Lung Involvement in ANCA-Associated Vasculitis

10

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10.1 Introduction

This chapter focuses on the clinical presentation, diagnostic evaluation, and specific management issues associated with the various aspects of pulmonary parenchymal and tracheobronchial involvement of GPA and MPA. We emphasize the pulmonologist's perspective and refer to general treatment recommendations of GPA and MPA only briefly when necessary. Diagnosis and management of EGPA is covered elsewhere in this book.

10.2 Necrotizing Granulomatous Inflammation of the Lung

Disease manifestations caused by necrotizing granulomatous inflammation are the hallmark and disease-defining feature of GPA, setting GPA apart from MPA and EGPA [1]. In the lung, the pathognomonic histopathologic features of GPA include neutrophilic microabscesses, fibrinoid necrosis, palisading histiocytes, and giant cells forming a granulomatous inflammation pattern that is often called "geographic necrosis" [2]. Areas involved with this type of necrotizing granulomatous inflammation may encroach on vessel walls or contain focal vasculitis, thrombosis, and fibrous obliteration of vascular lumina. Other more non-specific histopathologic features have also been reported to occur rarely in GPA, including organizing pneumonia, bronchocentric inflammation, and occasionally prominent eosinophils in the inflammatory infiltrates [3, 4].

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Radiographic correlates of the necrotizing granulomatous inflammation are solitary or multiple pulmonary nodules or mass lesions with or without cavitation or non-specific pulmonary infiltrates that are radiographically indistinguishable from pneumonia (Fig. 10.1). A peribronchial distribution of the inflammatory lesions can often be seen by computed tomography (Fig. 10.1) [5]. Fibrotic changes are usually not a radiographic feature associated with GPA, but rather with MPO-ANCA associated MPA (see below).

The differential diagnosis of these lesions is broad, particularly when they are the only disease manifestations in a given patient [5]. Infections, including fungal infections, such as histoplasmosis, coccidioidomycosis and, to a lesser degree, blastomycosis are endemic in certain defined areas of the world. Nocardia infections can occur in immunocompetent patients and mimic the pulmonary presentation of GPA [6, 7]. Cryptogenic organizing pneumonia can be radiographically indistinguishable from GPA limited to the lung. This differentiation is further complicated by the fact that organizing pneumonia has been described as a rare histopathologic occurrence in GPA [4]. Malignancy, including metastatic disease and lymphoproliferative disorders, can cause multiple bilateral pulmonary nodules and therefore also needs to be considered in the differential diagnosis. Particularly, lymphomatoid granulomatosis, a rare angiocentric and angiodestructive, Epstein Barr virus-related T-cell-rich B-cell lymphoma can mimic GPA because, like GPA, it often affects different extra-pulmonary organs [8, 9].

Microbiologic studies and cytology performed on sputum samples or samples obtained during bronchoscopy procedures are usually helpful in the differential diagnostic evaluation. Transbronchial biopsies can provide tissue samples that are supportive of a diagnosis of GPA in about 50% of patients who have other supportive clinical features or ANCA [10]. Tissue samples obtained by transbronchoscopic biopsy are diagnostic by themselves in up to a quarter of patients [10]. A CT-guided

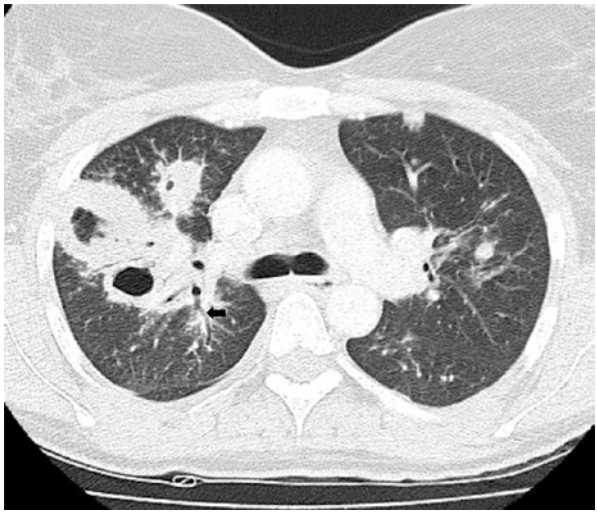

Fig. 10.1 Necrotizing granulomatous lung lesions of GPA. Typical computed tomography cut from a 67-year-old woman with GPA showing multiple bilateral nodules and cavitating mass lesions as well as peribronchial inflammation (black arrow)

core needle biopsy is preferred to transbronchial biopsies when the lesions are very peripheral. A video-assisted thoracoscopic lung biopsy has the highest diagnostic yield for GPA, but it is also associated with the highest morbidity and should therefore be used very judiciously.

The pulmonary parenchymal lesions caused by the necrotizing granulomatous inflammation may be asymptomatic, and they may not lead to measurable impairment of lung function. Consequently, they may be a serendipitous radiographic finding in newly diagnosed patients. For the same reason, any screening for disease activity during follow-up of patients with AAV must include chest imaging even if the patient does not endorse any respiratory symptoms.

Cough and minor hemoptysis are symptoms that may be associated with such lesions having access to subsegmental bronchi. The development of cavitation as a consequence of necrotizing granulomatous inflammation also signals involvement of a draining airway. Air-fluid levels within cavitary lesions are usually a sign of bacterial superinfection and should prompt a careful microbiologic evaluation and appropriate antibiotic therapy.

The disease manifestations caused by necrotizing granulomatous inflammation usually progress more slowly than capillaritis-related disease manifestations (see below), are not life-threatening, and they rarely cause irreversible lung damage. Therefore, patients who only have these disease manifestations are categorized for treatment stratification as having "non-severe" disease, implying that the combination of glucocorticoids with weekly methotrexate should be tried as first-line remission induction therapy [11]. Patients who fail this regimen usually respond well to the combination of glucocorticoids and rituximab [12, 13]. Sometimes, if the overall pulmonary disease burden is deemed extensive, treatment following the recommendations for "severe" disease using the combination of glucocorticoids with cyclophosphamide or rituximab may be appropriate [11]. Since most of the patients with such "severe" disease are PR3-ANCA-positive and have a very highly likelihood of relapse, management with rituximab from the get-go may be preferable.

10.3 Tracheobronchial Inflammation of GPA

In GPA, tracheobronchial involvement (Fig. 10.2) has been reported in 15–55% of cases, but it is usually not a feature of MPA [14]. Patients with tracheobronchial disease, including subglottic inflammation and subsequent stenosis, most commonly have PR3-ANCA, but may have MPO-ANCA or be ANCA-negative. The tracheobronchial inflammation is thought to be the result of necrotizing granulomatous inflammation, but confirmation by biopsy is rare. Therefore, we acknowledge that, whether tracheobronchial involvement is reported as a feature of GPA or MPA in cohort reports depends on the clinician's acceptance and application of different disease definitions and clinical surrogates of GPA-defining necrotizing granulomatous inflammation [15–17].

One characteristic feature of the tracheobronchial inflammation of GPA is its localized or patchy distribution throughout the airway with affected areas

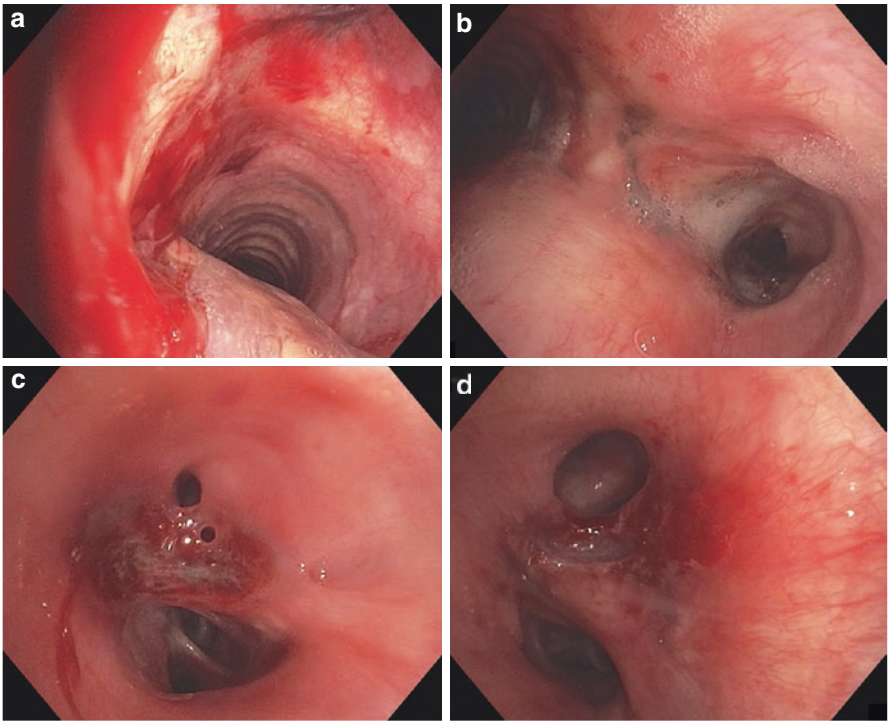

Fig. 10.2 Tracheobronchial involvement of GPA. (Panel **a**) Significant erythema and friable mucosa in the immediate subglottic region. (Panel **b**) Scarring of the main carina which is significantly broadened, but the entrance to the right main stem bronchus is widely patent. (Panel **c**) Anterior segment of the right lower lobe occluded by a web with two pin holes. The other segments appeared normal. (Panel **d**) The bronchoscopically introduced microknife was used to make a couple of cuts in the anterior segment of the right lower lobe leading to significant improvement of the lumen (**d**)

right next to entirely normal appearing airways. The subglottic region is most commonly involved, but airway inflammation may occur at any level of the tracheobronchial tree from the trachea down to the subsegmental airways. The inflammation of affected airways can consist of mucosal erythema, edematous swelling, friability, ulcerations, or so-called cobble-stoning. The inflammation is often circumferential. If it is transmural, it is detectable by CT imaging of the chest. If the cartilage of the airways is damaged by the inflammation, tracheo- or bronchomalacia with significant expiratory dynamic airway collapse may be the result. Alternatively, the acute inflammation as well as subsequent scarring occurring with immunosuppressive therapy can cause stenosis of the affected airway or complete occlusion.

The differential diagnosis of the tracheobronchial inflammation of GPA may be difficult in patients who do not have other typical organ manifestations of GPA or typical PR3- or MPO-ANCA. Relapsing polychondritis [18], inflammatory bowel

disease [19, 20], and sarcoidosis [21] should be considered as alternative diagnoses in such patients, and infections, particularly with fungal organisms, should be ruled out.

Symptoms that can occur as the result of airway inflammation of GPA include cough, streaky hemoptysis, stridor, localized wheezes, and dyspnea. Early inflammatory lesions remain often undetected because they do not cause significant airway obstruction. The presence and degree of stridor, localized wheezes, or dyspnea depend on the localization and severity of large airway obstruction.

The diagnostic approach is determined by the degree of suspicion for the presence of airway inflammation as well as by the symptoms of the patient. Pulmonary function testing, bronchoscopic inspection of the airways, as well as three-dimensional reconstruction of computed tomography images are important components of the diagnostic evaluation [14]. Inspiratory and expiratory flow-volume tracings allow the detection of airway stenoses and an estimate of their functional severity. When assessing and following airway stenosis in patients with GPA, measurements of the maximum voluntary ventilation during pulmonary function testing or of the peak expiratory flow, using a peak flow meter, are very useful for determining the degree of airflow limitation. Serial pulmonary function testing during follow-up is helpful in assessing the effects of medical therapy or of bronchoscopic interventions on airway patency. Pulmonary function testing is indicated for any patient with GPA who has respiratory symptoms such cough, dyspnea, or hemoptysis. It should also be pursued in any patient who has radiographic abnormalities of the pulmonary parenchyma or the airways, regardless of the presence or absence of symptoms.

Bronchoscopic inspection of the airways is indicated for patients with respiratory symptoms, abnormalities on pulmonary function testing, or on chest imaging studies. Bronchoscopy is indispensable for (1) the assessment and mapping of inflammatory lesions in the tracheobronchial tree, (2) planning of any therapeutic interventions, (3) to obtain specimens for microbiologic studies, and (4) to assess the effect of therapy on the airways. The so-called "virtual bronchoscopy" or three-dimensional reconstruction of CT images of the airways plays a significant role in the planning of dilation procedures or stent placement as it is important to assess airway patency distal to tight stenosis that cannot accommodate a pediatric bronchoscope [22].

The treatment of tracheobronchial involvement of GPA often poses specific challenges. First, tracheobronchial inflammation may be more resistant to systemic immunosuppressive therapy compared to other disease manifestations. Second, symptoms of progressive airway obstruction may be the result of scarring or damage rather than of persistent inflammation, explaining their resistance to immunosuppressive therapy and calling for other interventions, such as dilation procedures or stent placements for airway stenosis or the application of continuous positive airway pressure (CPAP) treatment in patients with tracheo- or bronchomalacia. Third, localized persistent infections with organisms such as *Staphylococcus aureus* or *Pseudomonas aeruginosa* may be persistent "antigenic drivers" of the autoimmune inflammation unless addressed with appropriate antimicrobial therapy. For this reason, potential pathogens identified by bronchoscopic sampling of the airway

secretions are treated based on antimicrobial susceptibility results in our practice. Finally, to suppress airway inflammation while minimizing cumulative systemic glucocorticoid exposure, we also advocate for the use of high-dose inhaled glucocorticoids in patients with tracheobronchial disease.

10.4 Pulmonary Capillaritis and Diffuse Alveolar Hemorrhage

GPA and MPA represent the most common causes of capillaritis of the lung leading to diffuse alveolar hemorrhage (DAH) [23] (Fig. 10.3). About a quarter of patients with GPA or MPA will present with or experience DAH during the course of their disease [13, 24]. By contrast, DAH occurs rarely (0–10%) in EGPA, where it seems to be linked to the presence of MPO-ANCA [25–27]. The clinical presentation of DAH is non-specific, consisting of various degrees of dyspnea, hypoxemia, diffuse alveolar filling defects detectable by chest imaging studies, and anemia. Cough may not be a prominent feature, and hemoptysis is absent as presenting feature in a third of patients with DAH [28, 29].

If suspected, DAH should be confirmed or ruled out. This is usually accomplished by bronchoscopy with bronchoalveolar lavage (BAL). At the same time, the BAL procedure offers the opportunity to collect specimens for detailed microbiologic studies

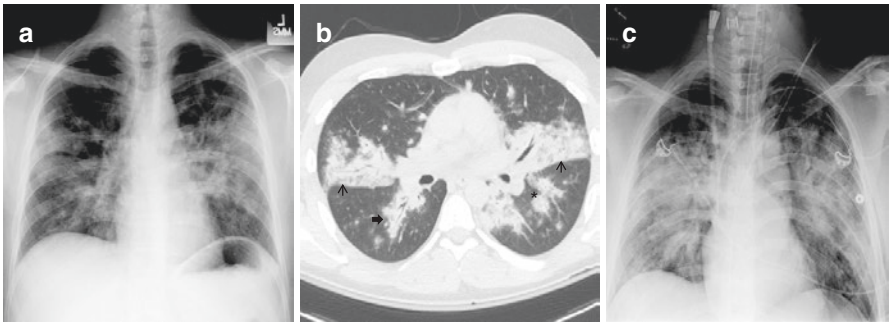

Fig. 10.3 Diffuse alveolar hemorrhage. (Panel **a**) Chest roentgenogram of a 20-year-old man with known GPA, PR3-ANCA-positive, presenting with cough, fever, malaise, and arthralgias, but without hemoptysis, to the emergency department on Day 1. Hemoglobin is 11.0 g/dL and oxygen saturation on room air is 94%. The patient is given antibiotics and dismissed for further outpatient evaluation the next day. (Panel **b**) Computed tomography is performed the next day (day 2) showing typical features of diffuse alveolar hemorrhage, including dense infiltrates and consolidation with air bronchograms, partially respecting lobar borders (thin arrows). Nodules (star) and peribronchial inflammation (bold arrow) are radiographic features that point toward GPA as underlying cause of the hemorrhage. The patient is admitted to the intensive care unit. (Panel **c**) Rapid progression of hemorrhage by day 3. Hemoglobin is now 8.0 g/dL, and the patient is intubated and receives mechanical ventilation. This patient also suffered bilateral pneumothoraces requiring placement of chest tubes. This case illustrates how quickly patients with diffuse alveolar hemorrhage can progress from a relatively indolent clinical presentation to respiratory failure requiring intensive care

for the identification or exclusion of an infection. If the bleeding originates with the alveolar space, successively returned BAL aliquots turn bloodier. In contrast, if the bleeding source is in the large airways, the first returned aliquot is the bloodiest, and subsequent aliquots of return become clearer. A negative BAL does not rule out that the diffuse alveolar filling defect on chest imaging is caused by DAH or capillaritis as the bleeding may have stopped by the time the BAL is performed. However, in that case, at least 20% of alveolar macrophages should stain positive for iron deposits, which is a well-accepted BAL criterion for alveolar hemorrhage [30]. However, this criterion is not entirely specific for DAH as up to a third of patients with diffuse alveolar damage may also have more than 20% hemosiderin-laden macrophages in their BAL fluid [31]. In very acute situations, iron-laden alveolar macrophages may not yet be detectable, as it is assumed to take a minimum of 24–48 h for the macrophages to engulf the hemoglobin and turn positive on iron stains; this is based on a study in mice in which hemosiderin was first detectable in alveolar macrophages on day 3 following intranasal blood instillation [32]. The percentage of hemosiderin-laden macrophages was not identified as a predictor of progression to respiratory failure in DAH caused by AAV, but the presence of greater than 30% neutrophils on the BAL differential cell count was an independent risk factor for development of respiratory failure, probably because it is an indirect marker for the severity of the interstitial inflammation [28]. Bronchoscopy and BAL should only be performed in clinical setting where the level of care can easily be escalated, as the procedure may result in temporary acute worsening of the patient's respiratory status requiring a higher level of respiratory support including intubation and mechanical ventilation.

The differential diagnosis of DAH related to AAV depends on when it occurs in the patient's disease course. If DAH is the first presentation of the disease, all other possible causes of DAH need to be considered until the diagnosis of AAV is substantiated. Once respiratory support is assured and adequate oxygenation has been secured, the first decision to make is whether and when to initiate therapy with high-dose glucocorticoids (usually in the form of 1–3 pulses of 500–1000 mg of intravenous methyl-prednisolone). This decision depends on whether an immunologic cause of the DAH is suspected or not. Any combination of the four factors, including the presence of (1) respiratory symptoms exceeding 11 days prior to presentation, (2) constitutional symptoms such as fatigue and/or weight loss, (3) arthralgias or arthritis, and (4) proteinuria of greater than 1 g per liter, has been identified as having a very high positive predictive value for an immunologic cause of DAH, which should prompt the institution of glucocorticoid therapy [33, 34].

The diagnosis of a specific immunologic cause of DAH including GPA, MPA, or EGPA can usually be established when the complete clinical context is considered in conjunction with specific serological testing for the specific autoimmune conditions that can cause alveolar hemorrhage. A lung biopsy is usually not necessary and is associated with a very unfavorable risk-to-benefit ratio. If tissue confirmation is needed for a diagnosis of GPA or MPA, it can usually be obtained in a safer manner from other organs such as skin, nose and sinuses, or kidneys. A kidney biopsy may also provide additional valuable prognostic information, which a lung biopsy cannot [35–37].

If DAH is suspected in an established patient with GPA or MPA because of the clinical presentation of dyspnea, hypoxemia, and radiographic alveolar filling defects, the differential diagnosis includes infection, particularly if the patient is being treated with immunosuppressive agents, drug toxicity, and other unrelated co-morbidities. Again, bronchoscopy with BAL is indicated in such patients.

DAH is a severe disease manifestation of GPA and MPA, which can rapidly progress to respiratory failure threatening the patient's life. Mortality rates reported in the largest most recent series range from about 10% to 25% [28, 38]. If patients survive the original episode of DAH, their response to treatment is similar to that of patients with all other disease manifestations of GPA and MPA in aggregate [13, 28]. In most cases, the lung parenchyma also recovers without significant loss in lung function [28, 39]. Early detection of DAH and prompt implementation of definitive therapy is the key to curb the early mortality associated with DAH caused by GPA or MPA.

A multivariate analysis conducted in a cohort of 73 patients with DAH caused by GPA or MPA has identified three risk factors portending a high likelihood of progression to respiratory failure requiring ventilatory support. They include an oxygen saturation measured by pulse oximetry (SpO_2) to fraction of inspired oxygen (FiO_2) ratio of <450 (OR 74, 95% CI 9–180) measured at the time of first presentation, a C-reactive protein level >25 mg/dL (OR 7.4, 95% CI 1.7–48), and the presence of >30% neutrophils on the differential cell count of the BAL fluid (OR 6.4, 95% CI 1.6–34) [28]. Consequently, the SpO_2:FiO_2 ratio should be determined in any patient with vasculitis presenting with dyspnea or with a pulmonary infiltrate even in the absence of dyspnea or hemoptysis, so that the appropriate level of care can be chosen for the implementation of further diagnostic and therapeutic interventions.

Patients with DAH caused by GPA or MPA respond well to standard therapy for severe disease manifestations. The response of patients with DAH to the application of 1–3 daily pulses of 1 g of intravenous methyl-prednisolone followed by oral prednisone in combination with either rituximab (RTX) or cyclophosphamide (CYC) was equivalent to that of the entire trial cohort in the RAVE trial [13]. An analysis of a large single-center cohort (n = 73) showed similar early response rates and hospital survival in patients treated with RTX or CYC. Complete remission, defined as a Birmingham Vasculitis Activity score of 0 and complete discontinuation of prednisone by 6 months, was superior in patients treated with RTX compared to those treated with CYC (89% versus 68%, $p = 0.02$), even in the subset of patients who required mechanical ventilation ($n = 31$, 83% with RTX versus 42% with CYC, $p = 0.02$), a group of patients that was excluded from enrollment into the RAVE trial [28].

The addition of plasma exchange (PLEX) to standard immunosuppressive therapy has been advocated to curb the early mortality associated with DAH in the setting of AAV based on a single report of 20 patients treated with PLEX and surviving the initial hospitalization [40]. However, a larger single-center cohort analysis of 73 patients, 32 of which were treated with PLEX, did not identify any benefit derived from PLEX after adjustment for the disease severity and treatment (RTX versus CYC) [28]. Results from a large multicenter randomized controlled trial comparing

PLEX to no PLEX in AAV also showed no benefit of PLEX in the subset of patients with DAH [41]. Consequently, the addition of PLEX to standard immunosuppressive therapy can no longer be advocated.

10.5 Interstitial Lung Disease and ANCA with or Without MPA

An association between fibrotic interstitial lung disease (ILD) and MPO-ANCA and MPA is increasingly recognized but remains poorly understood [42–44]. Case reports and case series from all over the world have documented interstitial lung disease in patients who are ANCA-positive. MPO-ANCA is the predominant ANCA type encountered in the context of interstitial lung disease. In contrast, PR3-ANCA occurs rarely. The patients with PR3-ANCA may or may not have abnormal markers of inflammation or typical signs of vasculitis (MPA) in other organs. Careful review and analysis of these reports indicate that in the majority of cases, the interstitial lung disease either has radiographic and histopathologic features of nonspecific interstitial pneumonitis (NSIP) (Fig. 10.4a, b) or of usual interstitial pneumonia (UIP) (Fig. 10.4c, d). However, atypical features including follicular bronchiolitis have also been reported. The available reports suggest the following common themes:

1. Patients who are MPO-ANCA-positive with ILD have a 25% chance of subsequently developing clinical features of MPA [45, 46]. This progression to MPA has been documented for MPO-ANCA, but has not been observed for PR3-ANCA [45].
2. The lung disease seems to precede the development of frank MPA. This is most clearly documented for lung fibrosis with radiographic patterns of UIP [43].
3. Patients who present with a radiographic pattern of NSIP show a response to immunosuppressive therapy of their ILD, whereas patients with UIP appear unresponsive to immunosuppressive therapy, and the lung continues to decline as expected for idiopathic pulmonary fibrosis.
4. Patients with overt manifestations of MPA, with or without alveolar hemorrhage superimposed on their ILD, show a clinical response to immunosuppressive therapy of the vasculitis disease manifestations as expected for MPA. If overt MPA is present, the ILD may respond to immunosuppressive therapy if the fibrosis has features of cellular NSIP. However, if the patient's lung fibrosis is of the UIP variety, no response to immunosuppression can be expected for the pulmonary fibrosis. It remains unclear, whether such patients with UIP would benefit from treatment with anti-fibrotic agents.

Based on these observations, pulmonologists at Mayo Clinic have adopted the empiric clinical management approach to patients with MPO-ANCA and ILD summarized in Table 10.1. This clinical approach assures that patients who have overt features of MPA receive appropriate therapy for severe disease manifestations of

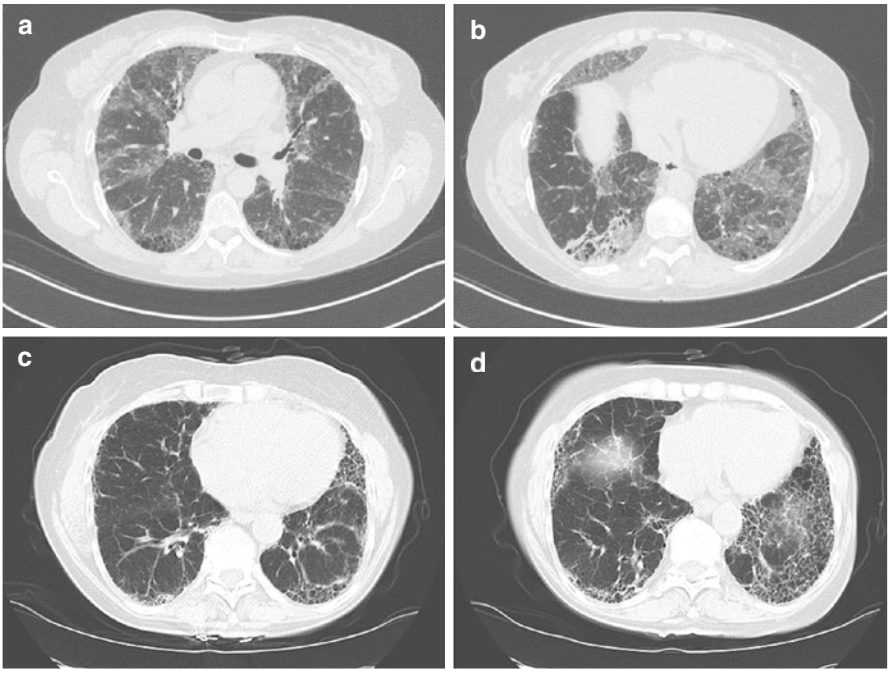

Fig. 10.4 Interstitial lung disease associated with MPO-ANCA. (Panel **a** and **b**) Chest computed tomography cuts from a 49-year-old patient with a 4-year history of MPO-ANCA-positive interstitial lung disease showing bilateral diffuse ground-glass infiltrates in the upper and lower lobes. Cystic scarring is also seen in the lower lobes posteriorly with some traction bronchiectases. These features are consistent with nonspecific interstitial pneumonitis. The cystic fibrotic lesions are too large to be called honeycombing. Two years following the diagnosis of interstitial lung disease, the patient developed mononeuritis multiplex and glomerulonephritis despite receiving low-dose prednisone and mycophenolate mofetil. (Panel **c** and **d**). Chest computed tomography cuts obtained from a 76-year-old lady who presented with cough and shortness of breath, an elevated sedimentation rate and C-reactive protein, and a positive MPO-ANCA test result, but without any other organ symptomatology. The images show fibrotic changes, including honeycombing and traction bronchiectases with a lower lung predominance and peripheral distribution and complete absence of ground-glass infiltrates; these features are typical for usual interstitial pneumonia (UIP). Review of old chest X-rays revealed the presence of fibrotic changes in the lower lungs dating back 4 years. She never developed any signs or symptoms of MPA, and died 5 years later of an "acute exacerbation of IPF"

ANCA vasculitis in the form of remission induction therapy with glucocorticoids and cyclophosphamide or rituximab following the principles and guidelines of therapy for AAV [11].

Also, patients who present with an NSIP pattern will receive a trial of immunosuppressive therapy, even if no other organ disease manifestations of MPA are apparent. Since this immunosuppressive therapy is generally regarded as effective remission maintenance therapy for AAV, it may prevent the development of overt MPA in other organs while also preventing progression of the lung disease to irreversible fibrosis.

Table 10.1 Management of patients with MPO-ANCA and interstitial lung disease

Fibrosis pattern	Elevated markers of inflammation (ESR, DAH)	Extrapulmonary signs of vasculitis or DAH	Management
UIP	No	No	Observe and monitor for microhematuria[b]
UIP	Yes	No	Observe and monitor for microhematuria[a]
UIP	Yes	Yes	Treat for MPA[a,b]
NSIP	No	No	GCS plus MMF or AZA
NSIP	Yes	No	GCS plus MMF or AZA
NSIP	Yes	Yes	Treat for MPA[a]

[a]Standard immunosuppressive therapy following standard guidelines for MPA
[b]Consider anti-fibrotic therapy for UIP following guidelines for idiopathic pulmonary fibrosis
AZA azathioprine, *CRP* C-reactive protein, *DAH* diffuse alveolar hemorrhage, *ESR* erythrocyte sedimentation rate, *GCS* glucocorticoids, *MPA* microscopic poliangiitis, *MMF* mycophenolate mofetil, *NSIP* non-specific interstitial pneumonia, *UIP* usual interstitial pneumonia

At this point, we have not seen any beneficial effect of lung fibrosis of the UIP pattern in patients with MPO-ANCA, with or without features of MPA. Therefore, we do not believe that immunosuppressive therapy is beneficial or indicated in such patients in the absence of other overt features of MPA. However, since a sizable proportion of such patients will develop MPA later, and the development of renal disease can be slow and indolent, yet lead to irreversible renal insufficiency, we monitor patients for the development of glomerulonephritis by screening the urine for microhematuria at least on a monthly basis. This way, the development of glomerulonephritis is detected early, and effective therapy can be initiated before severe renal damage occurs. At the same time, such patients with UIP are not exposed to immunosuppressive therapy that could even be detrimental as shown in a randomized controlled trial of idiopathic pulmonary fibrosis [47]. As the UIP seems to precede disease manifestations of MPA in most patients, we do not consider the lung fibrosis a priori a disease manifestation of MPA, but rather a pre-existing comorbidity, and anti-fibrotic therapy may be an appropriate option for such patients with UIP.

10.6 Conclusion

Pulmonary parenchymal or tracheobronchial involvement is common in ANCA-associated vasculitis. The clinical presentation and symptoms including the severity of the disease depend on the underlying type of inflammation, on the affected tissue compartments, and on the ANCA-type and the clinical syndrome in which they occur. A conceptual separation into four main categories, including, (1) pulmonary parenchymal disease manifestations caused by the necrotizing granulomatous inflammation of GPA, (2) tracheobronchial inflammation often leading to airway compromise in the context of GPA, (3) diffuse alveolar hemorrhage as an

acute and severe disease manifestation caused by capillaritis in GPA or MPA, and (4) an association of interstitial lung disease and fibrosis with MPO-ANCA and MPA, is practical for clinicians, as such a categorization allows a systematic differential diagnostic approach and therapy that is appropriately targeted to individual patients.

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