Diffuse alveolar hemorrhage in systemic lupus erythematosus: An uncommon initial manifestation

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Abstract

It is uncommon for systemic lupus erythematosus (SLE) to present with diffuse alveolar hemorrhage (DAH) as the initial presentation. To diagnose this in a young male with no renal involvement is further uncommon. We report a case of a 16-year-old boy, who presented with hemoptysis and was eventually diagnosed as DAH with underlying SLE. Treatment with steroids and immunosuppressant helped in rapid recovery from this potentially life-threatening condition. This case highlights the need of defining diagnostic criteria for SLE in patients presenting as DAH and formulating guidelines for treatment of the same, especially in absence of co-existing lupus nephritis.

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Introduction

Systemic lupus erythematosus (SLE) is a common multisystem disease of middle-aged females presenting typically with cutaneous, rheumatological and renal manifestations. We present a case of a young boy who presented with diffuse alveolar hemorrhage (DAH) and was diagnosed as SLE, without active renal involvement. In view of no treatment guidelines for the same, he was treated with steroid and cyclophosphamide with a dramatic response and the patient went into remission.

Case Report

A 16-year-old boy presented with complaints of hemoptysis for 10-12 days and breathlessness for seven days. Hemoptysis was moderate in amount, 3-4 episodes per day, fresh red blood, not associated with bleeding from any other site. There was no history of fever or weight loss. Breathlessness was sudden in onset and progressive in nature with no postural variation. There was no orthopnea or paroxysmal nocturnal dyspnea.

There was no history of repeated childhood respiratory infections, episodes of cough with expectoration, treatment with antitubercular therapy and no history of palpitations, sweating or other symptoms suggestive of chronic heart or lung disease.

On examination, the patient was conscious and oriented to time, place and person. He was hemodynamically stable with tachycardia and tachypnea. His blood pressure was 110/70 mm of Hg, pulse 120/min and respiratory rate was 30/min. Pallor was present with no icterus, pedal edema or lymphadenopathy. Respiratory system examination revealed the use of accessory muscles of respiration and vesicular breath sounds with bilateral crackles all over the lung fields.

Hematological investigations revealed anemia with normal organ function tests with type 1 hypoxemic respiratory failure. Chest X-ray (performed on day 1 of admission) was suggestive of bilateral diffuse opacities (Figure 1a). This was confirmed by CT chest done on the subsequent day which revealed bilateral ground glass opacities and basal alveolar opacities (Figure 2). Given a previous report of hemoglobin demonstrating fall over one week, a provisional diagnosis of DAH was made, and the patient was planned for bronchoscopy.

Flexible bronchoscopy was suggestive of normal anatomy. Broncho-alveolar lavage (BAL) was negative for acid-fast bacilli (AFB), cartridge-based nucleic acid amplification test (CBNAAT), pneumocystis pneumonia (PCP), fungal mount and malignant cytology. There was no growth in pyogenic and

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mycobacterial culture. BAL cytology was suggestive of hemosiderin-laden macrophages.

In the course of hospital stay, the patient developed a skin rash. There was bilateral lower limb involvement, with maculopapular rash associated with mild itching (Figure 3a). On detailed history, the patient revealed that he had presented to a local doctor two months back with a papular rash on the skin in the lower limbs, taken some antihistaminic and homeopathic medications for the same and the lesions had partially healed. On further probing, the patient also revealed the history of fever with pain and swelling of the knee, elbow, and wrist joint along with the rash which had resolved in around one week with anti-inflammatory drugs. A skin biopsy was taken which was suggestive of fibrinoid necrosis with evidence of capillaritis (Figure 3b).

Immunological profile of the patient revealed negative ANCAs, negative IgM anticardiolipin, lupus anti-coagulant and IgM beta-2-glycoprotein 1, positive ANA in high titers, positive dsDNA and low complement levels (Table 1). Thus, fulfilling the

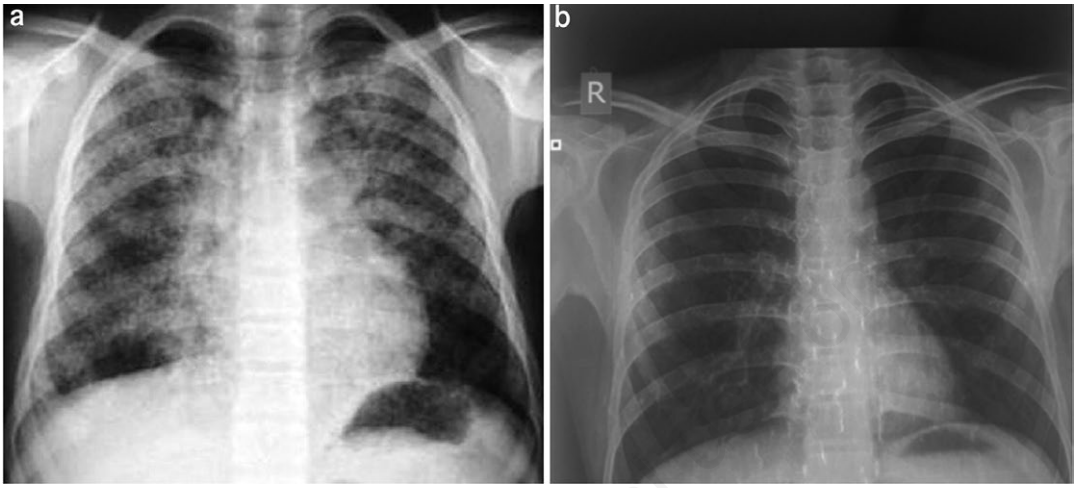

Figure 1. a) Initial chest X-ray on day 1 of admission showing bilateral diffuse opacities subsequently diagnosed as diffuse alveolar hemorrhage. b) Chest X-ray of the patient on discharge after ten days of the initial X-ray showing resolution of diffuse alveolar hemorrhage.

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Table 1. Hematological and other investigations.

Investigation	Admission	Discharge (day 10)
ABG- PH	7.48	7.41
PO_2	55	80
PCO_2	30	35
HCO_3	23	25
SO_2	88	99
Chest X-ray	Bilateral opacities	Normal
Urine examination	1+ Proteinuria by dip-stick examination 24 hour urine protein -100 mg% No cast or active sediment No red blood cells	Repeat 24 hour proteinuria - 20 mg%
Blood urea/creatinine	24/0.5	28/0.4
Hemoglobin (gram %)	9.0	10.9
Leucocyte coun	10000	8000
tPlatelet Count	3.1 Lac	3.2 Lac
INR	1.1	1.1
Immunological profile		
ANA(IIFA)		1:160 (positive)
ds DNA(EIA)		1:80 (positive)
Anti-RO/LA		Negative
Scl-70		Negative
c-ANCA(IIFA)		Negative
p-ANCA(IIFA)		Negative
C_3		8 (low) (range: 66-185 mg/dl)
C_4		11 (low) (range: 15-52mg/dl)
IgM anticardiolipin, Lupus anti-coagulant and IgM beta-2-glycoprotein 1		Negative

ABG, arterial blood gas; INR, international normalized ratio; ANA, antinuclear antibodies; C_3, C_4, complement 3 and 4; IIFA, indirect immunofluorescence; EIA, enzyme-linked immunosorbent assay.

classification criteria with two clinical and three immunological criteria, a final diagnosis of SLE with DAH with type 1 respiratory failure with skin rash with capillaritis was made. Kidney function tests and urine examination for proteinuria and active sediments were normal, and hence no kidney biopsy was indicated.

Patient was given methylprednisolone 1 gram for three days (day 4 to 6 from admission) and cyclophosphamide along with mesna 750 mg stat (on day 4 from admission). Hemoptysis of the patient resolved in 2 to 3 days and ABG improved with room air saturation of 99% by day 7 of admission. The patient tolerated the therapy well without any adverse events. The patient was discharged on day 10 from admission with oral prednisolone 30 mg, oral calcium supplementation and hydroxychloroquine. Chest X-ray at discharge (Figure 1b) showed resolution and skin rash also showed a dramatic response. The follow up strategy was to give 6 cycles of cyclophosphamide pulse therapy continuing with oral steroids. Subsequently, patient was planned to be maintained on tapering doses of oral steroids with azathioprine.

Discussion

Acute diffuse alveolar infiltration, a rare manifestation of SLE, is caused by various life-threatening conditions such as- acute lupus pneumonitis, acute infections and DAH [1]. Since the treatments for DAH and the other causes of acute diffuse alveolar infiltration are completely different, early recognition and prompt treatment improve survival of SLE-associated DAH (SLE-DAH). It is difficult to diagnose DAH early because of its abrupt onset and rapid progression, and the non-specific clinical symptoms and radiographic findings and progressive bloodier lavage can help in the same.

Lung involvement in the form of DAH is very rare in SLE patients, with estimated incidence of 1% to 5% in adult SLE patients, yet the mortality rate typically exceeds 50%, with recurrences reported even after survival of the initial bleed [2-4]. Also, 40-100% of these patients have coexisting lupus nephritis [5].

Our patient satisfied all the components of DAH and initially suspecting it to be ANCA associated vasculitis, was subsequently diagnosed as SLE. However, there was no evidence of associated lupus nephritis. On reviewing the available literature, there are guidelines available for treatment of ANCA associated vasculitis for DAH and SLE nephritis [6,7]. However, there are no guidelines for the treatment of ANA positive SLE with DAH, especially in patients with no evidence of nephritis. One reason for this is the rarity of such a presentation. In a large cohort study of around a thousand patients, 22 patients of SLE had DAH. All patients were treated with multiple agents- immunosuppression, corticosteroids, plasmapheresis, cyclophosphamide, rituximab, and mycophenolate mofetil given the absence of guidelines for treatment of the same [8]. On similar lines, we treated with steroids and cyclophosphamide and achieved a dramatic response.

In a cohort study of childhood SLE, only 7 of 410 patients had DAH. Most of these children were successfully treated with steroids, immunosuppressants like cyclophosphamide, rituximab, and intravenous immunoglobulin (IVIG). The average age of presentation was 14 years. However, more than 70% of these patients presented

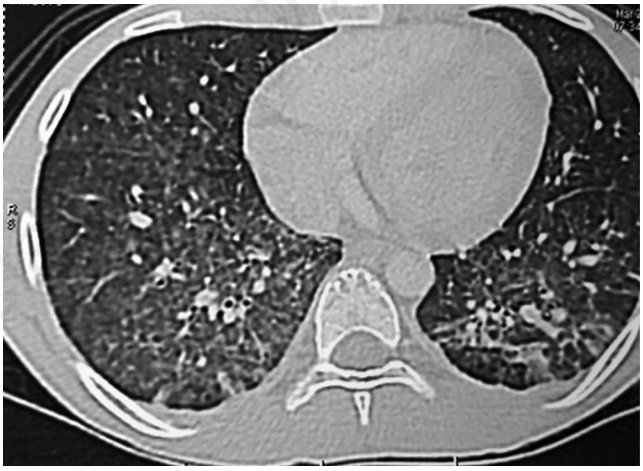

Figure 2. Chest CT scan showing bilateral ground glass haze along with basal alveolar opacities suggestive of diffuse alveolar hemorrhage.

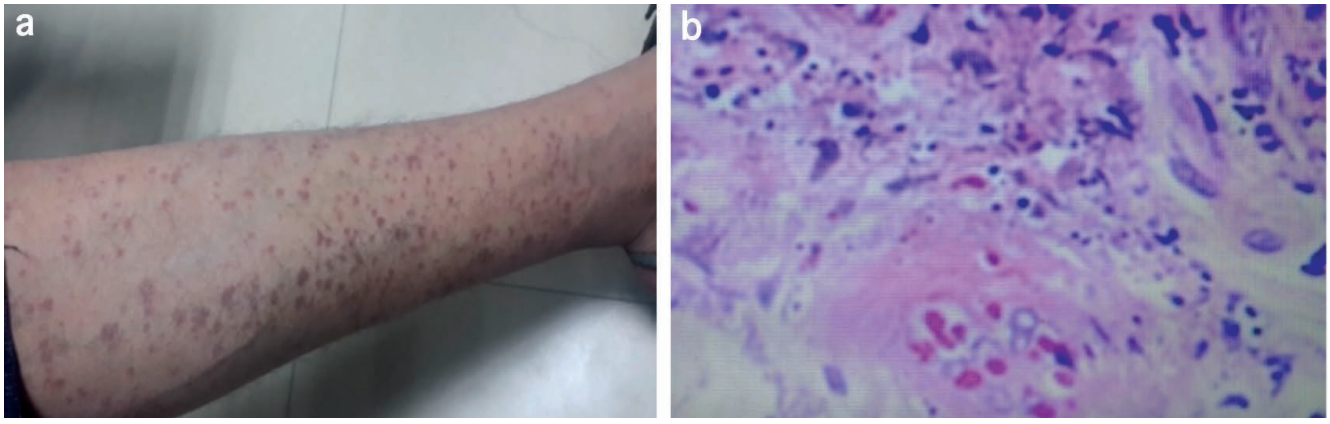

Figure 3. a) Maculopapular skin lesions on the extensor aspect of the leg of the patient developed during hospital stay. b) Skin biopsy in Hematoxylin & Eosin stain (40x magnification) showing capillary wall edema with dense neutrophilic infiltration with fibrinoid necrosis suggestive of capillaritis.

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with DAH within three months of diagnosis and majority of these children were males [9]. Both these points are reflected in our case also, and generalization of the same requires large-scale studies.

In view of absence of guidelines for our case of DAH in SLE without lupus nephritis and based on previous case reports, the authors plan to give the cycles of cyclophosphamide based on EULAR guidelines for anti-neutrophil cytoplasmic antibody (ANCA)-associated DAH. Even, the latest 2019 EULAR update on SLE does not mention treatment for pulmonary manifestations like DAH in SLE [10].

Besides, as SLE can have varied presentations, a strict watch on kidney function tests for worsening creatinine, hematuria, proteinuria, urine for active sediments will be done. The American College of Rheumatology (ACR) criteria for follow up of SLE without nephritis suggests monitoring blood pressure 3 every three months, and monitoring for dsDNA, C3, C4, urine analysis every 6 months. The authors plan to do this follow up every three months in this patient, as ACR itself documents that around 35% of SLE have renal involvement at start and more than half of the patients develop renal manifestations within the first decade [6].

Conclusions

DAH can be an initial presentation of SLE, especially in the young. Prompt diagnosis, urgent workup and the timely start of treatment largely determine the prognosis. Cyclophosphamide has improved survival of DAH on a large scale, and in the absence of clear guidelines from the literature, the approach to treatment remains individualized. Biopsy proven lupus is taken as a diagnostic criterion for SLE in presence of positive antinuclear antibodies (ANA) to promote early immunosuppression therapy to save the kidney. Another point to consider is whether we need a similar definition for SLE presenting as DAH, because mortality is high, if untreated.

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