Antineutrophil cytoplasmic antibody-associated interstitial lung disease: a review

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Abstract

Over the past three decades, an increasing number of publications have reported the association between interstitial lung disease (ILD) and anti-neutrophil cytoplasmic antibody (ANCA) or ANCA-associated vasculitis (AAV). With this increased awareness, we have reviewed the literature to date and provide an update in this narrative review. The vast majority of cases of ILD have been shown to be in the setting of positive anti-myeloperoxidase antibody and can be present in up to 45% of patients of microscopic polyangiitis, though cases of ILD associated with proteinase 3 ANCA have rarely been reported. Pulmonary fibrosis and ANCA positivity can occur with or without systemic involvement. The pathogenetic mechanisms establishing the relationship between ANCA and the development of pulmonary fibrosis remain unclear. Histologic and radiographic features of ANCA-ILD most commonly reveal usual interstitial pneumonia or non-specific interstitial pneumonia patterns, though other atypical features such as bronchiolitis have been described. ILD in the setting of AAV has been associated with worse outcomes, and thus early identification and treatment in these patients is appropriate. We advocate that ANCA antibody testing be performed as a baseline evaluation in patients presenting with idiopathic interstitial pneumonia. Suggested treatment of ANCA-ILD includes immunosuppression and/or antifibrotic agents, though supporting data and clinical trials to substantiate use of these therapies are needed.

Introduction

The association between interstitial lung disease (ILD) and anti-neutrophil cytoplasmic antibody (ANCA) or ANCA-associated vasculitis (AAV) has been increasingly recognised over recent years. Anti-neutrophil cytoplasmic antibodies are autoantibodies specific for antigens located in the cytoplasmic granules of neutrophils and lysosomes of monocytes [1]. ANCA-associated vasculitis is a heterogeneous group of systemic vasculitides that predominately affects small blood vessels. It comprises three different clinical syndromes: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA), with anti-myeloperoxidase (MPO) ANCA and MPA having the strongest association with ILD. Patients with ILD and ANCA positivity without other manifestations of systemic vasculitis have also been reported. Furthermore, ANCA-positive conversion has been described in patients with an initial diagnosis of idiopathic pulmonary fibrosis (IPF), with manifestations of systemic vasculitis occurring in some patients. Differences between ILDs secondary to AAV and isolated ANCA-positive idiopathic interstitial pneumonia (IIP) remain unclear.

This review outlines the clinical, radiographic and histopathologic features of ANCA/AAV-associated ILD, theories regarding pathophysiology of development of ILD in patients with ANCA positivity, as well as therapeutic strategies and future directions.
We performed a PubMed search for English language articles published between January 1990 and May 2021. The following terms were combined in the search method: ANCA, antineutrophilic cytoplasmic antibody, vasculitis, GPA, Wegener’s granulomatosis, MPA, MPO, proteinase 3 (PR3), lung manifestations, ILD, interstitial pneumonia, pulmonary fibrosis, lung fibrosis, computed tomography and histopathology. The full text of the resulting articles was retrieved and reviewed. Additional text references in publications were also reviewed. Published studies included in this review include data from >500 patients and are summarised in table 1 [2–32].

Epidemiology
The association between ILD and ANCA or AAV was first reported in two patients with pulmonary fibrosis and MPO-ANCA positive MPA by NADA et al. in 1990 [2]. A Japanese retrospective study was subsequently published in 1995 describing the characteristics of 46 patients with positive anti-MPO antibodies, of which 43% demonstrated findings of ILD [3].

Geographic variation in AAV incidence has been described, with a greater percentage of MPO-ANCA positive patients in Asian populations than in European populations, where GPA and PR3 ANCA positivity is more commonly seen [33]. A prospective study comparing incidence and characteristics of AAV between Japan and Europe found no significant difference in the annual incidence of AAV between Japan and the UK (22.6 million versus 21.8 million adults), though the annual incidence of MPA in Japan was higher than that in the UK (18.2 million versus 6.5 million adults), while GPA was predominant in the UK (14.3 million adults versus 2.1 million in Japan) [34]. A higher ratio of MPO antibody was also reported in Japan than in the UK (83.7% versus 30%, p<0.001) [34]. Additional epidemiologic studies in other Asian countries have also demonstrated a higher ratio of MPO-ANCA to P3-ANCA positivity, as well as a higher prevalence of ILD [35–37]. The higher prevalence of ILD among patients with ANCA positivity in Asian countries such as China and Japan than in Europe may be attributed to the greater frequency of MPO-ANCA antibodies in this population [38].

AAV-ILD
Recent epidemiologic studies report prevalence rates of AAV of 300–421 per million persons [39]. Prevalence rates of ILD in patients with systemic vasculitis have been reported in up to 23% of GPA patients and 45% of MPA patients [10, 11, 13, 16, 18, 20, 24, 40, 41]. The onset of ILD occurs concurrently or precedes the development of full vasculitis syndrome in the majority of individuals. Prior studies reported ILD antedating AAV in 14–85% of patients, occurring simultaneously in 36–67% and occurring after AAV in 8–21% of patients [2, 7–9, 11, 15, 16, 18, 21, 30, 42, 43].

The age of onset of MPA-associated pulmonary fibrosis appears to be similar to IPF and is usually observed in patients aged 65 and older, while the onset of MPA in patients without ILD is typically closer to 55 years of age [2, 7–11, 18, 41, 44]. There is a suggestion of a slight male preponderance in patients with ANCA-associated ILD [2, 7, 8, 10, 11, 18].

ANCA-positivity with isolated ILD (ANCA-ILD)
The prevalence of ANCA positivity in patients with an initial presentation of interstitial pneumonia ranges between 4–36% for MPO-ANCA and 2–4% for PR3-ANCA [7, 8, 12, 14, 16, 21–23, 25, 28, 42, 45]. In one retrospective North American study involving 745 total patients with IPF, 25–33% of patients with an initial diagnosis of IPF with MPO-ANCA positivity developed clinical manifestations of vasculitis during a median follow-up period of 18 months [28]. Furthermore, studies have shown that approximately 10% of ANCA-negative IPF patients will seroconvert during follow up [14, 21, 23]. Cases of ANCA positivity and isolated pulmonary fibrosis without apparent development of systemic manifestations have also been described [23].

Pathogenesis and risk factors: current concepts
Genetic susceptibility
Emerging studies have identified variants associated with increased susceptibility to pulmonary fibrosis, with similarities between ANCA-ILD and familial IPF as well as other fibrotic ILDs. The mucin 5B (MUC5B) promoter, which is involved in airway clearance and bacterial host defence, is the strongest genetic risk factor for IPF and is observed in at least 50% of patients with the disease [46, 47]. The MUC5B variant has been shown to be associated with rheumatoid arthritis-ILD as well as fibrotic hypersensitivity pneumonitis [47, 48]. More recently, the MUC5B variant rs35705950T, the strongest susceptibility variant to IPF, was found to be increased in AAV-ILD patients compared to healthy controls in one Japanese study [49]. The MUC5B mutation was found in ANCA-ILD patients specifically, but not in AAV patients without ILD, suggesting possible shared pathogenetic mechanisms between other fibrotic ILDs [49].
| Reference, year, country       | Study description                                                                 | Number of patients | Mean age (years) | Male (%) | ILD (%) | Systemic vasculitis (%) | PF preceding AAV (%) | Median follow-up period (months) | ANCA specificity (%) | HRCT pattern                  |
|--------------------------------|----------------------------------------------------------------------------------|--------------------|-----------------|----------|---------|------------------------|---------------------|-----------------------------|-----------------------|--------------------------|
| **Nada et al. [2], 1990, USA** | PF in patients with pulmonary-renal vasculitis                                   | 3                  | 73              | 33       | 100     | 100 MPA                | 33 preceding, 67 concurrent | 120                        | 67 p-ANCA                | ND                      |
| **Arakawa et al. [3], 1995, Japan** | Pulmonary involvement in patients with MPO-ANCA                                  | 46                 | 61.1            | ND       | 43      | 28 MPA                 | ND                  | ND                          | 100 MPO                | ND                      |
| **Hiroruma et al. [4], 2000, Japan** | MPO+rapidly progressive GN during course of IPF                                 | 4                  | 67              | 50       | 100     | 100 MPA                | ND                  | ND                          | 100 MPO                | ND                      |
| **Eschun et al. [5], 2003, Canada** | PF presenting manifestation of MPA                                               | 6                  | 69.8 (63–78)    | 50       | 100     | 100 MPA                | 100                 | 36                          | 100 p-ANCA             | 3/6 UIP-like, 2/6 fibrotic NSIP, 1 ND |
| **Homma et al. [6], 2004, Japan** | PF in MPO-ANCA                                                                   | 31                 | 69              | 55       | 100     | 25 MPA                 | 100                 | 120                         | 100 MPO                | 84% UIP                 |
| **Foulon et al. [7], 2008, France** | ANCA-associated PF                                                               | 17                 | 66              | 71       | 100     | 41 MPA                 | 86 preceding, 14 concurrent | 57±41                     | 6/17 MPO, 1/17 PR3       | 100% UIP                |
| **Nouji et al. [8], 2009, Japan** | Comparison of ANCA-positive and -negative patients with PF                       | 19/53 with ANCA+ PF, 34/53 ANCA− PF | 69 (52–80) | 58     | 100     | 21 MPA                 | 100 preceding         | 1–90                      | 17/19 MPO, 2/19 PR3      | 73.3% UIP               |
| **Herrier et al. [9], 2009, France** | PF associated with AAV                                                           | 12                 | 70.7            | 75       | 100     | 83 MPA, 17 GPA         | 66 concurrent, 8 following AAV | 49.2 (7–116)          | 100 MPO 100             | 6/12 UIP, 1/12 NSIP, 5/12 ND |
| **Tzelepis et al. [10], 2010, Greece** | Prevalence and outcome of PF in MPA                                              | 36                 | 57              | 69       | 39      | 100 MPA                | 92 concurrent, 8 following AAV | 38±30                    | 85 p-ANCA, 8 p-ANCA +c-ANCA | 54% UIP, 31% NSIP        |
| **Arunkumar et al. [11], 2011, UK** | ILD and AAV                                                                      | 14                 | 67.3            | 71       | 100     | 100 MPA                | 14 preceding, 21 post     | 90                         | 100 MPO                | ND                      |
| **Tamao et al. [12], 2012, Japan** | IP associated with MPO-ANCA                                                      | 9                  | 62.1            | 66       | 100     | None                   | ND                  | 39.1                       | 100 MPO                | 66% UIP, 11% NSIP, 11% OP, 11% DAD |

Continued
| Reference, year, country | Study description | Number of patients | Mean age (years) | Male (%) | ILD (%) | Systemic vasculitis (%) | PF preceding AAV (%) | Median follow-up period (months) | ANCA specificity (%) | HRCT pattern |
|--------------------------|------------------|--------------------|-----------------|----------|---------|-------------------------|----------------------|-------------------------------|---------------------|-------------|
| Ahn et al. [13], 2012, Korea | Clinical features and outcomes of MPA | 55 patients with MPA, 13 with ILD (23.6%), 59.29±13.60 MPA, ND in ILD patients | 60% MPA, ND in ILD patients | 24 | 100 MPA | ND | 46.07 ±39.98 | 100 MPO | 84.6% UIP, 1 patient OP, 2 patients NSIP |
| Anno et al. [14], 2013, Japan | Incidence of MPO-ANCA and MPA in course of IPF | 61 patients with initial dx IPF, 9/61 ANCA+ | 69 (57–75) | 75 | 15 | 22 (2/9) MPA | 100 preceding | 40 (1–121) | 100 MPO | 78% UIP, 22% ND |
| Cornil et al. [15], 2014, France | PF in AAV | 49 | 66 (57–72) | 61 | 100 | 82 MPA, 18 GPA | 45 preceding, 43 concurrent, 12 post | 48 (14–88) | 88 MPO, 4 PR3 | 43% “typical” UIP, 14% “atypical” UIP, 7% fibrotic NSIP, 9.5% NSIP |
| Huang et al. [16], 2014, China | MPA+PF | 19 | 63.6 | 42 | 100 | 100 MPA | 68 preceding, 32 concurrent | 29.9 (8–93) | 100 MPO | 100% UIP |
| Yu et al. [17], 2014, China | CT image analysis before and after treatment of ANCA-ILD | 8 | 72.6 | 88 | 100 | ND | ND | ND | 75 MPO, 12.5 PR3+MPO, 12.5 PR3 | ND |
| Fernandez Casares et al. [18], 2015, Argentina | MPA associated with PF | 9 patients with PF out of 28 MPA patients | 60±14 | 56 | 32 | 100 | 56 preceding, 44 concurrent | 76±60 | 100 MPO | 89% UIP |
| Flores-Suárez et al. [19], 2015, Mexico | Survival in MPA patients with PF | 40 patients, 17 (42.5%) with PF | 54.2 (total cohort including non-PF) | 53 | 42.5 | 100 | 82 preceding | 43 (11–213) | 90 MPO-ANCA, 5 PR3, 2.5 MPO+PR3 | 88% UIP |

Continued
| Reference, year, country | Study description | Number of patients | Mean age (years) | Male (%) | ILD (%) | Systemic vasculitis (%) | PF preceding AAV (%) | Median follow-up period (months) | ANCA specificity (%) | HRCT pattern |
|--------------------------|------------------|--------------------|------------------|----------|---------|-------------------------|---------------------|-------------------------------|---------------------|--------------|
| Ono et al. [20], 2015, Japan | Characteristics of MPO-positive GPA patients | 14 patients with ILD out of 41 MPA patients | 72.3 (total cohort) | 44 | 34 | 100 | ND | 38.6 | 100 MPA (patients positive for MPO-ANCA) | 100% UIP |
| Kagiya et al. [21], 2015, Japan | ANCA positive conversion and MPA development in IPF patients | 504 PF, 36 ANCA+ | 73 | 61 | 100 | 9/36 ANCA positive with MPA | 100 preceding | 29 | 55 MPO, 45 PR3 | ND |
| Hosoda et al. [22], 2016, Japan | Clinical features of UIP with ANCA compared to IPF | 12 ANCA/UIP patients | 65.2 (48–74) | 67 | 100 | 25 MPA | 100 preceding | 72 (14–195) | 100 MPO | 100% UIP |
| Hozumi et al. [23], 2016, Japan | Clinical implication of PR3 in patients with IIPs | 16 PR3+ of 360 IIP | 72 | 75 | 100 | None | ND | 22 | 100 PR3 (MPA patients excluded) | 37.6% UIP/possible UIP, 31.3% NSIP, 31.3% “unclassifiable” CT pattern |
| Tashiro et al. [24], 2017, Japan | Characteristics and prognosis of MPA with bronchiectasis | 23 patients with ILD out of 45 patients with MPA | 72±9.2 | 100 | 51 | 100 MPA | ND | 52.9 (1–125) | 100 MPO | ND |
| Hozumi et al. [25], 2018, Japan | Clinical significance of MPO in patients with IIPs | 26 MPO+ of 305 patients | 70 | 77 | 100 | 24.3 MPA | 100 preceding | 69 | 100 MPO | 100% UIP/possible UIP |
| Juman et al. [26], 2019, UK | ILD associated with ANCA-positivity | 69 patients with ILD and 18 ANCA+ | 67 | 51 | 100 | 25 coexisting AAV | 59 preceding | ND | 55 p-ANCA, 45 c-ANCA, 23 MPO, 12 PR3 | ND |
| Baqir et al. [27], 2019, USA | Radiologic and pathologic characteristics of MPO-ILD | 58 (43–75) | 56 | 100 | 61 MPA | 61 (11/18) of patients with existing MPA, 3/18 developed MPA on follow up | 52 | 100 MPO | 22% UIP, 29% NSIP, 7% OP |
| Liu et al. [28], 2019, USA | Prevalence and significance of ANCA in IPF patients | 745 patients, 34 with ANCA+ | 67.9±8.9 | 53 | 100 | 5/34 ANCA+ patients with MPA | 100 preceding | 18.3 | 52 MPO, 26 PR3, 18 ND | 75% UIP/possible UIP |

Continued
### TABLE 1

| Reference, year, country | Study description | Number of patients | Mean age (years) | Male (%) | ILD (%) | Systemic vasculitis (%) | PF preceding AAV (%) | Median follow-up period (months) | ANCA specificity (%) | HRCT pattern |
|--------------------------|-------------------|-------------------|-----------------|---------|--------|-------------------------|----------------------|--------------------------|-----------------|-------------|
| Watanabe et al. [29], 2019, Japan | Prognosis of MPO-UIP in patients with AAV nephritis | 31 | 74 (58–88) | 52 | 100 | 97 MPA, 3 GPA | All cases had pre-existing ANCA nephritis | ND | 100 MPO | 100% UIP |
| Maillet et al. [30], 2020, France | UIP in AAV | 62 AAV-ILD | 66 | 55 | 100 | 85 MPA, 15 GPA | 52 preceding, 39 concurrent, 10 after | 40.5 (21–68) | 89 MPO, 5 PR3 | 63% UIP, 39% NSIP |
| Kwon et al. [31], 2020, USA | ILD in AAV patients | 24 (14 with MPA, 8 with GPA, 2 EGPA) | 73 (19–94) | 45.8 | 100 | 58 MPA, 33 GPA, 8 EGPA | 20.8 preceding, 45.8 concurrent, 33.3 after | 42 | 66.7 MPO, 33.3 PR3 | 50% UIP/probable UIP, 41.7% alternative diagnosis (25% fibrotic HP pattern, 12.5% NSIP, 4.2% OP), 8.3% indeterminate |
| Sun et al. [32], 2021, China | Clinical features and long-term outcomes of ILD with ANCA antibody | 80 | 60 | 45 | 38.7 MPA-ILD, 61.25 isolated ANCA-IIP | 38.75 MPA | ND | 40 | 56.25 MPO, 86 p-ANCA, 2.5 PR3, 13.75 c-ANCA | 8.75% UIP, 63.75% NSIP, 27.5% “unclassifiable” |

**Notes:**
- AAV: ANCA-associated vasculitis; ANCA: anti-neutrophil cytoplasmic antibody; c-ANCA: cytoplasmic ANCA; AAV: ANCA-associated vasculitis; CT: computed tomography; DAD: diffuse alveolar damage; dx: diagnosis; EGPA: eosinophilic granulomatosis with polyangiitis; GN: glomerulonephritis; GPA: granulomatosis with polyangiitis; HP: hypersensitivity pneumonitis; HRCT: high-resolution computed tomography; IIP: idiopathic interstitial pneumonia; ILD: interstitial lung disease; IPF: idiopathic pulmonary fibrosis; MPA: microscopic polyangiitis; MPO: myeloperoxidase; ND: not described; NSIP: non-specific interstitial pneumonia, OP: organising pneumonia; p-ANCA: perinuclear ANCA; PF: pulmonary fibrosis; PR3: proteinase 3; UIP: usual interstitial pneumonia (the most common pattern of ANCA-ILD).
Although the MUC5B variant rs35705950T has been shown to be more strongly associated with a usual interstitial pneumonia (UIP) pattern, this study did not specifically address this question [49, 50]. Moreover, other IPF susceptible alleles in the telomerase reverse transcriptase and desmoplakin genes were found to be associated with MPA, although these were surprisingly present irrespective of the presence of ILD [51].

Pathogenesis of AAV-ILD
Environmental factors such as smoking, silica exposure, Staphylococcus aureus infection and use of drugs (e.g., propylthiouracil and hydralazine) are identified risk factors associated with the development of AAV [52, 53].

AAVs are characterised by microvascular endothelial inflammation leading to extravascular inflammation, progressive injury, tissue destruction and fibrosis. GPA and MPA develop by the loss of immunological T cell and B cell tolerance to one of two neutrophil proteins, PR3 or MPO [39]. This loss of tolerance leads to the development of ANCA, which activate neutrophils. ANCA-activated neutrophils localise to vulnerable microvascular beds where they induce injury and release the autoantigen for presentation by antigen-presenting cells, antigen recognition by effector T cells, which mediate further injury [39].

More specifically, in ANCA-associated ILD, a direct role of MPO antibodies in the pathogenesis of pulmonary fibrosis has been implied [33]. In vitro activation of MPO by anti-MPO antibodies has been shown to lead to the production of oxidant products including hypochlorous acid, triggering fibroblast proliferation and extracellular matrix deposition in the distal pulmonary parenchyma [54–56] (figure 1 [19, 57]). Furthermore, FOUCHER et al. [55] observed patchy inflammatory cell infiltrates throughout the parenchyma of the lung in their MPO-induced rat model of AAV, suggesting that the presence of MPO antibodies trigger an autoimmune response including activation of neutrophils. ANCA-activated neutrophils locally release proteolytic enzymes such as elastase or neutrophil extracellular traps (NETs), contributing to pulmonary tissue injury and fibrosis [55, 56]. Though the exact mechanisms remain unknown, NETs have been shown to play an important role in the pathogenesis of AAV [56]. Patients with active AAV express higher levels of circulating NET remnants when compared to patients in remission [58, 59]. Furthermore, interleukin-17-bearing NETs have been shown to trigger human lung fibroblast activation and differentiation into myofibroblasts [58, 60]. NET release has been implicated in tissue injury and dysfunction in systemic autoimmune diseases, including systemic lupus erythematosus and AAV, and have been proposed as potential targets for novel drug therapies [58].

Other proposed mechanisms for the development of ILD in AAV include repeated episodes of alveolar haemorrhage leading to pulmonary fibrosis, as implied by the development of pulmonary fibrosis in some patients with chronic mitral valve stenosis or idiopathic haemosiderosis, as well as evidence that cell-free haemoglobin induces alveolar epithelial injury mediated through the redox transition of haemoglobin to higher oxidation states [61–65]. Furthermore, subclinical episodes of pulmonary haemorrhage in patients with ANCA vasculitis have been described via the presence of haemosiderin-laden macrophages in bronchoalveolar lavage (BAL) fluid in AAV and previous series have reported histologic evidence of acute or chronic haemorrhage in greater than half of lung biopsies [66]. However, this theory is contradicted by the fact that the majority of described cases of pulmonary fibrosis have preceded the onset of vasculitis development. Thus, it has conversely been proposed that pulmonary fibrosis itself could induce MPO-ANCA production as a result of neutrophil destruction during the chronic inflammation process, perhaps explaining the appearance of ANCA after the onset of ILD [33].

Diagnosis of ANCA-ILD
Pulmonary symptoms of ANCA-ILD are usually non-specific and include progressive dyspnoea and cough, although patients will occasionally present with more obvious pulmonary or extrapulmonary signs of systemic vasculitides such as haemoptysis, constitutional symptoms such as fever or weight loss, arthralgias, haematuria, skin lesions or peripheral neuropathy.

Laboratory findings
While the 2018 IPF guidelines recommend serologic testing for autoimmune disease, the guidelines do not include an ANCA panel to rule out connective tissue disease (CTD) in patients suspected to have IPF [67]. Testing for ANCA is typically not performed as part of the diagnostic work-up of IIP and has also not been included in the research criteria for interstitial pneumonia with autoimmune features (IPAF) due to its association with the vasculitides, rather than the CTD-ILD spectra of disorders [68]. Given the ill-defined criteria for CTD as well as the fine line between CTD and systemic vasculitides, this approach has been disputed by experts [69, 70]. ANCA positivity in patients with IIP can have prognostic implications including the risk of future development of AAV, as well as potential therapeutic implications including consideration of immunomodulating agents when appropriate. Our approach is to include ANCA as part of initial serologic
testing in the work-up of a patient presenting with ILD at the baseline evaluation. A 2020 international consensus on ANCA testing beyond systemic vasculitis supports this approach, suggesting that MPO-ANCA and PR3-ANCA be tested in all patients with IIP and may be included in the serological criteria for IPAF [69].

In addition to ANCA positivity, patients with AAV and ILD (most frequently MPA) will often have elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels, whereas those with pulmonary fibrosis with isolated ANCA positivity typically do not. A recent retrospective review of 80
patients with either MPA-ILD or isolated ANCA-positive IIP demonstrated that mean ESR and CRP levels were significantly higher in the MPA-ILD group than the ANCA-IIP group (ESR 69 versus 17, p<0.001) and (CRP 23.4 versus 2.44, p<0.001) [32]. Elevated ESR was independently associated with a poor prognosis in multivariable analysis, and the ANCA-IIP patients with elevated ESR/CRP had a worse prognosis than those with normal inflammatory markers, perhaps suggesting stratified treatment in these patients. Other previous studies have corroborated these results, finding that patients with isolated pulmonary fibrosis have similar inflammatory marker levels regardless of ANCA status [8, 14, 22, 23].

**Pulmonary function testing and BAL cellular findings**

Similar to other fibrotic interstitial pneumonias, both isolated ANCA-IIP and AAV-ILD are associated with a restrictive pattern with reduced total lung capacity, forced vital capacity (FVC) and diffusing capacity for carbon monoxide, though co-existing airflow obstruction can occasionally be observed in AAV-ILD [7, 8, 11, 15, 16, 18, 21, 26, 27, 31]. FVC and diffusing capacity have been shown to decline over time [11, 26, 31]. BAL cellular findings in patients with ANCA/AAV-ILD are often abnormal but non-specific, though data is limited. An increased cellular count with elevated neutrophils has been reported in most available studies evaluating BAL findings in positive ANCA/AAV-ILD, with some studies reporting elevated haemosiderin-containing macrophages (suggesting chronic haemorrhage) as well as lymphocytosis [7, 8, 15, 30].

**Imaging**

High-resolution computed tomography (HRCT) images are helpful for detecting findings of interstitial pneumonia in evaluating patients with pulmonary symptoms and positive ANCA antibody and/or AAV, as interstitial abnormalities can be present in a significant proportion of patients. In a large, multicentre Japanese study assessing the prevalence of chest computed tomography (CT) abnormalities in 150 patients with MPA, 66% of patients had interstitial lung abnormalities [71]. Another recent prospective Japanese study evaluating HRCT findings in 144 MPA patients identified CT abnormalities in 93% of patients, with 51% patients having interstitial pneumonia [72].

Commonly described radiographic imaging patterns of ANCA/AAV-ILD include ground glass opacities, reticulation, interlobular septal thickening, consolidation, nodular pattern and honeycombing [10, 15, 18, 26, 27, 30, 31, 73]. Airway lesions have also been reported and include bronchiolitis, bronchial wall thickening and bronchiectasis [71, 73]. Other described findings include combined pulmonary fibrosis and emphysema (CPFE) and pleural effusion [15, 71, 72].

The most frequent radiologic pattern in patients with ANCA positivity is UIP (up to 78% of cases), followed by non-specific interstitial pneumonia (NSIP) (ranging from 13–64% of cases). Other less commonly seen patterns include desquamative interstitial pneumonia-like pattern, organising pneumonia and CPFE [15, 30, 71, 72].

**Histopathology**

The histopathology of AAV has been well described in previous reports, with fibrinoid necrosis and inflammation of small vessels, sometimes accompanied by thrombosis, being the hallmark of acute injury in all forms of AAV [39]. In the lungs, neutrophilic capillaritis is common to all forms of AAV, with granulomatous inflammation being a defining feature of GPA and not present in MPA [66]. In studies evaluating the histopathologic features in AAV, features of interstitial fibrosis were found in 26% of patients with GPA, with 7% of those patients having pulmonary fibrosis as a major or dominant finding [66]. Another study identified interstitial lesions as a pathologic feature in 74% of patients with PR3 or MPO antibodies, with fibrosis present in 48% [74].

Few studies have specifically evaluated pathologic features of ILD cases associated with ANCA positivity. In a case series describing histopathologic specimens of nine patients with MPO-ANCA IIP, eight out of nine patients were described as having a UIP histologic pattern, with accompanied areas of NSIP [12]. Two patients had combined UIP and diffuse alveolar damage (DAD), and one patient was labelled as having a DAD pattern. Other features included small airway disease (in 9/9 patients) and lymphoid follicles in seven of the nine patients, suggesting some unique features when compared to IPF. None of the cases had findings of vasculitis [12]. Another study evaluating surgical lung biopsy (SLB) findings in 18 patients with IIP, and MPO-positivity showed similar findings, with a UIP pattern demonstrated in 56%, with 40% of the patients with a UIP pattern found to have additional inflammatory changes not typical of the UIP pattern in patients with IPF, including bronchiolitis, lymphoid hyperplasia, desquamative interstitial pneumonia and organising pneumonia [27].

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In a similar vein to the diagnostic work-up of ILD in other autoimmune diseases, SLB is likely unnecessary in pursuing a histopathological diagnosis in patients with ANCA positivity and interstitial pneumonia; although in cases with systemic involvement, renal, lung, skin or other tissue biopsy may be important in establishing the diagnosis of AAV [39]. In patients with isolated ANCA-positive IIP, particularly those with a radiographic UIP pattern, SLB would not be required for histopathologic confirmation, given the well-documented correlation between radiographic and histopathologic UIP [75–77].

The diagnosis of ANCA-ILD is best accomplished by a collaborative approach with input from multidisciplinary experts including a rheumatologist, pulmonologist with ILD expertise and a radiologist. Once the diagnosis of ANCA-ILD is established, our approach is to follow up with frequent clinical assessment to detect any new organ involvement, which can occur at any point in the disease course. We suggest investigations of extrapulmonary signs of systemic vasculitis (e.g., rhinosinusitis, haemoptysis, arthralgias, haematuria, skin lesions, neurologic dysfunction) with involvement of the appropriate disciplinary expertise as necessary. For those with AAV and existing systemic involvement, we suggest frequent urinalysis, circulating inflammatory markers and renal function be periodically assessed (i.e., every 1–3 months) to monitor disease status [78].

**Prognosis**

While the overall 5-year survival for AAV has significantly improved over the years following an improvement in the standardisation of immunosuppressive therapies, the presence of ILD in AAV, particularly with a UIP pattern, has been associated with significantly worse outcomes in patients with AAV. A recently published meta-analysis of 10 studies showed a 2.9-fold increased risk of death in patients with AAV-ILD when compared with the control group of AAV patients without ILD, with a higher relative risk (RR) value of death in the UIP group than in the non-UIP group (RR 4.36 versus RR 2.90) [79]. Another recently published study looking at outcomes of 80 patients with MPA-ILD demonstrated that those patients with higher fibrosis scores with presence of honeycomb lesions had significantly worse 5-year survival rates than those with lower scores [80].

Long-term outcomes are less described in those patients with isolated ANCA positivity and pulmonary fibrosis. The majority of available studies have reported similar prognoses between patients with pulmonary fibrosis despite ANCA positivity versus negativity, though a few studies demonstrated a worse prognosis in those patients with higher ANCA titres and inflammatory markers [7, 8, 14, 21–23, 28, 32]. Moreover, a recently published retrospective study of 80 patients with MPO antibodies and ILD in which 31 (38.75%) had MPA-ILD and 49 (61.25%) had isolated ANCA-positive IIP demonstrated that prognoses of ANCA-IIP with normal inflammation markers, ANCA-IIP with elevated inflammation markers and MPA-ILD were sequentially poorer [32]. Prospective long-term studies are needed for further evaluation as to whether isolated ANCA positivity in patients with IIP has a different impact on clinical course and survival compared to IPF.

**Treatment**

The treatment of ILD in the setting of ANCA positivity should be approached on an individualised basis, with multidisciplinary input from a rheumatologist and an ILD pulmonologist in order to optimise therapeutic strategies.

There have been numerous studies evaluating treatment in ANCA-associated systemic vasculitis, though there are no published controlled trials up to this point for the treatment of patients with AAV-ILD or with IIP and associated ANCA positivity [81–86]. In addition, the most recent European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association guideline recommendations for the management of AAV do not specifically address treatment strategies for this subset of patients [78]. An empirical management approach to patients with MPO-ANCA positivity and ILD proposed by the Mayo Clinic consists of immunosuppressive therapy per therapeutic guidelines of AAV in those with MPA, a trial of immunomodulating medications in those with NSIP pattern in the absence of other organ involvement and a suggestion against immunosuppressive therapy in those with UIP pattern without vasculitis manifestations given the lack of evidence of therapeutic benefit [33, 87].

**Immunomodulating agents**

Currently, there are few retrospective case series and case reports addressing the treatment of ANCA-ILD. Treatment of patients with systemic vasculitis involvement involves induction therapy using highly potent immunosuppressive drugs, with the goal of achieving remission, followed by maintenance therapy with the aim of preventing relapse [39]. The most commonly used immunosuppressive agents for patients with...
ANCA-ILD included mycophenolate, azathioprine, rituximab (RTX) and cyclophosphamide (CYC) [7, 8, 14, 15, 26, 28, 30–32].

The approach to managing patients with ANCA-ILD, particularly those without systemic vasculitis manifestations, is much less well defined and treatment with immunomodulating agents can be considered in this subgroup of patients based on limited data, particularly in cases with non-UIP patterns. In a retrospective study of 69 patients with ANCA-positivity and co-existing ILD (17 patients with AAV diagnosis), improvement in pulmonary function tests was demonstrated in those patients who were treated with immunosuppressive agents versus an overall decline in lung function in the no-treatment group [26]. On the other hand, immunosuppressants did not improve the prognosis of AAV-ILD in a recent study on 62 patients [30]. Another study of 49 AAV-ILD patients demonstrated that 1- and 5-year survival rates were significantly better in those who received glucocorticoids in combination with RTX or CYC as induction therapy than in those who were treated with corticosteroids alone [15].

**Antifibrotics**

There is growing evidence of the potential role of antifibrotic agents in the treatment of progressive fibrotic ILDs (PF-ILDs) other than IPF, especially in patients with a UIP pattern [88]. *Post hoc* analysis of the INBUILD study suggested a treatment benefit of the antifibrotic nintedanib across all sub-groups of patients with PF-ILD, including autoimmune ILD, though the trial was not powered to provide evidence to address this specific question [89]. Nonetheless, nintedanib has become increasingly used in clinical practice since its approval by the United States Food and Drug Administration for treatment of PF-ILDs other than IPF. Moreover, results of the recently published RELIEF study evaluating the efficacy and

![Flowchart](https://doi.org/10.1183/16000617.0123-2021)
safety of pirfenidone in 127 patients with PF-ILD other than IPF suggested attenuated disease progression by a significantly lower decline of FVC percentage in the treatment group over 48 weeks, although these results should be interpreted with caution as the study was terminated early due to slow recruitment [90].

There are no published studies specifically evaluating the role of antifibrotic agents in ANCA-ILD, though a pilot study (NCT03385668) is ongoing with the aim of evaluating the safety and the effectiveness of pirfenidone in patients with anti-MPO positivity and pulmonary fibrosis, with or without AAV. Still, pending much-needed evidence, combination therapy with immunosuppressive and antifibrotic drugs could be considered as a reasonable treatment option in patients with co-existing fibrosis and inflammatory disease (particularly in a patient with a fibrotic NSIP pattern), or monotherapy with an antifibrotic agent without immunosuppression in the setting of ANCA-ILD without systemic involvement and UIP pattern manifesting progressive disease. A suggested clinical approach to the diagnosis and management of patients with AAV-ILD or ANCA positivity in ILD is summarised in figure 2.

Conclusions
The presence of ILD is not uncommon in patients with AAV and has become increasingly recognised over the recent years. Anti-MPO antibody associated ILD occurs most frequently, with or without systemic manifestations, with pulmonary fibrosis often preceding development of frank systemic vasculitis. Despite an enhanced understanding of the disease pathophysiology, clinical manifestations and outcomes of this subset of patients with ANCA-ILD, much remains unknown regarding the pathogenetic mechanisms between ANCA positivity and the development of pulmonary fibrosis and disease progression.

Testing for ANCA is not typically included in the diagnostic work up of IIP and is not included in the research criteria for IPAF. Standardised international criteria are needed for the diagnosis and classification of all autoimmune-associated ILDs to allow for earlier identification and improved treatment strategies. Furthermore, prospective studies are needed to clarify the natural course and biologic implications of ANCA positivity in patients with IIP, including the likelihood of progression into systemic vasculitis as well as progressive pulmonary fibrosis and potential unique therapeutic implications in this cohort of patients.

Although the application of antifibrotic therapy to patients with progressive fibrotic lung diseases encompassing patients with autoimmune disease has provided additional treatment options for patients with autoimmune-associated pulmonary fibrosis, including ANCA-ILD, this continues to remain an area with a significant unmet research need. Controlled trials are needed to determine the safety and efficacy of treatment regimens in order to improve outcomes and quality of life, which are meaningful to this subset of patients.

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