

# Epidemiology and management of interstitial lung disease in ANCA-associated vasculitis

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## ABSTRACT

Antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) is a group of systemic vasculitides that predominantly affect small vessels, including granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA).

Pulmonary involvement is frequently observed in AAV patients, with various possible phenotypes in the different diseases. In the last years, among the possible types of lung involvement, a growing interest has been addressed to the interstitial lung disease (ILD).

Prevalence of ILD is higher in MPA than in GPA; in fact, ILD has been reported in up to 45% of MPA patients and in 23% of GPA. Anti-MPO antibodies are the main ANCA subtype associated to ILD, in about 46-71% of cases, while anti-PR3 antibodies are reported in 0-29% of patients.

High resolution computed tomography (HRCT) frequently detects interstitial lung abnormalities in AAV, up to 66% of patients with MPA, even if with an unclear clinical relevance, specifically in asymptomatic patients. Ground glass opacities, mainly consistent with diffuse alveolar haemorrhage (DAH), are the most frequent finding in MPA patients, but reticulations, interlobular septal thickening and honeycombing are also reported.

ILD significantly affects quality of life and survival, with mortality increased 2 to 4 times, particularly higher in MPA patients with pulmonary fibrosis.

Currently, immunosuppressive therapy is considered also as a possible treatment of ILD. However, a careful evaluation of progression and severity of lung involvement, should guide the treatment decision in the single patient.

In this review, we discuss the available evidence on clinical features, diagnostic work-up, prognosis and management of AAV-ILD.

## ANCA-associated vasculitis: introduction and classification criteria

Antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) is a heterogeneous group of systemic vasculitides that predominantly affect small vessels, including granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), together with renal-limited vasculitis, and eosinophilic granulomatosis with polyangiitis (EGPA) (1). AAV is associated with myeloperoxidase (MPO) or proteinase 3 (PR3) ANCA. However, cases of ANCA-negative AAV can occur, especially in EGPA but also in GPA (2). Although many classification criteria are available for AAV, a differential diagnosis between GPA and MPA is sometimes unreliable, and a diagnosis of unclassified form is occasionally made (3).

The different types of ANCA have been associated to different disease extent and severity, with regard to relapse risk, response to therapy, and patient outcome; therefore, some authors proposed to classify AAV on the basis of the "autoantibody profile", as "PR3-ANCA", "MPO-ANCA", or "seronegative" disease. Nevertheless, none of the ANCA specificities is pathognomonic for any clinical feature (2, 4).

A careful clinical assessment of patients, a screening for all potentially affected organs and a categorisation of disease severity remain the best approach to predict disease prognosis and to tailor the treatment, considering the complementary role of ANCA specificities and clinical phenotypes (3, 5).

Pulmonary involvement is frequently observed in AAV patients, and in the last years a growing number of evidence has been published on the interstitial lung involvement in these conditions.

In this paper, we review clinical features, diagnostic work-up, prognosis and management of interstitial lung disease (ILD) associated to AAV. The role of ANCA in patients with idiopathic interstitial pneumonias (IIPs) without an AAV will be also evaluated.

*Pulmonary features of granulomatosis with polyangiitis*

GPA is a systemic vasculitis characterised by granulomatous lesions and necrotising vasculitis with an incidence estimated as 4 to 21 cases/million. The peak incidence is in the fourth through seventh decades of life, without gender predominance (6, 7). Although any organs may be affected, the upper and lower respiratory tract, along with kidney, are the most frequently organs involved in GPA. Moreover, GPA represents the most common pulmonary vasculitis (8, 9). About 90% of patients affected by GPA presents heterogeneous pulmonary manifestations at high resolution computed tomography (HRCT), including lung nodules, segmental bronchial wall thickening, septal lines, consolidations, lobar bronchial wall thickening, and bronchiectasis (10).

Non-cavitated nodules, consolidations, pulmonary infiltrates, and ground glass opacities (GGO) are usually considered as features of mild parenchymal disease, while other lung complications, such as alveolar haemorrhage or cavitated nodules can be life-threatening and require an early diagnosis and prompt therapeutic approach (11).

Nodules are the most frequent pulmonary finding in GPA; they are bilateral, without regional predisposition, with different amount of granulomatous inflammation and necrotic tissue at histology. Nodules usually show a good response to treatment; however, they can be complicated by cavitation, especially in case of nodules larger than 2 cm with irregular margins, that can sometimes become infected (12). Bilateral irregular consolidations can

also be detected and generally represent granulomatous inflammation with necrosis and organising pneumonia. They are more frequently detected in wedge-shaped areas of peripheral consolidation abutting the pleura and mimicking pulmonary infarction (13).

Alveolar haemorrhage, with or without capillaritis, rarely represents the clinical onset of GPA, but it is recognised to be another cause of GGO or consolidation in this type of vasculitis. Globally, GGO are described in about 25% of patients (6, 14).

Besides pulmonary parenchymal manifestations, both upper and lower respiratory tracts can be involved in the course of GPA (15, 16). airway involvement is described in 95% of GPA. Many studies report tracheobronchial involvement, namely bronchial wall thickening, bronchiectasis of the small airways, but also segmental and subsegmental bronchial stenoses, expression of inflammatory damage (16). Finally, pleural effusion is considered the most common pleural manifestation in GPA patients; pleuritis, pleural nodules, and pneumothorax have also been described (15) (Table I; 6, 10-18).

*Pulmonary features of eosinophilic granulomatosis with polyangiitis*

EGPA is the least common among AAV with an estimated incidence of 0.5 to 6.8 cases/million (19). EGPA usually shows a prodromal phase, including rhinosinusitis and asthma; an eosinophilic phase with blood and tissue eosinophilia, is usually followed by the vasculitic phase (20). Sometimes, the different stages of disease overlap among them and are not distinguishable.

Asthma is the most common manifestation in EGPA; it can precede the onset of vasculitis by 3–9 years and often fulfils the criteria for severe asthma (21-23).

Eosinophilic pneumonia is relatively frequent in patients with EGPA, but may be underdiagnosed because of the mild clinical manifestations and transient pulmonary infiltrates responsive to corticosteroid therapy (24-26). Hypereosinophilic bronchiolitis may also be observed, and it is characterised by bronchiectasis and airway abnormali-

**Table I.** Airway and pulmonary manifestations in granulomatosis with polyangiitis.

<b>Upper airway manifestations</b>	
Sinusitis	61%
Nasal mucosa ulcers/crusting	up to 70%
Saddle nose	20-50%
Nasal mass	rare
Other (bone deformity)	
<b>Lower airway manifestations</b>	
Strictures and stenosis (usually subglottic)	15%
Bronchiectasis	13-20%
Other (ulcers, inflamed mucosa)	
<b>Pulmonary manifestations</b>	
Cavitated and noncavitated nodules	40-89%
Consolidations	30%
Ground glass opacities	25-50%
Diffuse alveolar haemorrhage	5-10%
<b>Pleural manifestations</b>	
Pleural nodules	rare
Pneumothorax	rare
Pleural effusion	12-20%

**Table II.** Airway and pulmonary manifestations in eosinophilic granulomatosis with polyangiitis.

<b>Upper airway manifestations</b>	
Nasal polyposis	50-76%
Eosinophilic rhinitis	
Chronic/recurrent rhinosinusitis	14-73%
<b>Lower airway manifestations</b>	
Asthma	95-100%
Stenosis	
Bronchiectasis	15-20%
Hypereosinophilic bronchiolitis	
<b>Pulmonary manifestations</b>	
Eosinophilic pneumonia	38-75%
Consolidations/Nodules	11-89%
Ground glass opacities	39-99%
diffuse alveolar haemorrhage	3-8%
<b>Pulmonary manifestations</b>	
Pleural effusion	12-22%

ties, such as centrilobular nodules and bronchial wall thickening (27).

Both vascular inflammation and eosinophilic infiltration contribute to organ damage, but the clinical presentation is heterogeneous and it is commonly characterised by non-specific systemic symptoms, including fever, fatigue, arthralgia and weight loss. Frequently, in patients with a previous history of asthma, EGPA is suspected only after the onset of eosinophilia and vasculitic manifestations (*i.e.* multiple mononeuritis or purpura). Less frequently, asthma can be concurrent to vasculitis or can be absent (28). (Table II; 17-31).

### *Pulmonary features of microscopic polyangiitis*

MPA mainly affects pulmonary and renal small-size vessels, and it is characterised by necrotising inflammation of blood vessels, circulating ANCA and absence of necrotising parenchymal inflammation on histopathology (32).

The prevalence of MPA varies between countries, with an annual incidence estimated as 18.2 cases/million in Japan and 6.5 cases/million in Europe. The mean age at diagnosis is 69 years in Japan and 60 years in the UK, without gender predominance (33, 34).

Although MPA shares several clinical features with GPA, systemic signs, such as weight loss, fever, and arthralgias are less frequent or mild (35). Moreover, differently by GPA, granulomas are always lacking (8).

Diffuse alveolar haemorrhage (DAH) secondary to pulmonary capillaritis is the main lung manifestation of MPA, ranging from incidental finding by imaging or bronchoalveolar lavage (BAL) to life-threatening acute respiratory failure (Fig. 1).

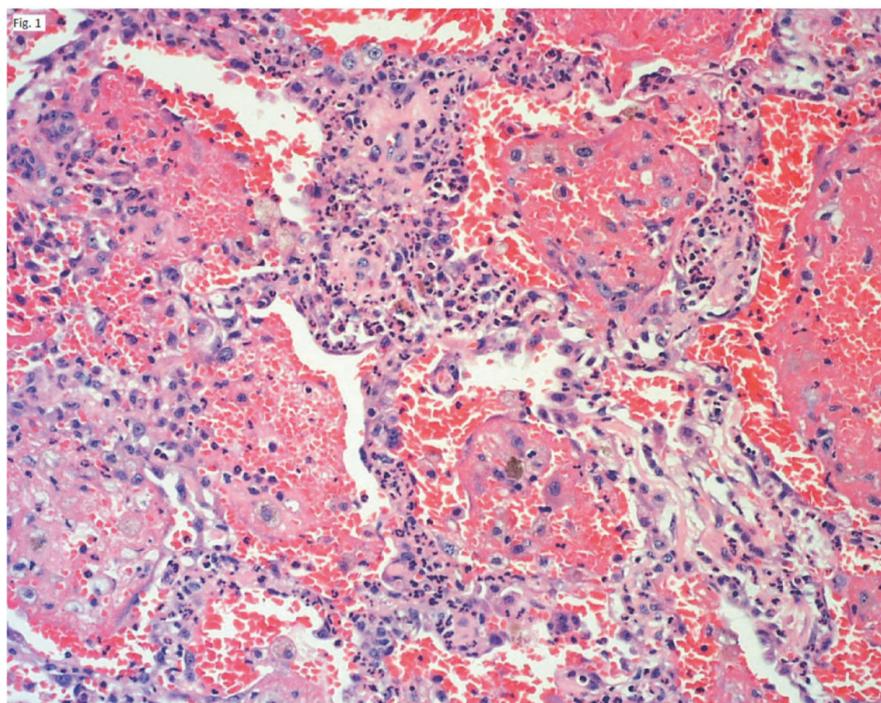
A variable degree of DAH may represent the only lung manifestation of MPA in many patients, with acute or subacute onset; occasionally, a chronic occult DAH at imaging is observed, with siderophages found at BAL (17, 18) (Fig. 2).

Most patients with DAH show dyspnoea progressing over a few days and nonspecific symptoms, such as cough and/or chest pain (18). Haemoptysis is a typical feature when present, but it is lacking in about one-third of cases (36, 37).

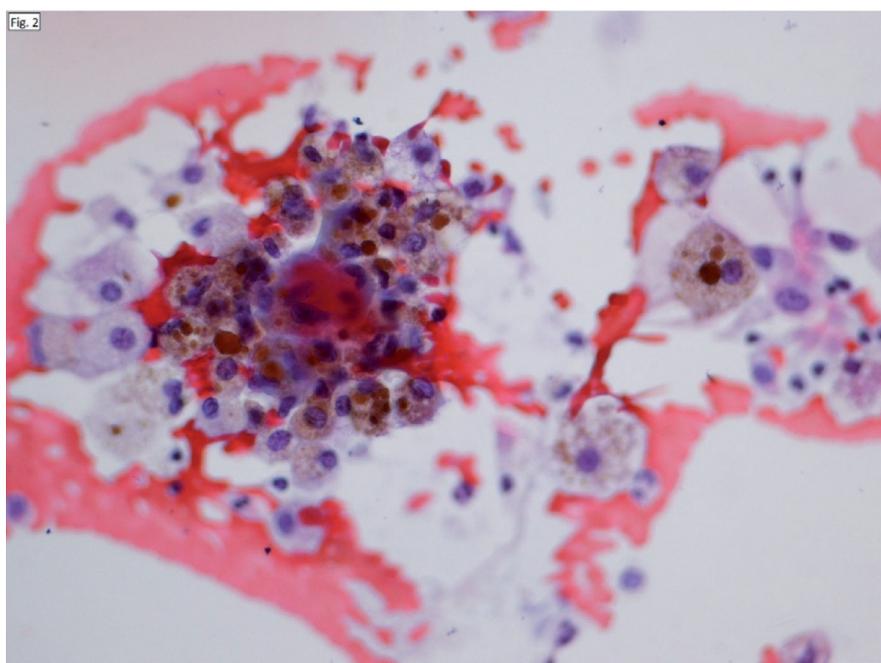
Chest-X-ray and HRCT are usually nonspecific, but the appearance of lung opacities at chest-X-ray and a reduction of haemoglobin or haematocrit over a few days are highly suggestive of DAH, even without haemoptysis (18).

Chest X-Ray may be normal or show patchy or diffuse bilateral airspace opacities and consolidation, usually widespread, sometimes prevalent in the peri-hilar areas and in the mid and lower lung zones (18, 38, 39).

GGO are the key feature at HRCT, without a characteristic distribution, and with patchy or uniform opacities. The presence of dense consolidations



**Fig. 1.** Acute pulmonary haemorrhage in a patient with microscopic polyangiitis, consisting in the intra-alveolar accumulation of fresh blood and fibrin with a few haemosiderin-filled macrophages. Notice the neutrophils in the alveolar septa (capillaritis). Haematoxylin-eosin, 100X.

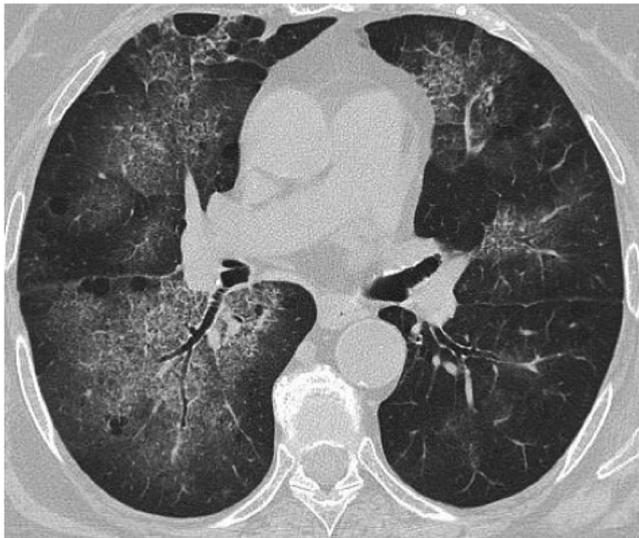


**Fig. 2.** Broncho-alveolar lavage fluid in a patient with ANCA-associated vasculitis presenting with alveolar haemorrhage, showing macrophages with coarse haemosiderin granules. Papanicolaou staining, 400X.

represents complete filling of the alveoli with blood (Fig. 3) (40, 41).

Diagnosis of DAH is usually confirmed by BAL fluid examination, showing erythrocytes, siderophages and excluding a concomitant infection (Fig. 2). An

increasingly haemorrhagic BAL after sequential sampling is specific for DAH and it is the best diagnostic test; when DAH began more than 2 days before, the presence of haemosiderin-laden alveolar macrophages (siderophages)



**Fig. 3.** Microscopic polyangiitis on HRCT. Large patchy area of ground glass opacity in patient predominantly distributed in the right lung. HRCT features are indeed not specific and diagnosis of pulmonary haemorrhage secondary to microscopic polyangiitis can be obtained only with corroboration from clinico-laboratory findings.

**Table III.** Airway and pulmonary manifestations in microscopic polyangiitis.

<b>Upper airway manifestations</b>	%
Sinusitis and nasal mucosa ulcers	rare
<b>Lower airway manifestations</b>	%
Bronchiectasis	32%
Hypereosinophilic bronchiolitis	55%
<b>Pulmonary manifestations</b>	%
Diffuse alveolar haemorrhage	10-55%
Uni- or bilateral pulmonary infiltrates	26-92%
Lung fibrosis/interstitial abnormalities	32-90%

$\geq 20\%$  confirms the diagnosis of DAH (17); the Golde score allows to quantify siderophages and a score  $>100$  is pathognomonic for DAH (42). Trans-bronchial biopsy is not mandatory for diagnosis, but, when performed, it shows a variable combination of blood, acute lung injury (*i.e.* fibrin, organising pneumonia), haemosiderin deposition and capillaritis. Finally, surgical lung biopsy is no longer used for its relative high risk and because it rarely helps to find the cause of bleeding (43). DAH should be always categorised as a severe complication of MPA because of the risk of a rapid progression to a life-threatening condition with a high mortality rate of 10% to 25% (37, 44, 45). An oxygen saturation measured by pulse oximetry (SpO<sub>2</sub>) to fraction of inspired oxygen (FiO<sub>2</sub>) ratio of less than 450 at the disease onset, a C-reactive protein  $>25$  mg/L, and a neutrophils count  $> 30\%$  on the BAL fluid have been identified as independent risk factors for the progression to respiratory failure (44, 45). Therefore,

the SpO<sub>2</sub>:FiO<sub>2</sub> ratio should be evaluated in any MPA patient presenting with dyspnoea or with a pulmonary infiltrate, even if haemoptysis is absent (45). (Table III; 17, 18, 41, 46-48).

### Interstitial lung disease in ANCA-associated vasculitis

#### Epidemiology of interstitial lung disease in ANCA-associated vasculitis

In 1990 Nada *et al.* reported for the first time the presence of ILD in 2 patients with ANCA-associated MPA (49). Subsequently, in 1994, the association between ILD and AAV was confirmed by Arinuma *et al.* in a Japanese study, showing that 43% of 46 MPO-ANCA-positive patients with connective tissue disease or glomerulonephritis showed ILD (50).

Geographic differences have also been described: ILD has been reported more frequently in Japanese cohorts with AAV compared to Western patients (46, 51-55). An increased frequency of alveolar haemorrhage and a higher prevalence of MPO-ANCA antibodies in Japanese patients have been proposed as possible explanation for these differences (56-58). However, considering only MPA patients the prevalence of ILD seems to be similar worldwide (46, 51, 52).

Prevalence of ILD is higher in MPA than in GPA (52, 59, 60); in fact, ILD has been reported in 23% of GPA patients (61) and up to 45% of MPA patients. Anti-MPO antibodies are the

main ANCA subtype associated to ILD, in about 46-71% of cases, while anti-PR3 antibodies are reported in 0-29% of patients (53, 54, 61, 62, 63, 64).

Patients with MPA-ILD show an age at onset similar to idiopathic pulmonary fibrosis (IPF), while MPA patients without ILD are generally younger (66 vs. 55 years, for MPA patients with and without ILD, respectively). There are no conclusive data about gender predominance, even if some series have reported a slight male predominance (60-65%) (46, 49, 51, 52, 59, 62, 63, 65-71). In contrast to other AAV, lung fibrosis is very rare in EGPA, and only one case has been described in 2006 (72).

#### Pathogenesis of interstitial lung disease in ANCA-associated vasculitis

Several hypotheses have been proposed as possible pathogenetic pathways for lung fibrosis in AAV.

Repeated episodes of intra-alveolar haemorrhage have been suggested as a possible trigger for an exuberant reparative mechanism (73-75). Although this hypothesis has not yet been confirmed, markers of chronic alveolar bleeding have been found to be increased in BAL fluid and histologic specimens of AAV-ILD subjects (76-77), unlike patients with ILD related to other autoimmune diseases (75).

Furthermore, MPO-ANCA may play a direct role in the pathogenesis of lung fibrosis (78-80), while PR3-ANCA seems not to be associated to ILD.

MPO-ANCA may contribute to pulmonary tissue injury through the production of major oxidant products, resulting from the activation of MPO (80). Furthermore, ANCA-activated neutrophils locally release proteolytic enzymes, such as elastase (78), or neutrophil extracellular traps (NETs), produced during a distinct form of cell death, named NETosis (81). NETs are able to activate lung fibroblasts and promote their differentiation into myofibroblasts (82).

Pulmonary damage could also be induced by eosinophils, as proven by the report of extensive eosinophilia in specimens of ANCA-IPF (83-85). Moreover, lung fibroblasts might influ-

ence function and survival of eosinophils (84).

On the other side, ILD itself could induce MPO-ANCA production, potentially explaining the appearance of ANCA after the onset of ILD. Tobacco toxicity and chronic lung parenchymal ischaemia could be other relevant factors, stimulating MPO expression in epithelial cells (62, 86-88), while pro-inflammatory cytokines could trigger an autoimmune response against MPO normally expressed by activated neutrophils (87). In predisposed subjects, the consequent production of MPO-ANCA could lead to AAV.

Finally, a Japanese study has recently proposed an association between usual interstitial pneumonia (UIP) pattern in AAV and the single nucleotide polymorphism rs35705950(G/T) in the promotor region of MUC5B, encoding mucin 5B (89). An association between this polymorphism and UIP has been already described in IPF (90) and UIP related to rheumatoid arthritis (91), suggesting a similar pathogenetic pathway for UIP, independently by the associated condition.

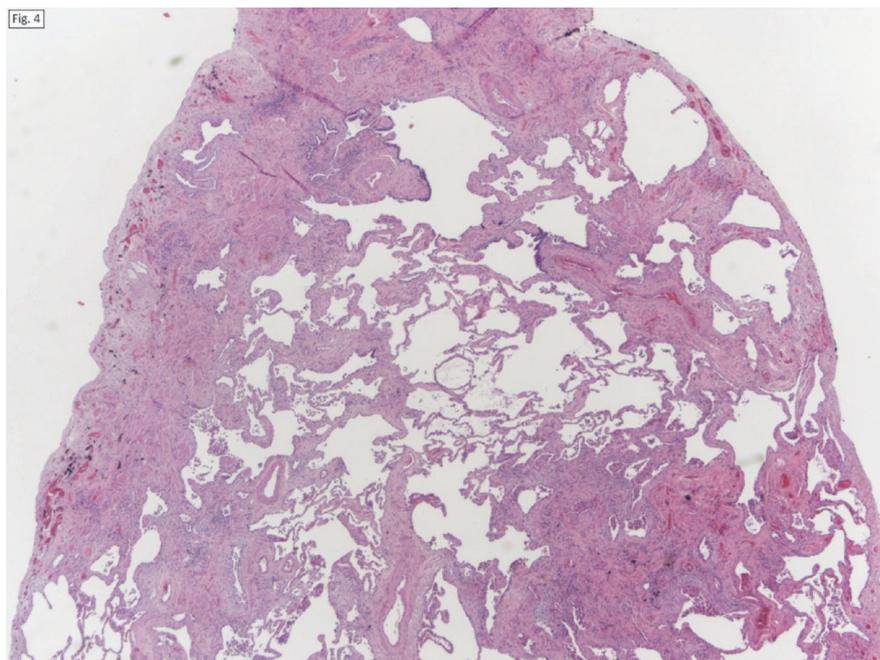
#### *Clinical manifestations of interstitial lung disease in ANCA-associated vasculitis*

Progressive dyspnoea and non-productive cough are the main symptoms of ILD-related to AAV (63, 65, 92, 93), such as in IIPs.

Other possible manifestations are associated with the specific type of vasculitis, particularly alveolar haemorrhage and haemoptysis or constitutional symptoms, such as fever and weight loss (63, 86, 92).

Vasculitic involvement is common in skin (8-31%), peripheral nervous system (8-53%), joints and muscles (23-31%) and kidney (57-100%) in patients with MPA or GPA (Fig. 5) (51, 52, 60, 62, 94).

Interestingly, some authors described less severe systemic involvement in patients with MPA-ILD compared to patients without, namely lower erythro-sedimentation rate, higher haemoglobin levels, a lower frequency of diffuse alveolar haemorrhage, peripheral nerve and kidney involvement (46, 66).



**Fig. 4.** Surgical lung biopsy in a patient with IPF and p-ANCA positivity, developing a vasculitis with features of microscopic polyangiitis. The biopsy shows a classical UIP, consisting in the combination of patchy fibrosis and fibroblastic foci (barely visible at this magnification). This sort of histology is identical to UIP in patients with IPF and no clinical features of vasculitis. Haematoxylin-eosin, 40X.

**Fig. 5.** Surgical lung biopsy in a patient with the combination of IPF and granulomatosis with polyangiitis.

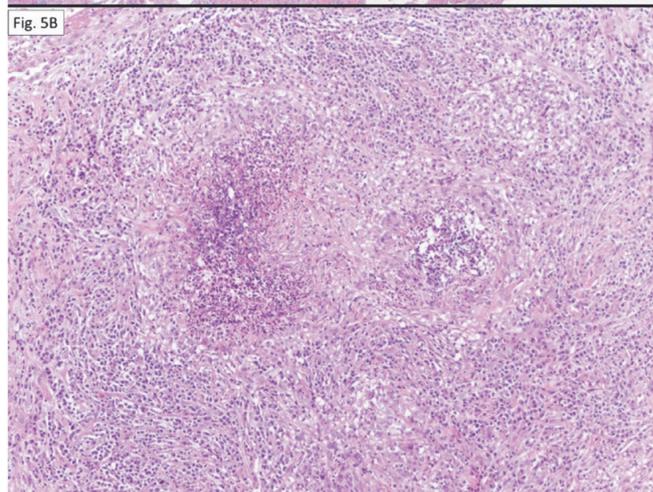
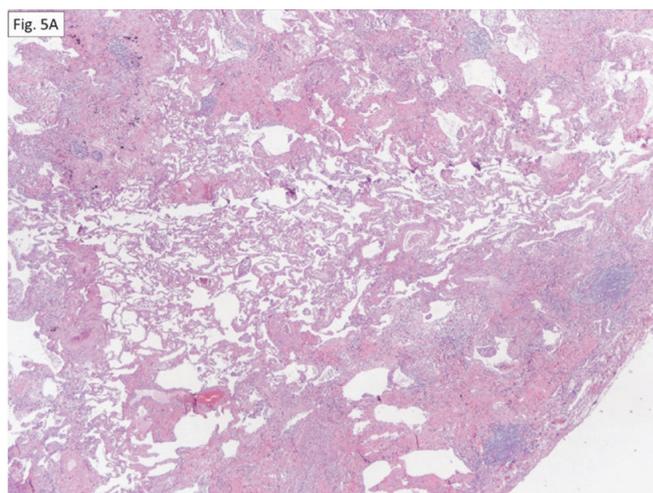
Part of the biopsy shows a fibrosing ILD with UIP pattern, consisting in patchy scarring and fibroblastic foci (A).

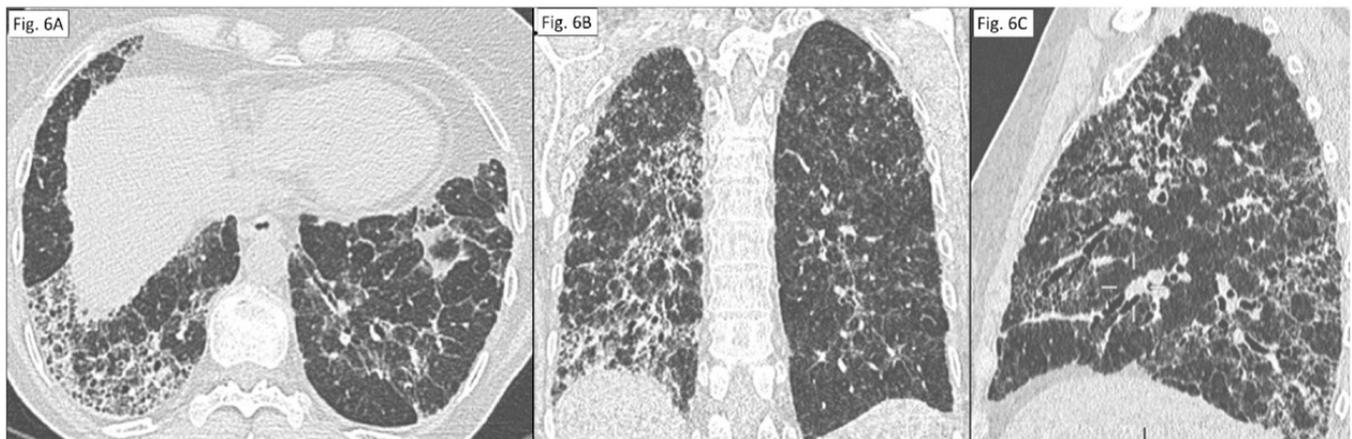
Focally an inflammatory nodule was present, with scattered suppurative foci with palisading histiocytes (B).

p-ANCA were positive and no microorganisms were found.

A: haematoxylin-eosin, 20x.

B: haematoxylin-eosin, 100x.





**Fig. 6.** Pulmonary fibrosis in ANCA-associated vasculitis. Axial CT image (A) shows reticular abnormalities with traction bronchiectasis predominantly distributed in the right lower lobe. Both coronal (B) and sagittal (C) reformatted images more clearly depict the traction bronchiectasis and the widespread distribution of the reticular abnormalities throughout the lung (courtesy of Valentini A, IRCCS Fondazione Policlinico San Matteo, Pavia, Italy).

Among 33 MPA ANCA-positive patients, Tzelepis *et al.* detected ILD in 12 (36%) at disease onset, while only one other developed it later (51, 95). All had renal involvement (necrotising, segmental glomerulonephritis) and, more importantly, patients with ILD had a worse prognosis (51, 95).

#### *Imaging of interstitial lung disease in ANCA-associated vasculitis*

HRCT frequently detects interstitial lung abnormalities (ILAs) in AAV, in particular in MPA patients (96), even if the clinical meaning of ILAs occurring in asymptomatic patients is nowadays difficult to be established (97).

In 150 unselected, untreated MPA cases, HRCT showed at least one lung abnormality in 97% of patients, including ILAs in 66% (98). Interestingly, similar results have been reported in 62 MPO-ANCA positive patients with or without MPA. Among them, 77% showed HRCT abnormalities suggestive for interstitial involvement (99).

GGO are the most frequent findings in MPA patients (up to 90% of patients), but reticulations, interlobular septal thickening and honeycombing are also frequently reported (51, 52, 94, 98, 99). Moreover, airway abnormalities have been reported in 32–55% of cases, mainly bronchiolitis, bronchial wall thickening or bronchiectasis (Fig. 3) (51, 98).

In particular, UIP pattern is described in almost half of patients, while non-specific interstitial pneumonia (NSIP)

is described in less of a third of cases and desquamative interstitial pneumonia in about 15% (46, 51, 52, 59, 60).

In a recent French cohort of AAV and ILD, 38/62 patients (61%) showed an UIP pattern, while the other 24 (39%) a NSIP pattern at HRCT (Fig. 6) (100). Lung disease is usually symmetrical, predominantly involving the lower lobes and the peripheral areas of parenchyma (52, 59, 94, 99).

Combined pulmonary fibrosis with emphysema has also been reported in a few cases of MPA (60, 98, 101, 102). Finally, up to 40% of cases cannot be classified in any specific CT-pattern (46, 51, 52, 59, 60), also because of the coexistence of different patterns in the same patient.

#### *Prognosis of interstitial lung disease*

Many studies comparing MPA patients with and without ILD, reported a reduced survival for patients with ILD (51, 59, 62, 65, 103), with a mortality 2 to 4 times higher in MPA patients with pulmonary fibrosis (66,104) compared to AAV patients without ILD.

Primary causes of death include infections, progressive respiratory failure, and ILD-acute exacerbation (51, 52, 59, 60, 86). In a study by Fernandez Casares *et al.*, respiratory failure was the main cause of death in all MPA-ILD patients (46).

#### **ANCA-positive idiopathic interstitial pneumonias**

In 1999, Becker-Merok *et al.* described a case of IPF that developed in the fol-

lowing year a segmental pauci-immune glomerulonephritis and necrotising vasculitis of the peripheral nerves, including the presence of p-ANCA antibodies, which allowed to make a final diagnosis of MPA (105). In the next years, many other cases have been described (51, 52, 59, 62, 63, 65, 86, 93, 106–108), suggesting the possible association among IPF and MPO-ANCA with or without clinical manifestations for MPA (96). Patients positive for MPO-ANCA with idiopathic interstitial pneumonia (IIP) include individuals in whom ILD precedes MPA (51, 52, 59, 62, 63, 65, 86, 93, 106–108), but, also MPO-ANCA-positive patients that apparently never developed an AAV (64). ANCA can be frequently found in patients with IIPs; MPO-ANCA have been reported in 4–36% of patients with IPF or other IIP, while PR3-ANCA are rarer, being found only in 2–4% of cases (62–64, 86, 93, 94, 106–108). Patients with IPF can develop ANCA antibodies in 5–10% of patients negative at diagnosis (62, 63, 86, 106, 107). In various studies including IPF patients, MPA appeared ranging from 1.7 to 25.7% of patients during the follow-up (63, 86, 109).

ILD occurs concurrently or before the onset of vasculitis in a large proportion of patients. In particular, ILD precedes vasculitis in 14–85% of patients, and appears simultaneously with other organ involvement in 36–67%. Onset of ANCA-associated vasculitis precedes the diagnosis of ILD only in 8–21% of

cases (46, 49, 50, 52, 59, 62, 63, 66, 92, 94, 106, 107, 110-113). The interval between ILD and vasculitis, mainly MPA, may be very broad, ranging from a few months to 12 years.

In 2018, Hozumi *et al.* retrospectively reviewed 305 consecutive patients initially diagnosed as IIPs, identifying at baseline 16 ANCA-MPO-positive subjects, while other 10 patients developed MPO-ANCA in a mean follow-up of 3.9 years, for an overall prevalence of 8.5% (114). Among the 26 MPO positive patients, only 9 developed MPA, with a 5-year cumulative incidence for MPA of 24.3%. Of interest, MPA was more frequent in patients previously diagnosed as IPF (6.2%) rather than other IIPs (1%) (114). Considering only patients with an initial diagnosis of IPF, 11.3% were MPO-ANCA-positive and 40% of these subsequently developed MPA (Fig. 4) (114).

In another retrospective study, 12 patients with MPO-ANCA/UIP were compared with 108 IPF/UIP patients (93). Although this study was limited, by the low number of patients in MPO-ANCA/UIP group, the authors observed no differences in clinical, laboratory, radiological and lung function features at baseline, except a higher percentage of BAL neutrophils in MPO/UIP group ( $p=0.02$ ). Also, survival and frequency of acute exacerbations were the same between the 2 groups (93).

In two different North-American cohorts of IPF, ANCA were positive in 4% and 5.1% of cases, respectively. The 2 groups differed for the prevalence of PR3 antibodies; in the first, they were 57% (8/14 patients), while PR3 were recorded only in 2/20 patients (10%) in the other group. The comparison of clinical features between ANCA-positive and negative IPF patients showed only a prevalence of female sex in ANCA-positive group, but no differences in severity of lung disease at enrolment. However, compared with ANCA-negative IPF, ANCA-positive patients were significantly more likely to have GGO and moderate/severe honeycombing (115).

Finally, patients with pulmonary fibrosis developing MPA had higher ANCA titres than those without vasculitis,

suggesting a predictive value of ANCA on the appearance of vasculitis in IPF patients (63).

Conflicting data have been reported about the possible influence of ANCA on the survival of IPF patients. In fact, many authors described similar survival rates for patients positive or negative for ANCA (53, 62-64, 86, 93, 107). In particular, Zhao *et al.* observed no differences in survival rates at 1, 3 and 5 years between 73 MPA-UIP and 68 IPF patients (116). On the other hand, 5- and 10-year survival was significant lower in ANCA-positive patients in a large cohort of 504 patients with isolated pulmonary fibrosis (105). In this study, the main factors associated with increased mortality were PR3-ANCA, age >65 years and baseline DLCO <70% (105). Moreover, a correlation between ANCA titre and mortality has been reported by various authors (86). Nuzo showed a better survival in the low-titre (<50 EU) than high-titres (>50 EU) group in ANCA-positive lung fibrosis (63).

Finally, an age >65 years at AAV diagnosis, an alveolar haemorrhage at the time of AAV diagnosis and an UIP pattern (compared to NSIP) were independent factors associated with shorter survival in AAV-ILD patients (100).

#### **Therapeutic approach to interstitial lung disease**

Currently, only retrospective case series and a few case reports have been published and no controlled clinical trials have been performed for the treatment of ILD in patients with AAV-ILD or with IIP and isolated ANCA positivity (52, 59, 60, 65, 86, 93, 100, 105).

Despite conflicting data, standard therapy for AAV is considered also as a possible treatment in patients with ILD and includes mainly systemic glucocorticoids, cyclophosphamide, rituximab, mycophenolate mofetil, methotrexate and azathioprine (5). A study on 49 AAV-ILD patients suggested a longer survival for patients treated with glucocorticoids in combination with cyclophosphamide or rituximab compared to glucocorticoids alone (60). On the other hand, immunosuppressants did not improve the prognosis of AAV-ILD in a recent study on 62 patients and

also other reports confirmed the lack of effectiveness of immunosuppressants (52, 59, 65, 100)

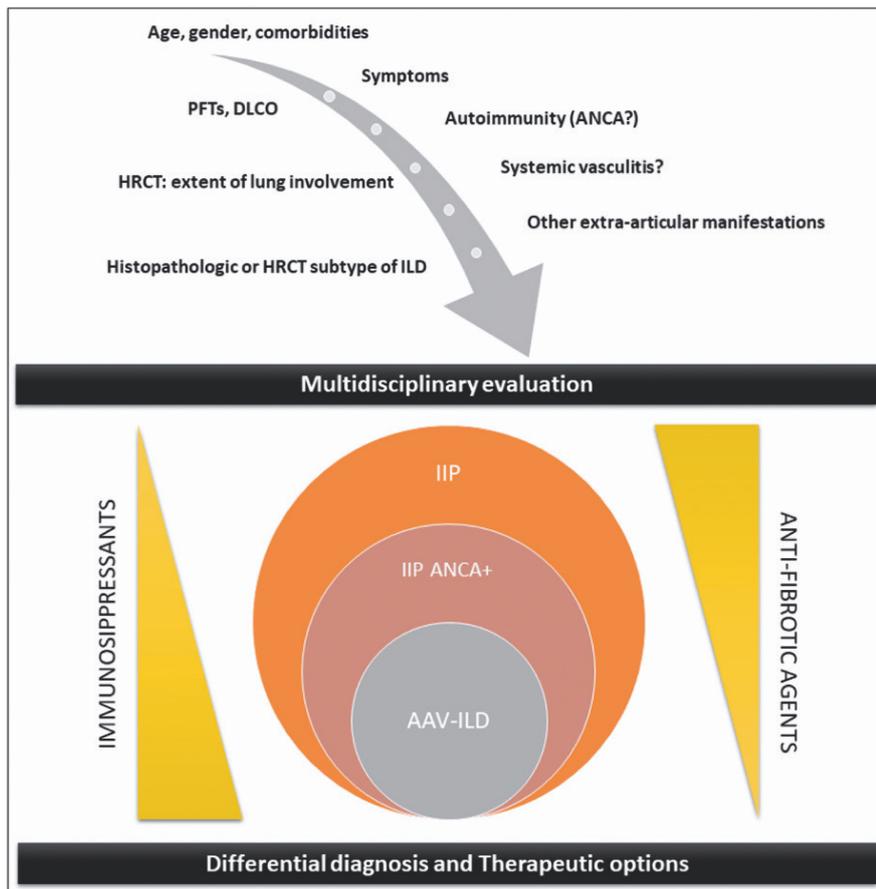
In patients with ANCA-positive ILD without vasculitis, the therapeutic approach should not differ by IIP (117), although some authors suggest the use of immunosuppressive drugs in these patients for a supposed autoimmune aetiology of the disease. Of interest, despite some conflicting data, immunosuppressive therapy administered for ILD does not seem to reduce the risk of subsequent development of AAV (86, 93, 105).

Moreover, in patients with an UIP pattern, the histologic and radiologic similarities with IPF (41, 96), as well as some common aetiopathogenetic background (90), may suggest the use of antifibrotic therapies, namely pirfenidone and nintedanib (118). Furthermore, given both the fibrotic and inflammatory aspects of AAV-ILD, a combination of immunosuppressive and antifibrotic drugs might be an opportunity for possible future therapeutic approaches (118).

A number of trials are currently evaluating the use of nintedanib and pirfenidone in patients with autoimmune fibrosing ILD other than IPF (119-124). Among them, the open-label study PIRFENIVAS is ongoing (NCT03385668) (123) with the aims to evaluate the safety and the effectiveness of pirfenidone in patients with MPO-ANCA-positive pulmonary fibrosis with or without AAV.

An empiric clinical management approach, proposed by the Mayo Clinic, consists in immunosuppressive therapy, according to therapeutic guideline for AAV, for patients with systemic vasculitis, as well as for patients with a NSIP pattern without vasculitis. In patients with a UIP pattern, but without vasculitis, immunosuppressive therapy is avoided and antifibrotic therapy may be considered (125).

In conclusion, a multidisciplinary approach including rheumatologist, pulmonologist, pathologist and radiologist and a careful evaluation of progression and severity of lung involvement, should guide the treatment decision; a “wait and see” approach can be proposed for non-symptomatic, non-progressive ILD patients.



**Fig. 7.** Proposed framework for the management and treatment of ANCA-associated vasculitis patients complicated by ILD. Therapeutic choice should derive by a multidisciplinary approach including rheumatologist, pulmonologist and radiologist. Use of immunosuppressants or, in selected patients, antifibrotic should be evaluated according to the activity and severity of vasculitic manifestations and ILD.

**Proposal for patient management and treatment**

The treatment of AAV-ILD should be tailored for each patient and multidisciplinary approach, including at least rheumatologist, pulmonologist and radiologist, is mandatory to optimise therapy and follow-up strategies. Early diagnosis, functional and radiologic follow-up of the lung involvement are necessary to identify patients with progressive disease (126, 127). In fact, the progression and the severity of ILD are the two main factors to be considered when a decision-making on treatment is requested. Patient’s age, radiologic or histo-pathologic pattern of ILD and subjective symptoms should also be carefully evaluated (128, 129). Moreover, when considering therapeutic options for patients with vasculitis, both pulmonary and extra-thoracic disease manifestations need to be assessed

and taken into account (Fig. 7). Comorbidities should be also considered for their possible influence on the short and long-term safety of the treatment (diabetes mellitus, osteoporosis, etc.) (130). In such challenging condition, given the heterogeneity in disease presentation, the multiple manifestations that may be present, and the broad range of disease severity, coordinated care is essential. In AAV-ILD patients, immunosuppressive drugs are usually the first choice. In particular, cyclophosphamide, mycophenolate mofetil, rituximab or azathioprine have been demonstrated efficacy on AAV and have also showed some evidence in ILD associated to rheumatic diseases (5, 131, 132). According to the results of INBUILD study, in patients with fibrotic pattern of ILD and without significant activity of vasculitis, it is reasonable to pro-

pose the therapeutic strategies for IPF, namely antifibrotic agents such as pirfenidone and nintedanib (117, 119, 133). In patients with fibrotic, progressive ILD and active vasculitis, the results of INBUILD study and some previous observations suggest the possibility of a combination therapy with both immunosuppressants and anti-fibrotic agents (119, 134-136). Finally, in asymptomatic patients with mild, non-progressive ILD, a “wait and see” approach is usually adopted (137).

**Conclusions**

The association between AAV and ILD is well-known, but not always investigated in these patients. Moreover, even if ILD significantly influence the prognosis and the quality of life of patients with AAV, ILD is not included in any activity or severity disease score proposed for AAV (namely BVAS, etc.), suggesting the need to review these scores in the light of the new knowledge on AAV-ILD (138). On the other hand, a search for ANCA is not usually included in the diagnostic work-up of IIP. Interestingly, ANCA have not been included in the research criteria for interstitial pneumonia with autoimmune features (IPAF), because its association with vasculitis rather than connective tissue diseases (139), and the current criteria do not allow to exclude an IPF in ANCA-positive patients with pulmonary fibrosis (139). For all these reasons, ANCA should be investigated in all patients with IIP due to the possible significant prognostic implications, both on survival and on the risk of developing an AAV (46, 49, 51, 52, 59, 62, 63, 66, 92, 94, 104, 105, 108-111). Waiting for the results of ongoing trials, the treatment of AAV-ILD remains an unmet clinical need. The evaluation of the single patient with a multidisciplinary approach including rheumatologist, pulmonologist, pathologist and radiologist is mandatory for a correct classification of these patients. Finally, prospective *ad hoc* study should clarify the natural history of AAV-ILD and the role of ANCA positivity in patients with IIP, other than the better therapeutic approach for the different groups of patients.

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