

## Early View

Original article

# Spectrum of childhood interstitial and diffuse lung diseases at a tertiary hospital in Egypt

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## **Spectrum of childhood interstitial and diffuse lung diseases at a tertiary hospital in Egypt**

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## **ABSTRACT**

**Background:** Childhood interstitial and diffuse lung diseases (chILD) encompass a broad spectrum of rare pulmonary disorders. In most developing middle eastern countries, chILD is still underdiagnosed. Objective: To describe and investigate patients diagnosed with chILD in a tertiary university hospital in Egypt.

**Methods:** We analyzed data of consecutive subjects (<18 years) referred for further evaluation at the Children's Hospital, Ain Shams University. Diagnosis of chILD was made in accordance with the chILD-EU criteria. The following information was obtained: demographic data, clinical characteristics, chest CT findings, laboratory studies, spirometry, BAL and histopathology findings.

**Results:** 22 subjects were enrolled over 24 months. Median age at diagnosis was 7 years (range 3.5-14 years). The most common manifestations were dyspnea (100%), cough (90.9%), clubbing (95.5%) and tachypnea (90.9%). Systematic evaluation led to the following diagnoses: hypersensitivity pneumonitis (n=3), idiopathic interstitial pneumonias (n=4), chILD related to chronic granulomatous disease (n=3), chILD related to small airway disease (n=3), postinfectious chILD (n=2), Langerhans cell histiocytosis (n=2), Idiopathic pulmonary hemosiderosis (n=2), granulomatous lymphocytic interstitial lung disease (n=1), systemic

sclerosis (n=1), familial interstitial lung disease (n=1). Among the subjects who completed the diagnostic evaluation (n=19), treatment was changed in 13 (68.4%) subjects.

**Conclusion:** Systematic evaluation and multidisciplinary peer review of chILD patients at our tertiary hospital led to changes in management in 68% of the patients. This study also highlights the need for an Egyptian chILD network with genetic testing, as well as the value of collaborating with international groups in improving health care for children with chILD.

**Keywords:** Childhood Interstitial Lung Disease, Childhood Diffuse Parenchymal Lung Disease (DPLD), Chronic granulomatous disease, Hypersensitivity pneumonitis in children, Granulomatous lymphocytic interstitial lung disease (GLILD) in children, bronchiolocentric pattern of interstitial pneumonia

## INTRODUCTION

Childhood interstitial and diffuse lung disease (chILD) is a term that describes a rare heterogeneous group of diffuse parenchymal lung diseases associated with considerable morbidity and mortality [1]. ChILD typically presents with tachypnea, hypoxemia, retractions, crackles, and failure to thrive [2]. The causes of chILD are numerous, they include toxic exposures, immune deficiency, systemic diseases, infections and genetic causes. In several cases the exact aetiology remains unknown [3]. Diagnostic testing to determine the exact chILD cause has many merits, such as avoiding unnecessary empiric treatment, initiating disease specific treatment and guide discussions with families regarding disease prognosis and duration of therapy. A systematic approach is recommended to identify the specific chILD diagnosis, starting with the clinical assessment, echocardiography and blood tests. Lung function testing may also be helpful [2]. Chest CT is considered the standard modality for radiologic

investigation as it confirms the diagnosis of chILD, identifies the disease extent, and may allow diagnosis without biopsy [4]. Genetic testing is also helpful in making the diagnosis and evaluating the recurrence risk for affected families [5]. If the diagnosis can't be made at this point, then invasive tests are required. Bronchoalveolar lavage (BAL) may be helpful in diagnosis of certain conditions such as pulmonary hemorrhage syndromes, Langerhans cell histiocytosis (LCH), pulmonary alveolar proteinosis, aspiration syndromes, and most importantly exclusion of infections [6]. Histopathological assessment of lung biopsies is also an important diagnostic tool when other investigations have not identified the precise chILD diagnosis [2]. At our hospital, we face many obstacles regarding the diagnosis of chILD cases, most importantly is the lack of a structured multidisciplinary approach. Before this study, the diagnostic evaluation for chILD wasn't unified in all cases and lung biopsies were not performed due to lack of facilities and expertise to interpret the results. The purpose of this study was therefore to reach the specific chILD entity by application of a systematic diagnostic evaluation for chILD cases referred at our hospital.

## **METHODS**

We performed an observational study of children diagnosed with chILD at the Paediatric Pulmonology Section, Children's Hospital, Ain Shams University, Cairo, Egypt over a 2-year period (2018-2020). At the time of enrolment, all patients were subject to a standardize diagnostic evaluation, aiming to reach a specific chILD diagnosis. Baseline data were collected just prior to the diagnostic evaluation. On presentation to our hospital, a fully informed parental consent was obtained prior to study inclusion. The study was approved by the Ethics Committee of Ain Shams University.

Inclusion criteria: clinical diagnosis of chILD syndrome i.e., satisfied the 2015 European taskforce chILD's definition [2]. All enrolled subjects had at least three of the following four criteria: (a) respiratory symptoms (e.g., cough, dyspnea, or exercise intolerance) (b) respiratory signs (e.g., resting tachypnea, retractions, respiratory failure, clubbing or failure to thrive); (c) hypoxemia (oxygen saturation <90%); and (d) diffuse radiological abnormalities. Patients with common causes of diffuse lung disease (i.e., cystic fibrosis, primary ciliary dyskinesia and congenital heart disease) were excluded from the study.

Data collected at baseline included patient demographics, family and neonatal history, initial and current history and symptoms, as well as the physical examination findings. Guided by history and physical examination, we sequentially chose the tests indicated, starting with non-invasive tests (NIT), such as blood tests, echocardiography, chest CT scan and lung function tests. Fan severity score [7] was recorded for each subject on presentation as follows: (1) Asymptomatic; (2) Symptomatic, normal oxygen saturation under all conditions; (3) Symptomatic, normal resting room air saturation, but hypoxemia <90% with exercise or sleep; (4) Symptomatic, hypoxemia <90% at rest; (5) Symptomatic, hypoxemia at rest and pulmonary hypertension. Blood tests were guided by the clinical assessment and they included complete blood picture, selected immune studies, hypersensitivity pneumonitis precipitins panel and viral serology (*for Epstein-Barr virus, cytomegalovirus and human immunodeficiency virus*). Genetic testing for chILD is not available in Egypt, and thus, it was not performed as a part of this study. Plain chest X-ray and CT scan were performed for all enrolled subjects (volumetric scan during inspiration, with a high resolution fine-cut spaced expiratory scan-HRCT). The images were interpreted by a consultant radiologist specialized in thoracic imaging (**A.M.O.**). If a specific diagnosis could not be established at this point, we then proceeded for invasive testing.

Bronchoalveolar lavage (BAL) was not performed as a routine procedure, it was indicated to investigate infectious agents or if diffuse alveolar hemorrhage was suspected, thereby potentially avoiding biopsy. Lung biopsy (Bx) was performed when a specific diagnosis could not be achieved through the methods described above. The lung Bx procedure was performed according to the chILD European protocols [2], via the open surgical technique. The obtained tissue was divided as follows: 20% was sent as a fresh tissue for microbial cultures (bacterial, mycobacterial, viral and fungal), and 80% was fixated by formalin to form wax blocks. Hematoxylin & Eosin stain (H&E) was routinely performed for all lung biopsy specimens, and further special stains were ordered as required. Electron microscopy studies for lung biopsy specimens were not done as they are not available in our hospital. As no chILD clinical or research network previously existed in Egypt, we chose to refer histological specimens for a second opinion overseas, which is a common practice among global chILD networks. Lung biopsy samples were reviewed independently by two consultant thoracic pathologists (**F.A.G.**) and (**A.G.N.**) and classified according to the global chILD schemes for paediatric interstitial and diffuse lung disease [1,2,6,8,9]. Cases with multiple or overlapping patterns were classified according to the dominant one, and any minor patterns were recorded. Further specific investigations were ordered for selected subjects guided by the histopathology results. Each individual case was subject to a multidisciplinary peer review to standardize diagnostic precision. Treatment plans were adjusted according to the corresponding final chILD diagnosis.

*Statistical Analysis:* Quantitative non parametric data were presented as median and inter-quartile range (IQR). Qualitative variables were presented as number and percentages. Height, weight and body mass index were converted to Centre for Disease Control Z-scores and percentiles.

## RESULTS

Over the study period, 22 patients were identified. The median age of symptom onset was 3.75 years (range: 0-11), while the median age at referral for diagnostic evaluation at our hospital was 7 years (range 3.5-14). Although 8 (36.4 %) subjects their symptoms started during the first 2 years of life, yet, specialist referral was delayed.

Dyspnea (100%, 22/22), cough (90.9%, 20/22) and recurrent pneumonias (77.3%, 17/22) were the most frequent symptoms in all studied patients. All enrolled subjects reported dyspnea on exertion, while 20 (90.9%) subjects reported dyspnea at rest as well. Cough was also a troublesome symptom. All 20 subjects who gave history of cough reported that their cough was dry, however, 8 of them reported frequent episodes of productive cough as well. In addition, 10 (45.5%) subjects had history of recurrent febrile episodes, refractory to routine antibiotic therapy. Furthermore, 7 (31.8 %) patients were falsely diagnosed with childhood asthma by primary care physicians and they were later on referred due to poor response to treatment. Other symptoms included anorexia, attacks of cyanosis, weight loss, haemoptysis and systemic manifestations. Digital clubbing (95.5%, 21/22), tachypnea (90.9%, 20/22), tachycardia (68.2%, 15/22) and failure to thrive (54.5%, 12/22) were the most commonly observed signs. Abnormal auscultatory findings included inspiratory fine crackles (90.9%, 20/22), wheeze (68.2%, 15/22), loud S2 (36.4%, 8/22). Also, chest deformities were noticed in 3 (13.6%) subjects. Median weight Z score, height Z score and BMI Z score among studied subjects were low (-2.17, -1.42 and -1.36 respectively). In addition, Lower weight and height Z-scores were significantly associated with lower SpO<sub>2</sub> levels in room air at rest and during sleep. 5 (22.7%) subjects had family history of interstitial lung disease. The clinical severity of the disease was assessed using Fan scoring system and we found that 5 (22.7 %) of studied patients were categorized as score 2,

1 (4.5%) subject was categorized as score 3, 8 (36.4%) as score 4 and 8 (36.4%) as score 5. Among the study group, 8 (36.4%) subjects had pulmonary hypertension by echocardiography on initial assessment.

Plain Chest X-ray findings were generally non-specific. A comparison between chest X-ray and corresponding chest CT findings among enrolled subjects is provided in supplementary table-1. The predominant abnormality identified by chest CT was the presence of ground glassing (90.9%). Other common abnormalities included septal thickening (50%), air trapping (40.9%), mosaic attenuation (31.8%), reticulations (27.3%) and consolidation (22.7%). Less common features included tree in bud pattern, honeycomb cysts, nodules, air filled cysts, hyperinflation, traction bronchiectasis, crazy paving, lymphadenopathy and emphysematous changes.

Only 14 (63.6%) subjects were able to perform spirometry and the rest were too dyspneic or too young to perform the test. Of the subjects who could perform the test, 9 (64.3%) subjects showed restrictive pattern, 3 (21.4%) showed mixed obstructive and restrictive pattern; While 2 (14.3%) subjects had normal spirometry results.

We managed to make a specific diagnosis without a lung biopsy in four patients. One patient was diagnosed with post-tuberculous chILD based on clinical evaluation and non-invasive tests, and another patient was diagnosed with chronic granulomatous disease based on the result of dihydrorhodamine (DHR) test. Two other patients had a history of recurrent hospitalization for severe microcytic hypochromic anemia requiring blood transfusion, following several attacks of haemoptysis, and they were diagnosed with idiopathic pulmonary hemosiderosis (IPH) by BAL after exclusion of all other causes of diffuse alveolar hemorrhage. More details regarding the BAL findings are provided in supplementary table-2.

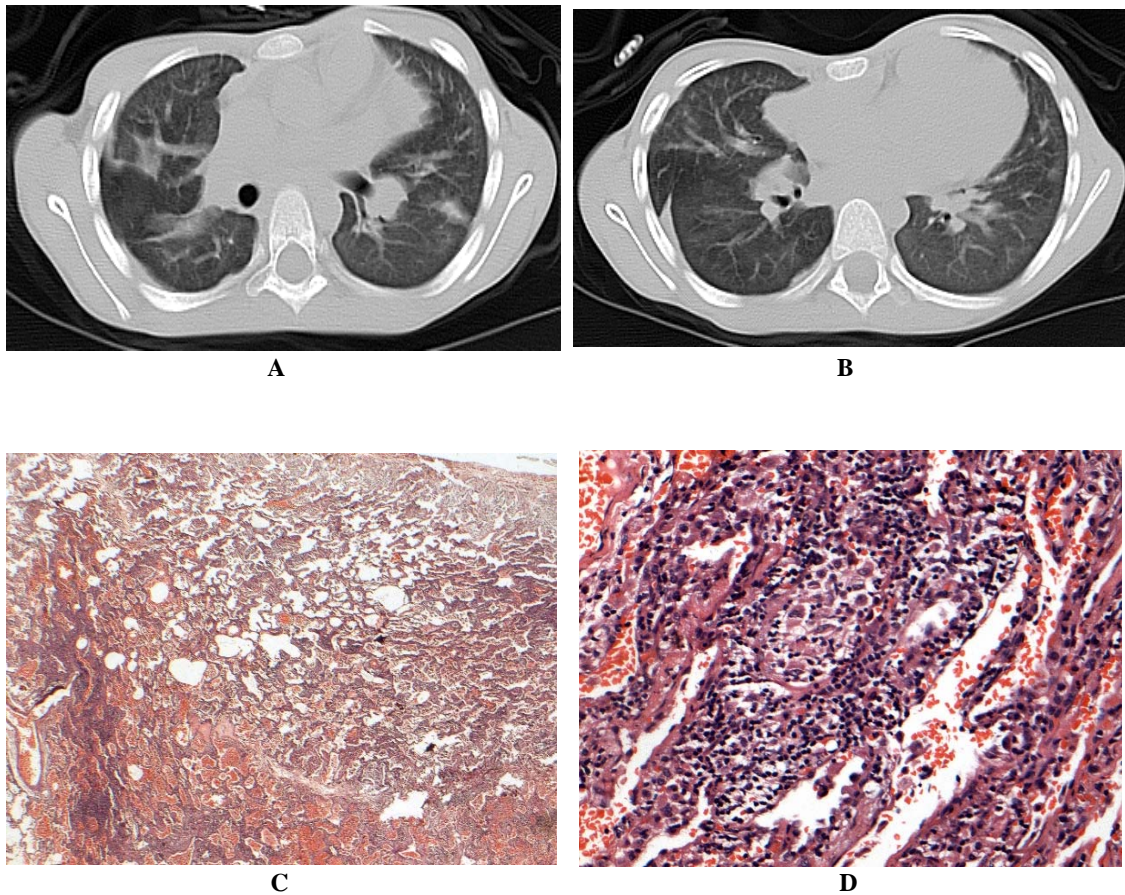
Open Lung biopsy was performed in 15 (68.2%) subjects. Median duration of intensive care unit (ICU) admission post-operative was 1 day (range 1-4 days) and median duration of hospital stay postoperative was 6 days (range 3-14 days). To treat any potential post-operative air-leak, a routine intercostal drainage was left insitu in all subjects. It was removed 1-2 days post-operative if there was no evidence of ongoing air-leak. Five children (33.3%) experienced complications following the procedure. Three (20%) had pneumothorax with underlying lung collapse requiring ongoing chest drainage for a median of 8 days (range 7 - 21 days). One (6.7%) of these children subsequently developed pneumonia requiring parenteral antibiotic therapy and one subject had persistent pneumothorax and discharged 7 days post-operative on Heimlich valve for another 2 weeks. Two (13.3%) subjects developed acute exacerbation shortly after the biopsy procedure requiring systemic steroid therapy. No mortalities, hemorrhage, wound infection or need for intubation were recorded following the procedure.

The diagnostic evaluation was incomplete in 3 subjects. Two patients had imaging suggestive of Langerhans cell histiocytosis (LCH), but were lost after enrollment into the study (one death and one drop-out). The third patient refused to have the lung biopsy, however, a suggestive diagnosis of familial interstitial lung disease (ILD) of unidentified aetiology was made based on history, examination and non-invasive tests.

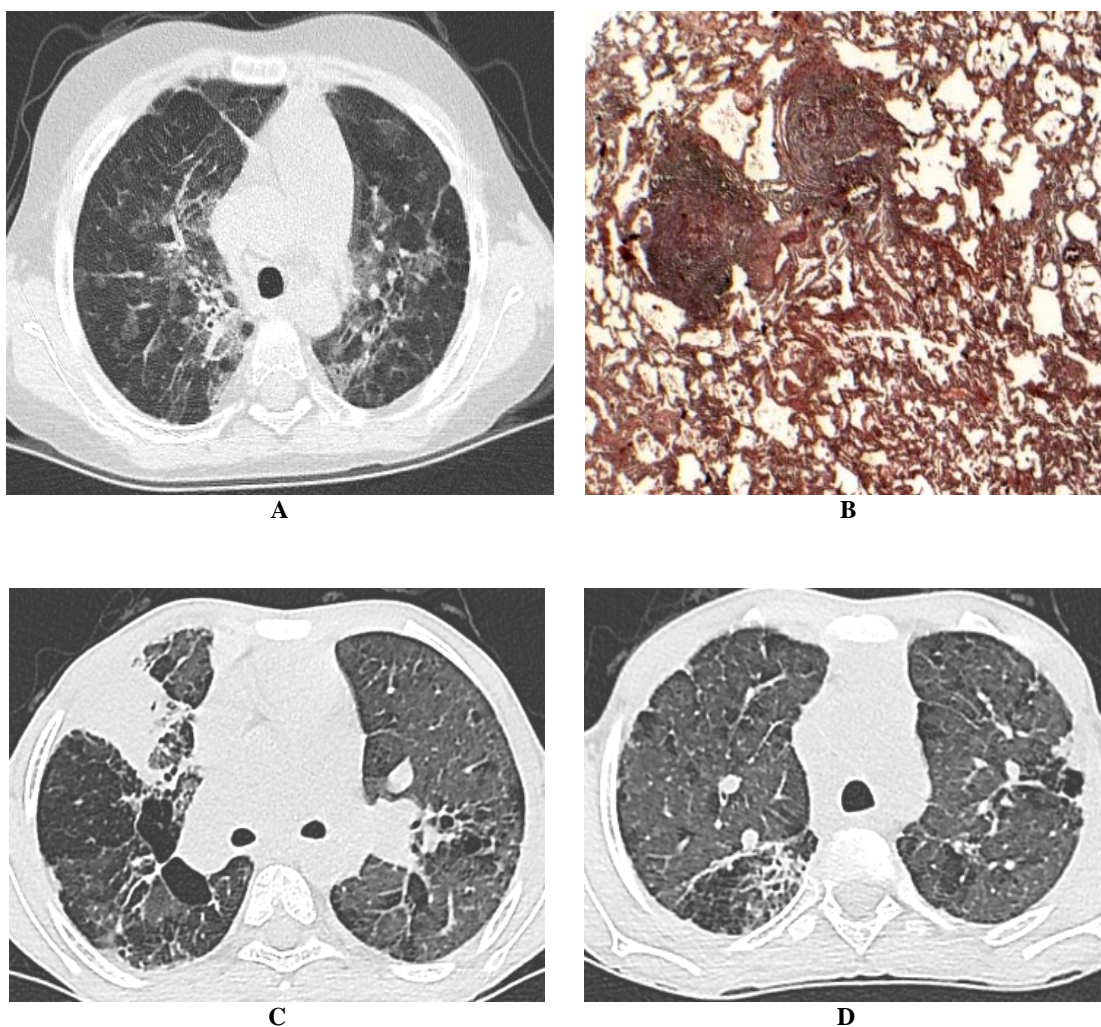
Enrolled subjects were classified according to their clinical, radiological, laboratory and histopathology features (Table 1; Figures 1-8).

Among the subjects who completed the diagnostic evaluation (n=19), treatment was changed in 13 (68.4%) subjects. Although the main stay of treatment before and after the diagnostic evaluation remained systemic corticosteroids, the added value that we were able to plan the duration of steroid therapy, and changed our perspective in management of subsequent

exacerbations. Highlights on treatment lines changes after the diagnostic evaluation is shown in supplementary table-3.



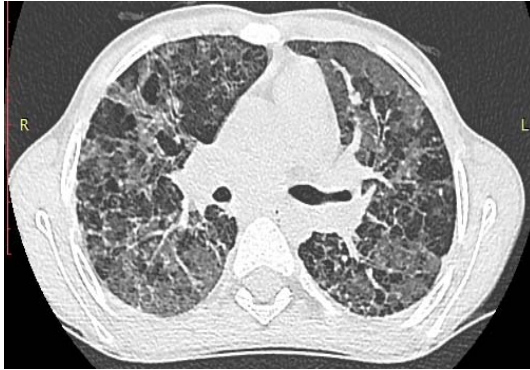
**Figure 1:** (*Subject 1*) 9 years old male patient was referred to us with possible diagnosis of chILD. He complained of recurrent attacks of dyspnea and dry cough. He also had a strong history of exposure to birds. On presentation, he was tachapenic and hypoxic (sats 88% at rest, in room air). He had marked failure to thrive with first degree clubbing and auscultation revealed wide spread fine crepitations. Echocardiography showed dilated right side with pulmonary hypertension. CT axial cut A. Shows Bilateral scattered subsegmental consolidative patches associated with few scattered atelectatic bands. B. Shows interlobular and fissural thickening. Histopathology shows C. Bronchocentric chronic inflammation (low power). D. High power shows a small poorly formed granuloma. (H&E, C x20, D x200). Overall, the features are consistent with hypersensitivity pneumonitis. There was a significant clinical improvement on elimination of bird exposure and systemic steroids.



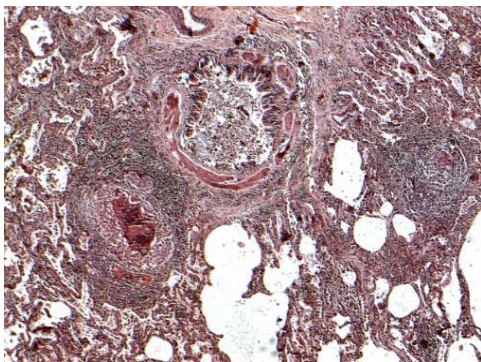
**Figure 2:** (*Subject 4: A, B*) Female patient, 5 years old, presented with severe failure to thrive and 3<sup>rd</sup> degree clubbing. She had profound hypoxemia (80% at rest, in room air), with wide spread fine crepitations and severe pulmonary hypertension. CT axial cut **A**. Shows Bilateral scattered central and peripheral patchy areas of GGO and septal thickening. This is associated with few areas of air trapping giving a mosaic pattern. Lung histopathology shows **B**. Granulomas surrounded by a rim of chronic inflammatory cells (H&E x20). Thorough immunological testing was performed after the Bx, and DHR test showed abnormal response confirming the diagnosis of Chronic Granulomatous Disease. (*Subject 5: C, D*) belongs to a 10-year-old male patient who was presented with chILD and later diagnosed with chronic granulomatous disease (CGD). He had severe initial clinical presentation with hypoxia at rest (in room air) and marked failure to thrive. CT axial cut **C**. Shows bilateral peripheral and central large patchy areas of GGO with areas of air trapping giving a mosaic pattern, associated with septal thickening and few mainly lower lobar emphysematous changes and central cystic changes. A large consolidative patch is noted affecting the anterior segment of the right upper lobe. **D**. Abnormal bronchial thickening and minimal tractional bronchiectasis. He was planned for Bx, but it was deferred as he started to suffer from recurrent skin and deep organ abscesses requiring surgical drainage. Further immune tests were done and DHR test showed abnormal response, confirming the diagnosis of CGD.



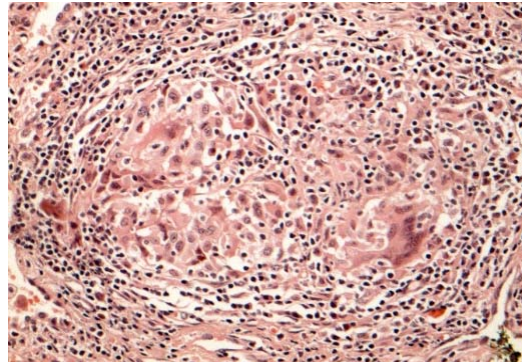
**A**



**B**

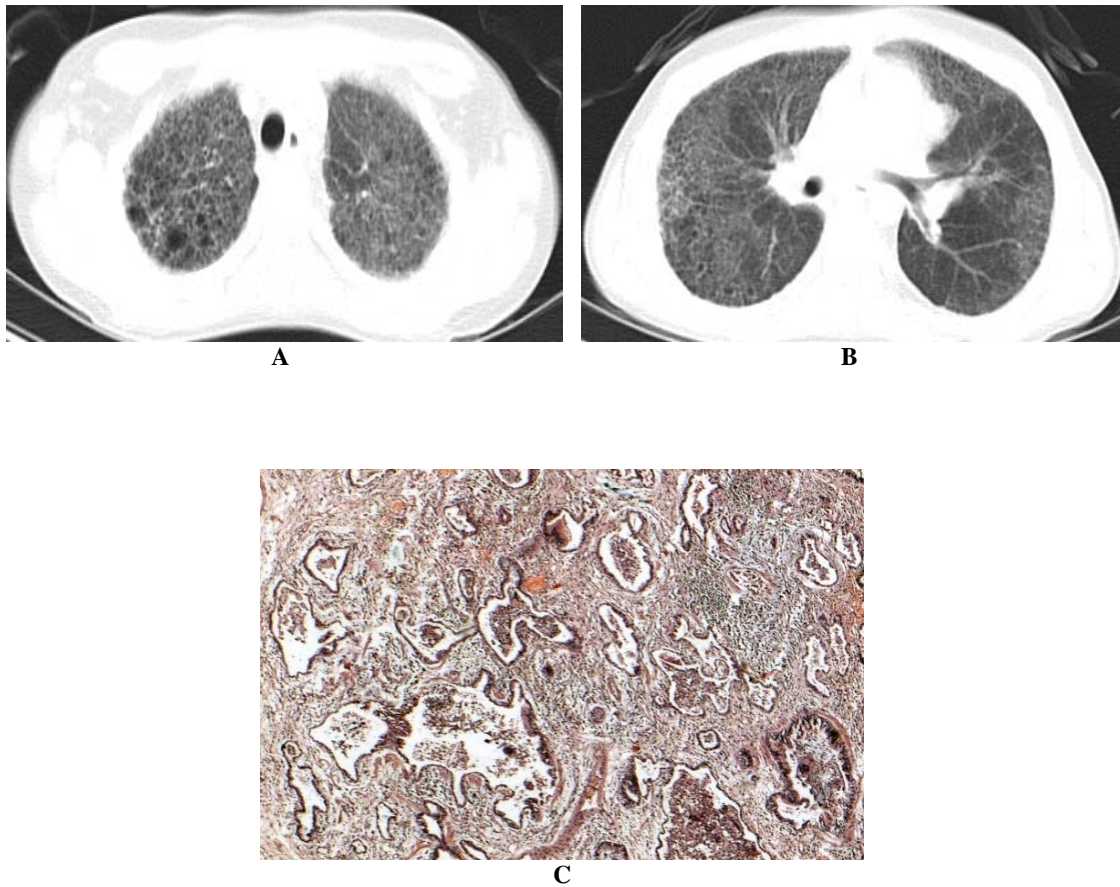


**C**

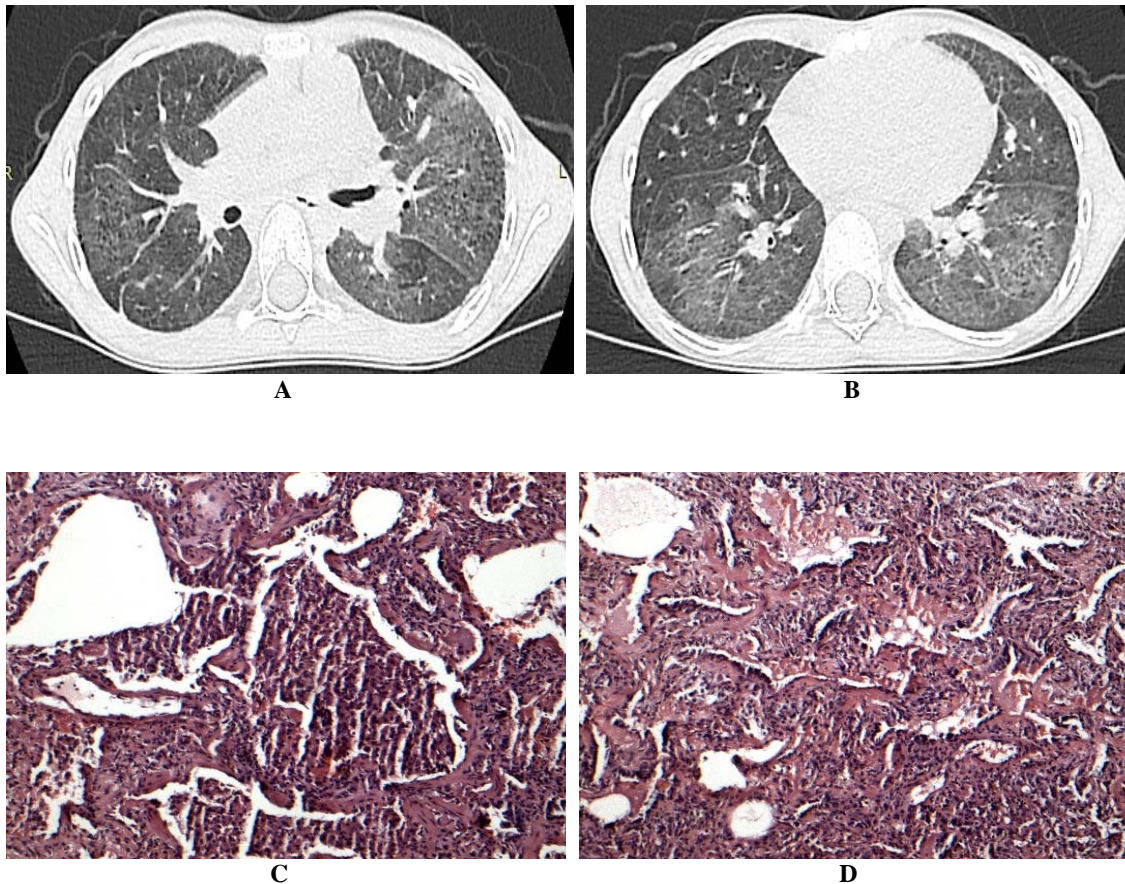


**D**

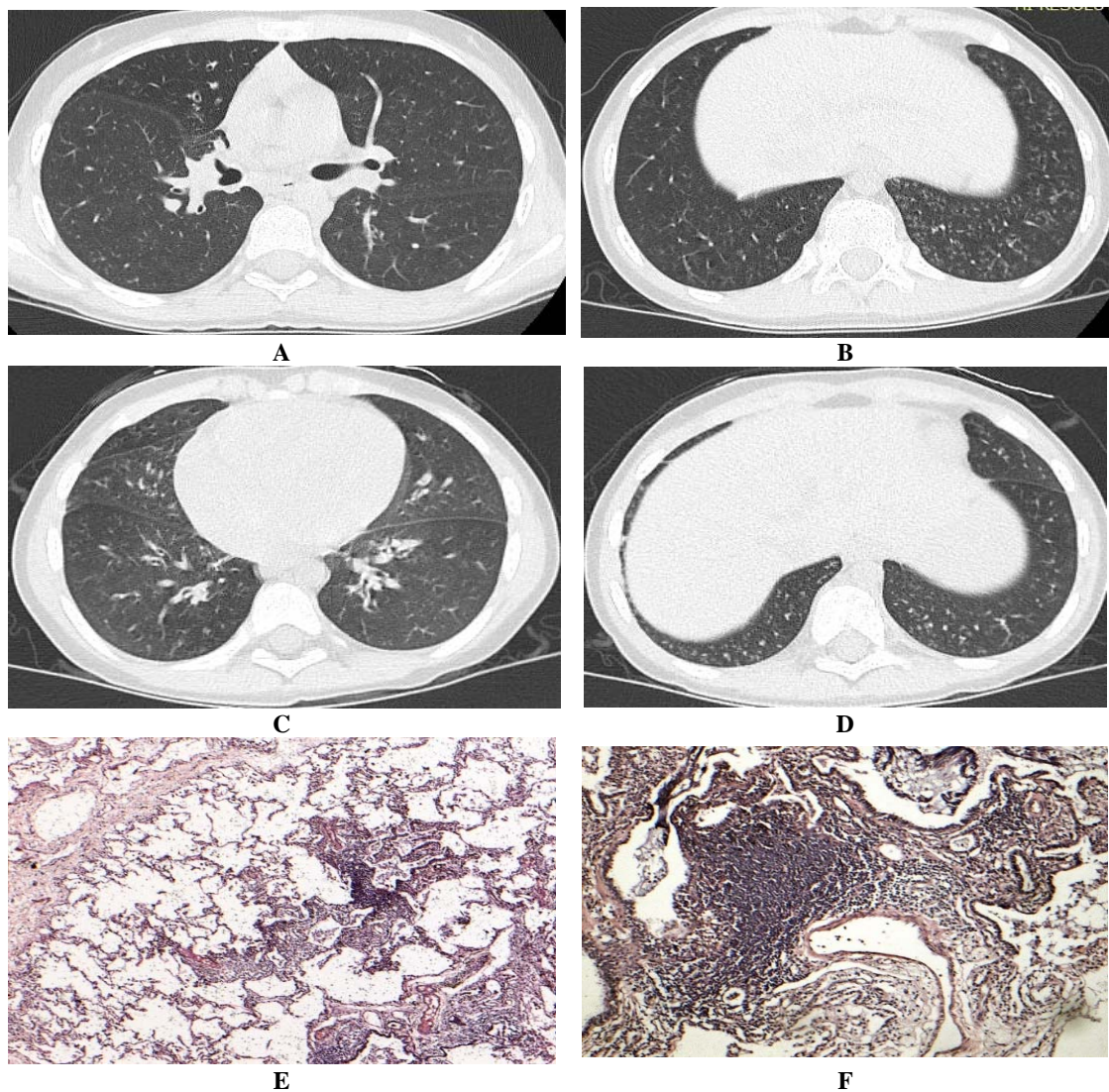
**Figure 3:** (*Subject 7*) Eight years old female patient had history of persistent dry cough and dyspnea. She is the second child for a first-degree consanguineous parents. In addition to the pulmonary symptoms, she had bouts of self limiting non-infective diarrhea and pustular skin lesions (**A**). She also had a history of PICU admission with severe sepsis that marked the disease onset. On presentation to us she was tachypneic, hypoxic with wide spread fine crepitations and wheeze by auscultation. Immunological profile showed elevated immunoglobulins and transient positivity of P-ANCA, which disappeared later on. CD markers shows borderline low natural killer cells and CD4 levels. Flow spirometry showed a restrictive pattern. CT axial cut **B**. shows bilateral mosaic appearance of both lung lobes (ground glass appearance alternating with areas of air trapping), with peri-bronchial wall thickening and pre-septal thickening. **C**. Histopathology shows bronchocentric inflammation and granulomatous inflammation. **D**. A high power of a granuloma. (H&E, Cx40 and D x200). Histopathology findings were consistent with Granulomatous lymphocytic interstitial lung disease (GLILD) spectrum. DHR test was normal and repeat immune studies showed persistent elevation of immunoglobulin levels, excluding underlying CVID.



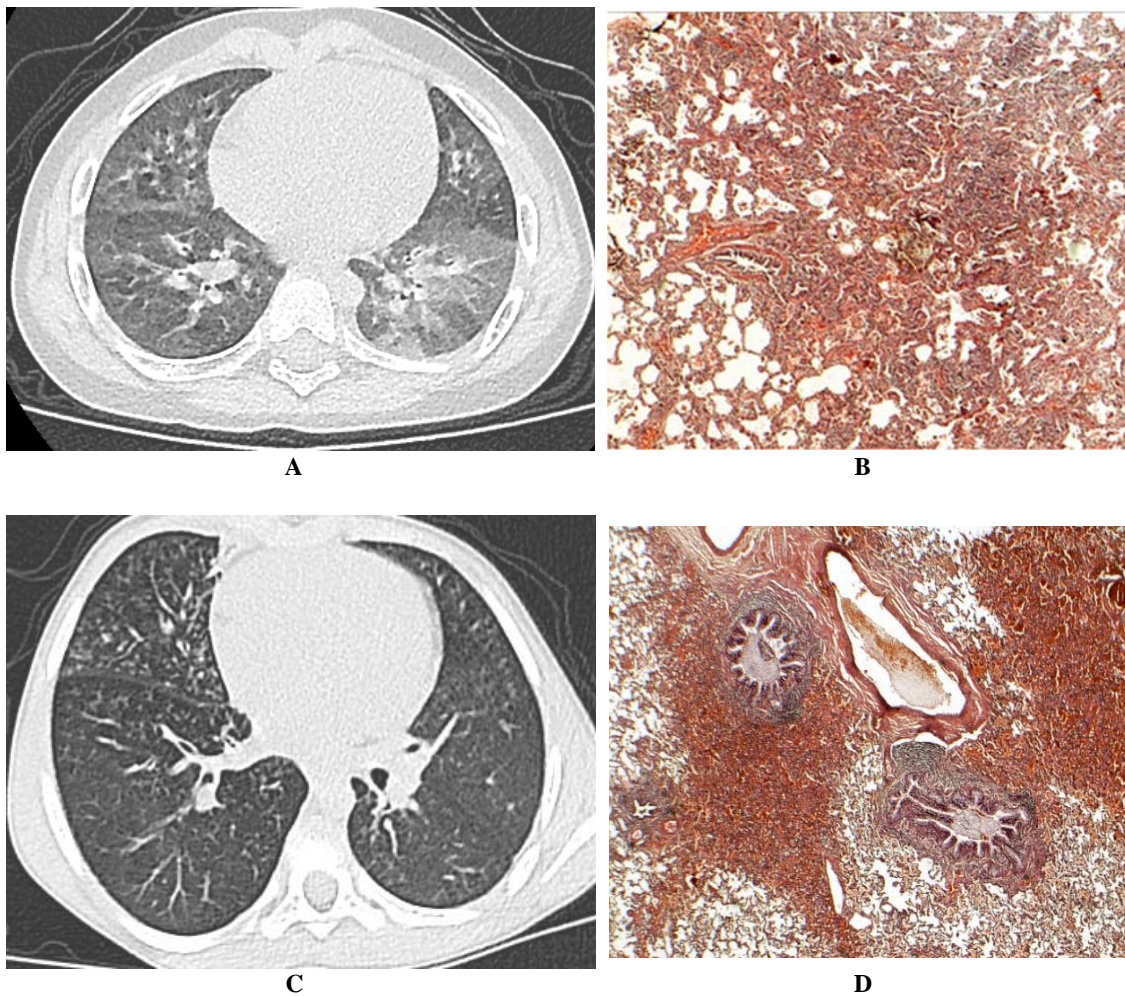
**Figure 4:** (*Subject 8*) female patient 8 years old was referred to us for further assessment. She complained of chronic dry cough and progressive dyspnea. She has a history of familial death with undiagnosed ILD in the fifth decade (uncle). On presentation to us she was tachycardic, tachapenic, hypoxic at room air (saturation 88%). She also had severe cachexia with 3<sup>rd</sup> degree clubbing. Echocardiography showed severe pulmonary hypertension with dilated right atrium and ventricle. CT axial cut shows A and B. bilateral predominantly upper lobar and peripheral GGO associated with peripheral reticular infiltration and honey combing. Histopathology shows C. Lung architecture is completely lost, with replacement by end-stage (honeycomb) fibrosis (H&E x40).



**Figure 5:** (*Subject 9*) female patient 7 years old, was referred to us for further assessment. She had a history of dyspnea shortly after birth, associated with failure to thrive. Her condition deteriorated to dyspnea at rest and attacks of cyanosis. On presentation, she was markedly distressed RR: 70/minute, HR: 150 BPM (tachycardia with gallop) and hypoxic (saturation 85% in room air, at rest). She also had 3<sup>rd</sup> degree clubbing and marked failure to thrive. She had bilateral fine crepitations on auscultation with accentuated second heart sound and tender hepatomegaly. Echocardiography showed dilated right ventricle and severe pulmonary hypertension. CT axial cut shows A. bilateral (predominantly upper lobar) subpleural and intraparenchymal microcysts and B. bilateral diffuse pulmonary GGO, with predominant affection of both lower lobes. Histopathology C. Shows predominance of alveolar macrophage accumulation. D. Shows diffuse and uniform interstitial chronic inflammation and mild fibrosis, characteristic of non-specific interstitial pneumonia. This mixed histological pattern (Fibrotic non-specific interstitial pneumonia and desquamative interstitial pneumonia) in the pediatric age group is suggestive of underlying surfactant protein disorder (H&E, C and D x100).



**Figure 6:** (*Subject 11-12*) Two affected siblings with history of grandparent death of undiagnosed ILD in the fourth decade. A and B: CT images from the older sibling. A. Diffuse pan-lobar pulmonary emphysema with areas of air trapping, abnormal bronchial wall thickening. B. Bilateral lower lobar scattered tiny ground glass nodules showing tree in bud appearance. C and D are CT images from the younger sibling. C. Air trapping and hyperinflation. D. Bilateral few peripheral lower lobar tiny ground glass nodules with few of them giving tree in bud appearance. The younger sibling was presented with a worse clinical picture (Severity Score 5) and her spirometry showed a restrictive defect. The older sibling is presented with significant symptoms, signs and hypoxia at rest and her spirometry showed mixed obstructive and restrictive defect, with negative reversibility test. E and F shows histopathology of the older sibling, with findings consistent with idiopathic BPIP. E. Low power shows peribronchiolar inflammation. F. Higher power shows peribronchiolar metaplasia. (H&E, E x40 and F x100). Grocott stain for fungi was negative. General causes of DPLD were thoroughly excluded as well as immune-deficiency and Alpha-1 antitrypsin deficiency. Although the specific cause for this histological pattern couldn't be precisely identified, but strong family history with 2 siblings having respiratory symptoms since birth and grandparent death due to ILD raises serious concerns for underlying genetic disorder.



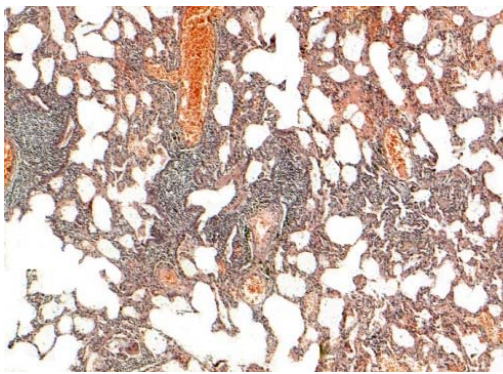
**Figure 7:** (*Subject 13: A, B*) Male patient referred to our hospital by the age of 8 years with history of worsening dyspnea and bouts of cyanosis. He had history of recurrent attacks of dyspnea and dry cough since birth, in addition to global developmental delay of unidentified aetiology. Initial diagnosis of bronchial asthma was made at primary care, yet, there was no significant improvement on conventional asthma management. On presentation to us, he was tachapenic and hypoxic (saturation 89% in room air, at rest). Examination revealed marked failure to thrive, in addition to fine crepitaions and wheeze by auscultation. CT axial cut shows **A**. Multiple scattered patchy areas of GGO alternating with few areas of air trapping giving a mosaic pattern. Histopathology **B**. Shows chronic bronchiolitis (H&E, Bx40). (*Subject 14: C, D*) CT axial cut **C**. Shows bilateral scattered tiny pulmonary GG nodules 2-3 mm in average showing centrilobular and peri-bronchial distribution. **D**. Histopathology shows chronic bronchiolitis with airway lumens focally containing mucin (H&E, D x20).



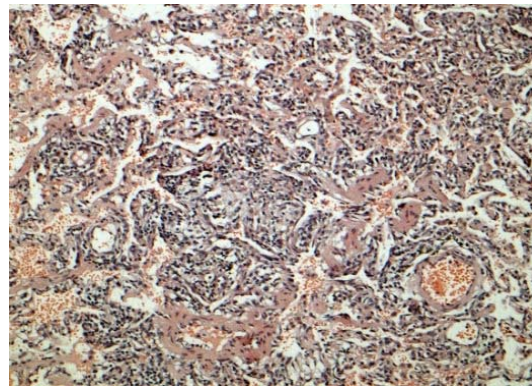
**A**



**B**



**C**



**D**

**Figure 8:** (*Subject 16*) 9 years old female, was referred to us for further assessment of her poorly controlled asthma. On presentation she had dyspnea and hypoxemia at rest with wide spread fine crepitations and wheeze by auscultation. She also had notable puffy fingers (**A**). Initial lab investigations were non-conclusive. CT axial cut shows **B**. Bilateral mainly lower lobar extensive ground glassing associated with few areas of air trapping, more evidently affecting the right lower lobe giving a mosaic pattern. Histopathology shows bronchocentric interstitial pneumonia **C**. Interstitial chronic inflammation, more marked around bronchovascular bundles (low power). **D**. An occasional focus of organising pneumonia is also noted. (H&E, C x40 and D x100). She also developed progressive digital tip ulcers, sclerodactyly, in addition to induration proximal to MCP (appeared later). Overall features confirm the diagnosis of Systemic Sclerosis (SSc).

**Table 1: Classification of enrolled subjects according to their clinical, radiological, laboratory and histopathology features.**

	History	Age (Yr) at start of symptoms	Age at referral (Yr)	Fan score	Spirometry	Chest CT	Histopathology	Significant Lab/BAL findings	Final opinion
1	Exposure to doves & chicken	4	9	5	RVD	Consolidation, septal thickening	GLD	-	Specific Dx: chronic HP
2	Exposure to doves & chicken	2.5	3.5	2	Not done*	Reticulations/ diffuse micronodules	GLD	Eosinophilia	Specific Dx: chronic HP
3	Exposure to doves/benzene/hookah	3.5	4	3	Not done*	GGO/ consolidation/ reticulations	Interstitial inflammation more marked around BVB	Eosinophilia	Specific Dx: subacute HP
4	Recurrent pneumonias	1	5	5	RVD	GGO/air trapping/ septal thickening	GLD	Elevated ESR/ DHR: defective response	Specific Dx: CGD (PID)
5	Recurrent skin abscesses /previous pulmonary TB infection	6.5	10	4	MVD	Multiple findings (figure 2)	Not done	Elevated ESR/ DHR: defective response	Specific Dx: CGD (PID)
6	Recurrent pneumonias	8	13	5	RVD	GGO/ air trapping/ septal thickening/ Reticulations/ consolidation	GLD	Elevated ESR/ DHR: defective response	Specific Dx: CGD (PID)
7	Recurrent pustular skin lesions	5	8	4	RVD	GGO/ air trapping/ septal thickening	GLILD	Elevated ESR/ Low NK cells & CD4/ Elevated immunoglobulins/Negative viral serology	Specific Dx: GLILD (non-CVID related)
8	Familial death of ILD (uncle) chILD onset after severe pneumonia	6	8	5	RVD	GGO/honey combing/reticulations	Severe fibrotic NSIP (honeycomb lung)	- Negative viral serology& immune studies - No evidence of microbial infection (by BAL)	Specific Dx: IP (fibrotic NSIP-honey comb lung) **
9	Dyspnea since birth	Since birth	7	5	RVD	GGO (with predominant affection of lower lobes), microcysts	mixed fibrotic NSIP & DIP	-	Specific Dx: IP (NSIP/DIP) **
10	GDD/familial death of undiagnosed ILD (sibling)	5.5	6	2	Not done*	GGO/ air trapping	NSIP (cellular)	-	Specific Dx: IP (NSIP)**
11	Familial death of undiagnosed ILD in the 4 <sup>th</sup> decade (grandparent)	Since birth	11	4	MVD	Emphysema/ Lower Lobes tiny GG nodules (tree in bud pattern)	BPIP	Negative immune studies	Specific Dx: IP (BPIP) **
12	Familial death of undiagnosed ILD in the 4 <sup>th</sup> decade (grandparent)	Since birth	5	5	RVD	Air trapping/hyperinflation/ Lower Lobes tiny GG nodules (tree in bud pattern)	Parents refused (P.S. case 11 and 12 are siblings)	Negative immune studies	Suggestive Dx: familial ILD of unidentified aetiology
13	GDD	Since birth	8	4	Not done*	GGO/air trapping	Chronic	-	Specific Dx: chILD related to

	History	Age (Yr) at start of symptoms	Age at referral (Yr)	Fan score	Spirometry	Chest CT	Histopathology	Significant Lab/BAL findings	Final opinion
							bronchiolitis/interstitial chronic inflammation		SAD with background IP#
14	GDD	0.25	5	4	Normal	GG nodules 2-3 mm (centrilobular and peri-bronchial distribution)	Chronic bronchiolitis/interstitial chronic inflammation	-	Specific Dx: chILD related to SAD with background IP#
15	NICU admission at birth for 2 months/ Full term	Since birth	14	2	MVD	GGO (few shows crazy paving)	Chronic bronchiolitis/interstitial chronic inflammation	-	Specific Dx: chILD related to SAD with background IP#
16	Puffy fingers/digital tip ulcers/ Sclerodactyly/ Induration proximal to MCP (late)	4	8	4	Not done*	Bibasilar GGO	BPIP+ focal OP	Abnormal nail fold capillaries	Specific Dx: Systemic sclerosis
17	Haemoptysis/ admitted twice for blood transfusion for severe microcytic anemia	4	5	2	Normal	GGO	Not done	BAL: HLM>60% of cells /other causes of DAH were excluded	Specific Dx: IPH
18	Haemoptysis/ admitted 6 times for blood transfusion for severe microcytic anemia	5.5	7	2	RVD	GGO	Not done	BAL: HLM>45% of cells /other causes of DAH were excluded	Specific Dx: IPH
19	Progressive dyspnea over 2 months	11	11	5	Not done*	Cysts (sparing CPA)/ GGO/ tiny nodules	death before any invasive tests	-	Suggestive Dx: LCH
20		1	3.5	4	Not done*	Cysts (sparing CPA)/ GGO	Dropped out	-	Suggestive Dx: LCH
21	History of pulmonary TB	3.5	4.5	5	Not done*	GGO/reticulations/atelectatic bands	clinically improving (not done)	Negative immune studies	Specific Dx: post infectious chILD (post tuberculous)
22	Start of disease following attack of severe pneumonia	6	6	4	RVD	GGO	OP & Reactive fibrous pleuritis	Negative immune studies	Specific Dx: post infectious chILD (organising pneumonia)

\*Not done: too young or too dyspneic to do the test or suffering from Global delay (non-cooperative). \*\*Further genetic testing required to exclude surfactant dysfunction mutation. #Future genetic studies are also warranted for this group as symptom onset was at birth or shortly after birth. Yr: year; BAL: bronchoalveolar lavage; MVD: mixed ventilatory dysfunction; RVD: restrictive ventilatory dysfunction; BVB: bronchovascular bundles; GLD: granulomatous lung disease; HP: hypersensitivity pneumonitis; GGO: ground glass opacity; NK: natural killer cells; CD markers: cluster of differentiation markers; DHR: dihydrorhodamine test; TB: tuberculosis; ESR: erythrocyte sedimentation rate; CGD: chronic granulomatous disease; PID: primary immune deficiency; GLILD: granulomatous lymphocytic interstitial lung disease; GDD: global developmental delay; NSIP: non-specific interstitial pneumonia; DIP: desquamative interstitial pneumonia; BPIP: bronchiolocentric pattern of interstitial pneumonias; NICU: neonatal intensive care unit; SAD: small airway disease; IP: interstitial pneumonia; MCP: metacarpophalangeal joint; GG: ground glass; HLM: hemosiderin laden macrophages; DAH: diffuse alveolar hemorrhage; IPH: idiopathic pulmonary hemosiderosis; CPA: costophrenic angle; LCH: Langerhans cell histiocytosis; Op: organising pneumonia.

## DISCUSSION

ChILD is a rare disease, with few cases reported in each specialized center annually. This is the first study to describe the diagnoses and characteristics of patients with chILD from one of the largest university hospitals in Egypt. Our study shows that systematic multidisciplinary review led to changes in management in the majority of cases diagnosed with chILD.

22 patients were referred to us from other hospitals for further evaluation, over a 24 months period. Although all enrolled subjects were older than 2 years at the time of referral to our hospital, the symptoms started during the first 2 years of life in one third of the patients. However, referral to a tertiary hospital was delayed, reflecting inadequate awareness of chILD amongst general pediatricians. Age of symptom onset is particularly important as it may provide a clue to the specific chILD. ChILD in infants younger than 2 years is more commonly related to developmental disorders, pulmonary interstitial glycogenosis and neuroendocrinal hyperplasia of the infancy. ChILD presenting after 2 years is more likely related to environmental exposures, systemic diseases and immune deficiency. Surfactant protein dysfunction mutations could present during infancy or later during childhood [10].

The clinical presentation of chILD is often non-specific and overlapping with many conditions. Among our study group the most common symptoms were dyspnea, cough and recurrent pneumonias. Although cough reported among chILD patients is classically dry [11], many of our cases reported super imposed attacks of productive cough which may have accompanied intercurrent infective exacerbations or development of traction bronchiectasis. In addition, almost one third of our patients were initially diagnosed with childhood asthma at primary care, and this should remind pediatricians to carefully assess difficult-to-treat asthma cases for possibility of an alternate diagnosis. Recurrent unexplained febrile episodes were also

common among our study group, this finding was observed among other chILD cohorts as well [10], and it should alert pediatricians for the possibility of chILD. Our findings of clinical presentation were similar to those reported in other series [12-14].

We found that thorough history and physical exam provided important information that aided in interpreting radiology and histopathology results. For instance, granulomatous lung disease was found in 5 patients, 2 patients had history of recurrent pneumonias and further immune studies confirmed the diagnosis of chronic granulomatous disease. While the other three patients had strong history of exposure to birds with improvement on steroid therapy and exposure elimination, confirming the diagnosis of hypersensitivity pneumonitis. Thus, confirmation of the diagnosis requires a multidisciplinary team work between clinicians, radiologists and pathologists.

In our study, we found that chest CT was useful in confirming the diagnosis of chILD, as well as identifying the disease distribution and helped in identifying a suitable biopsy site. However, the imaging was suggestive of the diagnosis in only two cases and no specific diagnosis was reached depending on the radiology alone. The predominant abnormality identified by chest CT among our study group was the presence of ground glass opacity (GGO). Similar findings are reported in the literature [10,13].

Bronchoscopy and BAL have an increasing role in the diagnosis of chILD. The primary value of Bronchoalveolar lavage fluid (BALF) analysis is exclusion of infection as the underlying cause of chILD. In addition, BALF high percentage of hemosiderin-laden macrophages is suggestive of diffuse alveolar hemorrhage syndromes, while BALF PAS-positive granular material with hypocellularity is suggestive of alveolar proteinosis. Furthermore, positive CD1a staining of BALF cells is highly suggestive of pulmonary histiocytosis. Many other

conditions may also be diagnosed with BAL such as eosinophilic lung disease, aspiration syndromes and sarcoidosis [6]. Hemosiderin-laden macrophages were found in BALF of the two subjects diagnosed with IPH, and they constituted more than 45% total cell count. Although the gold standard for IPH diagnosis is via lung biopsy, but it's rarely performed as BAL high percentage of haemosiderin-laden macrophages is considered a specific, sensitive and less invasive method for diagnosis of IPH in children [15].

Surgical lung biopsy plays an important role when other modalities fail to identify the specific chILD disease. Both open lung biopsy (OLB) and VATS (Video assisted thoracoscopic surgery) have been used to obtain samples for histopathology. The US chILD committee recommends VATS biopsy due to faster recovery time compared to OLB, however, the European guidelines do not make recommendations on the type of surgical approach [2,6]. In patients who had a diagnostic lung biopsy among our study group, we preferred the open surgical technique to ensure adequacy of the sampled tissue, and to avoid superficial non diagnostic biopsies.

Among the subjects who had an OLB in our study group, a routine intercostal drainage was left insitu in all subjects to treat any potential post-operative air-leak. This practice is recommended as it was noticed that many children with chronic interstitial lung disease develop an air-leak postoperative requiring chest drainage [16]. We report a shorter length of hospital stay (LOS) than other comparable series in the literature, but the complication rate is fairly similar [16,17]. In our study, we found that the procedure of open lung biopsy was safe with no mortalities or significant adverse events, even in patients with hypoxemia. The safety of OLB procedure was similar to other published cohorts [17,18].

We report three confirmed cases of hypersensitivity pneumonitis (HP) due to domestic bird's exposure, which shows that environmental factors play an important role in the development of chILD in our study group. Although HP is still considered a rare disease in children, yet, it has been increasingly reported in many chILD cohorts [12-19]. HP can be associated with exposure to a variety of finely dispersed environmental antigens, but avian exposure is by far the most common cause of HP in children, accounting for nearly two-thirds of the cases [20].

UpToDate there is no consensus for the diagnosis of HP in children, however, HP is suggested if there is a history of exposure to an offending antigen, prominent radiological features and positive precipitins test [19]. All 3 HP cases in our study had a strong history of exposure to birds, yet, they tested negative for the HP precipitins testing panel. This finding might be attributed to the fact that standard HP panels are often irrelevant to the patient's environment [21]. Thus, patient centered testing is recommended to avoid false negative results. The decision to refer for BAL was deferred, to avoid multiple invasive procedures requiring general anesthesia, as BALF CD4/CD8 ratio can be within the normal range in children [22]. Lung histopathology confirmed the diagnosis of HP in all 3 cases, and they improved dramatically on elimination of bird exposure and steroid therapy.

Three patients were presented with chILD and they were diagnosed with chronic granulomatous disease (CGD) after the diagnostic evaluation. They were presented solely with pulmonary manifestations of the disease, with less evident systemic symptoms. All 3 notably had severe clinical presentation with hypoxemia at rest and two had severe pulmonary hypertension. They also had recurrent pneumonias, associated with persistent elevation in erythrocyte sedimentation rate. ChILD seen in CGD patients could be a sequel to recurrent life-threatening

infections, or a result of sterile inflammation due to increased expression of proinflammatory molecules in genes encoding polymorphonuclear cells [23,24]. ChILD is considered to be a rare pulmonary complication among CGD patients, with few published case reports worldwide. The diagnosis of CGD in our study was made by dihydrorhodamine (DHR) test. However, future molecular and genetic studies are needed to identify the causal mutations. The major change in treatment for cases diagnosed with chILD related to CGD, that we added prophylactic antibiotics (most commonly used was trimethoprim-sulfamethoxazole) and antifungals (itraconazole/voriconazole). This is in addition to prompt management of any infection with aggressive antimicrobials. Immune related complications are also managed with corticosteroids and immunomodulatory therapies. Corticosteroids were sufficient in two cases, and mycophenolate mofetil was added in one subject due to poor response to steroids.

Additionally, we report a female subject with confirmed histological diagnosis of Granulomatous Lymphocytic Interstitial Lung Disease (GLILD), which wasn't related to common variable immune-deficiency (CVID). GLILD has been frequently reported in the literature as a complication for CVID in adults. However, in children many cases weren't linked to CVID. Recent data suggest that many children with GLILD do not fit the CVID criteria and they have a more severe disease in comparison to adults. Also, they require intensive treatment with corticosteroids or haemopoietic stem cell transplantation [25]. Our patient showed initial good response to steroid therapy, however immune-modulatory therapy was added due to frequent exacerbations.

Among the study group, 3 subjects had a predominant histological pattern of small air way disease, with a minor component of interstitial pneumonia. Small air way disease (SAD) has been recently classified as one of the causes of chILD, and it is frequently found to be the sole

abnormality in lung biopsy specimens of some chILD patients [9]. SAD can be associated with many diseases, but in many cases the exact cause is not clearly identified. Among our study group the cause of SAD couldn't be precisely identified.

We also report a female subject who was diagnosed with chILD related to systemic sclerosis (SSc). Pulmonary involvement in pediatric SSc is common, and it ranges from 30–70% [26]. Our case had typical radiological features of SSc as her imaging showed ground-glass opacities in a bibasilar distribution. Interestingly, her lung histopathology revealed a rare histological pattern that is bronchiolocentric pattern of interstitial pneumonia (BPIP). BPIP involves bronchiolocentric fibroinflammatory changes, it is reported to be the result of centrilobular injury due to toxic inhalation or from systemic disease manifesting with airway inflammation, such as collagen diseases [27].

The role of genetic factors in the development of chILD is evident [5]. We observed 5 cases with history of interstitial lung disease in closely related family members. One subject diagnosed with CGD after the evaluation, had a sibling death of similar condition. Two cases were siblings, of first-degree consanguineous parents and history of grandparent death in the fourth decade with undiagnosed ILD. The parents agreed a diagnostic lung biopsy for the older sibling only, and it revealed idiopathic BPIP. The exact cause of this histopathology pattern in such case could not be specifically identified. BPIP has not described in a familial setting, but this may reflect some form of genetic predisposition to an exogenous insult. After all, BPIP is still considered a rare subtype of interstitial pneumonia that requires further correlation with clinical studies [28]. The last 2 cases were diagnosed with interstitial pneumonia by histopathology as fibrotic NSIP with honeycomb fibrosis, and idiopathic NSIP.

Genetic studies have recently been recognized as a valuable non-invasive tool in chILD diagnosis. Genetic diagnosis is helpful in estimating recurrence risk and can help avoid lung Bx [6]. We reported cases with overall picture suggestive of surfactant protein dysfunction, yet, the specific genetic mutation could not be identified due to lack of genetic testing and histopathology electron microscopy studies, which was the major limitation of our study. Future international collaborations will be sought regarding appropriate genetic testing for selected cases.

Among our study group, the diagnostic evaluation changed treatment plans in 13 subjects. The overall diagnostic evaluation helped structure a plan for management and guide prognostic discussions with the parents and changed our perspective in management of subsequent exacerbations.

## **CONCLUSION**

We believe this study will help raise awareness of the burden of chILD in Egypt. It also highlights the need for introduction of genetic testing as well as establishment of a national chILD network, and collaboration with international groups to improve the health care for Egyptian children with chILD. Lung histopathology provided the most useful diagnostic information that directly contributed to change in treatment plans, in absence of genetic testing.

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**Supplementary table 1: Comparison between chest X-ray and corresponding chest CT findings among enrolled subjects.**

Subject	Chest X-ray	Chest CT
1	No definite pulmonary parenchymal lesions/ Cardiomegaly	Consolidation, septal thickening
2	Bilateral hazy reticulonodular opacities	Reticulations/ diffuse micronodules
3	Bilateral extensive (mainly central) consolidation patches/ Abnormal scattered opacities likely areas of ground glass	GGO/ consolidation/ reticulations
4	Right upper lobe heterogenous linear opacities (likely representing fibrosis). Otherwise, normal appearance of both lung parenchyma. Prominent pulmonary artery shadow suggestive of pulmonary hypertension.	GGO/air trapping/ septal thickening
5	Consolidation patch/ Linear opacities (suggestive of pulmonary fibrosis)/ Bilateral mainly central bronchial dilatation suggestive of bronchiectasis/ Abnormal increased density (suggestive of air trapping)	Multiple findings (figure 2)
6	Bilateral linear opacities (suggestive of fibrosis) / Atelectatic bands/ consolidation patch/ Bilateral scattered pulmonary reticular infiltration/ Enlarged pulmonary artery shadow (suggestive of pulmonary hypertension)	GGO/ air trapping/ septal thickening/ Reticulations/ consolidation
7	Diffuse bilateral pulmonary reticular infiltration	GGO/ air trapping/ septal thickening
8	Normal	GGO/honey combing/reticulations
9	Normal	GGO (with predominant affection of lower lobes), microcysts
10	Normal	GGO/ air trapping
11	Diffuse pulmonary emphysema (increased lung volume bilaterally)/ Diffuse decreased lung attenuation/ Ribbon shaped cardiac shadow and almost flattening of the diaphragms	Emphysema/ Lower Lobes tiny GG nodules (tree in bud pattern)
12	Mild bilateral increase in lung volume and decreased pulmonary attenuation	Air trapping/hyperinflation/ Lower Lobes tiny GG nodules (tree in bud pattern)
13	Bilateral lower zonal hazy pulmonary opacities	GGO/air trapping
14	Lower zonal and hilar reticulo-nodular infiltration	GG nodules 2-3 mm (centrilobular and peri-bronchial distribution)
15	Normal	GGO (few shows crazy paving)
16	Normal	Bibasilar GGO
17	Bilateral patchy pulmonary infiltrates	Bilateral extensive GGO
18	Bilateral hazy pulmonary infiltrates	GGO
19	Extensive diffuse bilateral pulmonary cystic spaces noted more evident affecting both upper lobes	Cysts (sparing CPA)/ GGO/ tiny nodules
20	Bilateral (mainly central) heterogenous opacities	Cysts (sparing CPA)/ GGO
21	Bilateral upper zonal linear opacities (suggestive of pulmonary fibrosis)	GGO/reticulations/atelectatic bands/left upper lobe calcific nodule *
22	Normal	GGO

GGO: ground glass opacity; GG: ground glass; CPA: costophrenic angle

\*subject 21: initial CT (at the time of pulmonary Tuberculosis infection) showed bilateral upper lobar GGO, air trapping and mediastinal lymphadenopathy.

**Supplementary Table 2: Bronchoscopy and bronchoalveolar lavage (BAL) indications, characteristics and other relevant investigations for selected cases.**

Subject	Indications of BAL	BAL characteristics	Other investigations
8	Disease onset after attack of severe unresolving pneumonia (suspicion of fungal/mycobacterial infection)	<ul style="list-style-type: none"> <li>– Gross appearance: Minimal mucosal inflammation</li> <li>– Cell count: 4 (x10<sup>4</sup>)/mL</li> <li>– Macrophage (%):40, Lymphocytes (%):55, neutrophil (%):5</li> <li>– Absent eosinophils</li> <li>– Gram stain &amp; ZN stain: negative</li> <li>– Bacterial, mycobacterial, viral and fungal C&amp;S: No growth</li> </ul>	<ul style="list-style-type: none"> <li>– EBV, CMV &amp; HIV serology: negative</li> <li>– Immune function studies: normal</li> <li>– Autoantibodies (ANA, anti-dsDNA &amp; ANCA): negative</li> </ul>
17	Recurrent attacks of haemoptysis with two admissions for blood transfusion for severe microcytic anemia	<ul style="list-style-type: none"> <li>– Gross appearance: Mild hyperaemic mucosa, rusty secretions arising from the RML, LUL &amp; LLL</li> <li>– Cell count: 4 (x10<sup>4</sup>)/mL</li> <li>– Neutrophils (%):4, Lymphocytes (%):10, Macrophages (%): 85; Many RBCS</li> <li>– Cytology: HLM constitutes &gt; 60% of BAL cells</li> <li>– Eosinophils, Lipid laden macrophages: absent</li> <li>– Gram stain &amp; ZN stain: negative</li> <li>– Bacterial, mycobacterial, viral and fungal C&amp;S: No growth</li> </ul>	<ul style="list-style-type: none"> <li>– HB:6.7 g/dL (microcytic, hypochromic anemia), platelet count:493 (10<sup>3</sup>/uL)</li> <li>– Serum ferritin &amp; TIBC: normal</li> <li>– Coagulation profile, LFTs &amp; RFTs: normal</li> <li>– Stool &amp; urine analysis: normal</li> <li>– ANA, anti-dsDNA &amp; ANCA: negative</li> <li>– Tuberculin test: negative</li> <li>– Immune function tests: normal</li> <li>– IgE specific for cow's milk protein: normal</li> <li>– Trial of elimination of cow's milk products: no clinical or radiological response</li> </ul>
18	Recurrent attacks of haemoptysis with six admissions for blood transfusion for severe microcytic anemia	<ul style="list-style-type: none"> <li>– Gross appearance: Mild hyperaemic mucosa</li> <li>– Cell count: 20 (x10<sup>4</sup>)/mL</li> <li>– Neutrophils (%):3, Lymphocytes (%):10, Macrophages (%): 85; Many RBCS</li> <li>– Cytology: HLM &gt;45% of BAL cells</li> <li>– Eosinophils, Lipid laden macrophages: absent</li> <li>– Gram stain &amp; ZN stain: negative</li> <li>– Bacterial, mycobacterial, viral and fungal C&amp;S: No growth</li> </ul>	<ul style="list-style-type: none"> <li>– HB:5.7 g/dL (microcytic, hypochromic anemia), platelet count: 510 (10<sup>3</sup>/uL)</li> <li>– Serum ferritin: low</li> <li>– TIBC: increased</li> <li>– Coagulation profile, LFTs &amp; RFTs: normal</li> <li>– Urine analysis: normal</li> <li>– Stool analysis: positive occult blood in stool</li> <li>– ANA, AntiDNA &amp; ANCA: negative</li> <li>– Tuberculin test: negative</li> <li>– IgE specific for cow's milk protein: normal</li> <li>– Immune function tests: normal</li> </ul>

ZN: Ziehl–Neelsen; C&S: culture and sensitivity; EBV: Epstein-Barr virus; CMV: cytomegalovirus; HIV: human immunodeficiency virus; ANA: antinuclear antibodies; Anti-dsDNA: anti-double stranded DNA, ANCA: Anti-neutrophil cytoplasmic antibodies, RML: right middle lobe; LUL: left upper lobe; RBCS: red blood cells; LLL: left lower lobe; HLM: haemosiderin laden macrophages; TIBC: total iron binding capacity; LFTs: liver function test, RFTs: Renal function tests.

**Supplementary table 3: Highlights on treatment changes after the diagnostic evaluation.**

Subject	Treatment after clinical evaluation & NIT*	Final opinion after Invasive tests/ specific immune tests	Treatment after diagnostic evaluation*	Additional notes
1	Systemic steroids (IV Pulse steroid therapy)	Specific Dx ( <b>by LBx</b> ): chronic HP	Exposure elimination +oral steroids (tapered over 9 months)	Complete resolution at the 9 months follow-up†
2	Antibiotics only	Specific Dx ( <b>by LBx</b> ): chronic HP	Exposure elimination +oral steroids (tapered over 6 months)	Complete resolution at the 6 months follow-up†
3	Antibiotics only	Specific Dx ( <b>by LBx</b> ): subacute HP	Exposure elimination + IV pulse steroids followed by oral steroids (tapered over 12 months)	Complete resolution at the 12 months follow-up†
4	Antibiotics + Systemic steroids (IV Pulse steroid therapy)	Specific Dx ( <b>by LBx +DHR</b> ): CGD	*Prophylactic antimicrobials (trimethoprim sulfamethoxazole & voriconazole) +continued low dose systemic steroids  *Mycophenolate mofetil was added#	Frequent exacerbations requiring parenteral antibiotics, antifungals & systemic steroids for stabilization
5	Antibiotics + Systemic steroids (IV Pulse steroid therapy)	Specific Dx ( <b>by DHR</b> ): CGD	Prophylactic antimicrobials (trimethoprim sulfamethoxazole and itraconazole) + continued low dose systemic steroids	
6	Antibiotics + Systemic steroids (IV Pulse steroid therapy)	Specific Dx ( <b>by LBx+ DHR</b> ): CGD		
7	Systemic steroids (IV Pulse steroid therapy)	Specific Dx ( <b>by LBx</b> ): non-CVID related GLILD	Systemic steroids Mycophenolate mofetil was added	Frequent exacerbations requiring pulse steroids
8	Systemic steroids (IV Pulse steroid therapy)	Specific Dx ( <b>by LBx</b> ): IP (fibrotic NSIP-honey comb lung)	No change (continued on systemic steroids, however, they were shifted to the oral route)	Hydroxychloroquine and azithromycin were added on follow-up due to frequent exacerbations
9	Combination therapy (pulse steroids+ Azithromycin+ hydroxychloroquine)	Specific Dx ( <b>by LBx</b> ): IP (NSIP/DIP)	No change (same treatment lines were continued after the diagnostic evaluation; However, the steroids were shifted to the oral route)	Oral steroids dose was adjusted (increased or decreased) according to the clinical condition
10	No specific treatment	Specific Dx ( <b>by LBx</b> ): IP (NSIP)	Monotherapy with Azithromycin	Improved clinically: treatment was stopped at the 3 months follow-up
11	Combination therapy (Oral steroids+ Azithromycin)	Specific Dx ( <b>by LBx</b> ): IP (BPIP)	No change (same treatment lines were continued after the diagnostic evaluation)	Improved clinically: treatment was gradually tapered and stopped
12	Systemic steroids (IV Pulse steroid therapy)	Suggestive Dx (clinical+ NIT): familial ILD of unidentified aetiology	Oral & inhaled steroids +Azithromycin	Frequent exacerbations requiring escalation in oral steroid dose

Subject	Treatment after clinical evaluation & NIT*	Final opinion after Invasive tests/ specific immune tests	Treatment after diagnostic evaluation*	Additional notes
13	Combination therapy (inhaled and systemic steroids, hydroxychloroquine and Azithromycin)	Specific Dx ( <b>by LBx</b> ): SAD with background IP	No change (same treatment lines were continued after the diagnostic evaluation)	Frequent exacerbations requiring pulse steroids
14		Specific Dx ( <b>by LBx</b> ): SAD with background IP		Improved clinically: Treatment was gradually tapered and stopped after 12 months
15		Specific Dx ( <b>by LBx</b> ): SAD with background IP		Improved clinically: Treatment was gradually tapered and stopped after 3 months
16	Systemic steroids (IV Pulse steroid therapy followed by oral steroids)	Specific Dx ( <b>by LBx+ further tests</b> ): Systemic sclerosis	Steroids were tapered and Mycophenolate mofetil was added	
17	Frequent blood transfusion	Specific Dx ( <b>by BAL</b> ): IPH	Oral steroids (tapered till remission)	
18	Frequent blood transfusion	Specific Dx ( <b>by BAL</b> ): IPH	Oral steroids (tapered till remission)	
19	No specific treatment	Suggestive Dx ( <b>by radiology</b> ): LCH	Death shortly after presentation	
20	No specific treatment	Suggestive Dx ( <b>by radiology</b> ): LCH	Dropped out	
21	Antibiotics + Antituberculous drugs	Specific Dx ( <b>clinical+ NIT</b> ): post tuberculous chILD	Oral steroids (tapered till remission) ^	
22	Antibiotics	Specific Dx ( <b>by LBx</b> ): post infectious chILD (OP)	Oral steroids (tapered till remission)	

\*We used the European protocols for diagnosis and initial management of chILD [2] as a guide for treatment, however, treatment plans were adjusted on case by case basis according to the clinical presentation, Fan score and the specific cause of chILD identified following the diagnostic evaluation. After the completion of diagnostic evaluation, we followed up the patients every 1-3 months at the pediatric pulmonology special clinic (follow up parameters included symptoms, signs, hypoxemia at rest and after exercise). Also, follow up echocardiography was done if the patient was originally presented with pulmonary hypertension, or if there was a clinical deterioration on follow up. Pulmonary function tests were also performed once yearly to evaluate disease progression. We are still following up enrolled subjects till the present time. † Complete resolution of clinical symptoms, signs with resolution of the radiological signs and normalization of pulmonary function tests on follow up. NIT: non-invasive tests; IV: intravenous; Dx: diagnosis; LBx: lung biopsy; BAL: bronchoalveolar lavage; HP: hypersensitivity pneumonitis; DHR: dihydrorhodamine test; TB: tuberculosis; CGD: chronic granulomatous disease; GLILD: granulomatous lymphocytic interstitial lung disease; NSIP: non-specific interstitial pneumonia; DIP: desquamative interstitial pneumonia; BPIP: bronchiolocentric pattern of interstitial pneumonias; ILD: interstitial lung disease; SAD: small airway disease; IP: interstitial pneumonia; IPH: idiopathic pulmonary hemosiderosis; LCH: Langerhans cell histiocytosis; Op: organising pneumonia. #Case 4: immunosuppression was started despite diagnosis of primary immune deficiency due to admission with frequent non-infective exacerbations refractory to pulse steroid therapy. ^ Subject 21: presented initially with a 6 months history of night fever and sweats. Initial CT showed bilateral upper lobar GGO, air trapping and mediastinal lymphadenopathy. Further investigations revealed positive tuberculin test (20 mm) and BALF culture showed positive M. Tuberculosis. Diagnosis of pulmonary TB was confirmed and she received antituberculous therapy. On further assessment she continued to have progressive dyspnea and dry cough one year post anti-TB treatment. Chest imaging was repeated and showed GGO, reticulations, atelectatic bands and calcified nodule. She continued to have progressive dyspnea and developed hypoxemia at rest. She fulfilled diagnostic criteria of chILD (persistent symptoms, signs, radiological changes and hypoxemia) after resolution of infection. Diagnosis of postinfectious chILD was made and she was started on systemic steroids with marked clinical improvement.