Case Report
Volume 3:6, 2021

Journal of Surgical Pathology and Diagnosis

ISSN: 2684-4575 Open Access

Tuberous sclerosis associated with pulmonary adenocarcinoma in situ: report of an unusual case and literature review

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Abstract

Our case represents a rare and perhaps unique and unusual occurrence of in situ lung adenocarcinoma in a patient who is a known case of tuberous sclerosis. We do not know, yet, if the association of lung adenocarcinoma and tuberous sclerosis is a coincidental finding or there is a casual relationship. However, further studies are warranted to highlight the nature of the linkage between the two conditions.

Keywords

Tuberous sclerosis • adenocarcinoma • lung • lymphangioleiomyomatosis • bilateral angiomyolipomas

Introduction

Tuberous sclerosis (TS) is a genetic disorder characterized by frequent occurrence of benign tumors, such as hamartomas which can occur in multiple organs like the skin, kidneys, eye, heart, brain and lungs. It was first described by Von Recklinghausen in 1862. TS is caused by loss-of-function and germline mutations in the TSC1 (also known as hamartin) or TSC2 (also known as tuberin) gene. It is inherited as an autosomal dominant trait in one-third of cases and occurs de novo (or as mosaicism to some extent) in the rest of the two-thirds. Classically, it presents during childhood with "Vogt triad" seizures, mental retardation and facial angiofibromas. So far, the most common reported pulmonary lesion in association with TS is lymphangioleiomyomatosis (LAM). We report herein, a rare case of an unusual association of TS with adenocarcinoma in situ of the lung. To the best of our knowledge, only one similar predominantly in situ case has been reported in the literature and this is the first one in Saudi Arabia. As this association is known to be rare and of uncertain pathogenesis, adding such a case would probably help to further document and clarify this association.

Case Report

G A 47-year-old female patient who is known to have tuberous sclerosis for the last ten years and had epilepsy, Hypothyroidism and bilateral angiomyolipomas was referred to the clinic at King Khalid University hospital for the evaluation of two suspicious subpleural pulmonary nodules. The patient had a history of lower limb edema with no clear etiology. The pulmonary nodules (Fig.1) were first identified on a chest computed tomography (CT) which was done during a systemic evaluation to rule out lymphatic obstruction because of her lower limb edema.

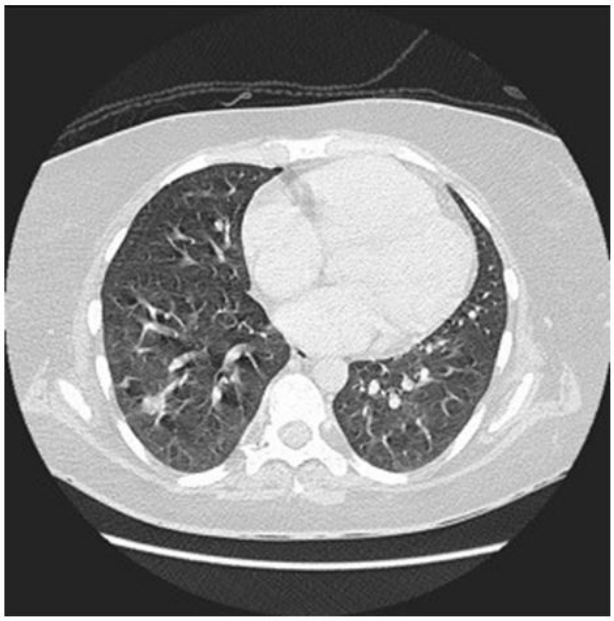

Figure 1: Cross-sectional CT scan of chest showing 13 mm indeterminate right lower lobe nodule.

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Received: 03 November, 2021; **Accepted:** 17 November, 2021**; Published:** 24 November, 2021

The patient also had a hepatic angiomyolipomas and a brain lesion. A lung biopsy was performed in order to know the nature of these nodules and to rule out malignancy. She had no respiratory symptoms prior to the lung biopsy. There were no other abnormal findings during physical examination and laboratory investigations.

Two wedge biopsies of lung were obtained from the right lower lobe. On macroscopic examination, there was an ill-defined firm tan lesion measuring 1.0 x 0.8 x 0.5 cm. Microscopically, it showed mucinous adenocarcinoma in situ of the lung which was predominantly lepidic in its growth pattern (Fig. 2 A and B). The tumor did not reach the pleural surface and was completely excised.

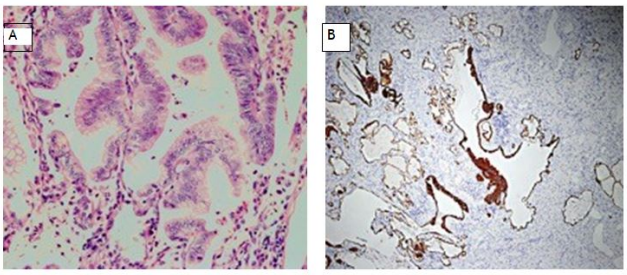

Figure 2: A)photomicrograph showing lepidic growth of mucinous epithelium along alveolar basement membranes. The features are consistant with adenocarcinoma in situ of lung. Hematoxylin & Eosin stain *200. B)In situ bronchioloalveolar carcinoma of lung stained for CK7. Immunohistochemical stain

*40.

A panel of immunohistochemical stains has been done. The stains showed a strong positive staining of the lepidic adenocarcinoma cells with Cytokeratin 7 and Napsin A. Stain for TTF1 was also focally positive in some cells (Fig. 2A and B). A final diagnosis of pulmonary adenocarcinoma in situ of lung was, subsequently rendered.

Results and Discussion

Tuberous sclerosis is a neurocutaneous syndrome characterized by widespread hamartomas in different organs such as brain, skin, eye, heart, lungs, liver and kidneys. TS tends to be highly variable when it comes to clinical presentation, ranging from asymptomatic to life-threatening conditions, thus, the Second International Tuberous Sclerosis Complex Consensus Conference was held to update the diagnostic criterias. According to recent studies, the incidence of TS is estimated to be 1 case per 6000 to 10, 000 live births while its prevalence is almost 1 in 20,000 [1].

Based on molecular genetics, TS is caused by an inactivation mutation of one of the two known TSC genes. TSC1 gene is located on chromosome 9q34, while the other TSC2 is on chromosome 16p13 both of these genes encode hamartia and tuberin proteins, respectively. These two proteins complex have an important role in cell growth regulation trough inhibiting mechanistic target of rapamycin (mTOR). Around one third of TS patients inherit the disease in an autosomal dominant manner, whereas in the two-thirds, it arises from a de novo germline mutation [2].

Different pathologies in multiple organs might be seen in case of TS, like renal angiomyolipoma, pulmonary Lymphandioleiomyomatosis (LAM), cardiac rhabdomyoma and Subependymal nodules, in addition to liver angiomyolipomas, facial angiofibromas and many more. The most common reported TS-associated lung lesion is Lymphangioleiomyomatosis (LAM) which usually presents in females as progressive dyspnea on exertion and recurrent pneumothorax. Although less frequently reported, multifocal micronodular pneumocyte hyperplasia (MMPH) and clear cell tumor of the lung can be seen as other TS pulmonary manifestations. MMPH is a rare pulmonary hamartomatous lesion composed of a scattered proliferation of type II pneumocytes with fibrotic interstitial thickening. It stains positive for cytokeratin and surfactant proteins A and B, but is negative for HMB-45, hormonal receptors and alpha smooth muscle actin [3].

Conclusion

Our literature review showed that lung adenocarcinoma in situ (previously called bronchiolo alveolar carcinoma) as not been known to be associated with tuberous sclerosis. Our case represents a rare and perhaps unique and unusual occurrence of in situ lung adenocarcinoma in a patient who is a known case of tuberous sclerosis. Five cases of pulmonary adenocarcinoma in TS patients have been described in the literature; only two of them were adenocarcinoma In Situ. 6-10 our patient did not show any atypical adenomatous hyperplasia component which can be interpreted as a precursor to the resultant lung adenocarcinoma [4]. We do not know, yet, if the association of lung adenocarcinoma and tuberous sclerosis is a coincidental finding or there is a casual relationship. However, we do agree with Takehiko et al that this association is most probably a result of the mutated TSC1 gene. Further studies are however, warranted to highlight the nature of the linkage between the two conditions. Following excision, our patient's remained well after 3 months of follow-up [5].

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How to cite this article: Alayed Doaa,AlroumaihAssem , Alrikabi Ammar cherkess. "Tuberous sclerosis associated with pulmonary adenocarcinoma in situ: report of an unusual case and literature review ." *J Surg Path Diag* 3 (2021) : 182