Research Article
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Lung ultrasound in children and adolescents with rheumatologic diseases in clinical practice

Abstract

Pulmonary complications from autoimmune diseases are rare in the pediatric age group, but with significant morbidity, compromising the patients' quality of life in adulthood. The objective of this study was to evaluate the presence of interstitial lung disease in pediatric rheumatologic patients with connective tissue diseases, who were submitted to investigation through lung ultrasound during outpatient follow-up. The medical records of 40 patients were reviewed from April 2014 to December 2021. The patients evaluated were those who had already undergone lung ultrasound and presented changes suggestive of interstitial lung disease and were submitted to complementary investigation with chest high-resolution computed tomography and pulmonary function tests. The sample consisted of 20 patients, 70% of whom were female. The average age was 14 years. Half of the patients with connective tissue diseases showed changes suggesting pulmonary fibrosis on lung ultrasound and underwent further investigation with chest high-resolution computed tomography and pulmonary function test. In this group, 40% had tomography with abnormal patterns in the lung parenchyma, suggestive of interstitial lung disease, predominantly with normal spirometry. Older age and longer duration of disease were statistically significant in the analysis between the group with both altered imaging tests and the 20 patients underwent lung ultrasound (p= 0.008 and p= 0.006, respectively). Lung ultrasound can be a valuable screening tool for the early detection of interstitial lung changes in pediatric collagenosis. Larger prospective and longitudinal studies are needed in the pediatric age group, so that its specificity for interstitial syndrome can be determined.

Keywords: ultrasound, childhood, adolescence, autoimmune diseases, interstitial lung disease

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Introduction

Pediatric rheumatologic diseases include several chronic inflammatory disorders, generally idiopathic, that affect children and adolescents' structures of the musculoskeletal system, blood vessels and/or other organs and tissues, with a potential impact on quality of life. Despite a partial understanding of the immunological mechanisms that cause child or adolescent's juvenile rheumatism, the great scientific advances in rheumatology in recent decades have opened a new perspective for affected patients, due to the possibility of early diagnosis and adequate treatment, basic requirements for achieving good prognosis and quality of life for patients.[1]

In recent years, ultrasound indications in pediatric rheumatologic patients have been widely discussed in the literature, making ultrasound a valuable extension tool for rheumatologic physical examination. Ultrasound can detect acute and subacute inflammatory activity in organs and tissues and guide local therapeutic interventions, such as joint infiltrations. In addition to the proven diagnostic sensitivity, ultrasound has shown advantages over other imaging methods, as it is safe, non-invasive, does not use ionizing radiation or pediatric sedation, in addition to being relatively low-cost.[2–4]

Pulmonary complications due to autoimmune diseases are rare in the pediatric age group and can be acute or chronic, with significant morbidity in the medium and long term, impairing patients' quality of life in adulthood, especially in insidious cases.[5] There are few studies on pulmonary lesions in children with rheumatic diseases, which incidentally, can affect all the system components, such as airways, vessels, parenchyma, pleura and respiratory muscles. Quality of life impairment may be related to the underlying disease, the drugs used in the treatment or be secondary to infections, among others. A study carried out in 14 pediatric rheumatologic patients showed that one third of the patients had some degree of abnormality in the pulmonary function test and/or radiological pattern, even in asymptomatic patients, suggesting a periodic performance of the pulmonary function test in all patients of the pediatric age group, even in the absence of respiratory symptoms.[6] Juvenile systemic lupus erythematosus (JSLE), juvenile systemic sclerosis (JSSc), juvenile dermatomyositis (JDM), mixed connective tissue disease (MCTD), juvenile Sjögren's syndrome (JSS) and juvenile idiopathic arthritis are pediatric rheumatologic diseases that can course with interstitial lung disease (ILD) and progression to pulmonary fibrosis, like in adults.[5] This retrospective study evaluated the presence of ILD in pediatric rheumatologic patients with connective tissue diseases at the Pediatric Rheumatology Unit of the Pontifical Catholic University of Campinas (PUC-Campinas), through lung ultrasound (LUS), discussing whether it could be a screening tool for the early detection of ILD, avoiding the periodic performance of the chest high-resolution computed tomography (HRCT) in this age group. Demographic data, chest tomography, spirometry and global disease activity were evaluated in patients who presented alterations on LUS.

Materials and methods

Population

Between April 2014 and December 2021, 496 pediatric patients (0-19 years of age) were admitted for rheumatologic evaluation at the Pediatric Rheumatology Unit of PUC-Campinas. Among them, 40 patients were diagnosed with connective tissue diseases (JSLE, JSSc, JDM, MCTD, JSS and juvenile localized scleroderma (JLSc) and were included in this retrospective study. Informed consent was obtained from all the children's parents and from all participants older than 12 years. This study was approved by the Human Research Ethics

Committee of the PUC-Campinas and was conducted in accordance with 1964 Helsinki Declarations standards.

Data collection

The medical records of patients were reviewed, according to the international classification criteria for childhood rheumatologic diseases. The patients evaluated were those who had already undergone LUS and presented changes suggestive of ILD, and were submitted to complementary investigation with chest HRCT and pulmonary function tests. Patients who had acute or chronic pulmonary infection during the periods of imaging exams and pulmonary function test, or those who had chronic lung diseases not associated with rheumatologic disease were excluded from this study.

Lung ultrasound

The LUS was performed by a rheumatologist specializing in ultrasound at our tertiary center. The Ultrasound equipment available at the Unit is an Esaote MyLab (Brazil, São Paulo), with a 3.5 to 10 MHz frequency linear transducer. LUS is a reliable tool to assess pulmonary fibrosis through the presence of B-lines.[7]. Multiple B-lines with diffuse and non-homogeneous distribution, and thickened, fragmented pleural line and the presence of subpleural cysts and nodules are findings compatible with pulmonary fibrosis. One of the simplified B-line assessment methods covers 14 intercostal spaces (ICS), distributed bilaterally between the second ICS of the parasternal line, fourth ICS of the medioclavicular, anterior axillary and midaxillary lines, and eighth ICS of the paravertebral, subscapular and posterior axillary lines. The proposed semiquantitative score for pulmonary fibrosis was: 0=normal (<5 B-lines), 1= mild pulmonary fibrosis (from 6 to 15 B-lines), 2= moderate pulmonary fibrosis (from 16 to 30 B-lines) and 3 = severe pulmonary fibrosis (>30 B-lines).[8–14]

Disease activity index assessment

JSLE: the clinical activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). JSLE inactive: 0; light activity: 1-5; moderate activity: 6-10; high activity: 11-19; very high activity: 20 or above.[15,16]

JDM: the clinical activity was assessed by the Disease Activity Score and muscle strength by the Childhood Myositis Assessment Scale and Manual Muscle Testing.[17–19] Serum levels of muscle enzymes evaluated, according to the kinetic method, were: aspartate aminotransferase (normal value <32 IU/L), alanine aminotransferase (normal value <33 IU/L), lactate dehydrogenase (normal variation 258-308 IU/L), creatine phosphokinase (<170 IU/L) and aldolase (normal value <7,6 IU/L).

JSSc: disease activity was assessed according to the Juvenile Systemic Sclerosis Severity Score proposed.[20]

JLSc: active disease was defined as the presence of enlarged lesion size, erythematous lesions or new lesions.[21]

MCTD: Disease activity was based on clinically predominant disease activity.[15–20]

Statistical analysis

Results are presented as median (variation) for continuous parameters and numbers (%) for categorical parameters. The Wilcoxon test was used to compare current age, disease duration, and global disease activity index between patients with abnormalities on both imaging tests and the overall study sample. $P < 0.05$ was considered statistically significant.

Results

Out of the 40 pediatric patients with connective tissue diseases, 20 underwent LUS. This group was represented by 8 patients with JSLE, 8 patients with JLSc, 2 patients with MCTD (JSLE and JSSc) and 2 patients with JDM. Fourteen (70%) patients were female. The patients' mean age was 14 years (9-18 years). Descriptive analyses of gender, age and duration of illness by group of rheumatologic conditions are shown in Table 1.

Table 1 Demographic data of patients evaluated by lung ultrasound.

	JSLE	JDM	MCTD	JLSc
N	8	2	2	8
Female gender (%)	75	50	100	75
Age (years)	14 (11-18)	16 (15-17)	17(17)	13.5 (9-16)
Disease duration (years)	3 (2-5)	9 (4-14)	3.5 (3-4)	5 (0-14)

Legends: N, number of patients; JSLE, juvenile systemic lupus erythematosus; JDM, juvenile dermatomyositis; MCTD, mixed connective tissue disease; JLSc, juvenile localized scleroderma

Ten (50%) of the 20 patients showed alterations suggestive of pulmonary fibrosis on the LUS, and were submitted to complementary investigation with chest HRCT and pulmonary function test. Of these, 4 (40%) exhibited chest HRCT with patterns of abnormality in the lung parenchyma (JLSc: 2, MCTD: 1 and JDM: 1), but with spirometry without evidence of a restrictive pattern. Descriptive results by disease group are shown in Table 2.

Table 2 Results of abnormal ultrasound assessment to assess interstitial pulmonary fibrosis in rheumatologic pediatric patients

Age (years)	Gender	Diagnosis	Disease duration (years)	LUS (SQS)	HRCT	Spirometry (restrictive pattern)
14	F	JSLE	5	Mild	Normal	
11	F	JSLE	2	Mild	Normal	X
12	F	JSLE	2	Mild	Normal	
17	F	MCTD	4	Mild	ILO	
17	M	JDM	14	Mild	ILO	
13	F	JLSc	4	Mild	Normal	
15	F	JLSc	5	Moderate	Normal	
17	F	JLSc	14	Mild	PN	

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Table Continued..

Age (years)	Gender	Diagnosis	Disease duration (years)	LUS (SQS)	HRCT	Spirometry (restrictive pattern)
16	F	JLSc	9	Moderate	PN	
12	F	JLSc	3	Moderate	Normal	

Legends: LUS, lung ultrasound; SQS, semi- quantitative score (mild: from 6 to 15 B-lines; moderate: from 16 to 30 B-lines); HRCT, high resolution computed tomography; F, female; JSLE, juvenile systemic

The comparative analysis between the group that presented both altered exams (LUS and HRCT) and the 20 patients underwent LUS shows that the age difference between the two groups is statistically significant, as the patients who presented alterations in both exams were, on average, 3 years older, in relation to the mean age of the 20 patients (p=0.008). In addition, that group with both altered exams had on average, 6.9 years more experience with the rheumatologic disease, in relation to the 20 patients evaluated (p=0.006). However, there was no statistical significance when comparing the global index of disease activity between the two groups (p=0.06). Table 3 summarizes this information.

Table 3 Difference of demographic data between the group that presented both altered exams (LUS and HRCT) and the 20 patients underwent LUS

Demographic data	Abnormal LUS and RCT (N=4)	Total sample (N=20)	P*
Current age (years)	16.75	13.75	0.008
Disease duration (years)	10.25	3.31	0.006
Global disease activity index (median)	0.75	0.81	0.06

Legends**:** N, number of patients; LUS, lung ultrasound; HRCT, high resolution computed tomography of the lung

*Wilcoxon´s test for the difference of medians

Discussion

To our knowledge, this is the first study to discuss the role of LUS in the early detection and monitoring of ILD in pediatric rheumatologic patients. A very relevant fact of this study is that 50% of the patients that presented signs of pulmonary fibrosis on LUS (2 JSLE and 3 JLSc) showed normal chest HRCT and spirometry without evidence of a restrictive pattern, which may suggest that the LUS may be able to detect early changes in the pulmonary interstitium, before the changes already well standardized by HRCT (Interlobular septal thickening, intralobular linear opacities, honeycombing, cystic airspace disease or bronchiectasis, nodules, granulomatous reaction, bronchiolitis, ground-glass opacity pattern, and consolidation).[22] Furthermore, although a patient with JSLE had a normal HRCT, mild pulmonary fibrosis was evidenced on LUS and spirometry revealed a mild restrictive pattern. The presence of positive anti-Sm and anti-ribonucleoprotein (RNP) antibodies in this patient is reported to increase the risk of ILD.[6]. The prevalence of ILD in JSLE is 3%; it usually has an insidious evolution.[6] In adults with systemic lupus erythematosus, the most common abnormality found on chest HRCT is ILD that was detected in 8%-70% of patients. However, the chronicity over time may explain these results. In asymptomatic patients, chest HRCT has been reported showing more signs suggestive of ILD than pulmonary function tests.[23] Studies on pulmonary function tests in pediatric lupus are limited, but a cohort of 60 patients showed that about 20% of patients under 20 years of age, had reduced diffusing capacity of the lungs for carbon monoxide (DLCO).[24] Spirometric evaluation studied in 21 JSLE patients without respiratory complaints demonstrated that when compared to healthy controls, lupus patients showed a significant restrictive pattern and small airway impairment.[25]

ILD rarely occurs in JDM, but it has a poor prognosis, with only 70% 5-year survival rate.[26,27] Although it may be asymptomatic, it clinically presents with chronic and progressive cough and dyspnea. In adults, ILD is dermatomyositis most frequent pulmonary complication, affecting 30 to 50% patients, and anti-Jo-1 antibody positivity has a high predictive value for this serious outcome.[22] In a case-control study with 59 JDM patients, 14% showed signs of ILD on chest HRCT and 26% evidenced a restrictive pattern on the pulmonary function test. It is reported that in these patients, asymptomatic lung disease can be diagnosed early through pulmonary function tests.[5,26,27] Interestingly, a patient with JDM in our study had alterations in lung images (LUS and HRCT) and normal spirometry, being asymptomatic, anti-Jo-1 negative and with a 14 years chronic clinical course, with well-controlled clinical and laboratory activities at the time of the study (Figure 1). This patient was using mycophenolate mofetil and hydroxychloroquine, having already used glucocorticoids, azathioprine, cyclophosphamide and immunoglobulin. The duration of the disease may justify these initial pulmonary findings and indicates the importance of periodic pulmonary LUS screening, saving the patient from periodic radiation with the use of HRCT scans.

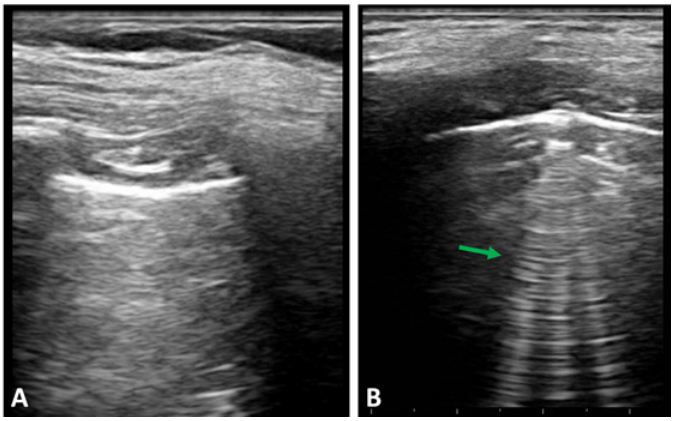

Figure 1 The score lung ultrasound evaluation in dermatomyositis patient with a total of B-lines to equal 8: (A) Left anterior axilar recess, without B-line and (B) Rigth posterior axilar recess, with B-lines (arrow).

Juvenile MCTD is a rare rheumatologic disease in the pediatric age group, representing only 0.1-0.5% of cases. In adults, 75% of patients with MCTD show pulmonary involvement. The pulmonary clinical course is variable, as it depends on the activity of associated diseases; however, pulmonary complications are potentially serious and cause a significant increase in mortality, especially if ILD is associated with pulmonary hypertension. Pulmonary involvement in systemic sclerosis is common in adults, affecting up to 90% of patients, whether due to pulmonary hypertension or ILD. The average survival in a patient who develops ILD is 5 to 8 years. JSSc is the connective tissue disease that most frequently involves the lungs in pediatric patients and usually occurs early in the initial course of the disease, evolving with rapid fibrosis. Lung disease is the most common cause of death in these pediatric patients. In childhood, in addition to the classic clinical

signs and symptoms of ILD, only 10-25% of children present X-ray changes, such as ground-glass opacities and reticular patterns on chest HRCT and pulmonary function tests considered more sensitive in the early detection of asymptomatic ILD, and the results of those tests are predictors of mortality. Pulmonary function tests reveal a restrictive pattern with reduced DLCO. Chest HRCT shows abnormalities in 90% of cases.[5,23,27] Out of our two patients with MCTD (both with JSLE and JSSc) and mean disease duration of 3.5 years, one showed mild pulmonary fibrosis on LUS and chest HRCT, with intralobular linear opacities, especially for more active systemic sclerosis, with capillaroscopy of a sclerodermic pattern, sclerodactyly, esophageal involvement, persistent Raynaud's phenomenon and irregular adherence to the use of all previously prescribed corticosteroid savers, making regular use only of glucocorticoids and hydroxychloroquine until the time of ultrasound evaluation (Figure 2).

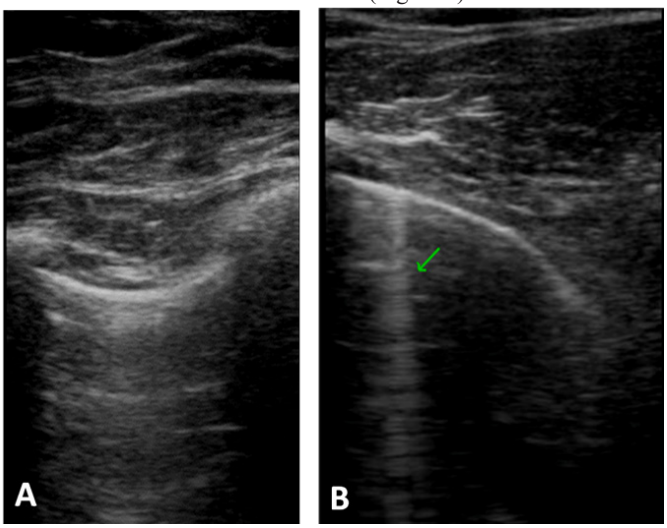

Figure 2 The score lung ultrasound evaluation in mixed connective tissue disease patient with a total of B-lines to equal 7: (A) Left anterior-axilar recess, without B-line; (B) Right paravertebral recess, with B-line (arrow).

Although JLSc is usually considered a disease confined to the skin and subcutaneous cellular tissue, extracutaneous manifestations occurred in almost 25% of children evaluated in a study with 750 pediatric patients. Respiratory involvement was reported in 5 patients. All had moderate dyspnea and/or persistent cough and one presented with pulmonary insufficiency. Pulmonary function tests showed a restrictive pattern in 3 patients and abnormalities in the DLCO in 2 patients. Chest HRCT revealed persistent basal infiltrates in 2 patients.[28] In our study, 5 out of 8 patients with LJSc (5 years mean disease duration) showed alterations on LUS, one patient with mild fibrosis and one with moderate fibrosis had sparse non-calcified nodules in the lung parenchyma on chest HRCT, that is, 40% of patients with abnormal ultrasound had tomographic abnormalities. None of these patients showed a restrictive pattern on spirometry.

LUS has stood out in clinical practice in recent years for its ability to detect and quantify pulmonary changes caused by ILD, and can be used as a screening tool to indicate the appropriate time to perform HRCT.[7,29,30] In addition, LUS can help monitor the progression of lung disease and assess the prognosis.[7] In adults, there are reports of a significant positive correlation between the ultrasound results of ILD and the semiquantitative score developed to assess the extent and severity of pulmonary fibrosis on chest HRCT.[31] Despite being represented by a small sample, 50% of our patients screened by LUS showed alterations suggestive of pulmonary fibrosis, and out of these patients, 40% had alterations in the lung parenchyma on chest HRCT. Due to the small sample evaluated, it was not possible to assess the potential impact of medications on the lung parenchyma, as already discussed in adult patients using methotrexate.[32,33] Although this is a retrospective study and limited on account of the number of patients, we conclude that the LUS is a highly sensitive method and a promising screening tool for early alterations in the lung parenchyma and may help in pulmonary monitoring in pediatric rheumatology clinical practice, saving many patients from periodic examinations with ionizing radiation. Furthermore, it can signal the need for therapeutic adjustments at an early stage, even in asymptomatic patients.

Conclusion

In conclusion, we suggest that LUS be part of the assessment of the clinical activity of pediatric collagenosis and that larger prospective and longitudinal studies be carried out, so that the specificity for interstitial syndrome in children and adolescents be determined, since ILD is rare in this age group and generally with insidious evolution.

Statements and declarations

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Availability of data and material

All data and materials comply with field standards.

Code availability

Software application or custom code support comply with field standards.

Authors' contributions

All authors have participated in the drafting of the manuscript and have read and approved its final version.

Ethics approval

This study was approved by the Human Research Ethics Committee of the Pontifícia Universidade Católica de Campinas (number 5.114.774, November 19th, 2021) and was conducted in accordance with 1964 Helsinki Declarations standards.

Consent to participate

Informed consent was obtained from all the children's parents and from all participants older than 12 years.

Consent for publication

Not applicable

Acknowledgments

None.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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