Pulmonary Pathologic Manifestations of Anti-Alanyl-tRNA Synthetase (Anti–PL-12)–Related Inflammatory Myopathy

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- Context.—Patients with anti–a-aminoacyl-tRNA synthetase syndrome (ARS), a subset of idiopathic inflammatory myopathy, have a high prevalence of lung involvement. Autoantibodies directed against alanyl-tRNA synthetase (anti–PL-12 Abs) represent 1 of the 8 autoantibodies currently described under the rubric of ARS.

- Objective.—To describe the clinical, radiographic, and pulmonary histopathologic findings in patients possessing anti–PL-12 autoantibodies.

- Design.—Patients with anti–PL-12 ARS were identified in the University of Pittsburgh Idiopathic Inflammatory Myopathy registry. Lung biopsies from 10 patients and lung explants from 2 patients with anti–PL-12 ARS were reviewed, together with chest computed tomography and clinical records.

- Results.—Patients primarily presented with dyspnea and variable combinations of cough, fever, mechanic’s hands, Raynaud phenomenon, and skin and muscle involvement. Chest computed tomography most commonly showed lower lung zone-predominant reticular infiltrates and traction bronchiectasis, with or without honeycomb change. Surgical lung biopsies and pneumonectomies for lung transplantation revealed usual interstitial pneumonia in 8 of 12 cases (67%), nonspecific interstitial pneumonia in 2 of 12 cases (17%), and organizing pneumonia in 2 of 12 cases (17%). Lymphoplasmacytic interstitial inflammation with lymphoid aggregates was common.

- Conclusions.—Lung disease is often the first manifestation of anti–PL-12 ARS. There are no pathognomonic histopathologic features to distinguish anti–PL-12 ARS-related lung disease from idiopathic variants of diffuse interstitial lung disease. Increased inflammation, lymphoid aggregates, and nonspecific interstitial pneumonia–like areas in a biopsy, as well as clinical features of mechanic’s hands, Raynaud phenomenon, arthritis, and fever, should prompt pathologists to suggest involvement by ARS.

Lung involvement, mostly in the form of ILD, is common in ARS, affecting up to 90% of patients with anti–PL-12 ARS. Most patients present with progressive dyspnea and cough. Although radiographic findings, including bibasilar fibrosis, ground-glass opacities, interlobular reticulation, and traction bronchiectasis, have been described, the corresponding histopathology has been poorly documented.

Here, we present the clinical and pathologic findings in 12 patients with anti–PL-12 antibodies, to our knowledge, the largest and most comprehensive study to date of pulmonary histopathologic features in anti–PL-12 ARS.

MATERIALS AND METHODS

The University of Pittsburgh’s Idiopathic Inflammatory Myopathy registry was searched for patients who, at the time of their initial clinical evaluation, were found to have anti–PL-12 antibodies. Anti–PL-12 was identified by radiolabeled protein immunoprecipitation, with positive results confirmed by RNA immunoprecipitation, as previously described.

Clinical features were extracted from this myositis registry, which encompasses more than 3 decades of prospective data and serum collected on consecutive outpatients and inpatients with myositis evaluated at the University of Pittsburgh (Pittsburgh, Pennsylvania). The extracted database was complemented by retrospective review of the electronic medical record. Patients possessing anti–PL-12 autoantibodies who were initially seen between January 1985 and December 2012 were included, regardless of their connective tissue disease (CTD) diagnosis. Patients with myositis met the diagnostic criteria of Bohan and Peter, whereas the...
### Table 1. Clinical Features of Patients With Anti–PL-12 Autoantibodies

| Case, No. | Age, y/SEX | Presenting Symptom | Myositis | Skin Disease | Raynaud | Arthritis | Mechanic’s Hands | Dysphagia | Fever | Clinical Diagnosis | Follow-up |
|-----------|------------|--------------------|----------|--------------|---------|-----------|------------------|-----------|-------|-------------------|-----------|
| 1         | 46/F       | Dyspnea            | –        | –            | +       | –         | –                | –         | –     | Sjögren           | Alive, 12 y |
| 2         | 52/F       | Dyspnea            | –        | +            | –       | +         | –                | –         | –     | UCTD              | Alive, lung transplant, 18-y follow-up, 7 y after transplant |
| 3         | 17/F       | Raynaud            | +        | –            | –       | –         | –                | –         | –     | PM                | Alive, 7 y |
| 4         | 57/F       | Dyspnea            | –        | +            | +       | –         | –                | –         | –     | UCTD              | Alive, lung transplant, 10-y follow-up, 5 y after transplant |
| 5         | 48/F       | Dyspnea            | –        | +            | –       | –         | –                | –         | –     | UCTD              | Alive, 8 y |
| 6         | 47/M       | Dyspnea            | +        | –            | –       | –         | +                | +         | –     | PM                | Dead, unknown |
| 7         | 64/F       | Dyspnea            | –        | SD           | +       | –         | +                | +         | –     | Overlap RA and SSc | Alive, 15 y |
| 8         | 59/F       | Dyspnea            | –        | –            | –       | –         | –                | –         | –     | UCTD              | Alive, lung transplant, 18-y follow-up, 11 y after transplant |
| 9         | 64/M       | Fever              | +        | SD           | +       | –         | –                | –         | –     | SSc               | Alive, 9 y |
| 10        | 35/F       | Dyspnea            | +        | –            | –       | –         | –                | –         | –     | UCTD              | Alive, 13 y |
| 11        | 60/M       | Fever              | –        | –            | –       | –         | +                | –         | –     | PM                | Alive, 6 y |
| 12        | 38/F       | Dyspnea            | –        | –            | +       | –         | –                | –         | –     | PM                | Alive, 20 y |

Abbreviations: PM, polymyositis; RA, rheumatoid arthritis; SD, sclerodactyly; SSc, systemic sclerosis; UCTD, undifferentiated connective tissue disease.

a ÷, present; —, absent.
b Age at time of (first) tissue sampling.
c Underlying systemic disease.

### Table 2. Radiographic and Histopathologic Features of Patients With Anti–PL-12 Autoantibodies

| Case, No. | Radiologic Diagnosis | Type of Biopsy | Lobes (Slides) | Main Pattern of Lung Disease | Secondary Histopathologic Features |
|-----------|----------------------|----------------|----------------|-----------------------------|-----------------------------------|
| 1         | UIP                  | 1. SLB         | 1. (3)         | 1. OP                       | 1. Grocott stains negative        |
|           |                      | 2. Tbbx (+5 y) | 2. (1)         | 2. Acute and chronic bronchitis | 2. Poorly formed nonnecrotizing granulomas; Grocott stain negative |
| 2         | UIP                  | BLT            | 5 (52)         | UIP                         | LPI, LA, few eosinophils; minimal vasculopathy |
| 3         | Subpleural fibrosis, Br’ectasis, and consolidation | SLB | 2 (8) | OP | Few plasma cells, few eosinophils |
| 4         | UIP                  | 1. SLB         | 5 (30)         | 1. UIP                      | 1. NSIP-like areas, numerous FF, LPI, LA, few eosinophils |
|           |                      | 2. BLT (+3 y)  |                | 2. UIP                      | 2. Widespread NSIP-like areas, multiple small calcifications, rare nonnecrotizing granulomas with giant cells associated with airways |
| 5         | UIP                  | SLB            | 2 (12)         | UIP                         | LPI, LA, few eosinophils, mild vasculopathy affecting small arterioles |
| 6         | UIP                  | SLB            | 1 (6)          | NSIP                        | Acute bronchopneumonia, mucoid impaction |
| 7         | UIP                  | SLB            | 2 (4)          | UIP                         | LA, eosinophilic pleuritis |
| 8         | UIP                  | SLT            | 2 (11)         | UIP                         | Rare stellate airway-centered scars, few eosinophils |
| 9         | UIP                  | SLB            | 1 (2)          | NSIP                        | OP, moderate No. of eosinophils, vasculopathy |
| 10        | UIP                  | SLB            | 1 (4)          | UIP                         | NSIP-like areas, LPI, rare nonnecrotizing granulomas, LA, few eosinophils |
| 11        | UIP                  | SLB            | 1 (6)          | UIP                         | LA, local OP, moderate No. of eosinophils, pleuritis |
| 12        | UIP                  | SLB            | 2 (10)         | UIP                         | LA, moderate eosinophil, vasculopathy, pleuritis |

Abbreviations: BLT, bilateral lung transplant; Br’ectasis, bronchiectasis; FF, fibrolastic foci; LA, lymphoid aggregates with or without germinal centers; LPI, lymphoplasmacytic inflammatory infiltrates; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; SLB, surgical lung wedge biopsy; SLT, single lung transplant; Tbbx, transbronchial biopsy; UIP, usual interstitial pneumonia.

a No. of lobes sampled (No. of slides available for study [hematoxylin-eosin]).
diagnoses of systemic sclerosis, Sjögren syndrome, undifferentiated CTD (UCTD), or other overlapping rheumatic syndromes were made clinically by experienced rheumatologists.

All variables (clinical, laboratory, radiographic, and pathologic) and organ system definitions were well defined and standardized in this registry. Organ involvement was defined as follows: (1) vascular, the presence of Raynaud phenomenon, digital pitting scars, ulcers and gangrene, or abnormal nailfold capillaries; (2) cutaneous, characteristic rashes of DM or sclerodactyly; (3) joints, objective joint swelling and tenderness; (4) muscle, objective, proximal muscle weakness, in addition to any one of the following: elevated serum creatine kinase, myopathic electromyogram, or myositis on muscle biopsy; (5) gastrointestinal, proximal or distal, esophageal dysmotility or small/large bowel involvement; (6) pulmonary, fibrosis on chest radiograph or high-resolution chest computed tomography; and (7) primary pulmonary artery hypertension, mean pulmonary artery pressure more than 25 mm Hg on cardiac catheterization or systolic pressure more than 40 mm Hg estimated by echocardiography in the absence of significant pulmonary and/or cardiac disease causing secondary pulmonary artery hypertension. Interpretations of chest computed tomographies were performed by thoracic radiologists at our institution.

Only patients for whom histology slides of lung tissue were available for review were included in the study. An average number of 12 slides stained with hematoxylin-eosin were available for study (median, 7; range, 2–52). The histopathologic pattern of lung involvement was classified according to the American Thoracic Society/European Respiratory Society consensus classification of idiopathic interstitial pneumonias.9,10 A clinical diagnosis of ILD required restrictive physiology on pulmonary function testing and abnormal radiologic findings by high-resolution chest computed tomography characterized by at least one of the following: reticulation, traction bronchiectasis, honeycomb change, or ground-glass opacities.

RESULTS

Specimens from 12 patients were available for study; 10 patients had surgical lung biopsies (1 underwent bilateral lung transplantation 3 years later; 1 underwent transbronchial biopsy 5 years later; both were also available for review), and 2 patients underwent single and double lung transplantation, respectively.

The clinical features of the 12 patients with anti–PL-12 autoantibodies are shown in Table 1. The patients’ median age was 52 years (range, 17–64), with 9 woman and 3 men. Most patients presented with dyspnea (9 of 75; 67%) as their initial symptom. Four patients carried a diagnosis of PM, 5 had UCTD, 2 had systemic sclerosis, and 1 had Sjögren syndrome. The most common ARS features, other than dyspnea, were erythematosus skin rashes in 5 of 12 patients.
and another with features of aspiration. In the third case, with accompanying, presumably infectious, acute bronchitis, a few scattered, nonnecrotizing granulomas (Figure 2, B): 1

and one patient with NSIP. Three of 12 cases (25%) showed A), and a focal secondary finding in one patient with UIP pattern of lung disease in 2 of 12 patients (17%) (Figure 2, A and B). Pertinent negative findings were the absence of pneumonic consolidation, mural thickening of pulmonary arteries, and subpleural honeycomb change. One patient was deceased, but all living patients had active disease, mostly manifested as ILD. Three patients had undergone therapeutic lung transplant procedures depending on the criteria used.11 Nonspecific interstitial pneumonia is 4 times more common than UIP in patients with PM, whereas the difference is less than 2-fold in patients with DM, demonstrating the heterogeneity among patients with IIM in the degree and pattern of lung involvement.11 Historically, the pattern of disease predicts prognosis: organizing pneumonia offers a better prognosis than UIP does, whereas diffuse alveolar damage portends a particularly poor prognosis.12

Herein, we describe the histopathologic features of lung involvement in 12 cases of anti–PL-12 ARS, a distinct subset of IIM, although anti–PL-12 can be seen in clinical association with other CTD or UCTD. Our study provides 2 main findings: (1) there are no pathognomonic features that would allow for a definitive diagnosis of anti–PL-12 ARS based on the histopathologic features alone, and (2)

| Source, y | Age, y/ Sex | Clinical Features | Radiologic Features |
|-----------|-------------|-------------------|---------------------|
| Kummerfeldt et al,23 2013 | 32/F | Dyspnea, restrictive PFTs | Ill-defined, coalescent peripheral nodular densities at lung bases |
| Handa et al,24 2005 | 44/M | Mechanic’s hands, restrictive PFTs, PH | Bilateral basal reticular shadows |
| Koreeda et al,25 2010 | 61/F | PM, also Jo-1 antibodies | GGO and TB without HC with basilar and BVB predominance |
| Friedman et al,3 1996 | 26/F | Respiratory failure requiring MV | NR |
| Friedman et al,3 1996 | 38/F | Fever, cutaneous vasculitis, Raynaud | NR |
| Friedman et al,3 1996 | 47/M | Cough | NR |
| Hervier et al,8 2010 | 7 pts | Not apparent from data reported | Not apparent from data reported |
| Targoff et al,4 1990 | 38/F | Cough, chest pain, dyspnea | Intersitial infiltrates |
| Targoff et al,4 1990 | 64/M | PM/DM, Raynaud, heliotrope rash | Bibasilar infiltrates |
| Targoff et al,4 1990 | 53/F | PM/DM, synovitis, fever, rash, Raynaud | Bilateral infiltrates |
| Targoff et al,4 1990 | 56/F | PM/DM, arthralgia, rash, dyspnea | Bibasilar infiltrates |
| Takahashi et al,2 2007 | 21 pts (14 M, 7 F); mean age, 59 y | All IPF | NR |
| Kalluri et al,3 2009 | 12 pts (11 M, 1 F); median age, 52 y | 9 pts with PM/DM, 1 pt with PM/RA,2 2 pts with UCTD | 5 pts with UIP pattern 6 with NSIP pattern, 1 pt NA |
| Marie et al,26 2014 | NR | NR | NSIP pattern |
| Johnson et al,27 2014 | 5 pts (4 F, 1 M); median age, 50 y | 3 pts with PM, 2 pts with overlap syndrome | Reported mean CT scores showing moderate fibrosis and moderate ground glass |

Abbreviations: BVB, bronchovascular bundle; CS, corticosteroids; CT, computed tomography; DAD, diffuse alveolar damage; DM, dermatomyositis; GGO, ground-glass opacities; HC, honeycomb change; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; LAS, lymphoid aggregate; MMF, mycophenolate mofetil; MV, mechanical ventilation; NA, data not available to authors; NR, not reported; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; PFTs, pulmonary function tests; PH, pulmonary hypertension; PM, polymyositis; PME, postmortem examination; pt, patient; pts, patients; RA, rheumatoid arthritis; SLB, surgical lung biopsy; TB, traction bronchiectasis; Tbbx, transbronchial biopsy; UCTD, undifferentiated connective tissue disease; UIP, usual interstitial pneumonia.

a One patient having undergone transbrachial biopsy had polymyositis with RA and showed organizing pneumonia.
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12 patients (25%) in this cohort. In 2 patients, this finding suggests lung involvement by ARS. Their presence is not specific enough to strongly correlate with increased mean pulmonary artery pressures of 48 and 27 mm Hg, respectively, as determined by right heart catheterization. The third patient had no evidence of pulmonary hypertension by echocardiography. Pulmonary hypertension is a known complication of ARS. Kalluri et al observed pulmonary hypertension, inferred by means of echocardiography, in 9 of 31 patients (29%) possessing anti–PL-12 antibodies. The presence of anti–SSA in other autoantibodies, especially Sjögren syndrome–associated ILD, is better than a matched cohort of patients with idiopathic UIP with CTD-related UIP.

Table 3 summarizes the pulmonary histopathology of 46 anti–PL-12 cases in the English literature to date. Although the nomenclature is not uniform in these reports, about two-thirds of patients seem to have some form of cellular and/or fibrosing ILD. Follow-up was not available for many cases. The existing literature and our cohort confirm that diffuse alveolar damage is not only uncommon in IIM, in general, but also in anti–PL-12 ARS specifically. The only patient with diffuse alveolar damage reported in the literature also showed capillaritis and was found to have improved on glucocorticoids 8 months after the episode. One patient who died rapidly of respiratory failure may have had an acute lung injury resembling diffuse alveolar damage.

Distinguishing ILD arising in the setting of ARS from idiopathic variants of ILD is important because recent data show that survival by patients with myositis-associated UIP is better than a matched cohort of patients with idiopathic pulmonary fibrosis. Even within the group of ARS, patients with anti–Jo-1 autoantibodies seem to fare better than those with other anti–tRNA synthetase autoantibodies, such as anti–PL-12, predominantly because of worse pulmonary outcomes. Thus, considering an ARS in the setting of isolated ILD is valuable because lung disease is the presenting feature in a significant number of such patients. In rare cases, antisynthetase autoantibodies coexist with other autoantibodies, especially Sjögren syndrome–associated antibody anti–SSA. The presence of anti–SSA in patients with ARS may be associated with worse pulmonary outcomes. Moreover, ARS could be considered and correlated with increased mean pulmonary artery pressures of 48 and 27 mm Hg, respectively, as determined by right heart catheterization. The third patient had no evidence of pulmonary hypertension by echocardiography. Pulmonary hypertension is a known complication of ARS. Kalluri et al observed pulmonary hypertension, inferred by means of echocardiography, in 9 of 31 patients (29%) possessing anti–PL-12 antibodies.

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serologically assayed, even in patients with an established autoimmune disease other than myositis.

This study has limitations. We are a tertiary referral center for ILD and rheumatic diseases, as well as a lung transplant center. Our patient cohort may be skewed toward late-stage and progressive lung diseases, such as UIP. However, most of the patients in this study lived close to our center and were followed by rheumatologists within our medical center before referral for lung transplantation. Although UIP representing idiopathic pulmonary fibrosis in patients older than 50 years cannot be excluded with absolute certainty, we believe that the patients in this series most likely suffered from lung involvement by ARS rather than idiopathic disease because of the high prevalence of ILD in patients with ARS. Furthermore, our patients often experienced the onset of respiratory symptoms long before the diagnosis of ARS and lung biopsy. Two of our patients showed histopathologic features of NSIP in biopsy material. We cannot exclude that these patients were inadequately sampled, especially because the radiologic diagnosis of UIP has high predictive value. However, both biopsies were taken from the lower lobe, making missing UIP less likely if it were present. Finally, a limitation of this study, as seen with any study of this kind, is the lack of an age-matched comparison group showing idiopathic disease.

In summary, there are no pathognomonic histopathologic features to distinguish anti–PL-12 ARS-related lung disease from idiopathic variants of diffuse ILD. Clinical features of mechanic’s hands, Raynaud phenomenon, arthritis, and fever should prompt pathologists to suggest involvement by ARS. Because the prognosis of IIM-associated UIP appears to be better than that of idiopathic UIP treated with systemic immunosuppressive therapy, considering the possibility of lung involvement by ARS is important.

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Figure 2. Histopathologic features of anti–PL-12 antisynthetase syndrome: organizing pneumonia (A), nonnecrotizing granulomas (arrow) (B), interstitial eosinophils (C), and vasculopathy involving an arteriole (D) (hematoxylin-eosin, original magnifications ×100 [A and B] and ×200 [C and D]).
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Submissions Now Accepted for the CAP18 Abstract Program

Abstract and case study submissions to the College of American Pathologists (CAP) 2018 Abstract Program are now being accepted. Pathologists, laboratory professionals, and researchers in related fields are encouraged to submit original studies for possible poster presentation at the CAP18 meeting.

Submissions will be accepted until 5 p.m. Central Friday, March 9, 2018. Accepted submissions will appear on the Archives of Pathology & Laboratory Medicine Web site as a Web-only supplement to the September 2018 issue. The CAP18 meeting will be held from October 20 to 24 in Chicago, Ill.

Visit the CAP18 Web site (www.thepathologistsmeeting.org) and the Archives Web site (www.archivesofpathology.org) for additional abstract program information as it becomes available.