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Lymphocytic interstitial pneumonia and follicular bronchiolitis in children: A registry-based case series

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Abstract

Objectives: Pediatric lymphocytic interstitial pneumonia (LIP) and follicular bronchiolitis (FB) are poorly characterized lymphoproliferative disorders. We present and quantify demographics, radiological and histopathologic patterns, treatments and their responses, and outcomes in non-HIV-infected children with LIP and FB.

Methods: This structured registry-based study included a retrospective chart review, blinded analysis of imaging studies and lung biopsies, genetic testing, and evaluation of treatments and outcomes.

Results: Of the 13 patients (eight females) studied, eight had FB, four had combined LIP/FB, and one had isolated LIP; diagnoses were highly concordant between the pathologists. Most patients became symptomatic during the first 2 years of life, with a mean lag time to diagnosis of 4 years. The most common symptoms were coughing and respiratory infections (11 out of 13 each), dyspnea (10 out of 13), and wheezing (eight out of 13). Autoantibodies were found in eight out of 13 patients. In three patients, disease-causing mutations in the *COPA* gene were identified. CT revealed hilar lymphadenopathy (five out of 12), ground-glass opacity (eight out of 12), consolidation (five out of 12), and cysts (four out of 13). Systemic steroids as intravenous pulses (11 out of 13) or oral intake (10 out of 13) were the main treatments and showed high response rates of 100% and 90%, respectively. Within the mean observation period of 68 months, all children had chronic courses, eight out of 13 had severe diseases, two died, and one worsened.

Conclusions: Children with LIP/FB have chronic diseases that occurred in early childhood and were commonly associated with immune dysregulation as well as high

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morbidity and mortality. Early diagnosis and treatment may be crucial to improve the outcome.

KEYWORDS
COPA syndrome, immune dysregulatory disease, interstitial lung disease in children, rare pediatric lung disease

1 | INTRODUCTION

Lymphocytic interstitial pneumonia (LIP) and follicular bronchiolitis (FB) are overlapping benign lymphoproliferative disorders of the lung. Both disease forms are characterized by the presence of inflammatory hyperplasia of the bronchus-associated lymphoid tissue. However, the degree of lymphocytic infiltration varies, and the histopathological patterns of LIP and FB may coexist.[1,2] LIP and FB are assumed to be pathological immunologic responses to different triggers and are particularly associated with autoimmune and infectious diseases as well as immunodeficiency.[3,4] According to the classification scheme of Deutsch et al[5] and further differentiated by Griese et al[6] LIP and FB are categorized as DPLD (diffuse parenchymal lung disease)-related to reactive lymphoid lesions. Respiratory tract infections, cough, and dyspnea are presenting symptoms that do not allow differentiation from other interstitial lung diseases.[7,8] In children with AIDS, LIP is a common complication.[9] However, in children without HIV infection, LIP and FB are rare and poorly characterized conditions. Evidence is derived mainly from case reports and small case series, but these often lack structured analysis. Systematic evaluations are needed to improve timely diagnosis and treatment. We describe pediatric patients with LIP and FB by presenting and quantifying demographics, radiological and histopathologic patterns, treatments and their responses, and overall outcomes.

2 | METHODS

This study was a retrospective registry-based long-term analysis of a case series of children with FB and LIP.

2.1 | Patient selection

The Kids Lung Registry (KLR) is an international registry and management platform for children with diffuse lung diseases (www.childeu.net) including a peer review process for diagnosis.[6] We searched the database using the terms "lymphocytic pneumonia" and "follicular bronchiolitis." All children with histologically confirmed LIP or FB (n = 15) reported to the KLR between 1997 and 2016 were initially included in this study. All included children were treated in university hospitals or tertiary care centers and reported by these institutions to the KLR.

Charts were manually searched for demographic data, clinical findings (including symptoms, laboratory values, results of bronchoalveolar lavage [BAL] and associated diseases), and treatments and outcomes. The local specialist in each center assessed treatment response and the disease course as an overall clinical impression, taking into account all existing symptoms. We categorized the patients' long-term course as asymptomatic, symptomatic but improved, symptomatic and stable, symptomatic and worse, and deceased.

2.2 | DNA extraction and exome sequencing

We extracted genomic DNA from whole blood of 11 patients and, if available, from their respective parents. In two cases, DNA was not available. We isolated DNA from ethylenediaminetetraacetic acid (EDTA) blood using the QIAmp DNA Mini Kit (QIAGEN) according to the manufacturer's protocol. Exome sequencing was performed as previously described.[10] Variants in all known disease-causing genes were searched, considering the different patterns of inheritance.

2.3 | Histopathology

Two pathologists, specialized in children's interstitial lung disease, independently reassessed the blinded lung biopsies of all patients in a structured manner. LIP was defined by the presence of a dense, predominantly lymphocytic interstitial infiltrate that expands alveolar septa. In contrast, FB was diagnosed by a pattern of numerous lymphoid follicles associated with bronchioles and the immediate peribronchiolar interstitium.

We used a grading system, previously developed for tissue samples from patients with Sjögren's syndrome, to assess the presence and extent of LIP and FB.[11] Lymphocyte aggregates were defined as the aggregation of 50 or more lymphocytes per high-power field. Tissue was scored as grade 0 in the absence of lymphocyte aggregates, grade 1 with 0 to 1 aggregate/10 mm^2, grade 2 with greater than 1 aggregate/10 mm^2, grade 3 with greater than 1 aggregate/10 mm^2 and the presence of focal lymphoid interstitial pneumonia, and grade 4 with greater than 1 aggregate/10 mm^2 and the presence of diffuse LIP. Interrater agreement was calculated using the concordance correlation coefficient proposed by Lin et al[12] with the use of the R statistical package, version 3.4.3. In the Landis and Koch[13] classification of the strength of agreement, a coefficient of 0.61 to 0.80 reflects substantial and 0.80 to 1.0 indicates perfect agreement.

2.4 | Radiology

A pediatric radiologist, specialized in chest imaging, analyzed the blinded thoracic computed tomography (CT) scans in a structured manner. One scan could not be evaluated due to poor quality. The analysis included separate examinations of pleura, mediastinum, parenchyma, and airways based on the recommendations of the Fleischner Society.[14]

2.5 | Ethics statement

All parents or guardians of the children and all patients aged 8 years or older gave their informed consent to participate in the study. The study was approved by the Ethical Review Committee of the Ludwig-Maximilians University Munich, Germany (EK 111-13).

3 | RESULTS

All 15 patients (nine females) retrieved from the database were initially included in the analysis. According to the database, the children were diagnosed with isolated LIP in four, combined LIP/FB in five, and FB in six cases (Figure 1). Two patients were excluded from further evaluation after histopathologic re-evaluation of all lung biopsies. In one case, the tissue sample could not be assessed due to poor quality. In the other case, both pathologists diagnosed a nonspecific interstitial pneumonia pattern rather than LIP or FB. All six FB cases were confirmed. In one case, the original LIP diagnosis was changed to FB after re-evaluation. Combined LIP/FB was confirmed in three cases. In one case, the diagnosis was changed to LIP and in another to isolated FB. Of the 13 patients (eight females) eventually included, eight children had FB, four combined LIP/FB, and one isolated LIP (Figure 1). The mean observation period was 68 months; it ranged from 3 months to 14.8 years (median 42 months).

3.1 | Lag time to diagnosis and clinical findings

While the onset of chronic symptoms occurred on average at 2 years of age for LIP and at 4 months of age for FB, the mean age at diagnosis was noticeably higher (6.9 years for LIP and 5 years for FB; Table 1). The mean lag time between symptom onset and diagnosis was 4 years (range from 9 months to 12 years).

The most frequent symptoms were chronic cough (defined as >3 months) and recurrent respiratory infections in 11 out of 13 (85%) patients each. The majority of the patients presented with dyspnea (10 out of 13 [77%]), wheezing, failure to thrive, and retractions (69% each), tachypnea (62%), and crackles (54%). We found the following signs of advanced-stage disease at diagnosis: hypoxemia at rest in seven out of 13 (54%), clubbing in four out of 13 (31%), and pulmonary hypertension (mean pulmonary artery pressure defined as >25 mm Hg) in three out of 13 (23%; Table 1).

3.2 | Genetics, comorbidities, and laboratory findings

We found missense mutations in the coatomer-associated protein subunit alpha (*COPA*) gene on chromosome 1q23.2 in three patients (including one familial case):

1. Mutation 160283781G>A, c.841C>T, p.Arg281Trp. Boy with FB, 9-year old at diagnosis; delayed puberty, gynecomastia, and disruptive behavior disorder; anti-nuclear (ANA) and anti-neutrophil cytoplasmic antibodies (ANCA) positive. His mother carried the same mutation.
2. Mutation 160283903C>G, c.719G>C, p.Trp240Ser. Girl with LIP/FB, 14-year old; juvenile rheumatoid arthritis with positive ANA, ANCA, rheumatoid factor, anticardiolipin (ACA), and myeloperoxidase antineutrophil cytoplasmic antibodies (MPO-ANCA).
3. Mutation 160283903C>A, c.719G>T, p.Trp240Leu. Girl with LIP/FB, 2-year old; pectus excavatum and positive ANA titer.

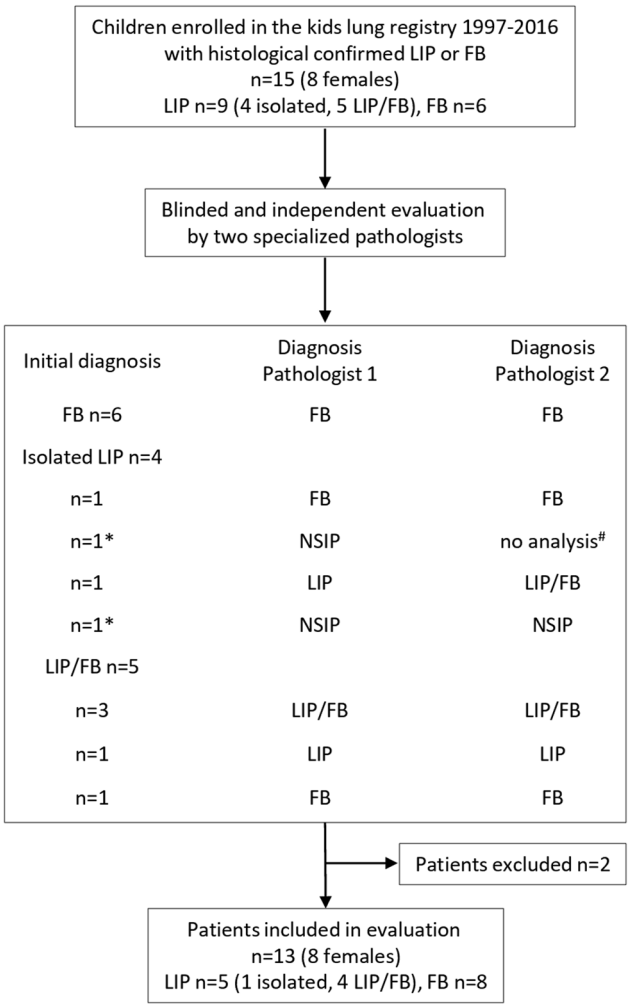

FIGURE 1 Study cohort. Subjects included were reported to the Kids Lung Registry between 1 Jan 1997 and 31 Dec 2016. Diagnosis before and after blinded re-evaluation by two specialized pathologists is shown. FB, follicular bronchiolitis; LIP, lymphocytic interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; *patients were excluded from further evaluation; #specimen quality was considered insufficient

TABLE 1 Demographics and clinical findings of patients with lymphocytic interstitial pneumonia or follicular bronchiolitis

	Patients, n (%)	
Patient demographics		
Sex (M/F)	5/8	
Mean/median age at onset (range), y	2.0/.04	(0.1-13)
Mean/median age at diagnosis (range), y	6.9/5.0	(1.2-17.3)
Mean/median lag time at onset to diagnosis (range), y	4.0/5.0	(0.9-12.0)
Symptoms and findings at diagnosis		
Cough	11 (85)	
Respiratory infections	11 (85)	
Dyspnea	10 (77)	
Wheezing	9 (69)	
Failure to thrive	9 (69)	
Retractions	9 (69)	
Tachypnea	8 (62)	
Hypoxemia, cyanosis	7 (54)	
Crackles	7 (54)	
Clubbing	4 (31)	
Fever	4 (31)	
Pulmonary hypertension	3 (23)	
Organomegaly (in total)	2 (15)	
Hepatomegaly	1 (8)	
Renomegaly	1 (8)	
Associated diseases		
Dermatitis/eczema	8 (62)	
Viral infections (in total)	4 (31)	
Rhino	2 (15)	
CMV	1 (8)	
Boca	1 (8)	
Autoimmune diseases (in total)	2 (15)	
Juvenile rheumatoid arthritis	1 (8)	
Celiac disease	1 (8)	
Immunodeficiency/dysregulation	1 (8)	
Familial	1 (8)	
Gastroesophageal reflux	1 (8)	
Laboratory tests		
BAL inflammatory markers (in total)	11 (85)	
Neutrophils	8 (62)	
Lymphocytes	6 (46)	
Eosinophils	5 (38)	
Autoantibodies (in total)	8 (62)	
ANA	8 (62)	
ANCA	3 (23)	
Other	1 (8)	
Blood inflammatory markers (ESR, CRP, leukocytosis)	3 (23)	
Surfactant disorders	0 (0)	

Note: Symptoms were recorded at diagnosis. Diseases were labeled as associated when they were pre-existing or coincided with disease onset. Precipitins to aspergillus and to bird antigens were available in 10 out of 13 children and were negative in all cases.

Abbreviations: ANA, anti-nuclear antibodies, ANCA, anti-neutrophil cytoplasmic antibodies; BAL, bronchoalveolar lavage; CMV, cytomegalovirus; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate

TABLE 2 Outcome of children with lymphocytic interstitial pneumonia or follicular bronchiolitis

Outcome	Patients, n (%)
Chronic course	13 (100)
Asymptomatic	0 (0)
Symptomatic, improved	3 (23)
Symptomatic, stable	7 (54)
Symptomatic, worse	1 (8)
Deceased[a]	2 (15)

Note: Assessment of the local specialist as clinical overall impression.
[a]One patient died 6 years after lung transplantation.

We did not find mutations in the cytotoxic T-lymphocyte antigen 4 (*CTLA4*), lipopolysaccharide-responsive and beige-like anchor protein (*LRBA*), signal transducer and activator of transcription 3 (*STAT3*), or transmembrane protein 173 (*TMEM173*) genes.

Associated diseases, defined as pre-existing or coinciding with disease onset, are listed in Table 1. Frequent laboratory findings were positive autoantibodies in eight out of 13 (62%) children and inflammation in the BAL in 11 out of 13 (85%).

3.3 | Course

All patients had a chronic disease course. No patient became asymptomatic, three out of 13 were symptomatic but improved, seven out of 13 were symptomatic and stable, one out of 13 was symptomatic and worse, and two patients died, one of whom was 6 years after she underwent lung transplantation (Table 2).

Eight children had a severe course, defined by the presence of at least one of the following criteria: death, lung transplantation, hypoxemia, and pulmonary hypertension. Neither presence of one of the LIP or FB histological patterns nor the extent of

TABLE 3 Chest CT (computed tomography) findings in children with lymphocytic interstitial pneumonia or follicular bronchiolitis

Compartment	Abnormality	Patients, n (%)
Mediastinum	Heart enlarged	1 (8)
	Enlarged med. lymph nodes	3 (25)
	Enlarged hilar lymph nodes	5 (42)
Parenchyma	Ground-glass opacity (in total)	9 (75)
	Diffuse	6 (50)
	Patchy	5 (42)
	Consolidation	5 (42)
	Cysts	4 (33)
	Mosaic attenuation	3 (25)
	Emphysema	2 (17)
	Reticular opacity	2 (17)
	Nodular opacity	2 (17)
	Hyperinflated secondary lobule	1 (8)
	Septal thickening	1 (8)
Respiratory tract	Traction bronchiectasis/ architectural distortion	3 (25)
	Bronchial wall thickening	2 (17)
	Tree-in-bud	1 (8)

Note: Enlargement of mediastinal lymph nodes was defined as greater than 7 mm in children up to 10 years of age and greater than 10 mm for children older than 10 years of age.

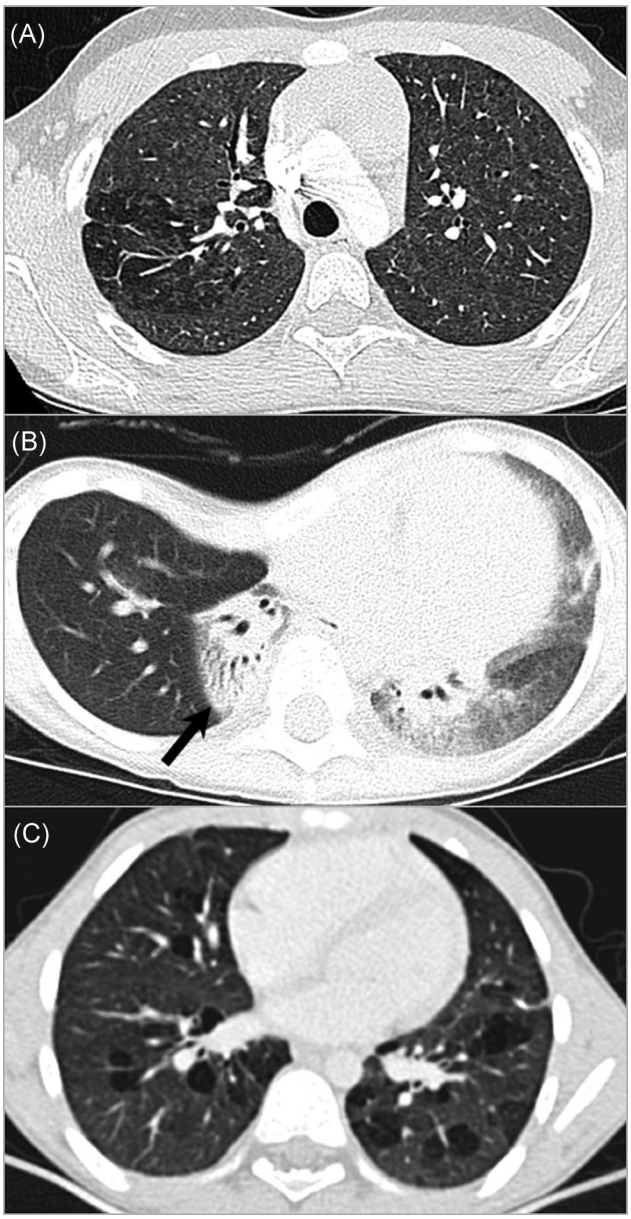

FIGURE 2 Common CT (computed tomography) findings in lymphocytic interstitial pneumonia (LIP) and follicular bronchiolitis (FB). All images were reconstructed in lung kernel with lung window settings (Width/Level 1500/−600 Hounsfield Units). A, Ground-glass opacity (GGO) in a 12-year old girl with LIP; 1.25-mm slice thickness. B, 4-year old girl with LIP/FB. Volume loss, consolidation, and traction bronchiectasis of the right lower lobe (arrow) as well as GGO on the left side are visible. Pectus excavatum; 5-mm slice thickness. C, Multiple thin-walled cysts in both lungs in an 8-year boy with FB; 2-mm slice thickness

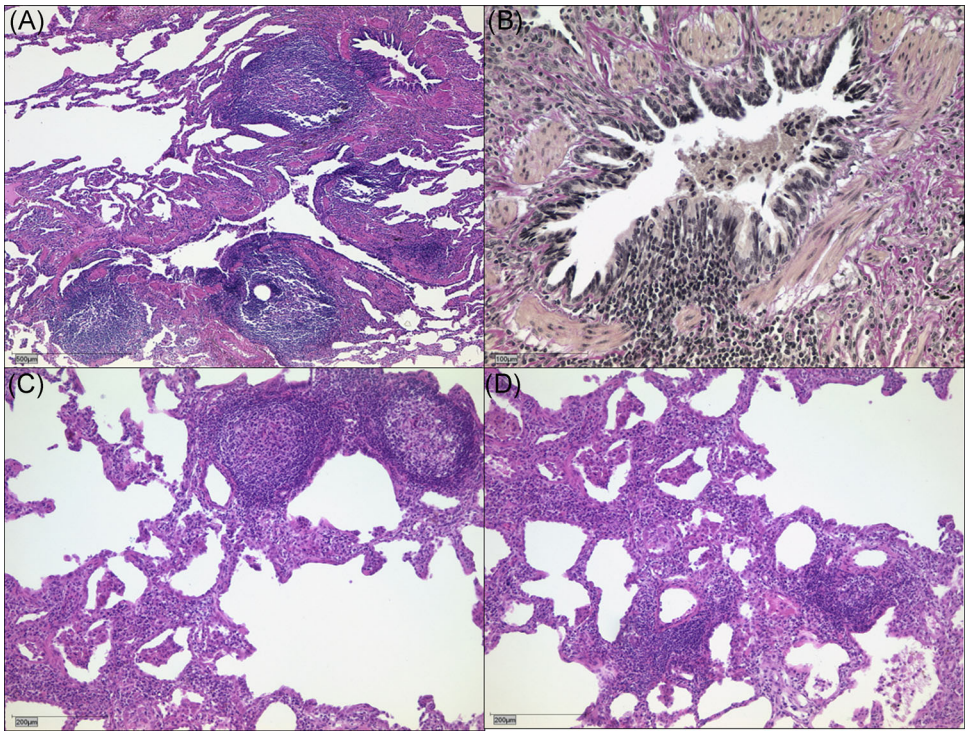

FIGURE 3 Histopathology of lymphocytic interstitial pneumonia (LIP) and follicular bronchiolitis (FB). A, FB with peribronchiolar lymphoid follicles and aggregates (hematoxylin & eosin [H&E] stain). FB with intraepithelial and bronchiolar wall infiltration as well as intraluminal exudate (Verhoeff van Gieson stain). C,D, Combined LIP and FB with peribronchiolar lymphoid follicles plus lymphocytic infiltrate expanding the alveolar septa (H&E stain) [Color figure can be viewed at wileyonlinelibrary.com]

infiltration was positively associated with the occurrence of severity criteria.

3.4 | Chest CT

The most common chest CT findings were ground-glass opacities: nine out of 12 (75%), consolidations five out of 12 (42%), cysts four out of 12 (33%), mosaic attenuation three out of 12 (25%), and traction bronchiectasis/architectural distortion three of 12 (25%; Table 3 and Figure 2). Hilar and mediastinal lymphadenopathy was present in five out of 12 (42%) and three out of 12 (25%) patients.

3.5 | Histopathology

Typical histopathological features are shown in Figure 3. According to the applied infiltration grading system, two to three patients were scored grade 1, five were scored grade 2, two were scored grade 3, and three to four patients were scored grade 4. The density of the lymphocytic infiltration is shown in Table 4. The pathologists agreed in all but one LIP case regarding whether there was additional FB. Concordance correlation coefficients were 1 (confidence interval [CI], 1-1) for LIP and 0.63 (CI, 0.20-0.85) for FB. Overall, the agreement of the infiltration density was very good for most samples. However, there were significant variances in three cases. The concordance correlation coefficient was 0.69 (CI, 0.34-0.87).

3.6 | Therapy

To assess response to treatment, local specialists used criteria similar to those reported by Bush et al.[15] They also included exercise

TABLE 4 Histopathological grading and extent of lymphocytic infiltration

Grade	Patients (n/n)		Extent of lymphocytic infiltration: lymphocytic aggregates/10 mm^2, mean (range)	
Pathologist	1	2	1	2
1	3	2	0.74 (0.38-0.94)	0.64 (0.27-1.0)
2	5	5	5.29 (1.23-11.88)	3.49 (1.48-6.0)
3	2	2	7.69 (6.4-8.97)	5.15 (1.96-8.33)
4	3	4	4.75 (2.31-7.24)	4.95 (2-6.67)

Note: Tissue was scored as grade 0 in the absence of lymphocyte aggregates; grade 1 with 0 to 1 aggregate/10 mm^2; grade 2 with greater than 1 aggregate/10 mm^2; grade 3 with greater than 1 aggregate/10 mm^2 and the presence of focal lymphocytic interstitial pneumonia (LIP); and grade 4 with greater than 1 aggregate/10 mm^2 and the presence of diffuse LIP.

TABLE 5 Drugs used for pediatric lymphocytic infiltration/follicular bronchiolitis, number of patients treated, total treatment time, and observed benefit

Drug	Route of administration	Patients treated, n (%)	Mean total treatment period, mo (range)	Benefit observed, n (%)
Steroid pulse	IV	11 (85)	15 (5-39)	11 (100)
Steroid	Oral	10 (77)	16 (1-36)	9 (90)
Steroid	Inhaled	5 (38)	65 (9-117)	5 (100)
Bronchodilator	Inhaled	5 (38)	43 (10-87)	4 (80)
Azithromycin	Oral	4 (31)	27 (11-64)	2 (50)
Azathioprine	Oral	4 (31)	26 (1-69)	2 (50)
Hydroxychloroquine/chloroquine	Oral	4 (31)	10 (7-13)	1 (25)
Methotrexate	SC	3 (23)	10 (3-20)	1 (33)
Theophylline	Oral	3 (23)	30 (2-68)	3 (100)
Immunoglobulin	IV; SC	2 (15)	6 (1-10)	1 (50)
Cyclosporine	Oral	2 (15)	39 (27-50)	2 (100)
Mycophenolate	Oral	2 (15)	27 (6-48)	1 (50)
Montelukast	Oral	2 (15)	81 (48-113)	1 (50)

Abbreviations: IV, intravenous; SC, subcutaneous.

capacity and general condition in the evaluation. However, parameters were not consistently quantified in the charts. The most frequently used therapy were steroid pulses in 11 patients (85%). Steroid pulses were defined as 10 to 30 mg/kg body weight of methylprednisolone administered intravenously on three consecutive days. A benefit was documented in all cases (Table 5). Oral steroids were used in 10 patients (77%), with a benefit noted in 90%. The third most common substances (38% each) were inhaled steroids (100% benefit) and inhaled bronchodilators (80% benefit). Azathioprine, azithromycin (benefit in 50% each), and chloroquine/hydroxychloroquine (benefit in 25%) were each used in four out of 13 of the patients. Several other utilized drugs are listed in Table 5. Due to the small sample size, a potential benefit could not be assessed. Adverse events were not systematically recorded in this study. We have no evidence from the records for drug-associated severe adverse events.

4 | DISCUSSION

This study, with a duration of almost 20 years, represents the largest pediatric LIP and FB case series to date and provides a comprehensive picture of the disorders. The children had chronic diseases with onset in early childhood that was commonly associated with immune dysregulation as well as high morbidity and mortality.

Etiologically, LIP and FB may be the result of immune dysregulation syndromes due to mutations in the genes *CTLA4*, *LRBA*, *STAT3*, *TMEM173*, and *COPA*.[16-22] We only detected *COPA* mutations in three children, all of whom had positive autoantibodies and one with arthritis.[20,21] However, five other children had autoantibodies and one patient had celiac disease, data that suggest other not-yet-defined underlying immune dysregulation conditions. While there have been no other significant changes in the diagnostic algorithm since the beginning of the study, new insights on genetic disorders should be included in the workup.

In this cohort, we observed a mean 4-year lag time between symptom onset and diagnosis. However, early diagnosis should always be sought to maintain all treatment options.[23,24] Disease rarity as well as nonspecific and diverse symptoms are diagnostic challenges and may be responsible for a delay in the diagnosis.[7,8,24-27] Symptoms of children's interstitial lung disease (chILD) are generally not specific and most entities have a similar pattern of findings.[28] However, we observed wheezing more frequently in our cohort than previously described.[24] This is a common symptom in early childhood, but may be the result of airway compression by a peribronchiolar lymphocytic infiltrate in FB and LIP.[1] All children in our cohort had persistent symptoms and at least three of the four criteria defining a chILD syndrome.[23] Therefore, children with persistent respiratory symptoms should undergo chest imaging, especially when red flags such as hypoxemia (more than 50% in our cohort) or signs of advanced-stage disease such as clubbing (31%) occur.

As a result of airway stenosis and air trapping, cysts may be found in the chest CT in LIP patients; this phenomenon can also occur in COPA syndrome.[4,22,29] The same mechanism, however, could explain why in our cohort FB-positive children predominantly had cysts. As the cysts developed in two children during the study, repeated CT should be considered in the follow-up.

In our study, half of the patients had hypoxemia and one-third had clubbing. These signs of advanced-stage disease are rarely described in adult patients, and thus their presence suggests a more

severe course in children[3,4] Besides, eight children had at least one of the severity criteria (death, lung transplantation, hypoxemia, and pulmonary hypertension). Consolidation in the chest CT, which was a frequent finding in our cohort, may also indicate a severe course as it can reflect intense infiltration or atelectasis.[7,30-32]

All patients in our cohort had a chronic course, two children with FB died, and one with combined LIP/FB worsened within the mean observation period of 68 months. Data about the long-term course of LIP/FB are very limited. In adults, the prognosis for patients with FB is described as relatively good.[33] The LIP course is more variable, with the majority of patients surviving for many years.[3,34] Case series of pediatric FB also showed predominantly favorable outcomes, with patients who are asymptomatic years after diagnosis.[7,35] Another previous series of pediatric LIP and FB reported ongoing disease in the majority of the patients at follow-up between 1 to 16 years.[8] In a longitudinal study about interstitial lung disease, none of the six children with LIP died over the follow-up period of 2 to 11 years.[26] In comparison, our data showed a significantly less favorable outcome, especially for FB.

The diagnosis of LIP and FB can be made with the routine stainings showing the lymphocytic infiltration. In this small cohort, we were unable to identify a relationship between the lymphocytic infiltration density and disease severity. However, the histopathological grading system may help to differentiate the disorders in cases with overlapping disease patterns, which can occur in up to 20% of patients.[1,4]

Systemic corticosteroids were the preferred therapy in our cohort, and the recipients showed high response rates. There are hitherto no randomized controlled trials for any treatment. Our observations support the empirical efficacy of systemic steroids and are in accordance with the suggested procedure of a recent Delphi consensus for children.[3,15,34] A subgroup of our cohort received inhaled steroids, and this treatment was assessed as beneficial in all cases. A benefit from inhaled steroids was also described in individual case reports.[36,37] Likewise, four out of five children benefitted from bronchodilator treatment, as previously reported in a few cases.[35] A subgroup received hydroxychloroquine and azithromycin; there was a positive response in some cases. Both drugs are listed in the chILD Delphi consensus.[15] In a recent literature review, Braun et al[38] identified 35 papers that reported a positive response to hydroxychloroquine in pediatric interstitial lung disease. The benefit was particularly high in LIP and some other diseases. Azithromycin was successfully used in individual cases in children and adults.[7,33]

The results of this study were limited by the sample size. The assessment of the clinical response to a drug was made by specialists in different centers and was not controlled for other medication changes in all cases. This design limits the significance of a documented benefit. Other limiting factors include the retrospective design and incomplete information on environmental exposures and infections.

In summary, children with LIP/FB had chronic and preponderantly severe diseases that occurred in early childhood and were associated with a high mortality rate. LIP/FB must be considered as a differential diagnosis in pediatric chronic lung disease, such as recurrent wheezing, and chest imaging should be considered early. The diseases were commonly associated with immune dysregulation, and in a subgroup, COPA syndrome was the underlying disease. Systemic steroids were the most common treatment, and there were high response rates. Due to the rarity of the condition, international cooperation will be helpful to build decent cohorts for future research to improve the clinical care of patients with LIP/FB.

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