Antineutrophil cytoplasmic antibody-associated interstitial lung disease: a review

Suha Kadura [ID] and Ganesh Raghu

Dept of Medicine, Center for Interstitial Lung Diseases, University of Washington, Seattle, WA, USA.

Corresponding author: Ganesh Raghu (graghu@uw.edu)

Shareable abstract (@ERSpublications)
Over the last three decades, an increasing number of publications have reported the association between interstitial lung disease and anti-neutrophil cytoplasmic antibody (ANCA) or ANCA-associated vasculitis. With this increased awareness, we have reviewed the literature to date and provide an update in this narrative review. https://bit.ly/3A8SGHZ

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].

TABLE 1 Published studies of anti-neutrophil cytoplasmic antibody associated interstitial lung disease

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
ARIMURA et al. [3], 1995, Japan	Pulmonary involvement in patients with MPO-ANCA	46	61.1	ND	43	28 MPA	ND	ND	100 MPO	ND
HIROMURA et al. [4], 2000, Japan	MPO+rapidly progressive GN during course of IPF	4	67	50	100	100 MPA	100	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
NOZU 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
HERVIER et al. [9], 2009, France	PF associated with AAV	12	70.7	75	100	83 MPA, 17 GPA	66 concurrent, 25 preceding, 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
ARULKUMARAN et al. [11], 2011, UK	ILD and AAV	14	67.3	71	100	100 MPA	14 preceding, 64 concurrent, 21 post	90	100 MPO	ND
TANAKA 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

TABLE 1 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
Ando 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
Comarmond 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

TABLE 1 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
Kagiyama 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 (MPO 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	53 MPO, 26 PR3, 18 ND	75% UIP/possible UIP

Continued

TABLE 1 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
Watanbe 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"

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 ANCAs, 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 patients with 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 vasculitis 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
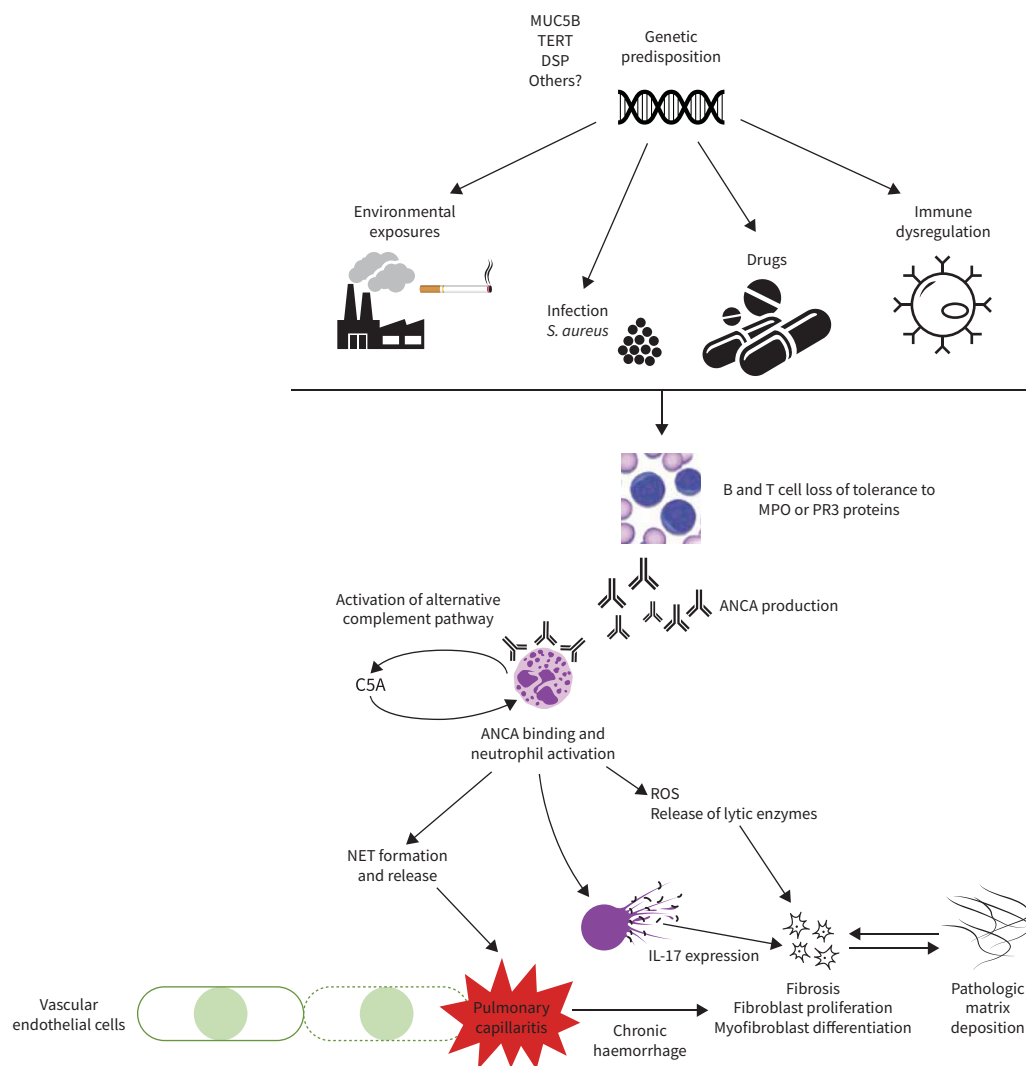
FIGURE 1 Schematic illustration of proposed concepts of pathogenesis in antineutrophil cytoplasmic antibody (ANCA)-mediated lung disease including pulmonary capillaritis and interstitial lung disease (ILD). The pathogenesis of ANCA-ILD is thought to involve an interplay of factors (including environmental exposures such as silica or cigarette smoke, drugs including hydralazine, infection, immune dysregulation) and genetic predisposition (such as *MUC5B*, telomerase reverse transcriptase, desmoplakin and others). These factors lead to the generation of an aberrant autoimmune response including loss of T- and B-cell tolerance and ANCA production. ANCA induces neutrophils to secrete chemoattractants which lead to activation of the alternative complement pathway, with anaphylatoxin C5A as an important player, leading to amplification loops and further priming of neutrophils [19, 57]. ANCA-activated neutrophils locally release reactive oxygen species (ROS), proteolytic enzymes such as elastase or neutrophil extracellular trap (NET) formation, which injures vascular endothelial cells leading to pulmonary capillaritis. Furthermore, interleukin-17 (IL-17)-bearing NETs have been shown to trigger human lung fibroblast activation and differentiation into myofibroblasts [60]. Other proposed mechanisms for the development of ILD in AAV include repeated episodes of alveolar haemorrhage leading to pulmonary fibrosis.

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, 32, 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].

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
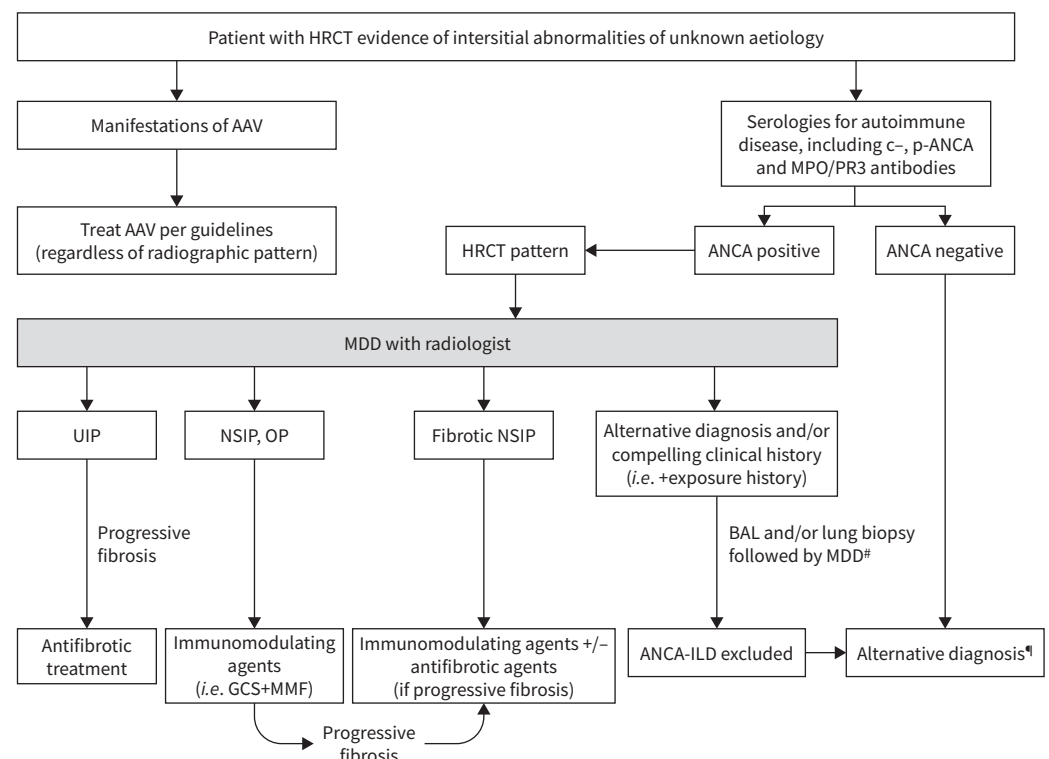

FIGURE 2 Suggested approach to diagnosis and treatment of antineutrophil cytoplasmic antibody (ANCA)-associated interstitial lung disease (ILD). HRCT: high-resolution computed tomography; AAV: ANCA-associated vasculitis; MDD: multidisciplinary discussion; UIP: usual interstitial pneumonia (the most common pattern of ANCA-ILD); NSIP: nonspecific interstitial pneumonia; OP: organising pneumonia, GCS: glucocorticoids; MMF: mycophenolate mofetil; #: Transbronchial biopsy (TBBx), cryobiopsy, or surgical lung biopsy (SLB), as per the treating clinician's discretion, local expertise and/or MDD; elective SLB in patients may be considered if TBBx and/or cryobiopsy is non-diagnostic in patients who are stable and are not at high risk for surgical complications. ¶: Pursue alternative diagnoses guided by appropriate clinical setting and guidelines (*e.g.*, idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, sarcoidosis, etc.).

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 in 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.

References

1   Falk RJ, Jennette JC. Anti-neutrophil cytoplasmic autoantibodies with specificity for myeloperoxidase in patients with systemic vasculitis and idiopathic necrotizing and crescentic glomerulonephritis. *N Engl J Med* 1988; 318: 1651–1657.

2   Nada AK, Torres VE, Ryu JH, *et al.* Pulmonary fibrosis as an unusual clinical manifestation of a pulmonary-renal vasculitis in elderly patients. *Mayo Clin Proc* 1990; 65: 847–856.

3   Arimura Y, Minoshima S, Tanaka U, *et al.* Pulmonary involvement in patients with myeloperoxidase specific-antineutrophil cytoplasmic antibody. *Ryumachi Rheum* 1995; 35: 46–55.

4   Hiromura K, Nojima Y, Kitahara T, *et al.* Four cases of anti-myeloperoxidase antibody-related rapidly progressive glomerulonephritis during the course of idiopathic pulmonary fibrosis. *Clin Nephrol* 2000; 53: 384–389.

5   Eschun GM, Mink SN, Sharma S. Pulmonary interstitial fibrosis as a presenting manifestation in perinuclear antineutrophilic cytoplasmic antibody microscopic polyangiitis. *Chest* 2003; 123: 297–301.

6   Homma S, Matsushita H, Nakata K. Pulmonary fibrosis in myeloperoxidase antineutrophil cytoplasmic antibody-associated vasculitides. *Respirol Carlton Vic* 2004; 9: 190–196.

7   Foulon G, Delaval P, Valeyre D, *et al.* ANCA-associated lung fibrosis: analysis of 17 patients. *Respir Med* 2008; 102: 1392–1398.

8   Nozu T, Kondo M, Suzuki K, *et al.* A comparison of the clinical features of ANCA-positive and ANCA-negative idiopathic pulmonary fibrosis patients. *Respir Int Rev Thorac Dis* 2009; 77: 407–415.

9   Hervier B, Pagnoux C, Agard C, *et al.* Pulmonary fibrosis associated with ANCA-positive vasculitides. Retrospective study of 12 cases and review of the literature. *Ann Rheum Dis* 2009; 68: 404–407.

10 Tzelepis GE, Kokosi M, Tzioufas A, *et al.* Prevalence and outcome of pulmonary fibrosis in microscopic polyangiitis. *Eur Respir J* 2010; 36: 116–121.

11 Arulkumaran N, Periselneris N, Gaskin G, *et al.* Interstitial lung disease and ANCA-associated vasculitis: a retrospective observational cohort study. *Rheumatology* 2011; 50: 2035–2043.

12 Tanaka T, Otani K, Egashira R, *et al.* Interstitial pneumonia associated with MPO-ANCA: clinicopathological features of nine patients. *Respir Med* 2012; 106: 1765–1770.

13 Ahn JK, Hwang J-W, Lee J, *et al.* Clinical features and outcome of microscopic polyangiitis under a new consensus algorithm of ANCA-associated vasculitides in Korea. *Rheumatol Int* 2012; 32: 2979–2986.

14 Ando M, Miyazaki E, Ishii T, *et al.* Incidence of myeloperoxidase anti-neutrophil cytoplasmic antibody positivity and microscopic polyangitis in the course of idiopathic pulmonary fibrosis. *Respir Med* 2013; 107: 608–615.

15 Comarmond C, Crestani B, Tazi A, *et al.* Pulmonary fibrosis in antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis: a series of 49 patients and review of the literature. *Medicine* 2014; 93: 340–349.

16 Huang H, Wang YX, Jiang CG, *et al.* A retrospective study of microscopic polyangiitis patients presenting with pulmonary fibrosis in China. *BMC Pulm Med* 2014; 14: 8.

17 Yu A-P, Chang J-X, Liu Y-J, *et al.* Computed tomography image analysis before and after treatment of anti-neutrophil cytoplasmic antibody—associated pulmonary interstitial fibrosis in 8 patients. *Clin Ther* 2014; 36: 2064–2071.

18 Fernandez Casares M, Gonzalez A, Fielli M, *et al.* Microscopic polyangiitis associated with pulmonary fibrosis. *Clin Rheumatol* 2015; 34: 1273–1277.

19 Flores-Suárez LF, Ruiz N, Rivera LMS, *et al.* Reduced survival in microscopic polyangiitis patients with pulmonary fibrosis in a respiratory referral centre. *Clin Rheumatol* 2015; 34: 1653–1654.

20 Ono N, Niiro H, Ueda A, *et al.* Characteristics of MPO-ANCA-positive granulomatosis with polyangiitis: a retrospective multi-center study in Japan. *Rheumatol Int* 2015; 35: 555–559.

21 Kagiyama N, Takayanagi N, Kanauchi T, *et al.* Antineutrophil cytoplasmic antibody-positive conversion and microscopic polyangiitis development in patients with idiopathic pulmonary fibrosis. *BMJ Open Respir Res* 2015; 2: e000058.

22 Hosoda C, Baba T, Hagiwara E, *et al.* Clinical features of usual interstitial pneumonia with anti-neutrophil cytoplasmic antibody in comparison with idiopathic pulmonary fibrosis. *Respirol Carlton Vic* 2016; 21: 920–926.

23 Hozumi H, Enomoto N, Oyama Y, *et al.* Clinical implication of proteinase-3-antineutrophil cytoplasmic antibody in patients with idiopathic interstitial pneumonias. *Lung* 2016; 194: 235–242.

24 Tashiro H, Takahashi K, Tanaka M, *et al.* Characteristics and prognosis of microscopic polyangiitis with bronchiectasis. *J Thorac Dis* 2017; 9: 303–309.

25 Hozumi H, Oyama Y, Yasui H, *et al.* Clinical significance of myeloperoxidase-anti-neutrophil cytoplasmic antibody in idiopathic interstitial pneumonias. *PLoS ONE* 2018; 13: e0199659.

26 Juman S, Haque S, Chaudhuri N. Interstitial lung disease associated with ANCA positivity: a retrospective analysis; *Eur Respir J*; 2019; 54: Suppl. 63, PA1362.

27 Baqir M, Yi EE, Colby TV, *et al.* Radiologic and pathologic characteristics of myeloperoxidase-antineutrophil cytoplasmic antibody-associated interstitial lung disease: a retrospective analysis. *Sarcoidosis Vasc Diffuse Lung Dis* 2019; 36: 195–201.

28 Liu GY, Ventura IB, Achtar-Zadeh N, *et al.* Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in north American patients with idiopathic pulmonary fibrosis. *Chest* 2019; 156: 715–723.

29 Watanabe T, Minezawa T, Hasegawa M, *et al.* Prognosis of pulmonary fibrosis presenting with a usual interstitial pneumonia pattern on computed tomography in patients with myeloperoxidase anti-neutrophil cytoplasmic antibody-related nephritis: a retrospective single-center study. *BMC Pulm Med* 2019; 19: 194.

30 Maillet T, Goletto T, Beltramo G, *et al.* Usual interstitial pneumonia in ANCA-associated vasculitis: a poor prognostic factor. *J Autoimmun* 2020; 106: 102338.

31 Kwon M, Lee AS, Mira-Avendano I, *et al.* Interstitial lung disease in antineutrophil cytoplasmic antibody–associated vasculitis patients: comparison with idiopathic pulmonary fibrosis. *J Clin Rheumatol* 2020; in press. [https://doi.org10.1097/RHU.0000000000001357].

32 Sun X, Peng M, Zhang T, *et al.* Clinical features and long-term outcomes of interstitial lung disease with anti-neutrophil cytoplasmic antibody. *BMC Pulm Med* 2021; 21: 88.

33 Sebastiani M, Manfredi A, Vacchi C, *et al.* Epidemiology and management of interstitial lung disease in ANCA-associated vasculitis. *Clin Exp Rheumatol* 2020; 38: Suppl 124, 221–231.

34 Fujimoto S, Watts RA, Kobayashi S, *et al.* Comparison of the epidemiology of anti-neutrophil cytoplasmic antibody-associated vasculitis between Japan and the U.K. *Rheumatology* 2011; 50: 1916–1920.

35 Oh JS, Lee C-K, Kim YG, *et al.* Clinical features and outcomes of microscopic polyangiitis in Korea. *J Korean Med Sci* 2009; 24: 269–274.

36 Chen M, Yu F, Zhang Y, *et al.* Clinical and pathological characteristics of Chinese patients with antineutrophil cytoplasmic autoantibody associated systemic vasculitides: a study of 426 patients from a single centre. *Postgrad Med J* 2005; 81: 723–727.

37 Wu C-S, Hsieh C-J, Peng Y-S, *et al.* Antineutrophil cytoplasmic antibody-associated vasculitis in Taiwan: a hospital-based study with reference to the population-based National Health Insurance database. *J Microbiol Immunol Infect* 2015; 48: 477–482.

38 Furuta S, Chaudhry AN, Hamano Y, *et al.* Comparison of phenotype and outcome in microscopic polyangiitis between Europe and Japan. *J Rheumatol* 2014; 41: 325–333.

39 Kitching AR, Anders H-J, Basu N, *et al.* ANCA-associated vasculitis. *Nat Rev Dis Primer* 2020; 6: 71.

40 Schirmer JH, Wright MN, Vonthein R, *et al.* Clinical presentation and long-term outcome of 144 patients with microscopic polyangiitis in a monocentric German cohort. *Rheumatology* 2016; 55: 71–79.

41 Shi J, Shen Q, Chen X-M, *et al.* Clinical characteristics and outcomes in microscopic polyangiitis patients with renal involvement: a study of 124 Chinese patients. *BMC Nephrol* 2019; 20: 339.

42 Kono M, Nakamura Y, Enomoto N, *et al.* Usual interstitial pneumonia preceding collagen vascular disease: a retrospective case control study of patients initially diagnosed with idiopathic pulmonary fibrosis. *PLoS ONE* 2014; 9: e94775.

43 Alba MA, Flores-Suárez LF, Henderson AG, *et al.* Interstitial lung disease in ANCA vasculitis. *Autoimmun Rev* 2017; 16: 722–729.

44 Guillevin L, Durand-Gasselin B, Cevallos R, *et al.* Microscopic polyangiitis: clinical and laboratory findings in eighty-five patients. *Arthritis Rheum* 1999; 42: 421–430.

45 Kang BH, Park JK, Roh JH, *et al.* Clinical significance of serum autoantibodies in idiopathic interstitial pneumonia. *J Korean Med Sci* 2013; 28: 731–737.

46 Wijsenbeek M, Cottin V. Spectrum of fibrotic lung diseases. *N Engl J Med* 2020; 383: 958–968.

47 Juge P-A, Lee JS, Ebstein E, *et al.* MUC5B promoter variant and rheumatoid arthritis with interstitial lung disease. *N Engl J Med* 2018; 379: 2209–2219.

48 Ley B, Torgerson DG, Oldham JM, *et al.* Rare protein-altering telomere-related gene variants in patients with chronic hypersensitivity pneumonitis. *Am J Respir Crit Care Med* 2019; 200: 1154–1163.

49 Namba N, Kawasaki A, Sada K-E, *et al.* Association of *MUC5B* promoter polymorphism with interstitial lung disease in myeloperoxidase-antineutrophil cytoplasmic antibody-associated vasculitis. *Ann Rheum Dis*. 2019; 78: 1144–1146.

50 Putman RK, Gudmundsson G, Araki T, *et al.* The *MUC5B* promoter polymorphism is associated with specific interstitial lung abnormality subtypes. *Eur Respir J* 2017; 50: 1700537.

51 Kawasaki A, Namba N, Sada K-E, *et al.* Association of *TERT* and *DSP* variants with microscopic polyangiitis and myeloperoxidase-ANCA positive vasculitis in a Japanese population: a genetic association study. *Arthritis Res Ther* 2020; 22: 246.

52 Scott J, Hartnett J, Mockler D, *et al.* Environmental risk factors associated with ANCA associated vasculitis: a systematic mapping review. *Autoimmun Rev* 2020; 19: 102660.

53 Gómez-Puerta JA, Gedmintas L, Costenbader KH. The association between silica exposure and development of ANCA-associated vasculitis: systematic review and meta-analysis. *Autoimmun Rev* 2013; 12: 1129–1135.

54 Guilpain P, Chéreau C, Goulvestre C, *et al.* The oxidation induced by antimyeloperoxidase antibodies triggers fibrosis in microscopic polyangiitis. *Eur Respir J* 2011; 37: 1503–1513.

55 Foucher P, Heeringa P, Petersen AH, *et al.* Antimyeloperoxidase-associated lung disease. An experimental model. *Am J Respir Crit Care Med* 1999; 160: 987–994.

56 Negreros M, Flores-Suárez LF. A proposed role of neutrophil extracellular traps and their interplay with fibroblasts in ANCA-associated vasculitis lung fibrosis. *Autoimmun Rev* 2021; 20: 102781.

57 Nakazawa D, Masuda S, Tomaru U, *et al.* Pathogenesis and therapeutic interventions for ANCA-associated vasculitis. *Nat Rev Rheumatol* 2019; 15: 91–101.

58 Frangou E, Vassilopoulos D, Boletis J, *et al.* An emerging role of neutrophils and NETosis in chronic inflammation and fibrosis in systemic lupus erythematosus (SLE) and ANCA-associated vasculitides (AAV): implications for the pathogenesis and treatment. *Autoimmun Rev* 2019; 18: 751–760.

59 Söderberg D, Kurz T, Motamedi A, *et al.* Increased levels of neutrophil extracellular trap remnants in the circulation of patients with small vessel vasculitis, but an inverse correlation to anti-neutrophil cytoplasmic antibodies during remission. *Rheumatology* 2015; 54: 2085–2094.

60 Chrysanthopoulou A, Mitroulis I, Apostolidou E, *et al.* Neutrophil extracellular traps promote differentiation and function of fibroblasts: NETs induce fibrosis via differentiation of fibroblasts. *J Pathol* 2014; 233: 294–307.

61 Birnbaum J, Danoff S, Askin FB, *et al.* Microscopic polyangiitis presenting as a "pulmonary-muscle" syndrome: is subclinical alveolar hemorrhage the mechanism of pulmonary fibrosis? *Arthritis Rheum* 2007; 56: 2065–2071.

62 Kay JM, Edwards FR. Ultrastructure of the alveolar-capillary wall in mitral stenosis. *J Pathol* 1973; 111: 239–245.

63 Le Clainche L, Le Bourgeois M, Fauroux B, *et al.* Long-term outcome of idiopathic pulmonary hemosiderosis in children. *Medicine* 2000; 79: 318–326.

64 Chintagari NR, Jana S, Alayash AI. Oxidized ferric and ferryl forms of hemoglobin trigger mitochondrial dysfunction and injury in alveolar type I cells. *Am J Respir Cell Mol Biol* 2016; 55: 288–298.

65   Borie R, Crestani B. Antineutrophil cytoplasmic antibody-associated lung fibrosis. *Semin Respir Crit Care Med* 2018; 39: 465–470.

66   Travis WD, Hoffman GS, Leavitt RY, *et al.* Surgical pathology of the lung in Wegener's granulomatosis. Review of 87 open lung biopsies from 67 patients. *Am J Surg Pathol* 1991; 15: 315–333.

67   Raghu G, Remy-Jardin M, Myers JL, *et al.* Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2018; 198: e44–e68.

68   Fischer A, Antoniou KM, Brown KK, *et al.* An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features. *Eur Respir J* 2015; 46: 976–987.

69   Moiseev S, Cohen Tervaert JW, Arimura Y, *et al.* 2020 international consensus on ANCA testing beyond systemic vasculitis. *Autoimmun Rev* 2020; 19: 102618.

70   Novikov P, Shchegoleva E, Akulkina L, *et al.* Diagnostic pitfalls and treatment challenges in interstitial pneumonia with autoimmune features: comment on the article by Wilfong *et al. Arthritis Rheumatol* 2019; 71: 651–652.

71   Yamagata M, Ikeda K, Tsushima K, *et al.* Prevalence and responsiveness to treatment of lung abnormalities on chest computed tomography in patients with microscopic polyangiitis: a multicenter, longitudinal, retrospective study of one hundred fifty consecutive hospital-based Japanese patients: CT lung abnormalities in microscopic polyangiitis. *Arthritis Rheumatol* 2016; 68: 713–723.

72   Suzuki A, Sakamoto S, Kurosaki A, *et al.* Chest high-resolution CT findings of microscopic polyangiitis: a Japanese first nationwide prospective cohort study. *Am J Roentgenol* 2019; 213: 104–114.

73   Homma S, Usui Y, Suzuki A, *et al.* Difference in chest HRCT findings in relation to ANCA subtypes in ANCA-associated vasculitis. *Eur Respir J* 2019; 54: Suppl. 63, OA5158.

74   Gaudin PB, Askin FB, Falk RJ, *et al.* The pathologic spectrum of pulmonary lesions in patients with anti-neutrophil cytoplasmic autoantibodies specific for anti-proteinase 3 and anti-myeloperoxidase. *Am J Clin Pathol* 1995; 104: 7–16.

75   Flaherty KR, Thwaite EL, Kazerooni EA, *et al.* Radiological versus histological diagnosis in UIP and NSIP: survival implications. *Thorax* 2003; 58: 143–148.

76   Kim EJ, Collard HR, King TE. Rheumatoid arthritis-associated interstitial lung disease: the relevance of histopathologic and radiographic pattern. *Chest* 2009; 136: 1397–1405.

77   O'Dwyer DN, Armstrong ME, Cooke G, *et al.* Rheumatoid arthritis (RA) associated interstitial lung disease (ILD). *Eur J Intern Med* 2013; 24: 597–603.

78   Yates M, Watts RA, Bajema IM, *et al.* EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. *Ann Rheum Dis* 2016; 75: 1583–1594.

79   Zhou P, Ma J, Wang G. Impact of interstitial lung disease on mortality in ANCA-associated vasculitis: a systematic literature review and meta-analysis. *Chron Respir Dis* 2021; 18: 147997312199456.

80   Matsuda S, Kotani T, Suzuka T, *et al.* Evaluation of poor prognostic factors of respiratory related death in microscopic polyangiitis complicated by interstitial lung disease. *Sci Rep* 2021; 11: 1490.

81   Stone JH, Merkel PA, Spiera R, *et al.* Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 2010; 363: 221–232.

82   Jones RB, Cohen Tervaert JW, Hauser T, *et al.* Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med* 2010; 363: 211–220.

83   Guillevin L, Pagnoux C, Karras A, *et al.* Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. *N Engl J Med* 2014; 371: 1771–1780.

84   Walsh M, Merkel PA, Peh C-A, *et al.* Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. *N Engl J Med* 2020; 382: 622–631.

85   Hiemstra TF, Walsh M, Mahr A, *et al.* Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial. *JAMA* 2010; 304: 2381–2388.

86   Smith RM, Jones RB, Specks U, *et al.* Rituximab as therapy to induce remission after relapse in ANCA-associated vasculitis. *Ann Rheum Dis* 2020; 79: 1243–1249.

87   Thompson GE, Specks U. Update on the management of respiratory manifestations of the antineutrophil cytoplasmic antibodies-associated vasculitides. *Clin Chest Med* 2019; 40: 573–582.

88   Flaherty KR, Wells AU, Cottin V, *et al.* Nintedanib in progressive fibrosing interstitial lung diseases. *N Engl J Med* 2019; 381: 1718–1727.

89   Wells AU, Flaherty KR, Brown KK, *et al.* Nintedanib in patients with progressive fibrosing interstitial lung diseases—subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. *Lancet Respir Med* 2020; 8: 453–460.

90   Behr J, Prasse A, Kreuter M, *et al.* Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase 2b trial. *Lancet Respir Med* 2021; 9: 476–486.