ABCA 3 mutation associated childhood Interstitial Lung Disease (chILD) presenting as Combined Pulmonary Fibrosis and Emphysema in siblings.

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Combined Pulmonary Fibrosis and Emphysema (CPFE) is a well-known entity in adults. However, the rare occurrences of Childhood Interstitial Lung Diseases (chILD) have documented CPFE only once in the literature. The association of ABCA3 mutation in CPFE is emerging.

We report a case of an 11-year-old boy who was symptomatic since the age of 3 years when his parents had noticed him to have breathlessness on exertion. His breathlessness has not been progressive and he continues to have a modified Medical Research Council (mMRC) grade I of breathlessness at 11 years of age. He had history of occasional dry cough since past 6 years. No complain of chest pain, fever or hemoptysis. No history of joint pain, rash, dryness of eyes or mouth, Reynaud's phenomenon. He had no history of repeated respiratory infections. No exposure to pets or pigeon droppings in neighborhood. On enquiry, similar complain of breathlessness was noted in his 6-year-old sister since past 2 years. His parents had a third-degree consanguineous marriage with two kids and no history abortions. He had normal developmental milestones and was sound academically. At the age of 4 years patient had undergone fundoplication surgery to prevent aspiration pneumonitis as it was considered contributory to his symptoms of lung disease.

His growth was stunted for his age with a weight of 28 kg and a height of 132 cm (Body Mass Index of 16). On clinical examination he had a pulse rate of 70 per minute and a respiratory rate of 20 per minute with a SpO_2 of 97 % at room air. Grade III clubbing was noted. On auscultation fine end inspiratory crackles were heard over bilateral infrascapular, infra axillary and mammary areas. A loud pulmonary component of second heart sound was heard over 2^{nd} intercostal space in right parasternal region. Other systems examination was unremarkable.

Patient had been following up with various respiratory care centers since past 7 years and the radiological investigations where suggestive of a diffuse lung parenchymal disease initially which had gradually progressed. His chest radiograph progressed from an apparently normal radiograph to development of bilateral reticular shadows involving all zones with a prominent pulmonary conus. Computed tomography (CT) chest had progressed from bilateral patchy ground glass opacities predominantly involving bilateral upper lobes to the development of bilateral interseptal thickening and centrilobular emphysematous changes particularly in upper lobe. (Fig 1 a and b). Spirometry was suggestive of mixed ventilatory defect and the lung volumes had declined gradually. (Fig 1 d) Diffusion lung capacity for carbon monoxide (DLCO) was reduced. Transthoracic echocardiography documented evidence of pulmonary hypertension. CT abdomen was normal. His routine blood investigations including total leukocyte count, liver enzymes, blood urea and serum creatinine were normal. Human Immunodeficiency Virus (HIV) tested negative. Antinuclear antibodies were negative. Alpha 1 antitrypsin level was normal. Sweat chloride was normal and CFTR gene showed no mutations. Bronchoalveolar lavage showed normal cytology and no evidence of infection. Periodic Acid Schiff (PAS) stain was positive. His serum test for granulocyte monocyte colony stimulating factor (GMCSF) antibodies was negative. Patient underwent video assisted thoracoscopic surgery (VATS) guided lung biopsy which showed fibroblastic foci and emphysematous dilatation of alveoli. His blood was tested for mutations of a panel of genes causing interstitial lung diseases.. A homozygous mutation of ABCA 3 gene was detected in exon 22, variant c.3137C>T (p.Ala1046Val).

In view of similar complains in his younger sister, she underwent a CT chest which showed evidence of diffuse parenchymal lung disease. (1 c) Her radiological picture resembled the initial radiological presentation of our case at her age. Her BAL stained positive with PAS while GMCSF antibodies were not detected. Her blood documented and identical ABCA 3 gene mutation.

A diagnosis of combined pulmonary fibrosis and emphysema was made based on histopathology and radiological picture. Familial nature of this disease was evident by the occurrence of similar disease in siblings and a history of consanguinity. The underlying etiology of this familial CPFE was documented to be a homozygous mutation in ABCA 3 gene. In view of the progressive nature of this disease, a lung transplant was considered and both patients were referred to a lung transplant center.

Interstitial lung disease in children are described under the acronym ‘chILD’. Prevalence of chILD has been reported to be about 1.5 to 3.6 cases per million.[1,2] Till now there is a single reported case of CPFE in pediatric population.[3] It was shown to be associated with ABCA3 mutation as well. The presentation of CPFE with ABCA3 mutation in siblings is being reported for the first time. As our awareness for chILD and CPFE improves we are likely to detect more such cases as well as use genetic studies to aid in the diagnosis.

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