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Combined pulmonary fibrosis and emphysema syndrome associated with *ABCA3* mutations

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ABSTRACT
We report a case of extensive upper-lobe emphysema and lower-lobe pulmonary fibrosis consistent with combined pulmonary fibrosis and emphysema (CPFE) syndrome in a non-smoker adult patient. Sequence analysis of surfactant protein C gene (*SFTPC*, MIM 178620) and ATP-binding cassette subfamily A member 3 gene (*ABCA3*, MIM 601615) identified no mutation in *SFTPC* gene but compound heterozygosity in *ABCA3* gene with c.3081_3092delinsCG, a new mutation, and the common mutation c.875A>T. This case suggests a potential contribution of surfactant metabolism dysfunction in the pathogenesis of this disorder.

To the Editor:

Here, we present the first report of combined pulmonary fibrosis and emphysema (CPFE) in adult patient being compound heterozygote for mutations of the ATP-binding cassette subfamily A member 3 gene (*ABCA3*, MIM 601615).

A 41-year-old non-smoker man, presented with dyspnea on mild exertion. The patient medical history indicated a neonatal respiratory distress, a gastro-esophageal reflux and pneumonia 8 years before which resolved with antibiotics. His physical examination revealed a mild pectus excavatum, finger clubbing and bilateral basal crackles. High-resolution computed tomography (HRCT) of the chest showed a voluminous emphysema in the upper zones of the lungs associated with honeycomb fibrosis and ground glass opacity in lower lobes, predominating in left lung (figure 1). The bronchoalveolar lavage differential cell count was: 67 % macrophages, 22 % neutrophils, and 8 % lymphocytes. Pulmonary function tests showed: total lung capacity 75%, vital capacity 50%, residual volume 134%; forced expiratory volume in 1 second, 49 %, diffusing capacity for carbon monoxide 38% of predicted values and forced expiratory volume in 1 s/vital capacity 74 %; PaO_2 on room air, was 96 mmHg. On 6-mn walk test the peripheral oxygen saturation decreased from 96 % at rest to 90 % after 630 m (80 % of predicted value). Lung biopsy was not performed. Doppler echocardiography showed normal heart cavities, with estimated systolic pulmonary arterial pressure of 37 mmHg. Serum alpha-1 antitrypsin levels, autoimmune markers (including anti-nuclear antibody, rheumatoid factor), and immunoglobulin pattern were normal.

This clinical presentation of CPFE in a young patient prompted us to screen mutations in genes causing surfactant dysfunction. After informed consent was obtained, sequencing analysis of surfactant protein C gene (*SFTPC*, MIM 178620) revealed no mutation. Sequence analysis of *ABCA3* gene identified two mutations: c.3081_3092delinsCG resulting in a serine to valine change at codon 1028 with the creation of a stop codon 103 aminoacids downstream (p.Ser1028Valfs*103) and the common mutation c.875A>T changing a glutamic acid to a valine at codon 292 (p.Glu292Val). None of these mutations were found in either the public polymorphism database or our controls. Two years after presentation, chest HRCT as well as lung function worsened and azithromycin (250 mg every other day) was initiated.

Pulmonary surfactant, a complex mixture of lipids and specific proteins located at the air-liquid interface, lowers alveolar surface tension thereby preventing alveolar collapse at the end of expiration. It is synthesized by alveolar type II cells, stored in lamellar bodies, and secreted by exocytosis. ABCA3 (ATP-binding cassette subfamily A, member 3) is expressed in the lamellar bodies of alveolar type II cells and is crucial to pulmonary surfactant storage and homeostasis. Several studies indicated a role of genes involved in surfactant metabolism in the development of diffuse lung diseases [1].

CPFE is a syndrome characterized by the coexistence of emphysema and pulmonary fibrosis in the same patient [2]. It typically occurs in male smokers and associates dyspnea, upper-lobe emphysema, lower-lobe fibrosis, and abnormalities of gas exchange. In absence of *SFTPC* mutation, previously associated with CPFE [3], we decided to analyze other genes involved in surfactant metabolism, such as *ABCA3*. Recessive loss-of-function mutations in *ABCA3* present as lethal surfactant deficiency in the newborn, whereas other recessive mutations in *ABCA3* can result in interstitial lung disease in older child [4]. Previous studies showed that homozygous or compound heterozygous *ABCA3* mutations led to abnormal processing and/or trafficking of the ABCA3 protein [5], alterations in ABCA3 protein functions such as ATPase activity [6], or impaired lipid transport [7]. As previously described, our patient had a less severe phenotype than that usually associated with *ABCA3*

mutations [4]. These variations in the clinical and radiological features may be related to the nature of the mutation. Our patient was found to be compound heterozygous for *ABCA3* mutations. The first one is the common mutation p.Glu292Val which is found in heterozygous form with a frequency of less than 1 % [8] and has been previously reported associated with a mild lung disease. The second one has not yet been described but is expected to be a disease-causing mutation as it introduces a premature termination codon likely to be associated with markedly reduced mRNA levels due to nonsense-mediated degradation. Such a “null” allele precludes any functional ABCA3 from being made resulting in abnormal lamellar bodies but should be less deleterious in combination with the mild mutation p.Glu292Val. Interactions with variants in other genes and/or with external factors such as viral or bacterial infections, as observed in our case, may also influence the observed phenotype [9].

The phenotype of our patient is very similar to that observed in the case reported by Cottin et al. carrying *SFTPC* mutations. The patient is non-smoker and the emphysematous lesions are voluminous and localized mostly in the upper lobes whereas asymmetric fibrosis lesions are predominant in the lower lobes.

There is no specific treatment of the CPFE syndrome. Supported immunosuppressive therapy was not indicated in this case without evidence of active inflammation. Improvement of severe interstitial lung disease in a young patient with ABCA3 deficiency has been reported after treatment of azithromycin, an azalide macrolide antibiotic characterized by a nitrogen in the macrolide ring [10]. Although, there is no evidence of efficacy of azithromycin in CPFE, the worsening of our patient's respiratory status together with the safety of this drug incited us to initiate this treatment in our patient.

To our knowledge, this is the first report of a phenotype of CPFE syndrome in adult patient carrying mutations of the *ABCA3* gene. Although further studies are needed to confirm the role of surfactant metabolism in CPFE, this result suggests that this syndrome may have an underlying genetic predisposition.

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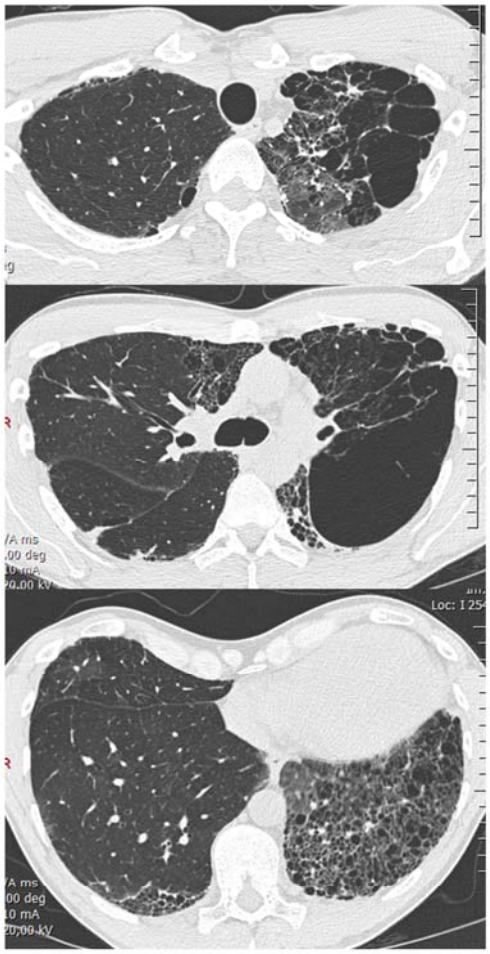
Figure 1

High-resolution computed tomography of the chest showing left upper lobe predominant emphysema associated with ground glass opacities and asymmetric honeycomb pattern in the lower zones.

Figure 1



Contributorship: RE conceived the experiment, drafted and coordinated the manuscript. CD, SS, PF participated in study design, and drafted the manuscript; ML performed genetic screening; AT is the referring clinician, participated in design and coordination of study and manuscript. All authors read and approved the final manuscript.

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Competing interests: none

The most important finding of our study:
We present the first report of combined pulmonary fibrosis and emphysema (CPFE) in an adult patient carrying compound heterozygote ABCA3 mutations.