Chronic Respiratory Failure in a Preterm Infant Heterozygous for a Potentially Damaging Variant in *SFTPC*

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Background

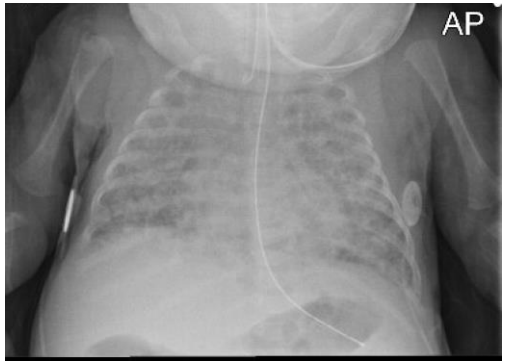
- Neonatal respiratory distress syndrome occurs due to insufficient endogenous surfactant production as a result of premature birth.
- Bronchopulmonary dysplasia (BPD) is a pulmonary developmental disorder related to preterm birth that can cause mild to severe lung disease.
- Heterozygous damaging variants in surfactant protein C gene (*SFTPC*) cause diffuse lung disease due to production of dysfunctional surfactant. Such cases present in childhood and later life, but rarely in infancy.
- We describe a preterm infant presenting at birth with severe respiratory distress and persistent respiratory failure, found to have a heterozygous variant of unknown significance (VUS) in *SFTPC.*

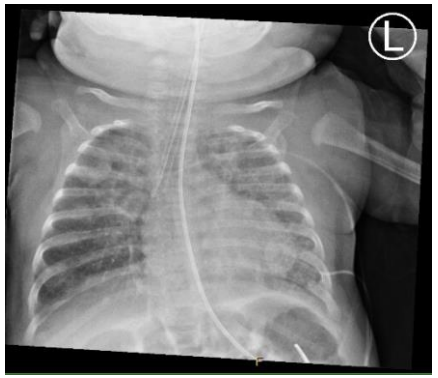
Clinical Course

- Female infant born at 26 weeks gestational age presented with respiratory distress at birth. She was intubated and given exogenous surfactant.
- She continued to require significant respiratory support, including high frequency jet ventilation, inhaled nitric oxide, repeated courses of ampicillin and gentamicin, and two courses of tapering intravenous dexamethasone with no significant improvement in respiratory status.
- Due to severity of respiratory failure, ILD work up was initiated. She was started on monthly pulse dose steroids of IV methylprednisolone (10 mg/kg/day for three days) and hydroxychloroquine (7 mg/kg daily), as these therapies have been reported helpful in *SFTPC*-related disease. She was subsequently able to tolerate some weaning of ventilator settings and fraction of inspired oxygen, but required tracheostomy placement to allow for chronic support.
- Patient had an episode of acute cardiorespiratory failure at home. Subsequently, she had a prolonged admission complicated by concerns for anoxic brain injury resulting in patient's death.

Results

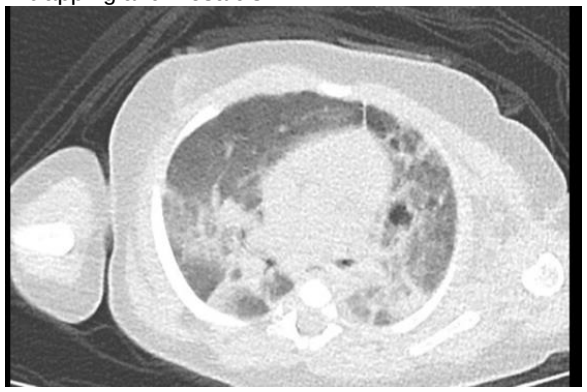
- Chest radiography below from before and after initiation of pulse steroids and hydroxychloroquine showing significant improvement of coarse granular opacities, which correlates with clinical improvement.

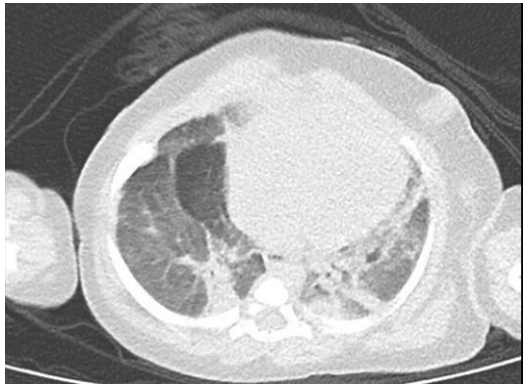




Results

- Chest CT showed significant lung disease with coarse opacities scattered throughout the lungs, most pronounced in the lower lobes. There are areas of scattered low attenuation suggestive of air trapping and mosaicism.





- Genetic testing for known causes of surfactant dysfunction and neonatal lung disease revealed a VUS (c.103C>T) in *SFTPC*. This variant is predicted to result in the substitution of cysteine for arginine at residue 35 (p.Arg35Cys).
- Echocardiograms revealed no signs of pulmonary hypertension.

Conclusions

Based on the severity of patient's lung disease, we propose that the patient's genetic variant contributed to and/or worsened her underlying BPD.

Discussion

- The *SFTPC* variant identified in our patient has not been reported as disease-causing in the literature, but is predicted to be damaging by *in silico* analyses, and has an allele frequency <1% in large population-based analyses. It has been observed that a "second hit" may precipitate lung disease in those with damaging *SFTPC* variants. We hypothesize that this patient's variant acted synergistically with her prematurity, hastening the development of diffuse lung disease related to surfactant dysfunction and/or leading to a severe BPD phenotype.
- The severity of the patient's respiratory disease correlates with the significant findings on chest CT. Her genetic findings could play a role in her response to steroids and hydroxychloroquine as her variant is outside the BRICHOS domain. Variants outside the domain are thought to have a more inflammatory component compared to those within the domain, which cause more amyloid deposition.
- A biopsy was not obtained due to patient's severe lung disease and concern that It would cause regression of her clinical progress. However, this was unlikely to provide information that would alter her treatment as she was improving clinically with the interventions.
- It is difficult to definitively know the significance of the genetic variant, however, it is important to highlight this variant as a comparison for future cases of SFPTC

References

- Johansson H et. Al. The Brichos domain of prosurfactant protein C. *Protein Science,* 2008.
- Kurland G, et al. An official American Thoracic Society clinical practice guideline. *Am J Respir Crit Care Med*. 2013.