Diffuse Alveolar Hemorrhage

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Diffuse alveolar hemorrhage (DAH) is often a catastrophic clinical syndrome causing respiratory failure. Recognition of DAH often requires BAL as symptoms are nonspecific, hemoptysis is absent in up to one-third of patients, and radiographic imaging is also nonspecific and similar to other acute alveolar filling processes. Once the diagnosis is established, the underlying cause must be established in order to initiate treatment. This review discusses the diagnosis of the underlying histologies and the clinical entities that are responsible for DAH as well as treatment options.

**Definition**

DAH is recognized by the clinical constellation of hemoptysis, anemia, diffuse radiographic pulmonary infiltrates, and hypoxemic respiratory failure. The underlying histopathology of DAH includes the presence of intraalveolar RBCs and fibrin and the eventual accumulation of hemosiderin-laden macrophages, which may take up to 48 to 72 h to accumulate. Of the histologies that are associated with DAH (pulmonary capillaritis, bland pulmonary hemorrhage, diffuse alveolar damage, and miscellaneous histology) pulmonary capillaritis is the most common.
Pulmonary capillaritis has a unique histopathologic appearance consisting of an interstitial neutrophilic predominant infiltration, fibrinoid necrosis of the alveolar and capillary walls, and leukocytoclasis. The infiltrating neutrophils undergo cytolysis, nuclear debris accumulates within the interstitium, and there is a subsequent loss of the integrity of the alveolar-capillary basement membrane (Fig 1). It is the disruption of the alveolar-capillary basement membranes that results in the accumulation of RBCs in alveolar spaces. There is a distinction between pulmonary capillaritis and pulmonary vasculitis. Pulmonary vasculitis refers to inflammation of the lung vessels of any size, whereas pulmonary capillaritis is confined to the microcirculation of the lung (alveolar capillaries, arterioles, and venules). However, both may be seen in systemic vasculitides and the connective tissue diseases.

Recently, there has been an effort to change the eponym of Wegener granulomatosis (WG) to a more scientific nomenclature of antineutrophilic cytoplasmic autoantibodies (ANCA)-associated granulomatous vasculitides and the connective tissue diseases. However, both may be seen in systemic vasculitides and the connective tissue diseases.

Recently, there has been an effort to change the eponym of Wegener granulomatosis (WG) to a more scientific nomenclature of antineutrophilic cytoplasmic autoantibodies (ANCA)-associated granulomatous vasculitides. This is not the first time that an eponym has undergone a change (eg, Loeffler Syndrome and simple pulmonary eosinophilia). Although the suggestion to develop an alternative name for WG may have evolved after the association of Dr Wegener and the Nazi regime, it is our opinion that the alternative should be used because it serves to describe the pathology, and eponyms do not describe the disease process.

**Etiology**

Injury to the alveolar microcirculation resulting in DAH may be localized to the lung (inhalation injuries, diffuse alveolar damage) or associated with a systemic disorder (vasculitis or connective tissue disease). The causes of DAH are listed in Table 1. There is a spectrum of disorders associated with DAH, but no prospective studies estimate its relative frequency. A review of 34 cases of histopathologically confirmed DAH indicated that capillaritis occurred in 88% of the cases. In one report, the most common clinical cause of DAH was WG (32%), followed by Goodpasture syndrome (13%), idiopathic pulmonary hemosiderosis (IPH) (13%), collagen vascular diseases (13%), and microscopic polyangiitis (MPA) (9%). In another series, isolated pauciimmune pulmonary capillaritis was the most common cause of DAH associated with capillaritis. In recipients of hematopoietic stem cell transplantation, DAH was reported to occur in 5% of 3,806 patients.

**Clinical Presentation and Diagnosis**

DAH appears at any age and often with an established associated disease. DAH may also be the initial manifestation of an underlying systemic disease. The cardinal sign of DAH, hemoptysis, may be a dramatic event or evolve over days to weeks; however, it may be initially absent in up to 33% of DAH cases. The natural course is unpredictable and varies in severity but always should be considered a potentially life-threatening event. The symptoms of DAH, other than hemoptysis, are nonspecific and include fever, chest pain, cough, and dyspnea. Nonpulmonary signs and symptoms are those that accompany the underlying systemic disease. In addition to history, physical examination, and routine laboratory studies, directed serologic testing for connective tissue disease and systemic vasculitis is useful for establishing the diagnosis (Table 2). In up to one-third of patients with DAH, hemoptysis is absent and the diagnosis is established after sequential BAL reveals worsening RBC counts. Moreover, a falling hematocrit should alert the clinician to the possibility of DAH. The chest radiograph findings are nonspecific and consist of an alveolar filling process that can be a patchy, focal, or diffuse alveolar filling process (Fig 2). Chest CT scans confirm the chest radiographic findings and more accurately define the extent of disease. Flexible bronchoscopy should be performed to establish the clinical diagnosis of DAH and to exclude infections. Progressively hemorrhagic BAL found in serial samples is diagnostic of DAH but not the underlying cause. Surgical lung biopsy may be required to establish the cause if serologic testing or clinical history is unrevealing. Transbronchial biopsies are usually insufficient. With recurrent episodes of DAH, interstitial fibrosis or an obstructive lung disease most compatible with emphysema can evolve.

**Specific Disorders Associated With DAH**

**Isolated Pauciimmune Pulmonary Capillaritis**

Isolated pauciimmune pulmonary capillaritis is a small-vessel vasculitis that is confined to the lung and without clinical or serologic features of an associated systemic disease. In a series of 29 cases of biopsy-confirmed...
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is unknown but is reported to occur most commonly before the age of 30 years. In the pediatric population the incidence is reported to be 0.24 in 1 million. The histology lacks evidence of capillaritis and the alveolar basement membranes are thickened but remain intact. Recurrent episodes of DAH lead to release of iron into the lung resulting in an abundance of hemosiderin-laden macrophages. In advanced cases of IPH, the lungs develop a distinctive brown color due to the abundance of hemosiderin and have varying degrees of consolidation and fibrosis. The cause and pathogenesis is unknown; however, an immune process may be involved as IPH appears to respond to immunosuppressant therapy. Although IPH was included as a syndrome with DAH, it should be noted that it is a rare entity distinct in histology from other causes of DAH resulting from the microcirculation.

**ANCA-Associated Granulomatous Vasculitis**

ANCA-associated granulomatous vasculitis is a systemic vasculitis characterized by granulomatous inflammation of the upper and lower respiratory tract, necrotizing vasculitis, and the presence of ANCA. The ANCA associated with ANCA-associated granulomatous vasculitis is an antibody directed against cytoplasmic proteinase 3 (PR3). Demographic data obtained from the WG Etanercept Trial varied between the patients with limited vs severe disease. Patients with DAH were defined as having severe disease, were older (mean age of 50 ± 16 vs 41 ± 16 years), and were more likely to be men. DAH was identified in 25% of the patients with more severe disease. The pathogenesis of PR3-ANCA-positive vasculitis involves the cellular immune pathways resulting in granulomatous inflammation. The percentage expression of PR3 on the surface of neutrophils in patients with ANCA-associated granulomatous vasculitis correlates with higher rates of relapse. A retrospective analysis found rising titers of cytoplasmic-ANCA to have high sensitivity and specificity (93% and 97%, respectively) in predicting relapse or the presence of active disease. However, a recent prospective study had a specificity of 75% and a sensitivity of 71% for predicting relapse using rising titers. Patients with persistently high titers of PR3-ANCA after remission tend to have a higher risk of relapse than those who are ANCA negative. Current treatment is concentrated for the induction of remission using corticosteroids and cyclophosphamide. Maintenance therapy after remission is achieved either with methotrexate or azathioprine. Recently rituximab, a chimeric anti-CD20 monoclonal antibody, has been shown to induce remission in patients with refractory ANCA-associated granulomatous vasculitis, but should

### Table 1—Etiology and Histology of Diffuse Alveolar Hemorrhage

| Pulmonary capillaritis | ANCA-associated granulomatous vasculitis | Microscopic polyangiitis | SLE | Rheumatoid arthritis | Mixed connective tissue disorder | Scleroderma | Polymyositis | Primary antiphospholipid antibody syndrome | Henoch-Schönlein purpura | Behçet Syndrome | IgA nephropathy | Goodpasture syndrome | Idiopathic glomerulonephritis (pauciimmune or immune complex-related) | Acute lung transplant rejection | Idiopathic pulmonary fibrosis | Diphenylhydantoin | Retinoic acid toxicity | Autologous bone marrow transplantation | Myasthenia gravis | Cryoglobulinemia | Ulcerative colitis | Propylthiouracil | Bland pulmonary hemorrhage | IPH | Goodpasture syndrome | SLE | Coagulation disorders | Trimellitic anhydride | Isocyanate exposure | Penicillamine | Amiodarone | Nitrofurantoin | Mitral stenosis | Subacute bacterial endocarditis | Polyglanudular autoimmune syndrome | Multiple myeloma | Diffuse alveolar damage | Bone marrow transplantation | Crack cocaine inhalation | Cytotoxic drug therapy | SLE | Radiation therapy | ARDS |
|------------------------|-----------------------------------------|--------------------------|-----|---------------------|---------------------------------|-----------|-------------|------------------------------------------|-----------------------------|------------------------|---------------------|--------------------------|-------------------------------------------------|-----------------|----------------|----------------|----------------------------|--------------------------|-----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Pulmonary capillaritis | ANCA-associated granulomatous vasculitis | Microscopic polyangiitis | SLE | Rheumatoid arthritis | Mixed connective tissue disorder | Scleroderma | Polymyositis | Primary antiphospholipid antibody syndrome | Henoch-Schönlein purpura | Behçet Syndrome | IgA nephropathy | Goodpasture syndrome | Idiopathic glomerulonephritis (pauciimmune or immune complex-related) | Acute lung transplant rejection | Idiopathic pulmonary fibrosis | Diphenylhydantoin | Retinoic acid toxicity | Autologous bone marrow transplantation | Myasthenia gravis | Cryoglobulinemia | Ulcerative colitis | Propylthiouracil | Bland pulmonary hemorrhage | IPH | Goodpasture syndrome | SLE | Coagulation disorders | Trimellitic anhydride | Isocyanate exposure | Penicillamine | Amiodarone | Nitrofurantoin | Mitral stenosis | Subacute bacterial endocarditis | Polyglanudular autoimmune syndrome | Multiple myeloma | Diffuse alveolar damage | Bone marrow transplantation | Crack cocaine inhalation | Cytotoxic drug therapy | SLE | Radiation therapy | ARDS |

ANCA = antineutrophilic cytoplasmic autoantibodies; IPH = idiopathic pulmonary hemosiderosis; SLE = systemic lupus erythematosus.

Pulmonary capillaritis, isolated pauciimmune pulmonary capillaritis was the most common cause of DAH. Overall, patients with isolated pauciimmune pulmonary capillaritis tend to have a better prognosis when compared with DAH occurring in the setting of a systemic vasculitis or collagen vascular disease.

**IPH**

IPH is a rare syndrome in which repeated episodes of DAH occur resulting in chronic anemia and pulmonary fibrosis. The incidence in the adult population is unknown but is reported to occur most commonly before the age of 30 years. In the pediatric population the incidence is reported to be 0.24 in 1 million. The histology lacks evidence of capillaritis and the alveolar basement membranes are thickened but remain intact. Recurrent episodes of DAH lead to release of iron into the lung resulting in an abundance of hemosiderin-laden macrophages. In advanced cases of IPH, the lungs develop a distinctive brown color due to the abundance of hemosiderin and have varying degrees of consolidation and fibrosis. The cause and pathogenesis is unknown; however, an immune process may be involved as IPH appears to respond to immunosuppressant therapy. Although IPH was included as a syndrome with DAH, it should be noted that it is a rare entity distinct in histology from other causes of DAH resulting from the microcirculation.

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patients who survive an episode of DAH their 1-year and 5-year survival is reduced to 82% and 68%, respectively.26-28 MPA can be distinguished from ANCA-associated granulomatous vasculitis by serologically demonstrating a perinuclear-ANCA directed against neutrophil myeloperoxidase (MPO-ANCA). Unlike ANCA-associated granulomatous vasculitis, the level of MPO-ANCA titers is not associated with disease activity.29 Recent animal studies suggest that MPO-ANCA, and to a lesser degree PR3-ANCA, may mediate disease by activating the alternative complement pathway, a self-sustaining pathway, and may lend new insight into the severity of disease in ANCA-positive diseases.30 Surgical lung biopsy is usually not

not be considered as first-line therapy in Wegener-associated DAH.22 Plasma exchange has also shown usefulness if instituted early in the disease course.23-25

**MPA**

MPA is a systemic vasculitis that is confined to the microvessels and is always associated with a focal segmental necrotizing glomerulonephritis. It is distinguished from ANCA-associated granulomatous vasculitis by the absence of upper airway involvement. DAH due to pulmonary capillaritis occurs in up to one-third of patients and represents the only pulmonary manifestation of MPA. DAH increases the mortality of MPA. In the acute setting, 30% of patients do not survive an episode of DAH; in those patients who survive an episode of DAH their 1-year and 5-year survival is reduced to 82% and 68%, respectively.26-28

### Table 2—Serologic and Radiologic Evaluation of Diffuse Alveolar Hemorrhage

<table>
<thead>
<tr>
<th>Nonspecific findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytosis</td>
</tr>
<tr>
<td>Any cause</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Cytotoxic drugs</td>
</tr>
<tr>
<td>Antiphospholipid syndrome</td>
</tr>
<tr>
<td>SLE</td>
</tr>
<tr>
<td>Increased sedimentation rate</td>
</tr>
<tr>
<td>Any cause</td>
</tr>
<tr>
<td>Urine red blood cell casts</td>
</tr>
<tr>
<td>Any systemic vasculitis</td>
</tr>
<tr>
<td>SLE, mixed connective tissue disease</td>
</tr>
<tr>
<td>Goodpasture syndrome</td>
</tr>
<tr>
<td>Abnormal PT, PTT, INR</td>
</tr>
<tr>
<td>SLE</td>
</tr>
<tr>
<td>Coagulation disorders</td>
</tr>
<tr>
<td>Drugs</td>
</tr>
<tr>
<td>Chest radiographic and CT scan infiltrates</td>
</tr>
<tr>
<td>Patchy or diffuse, often with apical and peripheral sparing</td>
</tr>
<tr>
<td>Any cause</td>
</tr>
<tr>
<td>Air bronchograms</td>
</tr>
<tr>
<td>Any cause</td>
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</tbody>
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| Specific findings                          |
| Connective tissue disease                  |
| Rheumatoid factor                          |
| Connective tissue disease                  |
| ANCA-associated granulomatous vasculitis    |
| Cytoplasmic-ANCA                           |
| ANCA-associated granulomatous vasculitis    |
| Microscopic polyangiitis (less common)     |
| Perinuclear-ANCA                           |
| Microscopic polyangiitis                   |
| ANCA-associated granulomatous vasculitis    |
| Specific radiologic findings on chest radiograph and/or CT scan |
| Kerley B lines                             |
| PVOD, mitral stenosis                      |
| Nodules, cavities                          |
| WG                                         |
| Rheumatoid arthritis                       |

**Figure 2.** Chest radiograph (A) and chest CT scan (B) showing diffuse nonspecific alveolar infiltrates in a patient with diffuse alveolar hemorrhage.
necessary in patients with suspected DAH in the setting of ANCA-positive disease provided infection has been excluded. Treatment, as with ANCA-associated granulomatous vasculitis, is glucocorticoids, cyclophosphamide, and plasmapheresis, and is the recommended regimen for induction of remission. Recombinant factor VIIa has been used to treat severe DAH in MPA with unremitting respiratory failure. The mechanism of factor VIIa treatment is the enhancement of thrombin generation on the surface of activated platelets at the sites of hemorrhage.

Systemic Lupus Erythematous

DAH occurs in 4% of patients with systemic lupus erythematous (SLE) admitted to the hospital and pulmonary capillaritis is usually the underlying cause. In an immunosuppressed patient with SLE, infectious pneumonia should be excluded as the cause of DAH. In the majority of DAH associated with SLE, glomerulonephritis is also present, and in 80% the DAH occurs in patients with known SLE. These are most often young females with a mean age of 27 years. The mortality had been previously reported to be as high as 50%; however, with the use of aggressive treatment with glucocorticoids and cyclophosphamide, the mortality associated with DAH in SLE is declining. DAH is distinguished from acute lupus pneumonitis using sequential BAL. Acute lupus pneumonitis presents with similar clinical and radiographic features as DAH; however, it also has systemic symptoms typical of an SLE flare and may be the only manifestation of the initial presentation of SLE. The histologic appearance of acute lupus pneumonitis is varied and includes diffuse alveolar damage, organizing pneumonia, nonspecific cellular pneumonia, or a combination of these histologic patterns, but capillaritis is not present. Immune complexes are frequently found in the lung. The deposition of immune complexes and the activation of complement within the lung are central to the development of parenchymal disease in SLE. Methylprednisolone is recommended (1-2 mg/kg/d in divided doses). High-dose pulse methylprednisolone (1 g given in divided doses for 3 days) can be given to those with DAH or acute lupus pneumonitis. Escalating treatment in steroid-resistant DAH includes azathioprine, cyclophosphamide, or intravenous γ globulin. The combination of high-dose intravenous methylprednisolone and cyclophosphamide anecdotally is the most effective combination. In refractory cases, plasmapheresis has been used; however, survival does not appear to be improved. In a patient with SLE who has established DAH, recurrences are to be expected.

Other Connective Tissue Diseases

DAH with underlying pulmonary capillaritis is an infrequent occurrence in mixed connective tissue disease, rheumatoid arthritis, polymyositis, dermatomyositis, primary antiphospholipid syndrome, and scleroderma. The DAH may be the presenting manifestation or complicate a preexisting disease. Treatment options are similar to those outlined for DAH in SLE.

Goodpasture Syndrome (Antiglomerular Basement Membrane Antibody Disease)

Goodpasture syndrome, also known as antiglomerular basement membrane antibody disease-associated DAH, is likely the result of autoantibodies directed against the NC1 domain of the α3 chain of the basement membrane collagen type 4. The clinical expression of the disease occurs only in the lungs and the kidneys. DAH is common in antiglomerular basement membrane disease, particularly in cigarette smokers. It is postulated that smoking mediates damage to the alveolar basement membrane, thus allowing the development of autoantibodies. Bland hemorrhage is the most common underlying histology, but pulmonary capillaritis is sometimes seen. Patients with Goodpasture syndrome tend to be men in their 20s who also smoke. More than 90% of patients with Goodpasture disease have circulating anti-basement membrane antibodies. In patients with negative circulating anti-basement membrane antibodies, a lung or renal biopsy with immunofluorescence revealing linear antibody deposition within the alveolar or glomerular basement membrane confirms the diagnosis. However, in up to 10% of patients with Goodpasture syndrome, DAH is present without renal involvement and is identical to isolated pulmonary capillaritis. Lung biopsy with immunofluorescence studies distinguishes the two. Treatment with immunosuppression and plasma exchange has improved outcomes in these patients. Rituximab, a chimeric anti-CD20 monoclonal antibody that has shown efficacy in the treatment of rheumatoid arthritis, should be considered in patients with ANCA-associated vasculitis that is refractory to standard therapy. Treatment with rituximab results in depletion of B cells that produce pathogenic autoantibodies and reduces the cellular interaction by decreasing both the production of cytokines that maintain mononuclear cells and the production of immune complex formations that help to sustain the disease.

Lung Allograft Rejection

Pulmonary capillaritis as a form of acute lung transplant rejection was first described in five patients in...
1998. Since then, the mechanism of the acute rejection with DAH has been studied further. A necrotizing, pauciinflammatory septal capillary injury pattern was noted. Immunofluorescent staining revealed a septal capillary deposition of antibodies specific for complement factors and immunoglobulin subtypes. Differentiating between acute cellular rejection and posttransplant capillaritis requires tissue biopsy and can be found concomitantly in >50% of cases. Isolated pulmonary capillaritis, however, is an infrequent occurrence (approximately 10% of all biopsies performed; M. Zamora, personal communication). Treatment consists of IV corticosteroids and plasmapheresis in severe cases.

**Bone Marrow Transplant**

Pulmonary complications develop in 30% to 60% of all bone marrow transplant recipients and are the cause of death in up to 60%. DAH occurs in approximately 5% of allogeneic and autologous recipients and has a reported mortality rate ranging from 50% to 100%. Of the recipients that develop DAH as a pulmonary complication and survive, the 6-month mortality is 38%.

The frequency of DAH does not appear to vary significantly with the type of hematopoietic stem cell transplant, with a reported frequency of 1% to 21% in autologous and 2% to 17% in allogeneic hematopoietic stem cell transplant recipients. Risk factors for the development of DAH in bone marrow transplant recipients include older age, total body radiation, myeloablative conditioning regimens, and severe acute graft-vs-host disease. Clinically, these patients present with hemoptysis less frequently compared with other causes of DAH with a rate of approximately 15%. Protective strategies, such as reducing the intensity of the conditioning regimen, do not appear to decrease the risk of DAH. The pathogenesis of DAH in bone marrow transplant recipients has yet to be clearly established, but it has been suggested that tissue injury, inflammation, and the associated cytokine release play important roles. Lung biopsy reveals diffuse alveolar damage and DAH. The majority of patients with DAH require mechanical ventilation and corticosteroids are the mainstay of treatment, although their effectiveness remains uncertain.

**Summary**

DAH is a clinicopathologic syndrome that results from a variety of conditions and should be considered a life-threatening event. Once believed to be a rare syndrome, DAH is being recognized with increasing frequency. A systematic approach to early recognition, establishment of diagnosis, and aggressive treatment likely decreases the morbidity and mortality associated with untreated or unrecognized DAH.

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