# Pulmonary involvement in microscopic polyangiitis

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**Purpose of review**

Microscopic polyangiitis is a systemic necrotizing vasculitis that affects small vessels, resulting in a wide spectrum of organ involvement including the kidneys and the lungs. This paper reviews recent insights and observations into the pathogenesis, clinical manifestations, and treatment of pulmonary involvement in microscopic polyangiitis.

**Recent findings**

The spectrum of clinical presentations ranges from antecedent interstitial fibrosis to frank hemoptysis secondary to capillaritis. Computerized tomography imaging reveals a variety of pulmonary findings, including ground-glass attenuation, consolidation, thickening of bronchovascular bundles, and honeycombing. Antineutrophil cytoplasmic antibodies are important in diagnosis as well as in the pathogenesis and prognosis of microscopic polyangiitis. There is more evidence to support the various therapeutic modalities currently used in pulmonary manifestations of microscopic polyangiitis, including induction therapy with cyclophosphamide, the use of other novel pharmacologic agents such as the tumor necrosis factor-$\alpha$ blockers and rituximab, and nonpharmacologic modalities such as plasmapheresis and ventilatory management.

**Summary**

The pulmonary manifestations of microscopic polyangiitis are diverse and often difficult to manage; however, as our understanding and experience grows so does our ability to successfully diagnose and treat these patients.

**Keywords**

alveolar hemorrhage, microscopic polyangiitis, pulmonary manifestations, vasculitis

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**Abbreviations**

| | |
|---|---|
| **ANCA** | antineutrophilic cytoplasmic antibodies |
| **ELISA** | enzyme-linked immunosorbent assay |
| **IIF** | indirect immunofluorescence |
| **MPA** | microscopic polyangiitis |
| **MPO** | myeloperoxidase |
| **MPO-ANCA** | myeloperoxidase ANCA |
| **P-ANCA** | perinuclear ANCA |
| **PR3** | proteinase 3 |
| **PR3-ANCA** | proteinase 3 ANCA |


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## Introduction

Microscopic polyangiitis (MPA) is a systemic necrotizing vasculitis that histologically affects small-caliber blood vessels and is without granulomatous formation. Although MPA was originally considered a subclass of polyarteritis nodosa, the Chapel Hill Consensus Conference in 1994 set a classification framework that differentiated MPA from polyarteritis nodosa on the basis of the presence (as opposed to the absence) of vasculitis in the arterioles, venules, or capillaries [1]. MPA is the most common antineutrophilic cytoplasmic antibody (ANCA)-associated small-vessel vasculitis and is further characterized by few or no immune deposits in the involved vessels.

Pulmonary involvement is a common feature of MPA and can present from fleeting focal infiltrates to massive lung hemorrhage and hemoptysis secondary to alveolar capillaritis [2]. We review recent observations on the causes, clinical presentation, and treatment of these pulmonary manifestations.

## Epidemiology

The incidence of MPA is approximately 1:100,000 per year, with a slight predominance in men and a mean age at onset of approximately 50 years [2]. Gonzalez-Gay *et al.* [3] applied the Chapel Hill Consensus Conference definitions retrospectively to a southern European population fulfilling the criteria for primary systemic vasculitis and confirmed that MPA is more prevalent than Wegener's granulomatosis and that there is an increasing incidence of primary systemic vasculitis with age. Mahr *et al.* [4] in a capture-recapture estimate in a French urban population determined a prevalence for MPA of 25.1 per million adults (95% CI 16–34). The kidneys are the most commonly affected organ in 90% of patients [2]. In a retrospective review of 36 patients with MPA, pulmonary involvement occurred in 22% and alveolar hemorrhage in 11% [5]. Lane *et al.* [6•] found pulmonary involvement in 29% and hemoptysis in 17% among 24 MPA patients.

## Cause

A genetic background is suspected for ANCA-associated vasculitides. Among 50 Japanese patients with MPA, there was a significant association of HLA-DRB1*0901 with MPA ($P = 0.0037$, OR 2.44, 95% CI 1.33–4.46) as well as with anti-myeloperoxidase (MPO) antibody ($P = 0.0014$, OR 2.44, 95% CI 1.41–4.22) [7]. Bartfai *et al.* [8] also noted a possible role of enhanced nterleukin-10 (-1082) polymorphisms in MPA patients (39% expressing the AA homozygous genotype) compared with healthy control individuals (10.5%; $P < 0.0001$). Furthermore, the AA

homozygous genotype was significantly more frequent in female individuals (62.5%) than in male individuals (20%, $P < 0.05$) [8].

Seasonal clusters of MPA cases occurring from April to May (29.5% of cases) and from October to January (39.5% of cases) ($P = 0.03$) suggest possible environmental factors [9]. Lane *et al.* [10] examined environmental risk factors in 75 patients with primary systemic vasculitis (12 with MPA) and 273 control individuals and found that farming in the index year was significantly associated with MPA (OR 4.3, 95% CI 1.9–21.6) and with the presence of MPO-ANCA (OR 4.3, 95% CI 1.5–12.7) but not with lifetime farming, silica, solvent, or metal exposure. Occupational exposure to asbestos has also been associated with positive test results for ANCA and the development of probable MPA [11,12].

One prevalent theory for the pulmonary damage seen in MPA stems from the pathogenic nature of ANCA. In response to proinflammatory cytokines, small quantities of ANCA antigens are translocated to the surface of neutrophils, which in turn activate primed neutrophils directly, causing injury to localized endothelial cells and alveolar hemorrhage secondary to extensive reactive oxygen species formation and degranulation of neutrophil constituents, including MPO [13]. MPO-ANCA can prevent the clearing and inactivation of MPO by ceruloplasmin as well, resulting in increased MPO activity [14]. Ando *et al.* [15••] noted that as serum MPO-ANCA titers decreased after treatment, pulmonary abnormalities improved, supporting the observation that MPO-ANCA may be closely related to the pathogenesis of pulmonary hemorrhage in MPA.

The pathogenicity of ANCA has been further demonstrated in a recent report of transplacental transfer of MPO-ANCA from a mother with MPA to a 33-week gestational age neonate that resulted in neonatal pulmonary hemorrhage and renal involvement [16•].

## Pathology of lung lesions

Open or thoracoscopic lung biopsy carries an increased risk of morbidity and mortality in critically ill patients. Biopsy specimens frequently demonstrate only necrotic tissue or show nonspecific inflammation and hemorrhage. Moreover, pulmonary capillaritis is a relatively nonspecific pathologic finding and may be seen in other conditions. Lung biopsy is generally not recommended in the setting of immune-mediated alveolar hemorrhage when a specific diagnosis can be established by biopsy of other tissues and by serum ANCA assays [17]. Alveolar hemorrhage, vasculitis with alveolar hemorrhage, pulmonary fibrosis, bronchitis, and bronchiolitis obliterans organizing pneumonia have been reported in surgical biopsies and autopsies of MPA patients [15••].

## Clinical features of pulmonary abnormalities

Agard *et al.* [5] found that the most common presenting clinical symptoms attributable to vasculitis in 36 MPA patients were general symptoms (fever, weight loss, asthenia) (61%), followed by myalgias (43%) and arthralgias (29%). Alveolar hemorrhage occurred in 11% of the patients. Although most MPA patients with alveolar hemorrhage have extrathoracic involvement, isolated alveolar hemorrhage has been reported. Cough, chest pain, and shortness of breath may be present, and in a retrospective review of 29 patients with MPA and alveolar hemorrhage, dyspnea was severe in 69% of patients and required immediate mechanical ventilation in 10% [17]. Hemoptysis is a common presenting feature, although it can occur late or even be absent in the face of significant alveolar bleeding [18,19]. Occasionally, MPA patients with chronic alveolar hemorrhage may experience lung fibrosis or obstructive bronchiolitis [20–22]. Pulmonary interstitial fibrosis can also be a initial manifestation of MPA, may predate the onset of vasculitis by several years, and seems to be associated with a poorer prognosis [23].

Other pulmonary presentations of MPA have been described in recent reports: a case of nonspecific interstitial pneumonia as an initial manifestation of MPA, a patient with MPA who had pulmonary aneurysms on angiogram and alveolar hemorrhage, a female patient with diffuse panbronchiolitis for 4 years before presenting with pulmonary hemorrhage and a positive MPO-ANCA, and a patient who presented with clinical signs of MPA and a highly positive perinuclear-ANCA (P-ANCA) who eventually received a diagnosis of bronchioloalveolar carcinoma by surgical biopsy [24–27].

### Chest radiograph

Chest radiographic abnormalities consist of patchy, bilateral airspace opacities caused by alveolar hemorrhage. Opacities are most commonly bilateral and involve the upper and lower parts of the lungs [17].

### Imaging

Ando *et al.* [15] reviewed the computed tomography (CT) findings in 51 MPA patients with pulmonary involvement. The most common CT findings consisted of ground-glass attenuation in 94% of patients, consolidation in 78%, thickening of bronchovascular bundles in 51%, and honeycombing in 37%. The extent of ground-glass attenuation corresponded to that of alveolar hemorrhage, interstitial chronic inflammation in the alveolar septa, and capillaritis. Consolidation corresponded to diffuse alveolar hemorrhage, and thickening of bronchovascular bundles corresponded with the infiltration of lymphocytes and mild fibrosis along the bronchovascular bundles.

Neumann *et al.* [28] reported the use of somatostatin receptor scintigraphy in differentiating active from inactive

pulmonary disease in ANCA-associated small vessel vasculitis with a specificity of 96% and a sensitivity of 86%. Additional studies are needed to confirm the usefulness of this imaging test.

#### Bronchoscopy

Bronchoalveolar lavage fluid in MPA patients with alveolar hemorrhage is typically grossly hemorrhagic and contains numerous erythrocytes. Perls's Prussian blue staining reveals a significantly elevated percentage of hemosiderin-laden macrophages (30%) [17].

#### Laboratory and antineutrophil cytoplasmic antibodies

Testing for ANCA is used to aid in diagnosis and to monitor inflammatory activity in small vessel vasculitides, including MPA, Wegener's granulomatosis, and Churg-Strauss syndrome. The International Consensus Statement on testing and reporting of ANCA recommends that ANCA are best demonstrated in these conditions by a combination of indirect immunofluorescence test (IIF) using normal peripheral blood neutrophils as substrate and by an enzyme-linked immunosorbent assay (ELISA) for proteinase 3 (PR3) and MPO [29]. The classic granular cytoplasmic ANCA pattern is due to antibodies to PR3, whereas ANCA that selectively stain the perinuclear area of neutrophils and monocytes (P-ANCA) are predominantly directed against MPO [30]. Most patients with MPA have positive MPO-ANCA, although PR3-ANCA may be also present in as many as 40% of patients, and approximately 10% can be ANCA negative.

Specific ANCA measured by ELISA can be particularly useful in differentiating vasculitis from diseases that may mimic systemic vasculitides, such as severe multiorgan dysfunction and parenchymal pulmonary disorders. Vassilopoulos *et al.* [31] examined ANCA prospectively in 99 patients with multiorgan dysfunction admitted to the medical intensive care unit, 29 outpatients with various lung disorders, and 18 Wegener's granulomatosis patients. ANCA were detected by IIF alone in 16% of multiorgan dysfunction patients and 17% of outpatients with various pulmonary disorders. Most these positive IIF specimens exhibited an atypical pattern (73% and 80%, respectively). When patients were tested by IIF and ELISA, however, only one patient with a nonvasculitic disorder was additionally positive for anti-MPO (compared with 78% of control patients with Wegener's granulomatosis), suggesting that the presence of ANCA by IIF alone was not specific for systemic vasculitis. Positive ANCA by IIF can be seen in rheumatoid arthritis, Felty's syndrome, systemic lupus erythematosus, ulcerative colitis, and other multisystem conditions, but most do not result in the production of PR3-ANCA or MPO-ANCA [32].

Recent conflicting reports on the specificity of ANCA in pulmonary tuberculosis are of particular concern, when the clinical similarities between tuberculosis and pulmonary manifestations of ANCA-associated vasculitides are considered. Flores-Suarez *et al.* [33] reported a positive ANCA in 44% of 45 tuberculosis patients by IIF and in 40% of patients by ELISA (33% displaying cytoplasmic ANCA/PR3-ANCA pattern and 7% P-ANCA/MPO-ANCA). By contrast, a larger study found that although 10% of tuberculosis patients had positive test results for ANCA by IIF, specific ELISA testing yielded only one PR3-ANCA positive serum, and no combined IIF-ELISA positivity was detected [34].

Other common laboratory abnormalities in MPA include a normocytic anemia, a mild to modest leukocytosis, and elevated inflammatory markers, including erythrocyte sedimentation rate and C-reactive protein [17].

## Therapy

The cornerstone of pharmacologic therapy of MPA remains systemic corticosteroids and cyclophosphamide. A treatment duration of at least 12 months of combined therapy has been empirically recommended. Recently, Guillevin *et al.* [35] confirmed this with a prospective trial comparing 6-monthly with 12-monthly cyclophosphamide pulses in combination with corticosteroids. Survival analysis showed a significantly lower relapse probability and higher event-free survival in the 12-monthly cyclophosphamide pulse group; however, prolonged exposure to cyclophosphamide has been associated with an increased risk of bladder cancer, hemorrhagic cystitis, and infertility. Jayne *et al.* [36] addressed this concern in a large prospective study investigating whether exposure to cyclophosphamide in patients with ANCA-associated vasculitis (60 of whom had MPA) could be reduced by the substitution of azathioprine at remission. All patients received standard therapy with corticosteroids and oral cyclophosphamide until remission was achieved (3–6 months) and then randomized to receive maintenance therapy with either azathioprine or continued cyclophosphamide. After 12 months, the patients in the cyclophosphamide group were switched to the same azathioprine regimen as the azathioprine group and were monitored for an additional 6 months. Both groups had statistically similar outcomes with regard to relapses, adverse events, and other disease activity indices, suggesting that the duration of exposure to cyclophosphamide may safely be reduced with the substitution of azathioprine. Other recent smaller trials and case reports have added to the growing body of evidence that mycophenolate mofetil as well as methotrexate may also have potential usefulness in the maintenance therapy of ANCA-associated vasculitides [37–39].

New but conflicting reports regarding the use of tumor necrosis factor-α inhibitors in ANCA-associated systemic vasculitis have been published. Booth *et al.* [40•], in an open-label, multicenter, prospective trial, examined the

safety and efficacy of infliximab as adjuvant therapy in both acute flares (study I) and persistent disease (study II) in patients with Wegener's granulomatosis and MPA. The two study groups achieved high rates of remission (88%) and, in study I, a 40% reduction in cumulative prednisolone dose compared with standard regimens; however, the results of the Wegener's Granulomatosis Etanercept Trial analyzing the efficacy of etanercept combined with a standard drug regimen found that there was no additional benefit with regard to rates of sustained remission, sustained periods of low-level disease activity, or the time required to achieve those measures [41•]. The successful use of rituximab in refractory ANCA-associated vasculitis has also been recently reported in 12 patients, although none had a diagnosis of MPA [42,43•]. Additional studies on the use of biologic agents in primary systemic vasculitis are needed.

### Control of hemorrhage

In patients with small vessel vasculitis, diffuse alveolar hemorrhage was the single most important predictor of mortality, and aggressive immunosuppressive therapy alone may not be adequate [44]. Plasma exchange combined with immunosuppressant agents can be used to the pulmonary hemorrhage associated with MPA [45,46]. Klemmer *et al.* [46] performed a retrospective review of patients with ANCA-associated vasculitis and diffuse alveolar hemorrhage, all of whom were treated with apheresis as well as induction immunosuppressive therapy (intravenous methylprednisolone, intravenous cyclophosphamide, or both). Diffuse alveolar hemorrhage resolved with prompt plasmapheresis in 20 of 20 patients (100%) with an average of 6.4 treatments. The successful use of recombinant-activated human factor VII in a patient with diffuse alveolar hemorrhage and MPA has also been recently reported [47].

### Ventilation

There has previously been little evidence on which to base ventilatory strategies for adults, although a rational approach is to limit excessive tidal volume or pressure changes that could damage further the fragile vasculature and exacerbate the alveolar hemorrhage [18]. Extracorporeal membrane oxygenation has been used successfully in a few cases [48,49]. Hayes-Bradely [50•] suggested that prone position ventilation could improve oxygenation by better ventilation-perfusion matching and improved drainage of blood from the dorsal lung.

## Course and prognosis

Few papers have specifically addressed the course and prognosis of pulmonary involvement in MPA. Diffuse alveolar hemorrhage has been reported in 12 to 30% of patients with MPA [47]. Pulmonary hemorrhage typically subsides within 3 to 7 days after the beginning of steroid therapy but can last longer [51]. Reports of newer adjuvant therapies document significantly shorter periods [45–47]. The relative risk of death is increased almost ninefold in patients with MPA if pulmonary hemorrhage is present and disease relapses are common, occurring in 11 to and 46% of patients, with most patients relapsing after 2 years [44,52]. The mortality rate was higher in MPA patients positive for cytoplasmic ANCA/PR3-ANCA than in those positive for P-ANCA/MPO-ANCA, which may reflect a particular predisposition of the former group to have worse renal survival and higher relapse rates [52,53].

## Conclusion

The cause of MPA remains unknown, but continued evidence suggests genetic and environmental factors as well as a pathogenetic role for ANCA in the pulmonary injury often observed. Although alveolar hemorrhage is the most common and potentially serious pulmonary manifestation of MPA, a variety of lung pathologic manifestations have been described. Cyclophosphamide, corticosteroids, or both remain the pharmacologic induction therapy of choice, but additional modalities such as plasmapheresis are often necessary in the critically ill phase. The usefulness of therapies such as factor VIIa, rituximab, and the tumor necrosis factor-α inhibitors have several potential benefits in treating the various aspects of pulmonary involvement in MPA, but they still require additional exploration before being fully endorsed.

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