Case Report

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Internal Medicine Section

A Case of Acute Breathlessness in Systemic Lupus Erythematosus: A Devastating Complication

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ABSTRACT

Diffuse Alveolar Haemorrhage (DAH) is a severe respiratory complication of Systemic Lupus Erythematosus (SLE) and is associated with high mortality. A drop in blood haemoglobin, dyspnoea, haemoptysis, diffuse infiltrates on chest imaging indicate this devastating diagnosis. The DAH is rare in SLE, even rarer in the early months in an undiagnosed patient. Defective phagocytosis, immune complexes, depletion of complement, and autoantibodies are the aetiologies. Immune complex induced alveolar capillaritis is the cause of DAH. This report was about a 28-year-old female, who presented with acute worsening dyspnoea on a background history of inflammatory joint pain, digital gangrene, alopecia, oral ulcers, and Raynaud's phenomenon. She was subsequently diagnosed as SLE with DAH. This case was rare as she presented with DAH in the early months of her disease. The patient was started on high dose steroid, cyclophosphamide, and plasmapheresis, but succumbed on day 14 of admission due to high disease activity and respiratory failure. DAH carries very high mortality rate even in the best centres, even when diagnosed early.

Keywords: Diffuse alveolar haemorrhage, Immune complex, Steroid

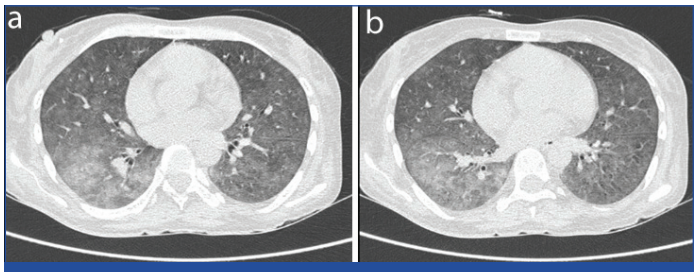
CASE REPORT

A 28-year-old female presented with inflammatory pain in multiple small and large joints for six months, blackish discolouration of the right index finger for six months, chest pain and breathlessness for three days before presenting to this centre. She was married and had two living children. The dyspnoea was sudden in onset, worsened over three days, not associated with cough or haemoptysis. The patient also reported alopecia, oral ulcers, and Raynaud's phenomenon. She was not on any treatment and had no significant family history.

On examination, the patient was afebrile, distressed, with a pulse rate of 140 beats per minute, regular and low volume; all peripheral pulses were felt. Her blood pressure was 90/60 mmHg, saturation was 95% at room air, with a respiratory rate of 34/min. She had six tender joints and a gangrenous right index finger with line of demarcation up to distal phalanx. Cardiovascular and respiratory systems were normal. On abdominal examination, there was diffuse tenderness in all quadrants, no organomegaly and normal bowel sounds. She had no neurodeficits.

Laboratory investigations showed a mild anaemia of 10.9 g/dL, normal leucocyte counts and platelets, normal liver, and renal functions. Arterial blood gas showed hypoxia (oxygen 60 mmHg), a carbon dioxide washout of 20 mmHg, normal bicarbonate levels initially. There was sinus tachycardia on electrocardiogram and chest X-ray showed bilateral inhomogeneous opacities. Coronavirus Disease 2019 (COVID-19) Reverse Transcription-Polymerase Chain Reaction (RT-PCR) was negative. Chest Computed Tomography (CT) showed bilateral lower zone inhomogeneous opacities [Table/Fig-1]. Pulmonary thromboembolism was ruled out on echocardiography and CT pulmonary angiography.

Her Antinuclear Antibody (ANA) by immunofluorescence was 3+ (homogeneous), and the blot test revealed presence of SmD1, U1SnRNP, double stranded Deoxyribonucleic Acid (DNA) (ds-DNA) antibodies. The ds-DNA titre was strongly positive (3+) with severe hypocomplementaemia (C3-18.9, C4-9.03). Antiphospholipid antibodies and Antineutrophilic Cytoplasmic Antibody (ANCA) were negative. Urine routine microscopy had 2+ protein, and 24 hours urine had nephrotic range proteinuria of 5.24 g. Ultrasonography



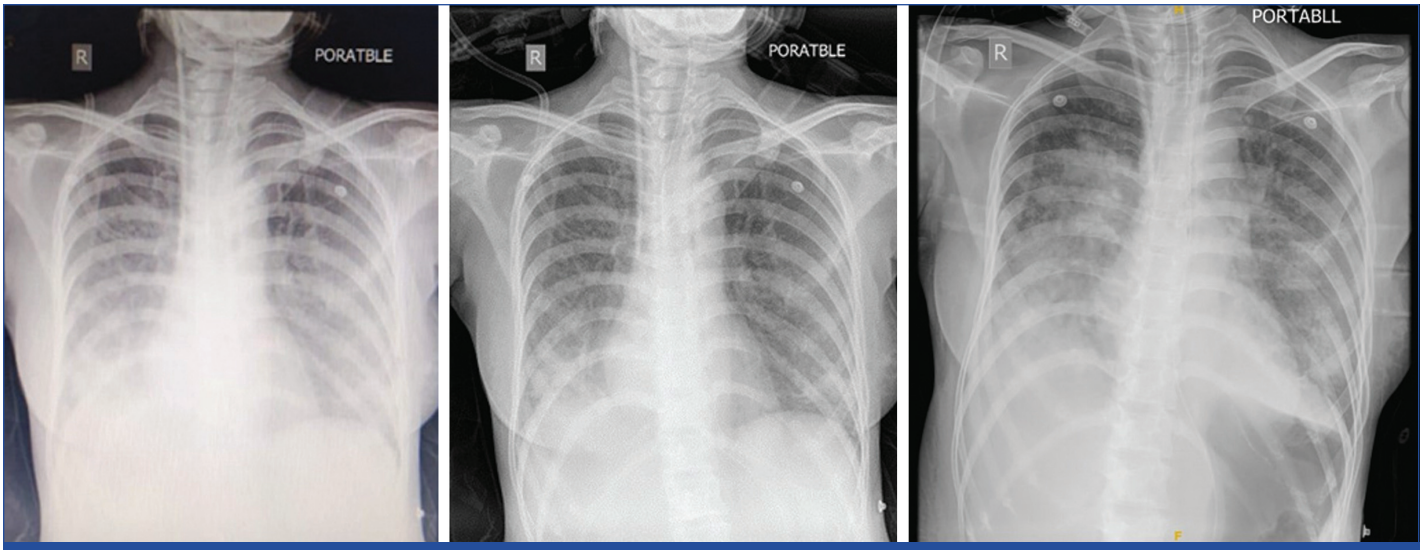
[Table/Fig-1a,b]: Computed tomography of thorax showing bilateral inhomogeneous opacities.

(USG) of the abdomen was normal. Serum amylase and lipase were normal based on these clinical and laboratory features, this patient was diagnosed as Systemic Lupus Erythematosus (SLE).

On day two, 2 g/dL fall in haemoglobin occurred and this indicated a possibility of diffuse alveolar haemorrhage. Thus, a final diagnosis of SLE with musculoskeletal, mucocutaneous features, lupus nephritis with Diffuse Alveolar Haemorrhage (DAH) was made and prompt treatment was started.

She was given oxygen at 4 litres per minute with nasal prongs and empirical ceftriaxone 1 g, 12 hourly, was started intravenously (i.v.). Pulse therapy was started on day 2, with i.v. methyl prednisolone 1 g for three days, and pulse cyclophosphamide i.v. 750 mg/m^2 body surface area, according to the National Institutes of Health (NIH) protocol [1]. Later, she was continued with oral prednisolone 1 mg/kg/day. The patient underwent five cycles of plasma exchange on alternate days, and improved after each cycle. On day 8, the patient's hypoxaemic respiratory failure worsened, and she was started on non invasive ventilation-pressure support, 100% Fraction of inspired oxygen (FiO_2) with Positive End Expiratory Pressure (PEEP) 8 mmHg. On day 10, she developed frank haemoptysis, hypoxaemic respiratory failure worsened further, and was intubated with Acute Respiratory Distress Syndrome (ARDS) settings of 100% FiO_2, high PEEP and low tidal volume.

Intravenous immunoglobulin therapy and further rituximab was planned, but unfortunately the patient succumbed due to continuing alveolar haemorrhage on day 14 of admission, after 6th cycle of plasmapheresis [Table/Fig-2-4].



[Table/Fig-2]: Chest X-ray before plasmapheresis with bilateral inhomogeneous opacities. **[Table/Fig-3]:** Chest X-ray after plasmapheresis with bilateral clear lung fields. **[Table/Fig-4]:** Final Chest X-ray with bilateral inhomogeneous opacities suggestive of massive DAH. (Images from left to right)

DISCUSSION

Systemic Lupus Erythematosus is a chronic autoimmune disease having clinical features of rashes, arthritis, glomerulonephritis, neurological, cardiovascular involvement, and lung manifestation [2]. Respiratory tract involvement occurs in 50-70% of SLE patients and includes pleuritis, infiltrating pneumonia, bronchiolitis obliterans, pulmonary hypertension, Antiphospholipid Syndrome (APS) and DAH [3]. Immune complex induced alveolar capillaritis is the aetiology of DAH [4].

The DAH is a severe, rare respiratory complication of SLE, rarer in the early months of the disease. It develops over hours to a few days and is the SLE-associated syndrome with highest mortality. Cardinal clinical features of DAH are a drop in blood haemoglobin, dyspnoea, haemoptysis, diffuse infiltrates on chest imaging, thrombocytopenia and C3 hypocomplementaemia. Methylprednisolone and cyclophosphamide are the common drugs used. Rituximab and plasmapheresis are the advanced therapies needed [3,4].

Dr. William Osler first described DAH in 1904 and it is one of the most devastating complications of SLE. Diffuse Alveolar Haemorrhage is more common in ANCA associated vasculitides and Antiphospholipid Syndrome (APS) [5]. The DAH is rare, ranging from 0.6% to 5.4% of all SLE patients. Possible aetiology is pulmonary capillaritis due to immune complexes which causes damage to basement membranes and leakage of erythrocytes into the alveolar space. Diffuse Alveolar Haemorrhage can lead to death in more than 50% cases in the best centres. Acute catastrophic haemoptysis, requirement of mechanical ventilation, infections and thrombocytopenia are responsible for mortality [6].

The SLE Disease Activity Index above 10, thrombocytopenia, C3 hypocomplementaemia, high anti-dsDNA titres, and leucopenia are associated with increased risk of DAH. Risk of DAH is increased with lupus nephritis, described in up to 80% of cases. Acute dyspnoea, hypoxaemia, occasionally with haemoptysis, drop in haemoglobin levels (by 1.5-2 g/dL), pulmonary interstitial or alveolar infiltrates could suggest DAH [6].

Methylprednisolone, cyclophosphamide, and plasmapheresis are the most frequently used modalities of treatment. A study found that corticosteroids were the most commonly used (98%) followed by cyclophosphamide (54%), plasmapheresis (31%), intravenous immunoglobulin (IVIG, 5%), mycophenolate (3%), rituximab (RTX, 6%) and stem cell transplantation (2%) [6-8].

Plasmapheresis is usually used for cases where there is inadequate response to high doses of corticosteroid and cyclophosphamide. In a study on 66 patients with autoimmune diseases subjected to plasmapheresis, 11 were cases of lupus with DAH. Of all patients (total 20) with DAH who were treated, 55% showed improvement [9]. Rituximab is a B cell targeted therapy which can be used in DAH but during acute DAH, there may not be sufficient time for the RTX therapy to act [10]. Usage of recombinant factor VIIa and extracorporeal membrane oxygenation (ECMO) has been considered in a few cases with uncontrolled bleeding. Newer treatment modalities such as RTX and mesenchymal stem cells (MSCs) should be undertaken in randomised trials [10]. Factor VIIa is given at a dose of 35-200 µg/kg, intravenously, either as a single dose or repeated doses every 2-4 hours. It can also be given by intrapulmonary bronchoscopy route with a total dose of 50-90 µg/kg [11,12].

Many case reports in the literature explain the high mortality of DAH. In 2018, a case report by Abdalla AO et al., of a 23-year-old female with SLE developed multiple episodes of DAH in spite of immunosuppression with steroids, cyclophosphamide and plasmapheresis [13]. A study by Martinez MU et al., in 2011, described mortality in 15 of 22 patients with DAH [14]. Tolaymat O and Berianu F, reported DAH in a 18-year-old male who presented with recurrent episodes of haemoptysis and was diagnosed with SLE, and was treated with immunosuppression and plasmapheresis and the patient improved gradually [15].

With recent advances, early diagnosis and prompt treatment with immunosuppression and plasmapheresis, survival rates have increased from approximately 25% in the 1980s to 67% in the current decade. Still, DAH is a catastrophic complication which carries high risk of mortality and requires high index of suspicion with prompt early treatment [6].

CONCLUSION(S)

In critical care settings, DAH needs to be kept in mind in active cases of SLE to institute prompt treatment measures to combat this highly fatal complication.

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