A novel genetic variant of pulmonary alveolar microlithiasis

Sir,
Pulmonary alveolar microlithiasis (PAM) is thought to be a rare hereditary lung disease caused by solute carrier family 34-member 2 (SLC34A2) gene mutations. SLC34A2 gene is composed of 13 exons and is located on chromosome 4p15, which was first identified in 2006. PAM is inherited through an autosomal recessive pattern. The gene is expressed in several epithelial tissues, mainly alveolar Type II cells, as the principal sodium-dependent phosphate transporter. Therefore, mutations in this gene can lead to defective phosphate uptake and subsequently intra-alveolar microliths formation. Here, we present a case of PAM which was discovered incidentally in a tertiary care hospital in Bahrain.

A 23-year-old male college student, not known case of any medical illness, presented with a history of fever (38°C), productive cough of 2-day duration. He was not on any medications and had no addictions. There was no known history of genetic disorders in his family. Clinical examination was unremarkable and chest X-ray (CXR) showed bilateral nodular opacities [Figure 1]. The patient was admitted in an isolation facility and investigated. Nasopharyngeal swab for reverse transcriptase-polymerase chain reaction (PCR) was positive for influenza B, serology panel for atypical pneumonia showed features of past infection with mycoplasma pneumonieae and multiple sputum smear examinations for acid-fast bacilli were negative. The patient was treated with appropriate supportive measures to which he showed symptomatic improvement with no changes in his CXR. High-resolution computed tomography (HRCT) [Figure 2a and b] showed diffuse bilateral sand-like calcifications throughout the lungs involving all lobes and all segments with superimposed regions of ground-glass opacity. The pleural surfaces were seen as a black line between the high-density ribs and the high-density lung and between the heart and high-density lung. Diffuse pleural calcifications were also noted. These findings were suggestive of PAM. The patient refused lung biopsy procedure; however, he accepted a genetic testing. Given the clinical and the radiological findings of our patient, which were suggestive of PAM, next-generation sequencing of the SLC34A2 gene was performed where we identified a homozygous c.1493G>T p.(Gly498Val) mutation. To the best of our knowledge, this genetic variant has not been described so far in the literature, therefore classified as a variant of uncertain significance. To determine the pathogenicity of the identified mutation, molecular genetic segregation analysis of other family members was suggested. The patient’s 18-year-old sister was found to have similar radiographic findings, despite being asymptomatic. Therefore, genomic deoxyribonucleic acid screening for the identified variant was performed using PCR amplification of the corresponding exon, which revealed the same homozygous mutation. This finding has increased the likelihood of the pathogenicity of the new variant, which could be confirmed by investigating the carrier status of a heterozygous mutation in the parents. Unfortunately, genetic testing of the parents and other unaffected siblings was not possible due to the limitation of resources.

PAM has been reported in <1100 cases worldwide. The majority of reported cases were from Italy, Turkey, China, Japan, India, and United States (United States has the highest number of reported cases). PAM affects both sexes, although there is a slight male predominance with most of the patients diagnosed while being young.

Figure 1: Chest X-ray posteroanterior view of the patient: Numerous calcified micronodulations involving both lungs

Figure 2: (a) Coronal reconstructed high-resolution computed tomography image of chest: Numerous fine sharply defined sand-like calcified micronodulations with “sandstorm” like appearance, extensively involving both lungs. There is marked nodularity along the fissures and the pleura. (b) Axial high-resolution computed tomography image of the chest at the level of the aortic arch: Similar pattern of calcified micronodulations
PAM is characterized by the accumulation of calcium phosphate microliths in alveolar spaces. Mutation in SLC34A2 gene results in the loss of sodium-phosphate transporter Type 2b leading to accumulation of phosphate within the alveoli and consequently microliths formation. Genetic study of SLC34A2 in our patient revealed a homozygous c.1493G>T p. (Gly498Val) mutation, a genetic variant of uncertain significance which has not been previously reported in the literature. The patient’s sister was found to have the same genetic mutation as well. In families, the transmission is usually in horizontal pattern and in the case of vertical transmission, it is strictly related to consanguinity. In our case, there was no consanguinity in the patient’s parents.

PAM is characterized by clinicoradiological dissociation with patient having mild symptoms and CXR showing extensive lung involvement. Most of the patients are asymptomatic at the time of diagnosis. The clinical course of the disease is variable with most of the patients having a static or slow progression. The typical CXR findings include sand-like micronodulation of calcific density bilaterally, giving a “sandstorm” appearance, mostly in middle and lower lung zones. HRCT may reveal calcified micronodules, ground-glass opacities, interlobular septal thickening, pleural and subpleural calcification, and cystic changes. So far, there has not been any proven therapeutic method to alter the progression of PAM. Lung transplantation is the only curative treatment for patients with PAM.

We have presented a novel genetic variant of PAM, a rare autosomal recessive disorder, associated with intra-alveolar calcification caused by SLC34A2 genetic mutation. In patients with characteristic clinicoradiological features, familial involvement and mutations documented on genetic testing, the need for invasive biopsy procedures may be obviated.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.