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Diffuse alveolar hemorrhage in childhood-onset systemic lupus erythematosus: a severe disease flare with serious outcome

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Abstract

Objective: To evaluate prevalence, clinical manifestations, laboratory abnormalities and treatment in a multicenter cohort study including 847 childhood-onset systemic lupus erythematosus (cSLE) patients with and without diffuse alveolar hemorrhage (DAH), as well as concomitant parameters of severity.

Methods: DAH was defined as the presence of at least three respiratory symptoms/signs associated with diffuse interstitial/alveolar infiltrates on chest x-ray or high-resolution computer tomography and sudden drop in hemoglobin levels. Statistical analysis was performed using Bonferroni correction ($p < 0.0022$).

Results: DAH was observed in 19/847 (2.2%) cSLE patients. Cough/dyspnea/tachycardia/hypoxemia occurred in all cSLE patients with DAH. Concomitant parameters of severity observed were: mechanical ventilation in 14/19 (74%), hemoptysis 12/19 (63%), macrophage activation syndrome 2/19 (10%) and death 9/19 (47%). Further analysis of cSLE patients at DAH diagnosis compared to 76 cSLE control patients without DAH with same disease duration [3 (1–151) vs. 4 (1–151) months, $p = 0.335$], showed higher frequencies of constitutional involvement (74% vs. 10%, $p < 0.0001$), serositis (63% vs. 6%, $p < 0.0001$) and sepsis (53% vs. 9%, $p < 0.0001$) in the DAH group. The median of disease activity score (SLEDAI-2 K) was significantly higher in cSLE patients with DAH [18 (5–40) vs. 6 (0–44), $p < 0.0001$]. The frequencies of thrombocytopenia (53% vs. 12%, $p < 0.0001$), intravenous methylprednisolone (95% vs. 16%, $p < 0.0001$) and intravenous cyclophosphamide (47% vs. 8%, $p < 0.0001$) were also significantly higher in DAH patients.

Conclusions: This was the first study to demonstrate that DAH, although not a disease activity score descriptor, occurred in the context of significant moderate/severe cSLE flare. Importantly, we identified that this condition was associated with serious disease flare complicated by sepsis with high mortality rate.

Keywords: Diffuse alveolar hemorrhage, Childhood, Systemic lupus erythematosus, Multicenter study

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Introduction

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease characterized by the involvement of several organs and systems [1–3]. Pleuropulmonary manifestations were described as initial feature from 17 to 42% childhood-onset SLE (cSLE) patients, particularly mild to moderate pleuritis [1, 3–5]. These respiratory complications may be classified as acute or chronic [6].

Of note, diffuse alveolar hemorrhage (DAH) is an acute, rare and life-threatening pulmonary manifestation characterized by sudden onset of respiratory symptoms, such as dyspnea; hypoxemia; hemoptysis; tachycardia and/or cough; associated with new lung infiltrates on chest x-ray (CXR) or high-resolution computer tomography (HRCT); and sudden drop in serum hemoglobin levels [7, 8].

Data of DAH in cSLE patients are limited due to the small representation of this complication in previous case series or the focus on the comparison to adult SLE, precluding an accurate analysis of associated factors and outcomes in patients with and without this severe complication [4, 7–15].

Therefore, the objective of the present multicenter cohort study was to assess the prevalence and the possible DAH association with demographic, clinical manifestations, laboratory abnormalities, disease activity score, treatments and outcomes in a large cSLE population.

Methods

This was a retrospective multicenter cohort study including 1017 patients followed in 10 Pediatric Rheumatology tertiary referral services in São Paulo state, Brazil. One hundred and sixty five patients were excluded due to: incomplete medical charts ($n = 96$), undifferentiated connective tissue disorder with 3 or fewer American College of Rheumatology (ACR) criteria ($n = 43$), isolated cutaneous lupus erythematosus ($n = 11$), neonatal lupus erythematosus ($n = 8$), drug-induced lupus ($n = 5$) and mixed connective tissue disease ($n = 2$). Therefore, this study group comprised 852 cSLE patients. All of them fulfilled the ACR criteria for SLE [16], with disease onset before the age of 18 [17].

An investigator meeting was held for protocol training according to the clinical parameters definitions and disease activity tool scoring, as previously reported [3, 18]. Patient's medical charts were systematically reviewed according to demographic data, clinical characteristics, DAH features, laboratorial abnormalities, therapies and outcomes.

DAH was defined as the presence of at least three respiratory symptoms and signs (dyspnea, hypoxemia, hemoptysis, tachycardia and/or cough) associated with diffuse interstitial and/or alveolar infiltrates on CXR or

HRCT, and sudden drop in hemoglobin level at least of 1.5 g/dL [7, 10, 11]. Bronchoalveolar lavage with hemosiderin-laden macrophages evidence was also recorded [14]. Patients were divided in two groups with similar disease duration: cSLE patients with DAH (assessed at DAH diagnosis) and cSLE patients without DAH (assessed at last visit).

Descriptors and definitions of SLE Disease Activity Index 2000 (SLEDAI-2 K) score were used to characterize disease parameters and to calculate disease activity score [19]. Custom definitions were defined as previously reported [3, 18]. Neuropsychiatric lupus included 19 syndromes according to ACR classification criteria [20]. Antiphospholipid syndrome was diagnosed taking into account the presence of arterial and/or venous thrombosis concomitant to high titers of antiphospholipid antibodies [21]. Macrophage activation syndrome was diagnosed considering the preliminary cSLE diagnostic guidelines, requiring the presence of at least one clinical plus two laboratorial criteria [22].

Laboratorial assessment included complete blood cell count and urine test. Anti-double-stranded DNA (anti-dsDNA), IgG and IgM anticardiolipin antibodies (aCL) were carried out at each center and the cutoff values were considered valid. Lupus anticoagulant was detected according to the guidelines of the International Society on Thrombosis and Hemostasis [23].

Drug treatment data (prednisone, intravenous methylprednisolone, chloroquine diphosphate, hydroxychloroquine sulfate, methotrexate, azathioprine, cyclosporine, mycophenolate mofetil, intravenous cyclophosphamide and intravenous gammaglobulin) were also recorded.

Statistical analysis

Results were presented as an absolute number (frequency) for categorical variables and median (range) or mean \pm standard deviation (SD) for continuous variables. Categorical variables comparisons were assessed by Pearson χ -Square or Fisher's exact test. Continuous variables from cSLE patients with and without DAH were compared by Mann-Whitney test or t test as appropriate. Statistical analysis was performed using Bonferroni correction ($p < 0.0022$).

Results

DAH was observed in 19/847 (2.2%) cSLE patients. Cough, dyspnea, tachycardia and hypoxemia occurred in all 19 cSLE patients with DAH; hemoptysis in 12/19 and endotracheal tube bleeding in 14/19. New infiltrates on CXR or HRCT and hemoglobin drop at least of 1.5 g/dL were evidenced in all cSLE patients with DAH (Table 1). Bronchoalveolar lavage was performed in two cSLE patients and hemosiderin-laden macrophage was observed in both of them.

Table 1 Demographic, clinical manifestations and imaging in 19 childhood-onset systemic lupus erythematosus (cSLE) patients with diffuse alveolar hemorrhage

Patient	Disease duration, Months	Cough	Dyspnoea	Tachycardia	Hypoxemia	Hemoptysis/bleeding in endotracheal tube	New Infiltrates CXR or HRCT	Drop Hgb/dL
1	60	+	+	+	+	+ / +	+	1.8
2	151	+	+	+	+	+ / +	+	1.5
3	5	+	+	+	+	+ / +	+	2.0
4	0	+	+	+	+	+ / +	+	1.6
5	33	+	+	+	+	+ / +	+	1.9
6	0	+	+	+	+	+ / +	+	2.7
7	3	+	+	+	+	+ / +	+	1.7
8	90	+	+	+	+	+ / -	+	2.5
9	42	+	+	+	+	+ / +	+	4.5
10	4	+	+	+	+	+ / +	+	3.0
11	0	+	+	+	+	- / -	+	3.2
12	47	+	+	+	+	- / +	+	1.5
13	5	+	+	+	+	- / +	+	1.5
14	0	+	+	+	+	+ / -	+	2.0
15	0	+	+	+	+	- / +	+	7.0
16	0	+	+	+	+	- / -	+	2.0
17	3	+	+	+	+	- / +	+	2.0
18	1	+	+	+	+	- / -	+	1.7
19	0	+	+	+	+	+ / +	+	8.0

CXR Chest x-ray, HRCT High resolution computer tomography, Hb Hemoglobin, ND Not done

Regarding outcomes, hospitalization in pediatric intensive care unit occurred in 17/19 cSLE patients with DAH and mechanical ventilation in 14/19. DAH associated with sepsis was observed in 10/19 cSLE patients. Concomitant macrophage activation syndrome was evidenced in 2/19 patients. Death was observed in 9/19 cSLE patients. The median duration between DAH onset and death was 2 days (0.5–25). Blood erythrocyte transfusion and broad-spectrum antibiotics were administered in all cSLE patients with DAH. Intravenous methylprednisolone pulse therapy was used in 18/19 cSLE and intravenous cyclophosphamide in 9/19 (Table 2). None of them had recurrence of DAH.

Further comparison between cSLE patients with DAH compared to 76 cSLE control patients without DAH with same disease duration [3 (1–151) vs. 4 (1–151) months, $p = 0.335$], showed significantly higher frequencies of constitutional involvement (74% vs. 10%, $p < 0.0001$), serositis (63% vs. 6%, $p < 0.0001$) and sepsis (53% vs. 9%, $p < 0.0001$) in the former group. The median of SLEDAI-2 K was significantly higher in cSLE patients with DAH compared to cSLE patients without this complication [18 (5–40) vs. 6 (0–44), $p < 0.0001$]. Frequencies of nephritis and neuropsychiatric involvements were similar in both groups ($p > 0.0022$) (Table 3).

The frequencies of thrombocytopenia (53% vs. 12%, $p < 0.0001$), intravenous methylprednisolone (95% vs. 16%, $p < 0.0001$) and intravenous cyclophosphamide (47% vs. 8%, $p < 0.0001$) were also significantly higher in the former group. The median of prednisone dose was higher in cSLE patients with DAH compared to those without DAH [1.4 (0.3–2) vs. 0.5 (0.03–3) mg/Kg, $p < 0.0001$] (Table 4).

Discussion

This is the largest study to evaluate DAH, a rare and acute life-threatening pulmonary manifestation, in cSLE population.

The multicenter study design with a large cohort of children and adolescents patients allowed a more precise assessment of this rare and severe cSLE respiratory complication. An investigator meeting was also taken in place to standardize the protocol study in all centers. However, the limitation was the retrospective design with potential missing data.

The prevalence of DAH in cSLE patients in the present study was similar to other reports, varying from 2 to 5% [6, 7, 24]. Diagnosis of this condition included the typical respiratory symptoms and signs, drop in hemoglobin levels and the radiographic evidence of pulmonary infiltrates, as well as the assessment of

Table 2 Outcomes and immunosuppressive treatment in 19 childhood-onset systemic lupus erythematosus (cSLE) patients with diffuse alveolar hemorrhage

Patient	ICU	Mechanical ventilation	Sepsis	MAS	Death	IV methylprednisolone pulse therapy	IV cyclophosphamide
1	+	+	+	-	+	+	-
2	+	+	+	-	-	+	+
3	+	+	+	-	+	+	-
4	+	+	+	-	-	+	+
5	+	+	-	-	+	+	-
6	+	+	-	-	-	+	+
7	+	+	+	-	+	+	+
8	+	-	+	-	+	+	+
9	+	+	-	-	+	+	-
10	+	+	-	-	-	+	+
11	+	-	-	-	-	+	-
12	+	+	-	+	+	+	-
13	+	+	-	-	+	-	-
14	+	-	+	-	-	+	+
15	+	+	+	+	-	+	+
16	-	-	+	-	-	+	-
17	+	+	+	-	-	+	+
18	-	-	-	-	-	+	-
19	+	+	-	-	+	+	-

ICU Intensive care unit, MAS Macrophage activation syndrome, IV Intravenous

Table 3 Demographic data, clinical manifestations and disease activity score in childhood-onset systemic lupus erythematosus (cSLE) patients according to the presence of diffuse alveolar hemorrhage (DAH)

Variables	With DAH (at diagnosis) (n = 19)	Without DAH (at last visit) (n = 76)	P
Demographic data			
Female gender	14 (74)	66 (87)	0.172
Disease duration, months	3 (1–151)	4 (1–151)	0.335
Current age, years	13 (9–18)	13 (3–23)	0.889
Current clinical manifestations			
Constitutional	14 (74)	8 (10)	< 0.0001*
Mucocutaneous	9 (47)	31 (41)	0.614
Musculoskeletal	5 (26)	8 (10)	0.127
Serositis	12 (63)	5 (6)	< 0.0001*
Neuropsychiatric	4 (21)	11 (14)	0.491
Nephritis	16 (84)	42 (55)	0.033
Current autoimmune thrombosis (APS), n = 90	0/16 (0)	1/74 (1)	1.000
Sepsis	10 (53)	7 (9)	< 0.0001*
Macrophage activation syndrome	2 (10)	2 (3)	0.113
Death, n = 94	9 (47)	15/75 (20)	0.020
Current disease activity			
SLEDAI-2 K, n = 82	18 (5–40)	6 (0–44)	< 0.0001*

*P-value according to Bonferroni correction for multiple comparisons ($p < 0.0022$). Results are presented in n (%) and median (range), APS Antiphospholipid syndrome, SLEDAI-2 K Systemic Lupus Erythematosus Disease Activity Index 2000

Table 4 Current laboratory tests and drug therapy of childhood-onset systemic lupus erythematosus (cSLE) according to the presence of diffuse alveolar hemorrhage (DAH)

Variables	With DAH (at diagnosis) (n = 19)	Without DAH (at last visit) (n = 76)	P
Current laboratory exams			
Autoimmune hemolytic anemia	5 (26)	8 (10)	0.127
Thrombocytopenia, < 150,000/mm ³ , n = 93	10 (52)	9/74 (12)	< 0.0001*
Anti-ds-DNA, n = 75	8/13 (61)	30/62 (48)	0.544
Drug therapy			
Prednisone current dose, mg/Kg, n = 82	1.4 (0.3–2)	0.5 (0.03–3)	< 0.0001*
Intravenous methylprednisolone	18 (95)	12 (15)	< 0.0001*
Antimalarial drugs	14 (74)	41 (54)	0.193
Azathioprine	2 (10)	16 (21)	0.513
Mycophenolate mofetil	1 (5)	5 (6)	1.000
Intravenous cyclophosphamide	9 (47)	6 (8)	< 0.0001*

*P-value according to Bonferroni correction for multiple comparisons ($p < 0.0022$). Results are presented in n (%) and median (range), anti-ds-DNA – anti-double-stranded DNA antibodies

hypoxemia due to acute respiratory distress [7]. In addition, in two of our cSLE patients the presence of haemosiderin-laden macrophages in the absence of bloody fluid suggested recent bleeding [6], analyzed by the bronchoalveolar lavage.

We demonstrated that DAH, although not a disease activity score descriptor of SLEDAI-2 K [19], was associated with high moderate or severe disease activity scores, particularly thrombocytopenia, serositis and constitutional involvement. In contrast to previous reports DAH was not associated with lupus nephritis [13].

Of note, we identified that DAH was a severe manifestation requiring pediatric intensive care unit hospitalization and mechanical ventilation for the vast majority of our patients. We extended previous observation of high frequency of severe infection in adults/cSLE patients with DAH [7], thus demonstrating the catastrophic nature of DAH, since more than half of cSLE patients developed concomitant sepsis.

Reinforcing this finding of poor outcome, 10% of the cSLE patients were diagnosed with concomitant macrophage activation syndrome. In fact, this is a rare condition characterized by an excessive activation and proliferation of T lymphocytes and macrophages with massive hypersecretion of proinflammatory cytokines, and may induce severe hemorrhages [25, 26].

We observed a high mortality rate in cSLE patients with DAH, as also observed in other studies [6, 10, 11]. This unfavorable outcome revealed that sepsis and macrophage activation syndrome may have contributed to the death of more than half of the patients.

Early detection of this severe pulmonary complication, prompt immunosuppressive agents treatment [9, 15, 27],

empirical antibiotics and mechanical ventilation are therefore essential to improve cSLE outcome [6, 7].

Conclusion

This was the first study to demonstrate that DAH, although not a disease activity score descriptor, occurs in the context of significant moderate/severe cSLE flare. Importantly, we identified that this condition is associated with serious disease flare complicated by sepsis and high mortality rate.

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Availability of data and materials

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Authors' contributions

All authors analyzed and interpreted the patient data regarding autoimmune hepatitis in childhood onset systemic lupus erythematosus. GB, EB and CAS were the major contributor in writing the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by our Ethics Committee.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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