termed the "antisynthetase syndrome."[3,4] Other antibodies in the anti-aminoacyl-tRNA synthetase group include anti-PL-7, anti-PL-12, anti-EJ, anti-OJ, anti-KS, anti-YRS, and anti-Zo. Although less common than anti-Jo-1, they share similar clinical features. We describe a cohort of anti-PL-12-positive patients, which is the third most common anti-aminoacyl-tRNA synthetase described in the literature,[4,5] and compare them to previously reported cases.

Materials and Methods

We performed a retrospective chart review of all anti-PL-12-positive patients at the following four tertiary care institutions: Medical University of South Carolina (MUSC); University of Pittsburgh Medical Center (UPMC); Johns Hopkins Medical Center (JHMC); and Brigham and Women's Hospital (BWH). Serologic testing was done at specialty laboratories by radio immunoprecipitation (IP) assay for MUSC and BWH. The sera at both UPMC and JHMC were analyzed by IP at university research laboratories. At UPMC, anti-PL-12 was verified by radiolabeled protein IP, with positive results confirmed by RNA IP. All patients testing positive for anti-PL-12 from 2000 to 2007 underwent a detailed retrospective chart review that included clinic and hospital notes, conventional chest CT scan or high-resolution CT (HRCT) scan of the chest, pulmonary function testing, pulmonary histopathology, and laboratory data. Treatment intervention and response to therapy were also recorded when available. Chest CT scans were independently interpreted by three pulmonologists; differences were resolved by consensus. Lung pathology at MUSC, JHMC, and UPMC was reviewed by a pulmonary pathologist, and for BWH reports were reviewed and accepted. PM or DM was diagnosed if patients met the published criteria of Bohan and Peter[6] for probable or definite disease. Subclinical myositis was defined as an elevation in serum creatine kinase and/or aldolase levels without proximal muscle weakness.[7]

ILD was diagnosed if any of the following conditions were present on CT scans: interlobular septal thickening; honeycombing; traction bronchiectasis; and/or ground-glass opacities. ILD was also diagnosed with biopsy confirmation of nonspecific interstitial pneumonitis (NSIP), usual interstitial pneumonitis (UIP), or organizing pneumonia (OP).[8,9] Pulmonary restrictive physiology was defined by an FVC < 80% predicted and an FEV_1/FVC ratio of > 70% on spirometry. Impaired diffusion was defined as a diffusing capacity of the lung for carbon monoxide of < 75% predicted.

Mechanic's hands were defined by the presence of characteristic hyperkeratotic and/or nonpruritic erythema on the lateral and palmar aspects of the hands and fingers with fissuring and scaling of the skin.[10]

We searched the English-language literature using the following free-text search words on MEDLINE from its inception through June 2007: "PL-12 antibody"; "Anti-PL-12"; "alanyl-tRNA synthetase"; "polymyositis"; "dermatomyositis"; and "autoantibody." The Cochrane Library EMBASE, CISCOM, and AMED databases were also examined for additional references. We also supplemented the literature search with references from the retrieved manuscripts and by consultation with experts. The institutional review boards at the respective institutions approved this study.

Results

Thirty-one patients with anti-PL-12 were identified (Table 2), as follows: UPMC, 14 patients; MUSC, 9 patients; JHMC, 5 patients; and BWH, 3 patients. The median age at diagnosis was 51 years (range, 22 to 87 years). There were 25 females (81%) and 16 African Americans (52%), 14 whites (45%), and 1 Hispanic patient (3%). Ninety percent had an underlying CTD. Ten patients (32%) had PM, 6 patients had DM (19%), and 5 patients (16%) had overlap syndromes with features of an IIM and a second CTD. These three conditions accounted for 68% of the cases. The other CTD diagnoses were undifferentiated CTD (five patients; 16%) and systemic sclerosis (two patients; 6%). Three patients

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