Alveolar growth abnormality in an infant with atrial septal defect: a case report

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Abstract
Alveolar growth abnormality is a rare paediatric diffuse lung disease. We report a case of a term girl with atrial septal defect and respiratory failure in early infancy. Lung biopsies demonstrated alveolar simplification. Timely surgical correction of atrial septal defect was temporally associated with resolution of respiratory symptoms.

Keywords: Atrial septal defect, growth abnormality, interstitial lung disease, paediatric, respiratory failure

Introduction
Atrial septal defect (ASD) is an uncommon cause of heart failure or respiratory distress in early infancy. We presented a case of ASD complicated by alveolar simplification leading to intractable respiratory failure.

Case report
A 3600-gram Chinese female was born to a Gravida one lady with an uncomplicated pregnancy at gestation 38 weeks by elective caesarean section. She had an uneventful perinatal course and was discharged home on day 3 of life. Family history was unremarkable and there was no parental consanguinity. At 2 months old, she presented to the hospital with coryzal symptoms and dyspnoea, and she was admitted with a presumptive diagnosis of acute bronchiolitis. On examination, she did not have dysmorphism. The oxygen saturation was initially 97% on room air. Heart rate was 150 beats per minute and respiratory rate was 50-60 breaths per minute. An ejection systolic murmur was detected. There were diffuse fine crackles and occasional wheeze over bilateral lung fields on auscultation. Liver was palpable 2 cm below right costal margin. Chest radiograph showed haziness over bilateral upper lobes (Figure 1). White cell count was 13.8x10^9/L, neutrophil and lymphocyte was 6.1 and 7.1x10^9/L respectively. C-reactive protein was <0.6 mg/L. Blood culture did not reveal any bacterial growth. Nasopharyngeal aspirate was negative for common respiratory viruses. Culture of nasopharyngeal swab for Bordetella pertussis was negative. Complement fixation test for antibody titres against respiratory pathogens including Mycoplasma pneumoniae was also negative. Echocardiogram showed a large secundum ASD, a small patent ductus arteriosus (PDA), enlarged right atrium and right ventricle, and evidence of pulmonary hypertension. Inhaled bronchodilator was tried and diuretics for heart failure were commenced. Surgical repair of ASD and PDA was planned after stabilisation of her pulmonary condition.

Unfortunately, our patient remained tachypnoeic and developed oxygen dependency requiring oxygen of 0.5-1 L/min via nasal cannula to maintain her saturation 95% or above despite an empirical course of amoxicillin/clavulanic acid. Computed tomography (CT) of thorax performed at 4 weeks after admission showed extensive collapse consolidation and ground glass opacification in both lungs, involving posterior segment of the right upper lobe, apical segment of the right lower lobe, posterior segment of the right lower lobe, multiple subsegmental regions of the left upper lobe and lingula, and most of the left lower lobe (Figure 2).

No infectious causes could be identified to account for the extensive consolidative changes on CT. Assessment by speech therapist demonstrated signs of dysphagia and aspiration. Flexible bronchoscopy was carried out which showed normal anatomy. Bronchoalveolar lavage detected fat laden macrophages though latter was not quantified. Although, 24-hour pH study and milk scan...
did not demonstrate gastro-esophageal reflux (GER) or evidence of aspiration, subsequent water-soluble contrast study did reveal evidence of GER. Oral feeding was replaced by nasogastric tube feeding. Workup for immune disorders including immunoglobulin pattern and lymphocyte subset did not suggest an underlying immunodeficiency.

Two months after the initial admission, our patient had an aspiration event and ended up requiring non-invasive ventilatory support and intensive care at 4 months of age. CT thorax showed that both lungs were heterogeneous in density with multifocal areas of hyperlucency suggestive of air trapping and the overall features were suspicious of post infection bronchiolitis obliterans. Unfortunately, she further deteriorated and required invasive ventilation 1 week later. Echocardiogram showed evidence of pulmonary hypertension and sildenafil was started. Two tracheal aspirates were positive for *Mycoplasma pneumoniae* DNA with PCR test, and a course of macrolide treatment was given. However, there was no clinical improvement and the patient remained ventilator dependent.

Lung biopsy was performed via thoracotomy because of persistent respiratory symptoms and radiographic changes. However, this first lung biopsy was not diagnostic. There was no significant inflammatory process and the features of bronchiolitis obliterans were not apparent in the biopsy. With the clinical evidence of dysphagia and GER, besides infection, aspiration was considered as an important culprit leading to bronchiolitis obliterans and respiratory failure, therefore gastrostomy and fundoplication were also performed.

With the working diagnosis of bronchiolitis obliterans syndrome, a trial of pulse methylprednisolone 30 mg/kg/day was given intravenously for 3 consecutive days and daily oral azithromycin 10 mg/kg was also started. Our patient was successfully extubated to nasal continuous positive airway pressure (nCPAP) within 12 hours after completion of the first course of methylprednisolone but then required re-intubation and invasive ventilation 1 week afterwards due to respiratory failure.

In view of the large ASD with significant pulmonary hypertension, early surgical repair of ASD was sought. Surgical closure of the ASD and ligation of the PDA were performed at 6 months of age. Open lung biopsy was repeated at the same surgery. The patient could be extubated to nCPAP 5 days after the operation. Echocardiogram repeated after the operation showed satisfactory left ventricular contraction with no residual ASD or PDA. NCPAP was removed 8 days after the operation and the infant remained well in room air with normal oxygen saturation. Our patient was eventually discharged at 7 months of age without the need of oxygen supplement. With training, she was able to feed orally without aspiration, and gastrostomy tube was

Figure 1. Chest radiograph (AP view) on admission demonstrated interstitial lung markings bilaterally especially in both upper lobes.

Figure 2. Axial high-resolution computed tomography thorax images. Image at 4 weeks after admission demonstrated extensive collapse consolidation and ground glass opacification in both lungs.
removed at 10 months old. She is now 2 years old and continues to do well without respiratory symptoms. Both lung biopsies were subsequently reviewed by a paediatric pulmonary pathologist. In the first biopsy, the lung parenchyma showed evidence of alveolar growth abnormality (alveolar simplification), characterised by distention of alveolar ducts, focal distention of peripheral airspaces, and mildly deficient septation in the subpleural airspaces (Figure 3). The pulmonary vasculature had no discernible abnormalities despite patient’s clinical history of ASD and pulmonary hypertension. There was no evidence of airway fibrosis to suggest bronchiolitis obliterans syndrome. There was no misalignment of pulmonary veins to suggest alveolar capillary dysplasia. Airway or interstitial inflammation was not seen, and no bacterial, fungal or mycobacterial organisms were identified. A Bombesin immunostain demonstrated an appropriate number of airway neuroendocrine cells, therefore neuroendocrine cell hyperplasia of infancy (NEHI) was unlikely. The second lung biopsies basically showed similar findings although the enlargement and simplification of airways were more exaggerated. In the second set of biopsies, there was a very minor component of pulmonary interstitial glycogenosis; however, this change was not likely to be physiologically significant for our patient. In summary, the major finding detected in these two sets of lung biopsies was the presence of alveolar simplification of mild to moderate degree, which was most likely secondary to the atrial septal defect.

Discussion

Diffuse lung disease in children comprises a heterogeneous group of rare lung disorders that contribute to considerable morbidity and mortality.\(^1,2\) Alveolar growth abnormality was the most common diffuse lung disease category represented in the lung biopsy reviews by Deutsch et al and Langston & Dishop with an overall mortality of 34%.\(^1,2\) It is characterised by prenatal or postnatal defective alveolarisation, resulting in variable alveolar simplification with deficient alveolar septation, often most prominently subpleurally.\(^1\) Abnormalities of alveolarisation are largely secondary and may be seen in a wide variety of circumstances, including pulmonary hypoplasia, chronic lung disease of prematurity, congenital heart disease and chromosomal abnormalities.\(^1,2\) In contrast to pulmonary hypoplasia and prematurity, the mechanisms resulting in alveolar simplification in congenital heart disease and chromosomal disorders are not completely understood. Intrauterine haemodynamics within the pulmonary vasculature may influence the degree of alveolarisation in children with congenital heart disease.\(^4\)

Hypoxaemia and tachypnoea are the most common symptoms and a significant number of children also have gastro-esophageal reflux, pulmonary hypertension and poor growth.\(^2\) However, these are also common features shared in many diffuse lung diseases and other cardiopulmonary disorders. Our patient suffered from persistent and progressive respiratory symptoms which

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**Figure 3.** Histology. (a) Wedge biopsy of the lung revealed distended alveolar ducts (asterisk) and focal distention of peripheral airspaces (arrows). Some of the subpleural airspaces showed mildly decreased septation, consistent with mild alveolar growth abnormality (haematoxylin and eosin, 4x magnification). (b) Higher magnification of the same lung wedge biopsy showed distended airspaces accompanied by decreased alveolar septa (asterisks) (haematoxylin and eosin, 10x magnification).
could not be solely explained by the presence of ASD and heart failure. Underlying lung pathology had to be considered, which might have predisposed the patient to respiratory failure when infection or other insults to the lungs took place. Apart from alveolar abnormality, pulmonary interstitial glycogenosis (PIG), NEHI, bronchiolitis obliterans or even infection could share similar clinical features. Correct diagnosis of a particular disorder within the spectrum of diffuse lung diseases is vital in determining treatment plan and predicting disease prognosis. Children's Interstitial Lung Disease Research Network (CHILDRN) has developed a working clinical definition, labeled as chILD syndrome which may be used as a screening tool to identify children who may benefit from evaluation for possible interstitial lung disease. Lung biopsy should be considered when the less invasive tests are not diagnostic and the child has persistent symptoms of at least 2 months or when the disease is progressively worsening. Consensus in handling lung biopsies is also important to optimise the diagnostic yield of lung biopsies. In this case of alveolar growth abnormalities, proper biopsy formalin inflation is particularly important which allows the alveoli to re-expand and facilitates the assessment of alveolar architecture and interstitium.

Aetiology of PIG is currently unclear. However the frequent presence of PIG in other forms of lung injury supports that it may be a non-specific reactive feature in the infant lung related to lung development and injury. In our case, the lung biopsy was performed after a period of mechanical ventilation, therefore whether the component of PIG was primary or secondary remains uncertain.

Our patient with atrial septal defect presented with persistent respiratory symptoms. Lung biopsies confirmed the diagnosis of alveolar growth abnormality and excluded other important differential diagnoses. Development of respiratory failure and prolonged ventilator dependency could be attributed to multiple factors including underlying alveolar growth abnormality, ASD, infection, GER and aspiration. Significant clinical improvement followed timely repair of the ASD which has likely stabilised the cardiopulmonary haemodynamics while management of GER and aspiration prevented further damage to the lungs. Efficacy of systemic corticosteroid therapy in alveolar growth abnormalities has not been well studied. Given the potential adverse effect on postnatal lung growth and neurodevelopment, it is important to weigh the benefits and risks before initiating corticosteroid therapy.

This case illustrates the importance of considering rare diffuse lung disease in infants with risk factors and suspicious clinical features. Further studies and investigations will be required to define the most suitable therapeutic strategies for alveolar growth abnormalities.

References