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An *SFTPC* gene mutation causes childhood interstitial lung disease: first report in the Arab region

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Summary

Background: Surfactant protein C dysfunction is one of the causes of childhood interstitial lung disease but has not previously been reported in Arabian countries.
Case presentation: A six-year-old girl had presented at the age of eight months old with bronchiolitis followed by a persistent cough, dyspnea and hypoxaemia. She was found to have gastroesophageal reflux disease, but her symptoms did not resolve despite her therapy being optimised. Further tests, including a chest computed tomographic scan, lung biopsy and genetic testing, confirmed a diagnosis of surfactant protein C dysfunction.
Conclusion: We report the first case in the Arab region of childhood interstitial lung disease caused by surfactant protein C deficiency.

Keywords

surfactant, protein C, SFTPC, interstitial, child

Background

We report the first case of childhood interstitial lung disease secondary to surfactant protein C (SFTPC) dysfunction in our region. Childhood interstitial lung disease contains a group of disorders that cause diffuse lung disease with a constellation of persistent findings, including coughing, respiratory distress, hypoxaemia and diffuse radiological changes. One of the sets of disorders that cause childhood interstitial lung disease in infancy is surfactant dysfunction disorders. For infants beyond the neonatal period, the most common causes are mutations in *SFTPC* and ATP-binding cassette subfamily A member 3 (*ABCA3*).[1] While *ABCA3* mutations are more prevalent in the Arabian region, there have been no reports of *SFTPC* mutations in this region.[2]

Case report

Our patient was a six-year-old girl who had presented at the age of eight months to our hospital with persistent symptoms of cough, dyspnea and hypoxaemia since she was two months old. She had an unremarkable neonatal history, which was the result of a full-term pregnancy, and had a birth weight of 2.4 kg. Her symptoms led to an initial diagnosis of viral bronchiolitis. However, her dyspnea persisted, and her condition further deteriorated during successive viral infections. Her parent complained that she suffered from recurrent vomiting, choking and symptoms suggestive of aspiration. The parents were first-degree consanguineous cousins, but there was no family history suggestive of chronic respiratory diseases.

On clinical examination, she was in respiratory distress, was failing to thrive and had a weight below the third percentile. Her height and head circumference were normal. No dysmorphism was noted, and clubbing was not initially present. Her vital signs showed tachypnea and hypoxaemia, and clear chest auscultation was observed. On cardiovascular examination, there was no murmur and no initial finding suggestive of pulmonary hypertension.

Her initial basic laboratory workup was normal apart from a nasopharyngeal polymerase chain reaction that was positive for rhinovirus. Chest X-rays showed diffuse bilateral ground glass opacity (Figure 1). An echocardiography was unremarkable. Her immunological work up was normal, and a bronchoscopy showed a normal airway structure. A workup for gastroesophageal reflux disease revealed moderate gastroesophageal reflux disease in pH probe studies. She was managed accordingly, and because the patient did not respond to optimal medical therapy, we proceeded with fundoplication and gastrostomy tube insertion.

Nevertheless, within the following year, she continued to exhibit dyspnea without exertion and hypoxaemia. Thus, a diagnosis of childhood interstitial lung disease was suspected. A chest computed tomographic scan showed diffuse inhomogeneous bilateral

Figure 1. Diffuse bilateral airspace consolidation but no pleural effusion or pneumothorax are present. The nasogastric tube remains in place. The pH probe can be seen with the tip projecting to one vertebral level above the diaphragm.

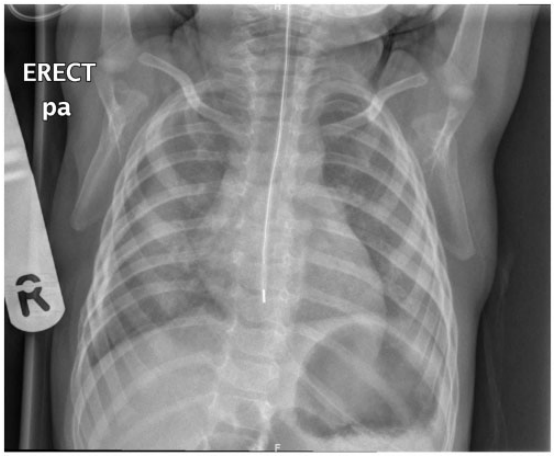
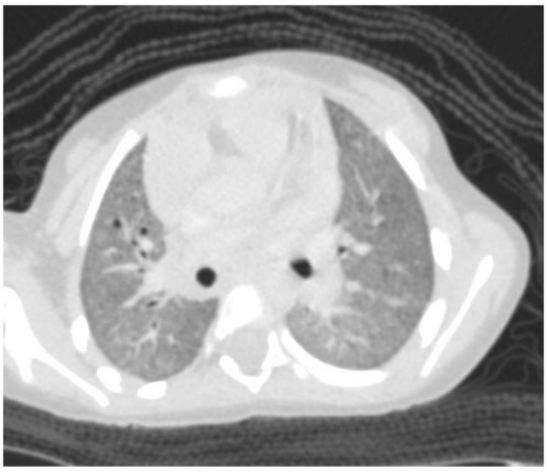


Figure 2. A computed tomographic scan showing diffuse bilateral inhomogeneous ground glass opacity. Small cysts can be seen scattered in the superior segments of both lower lobes and in the lateral segment of the middle lobe.



ground glass opacity with scattered small, thin-walled cysts in the superior segments of both lower lobes and the lateral segments of the middle lobe (Figure 2).

A wedge lung biopsy was obtained, which showed prominent large, irregular and cystic parenchymal distortion with marked thickening and fibrotic expansion of the interstitial spaces (Figure 3). The alveolar spaces showed moderate epithelial hyperplasia with

Figure 3. Lung biopsy showing interstitial expansion and cystic parenchymal distortion (arrows).

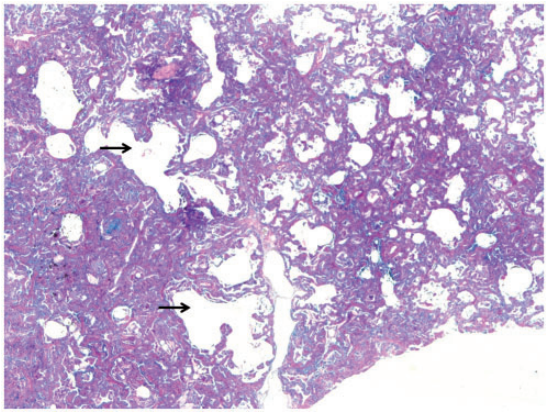
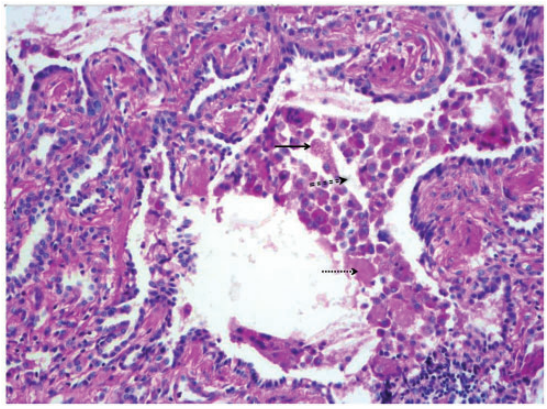


Figure 4. Foamy macrophages (solid arrow), lymphocytic infiltrate, cholesterol cleft (double-lined arrow) and eosinophilic globules (dotted arrow) with periodic acid–Schiff staining.



abundant foamy histiocytes, lymphocytic infiltrate and some areas with cholesterol clefts (Figure 4). Histiocytes also showed dense eosinophilic granules and occasionally globules of periodic acid–Schiff stain-positive proteinosis material (Figure 4). The airways showed mild epithelial hyperplasia and focal mild subepithelial fibrosis. These histological features are typical of genetic disorders of surfactant metabolism, and this morphological pattern at this age is most commonly associated with mutation in SFTPC. This diagnosis was confirmed by genetic testing, which showed a p.I73T pathogenic mutation located in coding exon 3 of the *SFTPC* gene, and no abnormalities were detected in the *ABCA3* or *NKX2.1* genes.

Currently, our patient is six years old. She was managed with six doses of monthly pulse therapy with hydroxychloroquine and azithromycin, which led to subsequent improvement in her respiratory status, as demonstrated by a decrease in her home oxygen requirement from 2 l/min to 0.5 l/min. She is also managed with supportive care, including nutritional, psychosocial and home care therapy. She was referred for the evaluation of lung transplantation.

Discussion

SP-C dysfunction is an autosomal dominant disorder caused by an *SFTPC* mutation that leads to childhood interstitial lung disease and was first reported by Nogee et al. in 2001.[3] The mechanism by which childhood interstitial lung disease manifests is not completely understood, but it has been suggested that it involves the accumulation of misfolded SP-C precursor proteins, which leads to the formation of protein aggregates, endoplasmic reticulum stress leading to the activation of apoptosis and release of pro-inflammatory cytokines.[3,4]

The presentation of SP-C dysfunction is widely variable at both its onset and its severity.[5] Patients usually present initially with viral bronchiolitis followed by symptoms including tachypnea, coughing, wheezing and hypoxaemia.[6,7] Gastroesophageal reflux disease is associated with SP-C dysfunction and has been reported to be present in 36% of cases.[7] Our patient presented initially with rhinovirus bronchiolitis, which was followed by a persistent cough, dyspnea and hypoxaemia. The presence of gastroesophageal reflux disease and recurrent aspiration delayed her diagnosis.

The most common radiological findings on high-resolution computed tomographic scan were ground glass opacity, which was observed in 100% of cases, followed by lung cysts, which were found in 40% of cases and were more prevalent in non-BRICHOS mutations. Other findings included interlobular septal thickening, air space consolidation, paraseptal emphysema and pulmonary nodules.[8] Our findings are consistent with the radiological abnormalities observed in SP-C deficiency, which include ground glass opacity and small, thin-walled lung cysts.

We confirmed the patient's diagnosis by genetic testing, which showed an *I73T* pathogenic mutation (c.218 T > C). This mutation, which is a non-BRICHOS mutation located in coding exon 3 of the *SFTPC* gene, is the most common mutation in this condition. This alteration results from a T to C substitution at nucleotide position 218 that leads to the replacement of a threonine by an isoleucine in codon 73.[5,7,9]

Histological patterns that are associated with the *SFTPC* mutation include chronic pneumonitis of infancy, nonspecific interstitial pneumonia, and alveolar proteinosis. Findings are largely influenced by biopsy timing.[7,10] The most common histopathological finding is interstitial expansion with or without cystic parenchymal distortion.[8,10] Other findings include hyperplasia of alveolar type 2 cells (in this case, foamy alveolar histiocytes were present), cholesterol clefts and periodic acid–Schiff stain-positive globules.[7,8,10] Our patient had similar histopathological findings, suggestive of an inherited disorder of surfactant metabolism most likely due to the *SFTPC* gene mutation.

To the best of our knowledge, our patient is the first case of SP-C dysfunction to be reported in the Arab region. However, other surfactant metabolism disorders have been reported, and among these, the *ABCA3* mutation is the most prevalent.[2] In conclusion, the *SFTPC* mutation is a known cause of childhood interstitial lung disease. Here, we establish the presence of this mutation in our demographic and show that its clinical, radiological and histopathological findings appear to be consistent with those described in the previous literature.

Declarations

Competing interests: None declared.

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Ethics approval: The Institutional Review Board (IRB) approved this study (IRB Log Number: 18-389). Written informed consent was obtained from the patient's father for the publication of this case report and all accompanying images.

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