Diffuse Alveolar Hemorrhage in the ICU

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Introduction

Alveolar spaces may fill with blood as a result of gross disruption of the delicate structures which form the alveolar-endothelial membrane. Collagen-vascular and immune diseases are the most common causes of diffuse alveolar bleeding, but several other underlying pathological conditions have been identified. Sometimes, the cause is obvious, as in patients with acute respiratory distress syndrome (ARDS) or those who have sustained chest trauma with lung contusion [1]. Occasionally, patients with pulmonary infections and pneumonia may present with severe diffuse alveolar bleeding [2, 3]. Patients with pulmonary metastases from solid tumors [4, 5], hematological malignancies [6, 7], and angio-sarcomas [8–10] may occasionally present with diffuse alveolar hemorrhage, while patients with allogeneic [11] and autologous bone marrow transplants [12] may also develop alveolar bleeding. Occasionally, alveolar spaces may fill with blood due to aspiration from a bleeding focus in the upper airways or from the upper digestive tract; usually, clinical evaluation will rule out this possibility. This chapter will focus primarily on clinical presentation, diagnosis and treatment of collagen-vascular and immune causes of diffuse alveolar bleeding, usually referred to as diffuse alveolar hemorrhage (DAH). Patients with collagen-vascular disorders usually develop signs and symptoms suggesting systemic disease. Although such clinical presentation may mimic endocarditis, sepsis and even malignancy, specific patterns can be suggestive of collagen-vascular diseases. Malaise, arthralgias, eye symptoms like episcleritis and uveitis, and skin changes, e.g., petechiae, palpable purpura, and leukocytoclastic vasculitis in vasculitic syndromes, butterfly-rash, notably in systemic lupus erythematosus, etc., usually lead in the right direction in the diagnostic work-up. Infrequently, however, DAH is the presenting sign of systemic disease. Close co-operation with specialists in the field of collagen-vascular and immune disorders may then help to reach a definitive diagnosis and install appropriate treatment.

Clinical Presentation and Management of DAH (Diffuse Alveolar Hemorrhage)

As the alveolar spaces fill with blood, the compliance of the respiratory system decreases, resulting in increased work of breathing; gas exchange is impaired with mismatching of ventilation and perfusion. Patients with DAH usually present with hemoptysis and dyspnea, and anemia is common, as a considerable amount of blood

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may be present in the alveolar spaces. Anemia may be aggravated if renal function is impaired. Some patients, however, never experience hemoptysis (Fig. 1). Physical examination may reveal pallor and dyspnea; rhales, rhonchi and inspiratory crepitations may be found on auscultation. Severe respiratory failure may ensue, necessitating admission to intensive care for mechanical ventilatory support.

Chest radiography shows opacification of an alveolar or acinar filling pattern, which may rapidly change within days. As such a radiographic pattern may also be encountered in ARDS and congestive heart failure, other diagnostic tests are necessary to reach a certain diagnosis in the absence of hemoptysis or frank anemia.

If the signs and symptoms are mild, one possible test would be to assess the transfer factor for carbon monoxide ($T_{L,CO}$) or when corrected for lung volume the carbon monoxide transfer coefficient K_{CO}, which is a test to assess the diffusing capacity. Carbon monoxide diffuses quickly across cell membranes, and binds quickly and irreversibly to hemoglobin which is normally only present in alveolar capillaries. K_{CO} is increased proportional to the surface available for gas exchange per unit of lung volume, and to the volume of blood present in the lung for carbon monoxide binding; and reciprocally proportional to the thickness of the alveolo-capillary membrane. As K_{CO} is higher than predicted if blood is present in the alveolar spaces, this test has been recommended to demonstrate the presence of alveolar bleeding [13–15]. In patients with respiratory failure, this test is not practical, and in intubated, mechanically ventilated patients, bronchoscopic bronchoalveolar lavage (BAL) is

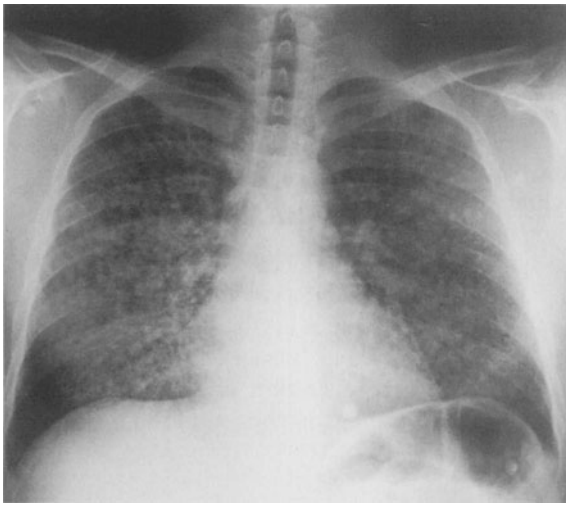

Fig. 1. Chest X-ray of male adult (23 yrs) who presented at the Emergency Dept with dyspnea, anemia, and renal failure with microscopic hematuria. He appeared to have anti-GBM antibodies, and was diagnosed with Goodpasture's disease. The same night, he needed intensive care admission and was admitted to our unit; he was on the unit for 102 days, was mechanically ventilated, needed dialysis, and was treated with plasma exchange and experimental immune absorption, along with immunosuppressive therapy (methylprednisolone, cyclophosphamide); eventually, he made a full recovery. During 6 years of follow-up, no relapse occurred

a relatively safe and easy method to obtain sampling from the alveolar spaces, and to diagnose alveolar bleeding [16]. During the procedure, the BAL fluid that is recovered from the alveolar spaces during gentle suctioning becomes more and more blood-stained [15, 17]. Often, previous episodes of bleeding can be demonstrated by the presence of hemosiderin-laden alveolar macrophages in the BAL fluid [18]. Microscopic cytological examination with appropriate staining, and culture of the BAL fluid may reveal specific causes of alveolar bleeding, like infection or ARDS. If these causes are ruled out, immune and collagen-vascular causes warrant immune-suppressive treatment, initially with methylprednisolone, 1 g iv once daily , for three or more days, when, usually, clinical improvement is observed in lung compliance, gas exchange and chest radiography. The prognosis and the decision to use other treatment modalities depend not only on the response to initial treatment, but also on the specific underlying disease.

Collagen-Vascular and Immune Diseases Causing Alveolar Bleeding

Vasculitis Syndromes: ANCA Group

This heterogeneous group of diseases is characterized by the presence of anti-neutrophil cytoplasmatic auto-antibodies (ANCA) in patients with necrotizing inflammation of vascular walls in histopathological specimens of affected tissues. These ANCA can be divided into two different fluorescence patterns: The 'classic' or cytoplasmic ANCA (c-ANCA) in which the ANCA appear to be directed at proteinase-3 (PR3) in appropriate enzyme-linked immunosorbent assays (ELISA); and a peri-nuclear fluorescence pattern (p-ANCA), in which these ANCA may be directed at many different neutrophil granulocyte target proteins. If the target protein is myeloperoxidase (MPO) or elastase, these ANCA have clinical significance in the context of suspected DAH. PR3 (c-ANCA) are strongly associated with Wegener's granulomatosis; both c-ANCA and PR3 (p-ANCA) are involved with the so-called ANCA-associated vasculitides, which comprise Wegener's granulomatosis, Churg-Strauss syndrome, and microscopic polyangiitis [19]. Before the detection of ANCAs were fully appreciated by clinicians, Wegener's granulomatosis was considered to be an uncommon cause of DAH [20–22]. At the Chapel-Hill conference, a new classification system for the vasculitis syndromes was proposed which has now become widely accepted [23]. Wegener's granulomatosis and microscopic polyangiitis are now recognized to be the predominant causes of immune DAH [24–27], while Churg-Strauss syndrome is an infrequent cause [28, 29]. The classic clinical presentation of Wegener's granulomatosis involves the triad ELK: E referring to ENT (upper airways or ear-, nose- and throat signs); L referring to the lung; and K to the kidney. The E-associated disorders usually result in major structural deformities in relapsing disease, with chronic necrotizing paranasal sinusitis, rhinitis commonly resulting in necrosis of the nasal septum with subsequent saddle-nose deformity, loss of hearing, and subglottic stenosis. Pulmonary involvement (L) may present with nodular, necrotizing lesions, massive confluent necrosis, endobronchial ulceration resulting in atelectasis, pleural space involvement, or DAH [15]. Renal abnormalities (K) present with microscopic hematuria, resulting from crescentic glomerulonephritis. Some patients with limit-

ed Wegener's granulomatosis may initially [30, 31], or during relapse [32], present with isolated DAH. The typical histopathological hallmark for Wegener's granulomatosis is the demonstration of necrotizing granulomas, a feature which is absent in microscopic polyangiitis. Clinically, the most important feature distinguishing microscopic polyangiitis from Wegener's granulomatosis is that in microscopic polyangiitis, ENT-involvement is restricted to mild rhinitis; and unlike in Wegener's granulomatosis, pulmonary involvement in microscopic polyangiitis is restricted to DAH [33]. In ANCA-associated DAH however, sometimes no surgical pathology is apparent, and therefore, an intermediate group referred to as ANCA-associated DAH has been postulated [15, 23].

Churg-Strauss syndrome is characterized by the presence of allergic asthma which invariably predates the onset of vasculitic changes, blood and sputum eosinophilia, and a varying degree of organ damage, with relatively frequent coronary artery involvement, due to necrotizing vasculitis [23, 34]. DAH in Churg-Strauss syndrome has only been reported occasionally [28, 29]. The diagnosis of the ANCA-associated vasculitis syndromes hinges on the clinical presentation, combined with histo-pathological evidence for necrotizing vasculitis, in combination with specific ANCA-immunofluorescence and ELISA results. There is one case report of anti-glomerular basement membrane (GBM) antibody-associated reno-pulmonary disease in which anti-MPO-antibodies were present [35].

Initial pulsed methylprednisolone treatment is followed by prednisolone in a tapering schedule of 1–2 mg/kg/d over several months. In Wegener's granulomatosis, and microscopic polyangiitis, this schedule is combined with cytotoxic treatment, typically with cyclophosphamide, 2 mg/kg/d, in a tapering schedule over a few months. Churg-Strauss syndrome can usually be managed with steroids alone [15].

Vasculitis Syndromes: Non-ANCA Group

The other vasculitis syndromes which are ANCA-negative, form a heterogeneous group of conditions for which no serological marker is available at present to help classify these patients.

In Henoch-Schönlein purpura (HSP), also referred to as IgA-associated vasculitis, the predominant feature is histo-pathological evidence of IgA granular deposits in vascular walls of affected tissues. Most patients are children who present with a post-streptococcal, self-limiting disorder with abdominal pain, diarrhea, skin purpura, and renal involvement [36]. Few patients, however, develop DAH [37–40]. There is one report suggesting that ANCA of the IgA-subclass may be involved in the pathogenesis [41], but this finding has not been confirmed by other research groups. Although HSP in children is usually self-limiting and needs no specific treatment, complicating DAH warrants treatment with steroids, initially with high-dosed methylprednisolone as in ANCA-associated DAH. The few patients who do not respond need more aggressive treatment such as cytotoxic agents or plasma exchange.

Essential mixed cryoglobinemia is a systemic vasculitic disorder characterized by cryoglobulins which can be demonstrated in the blood stream. It has now become clear that most of the older reports on essential mixed cryoglobinemia were not primary cases, but rather secondary to hepatitis C infection [42], or hematological ma-

lignancies [15, 23]. Patients usually present with arthralgias, purpura and glomerulonephritis; there is one report of complicating DAH [43].

Patients with Behçet's disease usually come from Mediterranean countries, notably Turkey, or from the far East, notably, Korea and Japan. Turkish patients usually present with the classical triad of ocular, oral and genital ulcerative lesions; in Japanese patients, abdominal symptoms prevail [44]. Occasionally, patients may present with pulmonary signs and symptoms. Most patients are male, and pulmonary artery aneurysms may develop [45–47]; DAH is uncommon [48]. Immunosuppressive treatment is commonly recommended although, unlike in ANCA-associated DAH, treatment effects are largely anecdotal, and relapses are common.

Occasionally, sarcoidosis may be complicated by necrotizing granuloma formation with capillaritis and DAH [49].

Anti-GBM Disease: Goodpasture's Disease and Idiopathic Pulmonary Hemosiderosis

The classic reno-pulmonary syndrome, first described by Goodpasture, now appears to account for only a minority of cases of DAH, as most of these cases appear ANCA-associated [26]. The typical finding is IgG-antibodies directed at components of the glomerular and alveolar basement membrane, notably in the non-collagenous 1 domain of the α3 chain of type IV-collagen (NC1α3-IV) in the bloodstream [26, 50, 51] and in surgical biopsy specimens [52]. Treatment with methylprednisolone alone is usually not sufficient to induce remission; immunosuppressive combinations with cytotoxic treatment and plasma exchange are often necessary. Relapses may occur, as in ANCA-associated vasculitis.

In idiopathic pulmonary hemosiderosis, GBM antibodies may occasionally be found. In this syndrome, alveolar bleeding is present without renal involvement, and the clinical presentation is usually mild [53, 54]; patients do not require intensive care unit (ICU) admission for treatment.

Connective Tissue Diseases

Systemic lupus erythematosus (SLE) is the most frequent cause of DAH in this group of diseases [55–59]. Patients usually present with Raynaud's sign and a butterfly rash. The classic diagnostic marker, anti-nuclear antibody (ANA), has high sensitivity but rather low specificity. Anti-double stranded DNA has a higher diagnostic potential. Most patients with SLE-associated DAH have had previous evidence of disease activity. Pulmonary involvement of the disease comprises a wide spectrum: Pleural effusion, interstitial lung disease, pulmonary vasculitis, and thrombo-embolic disease. Initial treatment with methylprednisolone is followed by cytotoxic agents and prednisolone, as in Wegener's granulomatosis.

Like SLE, mixed connective tissue disease (MCTD) is associated with ANA. MCTD is an uncommon disease, often accompanied by signs of pulmonary hypertension, and may occasionally be complicated by pulmonary hemorrhage [60, 61]. Raynaud's sign is usually present. Rheumatoid arthritis may cause diffuse interstitial pulmonary disease, rheumatoid pulmonary nodules, and pleural effusion, but rheumatoid

arthritis is an uncommon cause of DAH [60]. Peri-nuclear factor and the classic markers for rheumatoid arthritis help to establish the diagnosis. Progressive systemic sclerosis is associated with interstitial lung disease, and esophageal dysmotility is almost invariably demonstrable, even in the absence of dysphagia; patients are almost exclusively female. Although progressive systemic sclerosis may cause pulmonary alveolitis, DAH is rare [62]; there is one report on progressive systemic sclerosis with p-ANCA [63]. Poly-myositis, a cause of interstitial pulmonary disease, has been reported to be associated with DAH [64].

Drug-Induced Reno-Pulmonary Syndromes

Concomitant pulmonary and renal dysfunction is suggestive of the combination of one of the syndromes like Goodpasture's disease, microscopic polyangiitis or Wegener's granulomatosis, with DAH. Occasionally, drug-induced syndromes may mimic a reno-pulmonary syndrome [65], and BAL combined with bronchoscopic lung biopsies may help to resolve diagnostic dilemmas.

Conclusion

In patients admitted to the ICU with respiratory failure and suspected to have DAH, the first concern for the clinician is to rule out pulmonary infections, endocarditis and ARDS. If hemoptysis is absent, fiberbronchoscopy with BAL may help to diagnose DAH, and to rule out infections and ARDS. Signs and symptoms suggesting systemic disorders are usually present; malaise, arthralgias, skin abnormalities such as purpura, Raynaud's sign, and butterfly-rash, and eye involvement, point at collagen-vascular diseases, and help to differentiate between these clinical entities. Although the list of differential diagnoses is extensive, most cases are caused by pulmonary capillaritis resulting from Wegener's granulomatosis, microscopic polyangiitis, Goodpasture's disease or SLE. The serologic work-up therefore includes ANCA, ANA and GBM antibody tests. In typical cases, the diagnosis can be made without tissue biopsies, and treatment with pulsed methylprednisolone (1 g once daily) may result in rapid clinical improvement.

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