

## CASE REPORTS IN DIVERSE POPULATIONS

# Bronchial angiofibroma in tuberous sclerosis complex: A case report and literature review

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## Abstract

Cutaneous angiofibroma is part of the classic triad of tuberous sclerosis complex (TSC). Angiofibroma is rarely reported to affect the mucous membranes of the trachea and bronchus. Tracheobronchial angiofibroma is also a hamartomatous manifestation of TSC. Considering the paucity of literature describing tracheal lesions in TSC, more case reports are needed to guide treatment planning. This case report adds to the existing clinical literature and provides a reference for clinical diagnosis.

## KEYWORDS

case report, tracheobronchial angiofibroma, tuberous sclerosis complex

## 1 | INTRODUCTION

Tuberous sclerosis complex (TSC) is an autosomal dominant multisystemic disorder characterized by hamartomas in different organs, with an incidence of approximately 1/6000–10,000 live births (Northrup et al., 2013; Yang et al., 2017). Available reports on TSC were mostly related to cardiac rhabdomyoma, renal angiomyolipoma, skin changes, lymphangiomyomatosis, and multifocal micronodular pneumocyte hyperplasia, among others (Gupta & Henske, 2018; Randle, 2017). In 1979, a case of bronchial angiofibroma diagnosed bronchoscopically was reported in chest, in a patient with suspected TSC (Freedman et al., 1979). Here, we report a case of confirmed TSC complicated by bronchial angiofibroma that can serve as a reference for clinical diagnosis and treatment.

## 2 | CASE REPORT

A 57-year-old woman with unremarkable medical history presented with a productive cough that lasted for more than 4 months. Treatment with antitussive treatment was ineffective. Physical examination showed no rales in both lungs. Periungual and subungual fibromas (multiple hard reddish-brown vegetations) were observed; the damage

appeared as deep longitudinal stripes with obvious keratinization of the free nail edge (Figure 1a). Hypomelanotic patches of different sizes were scattered on both lower limbs and some of them were fused (Figure 1b). Numerous facial angiofibromas (hard and reddish-brown millet-like round papules and telangiectasias on both sides of the nasal alae) were also noted (Figure 1c). There were no fibrous cephalic plaque and shagreen patches.

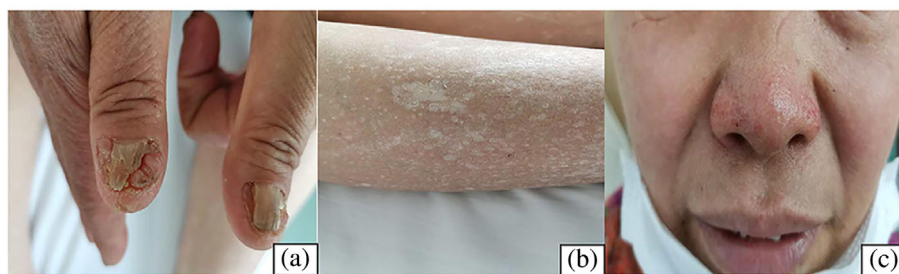
Hypomelanotic macules were observed on both lower limbs ( $\geq 3$ , at least 5 mm diameter). Facial angiofibromas ( $\geq 3$ ) and unguis fibromas ( $\geq 2$ ) were consistent with the three main features of clinical diagnosis recommended by the International Tuberous Sclerosis Complex Consensus Conference (Northrup et al., 2013).

The patient reported that the skin changes had developed 30 years earlier but were not treated; the patient's mother and sister also showed a skin appearance indicative of TSC, with periungual and subungual fibroma and hypomelanotic patches. However, the patient reported that her mother passed away and her sister refused to provide more information. The patient's parents did not have a consanguineous marriage.

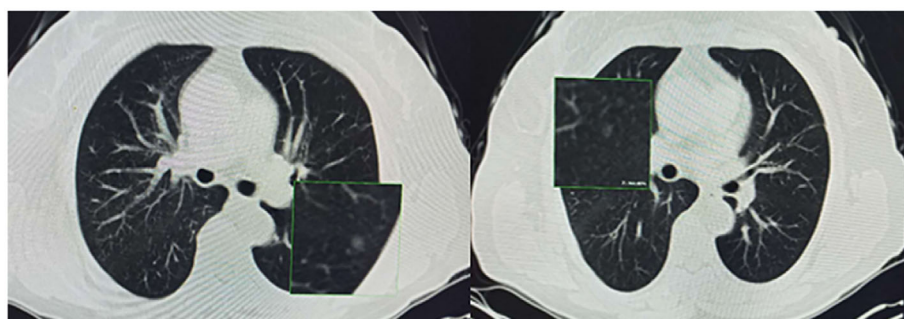
Laboratory blood examination showed no obvious abnormalities in tests for blood routine investigations, C-reactive protein, myocardial markers, blood coagulation, tumor markers, procalcitonin, immune indexes, and liver and kidney functions. Chest computed tomography

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**FIGURE 1** Clinical photographs of the patient. (a) Multiple hard reddish-brown vegetation on the fingernails. (b) Partially fused hypopigmented spots of different sizes on both lower limbs. (c) Multiple hard and reddish-brown millet-like round papules and telangiectasias, involving both sides of the nasal alae



**FIGURE 2** Chest computed tomography showing multiple nodules in both lungs, appearing as a partial ground glass shadow

(CT) identified multiple bilateral pulmonary nodules (Figure 2). Other manifestations of the condition (ophthalmic, cardiologic, neurologic, and nephrologic) were unremarkable. Bronchodilation and pulmonary function test results were negative. Bronchoscopy showed multiple smooth nodules of different sizes in the anterior wall of the bronchus, without involvement of the posterior wall (Figure 3). Pathological specimen analysis showed characteristic manifestations of angiofibroma such as dermal vasodilation, inflammatory lymphocyte infiltration, and perivascular fibrosis (Baykal et al., 2017; Bessis et al., 2018) (Figure 3b).

After obtaining informed patient consent, the peripheral venous blood of the patient was drawn. Genomic DNA was extracted by using the QIAamp DNA extraction kit, and its absorbance value and concentration were measured. Then the exons and intron boundaries of *TSC1* and *TSC2* genes were sequenced and analyzed after being captured twice and purified. The function, variation, and genetic pattern of each gene were analyzed, and the suspicious candidate mutations were obtained. Finally, the suspicious candidate mutation sites were amplified by PCR primers and verified by Sanger sequencing. The cDNA position is c.1030-2 and refseq ID is NM-000368.5. The base change is A>G (p.?). However, the effect of this variation on protein level is not clear. The results showed that the no pathogenic/likely pathogenic small sequence variant was identified in the coding regions of *TSC1* gene. However, an intronic variant (chr9:135786502) was identified in the Intron 10 of *TSC1* gene in a heterozygous state, which was predicted to affect splice site. (Figure 4).

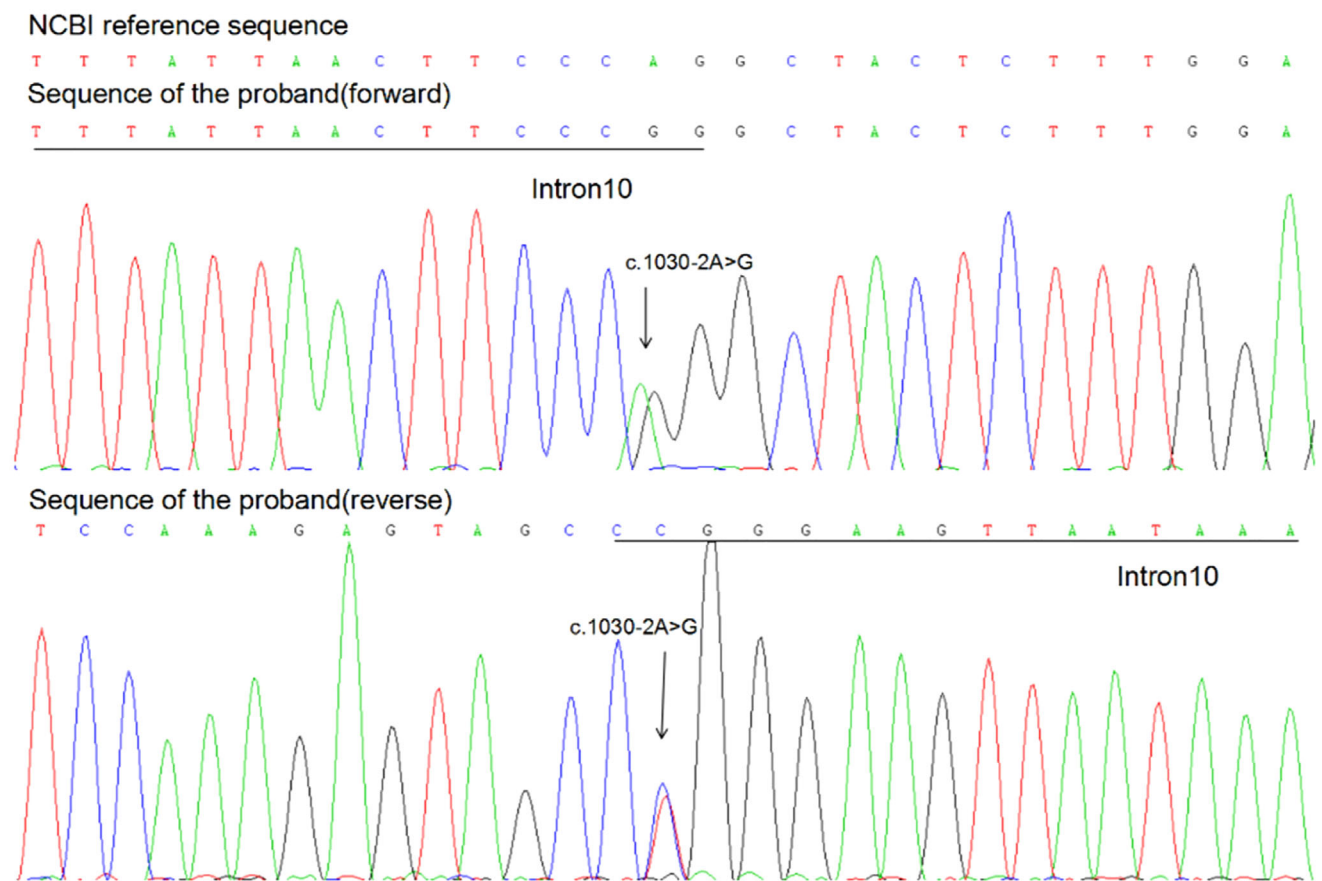
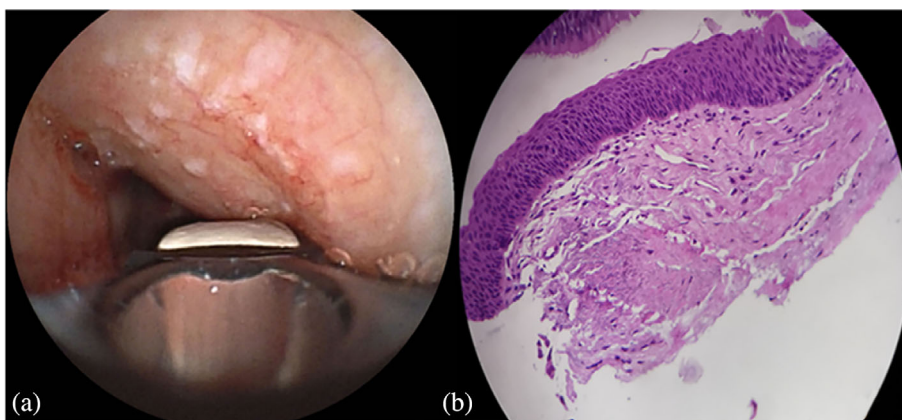
Compound methoxyphenamine capsules and paracetamol dihydrocodeine tablets were administered for 10 days for cough relief, and the patient's symptoms improved.

### 3 | DISCUSSION

During the first consultation, we noted multiple nodules on the fingernails and face. Subsequently, the patient was diagnosed with TSC during a dermatological consultation. Considering the possibility that similar nodules may have been present in the trachea, a stimulation of the medulla oblongata cough center could have led to development of cough. Furthermore, we considered that the main bronchial nodule was associated with TSC for the following reasons. First, TSC can involve multiple organs, and the involvement of the main bronchi and trachea cannot be ruled out. Second, bronchial angiofibroma has been reported in a patient with suspected TSC, providing precedence for bronchial involvement in this case. Third, the main bronchial nodules could have developed due to various causes, including tuberculosis, tracheal tumors, bronchial amyloidosis, and ossifying tracheobronchial disease. Combined with the clinical characteristics and the pathological findings, we temporarily excluded these diseases. Previous studies showed that the typical pathological manifestations of TSC were lymphocytic infiltration, perivascular fibrosis, and dermal vasodilation (Baykal et al., 2017; Bessis et al., 2018). Histopathological analysis of the bronchial nodules was consistent with our previous pathological results, confirming our earlier assumption.

To the best of our knowledge, this is the first report of a confirmed case of TSC complicated by bronchial and tracheal nodules. We retrospectively analyzed the similarities and differences between our case and previously reported suspected cases. First, the main complaint in both cases was chronic cough. Small papules with hard fusion could be observed on the face, but no lesions were found in other areas, such as the kidneys and the heart. Second, chest CT

**FIGURE 3** (a) Bronchoscopy: multiple smooth nodules of different sizes seen in the anterior wall of the main bronchus; (b) pathological analysis of the main bronchial nodule (HE, ×200): dermal vasodilation, inflammatory lymphocyte infiltration, and perivascular fibrosis



**FIGURE 4** The exon of *TSC1* identified no variant, but the position of Intron 10 (the position in the genome was chr9:135786502) was heterozygous, which was a splicing mutation

showed pulmonary nodules, whereas there were no typical signs of TSC involving the lung. Third, the bronchoscope showed numerous, scattered, whitish mucosal lesions in the trachea, and the pathological results showed multiple, scattered, dilated blood vessels surrounded by fibrous connective tissue, which were considered pathological manifestations of angiofibroma. Regarding differences, in the previously reported case, the patient had dyspnea and poor lung function due to long-term smoking. Second, the patient also had a history of epilepsy. Brain CT showed a small high-density area in the right

forehead region, suggestive of a meningioma. We believed that brain hamartomas associated with TSC was no exception.

The mutation of *TSC1* gene in this patient is a splicing mutation. This is expected to cause a change in the splicing site, resulting in a disorder of the encoded protein and loss of its normal function. The mutation of the modified site was not reported in the Human Gene Mutation Database (HGMD) database and was not included in the ESP6500siv2\_ALL (<https://evs.gs.washington.edu/EVS/>), Thousand Human Genome (1000g2015aug\_ALL) (<http://browser.1000genomes>).

org), and dbSNP147 databases. To the best of our knowledge, the heterozygous mutation of this locus, which can provide a new understanding for the gene diagnosis of TSC in the future, is not currently included in the gene bank.

Currently, specific targeted therapy with a rapamycin inhibitor has been found to delay a decline in lung function. There are no published studies on its efficacy to treat drug-treatable lesions in the main bronchus, which needs to be further investigated. From the previous cases and our case, interventional therapy under bronchoscopy was not feasible due to the presence of diffused lesions and the limited surgical scope.

This study has several limitations. The patient's relatives may have also had TSC, and the underlying molecular etiology could have been revealed by targeted analysis for the detected variant in the TSC1 gene (Northrup et al., 2013). If possible, after obtaining permission, the relatives of the patient should be diagnosed by genetic testing. Furthermore, a frequently reported characteristic of TSC is the progressive development of clinical manifestations and the involvement of multiple organs. Enteroscopy and bone radiography were not performed to exclude the involvement of other systems. Brain CT, magnetic resonance imaging, and other imaging modalities should be adopted regularly, with continued follow-up.

#### ACKNOWLEDGMENTS

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#### CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

#### AUTHOR CONTRIBUTIONS

Peikun Teng and Xuedong Liu conceived the study; Peikun Teng, Jing Liu, Deshun Liu, Wenfei Li, and Xuedong Liu analyzed the data; Peikun Teng, Jing Liu, and Xuedong Liu led the clinical study; Peikun Teng, Jing Liu, Deshun Liu, Wenfei Li, and Xuedong Liu wrote manuscript, and all authors revised and approved the manuscript.

#### DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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