acta medica

REVIEW

Pulmonary involvement in ANCA-associated vasculitis

Elif Durak Ediboğlu[1], Pınar Akyüz Dağlı[2], Deniz Köksal[3]

[1] Rheumatology Clinic, Hatay Training and Research Hospital, Hatay, Türkiye.

[2] Rheumatology Clinic, Gülhane Training and Research Hospital, Ankara, Türkiye.

[3] Department of Chest Disease, School of Medicine, Hacettepe University, Ankara, Türkiye.

Corresponding Author: Elif Durak Ediboğlu ▪ E-mail: eliff_durak@hotmail.com

This manuscript was peer-reviewed by Dr. Hakan Babaoğlu.

ABSTRACT

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) comprises systemic disorders, mainly GPA and MPA, characterized by small- and medium-vessel inflammation with frequent pulmonary involvement. Thoracic manifestations are diverse and include tracheobronchial disease, pulmonary nodules and cavitary lesions, diffuse alveolar hemorrhage, interstitial lung disease, bronchiectasis, and pleural involvement, each with distinct clinical and radiological features. Diagnostic evaluation requires integration of clinical findings, high-resolution CT, pulmonary function tests, bronchoscopy, and histopathology, while excluding infectious and malignant causes. Tuberculosis remains a major diagnostic challenge, particularly in endemic regions, due to overlapping clinical, radiological, and even serological features. Treatment typically involves high-dose glucocorticoids with cyclophosphamide or rituximab, with management tailored according to the extent and pattern of pulmonary involvement. Close monitoring is especially important in patients with MPO-ANCA positivity and interstitial lung disease, given the risk of progression to systemic vasculitis.

Keywords: ANCA-associated vasculitis, granulomatosis with polyangiitis, microscopic polyangiitis, pulmonary involvement.

INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) represents a group of systemic vasculitides that predominantly affect small and medium sized vessels [1]. AAV is classified into three main clinical subtypes, each characterized by distinct pathological, serological, and clinical features.

1. Granulomatosis with Polyangiitis (GPA), formerly known as Wegener's granulomatosis, frequently involves the kidneys as well as the upper and lower respiratory tracts.
2. Microscopic polyangiitis (MPA), which commonly affects the kidneys and lungs, is characterized by necrotizing vasculitis without granulomatous inflammation.
3. Eosinophilic Granulomatosis with Polyangiitis (EGPA), previously known as Churg-Strauss syndrome, is typically characterized by asthma, peripheral blood eosinophilia, and multisystem organ involvement.

Each subtype exhibits a distinctive pattern of pulmonary involvement, which plays a pivotal role in establishing the diagnosis, guiding therapeutic strategies, and determining prognosis. This review discusses the main thoracic manifestations observed in GPA and MPA.

1. Tracheobronchial involvement

Tracheobronchial involvement is common in GPA and is characterized by inflammation of the tracheobronchial mucosa, which can lead to

ulceration, tracheo- and/or bronchomalacia, and subglottic stenosis. Mucosal lesions are typically segmental and focal, presenting with inflammation and mucosal ulceration, and may lead to fibrosis, stenosis, or airway malacia if cartilage is involved. Subglottic stenosis, defined as narrowing of the airway just below the vocal cords, is the most common tracheobronchial manifestation in GPA [2]. Symptoms such as stridor, hoarseness, and dyspnea require urgent evaluation and may necessitate tracheostomy in severe cases. Biopsy of tracheobronchial lesions often reveals non-specific mucosal inflammation and fibrosis, while overt vasculitis is rarely observed [3]. Treatment includes high-dose systemic glucocorticoids, cyclophosphamide, or rituximab. Airway obstruction secondary to fibrosis or scarring can be managed with balloon dilation, laser ablation, local steroid injections, cryotherapy, or rarely surgical interventions [3,4].

2. Pulmonary nodules, masses, and consolidations

Pulmonary nodules are common in GPA, although they may occur in all types of AAV. They are present in 40–70% of GPA patients at presentation, and are often bilateral, frequently associated with infiltrates or consolidations. Cavitation occurs in 20–50% of nodules [5,6]. These nodules are often subpleural, vary in size from a few millimeters up to 10 cm, and may cavitate as they enlarge. Cavities typically have thick, irregular walls and lack calcification. The halo sign, defined as ground-glass opacity surrounding a nodule, is frequently seen and indicates accompanying alveolar hemorrhage. Air bronchograms within nodules are also typical.

The differential diagnosis of pulmonary nodules and masses in GPA/MPA includes tuberculosis (TB), septic emboli, multiple abscesses, fungal infections, hematogenous metastases, lymphoma, and organizing pneumonia. Clinical, radiological, histopathological, microbiological, and serological findings are essential for establishing the correct diagnosis. Exclusion of malignancy is crucial before diagnosing AAV. Radiologically, the development of nodules and masses within days to weeks makes malignancy less likely. Importantly, TB and other infectious causes must be excluded to avoid misdiagnosis and inappropriate initiation of immunosuppressive therapy.

The diagnostic evaluation must encompass acid-fast bacilli (AFB) staining, fungal stains, and microbiological cultures [7]. In regions where TB is endemic, the differential diagnosis is particularly challenging due to overlapping clinical and radiological features of both diseases. In cases of large cavitary lesions, a negative sputum AFB smear may help rule out active TB. Detection of AFB in tissue samples is difficult, therefore real-time polymerase chain reaction (PCR) testing can be performed. However, clinicians should recognize that PCR results may remain positive for years in patients with a prior history of TB treatment, and a negative PCR result does not conclusively exclude TB [8]. Accurate diagnosis requires biopsy of pulmonary lesions, sputum microscopy, and a multidisciplinary evaluation. Interferon-gamma release assays (e.g., QuantiFERON-TB) and c-ANCA testing may aid in differentiating TB from GPA. Importantly, ANCA positivity can be observed in the context of TB infection, which may create a complex diagnostic dilemma [9].

The treatment of pulmonary nodules in AAV depends on the extent of disease involvement. Localized disease is typically managed with methotrexate and systemic corticosteroids, whereas systemic involvement requires a combination of high-dose glucocorticoids with either cyclophosphamide or rituximab. Although individual responses to therapy may vary, treatment should be continued as long as there is radiological evidence of lesion regression [1,3].

3. Diffuse alveolar hemorrhage

Diffuse alveolar hemorrhage (DAH) can be defined as the leakage of blood into the alveolar spaces due to increased capillary wall permeability from capillaritis, resulting in impaired oxygenation. Clinical manifestations may include dyspnea, hypoxemia, and anemia, depending on the severity of organ involvement. Hemoptysis is often absent or scant. DAH can cause life-threatening hypoxemia, making early diagnosis and prompt management essential. In patients suspected of DAH, chest radiography can be performed as the initial imaging modality; however, up to half of these patients may have normal radiographic findings [10]. If clinical suspicion persists, thorax CT should be performed. Typical CT findings include bilateral alveolar opacities, intra- and interlobular septal thickening, ground-glass opacities, and a

crazy-paving pattern. In the differential diagnosis of DAH, it is essential to consider not only other immune-mediated diseases, such as anti-glomerular basement membrane disease and IgA vasculitis, but also non-immune-mediated causes, particularly infections, coagulation disorders, and, hemodynamic factors. Bronchoalveolar lavage (BAL) is considered the gold standard for diagnosis and is also crucial to identifying infectious processes included in the differential diagnosis [3].

The primary treatment regimen consists of high-dose glucocorticoids in conjunction with either cyclophosphamide or rituximab. Mechanical ventilation and admission to the intensive care unit (ICU) may be necessary in severe cases. Plasmapheresis is not advised for routine use per EULAR guidelines [1].

4. Interstitial lung disease

AAV-associated interstitial lung disease (ILD) represents a pulmonary involvement that most commonly develops during the course of MPO-ANCA-positive AAV. Clinically, patients often present with nonspecific respiratory symptoms, such as progressive exertional dyspnea and a chronic nonproductive cough, which may evolve gradually over weeks to months. ILD can be identified either prior to the diagnosis of AAV or during follow-up. High resolution thorax CT typically demonstrates ground-glass opacities, reticular opacities, interlobular septal thickening, consolidation, and honeycomb patterns. In MPO-ANCA–positive AAV patients, the most frequently observed radiological pattern of ILD is the usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP) ,and, less frequently, desquamative interstitial pneumonia (DIP). Pulmonary function tests reveal a restrictive ventilatory defect accompanied by reduced diffusing capacity for carbon monoxide (DLCO) and decreased lung volumes.

At the time of diagnosis, ANCA positivity is detected in approximately 5–10% of patients with ILD [11]. In some patients, ANCA tests may be negative at diagnosis but become positive during follow-up. Notably, around 25% of MPO-ANCA positive ILD patients subsequently develop MPA [11-13]. Therefore, regular monitoring for systemic manifestations of AAV is strongly recommended in patients with MPO-ANCA positive ILD, even in the absence of extrapulmonary involvement.

There is currently no clear consensus regarding the use of immunosuppressive therapy in patients with positive MPO-ANCA and concomitant ILD. In cases of active MPA, immunosuppressive treatment should be initiated. However, in patients with ILD and positive ANCA, close monitoring for other organ involvement is essential, given the potential adverse effects of immunosuppressive therapy [13]. There are insufficient data regarding the efficacy of antifibrotic agents (nintedanib, pirfenidone) in AAV patients with interstitial fibrosis. In the recently published guideline on the treatment of progressive pulmonary fibrosis (PPF), antifibrotic therapy is recommended for PPF secondary to autoimmune ILDs, including vasculitides [14]. Nintedanib is the first-line agent recommended, whereas pirfenidone is considered a second-line option due to limited evidence.

5. Bronchiectasis

The association between bronchiectasis and AAV has been described in case reports and small case series [15,16]. The reported prevalence of bronchiectasis among patients with AAV varies considerably in the literature. A recent study reported a prevalence of 19% in patients with AAV [16]. In patients with MPA, the prevalence ranges between 16% and 37.9% [15-17]. Importantly, several studies have demonstrated a strong association between anti-MPO positivity and bronchiectasis [16].

Currently, there are no specific guidelines for the management of patients with both bronchiectasis and AAV. However, the presence of bronchiectasis should not preclude the use of intensive immunosuppressive therapies when clinically indicated [16,17]. Due to the high risk of respiratory infections, influenza and pneumococcal vaccinations are recommended. Even in patients without known airway colonization, bronchiectasis warrants careful monitoring for infection, especially during MPA follow-up. For patients with bronchial obstruction, bronchodilators may be used regularly. In cases of co-existing asthma, inhaled corticosteroids may be added. Airway clearance techniques should be taught by respiratory physiotherapists. Nebulized saline or sterile water can facilitate mucus clearance, especially if combined with pre-treatment using

bronchodilators in patients prone to bronchospasm. Regular use of mucolytics is not recommended, but intermittent use may be considered for patients with difficulty expectorating. If bacterial colonization (e.g., *Pseudomonas aeruginosa*) is detected, appropriate eradication therapy should be considered.

6. Pleural involvement

Pleural effusion or pleuritis is reported in approximately 5–20% of AAV patients, according to various case series [18]. Early recognition of pleural involvement may help prevent disease recurrence or progression to other organ systems.

Diagnostic Methods for Pulmonary Involvement in GPA/MPA

Diagnosis of pulmonary involvement in GPA/MPA requires a comprehensive approach that integrates clinical suspicion, serological testing, imaging modalities, fiberoptic bronchoscopy, and, when indicated, histopathological confirmation. The clinical spectrum is highly variable. While some patients may be asymptomatic, others may present with symptoms depending on the site of involvement, such as cough, dyspnea, hoarseness, stridor, sputum production, hemoptysis, and pleuritic chest pain, often accompanied by constitutional symptoms [19]. On physical examination, findings may range from subtle crackles, wheezes, decreased breath sounds in the presence of effusion, or overt signs of respiratory distress in severe cases.

Thorax CT plays a pivotal role in the evaluation of suspected AAV, allowing detailed assessment of pulmonary nodules, cavitations, subpleural lesions, airway inflammation, and stenoses, which conventional chest radiography often fails to detect [5]. It also provides more accurate visualization of ILD and DAH. A baseline CT scan is recommended prior to initiating immunosuppressive therapy to document the extent of pulmonary involvement. In patients with concomitant renal involvement, non-contrast CT is preferred to minimize the risk of contrast-induced nephropathy. Additionally, three-dimensional reconstruction of the tracheobronchial tree can further facilitate the evaluation of airway involvement, particularly in cases with stenotic lesions.

Pulmonary function tests provide valuable information in the assessment of respiratory involvement in AAV. Spirometry can help detect extrathoracic obstruction, such as subglottic stenosis, or intrathoracic obstruction in cases of tracheobronchial involvement. In patients with İLD, DLCO is typically reduced. For longitudinal monitoring of ILD, a combination of spirometry, DLCO measurement, and the six-minute walk test (6MWT) is recommended to assess functional impairment and disease progression [14].

Fiberoptic bronchoscopy is a useful tool in GPA patients with suspected tracheobronchial involvement, allowing targeted biopsies from inflamed mucosa or lung parenchyma. However, due to the small size of these samples, histopathological evidence of granulomatous vasculitis may not always be detected, and a negative result does not exclude the diagnosis of GPA. Although capillaritis can sometimes be observed in biopsies from patients with DAH, the invasiveness and associated risks of lung biopsy generally limit its use as a routine diagnostic procedure. In cases of suspected DAH, BAL from the affected segment can provide important diagnostic information. A progressively bloody return on sequential lavage aliquots is suggestive of DAH. Cytological analysis revealing ≥20% hemosiderin-laden macrophages is considered diagnostic [20]. In addition, BAL allows for microbiologic evaluation to help exclude infectious causes, which is essential in the differential diagnosis of pulmonary involvement in AAV.

Lung biopsy may be indicated in patients presenting with pulmonary nodules, masses, or consolidation. CT-guided percutaneous or thoracoscopic approaches can be utilized; however, small tissue samples obtained via percutaneous biopsy may limit the diagnostic yield. Targeted biopsies from active, non-necrotic areas increase the likelihood of obtaining a definitive diagnosis. In GPA, histopathological examination typically demonstrates necrotizing granulomatous inflammation. To exclude granulomatous infections such as TB, appropriate special stains and microbiologic cultures should always be performed. Histopathologic examination provides critical insight into the pulmonary manifestations of AAV. In GPA, granulomas typically begin as

neutrophilic microabscesses, which may cause partial or complete vascular occlusion. Unlike the well-formed granulomas observed in TB or sarcoidosis, GPA granulomas are irregular and consist of multinucleated giant cells surrounded by plasma cells, lymphocytes, and dendritic cells. Biopsies often reveal central necrosis, palisading histiocytes, and multinucleated giant cells, with necrosis evolving into liquefactive or coagulative forms. Necrotizing or granulomatous vasculitis may also be present in small arteries and veins, frequently leading to vessel occlusion from granulomas or thrombi. In contrast, MPA lacks granulomatous inflammation, with pulmonary capillaritis representing its characteristic histologic hallmark.

REFERENCES

[1] Hellmich B, Sanchez-Alamo B, Schirmer JH, et al. EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update. Ann Rheum Dis 2024;83(1):30-47. https://doi.org/10.1136/ard-2022-223764

[2] Quinn KA, Gelbard A, Sibley C, et al. Subglottic stenosis and endobronchial disease in granulomatosis with polyangiitis. Rheumatology (Oxford) 2019;58(12):2203-2211. https://doi.org/10.1093/rheumatology/kez217

[3] Sacoto G, Boukhlal S, Specks U, Flores-Suárez LF, Cornec D. Lung involvement in ANCA-associated vasculitis. Presse Med 2020;49(3):104039. https://doi.org/10.1016/j.lpm.2020.104039

[4] Almuhanna A, Almahboob A, Alhussien A, Aljurayyed R, Alammar A. Current Therapeutic Approaches to Subglottic Stenosis in Patients With GPA: A Systematic Review. Ear Nose Throat J 2024;103(2):117-125. https://doi.org/10.1177/01455613211036246

[5] Castañer E, Alguersuari A, Gallardo X, et al. When to suspect pulmonary vasculitis: radiologic and clinical clues. Radiographics 2010;30(1):33-53. https://doi.org/10.1148/rg.301095103

[6] Feragalli B, Mantini C, Sperandeo M, et al. The lung in systemic vasculitis: radiological patterns and differential diagnosis. Br J Radiol 2016;89(1061):20150992. https://doi.org/10.1259/bjr.20150992

[7] Ohshimo S, Guzman J, Costabel U, Bonella F. Differential diagnosis of granulomatous lung disease: clues and pitfalls: Number 4 in the Series "Pathology for the clinician" Edited by Peter Dorfmüller and Alberto Cavazza. Eur Respir Rev 2017;26(145):170012. https://doi.org/10.1183/16000617.0012-2017

[8] Theron G, Venter R, Smith L, et al. False-Positive Xpert MTB/RIF Results in Retested Patients with Previous Tuberculosis: Frequency, Profile, and Prospective Clinical Outcomes. J Clin Microbiol 2018;56(3):e01696-17. https://doi.org/10.1128/JCM.01696-17

[9] Bossuyt X, Cohen Tervaert JW, Arimura Y, et al. Position paper: Revised 2017 international consensus on testing of ANCAs in granulomatosis with polyangiitis and microscopic polyangiitis. Nat Rev Rheumatol 2017;13(11):683-692. https://doi.org/10.1038/nrrheum.2017.140

[10] Cortese G, Nicali R, Placido R, Gariazzo G, Anrò P. Radiological aspects of diffuse alveolar haemorrhage. Radiol Med 2008;113(1):16-28. https://doi.org/10.1007/s11547-008-0229-x

[11] Kagiyama N, Takayanagi N, Kanauchi T, Ishiguro T, Yanagisawa T, Sugita Y. Antineutrophil cytoplasmic antibody-positive conversion and microscopic polyangiitis development in patients with idiopathic pulmonary fibrosis. BMJ Open Respir Res 2015;2(1):e000058. https://doi.org/10.1136/bmjresp-2014-000058

[12] Hozumi H, Oyama Y, Yasui H, et al. Clinical significance of myeloperoxidase-anti-neutrophil cytoplasmic antibody in idiopathic interstitial pneumonias. PLoS One 2018;13(6):e0199659. https://doi.org/10.1371/journal.pone.0199659

[13] Liu GY, Ventura IB, Achtar-Zadeh N, et al. Prevalence and Clinical Significance of Antineutrophil Cytoplasmic Antibodies in North American Patients With Idiopathic Pulmonary Fibrosis. Chest 2019;156(4):715-723. https://doi.org/10.1016/j.chest.2019.05.014

[14] Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 2022;205(9):e18-e47. https://doi.org/10.1164/rccm.202202-0399ST

[15] Gu Y, Zhang T, Zhu W, Han Y, Shi J. Prevalence and characteristics of bronchiectasis in ANCA-associated vasculitis: A systematic review and meta-analysis. Arch Rheumatol 2024;39(3):488-509. https://doi.org/10.46497/ArchRheumatol.2024.10352

[16] Néel A, Espitia-Thibault A, Arrigoni PP, et al. Bronchiectasis is highly prevalent in anti-MPO ANCA-associated vasculitis and is associated with a distinct disease presentation. Semin Arthritis Rheum 2018;48(1):70-76. https://doi.org/10.1016/j.semarthrit.2017.12.002

[17] Lhote R, Chilles M, Groh M, et al. Spectrum and Prognosis of Antineutrophil Cytoplasmic Antibody-associated Vasculitis-related Bronchiectasis: Data from 61 Patients. J Rheumatol 2020;47(10):1522-1531. https://doi.org/10.3899/jrheum.190313

[18] Thompson GE, Bourne MH, Casal Moura M, et al. Pleuritis and Pericarditis in Antineutrophil Cytoplasmic Autoantibody-Associated Vasculitis. Chest 2021;160(2):572-581. https://doi.org/10.1016/j.chest.2021.02.049

[19] Gómez-Puerta JA, Hernández-Rodríguez J, López-Soto A, Bosch X. Antineutrophil cytoplasmic antibody-associated vasculitides and respiratory disease. Chest 2009;136(4):1101-1111. https://doi.org/10.1378/chest.08-3043

[20] Maldonado F, Parambil JG, Yi ES, Decker PA, Ryu JH. Haemosiderin-laden macrophages in the bronchoalveolar lavage fluid of patients with diffuse alveolar damage. Eur Respir J 2009;33(6):1361-6. https://doi.org/10.1183/09031936.00119108