Interstitial Lung Disease with ANCA-associated Vasculitis

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ABSTRACT: The association between interstitial lung disease (ILD) and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), particularly microscopic polyangiitis (MPA), has been described in a number of case reports and case series reports in the last 2 decades. In addition, patients with pulmonary fibrosis and ANCA positivity but without other manifestations of systemic vasculitis have also been reported. Pulmonary fibrosis was clinically manifested at the time of diagnosis in the majority of AAV patients that developed this condition. Moreover, ANCA-positive conversion occurs in patients initially diagnosed with idiopathic pulmonary fibrosis, and as a result, other manifestations of systemic vasculitis develop in some of these patients. There is significant predominance of myeloperoxidase (MPO)-ANCA and MPA in patients with AAV and ILD. Radiological and pathological findings generally demonstrate usual interstitial pneumonia (pattern) in the lungs of these patients. In most studies, AAV patients with ILD have a worse prognosis than those without it.

KEYWORDS: interstitial lung disease, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, microscopic polyangiitis

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Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is characterized by pauci-immune necrotizing vasculitis of the small blood vessels,[1] which comprise three different clinical syndromes: eosinophilic granulomatosis with polyangiitis (EGPA, previously called Churg-Strauss syndrome), granulomatosis with polyangiitis (GPA, previously called Wegener's granulomatosis), and microscopic polyangiitis (MPA). Patients with AAV are usually defined and classified according to the European Medicines Agency (EMEA) algorithm.[2] This uses an algorithm to classify vasculitis and utilizes the American College of Rheumatology (ACR) criteria (1990) and the Chapel Hill Consensus Conference definitions.[1] Despite the common association with ANCA, however, these disease entities differ significantly in their clinical features and possibly in underlying pathophysiology. A lung lesion is a very common and important clinical feature in AAV. The association between interstitial lung disease (ILD) and AAV, particularly MPA, has been described in a number of case reports and case series reports in the last 2 decades. In addition, patients with pulmonary fibrosis and ANCA positivity but without other manifestation of systemic vasculitis have also been reported. The association between ILD and ANCA/AAV has received increasing attention both clinically and pathophysiologically. In this article, the association between ILD and ANCA/AAV is thoroughly reviewed. Studies included in this review are summarized in Table 1.

Epidemiology

Nada et al reported 2 patients with pulmonary fibrosis and p-ANCA-positive MPA in 1990.[3] An association between AAV or ANCA and ILD has since been demonstrated. The association between ILD and AAV or ANCA in many patients was first reported in a Japanese study by Arinuma et al in 1994.[4] In this retrospective study of 46 myeloperoxidase (MPO)-ANCA-positive patients with collagen-vascular disease or glomerulonephritis, 20 (43%) of the MPO-ANCA-positive patients had ILD. Of the 20 patients with ILD and MPO-ANCA, 9 had MPA and 4 had crescentic glomerulonephritis. ILD was diagnosed before the onset of renal diseases in 7 patients, whereas ILD never developed after the diagnoses of renal diseases in the study population. Since then, several studies have reported similar findings from Japan[5–9] and other countries[10–15]; however, it is still recognized that ILD is more frequently associated with ANCA-positive Japanese patients than Western patients.[16] In a Japanese nationwide rapidly progressive glomerulonephritis (RPGN) survey, 301/1147 (26.2%) patients with AAV had ILD.[5] In another Japanese nationwide, prospective, inception cohort study

Table 1. Summary of published studies of interstitial lung disease with ANCA-associated vasculitis.

COUNTRY	YEAR	SETTING*	TOTAL	ILD	AAV CLASSIFICATION†			ANCA SPECIFICITY†		UIP PATTERN ON HRCT†	REFERENCE
					MPA	GPA	EGPA	MPO	PR3		
Japan	1995	MPO-ANCA positive patients with collagen-vascular disease and glomerulonephritis	46	20	13‡	0	0	20	0	N.D.	4
Japan	2015	Rapidly progressive glomerulonephritis (RPGN)	1147	301	N.D.			291	20	N.D.	5
Japan	2014	Prospective, inception cohort study of AAV	156	61	37‡	3	2	60	3	N.D.	6
Japan	2013	Consecutive patients with idiopathic pulmonary fibrosis (IPF) initially without AAV	61	61	2§	0	0	9¶	0	N.D.	7
Japan	2015	Idiopathic pulmonary fibrosis (IPF) initially without AAV	504	504	9§	0	0	35**	30**	N.D.	8
Japan	2004	Patients with MPO-ANCA and pulmonary disorders	43	31	8	0	0	31	0	N.D.	9
United Kingdom	2011	AAV	510	14	14	0	0	14	0	8	10
Greece	2010	Consecutive patients with MPA	33	13	13	0	0	12	1	7	11
Argentina	2015	MPA	28	9	9	0	0	9	0	8	12
France	2009	ILD with AAV (from the database of the French Vasculitis Study Group)	(517)	12	10	2	0	12	0	6	13
France	2008	ILD with positive ANCA	17	17	7	0	0	6	1	17	14
France	2014	ILD with AAV	49	49	40	9	0	43	2	24††	15

Note: *If not indicated otherwise, the studies are retrospective. †These are numbers of cases among patients with ILD and ANCA/AAV. ‡Including renal-limited vasculitis. §MPA later developed in these IPF patients. ¶Including 6 seroconversion. **Including15 (MPO-ANCA) and 14 (PR3-ANCA) seroconversion, respectively. ††Including "typical" and "atypical" UIP pattern.
Abbreviations: ANCA; anti-neutrophil cytoplasmic antibody; AAV: ANCA-associated vasculitis; ILD: interstitial lung disease; MPA: microscopic polyangiitis; GPA: granulomatosis with polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis; MPO: myeloperoxidase; PR3: proteinase-3; UIP: usual interstitial pneumonia; HRCT: high-resolution computed tomography; N.D.: not determined.

of AAV (Remission Induction Therapy in Japanese Patients with ANCA-associated Vasculitides; RemIT-JAV), 61/156 (39.1%) patients had ILD.[6] In contrast, ILD was observed in only 14/510 (2.7%) AAV patients at a renal vasculitis clinic in London.[10] This discrepancy between Japan and other countries has been usually explained by the ethnicity and the predominance of MPO-ANCA (which will be discussed in later section of this review). In addition, the varied accessibility to computed tomography (CT) could somewhat affect the diagnostic rates of ILD, especially subclinical or very mild cases, and cases with "pulmonary limited vasculitis." According to the Organization for Economic Co-operation and Development (OECD) Health Statistics 2014 (http://stats.oecd.org/index.aspx?DataSetCode = HEALTH_STAT), the numbers of CT scanners per million population were 92.62, 29.26, 7.29, and 7.62 in 2002, and 101.28, 43.44, 8.95, and 13.49 in 2013 in Japan, United States, United Kingdom, and France, respectively. However, the prevalence of ILD among patients with MPA (not entire AAV) may actually be similar throughout the world. In a study of 33 consecutive MPA patients with RPGN and/or alveolar hemorrhage from Greece, pulmonary fibrosis was found in 13 (39%) patients.[11] In a study of MPA patients form Argentina, 9 of the 28 (32%) patients had pulmonary fibrosis.[12]

ANCA and AAV Phenotypes

Most of the studies have indicated that ILD developed more frequently in patients with MPO-ANCA-positive AAV, mainly in those with a diagnosis of MPA, compared to patients with proteinase-3 (PR3)-ANCA-positive AAV. In a Japanese nationwide RPGN survey, patients with MPO-ANCA (291/1088, 26.7%) were more frequently associated with ILD than patients with PR3-ANCA (20/114, 17.5%, $P = 0.03$).[5] In another Japanese nationwide, prospective, inception cohort study of AAV,[6] MPO-ANCA was more frequently associated with ILD than PR3-ANCA (60/130 vs. 3/18, $P = 0.02$), and the prevalence of ILD in patients with MPA/renal-limited vasculitis (37/78) was higher than that in patients with GPA (3/33) or EGPA (2/14). It is well recognized that patients with MPA and with positivity for MPO-ANCA are predominant in Japanese patients with AAV.[16] In fact, Fujimoto et al confirmed that there was no major difference in AAV incidence between Japan and the United Kingdom, whereas MPA and MPO-ANCA was more common in Japan and GPA and PR3-ANCA was more common in the United Kingdom.[17] Thus, this may contribute to the high prevalence of ILD in Japanese patients with AAV as described in the previous section. A renal vasculitis clinic in London reported that all 14 patients with AAV and ILD had MPO-ANCA and a clinical diagnosis of MPA.[10] The French Vasculitis Study Group reported MPO-ANCA in all of the 12 patients who had systemic vasculitis related to ANCA (10 MPA and 2 GPA) and pulmonary fibrosis.[13] Six university pulmonology French departments with an expertise in the field of ILD reported that they retrospectively detected 17 patients with pulmonary fibrosis and positive ANCA testing and that ANCA exhibited perinuclear fluorescence in 14 patients (6 with MPO-ANCA).[14] MPA was diagnosed in 7/17 patients. In a retrospective multicenter study by 16 French medical centers, 49 patients with pulmonary fibrosis associated with AAV were identified, and 43 patients had MPO-ANCA while 2 had PR3-ANCA, and 40 patients had MPA while 9 had GPA.[17] Thus, there is a significant predominance of MPO-ANCA and MPA in patients with AAV and ILD throughout studies from different countries.

Time Course

Pulmonary fibrosis was clinically manifested at the time of diagnosis in the majority of AAV patients that developed it. In a study of 33 consecutive MPA patients from Greece,[11] pulmonary fibrosis was present in 12 patients at the time of diagnosis, whereas pulmonary fibrosis developed in only one patient while on therapy 10 years after disease diagnosis. In most of the cases in a retrospective study of 17 patients presenting with pulmonary fibrosis and a positive ANCA testing by the French pulmonology group, lung fibrosis preceded the development of MPA by 1–10 years (if ever occurred), or the 2 diseases were diagnosed concomitantly.[14] In a French retrospective multicenter study including 49 patients with pulmonary fibrosis associated with AAV, the diagnosis of pulmonary fibrosis preceded the onset of vasculitis in 22 (45%) patients.[15] In a retrospective study of 61 consecutive Japanese patients with an initial diagnosis of idiopathic pulmonary fibrosis (IPF) at hospital presentation, MPO-ANCA was positive in 3 patients (5%) and MPO-ANCA positive conversion occurred in 6 patients (10%), of whom 2 were complicated by MPA.[7] The median duration between initial IPF diagnosis and conversion to MPO-ANCA positivity was 23 months (range, 0 to 71 months). In a retrospective study of 966 patients with IPF from Japan, ANCA was initially negative and measured repeatedly thereafter in 264 patients.[8] In these patients, MPO-ANCA and PR3-ANCA seroconversion occurred in 15 (5.7%) and 14 (5.3%) patients, respectively, and MPA developed in the 6 patients with seroconversion to MPO-ANCA. Collectively, the development of ILD after a diagnosis of AAV is very rare, whereas MPA developed in some patients with IPF with MPO-ANCA positivity at IPF diagnosis or with MPO-ANCA-positive conversion during follow-up; however, there is no consensus on whether patients with ILD and MPO-ANCA positivity but without other manifestations of systemic vasculitis should be called "pulmonary limited vasculitis" as a phenotypic variant of MPA.

Radiological Images of ILD

The French Vasculitis Study Group reported that there were signs of usual interstitial pneumonia (UIP) in 6 cases and non-specific interstitial pneumonia in one case, whereas the type of interstitial diffuse pneumonia was unspecified in 5 cases among the 12 patients with AAV and pulmonary fibrosis

by high-resolution computed tomography (HRCT).[13] In a retrospective study of 17 patients presenting with pulmonary fibrosis and a positive ANCA testing by the French pulmonology group, HRCT analysis showed honeycombing, reticular intralobular opacities and traction bronchiectasis in all the patients with some degree of ground-glass attenuation (usually limited), whereas air-space consolidation was rare.[14] In a French retrospective multicenter study including 49 patients with pulmonary fibrosis associated with AAV, 42/49 patients were retrospectively reviewed, and typical UIP was the main HRCT pattern (n = 18, 43%).[15] In a Japanese retrospective study of 31 patients with pulmonary fibrosis and MPO-ANCA, chest HRCT scan images showed reticulonodular shadows, honeycombing, and decreased lung volume, all of which were found predominantly in the lower and outer regions of the lung, and the histopathological pattern of pulmonary fibrosis could be classified as a UIP pattern in all 11 autopsied cases.[9] In another Japanese retrospective study of 61 patients with IPF, the initial HRCT scans of the 9 MPO-ANCA-positive patients showed subpleural reticular opacities, traction bronchiectasis, and honeycombing[7]; however, because these findings were also frequently observed in MPO-ANCA-negative cases, no differences were found between the 2 groups. A representative HRCT image of ILD with AAV is shown in Figure 1.

Pathological Findings of ILD

In a Japanese retrospective study of 31 patients with pulmonary fibrosis and MPO-ANCA, the histopathological features were analyzed in 15 patients: autopsy in 11, video-assisted thoracoscopic surgery (VATS) in 2, and trans-bronchial lung biopsy (TBLB) in 2.[9] In 13 patients, interstitial fibrosis was not confined to the alveolar walls but extended to the proximal interstitial tissues and interlobular septa. Honeycomb lesions were noted in 12 cases. The vasculitides were observed in pulmonary arterioles in 3 cases, in bronchial arteries in 3, and in capillaries presenting as alveolar hemorrhages in 2; however, vasculitis has almost never been pathologically proven in ILD/pulmonary fibrosis from other studies. For example, in the other Japanese retrospective study of 9 patients with IPF and MPO-ANCA,[7] the histologic pattern identified in the surgical lung biopsies in 6 patients was consistent with that of UIP, whereas alveolar hemorrhage or small vessel vasculitis was not observed. In addition, postmortem examination of the lung for 2 cases showed alveolar hemorrhage but no evidence of small vessel vasculitis.

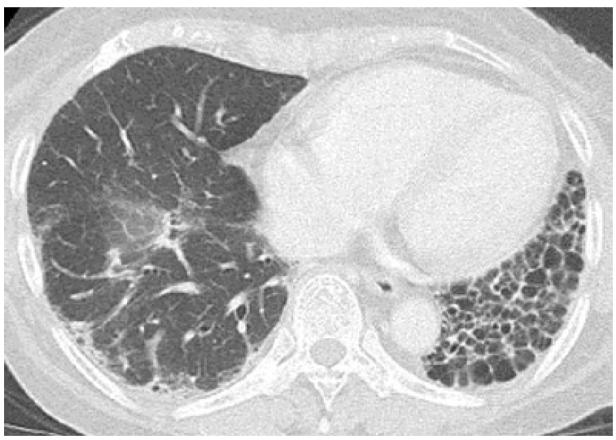

Figure 1. Representative high-resolution computed tomography scan in a patient with interstitial lung disease and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis. This patient was initially diagnosed with idiopathic pulmonary fibrosis, and myeloperoxidase-ANCA-positive granulomatosis with polyangiitis developed later.

Prognosis and Treatment

In most studies, AAV patients with ILD have a worse prognosis than those without it, and patients with pulmonary fibrosis and ANCA had as low a prognosis as patients with IPF without ANCA. The French Vasculitis Study Group reported that the respiratory status of 5 of the 12 patients with AAV and pulmonary fibrosis worsened, and 3 of them died from exacerbation of end-stage respiratory failure.[13] In a study of 33 consecutive MPA patients from Greece,[11] the presence of pulmonary fibrosis was associated with increased mortality ($P = 0.02$), with 6 deaths occurring in the fibrotic group (n = 13) and one occurring in the nonfibrotic group (n = 20). In the fibrotic group, most deaths were related to pulmonary fibrosis. In a Japanese retrospective study of 31 patients with pulmonary fibrosis and MPO-ANCA, a comparison of their institution's survival rates in MPO-ANCA-negative pulmonary fibrosis with collagen vascular diseases, cryptogenic fibrosing alveolitis, and MPO-ANCA-positive pulmonary fibrosis revealed that the 5-year survival rate of MPO-ANCA-positive pulmonary fibrosis was worse than in MPO-ANCA-negative pulmonary fibrosis with collagen vascular diseases and was the same for cryptogenic fibrosing alveolitis.[9] In a Japanese nationwide, prospective, inception cohort study of AAV, patients with ILD had significantly lower Birmingham Vasculitis Activity Scores (BVAS) than those without ILD ($P = 0.019$)[6]; however, it does not necessarily mean that AAV patients with ILD have a better prognosis because ILD is not included in these definitions. Actually, in another Japanese nationwide RPGN survey, the 5-year survival rate was 50.2% in the patients with ILD and 73.3% in those without pulmonary involvement; ILD was added as one of the predictors of 5-year mortality.[5] In contrast, in a retrospective study by the renal vasculitis clinic in London,[10] there was no difference in mortality between patients with MPA and ILD (n = 14) and those with MPA without ILD (n = 180) over the same time period ($P = 0.07$), which should be treated with some caution due to the small cohort size.

Currently, there is no specific treatment for patients with ILD and AAV/ANCA-positivity.[10] Corticosteroids and/or cyclophosphamide, cyclosporine, or N-acetylcysteine were administered to these patients[18]; however, their clinical benefit and indication are not well established. In a Japanese

retrospective study of 61 patients with IPF,[7] corticosteroids were administered more frequently in patients with MPO-ANCA than those without it (8/9 = 89% vs. 26/52 = 50%, $P = 0.036$). Immunosuppressants, including azathioprine, cyclophosphamide and mizorbine, were administered to 4 (44%) patients with MPO-ANCA-positive fibrosis and only one (2%) patient with ANCA-negative IPF. As for MPO-ANCA-positive fibrosis, 6 patients died during the follow-up period. Four patients died from the acute exacerbation of pulmonary fibrosis, one patient died of intractable pneumothorax, and one patient died from a cytomegalovirus infection. As for IPF, therapy was started for progressive respiratory failure in all patients. Eight patients died of an acute exacerbation of pulmonary fibrosis, 6 patients died of progressive respiratory failure, 6 patients died of pneumonia and 3 patients died of lung cancer. The median survival of patients with MPO-ANCA-positive fibrosis and IPF was 62 months (95% CI 29.13–94.87) and 63 months (95% CI 44.55–81.42), respectively. There was no significant difference between the 2 groups ($P = 0.93$). However, induction therapy with cyclophosphamide might improve the outcome.[15] In a French retrospective multicenter study including 49 patients with pulmonary fibrosis associated with AAV, the 3-year survival rate in patients treated with an immunosuppressant (cyclophosphamide or rituximab) combined with glucocorticoids as induction therapy was better than that in patients treated with glucocorticoids alone (94% vs. 64%, $P = 0.03$).

Possible Pathomechanisms

The association of ILD and ANCA or AAV does not seem to be fortuitous, considering its higher prevalence than in the average population. Although the pathogenesis of ILD in AAV remains poorly understood, 3 major hypotheses have been proposed by several groups on the development of ILD in patients with ANCA or AAV as summarized elsewhere by Kagiyama et al.[8] First, repeated episodes of alveolar hemorrhage due to pulmonary capillaritis could be the pathogenesis of pulmonary fibrosis.[13] Schnabel et al reported that subclinical alveolar bleeding was, indeed, a common finding in AAV.[19] Second, MPO-ANCA may play a direct role in the pathogenesis of pulmonary fibrosis. Guilpain et al suggested that oxidative stress, in particular the production of hypochlorous acid (HOCl) through the interaction of MPO with anti-MPO antibodies, could trigger the fibrotic process observed in MPA.[20] Foucher et al observed patchy inflammatory cell infiltrates throughout the parenchyma of the lung in their MPO-induced rat model of AAV and suggested that the presence of an anti-MPO directed autoimmune response contributes to generalized pulmonary tissue injury.[21] Third, to the extent that pulmonary fibrosis is clinically manifested at the time of diagnosis in the majority of patients, IPF may induce ANCA and AAV.[11] Namely, ANCA might be produced as a result of neutrophil destruction during the chronic inflammation process. In addition, tobacco smoke exposure may play an initiating role in the pathophysiology of the disease by activating epithelial cells and stimulating their MPO expression. In a Japanese retrospective study of 9 patients with IPF and MPO-ANCA, they were all smokers and frequently demonstrated low attenuation areas on their HRCT scans.[7] Similarly, in a retrospective study of 17 patients presenting with pulmonary fibrosis and a positive ANCA testing, 11 patients were either current or past smokers.[14] Furthermore, Churg et al suggested that acute exposure to cigarette smoke leads to macrophage activation and neutrophil recruitment, with consequent elastin and collagen degradation, resulting in accelerated matrix destruction and emphysema.[22]

Author Contributions

Conceived and designed the experiments: Y Katsumata, Y Kawaguchi, HY. Analyzed the data: Y Katsumata. Wrote the first draft of the manuscript: Y Katsumata. Contributed to the writing of the manuscript: Y Kawaguchi. Agree with manuscript results and conclusions: Y Katsumata, Y Kawaguchi, HY. Jointly developed the structure and arguments for the paper: Y Kawaguchi. Made critical revisions and approved final version: Y Katsumata, Y Kawaguchi, HY. All authors reviewed and approved the final manuscript.

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