Pulmonary Vasculitis

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KEYWORDS

- Diffuse alveolar hemorrhage • ANCA-associated vasculitis
- Granulomatosis with polyangiitis (Wegener) • Microscopic polyangiitis
- Antiphospholipid syndrome • Antiglomerular basement membrane disease
- Takayasu arteritis • Behçet syndrome

KEY POINTS

- Pulmonary vasculitis most frequently occurs in the context of antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis.
- In these disorders, pulmonary capillaritis with diffuse alveolar hemorrhage is the most common manifestation of small-vessel pulmonary vasculitis.
- Treatment of ANCA-associated vasculitis should be tailored to disease severity; diffuse alveolar hemorrhage represents a severe disease manifestation and warrants aggressive induction therapy.
- Pulmonary artery involvement in large vessel vasculitis such as Behçet syndrome and Takayasu arteritis may present as aneurysmal, thrombotic, or stenotic disease.

INTRODUCTION

Systemic vasculitis refers to a clinicopathologically heterogeneous group of diseases classified most commonly by the size of the inflamed vessels and the organ systems affected. Pulmonary vasculitis encompasses inflammation in the pulmonary vasculature, with involved vessels varying in caliber from large elastic arteries to capillaries. Small pulmonary capillaries are the vessels most commonly involved in vasculitis affecting the lung.[1] The antineutrophil cytoplasmic antibody (ANCA)–associated vasculitides (AAVs), which include granulomatosis with polyangiitis (GPA, formerly Wegener granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome), are the small-vessel vasculitides in which pulmonary vasculitis is most frequently observed and

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are the major focus of this article. Vasculitic involvement of the large pulmonary vessels, as may occur in Behçet syndrome and Takayasu arteritis (TA), is also discussed.

SMALL-VESSEL VASCULITIS

Diagnosis

Clinical presentation and physical examination

Although vasculitis of small pulmonary capillaries is the most common pathologic manifestation of pulmonary vasculitis, the clinical presentation is highly variable. Capillaritis and resultant destruction of the capillary-alveolar basement membrane leads to diffuse alveolar hemorrhage (DAH), characterized by extravasation of red blood cells into the alveolar spaces. A wide-spectrum of clinical signs and symptoms are associated with DAH; patients may be asymptomatic at presentation or present with acute respiratory failure. Symptoms usually arise over the course of several days, although more subacute presentations can occur. Most patients experience hemoptysis, although approximately one-third of patients with DAH do not report this condition at presentation.[2] Cough, fever, and dyspnea are other frequently occurring presenting manifestations. Similar to the presenting symptoms, physical examination findings in patients with DAH are typically nonspecific. Pulmonary auscultation may reveal decreased breath sounds or inspiratory crackles. Because DAH is the common denominator of many disease states injuring the pulmonary capillaries, specific clinical manifestations or examination findings suggestive of an underlying systemic disorder are discussed.

Laboratory findings

Anemia or a serially decreasing hemoglobin measurement is the most common laboratory finding in DAH, reflecting the accumulation of red blood cells in the alveolar spaces.[2] Leukocytosis or elevated inflammatory markers may be present, especially if the patient has an underlying systemic vasculitis. A retrospective analysis of almost 100 patients hospitalized for an initial episode of DAH suggested that a plasma lactate dehydrogenase (LDH) level greater than 2 times the upper limit of normal was an independent risk factor for in-hospital mortality.[3] In many cases, DAH is present as part of a pulmonary-renal syndrome with concurrent glomerular disease; thus, urinalysis may reveal elevated serum creatinine or active urine sediment levels. Specific serologic tests and detectable autoantibodies, which can be helpful in diagnosis, are highlighted in the discussion of the individual disease entities.

Radiology

Demonstration of bilateral air-space consolidation or opacities is the radiographic hallmark of DAH. Patchy, bilateral pulmonary infiltrates may be present on chest radiograph. Because the chest radiograph may be normal in DAH, a high-resolution computed tomography (CT) scan of the chest is recommended in patients with suspected DAH.[4] Chest CT often demonstrates ground glass opacities (GGOs) and can simultaneously rule out other causes of pulmonary hemorrhage, such as bronchiectasis or endobronchial tumor, in a patient with hemoptysis. In DAH, GGOs are often diffuse and bilateral; however, in approximately one-quarter of patients, the opacification is restricted to dependent areas of the lower lobes.[5] Imaging may lag behind clinical improvement and may take days to weeks to resolve after cessation of acute bleeding into the alveolar space. Following acute DAH, a radiographic pattern of septal thickening, known as crazy-paving, can occur, although, like GGO, this pattern is not specific for capillaritis or DAH.[6] Recurrent DAH can result in the development of pulmonary fibrosis, which is also readily apparent on high-resolution chest CT.

Bronchoalveolar lavage

Bronchoscopy accompanied by bronchoalveolar lavage (BAL) can confirm the diagnosis of DAH, which is particularly useful given the nonspecific clinical, laboratory, and radiographic presentation of DAH. Increasingly bloody return from serial BAL aliquots confirms acute alveolar hemorrhage. The presence of hemosiderin-laden macrophages on iron staining of the BAL fluid also supports DAH if more than 20% of the alveolar macrophages demonstrate iron staining. An additional advantage of BAL is the ability to concurrently rule out infection. Although BAL is useful in confirming hemorrhage, it has limited specificity in determining the underlying cause of DAH. Furthermore, BAL can fail to identify bleeding in some patients with DAH, most likely because of sampling error.

Histopathology

Guided-tissue biopsy from an affected organ is recommended to histologically confirm the diagnosis of small-vessel vasculitis whenever possible.[7] In the lung, targeted biopsy of radiographically abnormal lung parenchyma via either a thoracoscopic or open lung biopsy provides a high yield for diagnosis of small vessel vasculitis. Conversely, the efficacy of transbronchial biopsy in establishing the diagnosis of pulmonary vasculitis is less than 10%.[8] In a cohort of patients presenting with DAH who underwent open lung biopsy, capillaritis was documented in 88% of cases with a diagnosis of AAV or necrotizing small vessel vasculitis in 14 of 35 cases.[9] Neutrophilic aggregates interspersed within areas of hemorrhage and leukocytoclasia are seen in capillaritis. Histopathologic data must be interpreted in the context of known clinical and serologic data, and a final diagnosis can be further supported by immunofluorescence and with incorporation of other tissue histopathology if available.

Differential Diagnosis

DAH can result from a variety of insults to the lung including autoimmune, infectious, neoplastic and toxic causes.[10,11] Broadly, DAH can be divided into immune-mediated and non–immune-mediated causes (**Box 1**). This distinction has critical initial management implications, because immune-mediated processes usually accompany systemic disease and warrant prompt administration of immunosuppressive medications, typically beginning with corticosteroids. A thorough history, including review of systems, past medical history, travel and exposure history, and drug use (including both prescription medications and illicit drugs), is helpful in identifying an underlying cause of DAH. Patients with immune-mediated DAH are more likely to report constitutional symptoms and arthritis and have evidence of renal involvement at presentation.[12] Frequently encountered immune-mediated causes of pulmonary capillaritis are discussed later; this article does not include a discussion of DAH in systemic lupus erythematosus or rheumatoid arthritis, because pulmonary involvement in these disorders is discussed elsewhere in this issue.

ANCA-associated vasculitides

The AAVs, encompassing GPA, MPA, and EGPA, are a heterogeneous group of necrotizing small vessel vasculitides with a predilection for the lung and kidney. As a group, these diseases account for the major cause of vasculitis affecting the lung. With the goal of redefining the vasculitic syndromes with nomenclature reflective of the underlying pathogenesis, pathologic conditions, and clinical characteristics, the 2012 Chapel Hill Consensus Conference eliminated eponyms from the AAV nomenclature.[13] In this revised classification system, the presence of granulomatous inflammation in the respiratory tract is the fundamental difference between GPA and MPA,

Box 1
Selected causes of diffuse alveolar hemorrhage

Immune-mediated
Systemic vasculitis
- ANCA-associated vasculitis
  - Granulomatosis with polyangiitis
  - Microscopic polyangiitis
  - Eosinophilic granulomatosis with polyangiitis
  - Drug-induced ANCA-associated vasculitis
- IgA vasculitis/Henoch-Schönlein purpura
- Cryoglobulinemic vasculitis
- Behçet syndrome

Connective tissue disease
- Antiglomerular basement membrane disease/Goodpasture syndrome
- Antiphospholipid syndrome
- Systemic lupus erythematosus
- Rheumatoid arthritis

Other
- Stem cell transplantation
- Lung transplant rejection

Non–immune-mediated
Infection
Congestive heart failure
Acute respiratory distress syndrome
Mitral stenosis/valvular heart disease
Drug-induced disease
Coagulopathy/anticoagulant use
Pulmonary hemosiderosis

whereas the presence of eosinophilia with granulomatous inflammation is the distinguishing feature of EGPA (formerly Churg-Strauss syndrome).

As the name implies, this group of systemic vasculitides share an association with serologically detectable ANCAs. Circulating ANCAs with different immunofluorescence patterns and antigen specificities characterize GPA and MPA and are an important diagnostic tool in these diseases. A perinuclear (p-ANCA) or cytoplasmic (c-ANCA) pattern may be seen on indirect immunofluorescence. A positive immunofluorescence pattern should be followed up with an enzyme-linked immunosorbent assay (ELISA) for ANCAs specifically directed against proteinase-3 (PR3) or myeloperoxidase (MPO), which are associated with GPA and MPA, respectively, in greater than 80% of cases.[14,15] Only approximately half of patients with EGPA have detectable ANCAs; when ANCA positivity is seen in EGPA, ANCAs are directed against MPO 75% of the time.[16] ANCA pattern on immunofluorescence and ELISA specificity

must be interpreted together, because only combinations of c-ANCA with PR3 or p-ANCA with MPO have a high positive predictive value for GPA or MPA diagnosis. Certain drugs, infections, and malignancies can cause ANCA positivity; thus, the diagnostic utility of ANCAs depends on the clinical setting in which testing occurs. In patients presenting with DAH or a pulmonary-renal syndrome, ANCA positivity is highly suggestive of AAV and can help elucidate the underlying cause of DAH.

Some form of pulmonary involvement occurs in most patients with AAV, and may range from asymptomatic pulmonary nodules to fulminant respiratory failure, as may occur in approximately 25% of patients with AAV and DAH.[17] Approximately 85% of patients with GPA and MPA will have pulmonary involvement during their disease course,[18] whereas asthma is the hallmark feature of EGPA, occurring in more than 90% of patients.[19] Although overlap exists, those with GPA are more likely to develop nodules or cavitary lung disease, whereas interstitial disease and pulmonary fibrosis occur more frequently in MPA (**Table 1**). Furthermore, pulmonary involvement at disease presentation may predict long-term development of damage, with one study suggesting that those with pulmonary disease at AAV diagnosis had significantly higher damage scores at 2 years than those without pulmonary disease at presentation, and had an increased likelihood of developing pulmonary fibrosis.[20] An estimated 25% of those with DAH at presentation will have persistent abnormalities on pulmonary function testing.[21]

A recent systematic review analyzed more than 200 patients with AAV who had DAH with a reported incidence of 8% to 36%[17]; DAH occurred most frequently in those with MPA, who constituted 52% of the cohort, whereas DAH was rare in EGPA (6%). Other cohorts of patients with AAV and DAH have been more enriched for GPA than MPA.[22] DAH also occurs in children with AAV, with a reported incidence of 40% in one small series of pediatric patients with MPA.[23]

Extrapulmonary disease often accompanies pulmonary vasculitis in AAV and should be evaluated for in patients with suspected AAV and DAH. Fevers, arthralgia/arthritis, myalgia, and weight loss related to underlying systemic vasculitis often occur with DAH. Granulomatous involvement of the otolaryngologic system, including rhinosinusitis, serous otitis, and subglottic inflammation, occurs in greater than 90% of patients with GPA and is commonly a feature at disease presentation.[18] As such, a focused history and examination can gauge disease activity in this domain and, in conjunction with other clinical and serologic data, can support the diagnosis of GPA. Thorough assessment for all organ systems involved in these systemic disorders is crucial for determination of disease activity and stratification of disease severity.

Renal disease in the form of rapidly progressive glomerulonephritis accompanies DAH in most patients with AAV[17,21,22,24]; thus, assessing for renal involvement with urinalysis, serum creatinine measurement, and possibly kidney biopsy, when indicated, can help confirm an AAV diagnosis and provide information for disease stratification and prognosis.[25] Unlike renal involvement, some studies suggest that DAH alone is not predictive of poor outcome or increased mortality,[22] although others have found

Table 1
Distinguishing pulmonary features in ANCA-associated vasculitides

AAV Subtype	Distinguishing Pulmonary Features
GPA	Nodules, cavities, endobronchial lesions
MPA	Interstitial lung disease, fibrosis
EGPA	Asthma, infiltrates, eosinophilic pleural effusions

that DAH increased the relative risk of death by a factor of 8 and is thus a strong predictor of early mortality in AAV.[17] Additional poor prognostic factors that have been identified in patients with AAV with pulmonary vasculitis include intensive care unit admission and mechanical ventilation.[26]

In approaching AAV therapy, a few critical treatment principles guide patient management. First, patients should be stratified by disease severity, with treatment tailored to severity of disease. Severe disease, defined as life- or organ-threatening manifestations, includes features such as DAH, rapidly progressive glomerulonephritis, mesenteric ischemia, scleritis, and nervous system involvement, and typically requires more aggressive therapy.[27] Limited disease, which encompasses all non–life- or organ-threatening manifestations, including mild renal or granulomatous or nodular pulmonary disease, may not require immunosuppression that is as potent. Similarly, disease flares or relapses should be characterized as limited or severe based on organ systems involved, and this distinction is considered when choosing therapy.

Historically, AAV was treated with cyclophosphamide-based regimens after the recognition that a regimen of daily oral cyclophosphamide and high-dose corticosteroids was effective for inducing remission in most patients, which transformed GPA and MPA from a uniformly fatal disease to a chronic relapsing disease with a dramatically reduced mortality of 25% at 5 years.[28] Subsequent appreciation of the toxicity associated with long-term cyclophosphamide use[18] led to the search for therapeutic regimens that minimized and/or avoided cyclophosphamide exposure. Therefore, treatment of AAV is divided into therapy aimed at inducing remission followed by use of remission-maintenance agents.

Corticosteroids remain part of all induction regimens in active or relapsing disease and are usually tapered once remission is attained. Some patients are maintained on low-dose corticosteroids during the maintenance period, although at most centers, the goal is complete discontinuation after remission induction. The optimal tapering regimen and duration of glucocorticoid treatment is not established.

As mentioned previously, cyclophosphamide in combination with high-dose corticosteroids was long considered the standard of care for remission-induction therapy in patients with severe AAV. Complete remission is attainable in greater than 75% of patients treated with oral cyclophosphamide at doses of 2 mg/kg/d (with dose reductions made for older age and renal insufficiency). Use of pulsed intravenous cyclophosphamide (15 mg/kg every 2–3 weeks) has comparable efficacy to oral cyclophosphamide, with the advantage of lower cumulative cyclophosphamide doses.[29] However, those treated with intravenous cyclophosphamide may have higher relapse rates than those treated with the oral formulation.[30] Thus, cyclophosphamide regimens are similar in their ability to induce remission, with possibly higher relapse rates associated with intravenous cyclophosphamide, which must be balanced with the higher rates of leukopenia and potential infection associated with daily oral regimens.

Targeting of B cells with rituximab, the monoclonal anti-CD20 antibody, has been demonstrated to be an effective therapy for remission induction in severe AAV.[31,32] Two randomized trials including patients with both newly diagnosed and relapsing severe AAV demonstrated that rituximab was noninferior to cyclophosphamide for remission induction. In the double-blind, double-dummy Rituximab in ANCA-Associated Vasculitis (RAVE) trial, a single course of rituximab (375 mg/m^2 weekly for 4 weeks) was compared with cyclophosphamide followed by azathioprine in 197 patients with AAV; all patients received high-dose intravenous corticosteroids at the beginning of the induction regimen. Patients with a serum creatinine level greater than 4 mg/dL or alveolar hemorrhage requiring mechanical ventilatory support were

excluded from RAVE. The criteria for noninferiority were met, with 64% of patients receiving rituximab versus 53% of those receiving cyclophosphamide achieving steroid-free disease remission at 6 months, with similar rates of flare and serious adverse events noted in both groups. Published concurrent to RAVE, the Rituximab Versus Cyclophosphamide in ANCA-Associated Renal Vasculitis (RITUXVAS) study was an open-label trial in patients with newly diagnosed AAV with renal involvement. Patients were randomized 3:1 to receive rituximab (375 mg/m^2 weekly for 4 weeks) plus 2 doses of intravenous cyclophosphamide or pulse intravenous cyclophosphamide alone along with background corticosteroids in both groups. At 12 months, 76% of patients in the rituximab/cyclophosphamide group and 82% of patients in the cyclophosphamide-only group had achieved sustained remission. Although rituximab-only regimens have not been studied extensively in patients with severe DAH and respiratory failure, a combination of rituximab and cyclophosphamide for critically ill patients with AAV may be beneficial.[33] Local pulmonary administration of activated factor VII has been used successfully to treat DAH.[34] Although factor VII use has been reported to provide local control of pulmonary hemorrhage in patients with AAV.[35] its use cannot supplant systemic therapy aimed at controlling the underlying disease.

Removal of the circulating pathogenic ANCAs with plasma exchange has been used as adjunctive therapy in patients with severe AAV, including those with active glomerulonephritis and DAH. Used in conjunction with standard induction therapy, plasma exchange may improve renal recovery in patients dependent on dialysis and those with severe renal disease but does not seem to improve overall survival.[36,37] No controlled trials of patients with AAV and DAH treated with plasma exchange have been reported, although retrospective data suggest that this therapy may provide benefit.[38] An international randomized controlled study to evaluate the efficacy of plasma exchange in patients with AAV, DAH, and/or severe renal disease is ongoing.[39]

In patients with limited disease, which by definition can include patients with pulmonary involvement whose oxygen saturation by pulse oximetry is greater than 92% or room air partial pressure of oxygen is greater than 70 mm Hg,[27] cyclophosphamide-free induction regimens are commonly used. Despite this definition, when alveolar hemorrhage is present, disease is typically categorized as serious, requiring more aggressive immunosuppressive therapy. Methotrexate can be used to induce remission in limited AAV. An open-label trial comparing methotrexate with cyclophosphamide randomized patients with newly diagnosed AAV and limited disease (including mild renal and pulmonary involvement) to either methotrexate, 15 to 25 mg weekly or oral cyclophosphamide.[40] The primary end point of remission at 6 months was achieved in 90% of methotrexate-treated patients and 94% of cyclophosphamide-treated patients, although patients on methotrexate took a longer time to achieve remission and had higher rates of relapse at 18 months, most of which occurred after therapy was tapered off.[41]

Most patients who receive cyclophosphamide induction therapy are switched to an alternative maintenance therapy after 3 to 6 months, depending on clinical response. Azathioprine and methotrexate are the principal conventional immunosuppressive agents used for remission maintenance in AAV. The efficacy and safety of azathioprine for maintenance were demonstrated in a study in which patients who had achieved remission on oral cyclophosphamide were randomized to continue treatment with cyclophosphamide at a lower dose or to switch to azathioprine.[42] No difference was seen in relapse rates at 18 months between the 2 treatment groups, nor was a difference in adverse events observed. Methotrexate and azathioprine were also compared in a head-to-head maintenance trial, in which the primary end point was

adverse events requiring discontinuation of therapy.[43] Rates of adverse events and relapse were similar between those receiving methotrexate and those taking azathioprine; thus, methotrexate and azathioprine seem to be comparably efficacious and safe maintenance agents in AAV. Conversely, when mycophenolate mofetil (MMF) was compared with azathioprine for maintenance, relapse rates were higher in the MMF treatment arm, with a hazard ratio of 1.69, but no difference was seen in serious adverse events.[44] Because MMF is less efficacious than azathioprine in preventing relapse, it is not routinely used as a first-line maintenance therapy in AAV, although it may have a role in treating patients with refractory disease or those intolerant of other agents.

Rituximab is an also an effective maintenance therapy for AAV. A follow-up of RAVE reported that complete remission rates at 12 and 18 months were comparable in patients who had received a single course of rituximab and those who received cyclophosphamide followed by azathioprine maintenance.[45] These data suggest that, given the prolonged duration of its biological effects, a single course of rituximab has comparable safety and efficacy to continuous conventional immunosuppressive therapy in remission induction and maintenance out to 18 months. The optimal dose and frequency of rituximab maintenance therapy remain unknown. Some studies support the use of a preemptive strategy of rituximab retreatment every 6 months,[46,47] whereas other investigators advocate for utility in the combination of B lymphocyte reconstitution and ANCA level in predicting relapse, and base the retreatment decision on these laboratory parameters.[48] More definitive studies comparing these rituximab retreatment strategies and a head-to-head comparison of rituximab and azathioprine for maintenance are currently underway.

Once remission is induced and patients are on maintenance therapy, structured clinical assessments with urinalysis and basic laboratory tests should be performed regularly to monitor for new organ involvement, treatment response, and drug toxicity.[7] Relapse is common in AAV, especially after discontinuation of immunosuppression. The optimal duration of maintenance therapy is unknown. Relapse rates, which approach 55% in some cohorts, are highest in the first few years after diagnosis; thus, maintenance immunosuppression is generally continued for approximately 2 years in most patients.[49] Duration of maintenance therapy should be individualized and balance the individual risk of relapse with treatment morbidity. The main cause of death in the first year of AAV diagnosis is infection, accounting for 48% of deaths compared with 19% caused by active vasculitis, and therefore the risk of immunosuppression is not trivial.[28] Patients with AAV have been shown to have higher rates of *Pneumocystis jirovecii* pneumonia (PCP) than other patients with autoimmune disease on similar immunosuppressive regimens. Although no guidelines exist, PCP prophylaxis should be considered in all patients with AAV receiving induction therapy with either cyclophosphamide or rituximab. Vaccination is an important infection prevention strategy for patients with AAV. Although no disease-specific or medication-specific vaccination guidelines are available for patients with vasculitis, the Centers for Disease Control and Prevention guidelines for immunocompromised individuals can be applied to those on immunosuppressive treatment for AAV.[50]

Antiphospholipid syndrome

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by vascular thrombosis and/or pregnancy morbidity occurring in the presence of serologically detectable antiphospholipid antibodies (aPLs). aPLs, which are autoantibodies directed against phospholipid-binding plasma proteins, include lupus anticoagulant (LAC), anticardiolipin antibody, and anti–β2-glycoprotein I (aβ2GPI) and should be

persistently positive when measured at least 12 weeks apart to meet criteria for APS.[51] APS may occur alone or in the setting of another autoimmune disease, most commonly systemic lupus erythematosus.

Although the most common clinical manifestations of APS are thrombosis and fetal loss, it is a multisystem disease with many noncriteria manifestations, including thrombocytopenia, skin ulcers, and nephropathy.[52] The pathogenic vascular lesions in APS are principally related to thrombosis or microangiopathy, and not inflammation, although vasculitis, such as capillaritis, may rarely be a component of APS.[53]

Pulmonary involvement with DAH is a rare but serious manifestation of APS.[54] DAH occurs more frequently in the catastrophic antiphospholipid syndrome (CAPS) than in classic APS.[55] The histopathologic pulmonary capillaritis in APS/CAPS is believed to be immune-mediated, with circulating aPLs implicated in the pathogenesis.[56] In the largest reported series of primary APS-associated DAH, which described 18 patients, histologic evidence of capillaritis was noted in all 3 patients who underwent surgical lung biopsy.[57] Bronchial alveolar lavage has shown that neutrophilia and neutrophils are often present in the alveolar space on biopsy specimens even if capillaritis is not seen.[58] These inflammatory pathologic findings in APS-associated DAH occur in the absence of thrombosis; thus, DAH is considered to be a nonthrombotic manifestation of APS.

The presumed inflammatory nature of DAH in APS has important therapeutic implications. Experts recommend prompt initial treatment of DAH with high-dose corticosteroids and temporary cessation of anticoagulation.[54,57] Additional immunosuppression is often needed, because recurrence and mortality are common. No controlled or prospective data are available to guide treatment of APS-related DAH; however, borrowing from the treatment of capillaritis in AAV, cyclophosphamide or rituximab are often the first-line agents used. In a recent retrospective series from the Mayo Clinic of 18 patients with primary APS-associated DAH, complete remission was achieved in 3 of 7 patients treated with cyclophosphamide and 5 of 8 patients treated with a rituximab-based regimen, whereas uncontrolled disease was observed in patients treated with azathioprine, MMF, intravenous immunoglobulin, or plasmapheresis.[57]

Antiglomerular basement membrane antibody disease

Antiglomerular basement membrane antibody disease (anti-GBM disease), also known as Goodpasture disease, is an immune complex–mediated small vessel vasculitis.[13] The cause of anti-GBM disease is unknown, but genetic factors affect susceptibility and environmental factors are associated with the disease.[59] The hallmark of disease is detectable anti-GBM antibodies, which are directed against and ultimately bind to the noncollagenous-1 domain of type IV collagen in the basement membrane.[60] Anti-GBM antibodies can be detected in the sera via an ELISA-based assay or can be demonstrated histologically in biopsy specimens of affected tissue.

Acute renal failure from rapidly progressive crescentic glomerulonephritis is the most common presenting feature of anti-GBM disease. Renal biopsy, which will demonstrate linear deposits of IgG under immunofluorescence, is more sensitive than serology in confirming the diagnosis and also provides prognostic information.[61] Anti-GBM disease can present as pulmonary-renal syndrome with DAH accompanying crescentic glomerulonephritis in approximately 50% of cases.[62–64] Patients presenting with DAH in the absence of frank renal involvement have a better prognosis and, according to some cohorts, are more likely to be younger than those with renal involvement.[62,65] Predominant pulmonary involvement is often associated with smoking, prior exposure to inhaled toxins, or pulmonary infection. Some researchers have speculated that these exposures may trigger disease by damaging the pulmonary

endothelium, which can expose the basement membrane and allow it to serve as an antigenic stimulus for anti-GBM antibody production and/or a binding target for circulating antibodies.

Renal involvement and risk for rapid progression to end-stage renal disease drives therapy in anti-GBM disease. High serum creatinine levels at baseline and percentage of crescents on renal biopsy confer a poor prognosis, highlighting the importance of early diagnosis and treatment, because most patients who require hemodialysis at presentation remain dialysis-dependent.[66] "Triple therapy" is considered the gold standard for anti-GBM disease treatment, with a regimen including corticosteroids, immunosuppressives, and plasmapheresis,[67] resulting in a 1-year survival rate approaching 90%.

Plasmapheresis to remove the pathogenic anti-GBM antibody is essential to the management of anti-GBM disease. Plasmapheresis is typically prescribed daily for 10 to 14 days or until anti-GBM antibodies are no longer detectable; albumin is the usual replacement fluid for exchanges but fresh frozen plasma can be used instead to replace coagulation factors in patients with active DAH.[68]

In a small controlled trial that randomized patients to receive corticosteroids with or without plasma exchange,[69] only 2 of 8 patients receiving plasma exchange developed end-stage renal disease, compared with 6 of 9 patients who received only immunosuppressives. Although this study was underpowered and therefore a significant result was not reached, it shifted the treatment paradigm to include plasmapheresis in most cases of anti-GBM disease. Use of plasmapheresis in patients who are already dialysis-dependent is debated, because longitudinal studies suggest a very low probability (<10%) for return of renal function in these patients.[65] The decision to use plasmapheresis in these patients should take into account the duration of renal failure and prognostic features on renal biopsy.

Similar to other vasculitic syndromes, the cornerstone of treatment is a regimen that includes high-dose corticosteroids and cyclophosphamide. Most of the experience using cyclophosphamide in anti-GBM disease is with the oral formulation given at a dosage of 2 mg/kg/d, again with adjustments made for creatinine clearance and older age.[65] Corticosteroids at a dose of 1 mg/kg are usually administered initially, with a slow tapering over the next several months pending the patient's clinical response. The successful use of rituximab either alone or in combination with cyclophosphamide has been reported.[70] Unlike in AAV, anti-GBM titers can correlate with disease activity and be used to determine duration of therapy; experts recommend continuation of steroids and maintenance therapy with azathioprine if anti-GBM titers remain elevated after 4 months of cyclophosphamide, whereas those with persistently negative titers on serial monitoring do not typically require maintenance medications.

A subset of patients have both anti-GBM and ANCA. This "double positivity" may occur in approximately 20% to 30% of patients with anti-GBM disease. When present, the ANCA specificity is usually directed against MPO. These patients tend to have more extrarenal involvement than those with pure anti-GBM disease, whereas clinically and histologically, their renal disease parallels that of other patients with anti-GBM disease.[71] Although some studies have suggested increased relapse rates and mortality in double-positive patients,[72] other cohorts show that renal survival in double-positive patients is similar to that in other patients with anti-GBM positivity and considerably worse than in those with only MPO positivity.[73]

LARGE VESSEL VASCULITIS

Vasculitic involvement of the large pulmonary arteries can cause aneurysmal changes, stenosis, or occlusion. Isolated pulmonary artery vasculitis is rare and

typically occurs in the context of a systemic vasculitis, such as Behçet's syndrome or TA.

Behçet Syndrome

Behçet syndrome is classified as a variable-vessel vasculitis, meaning small, medium, or large vessels in the arterial or venous system can be involved in the inflammatory process, although large vessel disease is most common. Recurrent oral and genital ulcers are a hallmark of Behçet syndrome. Other manifestations can include skin lesions, arthritis, uveitis, gastrointestinal ulceration, and vascular involvement.

Pulmonary artery aneurysms (PAAs) and/or thrombosis are severe manifestations of Behçet syndrome. Although PAAs are a rare manifestation of Behçet syndrome, occurring in less than 10% of patients, they are an independent risk factor for and important contributor to mortality.[74] Though Behçet syndrome has no gender predilection, pulmonary vascular involvement occurs almost exclusively in male patients. In a series of 47 patients with Behçet syndrome and pulmonary artery involvement, 34 had PAA, whereas 8 had PAA with concurrent pulmonary artery thrombosis and 13 had isolated pulmonary artery thrombosis.[75] Concurrent abnormalities in multiple branches of the pulmonary artery is a usual finding radiographically.

Patients with Behçet syndrome with pulmonary artery involvement most commonly present with hemoptysis; fever, dyspnea, cough, and pleuritic chest pain are also frequent presenting symptoms. Pulmonary artery involvement in Behçet syndrome can be diagnosed with several imaging techniques, including CT angiography, MR angiography and fluorodeoxyglucose F 18/PET scanning.[76–78] Extrapulmonary disease usually accompanies PAA. Pulmonary arterial disease is associated with peripheral vascular disease in approximately 75% of patients, typically presenting as thrombophlebitis with superficial or deep vein thrombosis.[79] Thrombi in Behçet syndrome are usually surrounded by an inflammatory infiltrate. Management of venous thrombosis in Behçet syndrome is controversial, with some experts supporting treatment with immunosuppression rather than anticoagulation and others suggesting a combination of immunosuppression with concurrent anticoagulation.[80]

Controlled studies of treatment for PAA in Behçet syndrome are lacking, although most series in the literature report a combination of high-dose corticosteroids with either cyclophosphamide, azathioprine, or infliximab.[74,81,82] Anticoagulation is sometimes used for patients with stenotic or occlusive disease. For refractory hemoptysis, surgical interventions such as endovascular embolization and even lobectomy have been reported.[83,84]

Takayasu Arteritis

TA is a granulomatous large vessel vasculitis predominantly affecting the aorta and its major branches. TA preferentially affects women younger than 50 years. Prevalence estimates of pulmonary arteritis in TA vary between 15% and 60%, which may partly reflect the asymptomatic nature of pulmonary artery involvement in many patients.[85,86] Pulmonary arteritis usually occurs in conjunction with disease in other large vessels, but isolated pulmonary arteritis in TA has been reported.[87]

Presenting symptoms of pulmonary artery involvement in TA include dyspnea, cough, chest pain, and hemoptysis.[88] Pulmonary arterial hypertension is an important complication of pulmonary arteritis seen in patients with TA. Because the presenting signs and symptoms of pulmonary involvement in TA may be nonspecific or even absent, imaging plays an important role in diagnosis. In one series examining 15 asymptomatic patients with TA, 60% had evidence of pulmonary vascular involvement on noninvasive imaging using perfusion and ventilation lung scintigraphy.[89] CT

angiography and MR angiography have largely supplanted conventional angiography in the assessment of pulmonary vascular disease, because of their noninvasive nature and ability to detect subtle changes in the vessel wall, which can help differentiate active disease from stenosis caused by previously damaged vasculature. The use of PET in assessment of aortic/large vessel disease in TA is an area of active investigation[90]; however, negative PET imaging results in patients with TA with known pulmonary artery involvement have been reported, with the hypothesized explanation that the diameter of the pulmonary arteries is less than the power of detection of PET.[91]

Treatment of pulmonary artery involvement follows the general treatment principles for TA, in that high-dose corticosteroids are typically the first-line agents.[92] Methotrexate or azathioprine is often used in conjunction with steroids. For refractory or life-threatening disease, cyclophosphamide has been used, although more recently, biologic agents such as infliximab, rituximab, or tocilizumab are often used as an alternative to cyclophosphamide.[93] Again, no controlled data or head-to-head comparisons on the use of these therapies in TA are available. Relapses are common when immunosuppression is tapered, and the optimal duration of therapy is also unknown. Surgical therapies, including angioplasty, stenting, bypass, and even pulmonary artery replacement, have been reported to manage pulmonary artery stenosis in TA.[94,95] Generally, surgical interventions should only be undertaken once the disease is quiescent, and even then restenosis is common.

SUMMARY

Many of the systemic vasculitides can cause inflammation of the pulmonary vasculature. Whether the small pulmonary capillaries or the pulmonary arteries are involved in the vasculitic process, presenting signs and symptoms may be nonspecific and a high index of suspicion is necessary to diagnose pulmonary vasculitis. Pulmonary vascular involvement usually represents a serious disease manifestation of systemic vasculitis requiring prompt treatment with corticosteroids and additional immunosuppressive agents.

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