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Diffuse Alveolar Hemorrhage without Extrapulmonary Manifestations: A Rare Presentation of Lupus

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Female, 31
Final Diagnosis: Lupus DAH
Symptoms: Shortness of breath
Medication: —
Clinical Procedure: —
Specialty: Pulmonology

Objective: Unusual clinical course

Background: Diffuse alveolar hemorrhage (DAH) is a life-threatening disorder resulting in hemorrhage into the lungs due to a variety of reasons. The underlying etiology for DAH is broadly divided into immune and non-immune mediated causes. Rheumatological disorders account for a small number of cases. Although hemoptysis is one of the alarming symptoms of DAH, it is absent in a third of the cases. Diagnosis often requires a conglomerate of history, clinical, and laboratory investigation and radiological studies.

Case Report: We describe a case of a 31-year-old female who had an atypical presentation of systemic lupus erythematosus (SLE) with primary lung involvement/DAH and no other organ involvement.

Conclusions: This case report illustrates the importance of awareness and early recognition of the complication that can prevent mortality.

MeSH Keywords: Bronchoalveolar Lavage Fluid • Hemorrhage • Lupus Erythematosus, Systemic

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Background

Diffuse alveolar hemorrhage (DAH) is a life-threatening condition which refers to hemorrhage originating from pulmonary microvasculature. This a clinicopathological syndrome resulting in alveolar filling of the blood. Pulmonary capillaritis is the most frequent histopathological pattern described. It can be associated with any condition that leads to inflammatory changes causing capillaritis [1]. Most common causes of pulmonary capillaritis are due to rheumatological disorders. DAH as a manifestation of systemic lupus erythematosus (SLE) occurs in 1% to 5% of SLE cases [1–3]. Extrapulmonary signs and symptoms of SLE frequently accompany DAH, with nephritis as the most common manifestation. SLE presenting as DAH without any other manifestations is very rare. We report a case of a young female patient without any prior history, who presented with bilateral infiltrates and bronchoscopy revealed DAH; investigations for DAH revealed SLE.

Case Report

A 31-year-old female presented to our emergency department (ED) with a one-week history of cough and shortness of breath. Her cough was productive with yellow sputum that was blood tinged only on a couple of occasions. She denied any fever, chills, night sweats, headache, runny nose, or sore throat. Shortness of breath was exertional, and her exercise tolerance had decreased from 10 blocks to few steps in the last week. The patient was also having normal menses without any excessive bleeding. She also admitted to having lost 15 pounds in one week associated with poor appetite. Her medical history included hypertension, which was well controlled. There was no significant family history. She denied using tobacco or any illicit drugs but admitted to drinking alcohol occasionally. She had no known allergies. Her only home medication was amlodipine. Her surgical history was significant for tonsillectomy. She has had two uncomplicated pregnancies resulting in two healthy children. She was hemodynamically stable on arrival to the ED with vitals: blood pressure was 157/100 mm Hg, heart rate 91 beats per minute, respiratory rate of 16 breaths per minute, temperature 36.7°C, and oxygen saturation 99% on room air. Physical examination revealed bilateral basal crepitus and loud P2 on auscultation of lungs and heart, respectively. The rest of the examination was unremarkable. Her laboratory investigations are summarized in Tables 1 and 2. The images of her Chest x-ray are shown in Figure 1.

She was started on antibiotics for suspected community acquired pneumonia. She developed hypoxia needing supplemental oxygen. A CT chest was performed, and the images are shown in Figure 2.

She underwent diagnostic bronchoscopy in the operating room under general anesthesia and her bronchoalveolar lavage (BAL) was consistent with DAH as shown in Figure 3.

Post procedure she needed ventilatory support. She was started on intravenous Solu-Medrol 1,000 mg daily. Autoimmune workup was consistent with the diagnosis of SLE. After five

Table 1. Laboratory values.

Parameters (units) (normal values)	Day 1 (on admission)	Day 2	Day 4
Hemoglobin (g/dL) (12.0–16.0)	7.7	8.1	7.9
Hematocrit (%) (42%–51%)	24.5	25	25
White cell count (k/uL) (4.8–10.8)	2.5	3.0	4.1
Platelet (k/uL) (150–400)	166	158	148
Prothrombin time (9.5–12.0)	12		
Partial thromboplastin time (26.1–33.8)	25.3		
International normalized Ratio (0.0–2.0)	1.1		
Serum sodium (mEq/L) (135–145)	139	138	137
Serum potassium (mEq/L) (3.5–5.0)	3.8	4.1	3.9
Serum bicarbonate (mEq/L) (24–30)	19	17	18
Serum blood urea nitrogen (mg/dL) (6–20)	11	6	7
Serum creatinine (mg/dL) (0.5–1.5)	0.8	0.7	0.7
Urine toxicology	Cannabinoids		
Serum creatinine kinase (unit/L) (mg/dL)	52		
Serum human chorionic gonadotropin (mIU/mL)	0.5		

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Table 2. Autoimmune workup.

Autoimmune workup	Results
Myeloperoxidase antibodies	Undetectable
Proteinase-3 antibodies	Undetectable
Antiscleroderma-70 antibody	Negative
Antinuclear antibody	Positive
Antinuclear antibody pattern	Speckled
Antinuclear antibody titers	1: 320
Anti-deoxyribonucleic acid antibody (IU/mL)	>300
Rheumatoid factor (IU/mL)	<14
Serum C3 complement (mg/dL)	17
Serum C4 complement (mg/dL)	5
Anti-Smith antibody	>8
Anti-ribonucleoprotein antibody	>8
Lupus anticoagulant	Negative
Anti-cardiolipin antibodies	Negative

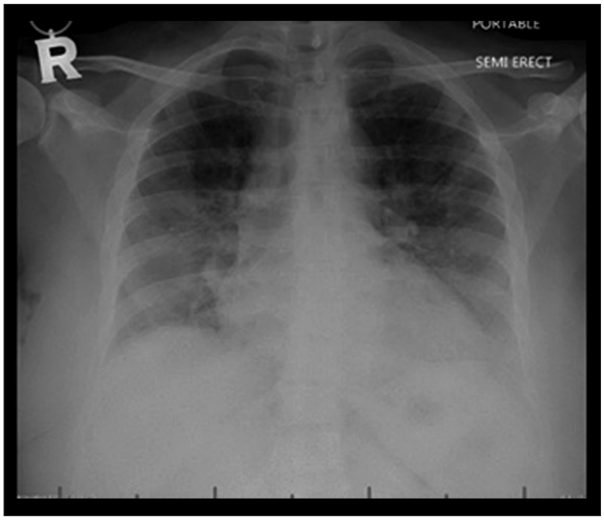

Figure 1. Chest x-ray showing bilateral lower lobe infiltrates.

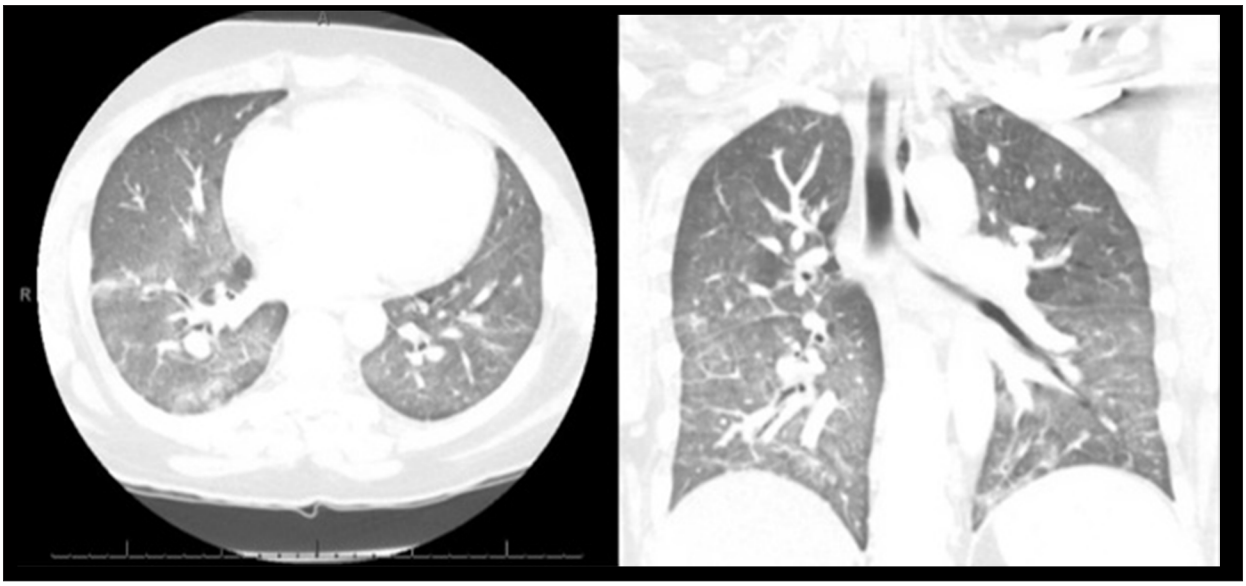

Figure 2. Computed tomography of the chest showing diffuse bilateral interstitial pattern with areas of more confluent ground glass density in the lower lobes.

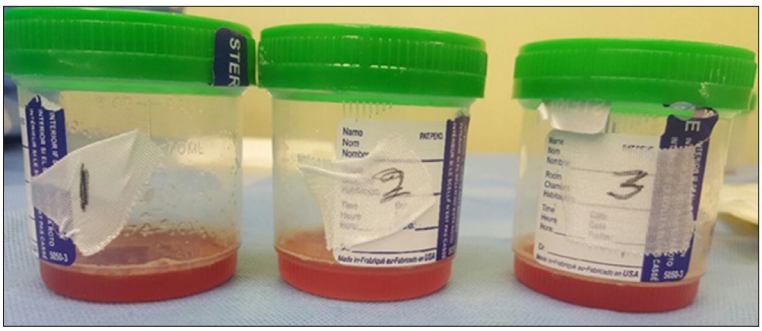

Figure 3. Sequential bronchoalveolar lavage (BAL) consistent with diffuse alveolar hemorrhage.

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days of intravenous Solu-Medrol, she was switched to tapering doses of oral steroids and mycophenolate was started. She responded to therapy and was successfully extubated. She symptomatically improved and was discharged. She was followed in pulmonary and rheumatology clinics post discharge without any recurrence in symptoms and is doing well.

Discussion

DAH is a devastating clinical syndrome characterized by a falling hematocrit, respiratory insufficiency, and radiographic evidence of pulmonary infiltrates. Pulmonary capillaritis is the instigating agent in a majority of cases. Common diseases resulting in DAH include granulomatosis with polyangiitis, Goodpasture syndrome, idiopathic pulmonary hemosiderosis, collagen vascular diseases, and microscopic polyangiitis. DAH is a rare manifestation in SLE seen in 4% of patients with SLE admitted to the hospital. DAH, as a presenting manifestation of childhood SLE, was reported in 29% of cases in one study [4]. In most case series of DAH in lupus, the diagnosis of SLE was established, although in 10% to 20% of cases, DAH was a presenting manifestation, all of these patients had extrapulmonary manifestations [2,5].

Pathogenesis

The three histologic patterns recognized in alveolar hemorrhage are: pulmonary capillaritis, bland pulmonary hemorrhage, and diffuse alveolar damage. Pulmonary capillaritis is the most frequent pattern described. The underlying etiology is broadly divided into immune and non-immune mediated causes [6]. Occasionally, recurrent episodes of DAH with no apparent etiology are seen, called idiopathic hemosiderosis. Two types of DAH are seen in SLE: “bland alveolar hemorrhage” i.e., capillaritis without any evidence of vasculitis, and capillaritis with vasculitis. Although the former is thought to be more common, the latter is seen in 80% of cases at autopsy. Immune complex deposits can be seen in both types of DAH and appear to be similar to lupus manifestations of the kidney [1].

Clinical features

The clinical manifestations of DAH are rather vague respiratory symptoms including that of cough and dyspnea. Although hemoptysis is one of the alarming symptoms of DAH, it is absent in a third of the cases with DAH; hence, high index of suspicion is paramount in patients with DAH [6,7]. Anemia or a drop of hematocrit level with no obviously bleeding source, along with low serum C3 complement levels and hypoxia are independent predictors of DAH in SLE [6,8]. A study by Kazzaz et al. showed many factors that predicted DAH in SLE patients including thrombocytopenia, cardiac valve disease, low C3 complement, leucopenia, neuropsychiatric features, hemolysis, arterial thrombosis, lupus anticoagulant, secondary APS, and low C4 complement by univariate analysis; however, multivariate analysis was significant for thrombocytopenia and low serum C3 complement levels [9]. Poor prognostic markers for DAH include renal failure, thrombocytopenia, concomitant infection, neuro-psychiatric illness, use of cyclophosphamide, and requirement of mechanical ventilation [2,10–12]. Other predictors of DAH include Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [12,13].

Chest imaging

Chest imaging, x-ray, and high resolution computed tomographic (HRCT) features are non-specific showing opacities that cannot be differentiated from other consolidative processes; however, the presence of pleural effusion eliminates the diagnosis of DAH. Evolution of opacities for the worse or the better is rapid and is notable in 48 hours [1]. The resolution of radiographic infiltrates is faster than seen in pneumonia, and slower than that of pulmonary edema [6].

Diagnosis

Diagnosis of DAH requires fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) with evidence of increasingly hemorrhagic return of bronchial washings from sequential BAL. Although not very specific, a clue for recent alveolar hemorrhage is intact erythrocytes in macrophages as opposed to hemosiderin laden macrophages in occult or chronic hemorrhages [14]. Histological diagnosis of DAH is evidenced by Golde score. It is the count of Prussian blue-stained macrophages graded from 1 to 4 based on the intensity of the stain among 100 cells under the microscope. Scores more than 100 are indicative of DAH. Scores more than 100 often correlated with siderophage of 67% [1]. Siderophages of more than 20% in BAL also have been shown to be strongly associated with DAH [1,6]. On the contrary, siderophage by itself has a less than optimum specificity for DAH as it can be seen in patients with congestive heart failure with chronic pulmonary edema. BAL must be further investigated for infectious and non-infectious causes, including cytological etiologies for DAH [1,6].

Lung biopsies, although considered gold standard for connective tissue disease (CTD) induced DAH, have become obsolete with the emergence of pertinent serological antibodies and prevalent radiological abnormalities. Moreover, invasive procedures for biopsy specimens do not alter the line of management and on the contrary, are associated with substantial risk of bleeding [1,6,15].

Pulmonary function tests

Isolated decreased DLCO (diffusion capacity of carbon monoxide) was found to be the most frequent abnormality followed

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by restriction and obstruction, respectively, when patients with SLE performed pulmonary function tests. Patients with SLE and no apparent pulmonary involvement had decreased DLCO, proposed as early manifestation or a milder form of lung involvement in SLE [16,17]. However, DLCO is temporarily supra-normal in cases of DAH, attributed to increased CO uptake by RBCs in the alveolar spaces [6].

Management

DAH is an autoimmune disease emergency and therapy should be initiated as soon as diagnosis is suspected or established. Intravenous methylprednisolone doses as high as 500 mg every six hours for four to five days followed by tapering doses to oral steroids have shown to be efficacious [18]. Off-label use of recombinant factor VIIa in refractory cases of DAH, immune and non-immune mediated, can be considered as has been shown in case reports and case series. It can be administered intravenously or bronchoscopic endobronchial instillation [19–23]. Plasma exchange therapy is reserved for patients with refractory hypoxic respiratory failure requiring ventilator support and has been endorsed by the American Society of Apheresis, and is recommended to be performed daily or on alternate days for at least two weeks. Long term benefits remain skeptical [24].

In intubated patients, supportive ventilatory care is followed. Lung protective ventilation is employed in patients presenting as ARDS. Extracorporeal membrane oxygenation (ECMO) has been reported to be used with survival benefit in patients with SLE-related DAH, [25,26].

Other immunosuppressants that have been reported to be used in CTD-related DAH with a trend towards optimal responses are: cyclophosphamide, azathioprine, mycophenolate mofetil, rituximab, methotrexate, etanercept, and imatinib [6,27–31]. Advanced treatments like umbilical cord-derived mesenchymal stem cell transplantation have come to light in the recent past, but more evidence is need before it can become the standard of care [32,33].

Conclusions

DAH is a catastrophic illness that is life threating with a high mortality rate. In patients presenting with DAH without any extrapulmonary manifestations, workup should include a collagen vascular profile. DAH is associated with SLE, and it seems to be rather under reported, secondary to lack of recognition as well as its rare occurrence. Awareness of this association irrespective of other more common extrapulmonary manifestation is of utmost importance not only because of its association with high rates of mortality but also because appropriate early interventions can drastically reduce mortality.

Conflict of interest

None.

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