Update on Diffuse Alveolar Hemorrhage and Pulmonary Vasculitis

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- Pulmonary vasculitis • Diffuse alveolar hemorrhage • ANCA-associated vasculitis
- Granulomatosis with polyangiitis • Microscopic polyangiitis
- Eosinophilic granulomatosis with polyangiitis

KEY POINTS

- Diffuse alveolar hemorrhage (DAH) represents the most common and potentially life-threatening manifestation of pulmonary vasculitis.
- Identification and treatment of the underlying cause of DAH are crucial for therapeutic success.
- Pulmonary vasculitis, including antineutrophil cytoplasmic antibody–associated vasculitis (AAV), represents the most common immune-mediated cause of DAH.
- Rituximab has an increasing role in the treatment of AAV, particularly in patients with severe relapsing or refractory disease.

Pulmonary vasculitis is characterized by inflammation and necrosis of the pulmonary blood vessels. Even though it can involve all parts of the pulmonary vasculature, pulmonary arteries, capillaries, and pulmonary veins, it most commonly affects the pulmonary capillaries. Diffuse alveolar hemorrhage (DAH), characterized by the widespread extravasation of red blood cells into the pulmonary alveolar spaces, is the most common clinical manifestation of pulmonary vasculitis (**Fig. 1**). DAH is typically attributable to disseminated injury of the pulmonary capillaries. It is associated with a disruption of the alveolar and capillary basement membranes facilitating the entry of red blood cells into the alveoli. Independent of the underlying cause, pulmonary capillaritis represents the most common histologic finding if lung-tissue biopsies are

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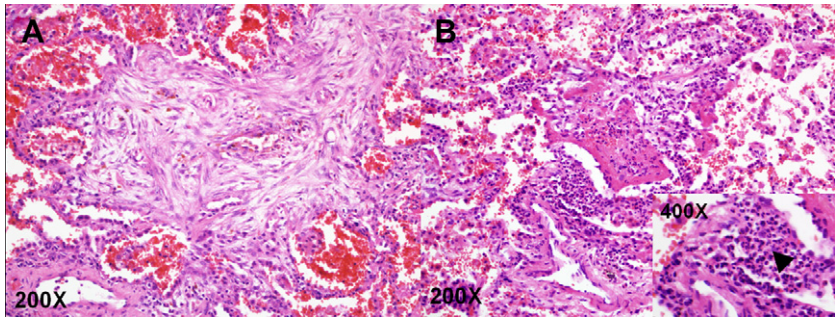

Fig. 1. Pathologic findings of diffuse alveolar hemorrhage. (*A*) Organizing diffuse alveolar hemorrhage with hemosiderin-laden macrophages with surrounding fibrosis. (*B*) Pulmonary capillaritis. Arrowhead indicates leukocytoclastic inflammation. (*Courtesy of* Dr MC. Aubry, MD, Mayo Clinic, Rochester, MN.)

obtained in these patients (see **Fig. 1**).[1] DAH can occur in the context of various systemic disorders or present in isolation. The etiology of DAH can be broadly divided into immune-mediated and non–immune-mediated causes.

As a group, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) represents the most common cause of pulmonary vasculitis. Even though all these diseases remain idiopathic, over the last few decades our understanding of their pathogenesis has improved significantly. In a recent effort to eliminate eponyms and establish more descriptive disease names reflective of the associated pathology and disease associations, a new nomenclature for AAV was proposed by an international expert panel.[2] Wegener's granulomatosis was renamed as granulomatosis with polyangiitis (Wegener's) GPA, highlighting the granulomatous nature and vascular inflammation associated with the disease as well as its similarities to microscopic polyangiitis (MPA). To emphasize the contribution of eosinophilic inflammation and the resemblance to GPA, Churg-Strauss was renamed as eosinophilic granulomatosis with polyangiitis (Churg-Strauss) EGPA.[2]

CLINICAL PRESENTATION AND DIAGNOSIS OF DAH

The clinical presentation of DAH is highly variable. Patients can present within a spectrum ranging from asymptomatic radiographic abnormalities to severe life-threatening respiratory failure. Even though the majority of patients experience a variable degree of hemoptysis, approximately one-third of all patients with DAH are lacking this symptom.[3] Other common symptoms include dyspnea, cough, fever, and chest pain. Laboratory studies frequently demonstrate anemia and/or decreasing hemoglobin values as a marker of intrapulmonary blood loss.[4,5] In addition, patients presenting with DAH frequently report signs and symptoms related to an etiologically related systemic disorder. Such abnormalities may include rashes, ocular, sinus, nasal, or ear symptoms, airway obstruction, renal dysfunction owing to glomerular inflammation characterized by an active urinary sediment, neurologic symptoms such as mononeuritis multiplex, inflammatory arthritis, muscle weakness, and many other symptoms. Patients presenting with DAH and concurrent glomerulonephritis are typically classified as pulmonary-renal syndrome. The vast majority of these cases are attributable to immune-mediated causes, most frequently AAV, systemic lupus erythematosus (SLE), or anti–glomerular basement membrane antibody (anti-GBM) syndrome. A careful history including review of systems, review of exposures, and

medical history, as well as a comprehensive physical examination are critically important for the characterization of any underlying systemic disease causing DAH.

Imaging studies, specifically high-resolution computed tomography, provide additional information to support a diagnosis of DAH (**Fig. 2**). However, radiologic findings are frequently nonspecific and subject to change throughout the course of the disease. Typical patterns include focal or diffuse areas of ground-glass opacification and/or consolidation as a consequence of alveolar filling. On cessation of the alveolar bleeding, most of the associated radiologic abnormalities resolve within a few days to weeks. The resolution of this process is slower than that of the infiltrates related to pulmonary edema but faster than the disappearance of the inflammatory/infectious radiologic changes observed in pneumonias. During the resolution of the acute hemorrhage, "crazy paving" with associated interlobular septal thickening may become more prominent.[6,7] Additional radiologic abnormalities may be attributable to many of the underlying systemic disorders or represent infectious complications related to systemic immunosuppression. Some of these findings include cavitating pulmonary nodules and masses and large-airway inflammation and stenosis caused by granulomatous inflammation in GPA, fibrosis and bronchiectasis in MPA, airway inflammation and inflammatory infiltrates in EGPA, and pleural effusions in SLE (see **Fig. 2**).

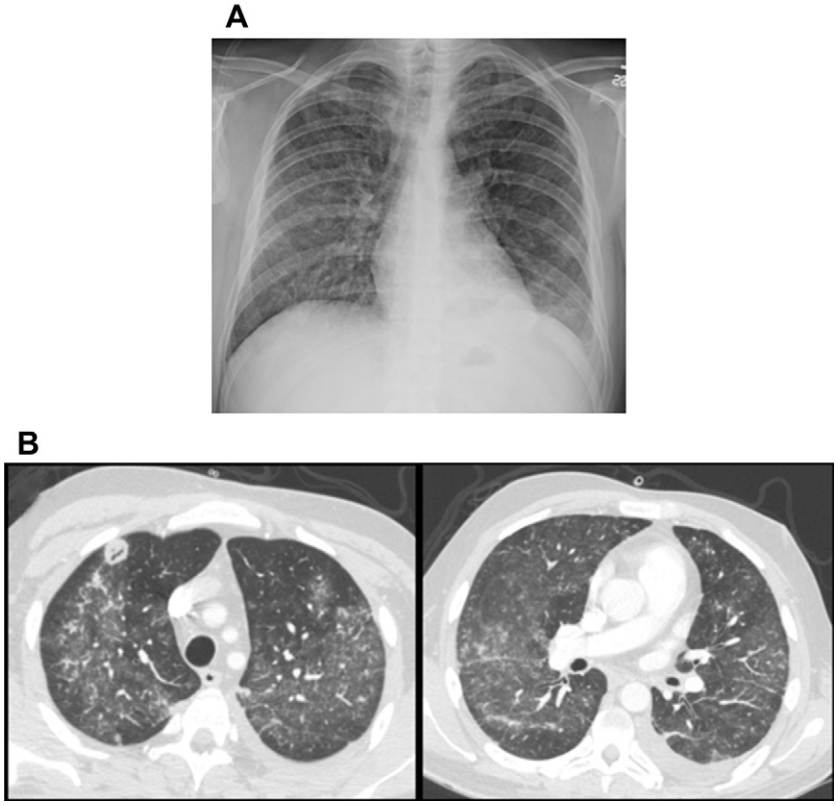

Fig. 2. Radiographic findings of diffuse alveolar hemorrhage. (*A*) Chest radiograph shows bilateral patchy infiltrate. (*B*) Computed tomography images show bilateral ground-glass infiltrates with associated necrotizing nodule in right upper lobe.

Because of the relatively nonspecific nature of the clinical-radiologic signs and symptoms of pulmonary vasculitis, additional laboratory tests and bronchoscopy with bronchoalveolar lavage (BAL) are frequently required to accurately diagnose and optimally manage patients with DAH. Laboratory studies typically include: complete blood count with differential, coagulation studies, serum creatinine and blood urea nitrogen, ANCA testing (by indirect immunofluorescence [cytoplasmic ANCA and perinuclear ANCA] and antigen-specific enzyme-linked immunosorbent assay [PR3-ANCA and MPO-ANCA]), anti-GBM antibodies, antinuclear antibodies (ANA), anticyclic citrullinated peptide antibodies (anti-CCP), rheumatoid factor (RF), antiphospholipid antibodies, creatine kinase, urinalysis with urinary sediment, and urine drug screen.

A transient, reversible increase in the diffusing capacity for carbon monoxide (DLCO) has been previously reported in patients with DAH.[8] This increase is attributed to the enhanced uptake of carbon monoxide by extravascular blood. However, because of the acute onset, the often severe clinical manifestations of DAH, and a lack of comparison baseline DLCO values, DLCO measurements are not routinely used to evaluate patients with suspected DAH.

The purpose of bronchoscopy with BAL is primarily to confirm the presence of intra-alveolar blood, exclude the large airways as a source of bleeding, and rule out infection. Alveolar blood results in an increasingly hemorrhagic appearance of consecutive BAL aliquots.[4] BAL iron staining revealing the presence of greater than 20% hemosiderin-laden macrophages (HLM) among all alveolar macrophages provides additional support for a diagnosis of DAH.[9] However, it is important that in cases of acute hemorrhage, increasingly bloody BAL returns may precede the appearance of HLM. By contrast, HLM may be detectable in the BAL fluid weeks to months after the intra-alveolar red cells have disappeared. Unfortunately, the presence of HLM is not restricted to DAH and is also commonly seen in patients with diffuse alveolar damage.[10]

Because most established diagnostic criteria for pulmonary vasculitis (eg, the American College of Rheumatology criteria for GPA) do require the histologic confirmation of vascular inflammation by tissue biopsy, tissue transbronchoscopic (TBBx) or surgical biopsies are often considered to establish a diagnosis in these patients. However, the diagnostic yield of TBBx remains suboptimal, the histologic findings are frequently nonspecific, and the risks of the procedure commonly outweigh its benefits. Compared with TBBx, surgical lung biopsies have a higher diagnostic yield for pulmonary vasculitis. For example, capillaritis was present in 17% to 43% of surgical lung biopsies in patients with GPA; however, these procedures are also associated with a substantial risk for these patients.[11,12] Consequently, recent efforts have focused on the development of diagnostic criteria that use clinical, radiologic, and serologic information (eg, ANCA for AAV) to establish a diagnosis.[13]

DIFFERENTIAL DIAGNOSIS OF DAH

The etiology of DAH can be broadly divided into immune-mediated and non–immune-mediated causes (**Table 1**). The list of diagnostic considerations is long, and a careful history and physical examination represents a key component in the evaluation of these patients.

In a 28-year retrospective cohort of patients presenting with DAH, immune-mediated causes including vasculitis, anti-GBM disease, and other connective tissue disease were identified in 36% of patients (35 of 97). Twenty-five patients had a diagnosis of vasculitis. Among the non–immune-mediated causes, systolic or diastolic

Table 1
Differential diagnosis of diffuse alveolar hemorrhage

Immune Mediated	Non–Immune Mediated
ANCA-Associated Vasculitis	Cardiac disease
Granulomatosis with polyangiitis (GPA)	Left ventricular dysfunction
Microscopic polyangiitis (MPA)	Valvular disease
Eosinophilic granulomatosis with polyangiitis (EGPA)	Infection
Isolated pulmonary capillaritis	Medications
Anti–glomerular basement membrane antibody syndrome	Acute respiratory distress syndrome
Connective tissue disease	Idiopathic pulmonary hemosiderosis
Systemic lupus erythematosus	Coagulopathy
Rheumatoid arthritis	Radiation exposure
Inflammatory myopathies	Occupational exposure
Antiphospholipid antibody syndrome	Crack cocaine inhalation
Henoch-Schönlein purpura/IgA vasculitis	Bone marrow transplant[a]
Cryoglobulinemic vasculitis	
Behçet disease	
Lung transplant rejection	
Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis)	
Drug-induced vasculitis	
Bone marrow transplant[a]	

[a] In autopsy series of patients with bone marrow transplant with diffuse alveolar hemorrhage, there were complications of diffuse alveolar damage, rather than capillaritis, suggesting a non–immune-mediated mechanism of diffuse alveolar hemorrhage.

cardiac dysfunction of the left ventricle and valvular heart disease accounted for 27% (26 of 97) of the cases.[3] Similarly, among critically ill patients with DAH, vasculitis accounted for 19% (7 of 37) of all cases.[14] Because capillaritis, independent of the underlying etiology, represents the most common histologic finding in DAH, it is certainly possible that pulmonary vasculitis is responsible for up to 88% of these cases.[1]

Among DAH patients with pulmonary vasculitis, AAV including GPA, MPA, and more rarely, EGPA and isolated pulmonary capillaritis account for the majority of cases.[15] Although all AAV have been associated with pulmonary capillaritis and DAH, their frequency differs between the syndromes. The incidence of DAH ranges from 12% to 29% for MPA, 8% to 18% for GPA, and 0% to 4% for EGPA.[16–20] Other less frequent causes of immune-mediated pulmonary small-vessel vasculitis include Henoch-Schönlein purpura, capillaritis including connective tissue disease (SLE, inflammatory myopathies, and rheumatoid arthritis), antiphospholipid syndrome, and anti-GBM-disease. DAH is also increasingly recognized as a pulmonary complication of bone marrow transplantation. However, whether this represents an immune-mediated or non–immune-mediated phenomenon remains controversial.

ACUTE MANAGEMENT OF DAH

Acute management of DAH involves supportive care, including ventilatory support ranging from oxygen supplementation to mechanical ventilation.[21] The coagulation cascade should be evaluated, and identified coagulation abnormalities should be corrected accordingly. Commonly accepted targets include a platelet count greater than

50,000/μL and an international normalized ratio of less than 1.5. Depending on the cause of the coagulopathy, platelet transfusions, vitamin K and fresh frozen plasma are used for correction.

It is crucial to identify and treat the underlying etiology of the DAH. Non–immune-mediated causes are treated by addressing the cause (eg, heart-failure management or discontinuation of any causative drugs). To quickly control the inflammatory activity in immune-mediated DAH, prompt initiation of high-dose methylprednisolone therapy is critical. Because of the high mortality associated with DAH, glucocorticoids are frequently started while diagnostic test results are pending.

If a non–immune-mediated cause is not effectively controlled by supportive care or addressing the underlying etiology or when all other options are exhausted in immune-mediated cases that are refractory to aggressive initial immunosuppressive therapy, consideration can be given to recombinant factor VIIa (rVIIa). Several recent case reports and small case series suggest that rVIIa may represent a treatment option for refractory cases. rVIIa is approved by the Food and Drug Administration (FDA) for the prevention and management of hemorrhagic complications in patients with hemophilia A or B. However, it has also been used for hemostasis in patients without hemophilia. Activated factor VIIa is thought to bind to activated platelets and activate factor X, resulting in the generation of thrombin in a tissue factor–independent fashion. In refractory cases of immune-mediated and non–immune-mediated DAH, including cases attributable to pulmonary vasculitis, rVIIa has been successfully administered both systemically (intravenously) or bronchoscopically. The optimal dose and dosing intervals remain to be determined. Systemic administration usually involves the intravenous administration of 90 to 180 μg/kg as either a single dose or, if needed, repeated doses every 2 to 4 hours. Endobronchial therapy typically includes the bronchoscopic delivery of a total dose of 50 μg/kg of activated factor VIIa diluted in 50 mL of normal saline. During the procedure 25 mL are instilled into each of the mainstem bronchi.[22–25] It must be noted that this represents an off-label use of rVIIa. Thrombotic complications involving both arterial and venous events have been reported in some patients treated with rVIIa, and patients should be monitored carefully. This risk is further increased in the known prothrombotic state of AAV. Therefore, this agent should be used with great caution when treating AAV.[26]

Another option includes the inhibition of fibrinolysis with the plasminogen inhibitor aminocaproic acid. The addition of aminocaproic acid to corticosteroids in patients with post–bone marrow transplant DAH was demonstrated to result in a lower 100-day disease-related mortality rate in comparison with corticosteroids alone.[27]

ADVANCES IN THE TREATMENT OF AAV

The treatment of AAV is typically stratified based on disease extent/severity and disease activity. The disease extent is classified as either nonsevere (limited) or severe disease. Severe disease is defined as the presence of life-threatening and/or organ-threatening disease manifestations, which includes all cases of pulmonary vasculitis and DAH. Active disease typically requires the initiation of remission induction therapy. Once remission has been achieved (after 3–6 months of therapy) patients are transitioned to remission maintenance therapy. At present, a minimum of 18 months is the accepted duration of remission maintenance therapy. The optimal length is not yet known. However, it is being evaluated in a randomized clinical trial comparing 24 months with 48 months.

In patients with severe disease, the selection of the appropriate remission induction and maintenance regimens appears to be independent of a clinical diagnosis of GPA

or MPA. Recent clinical trials have stratified patients based on their ANCA type rather than the specific underlying diagnosis. ANCA are classified based on their target antigens (either PR3 or MPO) and their staining pattern by indirect immunofluorescence on ethanol-fixed neutrophils (cytoplasmic [c] or perinuclear [p]). The most common pattern is c-ANCA/PR3-ANCA (GPA), p-ANCA/MPO-ANCA (MPA and EGPA).

Remission Induction Therapy for Severe AAV

Historically AAV was almost universally fatal; however, over the past decades new treatment strategies resulted in a dramatic decrease in AAV morbidity and mortality. Disease severity typically dictates the aggressiveness of the treatment strategy used. Traditionally combination therapy with high-dose corticosteroids (intravenous high-dose methylprednisolone, 1000 mg/d for 3–5 days followed by oral prednisone, 1 mg/kg/d [maximum 80 mg/d] tapered over approximately 6 months) and oral cyclophosphamide (CYC), 2 mg/kg/d was used for almost all cases of severe GPA and MPA, including cases of DAH. Approximately 75% of patients treated with prednisone/CYC will achieve remission, but disease relapse rates are as high as 50%.[28] Unfortunately, this regimen carries a substantial risk of severe treatment-related toxicity. Treatment-related complications include leukopenia and neutropenia owing to bone marrow suppression, opportunistic infections, hemorrhagic cystitis, female and male infertility, bladder cancer, and hematologic malignancies.[29,30] To decrease the occurrence of these side effects, intermittent intravenous pulse-dose CYC has been compared with the daily oral administration of the drug. Despite a significant decrease in the cumulative CYC dose in patients treated intravenously, differences in the side-effect profile were limited to fewer non–life-threatening leukopenias in patients receiving intravenous CYC. There were no differences in remission induction.[31] However, the relapse rate was higher in the intravenous-pulse CYC group, a finding that was recently confirmed during the long-term follow up of the study.[31,32] Even though methotrexate (MTX) is effective for remission induction therapy in patients with nonsevere (limited) GPA, this should not be used in the setting of DAH.[33]

Despite major advances in AAV remission induction, morbidity and mortality of patients with pulmonary vasculitis/DAH remains high and disease relapses occur frequently. Although the precise role of ANCA in the pathogenesis of AAV remains unclear, increasing clinical and experimental data suggest that these antibodies are at least modifying the autoimmune response. The presence of ANCA varies with the phenotype and the extent of disease. Whereas ANCA is absent in up to 30% to 40% of patients with nonsevere (limited) AAV, they are almost universally detectable in patients with pulmonary vasculitis/DAH. Consequently, several new therapeutic approaches have recently focused on the elimination of ANCA by depletion of B lymphocytes as the precursors of antibody-producing plasma cells or the direct removal of circulating antibodies.

Plasma Exchange for AAV

In an uncontrolled retrospective cohort study, 20 patients with AAV and DAH underwent plasma exchange (PLEX) in addition to standard immunosuppressive therapy. This approach resulted in excellent patient outcomes; DAH resolved in all cases and only 1 of 20 patients (5%) died, compared with historical controls.[34] However, earlier other investigators had reported a high mortality (50%) among 14 patients with pulmonary-renal syndrome despite the use of PLEX in 12 of 14 patients.[34,35] Furthermore, in the MEPEX trial the addition of PLEX to immunosuppressive therapy was found to improve 12-month renal outcomes in AAV patients presenting with severe renal dysfunction (serum creatinine >5.8 mg/dL).[36] Nevertheless, according

to the recently reported long-term follow-up data, these benefits were not sustained. In accordance with the evidence-based guidelines of the American Society for Apheresis, the authors are currently using PLEX in AAV patients with DAH presenting with hypoxemic respiratory failure requiring either high-flow supplemental oxygen or mechanical ventilation.[37] PLEX is typically performed daily or on alternating days for 14 days. Each exchange involves 1 to 1.5 times the total plasma volume. The volume is replaced with albumin but fresh frozen plasma is used at the end of each treatment. Nevertheless, the therapeutic indications of PLEX in AAV specifically for patients with DAH and glomerulonephritis remains controversial and is currently being investigated in an international randomized controlled clinical trial, the Plasma Exchange and Glucocorticoids for Treatment of AAV (PEXIVAS; NCT00987389).[38]

Rituximab in AAV

Rituximab (RTX) is a monoclonal chimeric antibody targeting CD20, a cell-surface protein expressed on B lymphocytes. These cells are the precursors for ANCA producing short-lived plasma cells. Antibody-mediated modification and/or depletion of B lymphocytes represents the proposed mechanism for this approach to decrease autoantibody production and control disease activity. Based on this rationale, RTX was evaluated on a compassionate-use basis for patients with refractory AAV. RTX is highly effective in patients with refractory AAV.[39–42] Successful treatment has been reported in more than 200 patients in at least 19 uncontrolled studies.[43] Therapeutic failures are uncommon and usually occur in patients with otherwise specific disease manifestations that are difficult to treat, such as retro-orbital pseudotumor. These very encouraging results led to 2 randomized controlled trials evaluating the use of RTX for remission induction therapy in patients with severe AAV.

The RTX in AAV (RAVE) trial compared combination therapy of glucocorticoids plus RTX or glucocorticoids plus CYC. After remission was achieved, patients in the CYC group were transitioned (after 3–6 months) to azathioprine (AZA) to complete 18 months of remission maintenance therapy, whereas RTX-treated patients were observed in the absence of further therapy. The RAVE trial was a double-blind, double-dummy controlled trial with a primary end point of noninferiority. All patients received either 4 weekly infusions of 375 mg/m^2 RTX or 2 mg/kg/d oral CYC. Based on the primary outcome measure (complete remission at 6 months: a Birmingham Vasculitis Assessment Score = 0 in the absence of corticosteroid therapy), RTX was found to be noninferior to CYC for remission induction therapy for severe AAV, including patients with pulmonary vasculitis and DAH. However, it must be noted that patients with severe DAH causing respiratory failure requiring mechanical ventilation were excluded from participation in this study. Both medications demonstrated similar efficacy in the subgroup of patients with DAH. Rituximab was superior to CYC for remission induction in patients who had a severe disease flare at the time of enrollment.[44] Somewhat surprisingly, relapse rates were similar between the 2 treatment groups at 18 months despite the absence of any active remission maintenance therapy in the RTX group.[45] Patients treated with RTX had fewer protocol-defined adverse events. This difference was mainly due to an increased frequency of leukopenia in the CYC-treated patients. Based on these data, RTX became the first FDA-approved drug for remission induction therapy in AAV.

Another study, the RTX versus CYC in ANCA-associated renal vasculitis study (RITUXVAS), enrolled 44 patients with newly diagnosed AAV (GPA and MPA) with renal involvement. Remission induction therapy included corticosteroids in combination with either RTX (4 weekly doses of 375 mg/m^2) and 2 pulses of intravenous CYC (15 mg/kg with the first and the third RTX infusion) or monthly intravenous CYC pulses

for 3 to 6 months (control patients received 15 mg/kg intravenous CYC every 2 weeks $\times$ 3, followed by every 3 weeks thereafter until stable remission, minimum 6, maximum 10 doses). Patients were randomized at a 3:1 ratio to experimental treatment (RTX plus 2 intravenous pulses of CYC) versus control treatment (intravenous pulse treatment with CYC for 6 months, followed by oral AZA for remission maintenance). Low-dose corticosteroids (5 mg/d) were continued in both treatment arms through 18 months. Similar to the RAVE study, there was no difference in remission induction and relapse rates between RTX and CYC.[46] Long-term data regarding the efficacy and safety of RTX is beginning to become available.[42]

Remission Maintenance Therapy for AAV

Remission induction therapy alone regardless of regimen is insufficient to prevent relapses, and prolonged CYC treatment has been associated with unacceptable toxicities. Consequently, several different remission maintenance regimens have been investigated. In a landmark randomized controlled trial, maintenance therapy with AZA (2 mg/kg for 18 months) was demonstrated to be as effective as long-term CYC treatment.[47] MTX (25 mg weekly) has also been demonstrated to be effective as remission maintenance therapy for AAV, and a recent randomized trial showed its equal efficiency in comparison with AZA.[48,49]

Mycophenolate mofetil is another safe alternative for remission maintenance therapy. However, in a recent randomized controlled trial it was found to be inferior to AZA. Consequently it is mainly used as a second-line option for patients who have contraindications to AZA or MTX or who have failed the first-line remission maintenance options.[50,51]

The intermittent administration of RTX without corticosteroids may represent another option for remission maintenance treatment of AAV. RTX will be investigated as such in an upcoming randomized controlled trial. Meanwhile, recent data regarding the long-term use of RTX in patients with refractory AAV is very promising.[42]

MONITORING AND PROPHYLAXIS

To minimize treatment-related morbidity, preemptive monitoring of the appropriate laboratory parameters should be conducted at regular intervals. Pneumocystis pneumonia prophylaxis should be prescribed to all patients on high doses of glucocorticoids, CYC, AZA, MTX, mycophenolate mofetil, or RTX. All patients on long-term glucocorticoid therapy should be offered prophylactic therapy for osteoporosis. Furthermore, patients exposed to CYC should be monitored for the development of bladder cancer, and reproductive issues should be addressed in patients of childbearing age. All patients treated with MTX should receive folic acid supplementation.

SELECTED OTHER DISEASES ASSOCIATED WITH PULMONARY VASCULITIS AND DAH

Primary Antiphospholipid Syndrome

DAH represents a rare, frequently fatal nonthrombotic pulmonary complication of primary antiphospholipid syndrome (APLS). Pulmonary capillaritis without thrombosis has been demonstrated in lung biopsies from APLS patients presenting with DAH.[52] A proposed mechanism for the pathogenesis includes binding of antiphospholipid antibodies to endothelial cells, promoting the increased expression of endothelial cell adhesion molecules, neutrophil binding, and ultimately injury of alveolar capillaries and alveolar basement membrane.[52]

DAH in APLS is very difficult to treat. Historically, combination therapy of glucocorticoids and other immunosuppressants (CYC, AZA, or mycophenolate mofetil) is

combined with the intravenous administration of immunoglobulin G (IVIG) and/or PLEX.[52,53] However, a recent review of 17 consecutive cases of DAH in APLS demonstrated the limited success of aggressive standard immunosuppressive therapy in these patients. None of the patients treated with AZA or mycophenolate mofetil achieved remission, and remission was only seen in a subgroup of patients treated with CYC, IVIG, PLEX, or RTX.[54] A recent case report also demonstrated a potential role for RTX for patients with primary APLS and DAH.[55] In addition to these challenging decisions regarding the appropriate immunosuppressive therapy, the clinical management of these cases is typically complicated by the fact that many of these individuals are on therapeutic anticoagulation to treat previous thrombotic complications. Because the DAH almost universally requires at least the temporary discontinuation of the anticoagulation, these patients are at high risk for recurrent venous and/or arterial thrombosis.

Hematopoietic Stem Cell Transplant

DAH can complicate both allogeneic and autologous hematopoietic stem cell transplantation. It typically occurs early after stem cell transplantation.[56] The incidence of DAH is approximately 2%.[57,58] The mortality is commonly greater than 50% in these patients. Outcomes are worse in allogeneic transplants and in patients presenting with DAH more than 30 days after their transplant.[59] While risk factors for DAH (older age and treatment regimens including intensive pretransplant chemotherapy and total body irradiation) have been identified, the underlying pathogenesis remains poorly understood. Based on data from selected retrospective case series, the current standard therapy frequently includes high-dose corticosteroids, implying that the nature of this disease is immune mediated.[56] A diagnosis of DAH in these typically immunocompromised patients is characteristically established based on clinical, radiologic, and bronchoscopic data (respiratory decompensation in a patient with pulmonary infiltrates and BAL findings suggestive of DAH). Similar findings are also typically present in patients with diffuse alveolar damage with or without associated coagulopathy, both of which are frequently present after bone marrow transplant. Because of the associated risks, lung biopsies are usually not obtained in these patients. It is interesting that in a large autopsy series most of these cases demonstrated a histologic pattern of diffuse alveolar damage, and capillaritis was notably absent in all cases. This information argues against the immune-mediated nature of DAH in the context of bone marrow transplantation, and caution is warranted against the indiscriminate use of glucocorticoid therapy. This caution is especially important in a patient population with a high incidence of invasive fungal infections, in whom further immunosuppressive therapy may result in worse clinical outcomes.

SUMMARY

Pulmonary vasculitis most frequently manifests with DAH and represents its most common immune-mediated cause. The acute management of these patients primarily focuses on respiratory support and the correction of abnormalities in the coagulation cascade. A careful history taking and physical examination in conjunction with a focused laboratory investigation (including serologic testing for autoantibodies) frequently facilitates targeted therapy by identifying the underlying systemic disease. AAV, specifically GPA and MPA, represents the most common cause of pulmonary vasculitis and immune-mediated DAH. Because of their life-threatening nature, these cases are typically categorized as severe disease and treated accordingly. Based on the data from recent randomized controlled trials, RTX represents an equally effective

and likely less toxic alternative to CYC for remission induction therapy in these patients. The role of PLEX remains unclear, and appropriate patients should be considered for participation in clinical trials.

Patients with pulmonary vasculitis benefit from a multidisciplinary team approach, and expedited referral to an appropriate center with these resources should be considered for these patients. Further research is needed to continue to optimize the care of these challenging patients.

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