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Review

# Interstital lung disease in ANCA vasculitis

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ABSTRACT

Anti-neutrophil cytoplasmic antibodies (ANCA) vasculitides are immune-mediated disorders that primarily affect small blood vessels of the airway and kidneys. Lung involvement, one of the hallmarks of microscopic polyangiitis and granulomatosis with polyangiitis, is associated with increased mortality and morbidity. In recent years, several retrospective series and case reports have described the association of interstitial lung disease (ILD) and ANCA vasculitis, particularly those positive for ANCA specific for myeloperoxidase. In the majority of these patients pulmonary fibrosis occurs concurrently or predates the diagnosis of ANCA vasculitis. More importantly, these studies have shown that ILD has an adverse impact on the long-term prognosis of ANCA vasculitis. This review focuses on the main clinical and radiologic features of pulmonary fibrosis associated with anti-neutrophil cytoplasmic antibodies. Major histopathology features, prognosis and therapeutic options are summarized.



**Contents**



## 1. Introduction

Anti-neutrophil cytoplasmic antibodies (ANCA) are autoantibodies specific for antigens located in the cytoplasmic granules of neutrophils and lysosomes of monocytes [1]. The two major autoantigen targets are myeloperoxidase (MPO-ANCA) and proteinase 3 (PR3-ANCA). ANCA vasculitides (ANCA-V) are multisystem diseases characterized by necrotizing vasculitis that predominantly affects small vessels [2].

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The major clinicopathologic variants of ANCA-V are granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA), and single-organ ANCA-V, including renal-limited ANCA vasculitis (RLV). Pulmonary manifestations are a characteristic feature of ANCA-V [3], with the lung being involved in 85–90% of GPA patients during the course of their disease [4–6]. The frequency in MPA is slightly lower, with reported prevalence of 25–55% [7–9]. In both disorders, lung involvement has been associated with unfavorable outcomes [10–12].

During the last few years, an increasing number of publications have reported the association between interstitial lung disease (ILD) and ANCA vasculitis. The objectives of this review are 1) to describe the main clinical and radiologic manifestations of pulmonary fibrosis (PF) associated with ANCA, 2) to detail major histopathological findings and hypothesize physiopathogenic mechanisms involved in the development of this condition, and 3) to summarize the outcome and therapeutic options for affected patients.

We performed a MEDLINE search for English language articles published between January 1970 and September 2016. The search strategy combined the following terms: "vasculitis, ANCA, granulomatosis with polyangiitis, Wegener's granulomatosis, microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis, Churg-Strauss syndrome, myeloperoxidase or proteinase 3" and "interstitial lung disease, lung fibrosis, pulmonary fibrosis, lung manifestations, thoracic manifestations, interstitial pneumonia or computed tomography (CT)". Full text of relevant articles were retrieved and reviewed. Additional references quoted in these publications were checked. Data of >200 patients included in case series [13–27] and case reports [28–42] constitute the basis of this review.

## 2. Epidemiology

Interstitial lung disease associated with ANCA is usually observed in patients older than 65 years old. The average age at presentation seems to be higher in MPA patients with PF than in those with this systemic vasculitis described in general cohorts (66 vs 55 years, respectively) [7,8,13–27], but similar to that reported in cases of idiopathic PF (IPF) [43,44]. Regarding gender, some series have reported a slight predominance of men (60–65%), although this has not been confirmed in other studies [13–26].

Pulmonary fibrosis occurs concurrently or antedates MPA in the majority of affected individuals (Table 1). In previous reports, ILD precedes full vasculitis syndrome in 14–85% of patients, appeared simultaneously with other organ involvement in 36–67%, and was reported after ANCA-associated disease in 8–21% [13–20,40,42,45–50]. In those cases where PF was diagnosed before MPA, the time between both events ranges from a few months to 12 years. It must be noted that in most series PF was not biopsy-proven, and diagnosis was based on the combination of clinical findings, pulmonary function tests (PFT) and CT images.

Prevalence of ILD is higher in MPA than in GPA [15,18,51]. PF has been reported in 23% of GPA cases [52] and in 2.7–45% of MPA patients. In these cases, interstitial disease was usually identified at disease onset [7,11,17–20,48,53,54]. Importantly, there is a significant predominance of MPO-ANCA in published series, i.e., 46–71% of all cases compared to 0–29% for PR3-ANCA [13,27,51,52,54–56].

On the other hand, prevalence of ANCA in cohorts of individuals who initially presented with isolated pulmonary fibrosis ranges between 4%–36% for MPO-ANCA and 2–4% for PR3-ANCA [13,16,27,46,48,50,56–59]. During follow-up, 5–10% of ANCA negative patients developed autoantibodies against MPO or PR3 (incidence of 12 cases per 1000 person years) [13,16,46,50,58]. In the latter group, presence of other autoantibodies, such as rheumatoid factor, erythrocyte sedimentation rate (ESR) >40 mm/h, bronchoalveolar lavage (BAL) eosinophilia and increased areas of low attenuation on CT have been suggested as factors predicting the conversion to positive ANCA [58]. In large cohorts of patients with idiopathic PF, 1.7–25.7% developed full MPA (Table 1) [16,50,58]. Prospective studies are needed to clarify the precise prevalence and incidence of ILD in ANCA vasculitis.

Of relevance, frequency of ILD in ANCA vasculitis seems to be higher in Japan than in Western populations [17,18,20,54,55,60]. Reasons for this particular association may include a higher prevalence of MPO-ANCA positivity and increased frequency of lung involvement and diffuse alveolar hemorrhage [11,61,62].

## 3. Clinical manifestations

Major symptoms of patients with ANCA-positive isolated pulmonary fibrosis are progressive dyspnea (50–73%) and nonproductive cough (21–60%) [16,26,49,59]. Other manifestations such as pulmonary hemorrhage and hemoptysis (5%) or constitutional symptoms, i.e., fever (31%) and weight loss (5%) were observed less frequently [16,49,58]. In previous studies, ANCA titers did not correlate with the severity of PF [16]. In a small case series, clinical presentation of patients with PF and positive ANCA did not differ from their counterpart with negative autoantibodies [16,49,59].

In contrast, patients with ILD who fulfilled MPA criteria typically manifested with constitutional symptoms (approximately 80%) and extra-pulmonary disease (70–100%) [15]. In these cases, malaise (31–63%), fever (52–90%) and weight loss (52–58%) are frequently detected at diagnosis [17,18,48,51]. In addition, vasculitic involvement is common in the skin (8–31%), peripheral nervous system (8–53%), joints and muscle (23–31%) or kidneys (57–100%) [13,17,18,48,51]. Pulmonary manifestations include progressive breathlessness (30–100%), alveolar hemorrhage (21–49%) and chronic cough (23–84%) [15,17,18,20,48,51]. Of note, when comparing MPA patients with and without PF, some authors have reported that the first usually exhibited less severe systemic inflammatory response, manifested as lower ESR, higher levels of hemoglobin and importantly, reduced frequency of clinical evident diffuse alveolar hemorrhage, peripheral nerve and kidney involvement [19,20].

## 4. Laboratory findings and pulmonary function test

In patients with MPA and ILD, ESR and C-reactive protein (CRP) were increased at disease onset in 95% and 73–79%, respectively [48,51]. As expected, >60% of these cases also have abnormal urinalysis [48,50]. In contrast, marked elevations of ESR and CRP were not described in ANCA-positive PF. In this sense, most studies have found similar CRP levels in patients with initially isolated lung fibrosis irrespective of their ANCA status [16,56,58,59].

Measurement of lung function is an important part of the evaluation of individuals with ILD. These ancillary tests are used for assessing the pattern and severity of pulmonary involvement. In both lung-limited ANCA-associated PF and MPA patients with PF, a restrictive pattern with reduction in total lung capacity is the most frequent pattern reported in spirometry (62–80%) [13,15,16,18,20,48,50,51]. Co-existing airflow obstruction can be observed in one third of pulmonary function tests [18]. Other frequent findings include reduction of the diffusing capacity (DLCO) and mild hypoxemia at rest (50% of cases) [13,15,18,20,21,48,49]. During follow-up, PFT tend to deteriorate as ILD progresses. This was evidenced in a previous study of patients with ILD and ANCA vasculitis, where after a mean of 5 years, basal values of forced expiratory volume in 1 s (FEV1), vital capacity and DLCO were reduced in 29%, 23% and 46%, respectively [18].

BAL features include an increased cell count in 60% of patients, with neutrophilia being the most frequent finding (40–87% of cases) [13,16,51]. Lymphocytosis and eosinophilia were reported in 20% and 26%, respectively [13,16]. Evidence of acute or chronic alveolar hemorrhage was observed in half of the samples [13]. When compared to idiopathic PF, some authors have reported that those cases associated with ANCA exhibited an increased percentage of BAL neutrophils and eosinophils [58,59]; however, other studies have disputed these results [13,63].