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Case Report

CASE REPORT

A 32-year-old man with hypoxemia and bilateral upper-lobe predominant ground-glass infiltrates on chest imaging

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Abstract

Diffuse alveolar hemorrhage (DAH) is a rare, but potentially fatal, complication of antiphospholipid syndrome, and may present with acute and fulminant symptoms. We report a case of DAH presenting as sudden onset dyspnea in a gentleman with known antiphospholipid syndrome. Chest computed tomography angiography with pulmonary embolism protocol showed right lower lobe segmental filling defects, upper-lobe predominant diffuse ground-glass opacities, and centrilobular nodules bilaterally. The presence of DAH can be confirmed by bronchoalveolar lavage with serial aliquots, but this procedure typically does not elucidate the specific etiology for the hemorrhage. The treatment for patients with severe disease typically consists of a combination of immunosuppressive medications in the form of high-dose intravenous glucocorticoids plus rituximab, cyclophosphamide or mycophenolate; and/or plasma exchange. This case both provides an example of high-quality diagnostic imaging of diffuse alveolar hemorrhage as well as demonstrates the clinical and image-based improvement after treatment.

INTRODUCTION

Diffuse alveolar hemorrhage is the result of damage to the alveolar microcirculation, including arterioles, venules and capillaries, with subsequent bleeding into the alveoli. There are many immune and non-immune mediated causes of DAH, but the most common etiology is thought to be pulmonary capillaritis, which is due to neutrophilic infiltration of the capillary walls resulting in leukocytoclasis [1, 2]. We report a case of diffuse alveolar hemorrhage presenting as sudden onset dyspnea in a gentleman with known antiphospholipid syndrome and excellent response to aggressive therapy.

CASE PRESENTATION

A 32-year-old man with antiphospholipid syndrome (APS), recurrent deep venous thromboses (DVTs) and pulmonary emboli (PEs) currently maintained on warfarin therapy, presented with 1 day of progressively worsening exertional dyspnea and blood-streaked sputum. He denied chest pain or purulent sputum production. Three months earlier, he first presented with DVTs and PEs. At that time, laboratory studies showed elevated titers of phospholipid IgM at 45 MPL (normal: <15 MPL), phospholipid IgG at 68 GPL (normal: <15 GPL), Beta-2 glycoprotein antibody IgM at 84.6 U/mL (normal: <15 U/mL),

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antinuclear antibody (ANA) at 4.3 U (normal: ≤1 U), double-stranded DNA antibody (ds-DNA) at 253 IU/mL (normal: <30 IU/mL), proteinase-3 antibody(PR3) at 0.4 U (normal: <0.4 U) and myeloperoxidase antibody (MPO) at 0.9 U (normal: <0.4 U), with a positive p-Anticytoplasmic antibody (p-ANCA) and negative c-Anticytoplasmic antibody (c-ANCA). While there were no other clinical manifestations of an ANCA-associated vasculitis, given the severity of his clot burden, he was placed on empiric treatment with rituximab. He was also treated with hydroxychloroquine during that initial visit. He was started on warfarin therapy to treat the acute thromboembolic state. He was maintained on warfarin and rituximab up until the time of this admission and had remained in good clinical condition, including working full-time as a teacher…One month prior to presentation, transthoracic echocardiography excluded significant heart failure or valvular disease.

On physical examination, heart rate was 120 bpm with a blood pressure of 115/75 mmHg and a temperature of 37.1°C. Room air oxygen saturation was in the low 80 s, but improved to the low 90 s with face mask oxygen at 8 L per minute (Lpm). Lung auscultation revealed coarse bilateral inspiratory crackles greatest in the upper lobes. Integumentary, eye, cardiac, neurologic and musculoskeletal examinations were normal.

Chest computed tomography (CT) angiography with PE protocol showed right lower lobe segmental filling defects consistent with previously diagnosed PE, upper-lobe predominant diffuse ground-glass opacities, and centrilobular nodules bilaterally (Fig. 1). Laboratory studies showed a normal complete blood count, electrolytes and creatinine. The INR was slightly subtherapeutic at 1.9. Arterial blood gas was significant for a PaO_2 of 69.3 mmHg while on 8 Lpm of oxygen. Erythrocyte sedimentation rate and C-reactive protein were elevated at 64 mm/1 h (normal: 0–22 mm/1 h) and 54.5 mg/L (normal: ≤8 mg/L), respectively. Tests for ANA, ds-DNA, c-ANCA, p-ANCA, MPO, PR3 and anti-glomerular basement membrane (GBM) antibodies were all negative. The phospholipid and Beta-2 glycoprotein antibodies remained elevated. Urinalysis showed 1+ protein, but no red cells, white cells or casts.

Given the acute onset of this patient's symptoms, history of APS, and prior serologies suggesting the possible presence of an ANCA-associated vasculitis and/or connective tissue disease, the leading diagnosis on admission was diffuse alveolar hemorrhage (DAH) of uncertain etiology. In addition to DAH, our differential diagnosis also included community acquired pneumonia, rituximab-associated immunocompromised host viral pneumonia or *Pneumocystis jiroveci* pneumonia, rituximab-associated direct lung injury, and diffuse lung diseases such as cryptogenic organizing pneumonia, secondary organizing pneumonia (potentially connective tissue disease-associated), acute eosinophilic pneumonia, acute hypersensitivity pneumonitis, and less likely sarcoidosis [1].

Because of the concern for DAH, a bronchoscopy with bronchoalveolar lavage (BAL) was performed. The BAL fluid return became progressively more hemorrhagic on serial aliquots and was sent for Prussian iron staining, which revealed hemosiderin-laden macrophages (Fig. 2). A sample of the BAL was also sent for gram stain, culture and viral PCR, all of which were negative. At this point, the leading diagnosis was DAH, more likely secondary to APS than to microscopic polyangiitis (MPA) or a connective tissue disease. Given the bland urinary sediment, the lack of extrapulmonary manifestations, and the risk of temporarily discontinuing anticoagulation, it was felt that the overall risk to benefit ratio favored empiric treatment over obtaining a pulmonary or renal biopsy. Once the initial BAL results were available showing no evidence of active infection, treatment was urgently initiated with high-dose corticosteroids and plasma exchange.

The patient was continued on warfarin with the addition of intravenous methylprednisolone 1 g daily for 3 days followed by prednisone 60 mg daily, and was given five daily treatments with plasmapheresis. Following completion of plasmapheresis, mycophenolate was started due to the prior lack of response to rituximab. A lung biopsy was not performed because it was felt to unlikely change management and a relatively high-risk procedure, given the need for anticoagulation. With the above treatment, the patient made daily improvements based on clinical assessment and decreasing oxygen requirements. By the time of hospital discharge, he was breathing comfortably on room air, with substantial improvement on imaging (Fig. 3).

DISCUSSION

DAH typically presents in middle-aged males with cough and dyspnea, with or without clinical hemoptysis [2]. Laboratory evaluation may include non-specific findings. Other autoimmune serologies that may be helpful in determining the cause of DAH include testing for the presence of an ANCA-associated vasculitis, connective tissue diseases such as SLE, and anti-GBM disease [3]. In the proper clinical setting, such as in a patient with DAH and positive ANCA serologies, especially in the presence of typical extrapulmonary manifestations such as renal involvement, a tissue biopsy may not be necessary to establish a diagnosis [4]. If the etiology is less clear, then it may be necessary to obtain tissue from the lung or extrapulmonary organs.

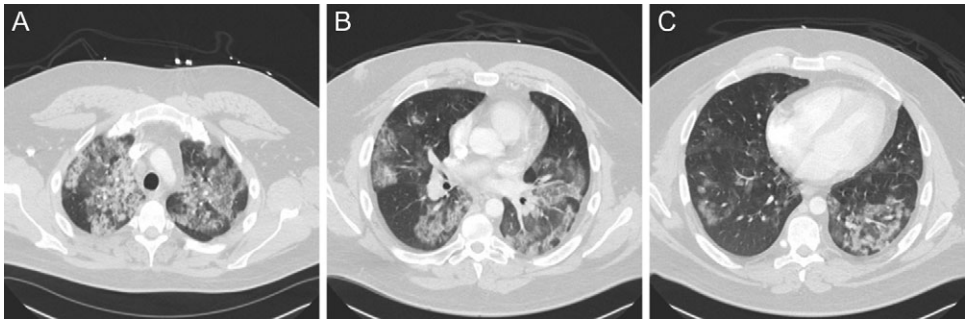

Figure 1: Contrasted chest computed tomography on hospital Day 1 displaying (**A**) the apices of the lungs, (**B**) the mid-lung zones and (**C**) the lung bases demonstrating upper-lobe predominant diffuse ground-glass opacities and centrilobular nodules.

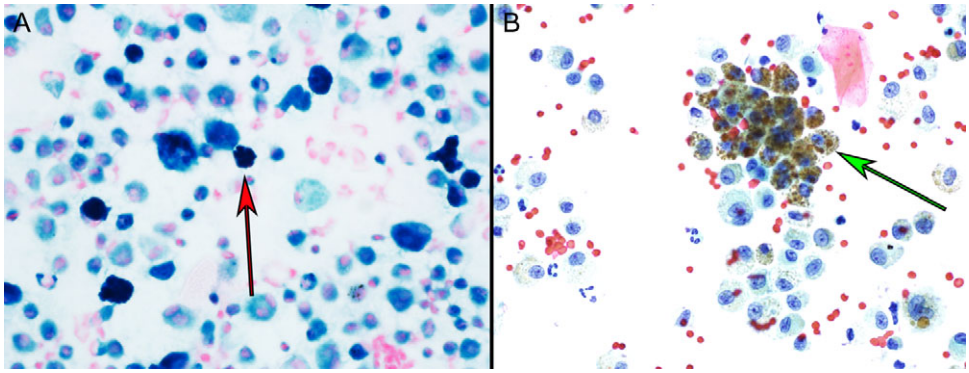

Figure 2: Hemosiderin-laden macrophages seen on bronchoalveolar lavage smears with (**A**) Prussian blue iron stain in which the hemosiderin stains a dark blue color inside the macrophages (red arrow) and (**B**) alcohol Papanicolaou stain in which the hemosiderin stains a brown color in the macrophages (green arrow). Each image is at ×40 magnification.

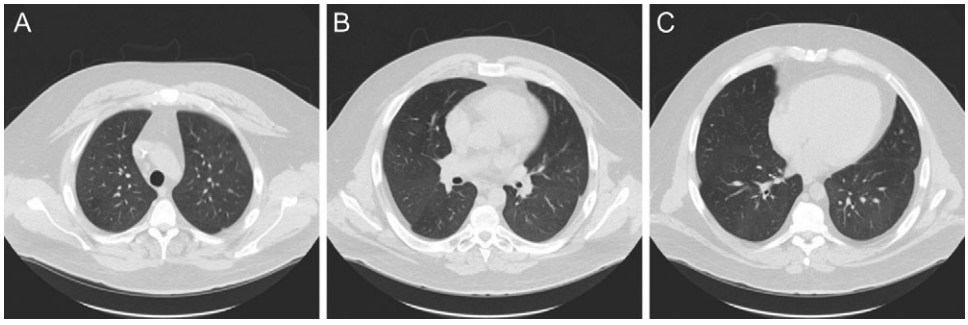

Figure 3: High-resolution chest computed tomography on hospital Day 5 displaying (**A**) the apices of the lungs, (**B**) the mid lung zones and (**C**) the lung bases demonstrating dramatic and rapid improvement of the ground-glass opacities after 5 days of treatment with high-dose glucocorticoids and plasma exchange.

The most common disorders associated with capillaritis-induced DAH are APS, granulomatosis with polyangiitis (GPA), MPA, systemic lupus erythematosus (SLE) and anti-GBM disease [2]. DAH is a rare complication of APS with an unknown prevalence [3–6]. These disorders frequently have overlapping clinical presentations and laboratory findings making it sometimes difficult to establish a definitive etiology for the DAH. In addition, it is important to note that a clinical diagnosis for these diseases can never be based purely upon laboratory testing. Rather, testing must always be correlated with the clinical presentation in order to arrive at a diagnosis. In our patient, there were serologic studies suggestive of disorders such as MPA or SLE. While these disorders frequently have extrapulmonary manifestations, they can present, as our patient did, with purely pulmonary manifestations. Other causes of DAH include bland pulmonary hemorrhage and diffuse alveolar damage.

Chest radiography in patients with DAH typically shows non-specific bilateral patchy or diffuse alveolar infiltrates. Imaging patterns on CT typically show diffuse, bilateral, ground-glass or consolidative opacities [3]. 'Ground-glass opacification' describes an appearance on chest CT of increased lung attenuation that appears hazy and allows visualization of the underlying blood vessels and airways. This appearance is created when air in the alveoli is replaced with another material such as blood (representing alveolar hemorrhage), inflammatory cells (representing pneumonia), fluid (representing edema), malignant cells (representing malignancy) or fibrosis (representing interstitial lung disease). Initially, during the more acute inflammatory phase of DAH, ground-glass opacities are frequently seen. Over time, particularly if not treated, interlobular septal thickening may develop [7]. The thickened septum and ground-glass opacities can on occasion form a 'crazy paving' pattern. With treatment, the ground-glass opacities and septal thickening typically clear up within 1–2 weeks [7]. However, without timely treatment, the disease process may progress to a non-specific form of pulmonary fibrosis.

The diagnosis of DAH is confirmed when serially collected BAL aliquots show increasing amounts of blood. BAL is also helpful in excluding other conditions which can mimic DAH on imaging, such as infections, alveolar proteinosis and pulmonary edema. Prussian blue iron staining may show hemosiderin-laden macrophages, with the diagnosis of DAH considered confirmed when >20% of 200 macrophages stain positive in a sample [8]. If the exact cause of DAH is indeterminate, a lung biopsy may become necessary.

The treatment options for DAH are based upon treating the underlying etiology [4, 8]. In the case of autoimmune or immune complex diseases, treatment typically consists of the combination of high-dose intravenous glucocorticoids, immunosuppressant agents (rituximab, cyclophosphamide or mycophenolate), and/or plasmapheresis. There are reports that the addition of plasmapheresis to these immunosuppressive agents may further improve survival, but most of the evidence is inferred from studies of severe renal vasculitis [9, 10].

In general, anticoagulation should not be stopped in patients with APS and DAH of whatever etiology, because the risk of developing further arterial and venous thromboembolic events is very high. In patients with DAH without APS,

anticoagulation should generally be withheld, with assessment made on a case by case basis. Blood products should be replaced as indicated.

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CONFLICT OF INTEREST STATEMENT

None declared.

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ETHICAL APPROVAL

No ethical approval required.

INFORMED CONSENT

The patient has given written consent for publication of this case report.

GUARANTOR

Michael Maniaci, MD, is a guarantor for the article.

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