Diffuse Alveolar Hemorrhage and Goodpasture’s Syndrome

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Abstract

Diffuse alveolar hemorrhage (DAH) represents a medical emergency. There are many causes of DAH, including Goodpasture’s syndrome, vasculitides, and collagen vascular disease. An organized approach to diagnosis is paramount. In patients suspected of having DAH due to Goodpasture’s syndrome, serologic evaluation searching for the presence of anti-basement membrane antibodies should be performed. If the diagnosis remains in question, emergent kidney biopsy should be obtained to demonstrate linear deposition of antibody along the glomerular basement membrane visible by direct immunofluorescence. Treatment of Goodpasture’s syndrome involves the combination of corticosteroids, cyclophosphamide or azathioprine, and plasmapheresis.

Diffuse alveolar hemorrhage (DAH) is a medical emergency, often leading to acute respiratory failure. Despite advances in the identification and management of DAH, it remains a highly morbid condition with substantial mortality. DAH is caused by a diverse group of disorders, among the most common of which is Goodpasture’s syndrome. Pulmonologists must be able to quickly identify the presence of DAH, expeditiously investigate potential underlying causes, and decide on therapy. This article reviews the clinical presentation of DAH and provides an approach to the identification of DAH and its underlying cause, with special attention given to one of the most common causes of DAH, Goodpasture’s syndrome.

Definitions

The term ‘diffuse alveolar hemorrhage’ refers to a distinct form of pulmonary hemorrhage originating from the pulmonary microcirculation, which includes the alveolar capillaries, arterioles, and venules. This definition distinguishes DAH from other causes of pulmonary hemorrhage, such as bronchiectasis, malignancy, or infection, in which hemorrhage often arises from the bronchial (systemic) circulation. Bleeding in these conditions can be brisk, quickly flooding the alveoli and mimicking the clinical and radiographic appearance of DAH.

Goodpasture’s syndrome, or anti-basement membrane antibody (ABMA) disease, is a clinical syndrome characterized by the combination of DAH and glomerulonephritis. In three-fourths of cases, the pulmonary and renal disease occur simultaneously, with the remainder split between isolated DAH and isolated glomerulonephritis. More than 90% of patients with Goodpasture’s syndrome have circulating serum ABMA (these antibodies are also commonly referred to as anti-glomerular basement membrane antibodies). The target of this antibody has been identified as the NC1 domain of the 3 chain of type IV collagen.

Etiology

The most common causes of DAH are listed in Table 1. A review of 34 cases of DAH found that approximately one-third were associated with Wegener’s granulomatosis. Goodpasture’s syndrome was the second most common etiology, accounting for 13% of cases.

Any source of injury to the alveolar microcirculation can theoretically cause alveolar hemorrhage. The injury may be primarily in the lung (e.g., pneumonia) or more generalized (e.g., vasculitis). Many cases of DAH are associated with a neutrophilic infiltration of the alveolar wall centering on capillaries and venules. This histopathologic observation is called ‘capillaritis’ and is most closely associated with the alveolar capillaries, arterioles, and venules. This definition distinguishes DAH from other causes of DAH, including Goodpasture’s syndrome. Pulmonologists must be able to quickly identify the presence of DAH, expeditiously investigate potential underlying causes, and decide on therapy. This article reviews the clinical presentation of DAH and provides an approach to the identification of DAH and its underlying cause, with special attention given to one of the most common causes of DAH, Goodpasture’s syndrome.

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with the systemic vasculitides and collagen vascular diseases. Although Goodpasture’s syndrome may be associated with capillaritis, it generally causes so-called ‘bland hemorrhage’ (i.e., showing no evidence of inflammation on biopsy).

The etiology of Goodpasture’s syndrome is unknown, but it is commonly associated with cigarette smoking, suggesting a potential causative role. Smoking likely increases the risk and severity of DAH by increasing alveolar permeability. The typical patient is a young male smoker, although older people, women, and nonsmokers can also be affected. Other associations include respiratory infections, such as influenza A2, and hydrocarbon products, such as petroleum, turpentine, and pesticides. There is a strong association with HLA-DRw2 and HLA-B7, which portend a poor prognosis.

Clinical Evaluation

There is nothing unique to the presentation of DAH in Goodpasture’s syndrome. Although demographics and urinary findings may suggest the diagnosis, it is only with further laboratory and histopathologic evaluation that the diagnosis is made. The following discussion is therefore relevant to DAH occurring in Goodpasture’s syndrome as well as to other causes.

History

The three most common presenting symptoms of DAH are hemoptysis, dyspnea, and cough. These are generally acute in onset, but occasionally they are subacute and recurrent. Many cases will not have this classic clinical presentation. Importantly, hemoptysis is not universally present at the time of initial evaluation, even in severe cases. Dyspnea is generally a result of ventilation-perfusion mismatch secondary to alveolar filling, although rarely anemia may contribute. Depending on the etiology of DAH, fever and signs and symptoms referring to a systemic vasculitis or collagen vascular disease may be present. Occasionally, complaints of decreased urine output or hematuria may be reported, suggesting a concomitant glomerulonephritis and raising the possibility of Goodpasture’s syndrome, systemic vasculitis, or collagen vascular disease (particularly systemic lupus erythematosus). As noted previously, youth, male gender, and current cigarette smoking are common findings in patients with Goodpasture’s syndrome. Most cases occur in men in their 20s and 30s.

Physical Examination

The physical examination is generally non-specific in DAH. The cardiac and pulmonary examinations are often normal, even in the setting of substantial alveolar filling due to hemorrhage. Inspiratory crackles are occasionally present and may be focal or diffuse. Clubbing is not present. Specific etiologies may be suggested by the presence of a diastolic murmur (mitral stenosis) or ocular, nasopharyngeal, and cutaneous evidence of vasculitis or collagen vascular disease. There are no physical findings specific to Goodpasture’s syndrome.

Radiology

The chest radiograph is almost always abnormal in DAH (Figure 1). Diffuse alveolar opacities are typically seen, although they can be focal and asymmetric. Pleural effusions are rarely seen. Although computed tomography is potentially useful in the evaluation of hemoptysis and is commonly obtained in patients presenting with this complaint, it has little role in the further evaluation of DAH.

Laboratory Evaluation

The laboratory evaluation is where the underlying etiology of DAH often becomes apparent. The hemoglobin is decreased in most cases of DAH, and leukocytosis may be seen. In Goodpasture’s syndrome, the serum creatinine may be elevated and the urine sediment active (i.e., dysmorphic red blood cells and/or red blood cell casts), suggesting a concomitant glomerulonephritis. Serum ABMA will commonly
(90%) be present. Serum anti-neutrophil cytoplasmic antibodies (ANCA) or serum markers of collagen vascular disease may be present and suggest alternative etiologies.

Pulmonary function testing is often not feasible given the severity of illness in many DAH patients. If performed, normal or mildly restricted patterns may be observed. In acute hemorrhage, the carbon monoxide diffusing capacity may be elevated, and this can be used to follow patients for evidence of recurrent hemorrhage once clinically stabilized.

**Histopathology**

**Lung Biopsy**

Surgical lung biopsy is highly preferable to transbronchial biopsy for the histopathological diagnosis of DAH due to its larger sample size and architectural preservation (Figure 2). True alveolar hemorrhage must be distinguished from other causes of red blood cell accumulation in the alveolar space, most commonly bleeding into the lung at the time of biopsy. Alveolar hemorrhage usually demonstrates intra-alveolar fibrin, hemosiderin in the alveolar walls, and hemosiderin-laden alveolar macrophages. Hemosiderin requires at least 48 h to develop and, if present, is helpful in distinguishing DAH from surgical trauma. Areas of mild interstitial thickening and occasional associated organizing pneumonia or diffuse alveolar damage may be present.

If Goodpasture’s syndrome is suspected and histopathology is required, kidney biopsy is generally preferred, but linear deposition of antibody along the alveolar basement membrane is generally visible by direct immunofluorescence of lung biopsy tissue. In other conditions, such as vasculitis and collagen vascular disease, capillaritis may be present. Typical histopathologic features of capillaritis include fibrin thrombi occluding capillaries in the alveolar septae, fibrinoid necrosis of the capillary walls, and interstitial accumulation of fragmented neutrophils and nuclear dust adjacent to alveolar capillaries. Capillaritis has been described in Goodpasture’s syndrome but is extremely rare.

**Kidney Biopsy**

In cases of Goodpasture’s syndrome without circulating ABMA, the diagnosis may require histopathologic confirmation. Kidney biopsy is generally preferable due to its lower morbidity and more consistent findings. As described previously for the lung, kidney biopsy in Goodpasture’s syndrome will demonstrate linear deposition of antibody along the glomerular basement membrane, visible by direct immunofluorescence (Figure 3). Even in the rare case of Goodpasture’s syndrome without clinically evident renal disease, kidney biopsy will still show the typical linear antibody deposition. Kidney biopsy is also useful for defining the presence and extent of glomerulonephritis in DAH associated with vasculitis, such as Wegener’s granulomatosis or microscopic polyangiitis.

**Diagnosis**

A thoughtful and thorough approach to the diagnosis of DAH is critical to appropriate management. In cases of DAH presenting with dyspnea or cough, the differential diagnosis includes congestive heart failure, pneumonia, and acute presentations of other diffuse parenchymal lung diseases. The presence of hemoptysis narrows this differential diagnosis.
significantly. In these patients, pseudohemoptysis (hemorrhage arising from the upper airway or gastrointestinal tract) must be excluded. Focal sources of pulmonary hemorrhage are common and must be considered (e.g., bronchitis, bronchiectasis, infection, and malignancy). As previously mentioned, most causes of hemoptysis can cause diffuse alveolar opacities if severe enough.

**History and Physical Examination**

Initial evaluation should focus on the qualitative and quantitative assessment of symptoms, such as hemoptysis, cough, and dyspnea. Comorbidities such as collagen vascular disease or existing pulmonary disease should be noted. A detailed drug and occupational history should be taken. Careful evaluation of the eye, nasal septum, and skin should be performed to search for evidence of systemic vasculitis. Importantly, DAH may represent the primary manifestation of an underlying systemic vasculitis or collagen vascular disease, so the absence of historical or physical evidence should not eliminate these as possible etiologies.

**Diagnostic Studies**

Initial diagnostic studies in patients suspected of having DAH should include chest computed tomography (because this may help identify alternative etiologies for pulmonary hemorrhage, such as bronchiectasis or bronchogenic cancer), complete blood count, and serum creatinine. Examination of the urinary sediment for evidence of glomerular injury cannot be overemphasized. In Goodpasture's syndrome, an active urinary sediment will often be the first clue to the diagnosis. If Goodpasture's syndrome is suspected, serum ABMA should be measured because their presence will confirm the diagnosis in up to 90% of patients. Serum ANCA, anti-nuclear, and anti-phospholipid antibodies should generally be sent along with ABMA in the evaluation of patients with DAH and evidence of concomitant glomerular disease.

**Bronchoscopy**

Bronchoscopy with bronchoalveolar lavage (BAL) is indicated in patients suspected of having DAH to both confirm the presence of true alveolar hemorrhage and exclude infection as an underlying etiology. An increasing number of red blood cells in sequential aliquots of bronchoalveolar lavage from the same subsegmental location is considered diagnostic of DAH. In addition, quantitative scoring of the hemosiderin concentration of alveolar macrophages, although labor-intensive and time-consuming, may add to the diagnostic specificity of BAL. Bronchoalveolar lavage specimens should routinely be sent for bacterial and fungal cultures, and when clinically indicated, viral and *Pneumocystis jiroveci* studies should be added.

**Biopsy**

Biopsy of the lung (usually via surgical biopsy) or kidney can be helpful in cases of DAH in which an underlying collagen vascular disease or vasculitis is suspected. In cases of suspected vasculitis, biopsy of the kidney shows focal segmental necrotizing glomerulonephritis. In Goodpasture’s syndrome, linear antibody deposition is seen.

**Current Therapy**

DAH is a medical emergency and definitive treatment requires identification of the underlying etiology. Hospitalization in an intensive care unit is appropriate for all newly diagnosed or suspected cases of DAH. Although exsanguination from uncontrolled hemorrhage is much less common in DAH than in conditions such as bronchiectasis or invasive fungal infection, significant hemorrhage can occur and patients should be aggressively resuscitated. Furthermore, respiratory failure requiring intubation and mechanical ventilation is common and often precipitous. (A discussion of specific recommendations for the treatment of DAH due to the most common etiologies is beyond the scope of this article.)

Aggressive treatment of Goodpasture's syndrome involves the combination of corticosteroids, cyclophosphamide or azathioprine, and plasmapheresis. This combination of therapies has proven effective even in patients who have already developed renal failure from their disease. In cases of Goodpasture's syndrome refractory to the previously mentioned therapies, responses to mycophenolate mofetil or anti-CD20 monoclonal antibody have been reported.

**Prognosis**

In Goodpasture’s syndrome, the majority of patients survive the initial presentation. A review of 29 cases of DAH due to Goodpasture's syndrome showed the 2-year survival rate to be approximately 50%. The degree of glomerular involvement on kidney biopsy and the degree of clinical impairment of renal function both had prognostic value. If less than 30% of glomeruli were involved and renal function was relatively preserved, patients had improved responsiveness to therapy and improved survival. If more than 70% of glomeruli were involved and abnormal renal function was present, patients were unresponsive to therapy and had increased mortality.

Further Reading


Introduction

The concept of histiocytosis X was proposed by Lichtenstein in 1953 and linked different clinical forms of the disease with the histological presence of eosinophilic granuloma. The definition of this group of diseases was based on morphological criteria detected by light microscopy and the term ‘histiocytosis X’ was proposed. This term embraces three major localized and generalized patterns of histiocytosis including a unifocal, multifocal, and disseminated variant. The unifocal variant (single site, single site) has previously been referred to as eosinophilic granuloma. This subtype commonly involves bones, lymph nodes, or lungs as a primary target. Children with localized disease tend to have bone involvement while adults have a greater propensity for lung involvement. The multifocal variant has been referred to in the past as Hand–Schüller–Christian disease. This variant usually affects younger patients and involves several sites in one organ system (single system, multiple sites). The organ system involved varies from one patient to another. A classic triad is skull lesions, exophthalmos, and diabetes insipidus. Other bones, the oral cavity, skin, lymph nodes, brain, lungs, and liver represent other organ systems that may be affected in different patients. Multiple foci of disease will be found in the particular organ system affected for a given patient. The disseminated variant was previously referred to as Letterer–Sewe disease and affects multiple sites in multiple organ systems. This is a potentially fatal systemic disease in children under 3 years of age. Typical manifestations include multisystem involvement of bones and organs and may include persistent fevers, irritability, anorexia, failure to thrive, purpuric rash, superinfection, diarrhea, pancytopenia, and life-threatening sepsis. However, this concept of histiocytosis X is no longer used due to the imprecise definitions of these terms, the recognition that the proliferating cells are Langerhans’ cells, and the growing recognition that

Langerhans’ Cell Histiocytosis (Histiocytosis X)

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Abstract

Langerhans’ cell histiocytosis (LCH) is a rare and pleomorphic disorder of the bone marrow-derived histiocytes that may involve the skin, bone, bone marrow, liver, spleen, lungs, and lymph nodes. The pathogenesis and etiology of LCH remain poorly understood. Whether LCH is a neoplastic disorder or a reactive process remains controversial. LCH is a disease with a broad spectrum of clinical presentations. All of the variants have in common the proliferation of cells that are morphologically, biochemically, and immunophenotypically indistinguishable from Langerhans’ cells. A definitive diagnosis of LCH can only be rendered when either there is demonstration of Birbeck granules on electron-microscopic study or there is the demonstration of CD1a expression with appropriate histological settings. The outcome and course of the disease are variable. LCH may in some cases regress on its own without treatment. In other situations, very minimal treatment will result in the resolution of symptoms and regression of the disease. The multisystem disease is treated with systemic chemotherapy but the treatment is still controversial.