Childhood interstitial lung disease: A case-based review of the imaging findings

Markus Wu, Priya Girish Sharma, Dhanashree Abhijit Rajderkar

Abstract:
Childhood interstitial lung disease (chILD) consists of a large, heterogeneous group of individually rare disorders. chILD demonstrates major differences in disease etiology, natural history, and management when compared with the adult group. It occurs primarily secondary to an underlying developmental or genetic abnormality affecting the growth and maturity of the pediatric lung. They present with different clinical, radiologic, and pathologic features. In this pictorial review article, we will divide chILD into those more prevalent in infancy and those not specific to infancy. We will use a case based approach to discuss relevant imaging findings including modalities such as radiograph and computed tomography in a wide variety of pathologies.

Keywords:
Alveolar capillary dysplasia, childhood interstitial lung disease, chronic lung disease of prematurity, congenital surfactant deficiency disorders

In accordance with the “Image Gently” campaign launched by the Society for Pediatric Radiology, pediatric chest computed tomography (CT) examinations at our institution are performed with a low-dose protocol employing lower kVp, and automatic mA modulation with 1 mm × 1 mm lung algorithm reconstruction. In the appropriate patient population and indications, high-resolution chest CT including inspiratory and expiratory phases are obtained.

In this pictorial review article, we will divide chILD into those more prevalent in infancy and those not specific to infancy. We will use a case-based approach to discuss relevant imaging findings including modalities such as radiograph and CT in a wide variety of pathologies that are encountered but are rare.

Childhood interstitial lung disease entities more prevalent in infancy

Alveolar capillary dysplasia
Alveolar capillary dysplasia with misalignment of the pulmonary

How to cite this article: Wu M, Sharma PG, Rajderkar DA. Childhood interstitial lung disease: A case-based review of the imaging findings. Ann Thorac Med 2021;16:64-72.
Pulmonary hypoplasia

Pulmonary hypoplasia is one of the alveolar growth abnormalities in which the bronchus and rudimentary lungs are present, while small airways, alveoli, and pulmonary vessels are decreased in size and number. It can be a primary phenomenon with intrinsic abnormal lung development, which is rare. Secondary pulmonary hypoplasia is much more common with compromised lung development due to intrauterine limitations on the thoracic space.[10] The most common cause of secondary pulmonary hypoplasia is congenital diaphragmatic hernia with abdominal organs occupying the thoracic space[11] [Figure 2]. Additional causes of secondary pulmonary hypoplasia include severe oligohydramnios (secondary to cystic renal dysplasia, prolonged rupture of membranes, or other genitourinary and placental abnormalities) and thoracic skeletal dysplasia (such as thanatophoric dysplasia and Jeune syndrome)[13] [Figures 3 and 4]. Imaging features include

low lung volumes, without evidence of ground-glass opacities or cysts. In addition, the associated causes of secondary pulmonary hypoplasia usually can be found.[13]

Chronic lung disease of prematurity

Chronic lung disease of prematurity is classically described in premature infants exposed to prolonged high-pressure mechanical ventilation and high concentrations of oxygen, resulting in airway smooth muscle hypertrophy, epithelial squamous metaplasia, peribronchial fibrosis, and hypertensive vascular changes.[14] Imaging findings include impaired lung aeration, bronchial wall thickening, coarse reticular pulmonary opacities, and cystic lucencies, with a combination of alveolar septal fibrosis, atelectasis, and hyperinflated lung, resulting in variable lung volumes.[15,16] Oftentimes chest radiographs are sufficient to make the diagnosis [Figure 5]. However, CT is a better modality to better characterize the disease, assess for complications, and perform preoperative/pretransplant assessment[17] [Figure 6].

There is a “new” type of chronic lung disease of prematurity seen in extremely premature (24–26 weeks gestation) infants given the improved ventilatory technique and survival.[18] These patients will have received prenatal corticosteroids and have been ventilated for shorter periods with new ventilator settings,[13] resulting in milder imaging abnormalities with less airway and vascular disease, and less fibrosis [Figure 7]. Histologically, this is seen as arrested lung development corresponding to the gestation of the infant at delivery.[19]

Trisomy 21-related interstitial lung disease

Trisomy 21 (Down syndrome) is one of the lung growth disorders associated with chromosomal abnormalities. These patients were found to have veins (ACD-MPV) is a diffuse development disorder characterized by deficient alveolar capillaries, prominent right-to-left intrapulmonary vascular shunt, malpositioning of the pulmonary veins adjacent to the pulmonary arteries within the bronchovascular bundles, pulmonary lymphangiectasia, as well as muscular hypertrophy of the intralobular pulmonary arterioles, and resultant maldevelopment of the pulmonary lobules.[6] In addition, ACD-MPV is often associated with cardiovascular, gastrointestinal, or genitourinary system anomalies.[9] Genetic mutations and deletions within the Forkhead box transcription factor gene cluster on 16q24.1 have been reported in up to 40% of infants with ACD-MPV.[8,9] Imaging features include progressive ground-glass opacification, with occasional pneumothorax or pneumomediastinum secondary to air leaks. Interlobular septal thickening and peribronchovascular thickening can be seen in associated lymphangiectasia [Figure 1].[1,10] Diagnosis requires biopsy and genetic testing. It is near universally fatal secondary to progressive respiratory failure if lung transplantation is not performed in time.[11]
decreased alveolar number and smaller alveolar surface area, as well as small peripheral subpleural cysts. On imaging, these cysts measure 1–2 mm in size and are subpleural along the lung periphery, fissures, and bronchovascular bundles.[20,21] [Figure 8]. They have been reported to involve the anteromedial portion of the lungs.[20] Histologically, these cysts are enlarged subpleural airspaces in continuity with the proximal airways.[22] The etiology is unknown but thought to be related to pulmonary hypoplasia with Down syndrome.[23]

**Congenital surfactant deficiency disorders**

Surfactant deficiency disorders are caused by mutations in several genes, including genes for surfactant protein B, surfactant protein C, adenosine triphosphate–binding cassette transporter protein A3, thyroid transcription factor 1, and colony-stimulating factor 2 receptor (CSF2RA or CSF2RB).[5,24] Histologically, these genetic surfactant deficiency disorders are similar irrespective of the gene involved. Typical features include type 2 pneumocyte hyperplasia and varying degrees of intra-alveolar macrophages, proteinosis, or lipoproteinosis. On imaging, these patients present with low lung volumes and diffuse ground-glass opacities. Additional findings include cysts, and interlobular septal thickening with a crazy-paving pattern. Associated pectus excavatum has also been reported, which is hypothesized to be the sequelae of chronic restrictive lung disease in the developing chest wall [Figures 9-11].

**Childhood Interstitial Lung Disease Entities Not Specific to Infancy**

**Noonan-related pulmonary lymphangiectasia**

Noonan syndrome is an autosomal dominant congenital disease characterized by RASopathy (Ras/mitogen-activated protein kinase) mutation. It has similar clinical features to Turner syndrome.[25] Various abnormalities of the lymphatic system have been reported in patients with Noonan syndrome including intestinal lymphangiectasis, lymphedema, and pulmonary lymphangiectasis.[26,27] It is caused by dilation and proliferation of the lymphatic channels due to incompetent valves, or agenesis of the valves, with absence or interruption of the thoracic duct. Imaging findings include interlobular septal thickening, ground glass opacification, pleural effusions, or chylothorax [Figure 12].
Blau syndrome – “pediatric sarcoidosis”
Blau syndrome classically presents in early childhood (under the age of 4 years) as a triad of granulomatous dermatitis, arthritis, and uveitis.[28] Recent studies have shown that Blau syndrome and early-onset sarcoidosis are the familial and sporadic forms, respectively, of the same disease.[29] Blau syndrome and early-onset sarcoidosis contrast with the adult-like form of sarcoidosis, which presents in older children and adolescents, clinically manifesting with systemic features of fever, weight loss, hilar adenopathy, and pulmonary infiltration.[30]Interstitial lung disease is a major feature in adults but not in children. Pulmonary involvement is rare and includes ground glass opacities in the both upper and lower lobes, adenopathy of axillary nodes, and bronchial granulomas [Figure 13].

Bronchiolitis obliterans
Bronchiolitis obliterans is a rare, fibrosing form of chronic obstructive lung disease that follows a severe insult to the lower respiratory tract and results in narrowing and complete obliteration of the small airways. Bronchiolitis obliterans in children is most often seen following a severe lower respiratory tract infection, most commonly adenovirus. It is also a known complication following lung transplantation, bone marrow, or hematopoietic stem cell transplantation. Microscopically, this corresponds to fibrosing inflammatory processes around the lumen of the bronchioles resulting in concentric narrowing and obliteration of small airways.[1] On imaging, bronchial wall thickening, ill-defined centrilobular nodular opacities, air trapping, and central bronchiectasis are common findings [Figure 14].

Organizing pneumonia
Organizing pneumonia (used to be described as bronchiolitis obliterans with organizing pneumonia) is histopathologically characterized by granulation tissues within small airways, alveolar ducts, and alveoli and by chronic inflammatory cell infiltration in alveolar walls.[31] When the cause is unknown, organizing pneumonia is classified as primary or cryptogenic. When a cause can be found, it is classified as secondary. Secondary causes include infection, drug reactions, collagen vascular disease, and after toxic-fume inhalation.[32] Common imaging findings include lower lung zone predominant
consolidation, patchy ground glass opacities in a subpleural or bronchovascular distribution, centrilobular nodules 3–5 mm in size, bronchial wall thickening and cylindrical bronchiectasis with air bronchograms, and pleural effusions [33] [Figure 15].

**Adenovirus interstitial pneumonia**

Adenovirus accounts for 5%–10% of acute respiratory infections in the pediatric population while it only accounts for <1% of respiratory illnesses in adults. [34] Adenovirus has its greatest effect in the terminal bronchioles and causes bronchiolitis and bronchiectasis. [35] The bronchiolitis may be necrotizing and result in a necrotizing bronchopneumonia. This is an increasing cause of morbidity and mortality in the immunocompromised pediatric population and has been documented in those who are post liver or kidney transplantation. [36] Swyer-James-MacLeod syndrome is considered to be an acquired disease secondary to adenovirus infection in childhood. [37] Imaging findings include patchy areas of consolidation in a segmental distribution with ground glass opacities [Figure 16], lobar collapse common in children, especially the right upper lobe [38] [Figure 17].

**Chronic Eosinophilic Pneumonitis**

Chronic eosinophilic pneumonia is a rare pediatric respiratory disease [39] and characterized by a significant infiltration of the alveolar spaces and interstitium by eosinophils, with conservation of the normal lung structure. Respiratory symptoms usually last more than 2 weeks duration. The diagnosis is based on the demonstration of alveolar eosinophilia on bronchoalveolar lavage, and/or blood eosinophilia, with exclusion of other known causes of eosinophilia. [40] Pathology shows that exudate rich in eosinophils fills the lung interstitium and alveoli. [41] On imaging, peripheral nonsegmental pulmonary consolidations in mid to upper lung predominance are usually seen [Figure 18]. Chronic eosinophilic pneumonia has an excellent response to steroids.

**Pneumocystis Pneumonia**

Pneumocystis pneumonia is caused by *Pneumocystis jiroveci* and most commonly occurs in immunocompromised children status post allogeneic hematopoietic stem cell transplantation, solid organ transplantation, or with congenital immunodeficiency syndromes and HIV. Subclinical infection is very common in immunocompetent children; two out of three children have antibodies by the age of 4 years. [42] Imaging features on CT include ground glass opacities, predominantly in the mid lung or perihilar region with peripheral sparing, and reticular opacities or interlobular septal thickening with crazy paving pattern [Figures 19 and 20]. Poorly ventilated zones are more prone to infection. Pneumatoceles can develop in 30% of cases. In patients treated with prophylactic medications, it can have an atypical appearance such as tree in bud nodules, lymphadenopathy, and pleural effusions. [43]

**Chlamydia Pneumonia**

*Chlamydia pneumoniae* is a common atypical respiratory
A pathogen found in children 5–15-year-old with an incubation period of approximately 21 days. It causes outbreaks in closed populations such as schools and coinfection with mycoplasma or streptococcus is common. Imaging appearance is variable. Airspace consolidation with or without centrilobular or peribronchovascular nodules is often seen and nonspecific. The presence of centrilobular or peribronchovascular nodules or bronchovascular bundle thickening without consolidation and with hyperexpansion or airway dilatation is more specific to *Chlamydia pneumoniae* pneumonia when compared to other atypical pneumonias[45] [Figure 21].

**Vaping-Associated Lung Disease**

Electronic cigarette or vaping product use-associated lung injury (EVALI) has become a serious public health
problem with significant morbidity and mortality in young adults.[46] These patients present with respiratory symptoms such as dyspnea, as well as systemic symptoms including fever, myalgias, nausea/vomiting, and...
fatigue. Bronchoalveolar lavage in these patients shows increased neutrophils and lipid-laden macrophages. Imaging plays a vital role in the initial detection and evaluation of progression of EVALI. There are several imaging patterns of EVALI in adults including diffuse alveolar damage, lipoid pneumonia, acute eosinophilic pneumonia, and organizing pneumonia.\textsuperscript{[47-49]} In the adolescent population, the most common reported pattern is diffuse alveolar damage, which manifests as bilateral ground-glass opacities and consolidation with subpleural and lobular sparing, in a lower lobe predominance\textsuperscript{[50]} [Figures 22 and 23]. The reversed halo sign (atoll sign) has been reported in pediatric patients with EVALI.\textsuperscript{[51]}

Conclusion

chILDs encompass a large variety of both rare and more common pulmonary pathologies. Pathologies can be divided into two broad categories: Those associated or identified during infancy and those not specific to infancy. Genetic mutations play a large role in the pathogenesis and presentation of chILD and should be kept in mind. Knowledge of these pathologies allows for a multidisciplinary approach by pediatric radiologists, pulmonologists, and clinicians to provide appropriate and timely management.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Semple TR, Ashworth MT, Owens CM. Interstitial lung disease in children made easier...well, almost. Radiographics 2017;37:1679-703.
2. Griese M, Haug M, Brasch F, Freihorst A, Lohse P, von Kries R, et al. Incidence and classification of pediatric diffuse parenchymal lung diseases in Germany. Orphanet J Rare Dis 2009;4:26.
3. Kornum JB, Christensen S, Grijota M, Pedersen L, Wogelius P, Beiderbeck A, et al. The incidence of interstitial lung disease 1995-2005: A Danish nationwide population-based study. BMC Pulm Med 2008;8:24.
4. Das S, Langston C, Fan LL. Interstitial lung disease in children. Curr Opin Pediatr 2011;23:325-31.
5. Kurland G, Deterding RR, Hagood JS, Young LR, Brody AS, Castle RG, et al. An official American Thoracic Society clinical practice guideline: Classification, evaluation, and management of childhood interstitial lung disease in infancy. Am J Respir Crit Care Med 2013;188:376-94.
6. Bishop NB, Stankiewicz P, Steinborn RH. Alveolar capillary dysplasia. Am J Med Genet A 2010;152A: 1257-62.
7. Tonson la Tour A, Spadola L, Sayegh Y, Combescure C, Pfister R, Argiroffo CB, et al. Chest CT in bronchopulmonary dysplasia: Clinical and radiological correlations. Pediatr Pulmonol 2013;48:693-8.
8. Northway WH Jr. Bronchopulmonary dysplasia: Twenty-five years later. Pediatrics 1992;89:969-73.
9. Joshi AJ. The new BPD: An arrest of lung development. Pediatr Res 1999;46:641-3.
10. Biko DM, Schwartz M, Anupindi SA, Altes TA. Subpleural lung cysts in Down syndrome: Prevalence and association with coexisting diagnoses. Pediatr Radiol 2008;38:280-4.
11. Gonzalez OR, Gomez IG, Recalde AL, Landing BH. Postnatal radiologic-pathologic correlation. Radiographics 2010;30:1721-38.
12. Lee EY. Interstitial lung disease in infants: New classification system, imaging technique, clinical presentation and imaging findings. Pediatr Radiol 2013;43:3-13.
13. Aukland SM, Halvorsen T, Fosse KR, Daltveit AK, Rosendahl K. Congenital lung abnormalities: Embryologic features, prenatal diagnosis, and postnatal radiologic-pathologic correlation. Radiographics 2010;30:1721-38.
25. Ford JJ, Trotter CW. Noonan Syndrome Complicated by Primary Pulmonary Lymphangiectasia. Neonatal Network 2015;34:117-25.

26. Hernandez RJ, Stern AM, Rosenthal A. Pulmonary lymphangiectasis in Noonan syndrome. AJR Am J Roentgenol 1980;134:75-80.

27. Noonan JA, Walters LR, Reeves JT. Congenital pulmonary lymphangiectasis. Am J Dis Child 1970;120:314-9.

28. Rose CD, Martin TM, Wouters CH. Blau syndrome revisited. Curr Opin Rheumatol 2011;23:411-8.

29. Rose CD. Blau syndrome: A systemic granulomatous disease of cutaneous onset and phenotypic complexity. Pediatr Dermatol 2017;34:216-8.

30. Becker ML, Martin TM, Doyle TM, Rosé CD. Interstitial pneumonitis in Blau syndrome with documented mutation in CARD15. Arthritis Rheum 2007;56:1292-4.

31. Lee JW, Lee KS, Lee HY, Chung MP, Yi CA, Kim TS, et al. Cryptogenic organizing pneumonia: Serial high-resolution CT findings in 22 patients. AJR Am J Roentgenol 2010;195:916-22.

32. Kligerman SJ, Franks TJ, Galvin JR. From the radiologic pathology archives: Organization and fibrosis as a response to lung injury in diffuse alveolar damage, organizing pneumonia, and acute fibronous and organizing pneumonia. Radiographics 2013;33:1951-75.

33. Faria IM, Zanetti G, Barreto MM, Rodrigues RS, Araujo-Neto CA, Silva JL, et al. Organizing pneumonia: Chest HRCT findings. J Bras Pneumol 2015;41:231-7.

34. Franquet T. Imaging of pulmonary viral pneumonia. Radiology 2011;260:18-39.

35. Becroft DM. Bronchiolitis obliterans, bronchiectasis, and other sequelae of adenovirus type 21 infection in young children. J Clin Pathol 1971;24:72-82.

36. Chong S, Lee KS, Kim TS, Chung MJ, Chung MP, Han J. Adenovirus pneumonia in adults: Radiographic and high-resolution CT findings in five patients. AJR Am J Roentgenol 2006;186:1288-93.

37. Müller NL. Unilateral hyperlucent lung: MacLeod versus Swyer-James. Clin Radiol 2004;59:1048.

38. Chiu CY, Wong KS, Huang YC, Lin TY. Bronchiolitis obliterans in children: Clinical presentation, therapy and long-term follow-up. J Paediatr Child Health 2008;44:129-33.

39. Nathan N, Guilleminot N, Aubertin G, Blanchon S, Chadelat K, Epaud R, et al. Chronic eosinophilic pneumonia in a 13-year-old child. Eur J Pediatr 2008;167:1203-7.

40. Marchand E, Cordier JF. Idiopathic chronic eosinophilic pneumonia. Orphanet J Rare Dis 2006;1:11.

41. Tassinari D, Di Silverio Carulli C, Visciotti F, Petrucci R. Chronic eosinophilic pneumonia: A paediatric case. BMJ Case Rep. 2013. p. 2013.

42. Pyrgos V, Shoham S, Roilides E, Walsh TJ. Pneumocystis pneumonia in children. Paediatr Respir Rev 2009;10:192-8.

43. Pitcher RD, Zar HJ. Radiographic features of paediatric pneumocystis pneumonia A historical perspective. Clin Radiol 2008;63:666-72.

44. Hammerschlager MR. Chlamydia trachomatis and Chlamydia pneumoniae infections in children and adolescents. Pediatr Rev 2004;25:43-51.

45. Nambu A, Saito A, Araki T, Ozawa K, Hiejima Y, Akao M, et al. Chlamydia pneumoniae: Comparison with findings of Mycoplasma pneumoniae and Streptococcus pneumoniae at thin-section CT. Radiology 2006;238:330-8.

46. Abbara S, Kay FU. Electronic cigarette or vaping-associated lung injury (EVALI): The tip of the iceberg. Radiol 2019;1:e190212.

47. Henry TS, Kanne JP, Kligerman SJ. Imaging of vaping-associated lung disease. AJR Am J Roentgenol 2020;214:498-505.

48. Sechrist JW, Kanne JP. Vaping-associated lung disease. Radiology 2020;294:18.

49. Henry TS, Kligerman SJ, Raptis CA, Mann H, Sechrist JW, Kanne JP. Imaging findings of vaping-associated lung injury. AJR Am J Roentgenol 2020;214:498-505.

50. Thakrar PD, Boyd KP, Swanson CP, Wideburg E, Kumbhar SS. E-cigarette, or vaping, product use-associated lung injury in adolescents: A review of imaging features. Pediatric Radiol 2020;50:338-44.

51. Artunduaga M, Rao D, Friedman J, Kwon JK, Pfeifer CM, Dettori A, et al. Pediatric chest radiographic and CT findings of electronic cigarette or vaping product use-associated lung injury (EVALI). Radiology 2020;295:430-8.