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ORIGINAL ARTICLE

Subclinical Pulmonary Hypertension in Childhood Systemic Lupus Erythematosus Associated with Minor Disease Manifestations

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Abstract The aim of this study was to evaluate pulmonary hypertension (PH) in 852 childhood-onset systemic lupus erythematosus (cSLE) patients. This was a large multicenter study conducted in 10 Pediatric Rheumatology Services of São Paulo state, Brazil. PH was defined as systolic pulmonary artery pressure >35 mmHg and/or measurement of the mean pulmonary artery pressure >25 mmHg and/or diastolic pressure >15 mmHg by transthoracic echocardiogram. Demographic data, clinical manifestations, disease activity score (SLEDAI-2K), disease damage score (SLICC/ACR-DI) and treatments were also evaluated. Statistical analysis was performed using Bonferroni correction ($p < 0.002$). PH was observed in 17/852 (2%) cSLE patients. Effort dyspnea occurred in 3/17, chest pain in 1/17 and right ventricle dysfunction in 3/17 cSLE patients. None had pulmonary thromboembolism or antiphospholipid syndrome. Further comparison between 17 cSLE with PH and 85 cSLE control patients without PH with similar disease duration [15 (0–151) vs. 15 (0–153) months, $p = 0.448$], evaluated at the last visit, revealed higher frequencies of fever (47 vs. 9%, $p < 0.001$), reticuloendothelial manifestations (41 vs. 7%, $p < 0.001$) and serositis (35 vs. 5%, $p = 0.001$) in the former group. Frequencies of renal and neuropsychiatric involvements and antiphospholipid syndrome, as well as the median of SLEDAI-2K and SLICC/ACR-DI scores, were comparable in both groups ($p > 0.002$). Normal transthoracic echocardiography was evidenced in 9/17 (53%), with median cSLE duration of 17.5 months (1–40) after PH standard treatment. PH was a rare manifestation of cSLE occurring in the first two years of disease. The majority of patients were asymptomatic with mild lupus manifestations. The underlying mechanism seemed not to be related to pulmonary thromboembolism and/or antiphospholipid syndrome.

Keywords Pulmonary hypertension · Childhood systemic lupus erythematosus · Lung · Multicenter cohort

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Introduction

Systemic lupus erythematosus (SLE) is a rare chronic autoimmune illness with variable disease manifestations and outcomes, and may affect the lungs and pulmonary vessels [1–4].

Pulmonary involvement has been reported in 7–31% childhood-onset systemic lupus erythematosus (cSLE) patients [2–4], mainly pleural effusions, pleuritis and pneumonitis [2, 5, 6].

Of note, pulmonary hypertension (PH) is a severe lung manifestation and has been described as case reports and case series in cSLE populations [3, 7–9]. However, to our knowledge there is no study evaluating PH in a large multicenter cohort of cSLE patients.

Thus, the aim of this study was to evaluate the prevalence and the possible association of PH with demographic data, clinical manifestations, laboratory abnormalities, disease activity/damage scores and treatments in cSLE patients.

Methods

This was a retrospective multicenter cohort study including 1017 patients with cSLE followed in 10 Pediatric Rheumatology tertiary referral services of 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, the study group comprised 852 patients with cSLE. All patients fulfilled the American College of Rheumatology (ACR) lupus criteria [10] with disease onset before 18 years of age and current age up to 25 years old. Committee for Research Ethics of each center approved the study.

A consensus was achieved among the participating centers in the study to delineate the protocol according to the clinical definitions, disease activity/damage tools scoring and outcomes parameters. Investigators in each center used the same database, and data collection was conducted locally.

Each cSLE patient underwent at least one transthoracic echocardiogram at diagnosis or during follow-up. The local pediatric cardiologists performed all the transthoracic echocardiogram, unaware of cSLE diagnosis. Our study group had access to their final medical reports. The reader of the echocardiogram was "blinded" to PH diagnosis. PH was defined as pulmonary artery systolic pressure >35 mmHg and/or mean pressure >25 mmHg and/or diastolic pressure >15 mmHg. The pulmonary systolic pressure was estimated via the peak velocity of the tricuspid regurgitation jets, and the diastolic pressure was estimated via the peak end-diastolic velocities of the pulmonary regurgitation jets as interrogated by Doppler. The right atrial pressure was assumed to be 5 mmHg [11–13].

Medical charts for demographic data, clinical features, laboratorial findings, disease activity/damage scores and treatments were systematically reviewed. Patients were divided into two groups with similar disease duration: cSLE patients with PH and cSLE patients without PH. Reticuloendothelial involvement included lymphadenopathy (peripheral lymph node enlargement >1.0 cm), hepatomegaly [based on physical examination with liver edge ≥2 cm below the right costal margin or imaging (ultrasound or computer tomography)] and splenomegaly [based on physical examination with palpable spleen or imaging (ultrasound or computer tomography)] [3]. Neuropsychiatric lupus included 19 syndromes according to ACR classification criteria [14]. Antiphospholipid syndrome was diagnosed according to the presence of arterial and/or venous thrombosis and antiphospholipid antibodies [15]. High blood pressure was defined as systolic and/or diastolic blood pressures ≥95th percentile for gender, age and height on ≥3 occasions [16].

Laboratorial assessment included C-reactive protein (CRP), complete blood cell count and urine examination. Anti-double-stranded DNA (anti-dsDNA) autoantibodies and anticardiolipin antibodies (aCL) IgG and IgM assessments were carried out at each center. The cutoff values were considered valid according to the manufacturer kit. Lupus anticoagulant was detected according to the guidelines of the International Society on Thrombosis and Hemostasis [17].

SLE disease activity was scored using SLE Disease Activity Index 2000 (SLEDAI-2K) [18] and cumulative damage through the Systemic Lupus International Collaborating Clinics/ACR-Damage Index (SLICC/ACR-DI) [19]. Drug treatments, such as prednisone, intravenous methylprednisolone, antimalarials and immunosuppressive agents were also registered. Diuretics, digoxin, vasodilators and endothelin receptor antagonists were also recorded.

Statistical Analysis

Results were presented as an absolute number (frequency) for categorical variables and median (range) or mean ± SD for continuous variables. Categorical variables comparisons were evaluated by Pearson Chi-square or Fisher's exact tests. Continuous variables from cSLE patients with and without PH were compared by Mann–Whitney test. The significance levels of the independent variables were set at 5% ($p < 0.05$). Holm–Bonferroni correction for multiple comparisons was used to adjust the significance level ($p < 0.002$).

Results

PH was observed in 17/852 (2%) cSLE patients, mainly in the first two years of disease. Effort dyspnea occurred in 3/17 (18%), chest pain in 1/17 (6%) and right ventricle

dysfunction by transthoracic echocardiogram in 3/17 (18%) cSLE patients. None of the subjects had pulmonary thromboembolism, digital clubbing, cyanosis or congestive heart failure. Concomitant invasive fungal infection was observed in 2/17 (12%) cSLE patients. None of cSLE patients underwent cardiac catheterization.

Further comparison between 17 cSLE with PH and 85 control cSLE without PH with similar disease duration [15 (0–151) vs. 15 (0–153) months, $p = 0.448$] revealed higher frequencies of fever (47 vs. 9%, $p < 0.001$), reticuloendothelial manifestations (41 vs. 7%, $p < 0.001$) and serositis (35 vs. 5%, $p = 0.001$) in the former group. Pericarditis was observed in 3/17 (18%) cSLE patients with PH and pleuritis in 4/17 (23%). Frequencies of renal and neuropsychiatric involvements and antiphospholipid syndrome, as well as the median of SLEDAI-2K and SLICC/ACR-DI scores, were similar in both groups ($p > 0.002$) (Table 1).

Laboratory parameters, autoantibodies and treatments in cSLE patients with and without PH are shown in Table 2. The median of CRP and the frequencies of autoimmune hemolytic anemia, lymphopenia, thrombocytopenia, autoantibodies and treatment were similar in both groups ($p > 0.002$) (Table 2).

Regarding treatment for PH, prednisone was administered in 17/17 (100%), intravenous methylprednisolone in 6/17 (35%), immunosuppressive agents in 9/17 (53%), antimalarial drugs in 9/17 (53%), vasodilators in 11/17 (65%) and diuretics in 5/17 (29%). Oral sildenafil was used in 2/17. None of the patients received digoxin, bosentan and other endothelin receptor antagonists.

During follow-up, at least one additional transthoracic echocardiogram was performed in all patients. Normal transthoracic echocardiography was evidenced in 9/17 (53%), with median disease duration of 17.5 months (1–40 months) after PH diagnosis and treatment.

Discussion

This was the first study evaluating PH in a large cohort of cSLE patients and clearly demonstrated that PH was a rare and subclinical involvement in cSLE associated with mild disease manifestations.

The strongest point of our study was the large cohort of cSLE patients, allowing a more accurate evaluation of this rare manifestation, and we found that the frequency was similar as previously reported [7, 20]. Transthoracic echocardiography was used herein as the diagnostic tool to define PH [21]. The main limitation was the missing data due to retrospective analyses. Targeted PH medications, such as endothelin receptor antagonists, were unavailable for cSLE patients.

Lupus is a multisystem disease, and the most frequent cardiopulmonary manifestations reported are pericarditis

Table 1 Demographic data, clinical manifestations, disease activity and disease damage scores in childhood-onset systemic lupus erythematosus (cSLE) patients with and without pulmonary hypertension (PH)

Variables	cSLE with PH ($n = 17$)	cSLE without PH ($n = 85$)	*P*
Demographic data			
Age at diagnosis, years	14.5 (8.8–20)	14.5 (3.3–23.2)	0.673
Female gender	15 (88)	67 (79)	0.513
Disease duration, months	15 (0–151)	15 (0–153)	0.448
Fever	8 (47)	8 (9)	<0.001*
Reticuloendothelial involvement	7 (41)	6 (7)	<0.001*
Mucocutaneous involvement	10 (59)	39 (46)	0.427
Musculoskeletal involvement	5 (29)	6 (7)	0.017
Serositis	6 (35)	4 (5)	0.001*
Neuropsychiatric involvement	1 (6)	13 (15)	0.455
Nephritis	6/16 (37)	21 (25)	0.356
Arterial hypertension	8 (47)	12 (14)	0.004
Antiphospholipid syndrome	1 (6)	0 (0)	1.000
Disease activity and disease damage scores			
SLEDAI-2 K	10 (0–41)	6 (0–35)	0.067
SLICC/ACR-DI	0.5 (0–3)	0 (0–4)	0.384

* *P* value according to Bonferroni correction for multiple comparisons ($p < 0.002$). Results are presented in *n* (%) or median (range), SLEDAI-2K—Systemic Lupus Erythematosus Disease Activity Index 2000, SLICC/ACR-DI—Systemic Lupus International Collaborating Clinics/American College of Rheumatology-Damage Index

Table 2 Laboratory parameters, autoantibodies and treatments in childhood-onset systemic lupus erythematosus (cSLE) patients with and without pulmonary hypertension (PH)

Variables	cSLE with PH ($n = 17$)	cSLE without PH ($n = 85$)	P
Laboratory parameters			
CRP, mg/L	25.5 (6–407)	0.5 (0–260)	0.004
Autoimmune hemolytic anemia	4/16 (25)	6 (7)	0.049
Lymphopenia, <1500/mm^3	6 (35)	17/79 (21)	0.228
Thrombocytopenia, <150,000/mm^3	4 (23)	8/81 (10)	0.213
Autoantibodies			
Anti-dsDNA	6/12 (50)	27/68 (41)	0.752
Lupus anticoagulant	0/12 (0)	4/28 (13)	1.000
IgM anticardiolipin	2/4 (50)	4/32 (12)	0.121
IgG anticardiolipin	2/4 (50)	8/32 (25)	0.304
Treatments			
Glucocorticosteroid			
Prednisone dose, mg/kg/day	1.2 (0.2–2.0)	0.38 (0.05–3.3)	0.008
Intravenous methylprednisolone	6 (35)	12 (14)	0.073
Antimalarial drugs	9 (53)	53 (62)	0.587
Immunosuppressive agents	9 (53)	41 (48)	0.794

* P value according to Bonferroni correction for multiple comparisons ($p < 0.002$)

Results are presented in n (%) or median (range), *CRP* C-reactive protein

and pleuritis, generally subclinical with small effusion volumes, rarely causing pericardial tamponade and respiratory insufficiency [3, 4]. Of note, serositis occurred in more than a third of patients with PH in the context of a high disease activity score (SLEDAI-2K). This finding suggested the presence of multiple targets in lung and heart tissues, possibly as consequence of systemic autoimmune inflammation and/or vasculitis [22–24]. In contrast, no association with other major organ involvements was observed in cSLE patients, regardless of previous reports of higher frequency of nephritis in adult SLE patients with PH [23–25].

The prevalence of PH in cSLE patients was low (2%) and comparable to the reported in adult lupus patients [23, 25]. Interestingly, the majority of patients were asymptomatic for PH and other signs and symptoms, such as serositis or arterial hypertension, needing transthoracic echocardiography procedure.

With regard to underlying pathogenic mechanisms of PH in cSLE, no association was observed with antiphospholipid syndrome, contrasting to the reported higher incidence of PH in antiphospholipid antibody positive lupus [26]. Likewise, thromboembolism, the leading cause of PH in adult SLE [27], was not observed in cSLE patients. Therefore, treatment of PH in cSLE patients did not take into account these two treatable causes of PH and targeted lupus systemic activity with high dose of glucocorticosteroid, immunosuppressive drugs and vasodilators [28, 29].

Interestingly, our study suggests that PH may be a reversible manifestation after treatment, since transient PH was observed in almost half of cSLE patients after follow-up. This finding is in contrast with the reported severity of PH in adult SLE patients, whose complication is life threatening, as well as an independent predictor of patients' survival [24].

In conclusion, PH is a rare manifestation of cSLE occurring in the first two years of disease. The majority of patients are asymptomatic with mild lupus manifestations. The underlying mechanism seems not to be related to pulmonary thromboembolism and/or antiphospholipid syndrome.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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