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Case Report

Alk-Rearranged Adenocarcinoma Arising in Lung Lymphangioleiomyomatosis of a Patient with Tuberous Sclerosis Complex: Case Report and Plausible Explanations

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Abstract

Tuberous Sclerosis Complex (TSC) is a rare genetic autosomal dominant syndrome caused by the inactivation of the tumor-suppressive genes TSC1 and TSC2. Clinical manifestations are variable and only rare malignant neoplasms are described in the literature. We underline the plausible molecular mechanisms shared by the TSC, lymphangioleiomyomatosis and lung adenocarcinoma. We describe a case of an ALK-mutated adenocarcinoma in a 54-year-old woman affected by TSC, treated with old antiepileptic drugs since childhood. The patient was treated with Crizotinib with a size reduction in the six-month follow-up. In our case a synergic influence of both TSC and ALK mutation in addition to sporadic events as a plausible action of old antiepileptic drugs, could cause an increased effect in stimulating cell-cycle and proliferation. We emphasize the importance of surveillance in these susceptible patients and in-depth genetic screening in case of malignancy for a more correct target therapy.

Abbreviations

TSC: Tuberous Sclerosis Complex; mTOR: Mammalian Target of Rapamycin; ALK: Anaplastic Lymphoma Kinase; LAM: Lymphangioleiomyomatosis; TTF1: Thyroid Transcriptional Factor 1; EGFR: Epidermal Growth Factor Receptor; PET: Positron Emission Tomography; m-TORC1: Mammalian Targets of Rapamycin Complex 1; GGO: Ground-Glass Opacities

Keywords: ALK-Rearrangement; Lung Adenocarcinoma; Tuberous Sclerosis

Introduction

Tuberous Sclerosis Complex (TSC) is a rare genetic autosomal dominant syndrome caused by the inactivation of the tumour-suppressive genes TSC1 and TSC2 [1]. Deletions, insertions and point mutations affecting these genetic loci result in a dysfunction of the signaling pathway of the mammalian Target of Rapamycin (mTOR), a serine-threonine kinase involved in cell proliferation and differentiation. Clinical manifestations associated with the disease are extremely variable, consisting of a constellation of symptoms related to widespread and usually

benign tumors [1]. We present the case of a 54-year-old woman with classic skin and nervous system symptoms of TSC who developed multiple lung nodules during the four-year follow-up who finally diagnosed as ALK-positive malignant adenocarcinoma. To the best of our knowledge, lung cancer in TSC and LAM has rarely been described (Table 1) [2-5]. We speculate a plausible explanation for the distinct molecular phenotype we detected in our case.

Author	Year	Histotype	Genetic screening	Follow-up
Present case	2017	NSCLC (on citology)	EGFR negative	Disease is slightly progressing. Alive after 10 month follow-up
Gorospe Sarasùa L (2*)	2017	NSCLC (on biopsy)	Not investigated	Unknown
Gironés R (3*)	2015	Poorly differentiated adenocarcinoma	EGFR negative	Recurrences after 1and 2 years. No more nodules and stabilization of LAM after 7 years.
Carneiro C et al. (4*)	2011	Bronchoalveolar carcinoma	Not investigated	Unknown
Casola M et al. (5*)	1983	Bronchoalveolar carcinoma	Not investigated	Unknown
*The numbers identify the reference for each case. Table Abbreviations: NSCLC: Non-Small Cell Lung Cancer; EGFR: Epidermal Growth Factor Receptor; LAM: Lymphangioleiomyomatosis				

Table 1: Clinicopathologic features of reported cases of cancers coexisting with LAM or TSC.

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A 54-year-old woman with a well-known history of TSC in treatment for many years with antiepileptics presented to our hospital for routine follow-up of lymphangioleiomyomatosis (LAM). In 2013 a single left perihilar lower nodule was detected. The nodule increased in size in 2015 and 2016 when other bilateral nodules were found. In autumn 2016 the patient had a cough with non-purulent sputum and occasionally hemoptysis. A bronchoscopic biopsy of the lower left lobe was programmed to achieve a final diagnosis. The microscopic examination of the bronchial biopsy was uninformative (Figure 1a) while the cytological specimens revealed a large number of dysmorphic Thyroid Transcriptional Factor 1 (TTF1) immunoreactive cells organized in papillary and micro papillary structures (Figure 1b, c). Thus, the diagnosis of non-small cell lung cancer in favour of adenocarcinoma was made. Following the recent guidelines, Epidermal Growth Factor Receptor (EGFR) mutation analyses for Anaplastic Lymphoma Kinase (ALK), were carried out.

No mutation for exons 18, 19, 20 and 21 in EGFR was detected while a strong immunopositivity for ALK (clone D5F3, Ventana) with a score of 3 was revealed (Figure 1d). The review of previous radiological examinations compared to the latest ones showed an area of parenchymal consolidation in the left lung extending to the apical segment of the lower lobe and involving the hilum. These findings were consistent with numerous nodules and ground-glass images both in the same lobe and in the contralateral ones. In both non neoplastic lungs, multiple thin-walled small parenchymal cysts were detected. For a complete diagnostic screening a Positron Emission Tomography (PET) was done and multiple bilateral angiomyolipomas and a bone involvement were reported. The patient was treated with Crizotinib with a size reduction in the six-month follow-up. After a period of suspension due to clinical exacerbation, the treatment was recently resumed. The patient was still alive after 10 months even if the disease was slightly progressing.

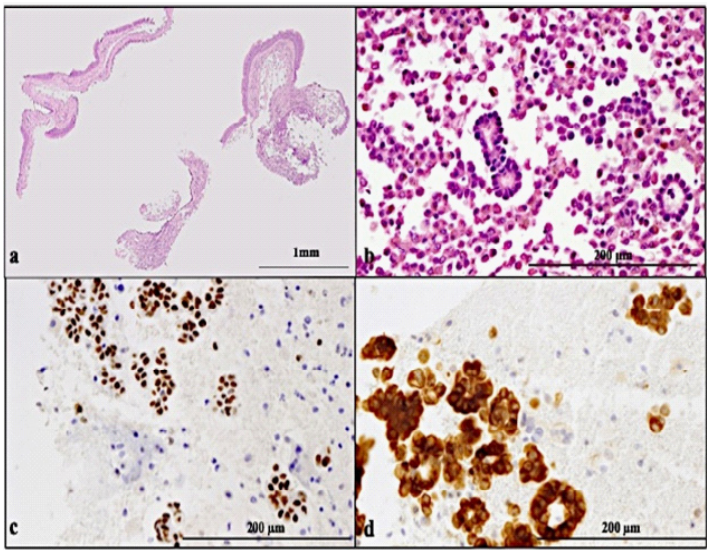

Figure 1: Hematoxylin and Eosin (H/E) stain: bronchial biopsy with no evidence of neoplastic aggregates (original magnification X25) **(a)**; pseudopapillary neoplasia (original magnification X100) with classic pseudo papillae (original magnification X200) **(b)** in broncho-alveolar lavage. Immunohistochemical (IHC) stain: strong nuclear positivity for TTF1 in neoplastic cells (original magnification X200) **(c);** homogeneous strong granular cytoplasmatic expressionALK-immunoreactivity throughout the tumor (original magnification X200) **(d)**

Discussion

TSC is a rare autosomic dominant syndrome with multisystemic manifestations. The kidney, heart, lung, skin, central nervous system, eyes and pancreas are most frequently involved [1]. Its pathogenesis is caused by a mutation that occurs in TSC1 and TSC2 genes, on chromosomes 9q34 and 16p13, codifying for hamartin and tuber in, respectively. The two proteins collaborate in forming a multi-protein complex (TSC complex) which works as a GTP-ase-activating protein on Rheb that in turn inhibits mammalian targets of rapamycin complex 1 (m-TORC1) signaling. Through linking to mTOR, it is involved in activating translation and protein synthesis because of phosphorilation of the initiating factor 4E-binding protein. A dysfunction in the TSC complex leads to an over-activation of mTOR signaling contributing to a cell-cycle deregulation both in differentiation and proliferation [6].

In this genetic alterate background, the abnormal smooth muscle-like cells typical of lymphangioleiomyomatosis lose their physiological features in cell adhesion, motility, proliferation and survival thus behaving like metastatic elements. Other symptoms are related to the presence of hamartomas or rare cancerous hamartoblastomas. Our patient had shown many of the characteristic manifestations of TSC. Since childhood she had several dermatological lesions, angiomyolipomas and cortical tubers with subsequent epilepsy, treated with different antiepileptic drugs through her life. The link between the genetic syndrome of TSC and the development of malignant neoplasms is little known. In the recent literature, TSC has been reported to be associated to gastric [7], hepatocellular and testicular cancers [8,9], somatostatinoma [10], abdominalpelvic sarcoma [11], neurocutaneous and malignant melanoma [12,13]. Only few papers describe the coexistence of lung adenocarcinoma, pulmonary LAM and TSC [2-5]. In only one case analysis for EGFR was also investigated but not for the other biomarkers [3].

A common signaling pathway deregulation can be involved both in TSC and in lung cancerogenesis, through the intermediatory action of PI3K/Akt/mTOR/S6K on the cell-cycle. Continuous cell growth is both the basis of tissue accumulation and tumor development and progression [14]. Alk-mutation was also detected in the present case. Since ALK was found as rearranged in our patient, its altered kinase activity could have led to the activation of several downstream pathways, among which mTOR cascade. The activation of mTOR resulting in the downstream of phosphorilation of S6 kinase and S6 ribosomal protein leading to cell proliferation may be related to several environmental triggers, growth factors and genetic alterations [15]. In our case a synergic influence of both TSC and ALK mutation in addition to sporadic events as a plausible action of old antiepileptic drugs, could cause an increased effect in stimulating cell-cycles and proliferation. The evidence of ALK translocation in this case also had therapeutic relevance as she underwent target inhibition therapy (Figure 2).

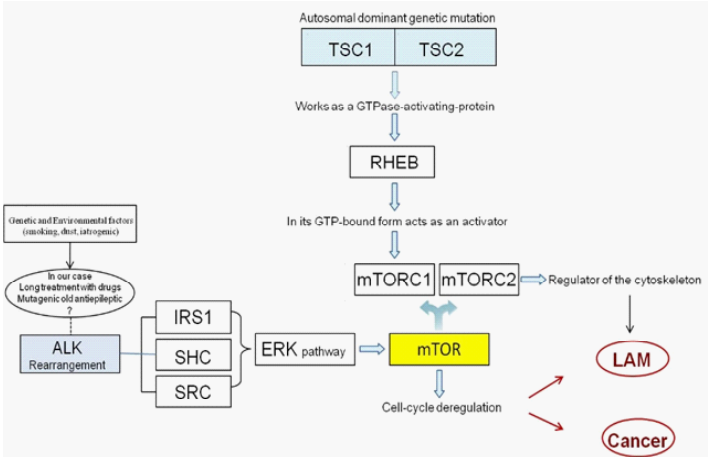

Figure 2: mTOR, ALK and LAM with cancer. The figures show a plausible molecular mechanism for mTOR over-activation leading to LAM and cancer (ALK: Anaplastic Lymphoma Kinase; IRS1: Insulin Receptor Substrate 1; SHC: SRC Homology 2 domain-containing; TSC: Tuberous Sclerosis Complex; RHEB: Ras Homolog Enriched in Brain; mTORC: Mammalian Target of Rapamycin Complex; mTOR: Mammalian Target of Rapamycin; ERK: Extracellular Signal-Regulated Kinase; LAM: Lymphangioleiomyomatosis)

We have reported a rare case of adenocarcinoma in a patient with TSC and LAM. Although TSC is not considered to be a risk factor for the onset of lung adenocarcinoma, a suspicious of a neoplasm should be kept in mind when nodularities and/or Ground-Glass Opacities (GGO) are detected, even in addition to interstitial involvement. Although rare, the occurrence of GGO or partially solid GGO should always be carefully investigated particularly in patients with genetic alterations predisposed to uncontrolled cell proliferation and/or subjected to such cancerogenic drugs as the old carbamade derivatives. Deep molecular investigation is now strongly advised, particularly in adenocarcinoma, to have advantages of the target therapies, as in our case.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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