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Antineutrophil cytoplasmic antibody-associated vasculitides: Clinical manifestations and pulmonary involvement

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Abstract:

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are necrotizing autoimmune vasculitis resulting from immune-mediated damage to small and medium-sized vessels. Three primary clinicopathological syndromes are defined in AAV: Granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). The disease may present as alveolar hemorrhage due to a systemic inflammatory response, purpuric rash due to vascular rupture, or segmental glomerular infarction due to vascular occlusion. The lungs are commonly affected organs in AAV, with lung involvement categorized into five main groups: pulmonary capillaritis characterized by granulomatous inflammation (lung nodules), tracheobronchial inflammation, diffuse alveolar hemorrhage (DAH), interstitial lung disease (ILD), and asthma. DAH and ILD are associated with a poor prognosis. The treatment goal is to achieve remission and prevent relapses.

Keywords:

ANCA-associated vasculitides, eosinophilic granulomatosis with polyangiitis, granulomatosis with polyangiitis, microscopic polyangiitis

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Introduction

Vasculitides are characterized by the infiltration of immune effector cells into blood vessels and surrounding tissues, leading to an inflammatory process. These conditions are associated with a significant incidence of constitutional symptoms and the potential for end-organ damage resulting from the narrowing or necrosis of vascular structures.[1]

Vasculitides are considered uncommon, with the primary form presenting with an annual occurrence rate of 20 to 100 cases per million individuals and a prevalence ranging from 150 to 450 cases per million people.[2] Due to their diverse

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nature, primary systemic vasculitides can potentially affect any organ within the body.[3] The lungs are commonly affected organs in systemic vasculitides, particularly in small-vessel antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV), which exhibit a higher propensity for lung involvement.[2,4] Vasculitides of large and medium vessels are less common, and their clinical manifestations have a less well-established spectrum. However, this type of vasculitide can also exhibit significant pulmonary involvement. This article discusses the clinicopathological features of AAV with pulmonary involvement.

Antineutrophil Cytoplasmic Antibody-Associated Vasculitides

ANCA-associated vasculitides refer to a specific category of autoimmune disorders distinguished by necrotizing vasculitis, minimal or absent deposits, and primarily immune-mediated damage to small blood vessels, including capillaries, venules, arterioles, and small arteries.[5] In relation to the systemic inflammatory response, it can give rise to an extensive spectrum of clinical manifestations and indications. Inflammatory states of vessels can lead to the occurrence of alveolar hemorrhage, a purpuric rash through vessel rupture, or segmental glomerular infarction through the occlusion of these vessels. Additionally, symptoms associated with microvascular damage to target organs or the mass effect of granulomas can also be observed.[6] ANCA-associated vasculitides include granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), and microscopic polyangiitis (MPA).[3,7]

Lung involvement occurs in approximately 30–50% of MPA patients, up to 60% in EGPA (including asthma in 95% of cases), and approximately 67–85% in GPA. Lung disease in AAV can occur in five main forms: granulomatous inflammation (lung nodules), tracheobronchial inflammation, diffuse alveolar hemorrhage (DAH), interstitial lung disease (ILD), and asthma. The incidence of these conditions varies. While the incidence of alveolar hemorrhage is 7.45% in GPA and 10–30% in MPA, it is rare in EGPA.[8] Pulmonary involvement in patients with AAV can be severe and can be considered a risk factor for mortality. The presence of DAH and ILD is associated with poor prognosis.[7]

Physiopathology of Antineutrophil Cytoplasmic Antibody-Associated Vasculitides

Antineutrophil cytoplasmic antibodies (ANCAs) are autoantibodies that specifically target myeloperoxidase (MPO) and proteinase 3 (PR3) antigens located in the cytoplasmic granules of neutrophils and the lysosomes of monocytes.[3,5] The production of ANCAs is influenced by the interaction of many factors, such as environmental factors, genetic susceptibility, and the immune system. Healthy individuals may possess natural autoantibodies targeting MPO and PR3. It has been suggested that silica, asbestos, infectious agents such as Ross River virus and *Staphylococcus* aureus, and some drugs such as propylthiouracil and hydralazine may play a role in the formation of pathogenic ANCAs.[3] Current research indicates a genetic predisposition to AAV.[3,9] Notably, variations in HLA genes play a significant role in determining autoimmune reactions to PR3 and MPO. Furthermore, epigenetic dysregulation of PR3 and MPO has been observed in the leukocytes of patients with AAV. This dysregulation leads to excessive expression of PR3 and MPO on the surface of neutrophils, which can trigger their activation by ANCAs, contributing to the breakdown of immune tolerance toward these proteins. Patients with AAV exhibit significant alterations in the regulatory functions of B and T cells. Specifically, autoreactive T lymphocytes targeting MPO or PR3 can serve as antigen-specific presenting cells, thereby triggering the production of pathogenic ANCAs by B cells. Patients with active AAV exhibit deficiencies in both the quantity and quality of B regulatory lymphocytes.[3]

Granulomatosis with Polyangiitis

GPA is characterized by necrotizing granulomatous inflammation affecting the upper and lower respiratory tracts, ears, and nose, along with necrotizing vasculitis predominantly affecting small- to medium-sized vessels, often involving necrotizing glomerulonephritis.[10] GPA is commonly associated with circulating PR3-ANCA and is the most common pulmonary vasculitis.[11] The disease course is highly variable. While some cases exhibit a slow progression, others may lead to organ failure and mortality due to rapidly developing multiorgan vasculitis.[12,13]

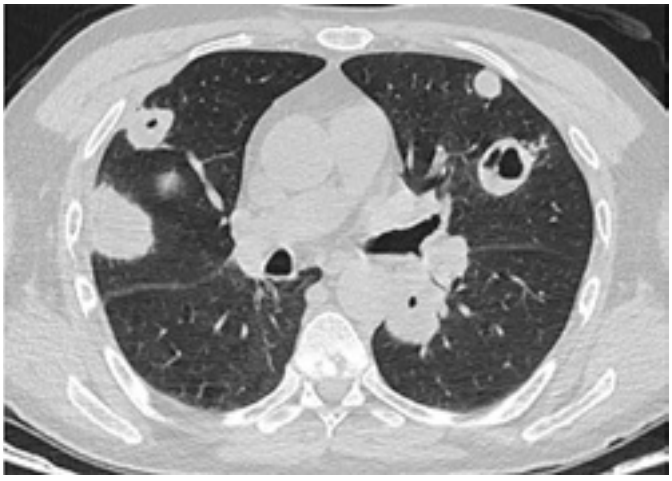

Figure 1: Nodules and cavities on thorax CT in granulomatosis with polyangiitis
CT: Computed tomography

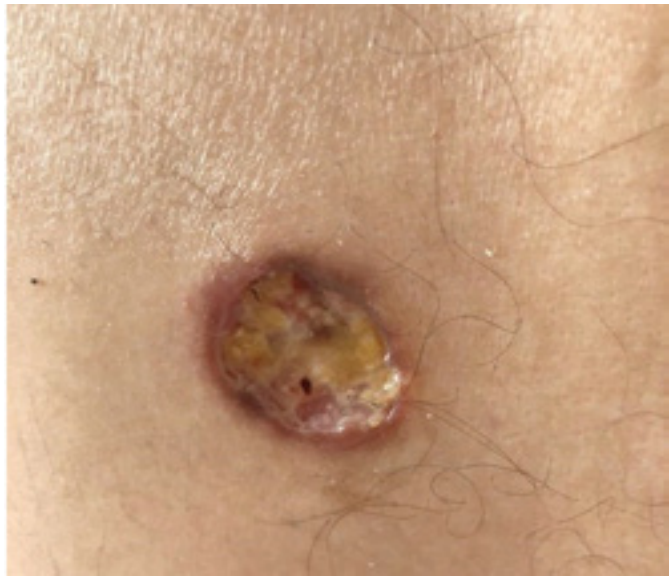

Figure 2: Necrotizing skin lesion in granulomatosis with polyangiitis

Clinical Findings

GPA typically presents with nonspecific disease symptoms, including fever, weight loss, malaise, polyarthralgia, and myalgia.[14] Upper respiratory tract (URT) involvement is observed in approximately 90% of the cases. The earliest symptoms of URT involvement include nasal congestion, mucosal tenderness, purulent discharge, nasal ulcerations, and epistaxis. Chronic rhinosinusitis can progress to nasal septum perforation, saddle nose deformity, serous otitis, and cutaneous fistulas.[14,15] Abnormalities are detected on sinus computed tomography in 85% of GPA cases.[12,13] Although conductive hearing loss due to nasopharyngeal disease is more common, sensorineural hearing loss may also occur. Sore throat or hoarseness should raise suspicion of vocal cord and pharynx involvement. Occasionally, adjacent structures to the URT, such as ulcers in the oral cavity, may also be affected.[16]

Pulmonary involvement is observed in 55–90% of cases.[13] The most common pattern of pulmonary involvement in GPA is nodules and mass lesions that can cavitate due to necrotizing granulomatous inflammation [Fig. 1]. Additionally, bilateral or unilateral lung infiltrates may also be observed.[17] Cases developing pleural effusion have also been reported. Although pulmonary fibrosis is more common in MPA among AAV, it can rarely be seen in GPA. Diffuse alveolar hemorrhage due to pulmonary capillaritis is a rare but potentially fatal complication of GPA.[18]

Subglottic stenosis can be observed in nearly 20% of cases and can be life-threatening. Inflammation and stenosis in the tracheobronchial tree may be present in a small proportion of cases with lung involvement.[17,19] Endobronchial disease does not typically cause obvious symptoms and may be incidentally observed on bronchoscopy. However, it may present with symptoms such as cough, hemoptysis, wheezing, dyspnea, or post-obstructive infection.

Kidney involvement develops at the onset of the disease in 40% of cases and within two years after beginning of the disease in 80% of patients.[12,20] Microscopic hematuria and proteinuria precede elevations in serum creatinine.[12] The most common renal lesion of GPA is segmental and focal glomerulonephritis. Rapidly progressive crescentic glomerulonephritis often develops, leading to end-stage renal disease.

Eye involvement is observed in approximately 20–50% of cases. Scleritis and conjunctivitis are most common, but episcleritis, peripheral ulcerative keratitis, and anterior uveitis may also occur. Tissue masses called pseudotumors may form in the retrobulbar area in 10–15% of patients. These may cause diplopia, proptosis, or vision loss.[13,19,20]

Skin involvement has been reported in 14–50% of cases. Palpable purpura, cutaneous nodules, ulcers, papules, vesicles, and subcutaneous nodules (granulomas) may be observed. Skin biopsies may show granulomatous vasculitis with necrosis, but leukocytoclastic vasculitis is more common.[13] Figure 2 illustrates a necrotizing skin lesion in GPA.

Neurological involvement is observed in 30–40% of cases. Both the central and peripheral nervous systems can be affected due to inflammation of the vasa nervorum. Mononeuritis multiplex or polyneuritis is the most common neurological manifestation. Cerebral or meningeal involvement occurs rarely in patients with GPA. Pachymeningitis is one of the serious manifestations of the disease and can cause irreversible damage despite adequate control of acute inflammation.[13,21–23]

Cardiac involvement is rare. Cardiomyopathy may develop due to small vessel involvement or inflammatory infiltration of the heart muscle. Pericarditis, valvulitis, coronary arteritis, and inflammatory pseudotumors may be observed.[24]

Laboratory and Diagnosis

Serum ANCA levels are elevated in most cases and typically correlate with disease activation. ANCA positivity is detected in 90% of cases with active generalized GPA and in 40–70% of those with localized disease. Among GPA patients with circulating ANCAs, nearly 90% are directed against PR3, while less than 10% are against MPO or other epitopes.[25,26]

High erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels are often associated with disease activation. However, these tests are nonspecific and may increase in some cases, such as infection.[12,13]

The diagnosis of GPA is established in patients with compatible clinical features, positive serological tests, histopathological evidence of necrotizing granulomatous vasculitis, and exclusion of other causes of vasculitis, such as drug-induced vasculitis.

Although the positivity of PR3-ANCA supports the diagnosis of GPA in cases with appropriate clinical, laboratory, and radiological findings, diagnosis ideally involves performing a biopsy from the area of involvement that is most accessible and histopathologically demonstrating the presence of vasculitis or granulomatous inflammation.[27]

The diagnostic value of the biopsy varies depending on the organ involved. Renal biopsy in patients with renal involvement yields a diagnostic accuracy of approximately 91.5%. It also aids in determining the prognosis of kidney disease. URT biopsies primarily show nonspecific inflammatory changes, with specific findings such as granulomas and vasculitis being less common. Lung biopsies yield variable results depending on the biopsy technique, with transbronchial biopsies being diagnostic in 12% of cases, while open lung biopsies offer higher diagnostic value.[28]

ANCA negativity does not completely exclude the diagnosis of AAV; ANCA negativity may be observed in some patients, especially in cases with renal-limited vasculitis or involvement limited to the respiratory tract.

There are currently no universally accepted diagnostic criteria for GPA. In 2022, the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) collaborated to introduce the 2022 ACR/EULAR criteria as a novel classification system for AAV. These criteria are not intended for diagnosing vasculitis alone but rather for classifying cases already diagnosed with vasculitis. When applying these updated criteria to potential AAV patients, it is essential to fulfill two primary requirements: confirming a diagnosis of small or medium vessel vasculitis and excluding other conditions that may mimic vasculitis. Table 1 displays the new classification criteria and cut off values for GPA, EGPA, and MPA according to the 2022 ACR/EULAR guidelines. Based on these criteria, a score of 5 or more allows existing vasculitis to be classified as GPA.[29]

Histopathology

GPA's fundamental histopathological finding is necrotizing vasculitis affecting arterioles, venules, and capillaries, along with granulomatous inflammation. Necrosis, microabscesses, fibrosis, and inflammation are evident in the parenchyma.[30,31] The walls of small vessels are infiltrated with mononuclear cells and neutrophils. Granulomatous vasculitis is characteristic but not always present. Fibrosis may be observed in the vessel wall, leading to luminal obliteration.[11]

Renal biopsy typically reveals segmental involvement of the glomeruli, with necrotizing inflammation and cellular crescents frequently observed. The direct immunofluorescence method can demonstrate pauci-immune glomerulonephritis, characterized by the absence or minimal presence of immune deposits. Granuloma-

Table 1: 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) Classification Criteria for granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA)

	GPA	EGPA	MPA
Clinical criteria			
Nasal passage involvement	+3		–3
Nasal polyps		+3	
Cartilaginous involvement	+2		
Conductive or sensorineural hearing loss	+1		
Obstructive airway disease		+3	
Mononeuritis multiplex		+1	
Laboratory criteria			
Positive test for cytoplasmic (anti-proteinase 3)-ANCA	+5	–3	–1
Positive test for myeloperoxidase-ANCA	–1		+6
Blood eosinophil count ≥1×10^9/liter	–4	+5	–4
Hematuria		–1	
Histological criteria			
Granuloma, granulomatous inflammation, or giant cells	+2		
Pauci-immune glomerulonephritis	+1		+3
Extravascular eosinophilic predominant inflammation		+2	
Radiological criteria			
Pulmonary nodules, mass, or cavitation on chest imaging	+2		
Fibrosis or interstitial lung disease on chest imaging			
Inflammation, consolidation, or effusion of the nasal/paranasal sinuses, or mastoiditis on imaging	+1		+3
Cut off total scores for the classification	**≥5**	**≥6**	**≥5**

ANCA: Antineutrophil cytoplasmic antibody

tous glomerulonephritis and necrotizing granulomas are rarely observed. The number of affected glomeruli, degree of crescent formation, glomerular destruction, and amount of sclerosis can provide insights into the potential recovery of renal function with treatment. Renal parenchymal involvement and tubulointerstitial nephritis are less commonly seen.[11]

Treatment

The treatment of GPA aims to achieve long-term remission. Therefore, it typically involves an initial induction phase to attain remission of active disease, followed by a maintenance phase to prevent relapse. Treatment approaches may vary depending on the severity of the disease and the affected organ systems. The presence of certain manifestations such as glomerulonephritis, cardiac involvement, mononeuritis multiplex, retro-orbital disease, central nervous system involvement, mesenteric involvement, pulmonary hemorrhage, and meningeal involvement suggests organ or life-threatening disease. Conversely, manifestations such as non-cavitating pulmonary nodules, nasal and paranasal disease without bone involvement, cartilage collapse, deafness or olfactory dysfunction, non-ulcerated skin involvement, episcleritis, and myositis (limited to skeletal muscle) do not typically suggest organ/life-threatening disease.[27]

In induction therapy for organ- or life-threatening disease, a regimen combining glucocorticoids with cyclophosphamide or rituximab is recommended. In cases of relapse, a combination of rituximab and glucocorticoids is preferred. For induction therapy in non-organ or life-threatening diseases, initial treatment with glucocorticoids combined with rituximab is recommended. Methotrexate and mycophenolate mofetil may also serve as alternatives to rituximab. The oral C5aR inhibitor avacopan, when combined with rituximab or cyclophosphamide, may be considered for remission induction in GPA to minimize glucocorticoid exposure.

Plasma Exchange (PLEX) may be added to treatment regimens to achieve remission in GPA, particularly in cases where serum creatinine levels exceed 300 μmol/L due to active glomerulonephritis. However, routine use of PLEX for treating alveolar bleeding in GPA is not recommended. PLEX is also indicated for patients positive for anti-glomerular basement membrane (anti-GBM) antibodies.

For most patients achieving remission after induction therapy, maintenance therapy with rituximab is recommended. Methotrexate and azathioprine are alternative options. Maintenance therapy is typically administered for 12–24 months following the induction of stable remission in patients newly diagnosed with GPA. Consideration for longer-term treatment should be given to patients with relapsed disease or those at high risk of relapse.[27]

Eosinophilic Granulomatosis with Polyangiitis

EGPA, previously known as Churg-Strauss Syndrome, is a rare immune-mediated inflammatory disorder affecting multiple body systems.[32] It is characterized by eosinophil-rich granulomatous inflammation and necrotizing vasculitis targeting small to medium vessels. This condition often presents with late-onset asthma, elevated eosinophils in the blood, and extrapulmonary manifestations.[10,33,34] Approximately 40% of EGPA patients test positive for ANCA (particularly p-ANCA), a distinctive feature that distinguishes it from GPA and MPA, where ANCA positivity is observed in 70–90% of cases.[32,34] Additionally, in some EGPA cases, there is an absence of evident pathological vasculitis, leading to classification within the category of eosinophilic lung diseases.[35] ANCA positivity tends to correlate with a higher occurrence of glomerulonephritis. Studies, such as those conducted by Sinico et al.,[36] have observed that ANCA-positive patients often exhibit renal involvement and systemic symptoms such as mononeuritis multiplex, purpura, and alveolar hemorrhage, while ANCA-negative patients more commonly experience pulmonary and cardiac issues, excluding alveolar hemorrhage. Although the precise etiology remains unclear, evidence suggests a contribution from genetic predisposition and immune dysregulation in the development of the disease.[37] Given the presence of asthma and eosinophilia, distinguishing EGPA from conditions such as allergic bronchopulmonary aspergillosis, chronic idiopathic eosinophilic pneumonia, parasitic infections, steroid-dependent asthma, and hypereosinophilic syndrome is crucial. The classical definition of EGPA, as outlined by Lanham et al.,[38] encompasses three phases: the prodromal phase, the eosinophilic phase, and the vasculitic phase. The prodromal phase, occurring 8–10 years before diagnosis, is marked by severe allergic rhinitis, sinusitis, and asthma. Subsequently, the eosinophilic phase is characterized by prominent peripheral blood eosinophilia, eosinophilic infiltration across various organs, and associated complications such as pulmonary infiltrates, gastrointestinal involvement, and eosinophilic cardiomyopathy leading to heart failure. The vasculitic phase often presents vasculitis-related features such as overt purpura, glomerulonephritis, and mononeuritis multiplex. However, these phases may overlap, and some patients may not manifest eosinophilic or vasculitic indications at all. Certain manifestations, such as thrombotic events, may not distinctly align with either eosinophilic or vasculitic mechanisms. It's important to note that the clinical presentation of EGPA varies significantly and may not strictly adhere to the outlined sequential stages.[32,38]

Clinical Findings

The respiratory system is frequently affected in EGPA, with approximately 90–95% of patients experiencing adult-onset asthma, often appearing years before other systemic symptoms. In some cases, asthma occurs concurrently with vasculitis. Asthma tends to become resistant to treatment and reliant on steroids before vasculitis develops. Eosinophilic pneumonia, in addition to asthma, occurs in about 40–70% of patients, presenting as patchy, peripheral, and migratory infiltrations visible on chest radiography.[32,39] High-resolution computed tomography reveals ground-glass opacities, small centrilobular nodules without cavitation, bronchial wall thickening, and the 'tree-in-bud' sign. Approximately 3–4% of patients may develop DAH, while pleural effusions might emerge due to eosinophilic pleurisy or congestive cardiac failure linked to eosinophilic cardiomyopathy.[32,40] URT involvement is also common, with paranasal sinusitis observed in about 70–80% of patients, along with rhinitis, nasal congestion, and nasal polyps.[41,42]

Cardiac manifestations, present in 27–47% of patients, exhibit considerable variability. Common findings include pericarditis and eosinophilic cardiomyopathy, alongside possibilities of arrhythmia, coronary vasculitis, and valvular defects. Cardiac involvement significantly influences both mortality and long-term morbidity. These pathologies might be overlooked due to their subclinical nature, emphasizing the importance of a systematic cardiac evaluation utilizing electrocardiogram, echocardiography, and N-terminal pro-BNP and troponin serum levels in all EGPA-diagnosed patients.[42,43]

Peripheral neuropathy, a hallmark of the vasculitic phase, occurs in 50–75% of patients, often as mononeuritis multiplex, typically unilateral or asymmetric. Skin lesions, occurring in 40–50% of patients, include petechiae, purpura, nodules, papules, urticarial lesions, and livedo reticularis. Biopsy of purpuric lesions generally indicates leukocytoclastic vasculitis.[39,41]

Renal involvement, less frequent (16–27%) than in other ANCA vasculitides, ranges from urinary abnormalities to rapidly progressive glomerulonephritis, typically characterized by pauci-immune necrosis and crescentic glomerulonephritis. EGPA's prognosis worsens when the kidneys are affected. Other systemic findings encompass fever, weight loss, joint and muscle pain, abdominal pain, diarrhea, gastrointestinal bleeding, and, in rare cases, central nervous system involvement.[39]

Laboratory and Diagnosis

Active EGPA typically manifests with significant peripheral eosinophilia, often exceeding 1.5×10^9/l or 10% of total white blood cells, indicating disease activity.[44] Moreover, the eosinophil percentage in bronchoalveolar lavage (BAL) usually exceeds 40%. While serum IgE and CRP levels elevate, they lack specificity for this condition.[38,39] In about 75% of active EGPA cases, heightened expression of IgG4 serves as a more reflective indicator of disease activity than IgE.[45] Although p-ANCA aids in diagnosing EGPA, its titers don't correlate with disease activity.[34,39]

Diagnosing EGPA lacks strictly defined criteria. The 2022 ACR/EULAR classification criteria suggest a score of 6 or higher for the EGPA classification. This diagnosis requires confirmation of small- or medium-sized vessel vasculitis and exclusion of other conditions that mimic vasculitis.[46]

Treatment

Initial treatment selection for EGPA relies heavily on evaluating mortality risks and disease severity through the five-factor score (FFS). This prognostic tool, updated in 2011, considers specific parameters: age over 65, cardiac failure, gastrointestinal involvement, renal impairment (stabilized peak creatinine ≥150 μmol/l or 1.7 mg/dl), and the presence or absence of manifestations related to the ear, nose, and throat (ENT), which are associated with a better prognosis. Individuals with a poorer prognosis (FFS ≥1) may begin treatment with a combination of immunosuppressants agents and glucocorticoids. Meanwhile, those with less severe disease (FFS=0) may initially undergo glucocorticoid therapy alone. For patients with organ- or life-threatening symptoms like eosinophilic alveolitis, DAH, or severe peripheral neuropathy, a combination of immunosuppressants and glucocorticoids is recommended as the first-line treatment.[32,47]

The suggested starting dose for glucocorticoids is 1 mg/kg/day of prednisolone for 2–3 weeks. Subsequently, the steroid dosage should be gradually tapered. By 3 months, the goal is to decrease the prednisolone dose to 0.3 mg/kg/day, followed by a further reduction to 0.15 mg/kg/day by 6 months. Maintenance doses should be adjusted carefully to effectively manage and prevent disease relapse. Drugs modifying the disease course, like methotrexate or azathioprine, prove beneficial in this context. In cases where glucocorticoids are used alone, maintaining a dose ideally below 7.5 mg/day of prednisolone is recommended to minimize the risk of steroid-related side effects. Cyclophosphamide is specifically suggested for inducing remission in life-threatening conditions or in patients with a poorer prognosis (FFS ≥1).[32,47]

Microscopic Polyangiitis

MPA is characterized by necrotizing vasculitis primarily impacting small blood vessels, often exhibiting minimal or absent immune deposits.[10] Friedrich Wohlwill documented two patients with a condition now described as MPA, distinct from classical polyarteritis nodosa in 1923.[48] MPA stands as a primary systemic vasculitis primarily affecting small pulmonary and renal vessels.[48,49] In the Chapel Hill International Consensus Conference of 2012, MPA was classified within the group of AAV.[8] The hallmark features of MPA encompass necrotizing inflammation impacting blood vessels of small and medium sizes, the presence of circulating ANCAs, and the absence of necrotizing parenchymal inflammation based on histopathological examination.[48,49] In patients with MPA, necrotizing glomerulonephritis is very commonly seen.[10] MPA is included among pulmonary-renal syndromes.[8] The reported incidence of MPA is documented to range from 2.7 to 94 cases per 1 million individuals.[50] A slight predominance in male individuals is observed, with a male-to-female ratio of 1.8:1, and the typical age of onset falls within the range of 50 to 60.[48,50]

Clinical Findings

As anticipated for a condition that impacts various organ systems, individuals affected by MPA can exhibit a wide array of diverse symptoms.[48] The clinical manifestations of MPA place it within the category of systemic vasculitides, signifying the potential involvement of multiple organs. Notably, the key organs predominantly affected by MPA are the kidneys and lungs.[50]

When these patients are diagnosed, more than 70% of them have constitutional symptoms such as fever and weight loss. The disease can manifest acutely, characterized by symptoms spanning from days to weeks, or follow a more gradual and subtle course prior to diagnosis. For instance, non-specific symptoms resembling flu-like illness or joint pain can be present for a prolonged period ranging from months to years before the eventual diagnosis is made.[48]

Pulmonary engagement is observed in 25–55% of patients with MPA. This involvement is marked by symptoms such as hemoptysis, alveolar hemorrhage, pulmonary infiltrates, pleural effusion, pulmonary edema, pleuritis, and interstitial fibrosis. A hallmark pulmonary manifestation in MPA is the occurrence of DAH attributed to pulmonary capillaritis, documented in 12–55% of patients. In cases where alveolar hemorrhage is present, chest radiographs typically depict scattered bilateral opacities within airspaces, commonly affecting both upper and lower lung regions.[48] ILD can also be observed at significant rates in cases of MPA.[8] Thorax CT shows DAH in MPA in Figure 3.

In MPA, renal symptoms are the most common manifestations. Glomerulonephritis is detected in approximately 80-100% of individuals during both the early stages and the progression of the disease. The most prevalent type of glomerulonephritis is the "pauci-immune" form of rapidly progressive glomerulonephritis. The clinical condition of patients can vary from asymptomatic hematuria to renal failure.[8]

Skin, gastrointestinal, and neurological systems can be affected in cases of MPA.[50] In 30–60% of patients, purpura, livedo reticularis, nodules, bullae, urticaria, and necrotic ulcers can develop symmetrically on the extensor surfaces of the limbs. Arthralgia frequently accompanies skin involvement.[51] Abdominal pain and bleeding can occur due to gastrointestinal involvement. Neurological involvement can manifest as peripheral neuropathy, mononeuritis multiplex, cerebral hemorrhage, pachymeningitis, and cerebral infarctions. Necrotizing vasculitis can be seen in a sural biopsy in 80% of affected patients. Sensorineural hearing loss can also be observed.[50] Symptoms and findings specific to the affected organ in MPA are presented in Table 2.

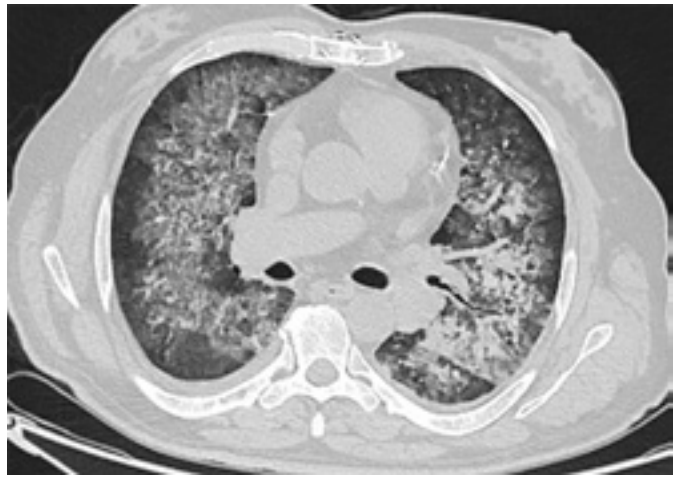

Figure 3: Diffuse alveolar hemorrhage on thorax CT in microscopic polyangiitis
CT: Computed tomography

Laboratory and Diagnosis

The clinical spectrum is very extensive. Comprehensive clinical, radiological, histopathological, and laboratory examinations are necessary.[8] There is no specific laboratory test for MPA. ANCAs are identified in only 50–75% of patients with MPA. Therefore, the absence of circulating ANCAs does not definitively exclude this diagnosis. ANCAs associated with MPA typically display a perinuclear staining pattern, which results from antibodies targeting MPO, and are detectable by the enzyme-linked immunosorbent assay (ELISA). Although immunofluorescence test (IFT) yields greater sensitivity, ELISA provides higher specificity in diagnosing MPA. Screening for vasculitis-associated ANCAs is conducted using an IFT. A complete blood count analysis reveals leukocytosis, anemia, and thrombocytosis. Elevated ESR, CRP, blood urea nitrogen, and serum creatinine levels are observed. The most commonly sampled tissues are those of the kidney, skin, and lung.[8]

Radiography has been proven to be effective in the detection of pulmonary involvement in MPA. The most prevalent finding observed in computed tomography

Table 2: Symptoms and findings observed in microscopic polyangiitis

Constitutional	Subtle onset, fever, weakness, and weight loss
Ocular	Ocular pain, scleritis, episcleritis, keratitis, ischemic optic neuropathy, orbital mass, and retinal artery thrombosis
Otorhinolaryngological	Sinusitis
Neurological	Mononeuritis multiplex, neuropathy, other non-specific neurological complaints, dermatomal localized motor, and sensory deficits
Cardiovascular	Hypertension, signs and symptoms of heart failure, myocarditis, and pericarditis
Pulmonary	Cough, hemoptysis, shortness of breath, crackles, bronchial breath sounds, alveolar hemorrhage, and interstitial lung disease
Renal	Hematuria, proteinuria, and rapid progressive pauci-immune glomerulonephritis
Gastrointestinal	Gastrointestinal bleeding, intestinal ischemia, and perforation
Dermal	Leukocytoclastic vasculitis and palpable purpura, livedo reticularis, skin ulcerations, necrosis and gangrene, necrotizing nodules, digital ischemia, and urticaria
Musculoskeletal	Arthralgia, myalgia, arthritis

is ground-glass attenuation (94%), indicative of alveolar hemorrhage and chronic interstitial inflammation of the alveolar septa, along with the presence of nodules with or without cavitation, as well as masses.[8,50] In recent times, an increasing number of studies have focused on a biomarker known as serum C-C motif chemokine ligand (CCL2), which is suggested to possess diagnostic and predictive capabilities in MPA-associated interstitial lung disease (MPA-ILD). Immunohistochemical staining has revealed pronounced CCL2 signals in CD68-/CD163 macrophages within the lungs of MPA-ILD cases. Targeting CCL2 in alveolar CD68-/CD163 macrophages might hold therapeutic potential as a strategy for ANCA-positive MPA-ILD.[8]

Bronchoscopy and BAL serve as additional diagnostic tools in DAH. In cases of acute DAH with a normal chest X-ray, bronchoscopy exhibits low sensitivity (<20%), but in those experiencing extensive hemoptysis, the sensitivity of this method exceeds 90%. BAL involves the examination for hemosiderin-laden macrophages, typically appearing within 24–48 hours following the onset of DAH. While the specific cut-off value for hemosiderin-laden macrophages in diagnosing DAH remains uncertain, the presence of >5% strongly indicates the presence of alveolar hemorrhage in individuals with AAV.[52]

The histological verification of vasculitis remains the gold standard in the diagnosis of MPA and should be pursued for every patient. Renal and surgical lung biopsies offer significant diagnostic value with a high success rate, with the former being particularly valuable for identifying glomerulonephritis and the latter assisting in the diagnosis of pulmonary vasculitis.[50] A defining observation in renal biopsies is the presence of focal segmental necrotizing glomerulonephritis, detected in up to 100% of cases. Glomerular crescents are also frequently observed, occurring in around 90% of patients. Immunofluorescence reveals minimal deposition of immunoglobulins or complement factors within the glomeruli and renal vessels, thus giving rise to the term "pauci-immune," distinguishing it from other small vessel vasculitis conditions, such as Henoch-Schönlein purpura, cryoglobulinemic vasculitis, and anti-glomerular basement membrane antibodies disease.[48]

There are no strictly accepted criteria for the diagnosis of MPA. By confirming the diagnosis of small- or medium-sized vessel vasculitis and excluding other medical conditions that may mimic vasculitis, cases scoring 5 or more according to the 2022 ACR/EULAR classification criteria are classified as MPA.[53]

Treatment

The therapeutic approach in MPA resembles that of GPA.[3] The use of the steroid-cyclophosphamide regimen leads to remission in approximately 90% of patients.[48,50] In patients with severe organ involvement or life-threatening symptoms, high doses of glucocorticoids, such as pulse glucocorticoids, are administered despite the increased risk of infection.[54]

The prognosis of MPA is influenced by kidney and lung involvement.[51] In the context of MPA, the five-year survival rate ranges from 45% to 76%, while the first-year relapse rate stands at 29%. A notable observation is that over 30% of patients experience a delay in diagnosis exceeding six months.[8]

Authorship Contributions

Concept – E.Ş.P., A.Ş., E.İ.; Design – E.Ş.P., A.Ş., E.İ.; Supervision – E.Ş.P., A.Ş., E.İ.; Literature search – E.Ş.P., A.Ş., E.İ.; Writing – E.Ş.P., A.Ş., E.İ.; Critical review – E.Ş.P., A.Ş., E.İ.

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There are no conflicts of interest.

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