Case Report

A Novel Mutation in TSC2 Gene: A 34-Year-Old Female with Pulmonary Lymphangioleiomyomatosis with Concomitant Hepatic Lesions

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Tuberous sclerosis complex (TSC) is an autosomal dominant disease resulting from mutation(s) in TSC1 or TSC2 genes. TSC is associated with the formation of hamartomas in the brain, heart, eyes, skin, kidneys, and lymphangioleiomyomatosis (LAM) of the lungs. LAM is almost restricted to women in reproductive age. Different mutations in TSC1 and TSC2 genes have been reported in the literature. Here, we present a female patient with TSC-LAM with a novel mutation in TSC2 gene. The patient also had multiple hepatic angiomylipomas, which is a relatively less-reported manifestation of the disease. The impact of this mutation on the pattern of disease presentation and response to treatment is not clear yet.

1. Case Presentation

The case is a 34-year-old woman, with the chief complaint of tightness of breath. Dyspnea had begun gradually 3 years before, was progressive in nature, and was not concomitant with cough, sputum, hemoptysis, pleuritic chest pain, wheeze, or weight loss. The patient had no history of smoking and her occupation did not expose her to environmental pollution or toxins. The patient was exposed to tuberculosis (TB) by her mother, who had inactive old TB. The patient had been previously referred to several other clinicians and, with diagnosis of asthma, was under treatment with multiple sprays. In spite of regular use of the sprays, her symptoms had not relieved. We asked for prior medical histories and patient claimed that she had history of epileptic attacks and was under treatment for her condition with valproate. In physical examination, lungs had generalized reduced respiratory sounds and were hyperresonant in percussion. Patient had hypomelanotic facial macules with fibrous facial plaques. Spirometry test conducted at our visit showed moderate obstructive ventilatory impairment (FEV1/FVC = 84%, FEV1 = 62% of the predicted values). The obstruction showed no significant response to bronchodilators (change in FEV1 after bronchodilator = 9% of the FEV1). Patient had no new brain magnetic resonance imaging (MRI) and the etiology of attacks was not clear. We recommended a brain MRI, which revealed multiple low-signal subependymal lesions less than 1 cm in size, beneath both right and left lateral ventricles along with multiple bilateral supratentorial subcortical flair hyperintense signal lesions (Figure 1). Electroencephalography was also obtained and no epileptic discharges were seen at the time. Also considering the history of TB exposure and her resistant dyspnea, a high-resolution computerized tomography (HRCT) of the chest was recommended; as a result, diffuse atelectasis of bronchioles in both lungs was seen along with multiple thin-walled cystic lesions distributed equally in all pulmonary zones (Figure 3). Our differential diagnoses for this finding were lymphangioleiomyomatosis, Birt-Hogg-Dube syndrome, pulmonary Langerhans’ histiocytosis, lymphoid interstitial pneumonia, amyloidosis, follicular bronchiolitis, and pulmonary adenocarcinoma. In abdominal cuts of a chest CT some very suspicious lesions were also seen in the liver and kidneys, which had the Hounsfield values of the
At this time, we decided to put the patient on sirolimus. Further ultrasound demonstrated subependymal lesions and no rhabdomyomas were detected in the heart. The patient's lung function tests are nearly left intact. FEV1/FVC = 59.4%, FEV1 = 64.4%, TLC = 75.8%, RV = 50.6% of the predicted values. It appears that pulmonary function has remained stable. No events of pneumothorax or epileptic attacks have occurred during this period. In the latest ultrasonography, shrinkage of the tuberous lesions in the liver is seen. Largest echogenic lesion in the right lobe of the liver (as mentioned above) has shrunken to 34 mm. Unfortunately, the size and echogenicity of the renal parenchyma has not changed significantly. Facial lesions have diminished, and patient no longer visits dermatologist for cosmetic purposes.

2. Discussion

Tuberous sclerosis complex (TSC) is an autosomal dominant disease resulting from mutation(s) in TSC1 (coding hamartin) or TSC2 (coding tuberin) genes. These genes are classified as tumor suppressor genes [2]. Variety of mutations in TSC1 and TSC2 genes have been mentioned in the literature [3, 4]. TSC is associated with the formation of hamartomas in different organs including cortical tubers, subependymal nodules and subependymal giant-cell astrocymoma in the brain (causing seizures, mental retardation), multiple retinal nodular hamartomas, hypomelanotic macules, facial angiofibromas, shagreen patch and periungual fibromas of the skin, cardiac rhabdomyomas, renal angiomylipoma (AMLs), and pulmonary lymphangioleiomyomatosis (LAM) [5]. This process causes progressive dysfunction of the involved organs, and current studies have shown the benefit of inhibition of mammalian target of rapamycin (mTOR). Sirolimus and everolimus both have shown promise in stabilizing and even improving the forced vital capacity and residual volume, reducing serum levels of VEGF-D, and shrinking the AMLs of the kidney [6, 7].

Serum VEGF-D level is correlated with the severity of lung involvement, measured as LAM CT grade, and is almost always higher in LAM patients, although in slightly lower in pulmonary cystic lesions-only patients. A prospective analysis of the MILES trial demonstrated reduce in VEGF-D levels following treatment with sirolimus and about 134 ml difference in FEV1 for each one-unit increase in VEGF-D baseline levels.

Here, we presented a female TSC-LAM patient with a novel mutation, detected in TSC2 gene. The patient also had multiple hepatic AMLs, which is a less-reported manifestation of the disease and may be due to her particular TSC2.
mutation [8]. Since the impact of this mutation on the pattern of disease presentation and response to treatment is not clear, we decided to report this case.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

References


