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Identification of the *BRAF* V600E mutation in a patient with sclerosing pneumocytoma: A case report

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ABSTRACT

Objectives: Sclerosing pneumocytoma (sclerosing hemangioma, SP) is a rare benign tumor of the lung with a low risk of recurrence. The genomic profile of SP is not well-known. Here we report gene mutation findings in a 17-year-old girl with SP.
Materials and methods: Immunohistochemistry (IHC), next-generation sequencing (NGS), and sanger sequencing were performed on the tumor tissue of this patient for pathological diagnosis and gene mutation analysis.
Results and conclusion: Two mutations were identified in the tumor tissue by NGS and sanger sequencing: *AKT1* E17K and *BRAF* (B-Raf proto-oncogene, serine/threonine kinase) V600E. This is the first case report of a *BRAF* V600E mutation in a patient with SP. This discovery extends our understanding of the pathogenesis of SP, and suggests the need for future testing of *BRAF* V600E in this rare tumor type.

1. Introduction

Sclerosing pneumocytoma (sclerosing hemangioma, SP) is a rare benign tumor of the lung that contains two cell types, stromal round cells and cuboidal surface cells. It is a well-circumscribed lung parenchymal lesion that is usually diagnosed in individuals aged 50 years and older, but also has been observed in younger individuals including adolescents. SP is more common in women, with a male:female ratio of 1:5. Although the genomic profile of SP is largely unknown, the *AKT1* (AKT serine/threonine kinase 1) E17K mutation has been reported with high frequency in SP. Mutations in *CTNNB1, ARID1B, APC, BLM, PLCG1,* and other genes also have been observed in SP [1]. We herein report a case of SP in a 17-year-old girl with both the *AKT1* E17K mutation and a novel mutation, *BRAF* (B-Raf proto-oncogene, serine/threonine kinase) V600E.

2. Case presentation

A 17-year-old girl presented in our clinic with a two-year history of cough and one-year history of bloody sputum. A chest computed tomography (CT) scan revealed multiple nodules of various sizes in both the upper and lower lobe of the right lung. The largest nodule had a diameter of 60 mm (Fig. 1). Pathological analysis of biopsied lung tissue confirmed the diagnosis of SP. The tumor was mixed with stromal round cells and cuboidal surface cells. Immunohistochemical staining showed that the stromal round cells were positive for ER, PR, Syn, Vim, TTF-1, EMA, and CK7, and focally positive for CD56 and CK. In addition, the cuboidal surface cells were positive for Vim, Syn, TTF-1, CK, EMA, CK7, and Ki67 (3%), focally positive for P63, and negative for CD31, CD34, CgA, and SMA (Fig. 2). The tumor did not increase in size over three months. The patient underwent thoracoscopic lobectomy of the right lung. In the process of pathological analysis, a tumor in the bronchus was identified by pathologist that was not presented in CT because of its size (1.5*1*1 cm). The tumor was diagnosed as mixed squamous cell and glandular papilloma. Immunohistochemical staining showed that the tumor cells were positive for CK7, TTF-1 and P63 (Supplementary Figure). Targeted next-generation sequencing (NGS) using a panel of 1021 genes was performed on the SP tissue. Somatic *AKT1* c.49G > A p.E17K (mutant allele frequency/MAF, 30.2%) and *BRAF* c.1799T > A p.V600E (MAF, 28.8%) mutations were identified, and *BRAF* V600E mutation was confirmed by sanger sequencing (Fig. 3).

Abbreviations: SP, sclerosing pneumocytoma; CT, computed tomography; IHC, immunohistochemistry; NGS, next-generation sequencing; AKT1, AKT serine/threonine kinase 1; BRAF, B-Raf proto-oncogene, serine/threonine kinase

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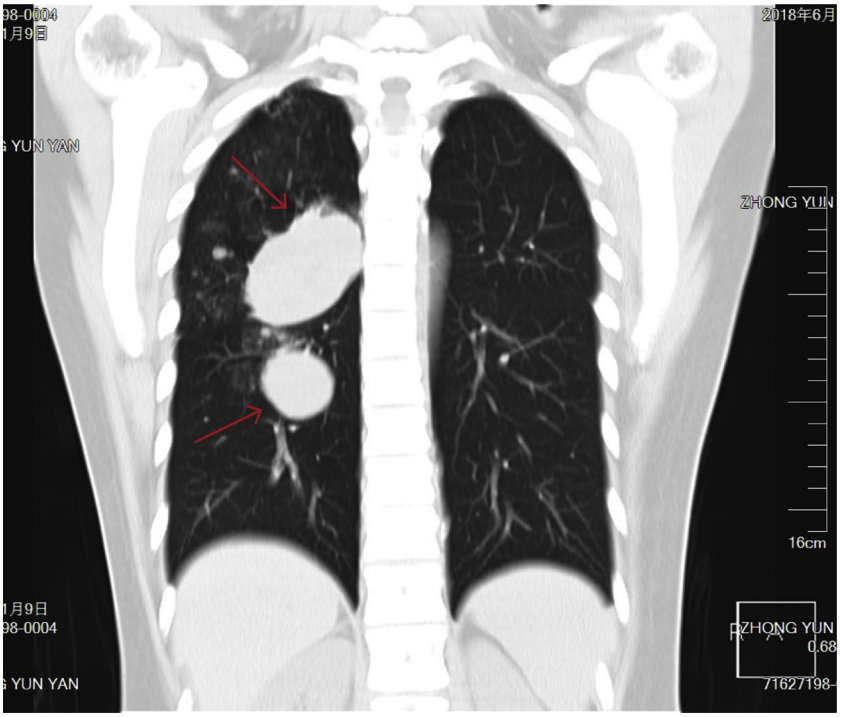

Fig. 1. Computed tomography (CT) scan. A chest CT revealed multiple nodules in the right lung of a 17-year-old female patient. SP were indicated with red arrows.

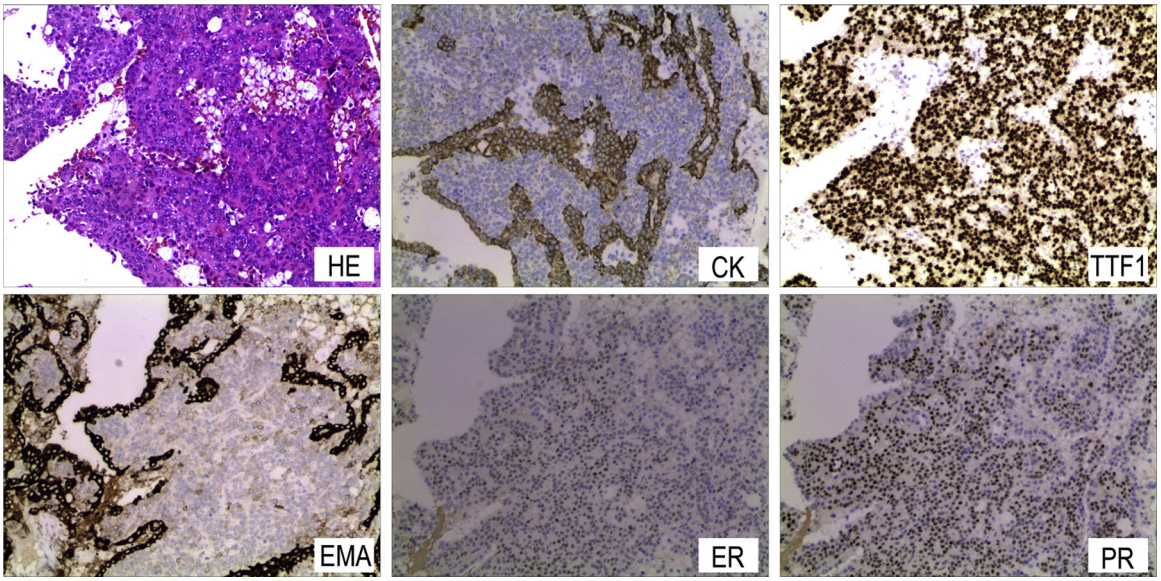

Fig. 2. Hematoxylin and eosin (HE) and immunohistochemical (IHC) staining of tissue from the larger one SP tumor (10×). Stromal round cells were present and positive for CK, TTF-1, EMA, ER, and PR. Cuboidal surface cells were present and positive for CK7 and TTF-1.

3. Discussion

SP is a benign lung tumor with mixed histological features. Genetic profiling of SP has been explored in the past few years. *AKT1* mutation occurred with high frequency in SP [1]. Allelic losses of *p16* and *Rb* loci were observed in SP patients [2]. *PTEN* germline mutation (c.388C > T) was identified in a 13-year-old female SP patient [3]. Multifocality tumors, lymph nodes and distant organ metastasis are rare in SP cases. Gastric metastasis was reported in a 72-year-old female SP patient with high Ki-67 proliferation index [4].

This is the first case report of the *BRAF* V600E mutation in SP. BRAF is a member of the Raf kinase family of growth signal transduction protein kinases, which plays an important role in regulating the MAPK/ERKs signaling pathway and affects cell division, differentiation, and secretion. V600E is the most common functional mutation of *BRAF*. The *BRAF* V600E mutation has been reported in a wide range of cancer types, including papillary thyroid cancer, melanoma, colorectal cancer, and non-small-cell lung carcinoma. Cancer patients with the *BRAF* V600E mutation usually have poorer clinical outcomes than those who do not have this mutation [5–7]. Ciliated muconodular papillary tumors genomic research demonstrated *BRAF* V600E was common in this pulmonary tumor [8]. *BRAF* V600E also has been reported with high frequency (63%) in ameloblastoma, a benign but locally infiltrative odontogenic neoplasm [9].

These findings suggest that SP has different molecular characteristics and same tumorigenesis mechanisms with other pulmonary

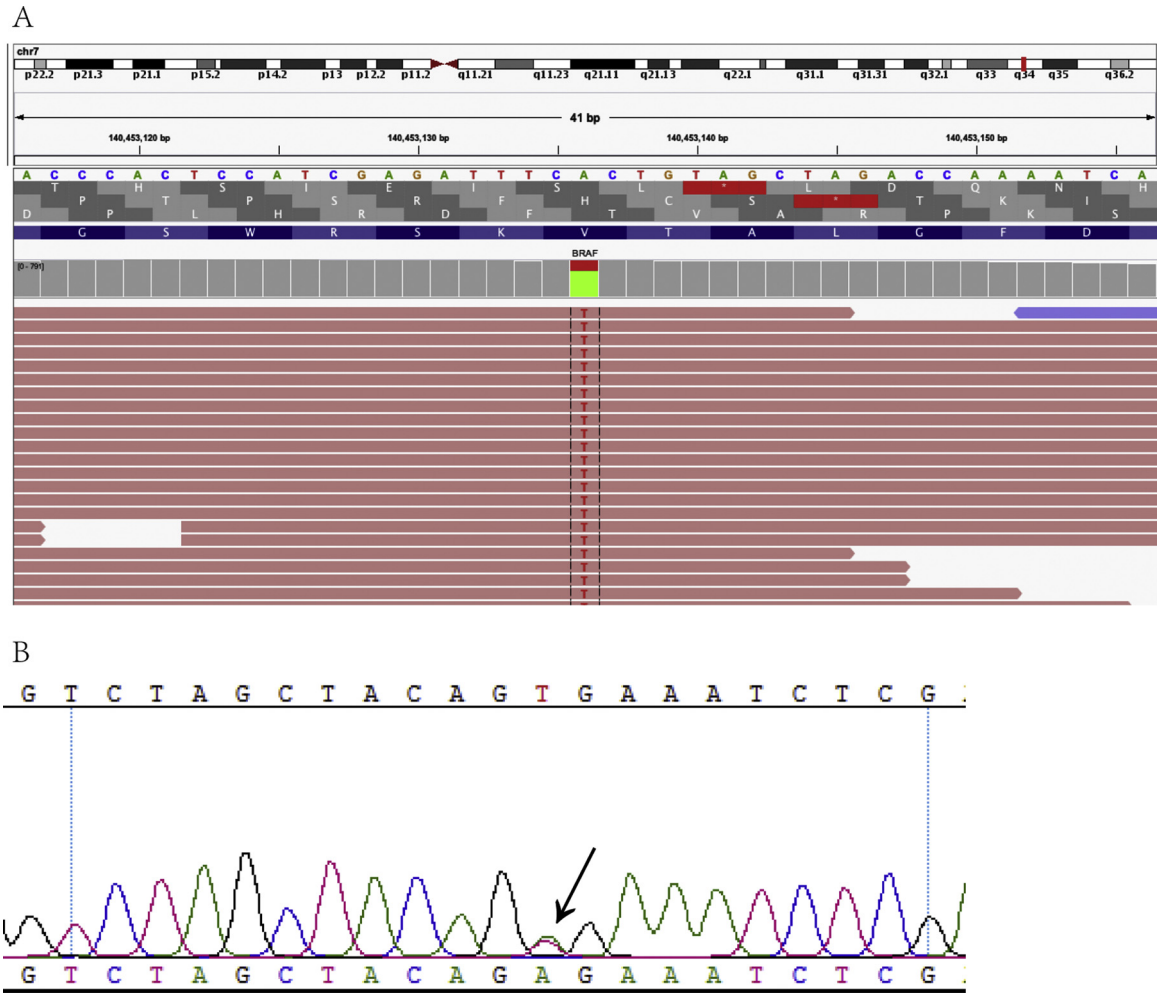

Fig. 3. Representative results of the *BRAF* mutation analysis. (A) The integrated genomics viewer (IGV) shows the c.1799T > A (p.V600E) mutation in the *BRAF* gene by next-generation sequencing. (B) Sanger sequencing revealed a c.1799T > A (p.V600E) mutation in the *BRAF* gene.

tumors, maybe results in distinct clinical features. The patient in our case had an earlier age at onset of SP than most patients. It is yet unknown whether this patient will have a recurrence of SP, which is very rare and occurs years after resection, we will continue to follow up [10,11].

4. Conclusion

In summary, we report an early-onset case of SP that exhibited the *BRAF* V600E mutation. Prior genomic profiling of SP has been limited. Our discovery extends understanding of the pathogenesis of SP. Our findings suggest that screening for the *BRAF* V600E mutation is warranted when a patient is diagnosed with this rare tumor type.

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Ethics

This study was approved by the institutional ethics review board of Dongguan people's hospital. The patient provided written informed consent for specimen collection, genetic testing, and use of this information for research purposes.

Declaration of Competing Interest

The authors declared that they have no conflicts of interest to this work.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.09.004.

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