# Pulmonary Fibrosis in Antineutrophil Cytoplasmic Antibodies (ANCA)-Associated Vasculitis

## A Series of 49 Patients and Review of the Literature

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**Abstract:** Pulmonary fibrosis (PF) is an uncommon manifestation observed in patients with antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV), particularly microscopic polyangiitis (MPA). While patients with PF associated with AAV seem to have a worse prognosis, these patients have been described only in case reports or small retrospective case series. In this retrospective multicenter study, we report the main features and long-term outcomes of patients with PF associated with AAV, fulfilling the American College of Rheumatology criteria and/or Chapel Hill definitions. Forty-nine patients (30 men [61%]; median age at diagnosis of AAV, 68 [interquartile range, 58–73] years) with PF associated with AAV were identified. Forty (81.6%) patients had MPA and 9 (18.4%) had granulomatosis with polyangiitis. The diagnosis of PF preceded the onset of vasculitis in 22 (45%) patients. Usual interstitial pneumonia was the main radiologic pattern (n = 18, 43%). ANCA were mostly of antimyeloperoxidase specificity (88%). All patients were treated with glucocorticoids as induction therapy, combined with cyclophosphamide (CYC) (n = 36, 73.5%) or rituximab (RTX) (n = 1, 2%). Factors associated with mortality included occurrence of chronic respiratory insufficiency (hazard ratio [HR], 7.44; 95% confidence interval [CI], 1.6–34.5; p = 0.003), induction therapy with glucocorticoids alone (HR, 2.94; CI, 1.05–8.33; p = 0.04), and initial weigh loss (HR, 2.83; CI, 1.05–7.65; p = 0.041). The 3-year survival rate in patients treated with glucocorticoids alone or combined with an immunosuppressant (CYC or RTX) as induction therapy was 64% (95% CI, 41–99) and 94% (95% CI, 86–100), respectively (p = 0.03). After a median follow-up of 48 months [interquartile range, 14–88 mo], 18 (37%) patients died, including 11 related to respiratory insufficiency. PF is a rare manifestation of AAV with a very poor prognosis. Induction therapy with CYC might improve the outcome.

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**Abbreviations**: ANCA = antineutrophil cytoplasmic antibodies, AAV = antineutrophil cytoplasmic antibodies-associated vasculitides, BAL = bronchoalveolar lavage, CI = confidence interval, CPFE = combined pulmonary fibrosis-emphysema, CYC = cyclophosphamide, EGPA = eosinophilic granulomatosis with polyangiitis, GPA = granulomatosis with polyangiitis, HR = hazard ratio, HRCT = high-resolution computed tomography, IQR = interquartile range, MPA = microscopic polyangiitis, MPO = myeloperoxidase, NSIP = nonspecific interstitial pneumonia, PF = pulmonary fibrosis, RA = rheumatoid arthritis, RTX = rituximab, UIP = usual interstitial pneumonia.

## INTRODUCTION

ANCA-associated *vasculitides* (AAV) are a type of systemic necrotizing vasculitis affecting small- and medium-sized vessels and can be associated with the presence of antineutrophil cytoplasmic antibody (ANCA).[22] AAV represent a

heterogeneous group of diseases including microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA, formerly Wegener's), and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome). The specific clinical phenotypes of these 3 distinct AAV are often distinguished based on initial presentation and ANCA specificity. Because of therapeutic considerations involving the use of glucocorticoids alone or combined with cyclophosphamide (CYC) or rituximab (RTX), the identification of characteristics at AAV diagnosis as prognostic factors is a major concern for clinicians. Conventional treatment of AAV includes a strategy of remission induction using glucocorticoids alone or combined with CYC or RTX,[23,36] depending on characteristics at AAV diagnosis and the severity of initial manifestations that are not consensually defined,[14] followed by maintenance therapy using azathioprine or methotrexate.[32]

Pulmonary fibrosis (PF) occurs in variable frequency in connective tissue diseases such as systemic sclerosis, rheumatoid arthritis (RA), polymyositis/dermatomyositis, and mixed connective tissue disease, and is often associated with a poor prognosis.[7,10,16,24] PF is an uncommon manifestation also observed in patients with AAV, particularly microscopic polyangiitis.[13,17,20,31,41] Patients with PF and AAV have been reported only in different small retrospective case series but tend to share characteristics such as male predominance, older age, the presence of myeloperoxidase (MPO)-ANCA, usual interstitial pneumonia (UIP) pattern, and poor prognosis. However, the pathogenesis of PF in AAV, the outcome and the possible link between PF, ANCA positivity and specificity, and vasculitis remain unclear. Moreover, the impact of therapeutic strategies on outcome of patients with PF and AAV has been analyzed only sporadically.

We conducted the current study to describe the main features and the long-term outcome of PF in AAV in a cohort of 49 patients.

## METHODS

### Patients

This retrospective multicenter study is based on 49 AAV patients with PF diagnosed and followed up in 16 medical centers, between January 1996 and June 2013. All patients were diagnosed as having AAV based on clinical, biological, radiologic and histologic findings (histologic evidence of small vessel vasculitis or segmental pauci-immune necrotizing glomerulonephritis), and according to the American College of Rheumatology criteria and/or Chapel Hill definitions.[21,22] The diagnosis and type of AAV were validated by the investigators (CC and DS), taking into account the entire follow-up period. The diagnosis and type of PF were validated by 2 radiologists (ALB and PG), experienced in interstitial lung disease. Baseline characteristics and outcome of pulmonary involvement and AAV were recorded. Patients with lung fibrosis with the presence of isolated ANCA but without evidence of systemic manifestation of vasculitis were excluded.

### High-Resolution Computed Tomography (HRCT) Evaluation

The characterization of the PF pattern was made by 2 chest radiologists (ALB and PG), and was based on the international consensus.[1] The 2 radiologists (ALB and PG) were blinded to the clinical and histopathologic data, however, they were aware

that the patients had PF and AAV. PF was defined as the presence of ground-glass opacities, reticular pattern, intralobular lines, traction bronchiectasis or honeycombing which persisted on repeat CT examination.[25,33] For each patient, HRCT patterns were classified as UIP, atypical UIP, combined PF-emphysema (CPFE), or nonspecific interstitial pneumonia (NSIP) with or without fibrosis. HRCT patterns were considered as UIP according to the following criteria: reticular pattern predominating associated with honeycombing in the subpleural areas of the lung bases. Atypical UIP were defined as bilateral and peripheral reticular pattern without honeycombing or bilateral honeycombing without lower lung predominance or honeycombing associated with ground glass opacity. CPFE were defined as emphysema predominating in the upper lobes and frequently, paraseptal and interstitial abnormalities suggesting PF in the lower lung zones. The HRCT pattern of NSIP was defined as ground-glass opacity predominant more or less associated fine reticulation without traction bronchiectasis or bronchiolectasis, without loss of the lung volume and without honeycombing. Fibrotic NSIP corresponded to reticular opacity predominant more or less associated with ground-glass opacity, with traction bronchiectasis or bronchiolectasis more or less associated with loss of lung volume, and absence of honeycombing. Then, the extension of the PF was evaluated according to MacDonald SL et al.[26] The chest radiologists scored (to the nearest 5%) the total extent of abnormal parenchyma (regardless of pattern) at 5 preselected levels: (a) origins of great vessels, (b) aortic arch, (c) carina, (d) between c and e, and (e) 1 cm above the dome of the right hemidiaphragm. These scores were then summed, and the mean was used for analysis. Where a reticular pattern was identified, a coarseness score was assigned as follows: grade 1, fine intralobular fibrosis predominating; grade 2, microcystic pattern with airspaces less than 3 mm in diameter; and grade 3, large cysts 3–6 mm in diameter. Scores were then summed (maximum score, 15).

### Literature Review

We performed a Medline (National Library of Medicine, Bethesda, MD) search using the term "microscopic polyangiitis" or "Wegener" or "granulomatosis with polyangiitis" or "Churg Strauss syndrome" or "ANCA" or "vasculitis" and "lung fibrosis" or "pulmonary fibrosis" or "interstitial pneumonia" to identify all articles published online, and we systematically searched the reference sections of these articles for further references. Our systematic literature search was limited to the English language. All published cases of AAV were then searched for descriptions of lung fibrosis characterized histologically, clinically, and/or radiologically. Using the data available in these articles, we tried to determine the frequency and main characteristics of lung fibrosis in AAV.

### Statistical Analysis

Data are expressed as median and interquartile range [IQR] for quantitative variables or counts and percentage (%) for categorical variables. Comparison between quantitative variables was performed using the nonparametric paired Wilcoxon test, and the Fisher exact test for categorical variables. Patient survival was analyzed using the Kaplan-Meier method and was compared using log rank tests. P values of less than 0.05 were considered to be significant. Tests were performed using SPSS Statistics v 17.0 for Windows (Chicago, IL).

# RESULTS

## Characteristics of Patients at Diagnosis of Vasculitis

We identified 49 patients with PF associated with AAV. Their demographic characteristics and main clinical manifestations at diagnosis are shown in Table 1. The median [IQR] age at diagnosis of AAV was 68 [58–74] years, with a male predominance (n = 30, 61%). Forty (82%) patients had MPA and 9 (18%) had GPA. No patients had EGPA. The diagnosis of PF preceded the onset of vasculitis in 22 (45%) patients, was concomitant in 21 (43%) and occurred subsequently in 6 (12%). The most common AAV manifestations at diagnosis included asthenia (63%), renal manifestations (57%), fever (52%), peripheral neuropathy (53%), and weight loss (52%). Alveolar hemorrhage defined by at least 20% of siderophages, was diagnosed in 23 (49%) patients, 14 of them had both alveolar hemorrhage and renal manifestations (only 7 were considered to have pulmonary-renal syndrome).

At diagnosis of AAV, one-third of patients had hypereosinophilia (that is, eosinophil count $\geq 500/mm^3$) (n = 15, 30.6%). Thirty-six (73%) patients had an inflammatory syndrome (that is, C-reactive protein >5 mg/L). All patients were tested for ANCA. Only 1 patient was ANCA negative and remained ANCA negative during the entire follow-up. Forty-three (88%) patients had MPO-ANCA. Two (4%) patients had proteinase 3-ANCA. Three (7%) patients had ANCA with unidentified specificity. Thirty-six of 49 (73.5%) had histologic findings supporting a diagnosis of AAV (vasculitis, granuloma, and/or pauci-immune necrotizing glomerulonephritis). Nineteen had kidney biopsies (sensitivity 17/19 = 89.5%). Nine underwent muscle biopsy (sensitivity 7/9 = 77.8%), 4 underwent nerve and muscle biopsies, 4 had nerve biopsy (both sensitivity 8/8 = 100%). Four had skin biopsy and 1 had ear, nose, and throat biopsy (sensitivity 3/4 = 75% and 1/1 = 100%, respectively). Two out of 4 with open lung biopsy had histologic findings supporting AAV (granuloma and/or capillaritis) and 1 other showed UIP.

## HRCT Patterns, Pulmonary Function Results, and Bronchoalveolar Lavage

Pulmonary characteristics at AAV diagnosis are summarized in Table 1 and Figure 1. The initial thoracic HRCT of 42/49 patients with PF and AAV were retrospectively reviewed. The HRCT pattern included typical UIP (n = 18, 43%), atypical UIP (n = 6, 14%), fibrotic NSIP (n = 3, 7%), CPFE (n = 9, 21.4%), NSIP (n = 4, 9.5%), and indeterminate (neither UIP nor NSIP although reticulation was present) in the remaining patients (n = 2, 4.8%) (see Figure 1). Patients with NSIP had a younger age at diagnosis of PF compared to patients with typical UIP or atypical UIP or fibrotic NSIP (median age, 47.5 [IQR, 35–58.5] vs 67 [IQR, 64–74.5 yr] years, respectively; p = 0.017). Patients with NSIP and CPFE had a lower coarseness score compared to patients with typical UIP or atypical UIP or fibrotic NSIP (median coarseness score of 4 [IQR, 2.25–5] and 6.5 [IQR, 6–8.25] vs 10 [IQR, 8–13], respectively; p = 0.015). A restrictive ventilatory defect at AAV diagnosis, as shown by a decrease of at least 20% of predicted total lung capacity, was observed in 33 out of 41 patients (80%) but was not associated with an increased risk of mortality (see Table 1). Despite the absence of statistically significant differences, total lung capacity and diffusing capacity for carbon monoxide at diagnosis tended to be more severely decreased in patients who died at the end of follow-up (see Table 1). We were able to follow-up total lung capacity in 22 patients, including 15 patients with lung disease relatively stable and 7 patients with progressive lung disease. Bronchoalveolar lavage (BAL) was performed in 33 patients. We found that 23 (70%) patients had siderophages in BAL.

## Long-Term Outcome

After a median follow-up of 48 [IQR, 14–88] months, vasculitis relapses occurred in 18 (37%) patients (Table 2). Among 31 cumulative relapses, we observed 7 (22.6%) with renal involvement and 4 (13%) with pulmonary-renal syndrome. At the end of follow-up, the median last dose of glucocorticoids was 15 [IQR, 6.5–30] mg/d. During follow-up, 13 (27%) patients had chronic respiratory insufficiency (that is, patients required long-term oxygen therapy), underlying the importance of respiratory damage in this patient population. Eighteen patients died, including 11 (61%) deaths caused by respiratory insufficiency. Among those who died from respiratory insufficiency, progressive lung fibrosis with respiratory failure was found to be the cause of death in 9 patients, including 2 evident fatal complications (1 pneumothorax and 1 pneumomediastinum). Respiratory infection of an immunocompromised patient was the cause of death in 2 other patients, including 1 Pneumocystis pneumonia after 2 months of initial treatment by glucocorticoids alone, and 1 cytomegalovirus pneumonia after 3 months of initial treatment by glucocorticoids combined with CYC. Other causes of death included kidney failure (n = 1, 5.5%) related to the vasculitis, myocardial infarction (n = 1, 5.5%), and unknown origin (n = 5, 28%).

## Factors Associated With Mortality

Factors associated with an increase rate of death (Table 3) included occurrence of chronic respiratory insufficiency (hazard ratio [HR], 7.44; 95% confidence interval [CI], 1.6–34.56; p = 0.003), induction therapy with glucocorticoids alone (HR, 2.94; 95% CI, 1.05–8.33; p = 0.04), weight loss (HR, 2.83; 95% CI, 1.05–7.65; p = 0.041), a higher eosinophil count at AAV diagnosis (HR, 1.32; 95% CI, 1.07–1.63; p = 0.0084), older age at diagnosis of AAV (HR, 1.09; 95% CI, 1.03–1.16; p = 0.004), and older age at diagnosis of PF (HR, 1.08; 95% CI, 1.02–1.13; p = 0.005).

## Treatment Regimen and Survival in PF-AAV

All patients were treated with glucocorticoids as induction therapy (n = 49, 100%), alone (n = 12, 24%) or combined with CYC (n = 36, 73.5%) or RTX (n = 1, 2%).

Overall survival was 88.7% (95% CI, 79.9–98.66) at 1 year, 86.3% (95% CI, 76.7–97.2) at 3 years, and 65.9% (95% CI, 52.1–83.3) at 5 years (Figure 2A). The 1-year survival rate in patients who received glucocorticoids combined with CYC or RTX as induction therapy was 94.1% (95% CI, 86.5–100.0) versus 73.3% (95% CI, 51.5–100.0) for those who received glucocorticoids alone, of 94.1% (95% CI, 86.5–100.0) versus 64.2% (95% CI, 41.3–99.6) at 3 years, and of 71.4% (95% CI, 56.2–90.6) versus 51.3% (95% CI, 27.6–95.5) at 5 years, p = 0.03, (Figure 2B). Maintenance therapy included azathioprine (n = 26, 53%), methotrexate (n = 3, 6%), mycophenolate mofetil (n = 7, 14%), or intravenous immunoglobulin (n = 2, 4%).

## Literature Review

To our knowledge, to date only 5 retrospective case-control studies,[13,17,20,31,41] 5 series,[9,18,29,30,34] and 9 case

**TABLE 1.** Baseline characteristics at vasculitis diagnosis of the 49 patients with PF and AAV, and according to mortality

| Characteristic | All (n = 49) | Alive (n = 31) | Dead (n = 18) | P |
|---|---|---|---|---|
| Age at diagnosis of AAV, median [IQR] years | 68 [58−73] | 66 [57−69] | 73 [66−79] | *0.004* |
| Age at diagnosis of PF, median [IQR] years | 66 [57−72] | 64 [56−68] | 71.5 [65−79] | *0.004* |
| Chronology of PF diagnosis in relation to AAV diagnosis | | | | 0.976 |
| Before AAV, n (%) | 22 (45) | 14 (45) | 8 (44) | |
| Same time, n (%) | 21 (43) | 13 (42) | 8 (44) | |
| After AAV, n (%) | 6 (12) | 4 (13) | 2 (11) | |
| Period between PF and AAV, median [IQR] months | 2 [0−24] | 5 [0−24] | 0 [0−16] | |
| Gender, male (%) | 30 (61.2) | 18 (58) | 12 (67) | 0.551 |
| Type of AAV : MPA / GPA, n (%) | 40 (82) / 9 (18) | 24 (77) / 6 (19) | 15 (83) / 3 (17) | 0.815 |
| Smoking history, n (%) | 26 (53) | 16 (52) | 10 (56) | 1.000 |
| Fever, n (%) | 25 (52) | 14 (45) | 11 (65) | 0.195 |
| Fatigue, n (%) | 31 (63) | 18 (58) | 13 (72) | 0.322 |
| Weight loss, n (%) | 25 (52) | 15 (48) | 10 (59) | 0.489 |
| Arthralgias, n (%) | 14 (29) | 12 (39) | 2 (12) | 0.095 |
| Myalgias, n (%) | 19 (39) | 14 (45) | 5 (28) | 0.229 |
| Renal manifestations, n (%) | 28 (57) | 19 (61) | 9 (50) | 0.441 |
| Central nervous system, n (%) | 1 (2) | 1 (3) | 0 | 1.000 |
| Peripheral neuropathy, n (%) | 26 (53) | 15 (48) | 11 (61) | 0.390 |
| Cutaneous manifestations, n (%) | 15 (31) | 12 (39) | 3 (17) | 0.107 |
| Cardiac involvement, n (%) | 2 (4) | 2 (6) | 0 | 0.526 |
| Gastrointestinal involvement, n (%) | 5 (10) | 3 (10) | 2 (11) | 1.000 |
| Ear, nose and throat involvement, n (%) | 11 (22) | 8 (26) | 3 (17) | 0.724 |
| Eye involvement, n (%) | 3 (6) | 2 (6) | 1 (6) | 1.000 |
| Pulmonary-renal syndrome, n (%) | 7 (14) | 5 (16) | 2 (11) | 1.000 |
| Hemoptysia, n (%) | 5 (10) | 4 (13) | 1 (6) | 0.639 |
| Chronic cough, n (%) | 21 (43) | 11 (35) | 10 (56) | 0.171 |
| Dyspnea, n (%) | 38 (78) | 24 (77) | 14 (78) | 1.000 |
| Crackles, n (%) | 36 (75) | 23 (77) | 13 (12) | 0.743 |
| Revised FFS | | | | 0.880 |
| FFS = 0 | 13 (27) | 8 (26) | 5 (28) | |
| FFS ≥ 1 | 36 (73) | 23 (74) | 13 (72) | |
| Creatinine (μmol/L) | 100 [71−180] | 103 [80−200] | 100 [70−142] | 0.280 |
| Clearance of creatinine, ml/min/1.73 m$^2$ | 63 [32−80] | 56 [25−75] | 67 [59−94] | 0.065 |
| CRP, mg/liter | 79 [31−116] | 79 [26−117] | 69 [39−114] | 0.977 |
| ESR, mm/first hour | 65 [45−82] | 57 [37−73] | 75 [60−97] | 0.818 |
| Hemoglobin, g/dl | 10.9 [9.8−12.8] | 10.9 [9.6−13] | 10.7 [10.4−11.3] | 0.586 |
| Platelets, /mm$^3$ | 336000 [268000−449000] | 313000 [268000−387500] | 382500 [282200−473500] | 0.239 |
| Leucocytes, /mm$^3$ | 9300 [7835−12450] | 8555 [7475−12420] | 10940 [9085−13100] | *0.036* |
| Lymphocytes, /mm$^3$ | 1595 [1233−2000] | 1600 [1400−2000] | 1490 [1108−2002] | 0.603 |
| Eosinophils, /mm$^3$ | 470 [114−718] | 250 [96−610] | 661 [278−949] | *0.041* |
| ANCA titer, UI/liter | 134 [76-184] | 135 [76−181] | 100 [78−568] | 0.571 |
| ANCA specificity, n (%) | | | | |
| pANCA | 33 (83) | 24 (83) | 9 (82) | 1.000 |
| cANCA | 6 (15) | 5 (17) | 1 (9) | 1.000 |
| MPO-ANCA | 43 (88) | 28 (90) | 15 (83) | 0.676 |
| PR3-ANCA | 2 (4) | 1 (3) | 1 (6) | 1.000 |
| unidentified | 3 (7) | 2 (7) | 1 (6) | 1.000 |
| ANCA negative | 1 (2) | 0 | 1 (6) | 1.000 |
| Bronchoalveolar lavage (n = 33) | | | | |
| cellularity, median [IQR] | 215000 [130000−350000] | 200000 [130000−322500] | 290000 [170000−445000] | 0.224 |
| macrophage, median [IQR] % | 73 [61−87] | 73 [61−89] | 68.5 [57.5−79] | 0.155 |
| neutrophils, median [IQR] % | 7 [3.5−17.5] | 7 [4.5−13.5] | 5.5 [1−22] | 0.569 |
| lymphocytes, median [IQR] % | 7 [4−12] | 6 [4.5−10.5] | 8 [3.5−12] | 0.982 |
| eosinophils, median [IQR] % | 2 [0−4] | 2 [0−4] | 1.5 [0−7] | 0.741 |
| siderophages, n (%) | 23 (70) | 16 (55) | 7 (39) | 0.300 |
| Restrictive findings on pulmonary function testing (n = 41) | 33 (80) | 21 (75) | 12 (92) | 0.398 |
| PFT findings | | | | |
| Total lung capacity, median [IQR] % predicted | 60.5 [60−85.75] | 79 [64.5−90.5] | 64.5 [43.75−80.75] | 0.156 |
| DLco, median [IQR] % predicted | 70.5 [55.25−80.25] | 74 [59.75−81.5] | 59 [43−70] | 0.082 |
| Forced vital capacity, median [IQR] % predicted | 74 [56.5−90] | 74 [56−95.25] | 84.5 [61−93.75] | 0.925 |
| FEV $_1$, median [IQR] % predicted | 76 [60.5−87.5] | 76 [62.75−93.25] | 80 [57.5−86] | 0.613 |
| FEV $_1$/FVC, median [IQR] % predicted | 78 [71.25−84.75] | 79.5 [74.75−87] | 76.5 [64.9−83.5] | 0.280 |
| Radiological patterns (n = 42) | | | | |
| Typical UIP, n (%) | 18 (43) | 12 (28.6) | 6 (14.3) | 1.000 |
| Atypical UIP, n (%) | 6 (14) | 4 (9.5) | 2 (4.8) | 1.000 |
| Fibrotic NSIP, n (%) | 3 (7) | 1 (2.4) | 2 (4.8) | 0.222 |
| NSIP, n (%) | 4 (9.5) | 3 (7.1) | 1 (2.4) | 1.000 |

**TABLE 1.** *Continued*

| Characteristic | All (n = 49) | Alive (n = 31) | Dead (n = 18) | P |
|---|---|---|---|---|
| CPFE, n (%) | 9 (21.4) | 8 (19) | 1 (2.4) | 0.232 |
| Unclassified, n (%) | 2 (4.8) | 1 (2.4) | 1 (2.4) | 0.528 |
| Extent, % | 8 [5−25] | 8 [5-25] | 6.5 [5.5-28] | 0.334 |
| Coarseness, (score /15) | 8 [5.5−10.5] | 8.5 [6-11] | 8 [5-9] | 0.816 |

Results are shown as number (%) or median [IQR].

Abbreviations: AAV = ANCA-associated vasculitis; CPFE = combined pulmonary fibrosis and emphysema; CRP = C reactive protein; DLco = diffusing capacity for carbon monoxide; ENT = ear, nose and throat; ESR = erythrocyte sedimentation rate; FEV 1 = forced expiratory volume in one seconde; FVC = forced vital capacity; NSIP = non specific interstitial pneumonia; PF = pulmonary fibrosis; PFT = pulmonary function test; SNG = segmental necrotizing glomerulonephritis; UIP = usual interstitial pneumonia.

reports[3–5,12,27,35,37,39,42] have been published. We excluded 7 articles: 1 case series of 2 patients in Japanese,[34] 3 case reports in Japanese,[38,40,43] 1 case report in French,[37] 1 case report in Spanish,[12] and 1 Chinese study[8] that included 15 (28%) patients with PF associated with GPA with MPO-ANCA, but data were insufficient concerning specific characteristics of patients with PF-GPA. In the literature limited to the English language (Table 4), a series of 65 patients with PF and AAV was available for analysis. Common demographic characteristics included age older than 65 years at diagnosis of AAV and a slight male predominance (65%). The diagnosis of PF preceded the development of vasculitis in 29 (54.7%) patients, was concomitant in 21 (39.6%), and occurred subsequently in 3 (5.6%). The most frequent extrapulmonary organ involved during AAV was the kidney (88%), followed by muscles in 23% and neuropathy in 18%. PF was diagnosed before AAV in 57%, at the same time in 38% and after in 5%. Radiologic patterns described were UIP in 83%, NSIP in 13%, and CPFE in 4%. ANCA had perinuclear and/or myeloperoxidase specificity in 94%. Seventy-two percent of patients received glucocorticoids combined with CYC as induction therapy. After a follow-up of 45 months, PF progressed in 35% and was stable or improved in 65%. Precise details on induction therapy received were available for 43 of 65 patients. Thirty-one (72%) patients received glucocorticoids combined with CYC as induction therapy. Deaths were 1.7-fold more frequent in patients who received glucocorticoids alone compared to those who received glucocorticoids combined with CYC as induction therapy: 10/12 (83%) versus 15/31 (48%), respectively. The global mortality rate was high (n = 32, 56%), mainly related to respiratory insufficiency (n = 14, 44%).

## DISCUSSION

PF is an uncommon but severe and therapeutically challenging manifestation of patients with AAV. However,
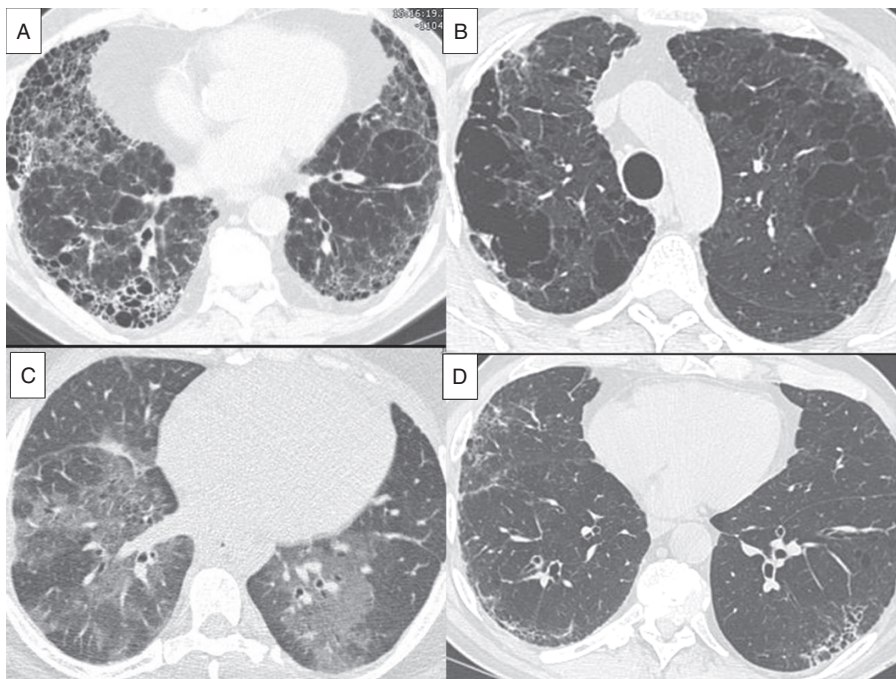


**FIGURE 1.** Representative high-resolution computed tomography showing typical features of the 3 major patterns of PF associated with AAV. Predominantly basal, subpleural reticular pattern with macrocystic honeycombing lesions in usual interstitial pneumonia (A). Centrilobular and paraseptal emphysema predominating in the upper lobes (B). Ground-glass opacities in a patchy distribution in nonspecific interstitial pneumonia (C), and reticular subpleural changes in the lower lobes, associated with few microcystic lesions suggesting honeycombing (D) in combined pulmonary fibrosis and emphysema syndrome.

**TABLE 2.** Induction therapy and outcome of the 49 patients with PF associated to AAV

|  | All (n = 49) |
| --- | --- |
| Induction therapy |  |
| Corticosteroids | 49 (100) |
| Cyclophosphamide | 36 (73.5) |
| Rituximab | 1 (2) |
| Plasma exchange | 3 (7) |
| Follow-up (months) | 48 [14−88] |
| Outcome |  |
| Relapses, n (%) | 18 (36.7) |
| End stage renal disease, n (%) | 4 (8.7) |
| Chronic respiratory insufficiency, n (%) | 13 (27) |
| Death, n (%) | 1 (36.7) |
| Causes of death |  |
| Respiratory insufficiency, n (%) | 11 (61) |
| Unknown origin, n (%) | 5 (28) |
| Renal insufficiency, n (%) | 1 (5.5) |
| Myocardial infarction, n (%) | 1 (5.5) |

Abbreviations: AAV = ANCA-associated vasculitis; PF = pulmonary fibrosis.

**TABLE 3.** Factors associated with death in patients with PF associated to AAV

| Parameters | HR (95% CI) | P |
| --- | --- | --- |
| Age at diagnosis of AAV | 1.09 (1.03-1.16) | *0.004* |
| Age at diagnosis of PF | 1.08 (1.02-1.13) | *0.005* |
| Gender | 1.18 (0.44-3.15) | 0.75 |
| Type of AAV | 0.57 (016-1.99) | 0.38 |
| Smoking history | 1.21 (0.48-3.07) | 0.69 |
| Fever | 1.96 (0.72-5.33) | 0.19 |
| Fatigue | 2.59 (0.92-7.34) | 0.073 |
| Weight loss | 2.83 (1.05-7.65) | *0.041* |
| Arthralgias | 0.29 (0.07-1.27) | 0.1 |
| Myalgias | 0.52 (0.18-1.45) | 0.21 |
| Renal manifestations | 0.72 (0.28-1.82) | 0.49 |
| Peripheral neuropathy | 2.08 (0.8-5.41) | 0.13 |
| Cutaneous manifestations | 0.46 (0.13-1.61) | 0.23 |
| Gastrointestinal involvement | 0.91 (0.21-4) | 0.9 |
| Ear, nose and throat involvement | 0.59 (0.17-2.07) | 0.41 |
| Eye involvement | 0.9 (0.12-6.92) | 0.92 |
| Pulmonary-renal syndrome | 0.83 (0.19-3.66) | 0.81 |
| Hemoptysia | 0.69 (0.09-5.22) | 0.72 |
| Chronic cough | 2.51 (0.94-6.69) | 0.067 |
| Dyspnea | 1.16 (0.38-3.56) | 0.79 |
| Crackles | 1.89 (0.65-5.48) | 0.24 |
| Revised FFS | 1.2 (0.67-2.14) | 0.54 |
| Clearance of creatinine, ml/min/1.73 m² | 1.01 (1-1.03) | 0.11 |
| CRP, mg/liter | 1 (0.99-1.01) | 0.9 |
| Hemoglobin, g/dl | 0.96 (0.8-1.14) | 0.64 |
| Eosinophil count, /mm³ | 1.32 (1.07-1.63) | *0.0084* |
| Restrictive findings on pulmonary function testing at diagnosis | 1.44 (0.18-11.21) | 0.73 |
| Radiological patterns |  |  |
| UIP or atypical UIP or fibrotic NSIP | 5.01 (0.63-39.92) | 0.13 |
| NSIP | 3.54 (0.21-58.61) | 0.38 |
| Extent | 1 (0.96-1.05) | 0.88 |
| Coarseness | 0.95 (0.8-1.14) | 0.57 |
| Induction therapy with corticosteroids alone | 2.94 (1.05-8.33) | *0.04* |
| Evolve to chronic respiratory insufficiency | 7.44 (1.60-34.56) | *0.003* |

Abbreviations: AAV = ANCA-associated vasculitis; CI = confidence interval; CRP = C-reactive protein; FFS = five-factor score; HR = hazard ratio; NSIP = non specific interstitial pneumonia; PF = pulmonary fibrosis; UIP = usual interstitial pneumonia.

little is known about factors that influence its prognosis. The identification of individual susceptibility and characteristics of at-risk patients may help to predict prognosis of PF and to develop adequate therapeutic approaches. Our results demonstrated that 1) PF is associated with a poor outcome in AAV, mainly related to respiratory insufficiency, and 2) induction therapy with CYC might improve the outcome. To our knowledge, this is the first study to report the main causes of mortality, the prognostic factors, and the impact of induction therapy on outcome in this patient population.

Regarding the high mortality (37%) mainly related to respiratory insufficiency observed in the current study, PF emerges as a leading cause of morbidity and mortality in AAV and may have crucial therapeutic implications. Indeed, the percentage of patients with a revised Five Factor Score (FFS) ≥1 was similar between the surviving patients and those who died (74% and 72%, respectively).[14] The revised FFS was
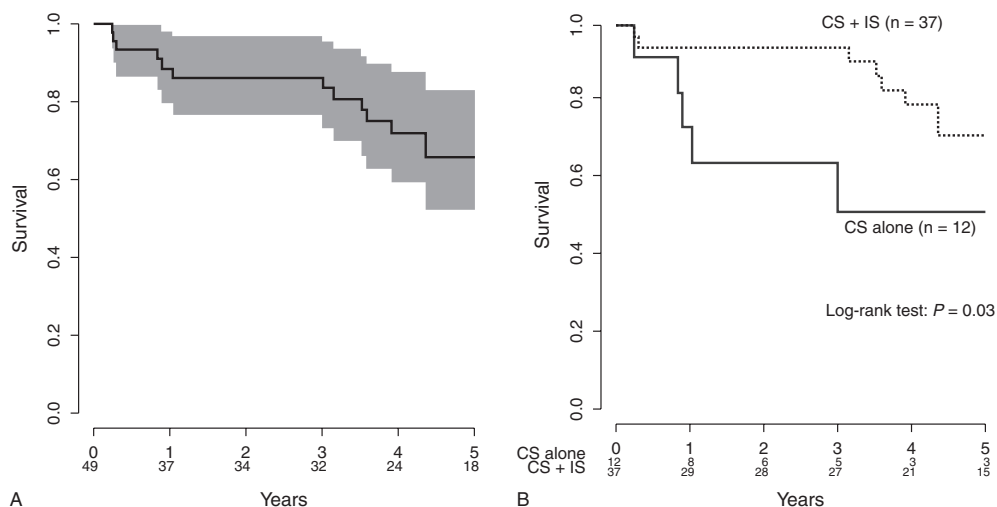


**FIGURE 2.** Kaplan-Meier survival curve of patients with PF associated with AAV (grey area = 95% CI) (A), and survival curves according to remission induction treatment with glucocorticoids alone ("CS alone," thick line) or combined with cyclophosphamide or rituximab ("CS + IS," dotted line) (B).

**TABLE 4.** PF Associated With AAV, Previous Reports

| | Gender (M/F) | Age at AAV diagnosis (Yrs) | ANCA specificity | Organ involvement | PF pattern | Induction therapy | PF Response Evolution | Follow-up | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| Homma S, n=8 | ND | ND | MPO (n=8) | ND | ND | ND | Progressed (n=2), stable or improve (n=6) | ND | ND |
| Foulon G, n=7 | 7M | 66 | 5 MPO, 1 lactoferrin, 1unidentified | 5 K, 2 S, 1 PNS, 1 Msc | 7 PF | CYC+ (n=5), CYCØ (n=2) | ND | 21-44-53-61-98-130-165 mths | alive (n=1, CYCØ), death (n=6, including 3 vasculitis and 3 ND) |
| Hervier B, n=12 | 9M/3F | 69.5 (64-78) | p-ANCA and MPO (n=12) | 8 K, 6 PNS, 3S, 4Msc, 1O, 2 ENT | 6 UIP (50%), 1 NSIP (8.33%), 5 ND | CYC+ (n=12) | Progressed (n=5), stable (n=5), ND (n=2) | 49 [7-116] mths | death (n=5, including 3 respiratory failure, 1 CMV pneumonia, 1 vasculitis) |
| Nozu T, n=4 | 2M/2F | [54-59-69-73] | MPO (n=4) | 4 K | 4 PF | CYC+ (n=1), CYCØ (n=3) | ND (n=1), Stable (n=3) | [1-3-37-90] mths | alive (n=2, including 1 CYCØ), death (n=2, renal failure in both) |
| Tzelepis GE, n=13 | 9M/4F | 57 | p-ANCA (n=11), p and c-ANCA (n=1), ANCA negativity (n=1) | 13 K, 4A, 6Msc, 1S, 1 GI, 1 PNS | UIP (n=7), NSIP (n=4), ND (n=3) | ND | Progressed (n=5) Stable (n=8) | 38±30 mths | alive (n=6), death (n=6, including 4 respiratory failures, 1 lung cancer and 1 sepsis) |
| Nada AK, n=3 | 1M/2F | [71-72-74] | p-ANCA (n=2), unspecified (n=1) | 3 K, 3 PRS, 1 Msc | bibasal interstitial infiltrates+pleural effusions, UIP (n=2) | CYCØ (n=3) | ND (n=1), stable (n=1), progressed (n=1) | 3 mths, 4 yrs, 7 yrs | death (n=3, including 1 renal failure, 1 perforated colonic diverticulum, and 1 ND) |
| Hiromura K, n=4 | 2M/2F | [48 -70-72-77] | MPO (n=4) | 4K, S | 2 PF | CYC+ (n=1) | ND | 4 mths, 5 mths, 19 mths, and ND for patient alive | alive (n=1, CYC+), death (n=3, including 1 pneumonia, 1 respiratory failure, 1HA) |
| Eschun GM, n=6 | 3M/3F | [63-64-67-68-79-78] | p-ANCA (n=6) | 6 K | UIP (n=4), NSIP (n=1), ND (=1) | CYCØ (n=3) CYC+ (n=5), CYCØ (n=1) | ND (n=2), stable (n=1), progressed (n=3) | 1-5-8 mths, 1 yrs, 7 yrs, ND | alive (n=1, CYC+), death (n=5, including 4 respiratory failures and 1 ND) |
| Nakabayashi K, n=1 | M | 72 | MPO | K, PNS, S, GI | UIP | ND | ND | 6 yrs | death (leukemia) |
| Becker-Merok A, n=1 | M | 65 | p-ANCA | PRS, K, PNS, S, Joint | bibasal fibrosis and small emphysematous lesions | CYC+ | stable | 24 mths | alive |
| Mansi IA, n=1 | F | 55 | p-ANCA | PRS, K, Joint, Uveitis | UIP | CYC+ | Improvement | ND | alive |
| Souid M, n=1 | M | 75 | MPO | K, Msc | ND | CYCØ then CYC+ 3 mths after | ND | 5 mths | death (respiratory failure) |
| Birnbaum J, n=1 | F | 77 | p-ANCA and MPO | Msc | atypical UIP | CYC+ | Improvement | 1 yrs | alive |
| Bhanji A, n=1 | F | 69 | p-ANCA and MPO | K | UIP | CYC+ and PE | improvement | ND | alive |
| Takato H, n=1 | F | 47 | MPO | K | UIP | CYC+ | stable | ND | alive (mycoplasma) |
| Tzouvelekis A, n=1 | M | 80 | p-ANCA and MPO | K | CPFE | CYC+ | stable | 2 yrs | alive |
| Total n=65 | 65% Male | 68 years | 94% p- or MPO-ANCA | 88% K, 23% Msc, 18% PNS | 83% UIP, 13% NSIP, 4% CPFE | (31/43) 72% CYC+ (ND for 22 patients) | 35%progressed, 65% stable or improve | 45 mths | 56% of death, caused by respiratory failure in (14/32) 44% |

Abbreviations: CPFE = combined pulmonary fibrosis and emphysema; CYC; CYC+ = patient who received corticosteroids combined with CYC; CYCØ = patient who received corticosteroids alone; F = female; IS = immunosuppressor; K = kidney; M = male; MPO = myeloperoxidase; Msc = muscle; mths = months; ND = no data; NSIP = non specific interstitial pneumonia; p-ANCA = perinuclear ANCA; PE = plasmatic exchange; PNS = peripheral neuropathy; PRS = pulmonary-renal syndrome; UIP = usual interstitial pneumonia; yrs = years.

not associated with death in univariate analysis. In contrast, our results suggest that glucocorticoids alone as induction therapy is associated with a higher risk of mortality in PF-AAV, compared to glucocorticoids associated with CYC or RTX (48.7% versus 28.6%, respectively, p = 0.03). Results obtained in our analysis of 33 cumulative patients from literature were similar, with 83% of mortality occurring in patients who received glucocorticoids alone versus 48% of mortality in patients who received glucocorticoids associated with CYC. The occurrence of long-term oxygen therapy increased by 7 times the odds of mortality in our PF-AAV patients. In the literature, the mortality rate in PF-AAV patients was high, reaching 56% of cases, and was mainly related to respiratory insufficiency.[9,17,18,35,41] Tzelepis et al[41] have compared the mortality of patients with MPO-ANCA positive MPA with and without PF and with similar severity of renal disease. Survival analysis using the Kaplan–Meier method showed a significantly higher mortality rate among MPA patients with PF.[41] The long-term outcome observed in our PF-AAV patients was variable. This variable prognosis of PF associated with AAV is an important difference compared with idiopathic PF, which is almost invariably a progressive disease.[6] Sex, smoking status, and clinical initial manifestations (except weight loss) did not influence survival in our PF-AAV cohort. In contrast with PF associated with RA, female sex was not associated with better outcome.[24] Smoking prevalence in our study (53%) was more important compared to the general population (around 20%), and tobacco could be a cofactor for the development of PF in patients with AAV. Older age at diagnosis of PF and of AAV was negatively associated with mortality. Reminiscent of a previous series of 12 PF-AAV patients where eosinophilia was present in the 5 cases whose condition worsened,[17] the eosinophil level was a poor prognostic factor. In our study, initial pattern on thoracic HRCT was not a prognostic factor.

This multicenter cohort of patients with AAV and PF underlines the high prevalence of MPA with MPO-ANCA specificity among this severe entity. Considering the poor prognosis of this association, it should impact modalities of assessment of pulmonary involvement, especially for earlier follow-up, because initial imaging features can show ground-glass opacities compatible with alveolar hemorrhage, but in the absence of repeated thoracic CT, it is impossible to distinguish from NSIP pattern. On the other hand, PF is often diagnosed before AAV and initially classified as idiopathic PF. These patients could benefit from a specific monitoring that could allow early detection of vasculitis.[13]

In our PF-AAV cohort, patients who received glucocorticoids combined with CYC or RTX as induction therapy had a better survival compared to those who received glucocorticoids alone. Awareness of the possible association of AAV and PF may be clinically relevant for physicians who manage patients with AAV, as well as for pneumologists who diagnose PF first. Nevertheless, no recommendation is currently available for the treatment of PF associated with AAV. A high dose of glucocorticoids is the cornerstone of treatment in AAV. It is recommended to add an immunosuppressant as induction therapy, either intravenous CYC or RTX in patients with severe manifestations of AAV.[11,19,28,36] Taken together, our results suggest that the association of glucocorticoids and CYC as induction therapy in patients with PF associated with AAV might be indicated.

Several hypothetical mechanisms may explain the pathogenesis of PF associated with AAV. First, small vessel vasculitis such as MPA and GPA commonly involve the kidney and lung, with alveolar hemorrhage being the commonest manifestation of pulmonary involvement. Thus, occult chronic alveolar hemorrhage might contribute to the development of PF in AAV.[5] MPO-ANCA might also play a role in the pathogenesis of PF in AAV. Guilpain et al showed that oxidative stress, in particular the production of hypochlorous acid through the interaction of MPO with anti-MPO antibodies, could trigger the fibrotic process observed in MPA.[15] Alternatively, PF is often the first manifestation of PF associated with AAV, and it may precede systemic symptoms of the vasculitis by months or even years. Thus, PF could be a contributing factor for development of autoimmunity, especially against MPO. Interestingly, this hypothesis is not applicable for advanced PF in RA, sarcoidosis, or systemic sclerosis, because it is often diagnosed when the connective tissue disease is already well established. The absence of EGPA with MPO-ANCA in the different PF-AAV cohorts remains unclear. The role of eosinophils has not been studied in PF associated with AAV. Yet, hypereosinophilia was frequently observed in AAV with PF (around 30%) and was associated with a worse prognosis. This biological specificity could be important as eosinophils through their destructive granule contents can cause significant tissue damage, resulting in inflammation and recruitment of inflammatory cells that may ultimately lead to fibrosis.[2,44]

Further studies are warranted to determine the incidence of AAV among patients with PF and isolated ANCA but no other evidence of systemic vasculitis at PF diagnosis. Whether the pulmonary fibrotic process interacts with the damaging process of vasculitis, and reciprocally, is still unknown. Our results highlight that in clinical practice, PF can precede AAV, and a thorough evaluation of those patients initially labeled as having idiopathic PF is critical. Some of those patients will indeed have an autoimmune-based parenchymal lung disease, and treatment options and prognosis can be affected.

In conclusion, the present study demonstrates that PF is a rare but clinically relevant manifestation occurring in association with AAV, especially among patients with MPA and with MPO-ANCA specificity. We identified the occurrence of chronic respiratory insufficiency, induction remission therapy with glucocorticoids alone, and high eosinophil count as prognostic factors. Despite a very poor prognosis, induction therapy with an immunosuppressant (CYC or RTX) might improve the outcome of patients with PF associated with AAV.

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