Subpleural Pulmonary Cysts in Children: Associations Beyond Trisomy 21

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April 26, 2023

Abstract

Background: Small air filled peripheral subpleural cysts are a well described feature of pulmonary anatomy at computerised tomographic (CAT) scan in children with Trisomy 21, yet only anecdotally described in association with other pathologies. The significance of these cysts is unknown. **Objective**: To investigate and explore the pathogenesis of these subpleural cysts in children. **Materials and Methods:** A retrospective review of 16 cases with subpleural cysts diagnosed on CT chest was performed. The distribution, location and ancillary CT findings were recorded. Hospital charts were reviewed for clinical details, especially cardiac abnormalities, pulmonary artery hypertension (PAH) and genetic associations. Histopathological and clinical correlative data were recorded. **Results:** 11/16 children (69%) were found to have an underlying chromosomal or genetic abnormality, six of whom had Trisomy 21. The remaining 5/16 cases (21%) had miscellaneous disorders without an identifiable genetic basis. The most common co-morbidities were cardiac abnormalities (81%) and PAH (62.5%). Regardless of their underlying etiologies, the cysts were present bilaterally in most cases (14/16, 88%). We observed both the postnatal development and the progression of cysts in our cohort . On long term follow-up, there were five deaths (31%) and six cases (38%) requiring maintenance oxygen therapy due to chronic hypoxia. Two cases (12.5%) became completely asymptomatic after correction of their underlying abnormalities. **Conclusion:** Subpleural cysts are not exclusive to Trisomy 21 and may be seen in other inherited or acquired causes, likely due to altered alveolar growth. We suspect these cysts are a sign of an underlying developmental disorder with variable clinical effect, especially in children with congenital cardiac disease.

Introduction

Interstitial lung diseases in the pediatric population are currently characterized using a contemporary combined clinical and pathological approach as proposed by Kurland et al, from the ChILD consortium. (1). Childhood interstitial lung diseases (chILD) are now recognised as distinct entities, owing to newly appreciated pathogeneses unique to the pediatric age group, particularly evident in younger children. Advances in the radiological, pathological and genetic bases in recent years have prompted distinction of specialized subgroups of diffuse lung diseases that present during infancy.

At the authors' institution, we have recently noted a radiographic pattern on computerised tomography (CT) of the chest, characterized by a rim of small 1-4 mm subpleural cysts at the periphery of the lungs. (images 1,2). The cysts are frequently but not exclusively symmetric and diffuse. The most frequently described diagnostic entity associated with these small air-filled cysts is Trisomy 21. (2, 3, 4, 5, 6, 7). Pathological specimens in children with Trisomy 21 have demonstrated cystic dilatations of the subpleural alveoli that communicate with dilated alveolar ducts. (2,7). There are only occasional case reports describing their occurrence in other genetic abnormalities, including Trisomies 10 and 18, and Filamen A mutation (3,8,9, 10)

We have seen this CT pattern of subpleural cysts in children without Trisomy 21. These are either primary (without any major lung abnormality) or in association with a co-existing cardiovascular abnormality. Through this retrospective analysis, we present a wider population manifesting subpleural cysts. We propose that these subpleural cysts are associated with pulmonary histological dysmaturity or immaturity, similar to that proposed in children with Down's syndrome (2). Though rare, there is currently limited literature regarding their further clinical associations and their evolution over time.

Materials and methods

This retrospective, observational, descriptive longitudinal study was approved by our institutional Research Ethics Board. We performed a free word search of our radiological report database using the terms "subpleural cysts", "peripheral cysts" or "subpleural blebs" over a 21-year period (2001-2022) at a tertiary level pediatric hospital. We limited the search to children under 3 years of age at their initial chest CT. Patient demographics, clinical information and laboratory work-up including genetics and histopathology were extracted from patients' charts. Echocardiographic and cardiac catherisation reports were reviewed for the documentation of underlying congenital heart disease (CHD) and/or pulmonary artery hypertension (PAH).

All CT scans, including studies acquired at external institutions, were performed on multi-detector scanners. Scanners differed with upgraded technology due to a long study duration of over 22 years. All cases were performed as helical scans, reconstructed to 2.5mm thickness for review of mediastinal/soft tissue windows using approximate window width 350, level 40 and reconstructed to 0.625-2.5mm thickness for review on a lung algorithm (approximate window-width 1500, level -500). Intravenous contrast was given in most cases, depending on the clinical question. Our primary endpoint was the presence or absence of multiple 1-4 mm air-filled subpleural cysts.

All studies performed at our institution utilised a CT dose-adjusted algorithm according to the body weight of the child. More recent studies were performed using CT scanners that provided additional automatic exposure control (AEC) with modulation of the tube-current depending on the thickness of the body part examined. As a result, mAs varied between 80-150 with a 120 kVp. As all patients were under the age of 4, scans were performed either using a "feed and sleep" approach, sedation or under general anaesthesia (GA). Non-GA cases were acquired in quiet breathing and GA cases were acquired in full inspiration, either via endotracheal tube or positive pressure mask. Prospective ECG-gated triggering was done in cases performed with a cardiac CT protocol.

All CT images were qualitatively analysed for the presence and distribution of subpleural cysts. The size of the largest cyst was recorded. The heart and mediastinal structures were evaluated for structural cardiac abnormalities, in correlation with data from echocardiographic examinations. Ancillary findings of mosaic attenuation, ground glass opacities and pleural effusion or pneumothorax were also recorded. Follow-up CT's in the available cases were compared for the interval status of cyst size and distribution. All images were analysed independently by three pediatric radiologists with a specialty interest in pulmonary imaging (33 years' experience, 3 years' experience, and a fellow in pediatric imaging). The radiologists were blinded to the clinical information and to each other's interpretations, with a consensus on final image interpretation.

Subpleural cysts were differentiated from subpleural lines seen in children with lymphatic distension due to lymphangiectasia by set criteria consisting of the lack of fissural thickening, lack of pleural effusions, lack of basal septal thickening creating typical hexagonal opacities, and lack of 'Kerley' lines in our cohort of children with peripheral cystic disease.

Demographic characteristics were summarized using descriptive statistics.

RESULTS

Sixteen children (ages 8d to 3y4m at first CT: 9M,7F) with subpleural cysts were identified during the study period over 22 years. Of these 16 children, 7 children received only a single CT examination. The remaining 9 children underwent multiple CT studies (up to three CTs in 4 children and four CTs in 1 child) at variable intervals depending on the clinical need. Of the 9 children who underwent repeat CT chest examinations, 7

occurred> 5 months after the first scan, and 6 children went on to have a third CT after an average of 12 months. One child had a fourth follow-up CT, performed 10 years after their initial CT.

Considering the known association with Trisomy 21, we divided the cases into two groups based on their genetic profiles (Table 1). The first group had an underlying genetic defect identified (n=11) while the second group had no identifiable genetic defect (n=5).

Findings of the CT scans are provided in Table 2. Of note, only 2 children manifested unilateral cysts. In the first child (case 12), cysts were only present on the left side. This child had left lower pulmonary vein stenosis and a smaller left lung. In the second child, (case 13), only right sided cysts were seen. This child had an absent right pulmonary artery and a smaller right lung.

While Trisomy 21 was the most common underlying genetic association when a genetic disorder was discovered (n=6/11), the cysts were found in other rare disorders, including one case of Kabuki syndrome and one case of Cornelia-de-Lange syndrome. The other 4 genetic abnormalities are listed. The remaining 5 children listed had other clinical pathologies which did not warrant genetic evaluation.

The most common clinical pathology in all these children was some form of congenital heart disease (14/16), most associated with left to right physiology (VSD or AVSD in 6/14, ASD in 6/11, PDA in 2/11, allowing for children with multiple defects). Pulmonary artery hypertension was recorded to be present in 8 children.

Two children who had no defined genetic abnormality were discovered to have these cysts in their teens, one with microscopic polyangiitis and one with hepatoportal sclerosis at birth of unknown etiology requiring liver transplantation (Image 2). Of note, this latter case had secondary hepatopumonary syndrome before liver transplantation.

While only a small number of children underwent follow-up CT scans for assorted reasons, it is noteworthy that in most cases (n=5/9) the number and size of cysts increased with time. (Image 1). The child with hypoplastic left heart syndrome (case 12) had 2 CTs performed in the first year of life that had no peripheral cysts, with the cysts only appearing on the 3rd CT at 2 years of age.

We could not find any significant correlation with ventilatory requirements. 7 cases required mechanical ventilation, usually in association with surgery for the underlying CHD. All 7 cases had underlying CHD, of which 5 were premature as well.

Pulmonary function tests were only performed in 2 teens, with contradictory results.

Indications for CT chest examination included evaluation of lung parenchyma in moderate to severe PAH (6/16), pre-operative evaluation of an underlying congenital heart disease (2/16), post-operative follow-up for worsening hypoxemia (2/16), and evaluation of recurrent upper respiratory tract infections (3/16). Other indications included evaluation of antenatally diagnosed pulmonary lymphangiectasia (1/16), concern for right-to-left shunting (1/16), and evaluation of non-specific dry cough and respiratory difficulty (1/16).

Histopathology was correlative in only two cases, both with Trisomy 21. The first was performed at the time of cardiac surgery (case 1) which demonstrated focal enlargement and simplification of subpleural alveolar spaces (image 3). The second was at autopsy (case 9) A third biopsy was performed in the teen with ANCA (Anti Neutrophil Cytoplasmic Antibodies) positive MPO positive microscopic polyangiitis, revealing pulmonary hemosiderosis without capillaritis.

Long term outcomes seemed to be more related to the child's underlying anomalies than to a pulmonary etiology. All 5 children who died had underlying CHD. Short term outcomes could not be associated with the presence of subpleural cysts due to the paucity of cases and to the complexity of confounding clinical variables including but not limited to prematurity, CHD, surgeries and intercurrent infections.

DISCUSSION

Alveolar growth abnormalities (AGA) usually present after birth and can occur as a result of multiple factors. They may be related to 1) pulmonary hypoplasia seen in situations limiting in utero lung growth, 2)

prematurity-related chronic lung disease, 3) term infants with early onset chronic lung disease, 4) children with congenital heart disease who have a normal karyotype, and 5) children with chromosomal abnormalities (including trisomy 21 with or without associated congenital heart disease, and other chromosomal abnormalities).

Regardless of the underlying etiology, AGAs share the common feature of alveolar growth arrest leading to alveolar simplification on histopathology. This simplified alveolar pattern is reminiscent of the rudimentary lung in fetal life, which has dilated alveolar sacculi. The overall reduced alveolar density results in a smaller gas-exchange surface area. Ancillary changes may occur in the surrounding interstitium, including pulmonary interstitial glycogenosis (PIG) and hypertensive arteriopathy in the pulmonary artery branches (11,12,13).

Cystic lung disease in Trisomy 21 was first reported by Joshi et al (14) in the autopsy specimens of two infants with AVSD. These were evident as multiple 2-4 mm sized cysts lining the subpleural surfaces of the lungs anteromedially, with cystic dilatation of the alveoli on microscopic examination. In a postmortem study by Gonzales et al (4), subpleural cysts were described in specimens of 18/89 (25%) children with Trisomy 21 (9 stillborn fetuses and 80 infants). Interestingly, none of the stillborn fetuses had subpleural cysts and only one neonate (3.5 weeks of age) was found to have subpleural cysts. The authors concluded that formation of the subpleural cysts occur due to immaturity/dysmaturity of alveoli in their later stages of development (phase of alveolarization). As such these changes were not present in fetal and neonatal life.

While this entity became reasonably well documented in association with Trisomy 21, our cohort shows subpleural cysts can be present in other conditions as well. Subpleural cysts are described with ancillary findings including interstitial glycogenosis and interstitial thickening in the regional interstitium, that can also be associated with alveolar growth abnormalities (12). However, the exact pathophysiological significance of subpleural cysts remains uncertain. Histopathological correlation places these cysts within the final stage of lung development of alveolarization, suggesting they are a form of altered alveolar growth. (2). The phase of alveolarisation is further divided into an 'early phase' of rapid alveolar growth that occurs from 36 weeks' gestation to 3 years of age, and a slower phase that continues into later childhood. This stage also holds importance in laying an effective gas-exchange unit. with thinning of the intervening mesenchyme and further apposition of the alveolar walls (1,9,15,16).

Interestingly, we observed 4 cases for whom an initial scan demonstrated no cysts, but subsequent scans showed the interval development of cysts. This supports the observations by Gonzales et al that these cysts can develop due to abnormalities affecting the alveolar development beyond their fetal stage of development.

Previous studies have demonstrated the youngest children with subpleural cysts to be as young as 2 weeks and 3 months of age, respectively (5,7). The youngest child with subpleural cysts in our study was an 8-day old infant with antenatally detected pulmonary lymphangiectasia.

From their large database of 8000 cases, Gonzales et al could find only two cases with subpleural cysts who did not have Trisomy 21, one of which had CHD. By contrast, Trisomy 21 was not the most common clinical entity in our study population. In fact, we found that most cases (67%) did not have Trisomy 21. This might be related to improved contemporary genetic analytic capabilities as compared to previous studies, or to CT related factors including improved spatial resolution and accessibility. Gyves et al (17) were the first to report that subpleural cysts in children with Trisomy 21 can be seen on CT alone, and not chest radiographs. We anecdotally found a similar low sensitivity of radiographic detection of subpleural cysts, suggesting a higher true incidence of these cysts given the limited indications for CT.

The size of these subpleural cysts has been described as 1-2 mm (4,7). This correlates with our findings of cysts between 1-2 mm in most cases at initial CT. Interestingly however, cysts did enlarge in subsequent CT's in children with follow-up imaging.

As can be seen in Table 2, bilateral lung involvement predominated. This is in concordance with the literature, where Biko et al. reported unilateral involvement in only one of the nine (11%) cases and Lim et al described unilateral involvement in only three of their ten cases (30%) with Trisomy 21. Bilaterality would

be expected in children with an abnormality of alveolar development, diffusely affecting the concomitantly developing lungs.

Pneumothorax was not observed in any of our cohort, despite the precarious subpleural location of these cysts, especially in the presence of positive-pressure ventilation. We also could not find any report of pneumothorax complicating these cysts in the literature. Microscopically, these cysts have definable walls of varying thickness, which may prevent their rupture. Histopathological findings from our study, as well as existing evidence from cases of Trisomy 21 (2) and Trisomy 18 (10), suggest that these abnormal alveoli indeed have thick walls. The intervening interstitium is also thickened in these cases due to the presence of a primitive capillary network. We believe that these features of dysplastic alveoli and rudimentary capillary network confer them with relative protection against the subsequent development of pneumothorax.

Although 66% of our cohort had a history of prematurity, the distribution of cysts did not suggest that these are attributable to prematurity alone. Parenchymal cysts in chronic lung disease of prematurity are more randomly distributed within the lungs. Paradoxically in our cases, these cysts predominantly or exclusively involved the subpleural lungs, thereby suggesting an alternate etiology.

The exact impact of these cysts on lung function remains elusive as their impact on the cardiopulmonary status is often difficult to ascertain. There remains ambiguity for the potential role, if any, of these alveolar growth abnormalities in the development of PAH.

We believe that these subpleural cysts represent dysplastic alveoli and alveolar ducts. The extent to which they contribute to respiratory compromise is likely variable and partially dependent on other underlying co-morbidities, particularly congenital heart disease. Limited cardio-respiratory reserve and vulnerable conditions could theoretically unmask the inability of these immature and dysplastic alveoli to provide an efficient gas-exchange unit. It has been proposed that this could worsen a hypoxemic state, which sets a vicious cycle of worsening PAH that in turn affects alveolar ventilation and vice-a-versa (2,11).

Our study demonstrates the non-specificity of subpleural cysts to Trisomy 21. As such, we believe that these cysts represent a growth abnormality of the lung that can be seen in other conditions, consisting of, in part, alveolar simplification, peripheral acinar enlargement and resultant overall pulmonary alveolar hypoplasia. CT can be performed to identify subpleural cysts as evidence of underlying lung maldevelopment.

The most significant limitation of our study is the small number of children who manifest subpleural cysts at CT. Due to a small sample size, we could not establish a definitive association of these cysts with co-morbidities and long -term outcome. Subsequent studies of larger sample sizes could help to clarify the role of this degree of pulmonary dysmaturity in cardio-respiratory compromise.

CONCLUSION:

Subpleural cysts are not unique to Trisomy 21 and can be seen in other congenital or acquired causes that may interfere with the growth of the alveoli. Their exact effect on pulmonary function by themselves remain to be ascertained.

Captions

Image 1

Subpleural cysts with interval progression in Trisomy 21 (Case 2) : (a,b) CT scan of 1y5m old male child shows small subpleural cysts in bilateral lungs with greater involvement of the left lung. (c,d) Follow-up CT at the age of 4 years 8 months reveals increase in the size of pre-existing cysts as well as new areas of involvement in the posterior portions of the lungs.

Image 2

CT scans of a child with biopsy proven capillaritis (a,b)(case 15) and a different child with idiopathic hepatic sclerosis (c,d)(case 16), both with subpleural cysts

Table 1

Clinical characteristics of the population, divided into Group A (identified genetic abnormality) and Group B (no identified genetic abnormality)

Table 2

CT findings with respect to size, number and distribution of subpleural cysts, as divided into Group A (identified genetic abnormality) and Group B (no identified genetic abnormality)

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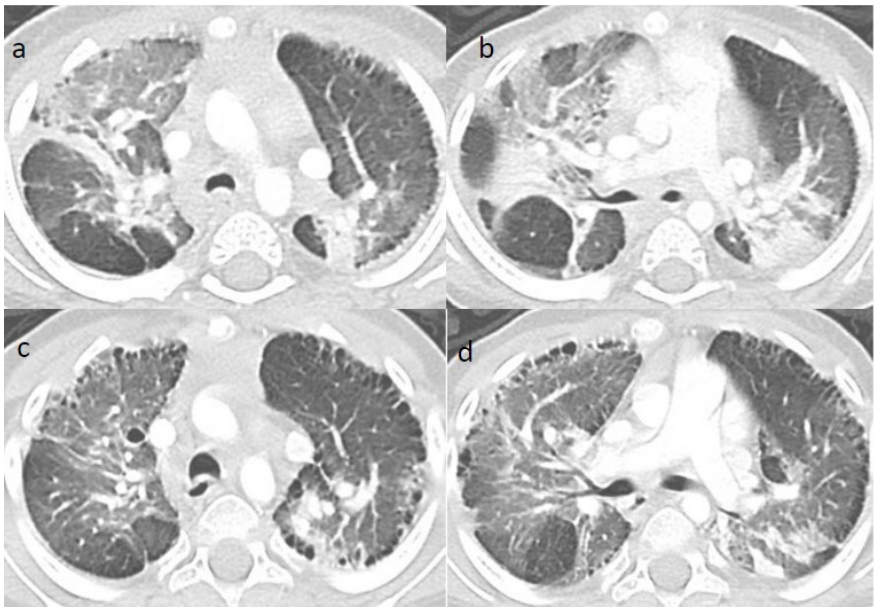

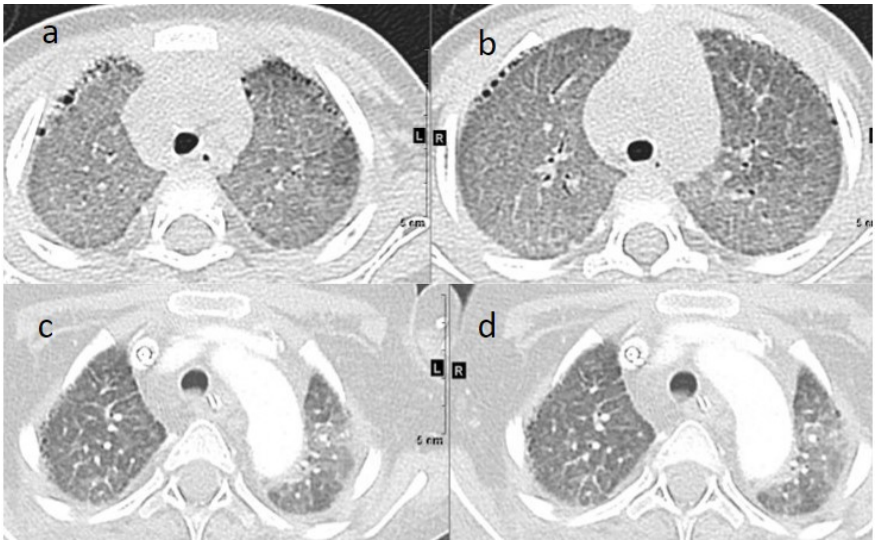

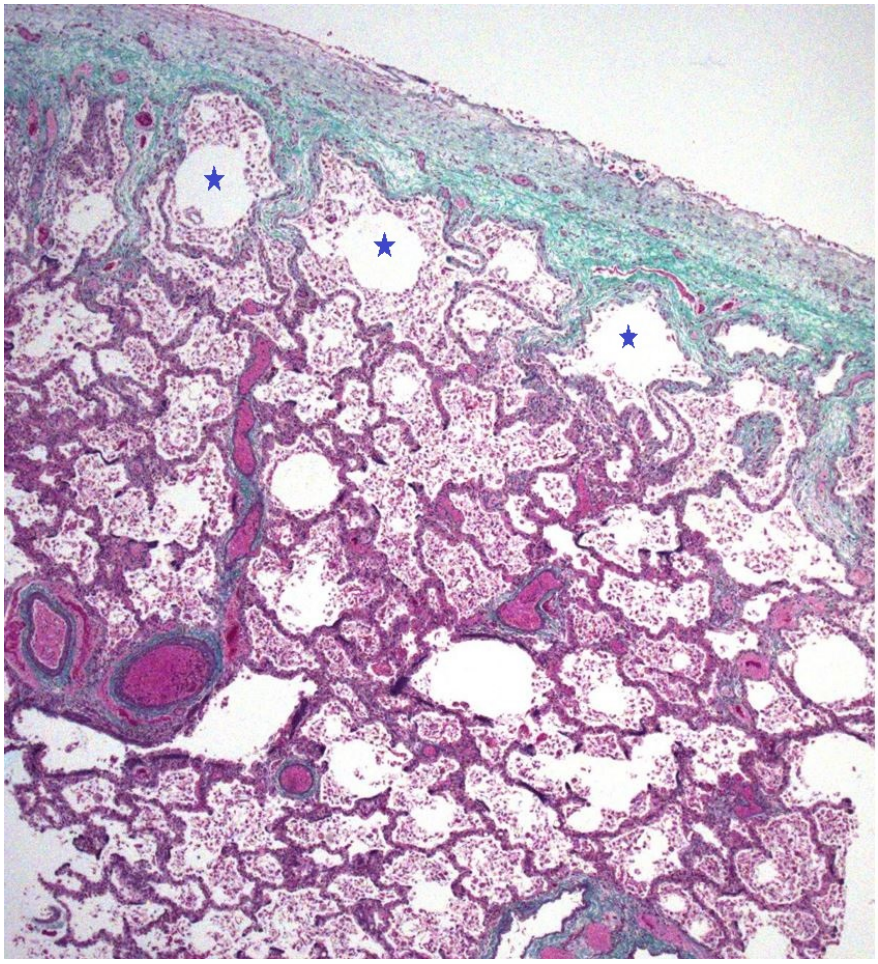

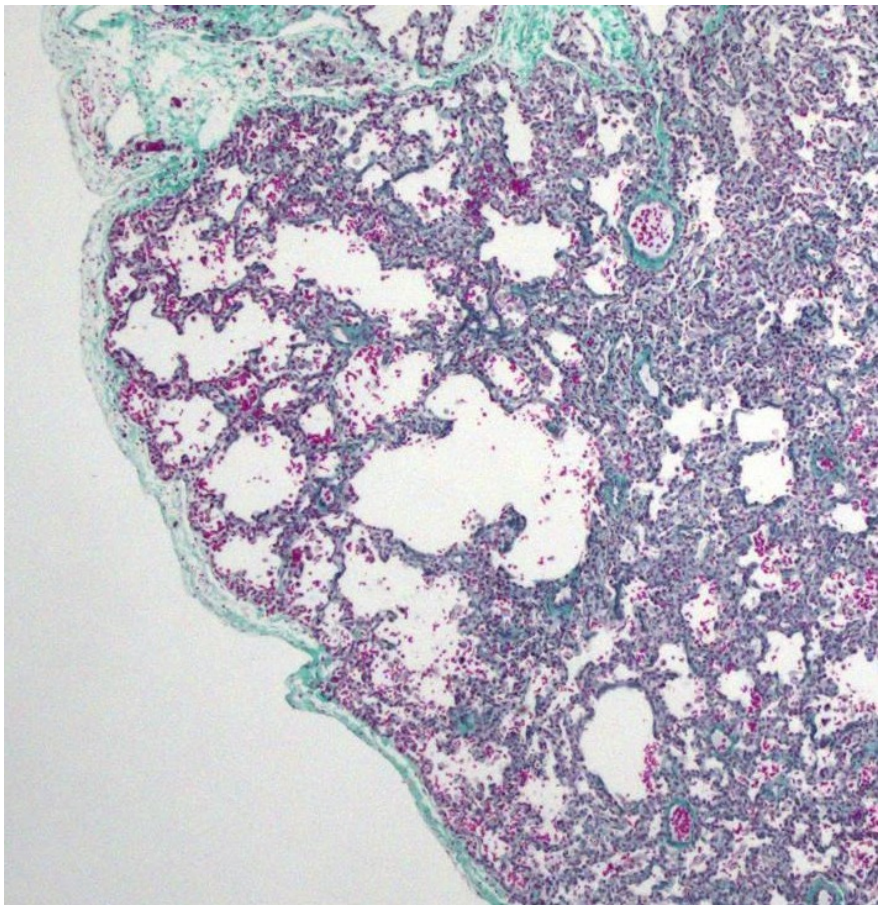

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