

# Tuberous Sclerosis Complex Presenting as Periungual Fibromas: A Rare Case Report and Literature Review

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**Background:** Tuberous sclerosis complex (TSC) is a rare autosomal-dominant disorder involving multiple organs including skin, brain, heart, lung, kidney and liver. It usually occurs as early as birth or even in utero, with rare cases diagnosed in their adulthood. Here, we present a rare adult case of TSC presenting as periungual fibromas (PF).

**Case Presentation:** A 67-year-old gentleman showed recurrence of multiple periungual polypoid tumors on all the toes of the right foot when presenting to our department. On physical examination, there were polypoid and verrucous protrusions on the nail fold side of the proximal toe. Computed tomography scan indicated multiple subependymal nodules and renal cyst. Pathological analysis for the polypoid tissues showed fibroepithelial-like lesions, epidermal hyperkeratosis, and acanthosis. Therefore, the patient was diagnosed with TSC presenting as PF.

**Conclusion:** We reported a rare case of TSC diagnosed in the adulthood based on the presence of PF, subependymal nodules, and renal cyst.

**Keywords:** tuberous sclerosis complex, periungual fibromas, renal cyst, subependymal nodule

## Introduction

Tuberous sclerosis complex (TSC) refers to a rare autosomal-dominant disorder that can affect any sex and ethnic group.<sup>1</sup> Generally, it is a rare condition with multi-organ involvement, including skin, brain, heart, lung, kidney and liver. As a genetic disease, the individuals born with TSC show signs as early as birth or even in utero,<sup>2,3</sup> with extremely rare cases being diagnosed in adulthood.

There are no definite clinical manifestations in the musculoskeletal tissues for the TSC patients. The dermatological manifestations are usually typical, including café au lait spots (CALs), angiofibroma, periungual fibroma, intraoral fibroma, and enamel pits.<sup>4</sup> The diagnostic criteria for TSC have been updated in 2021 by the International TSC Consensus Group, which mainly relies on clinical features and gene mutation analysis.<sup>5</sup> According to these criteria, pathogenic mutation of *TSC1* or *TSC2* gene constitutes a definite diagnosis. Besides, the presence of two major features or one major feature with at least two minor features could also make a definite diagnosis.<sup>6</sup> To date, the systemic treatment of TSC is mainly based on the mammalian target of rapamycin (mTOR) inhibitor; however, the optimal dose, appropriate serum concentration, treatment duration and long-term adverse events are still needed to be further explored. In this study, we reported a rare adult case of TSC presenting as periungual fibromas (PF). In addition, we performed

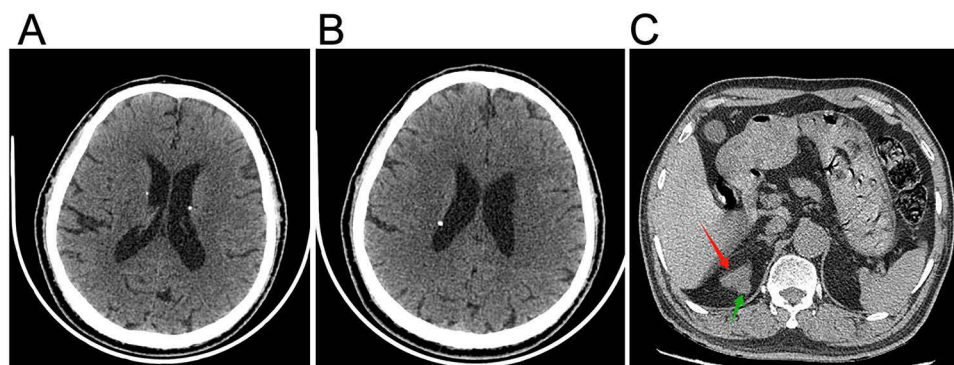
a comprehensive literature research, with an aim to screen the TSC patients presenting with PF, followed by analyzing their clinical and genetic features.

## Case Presentation

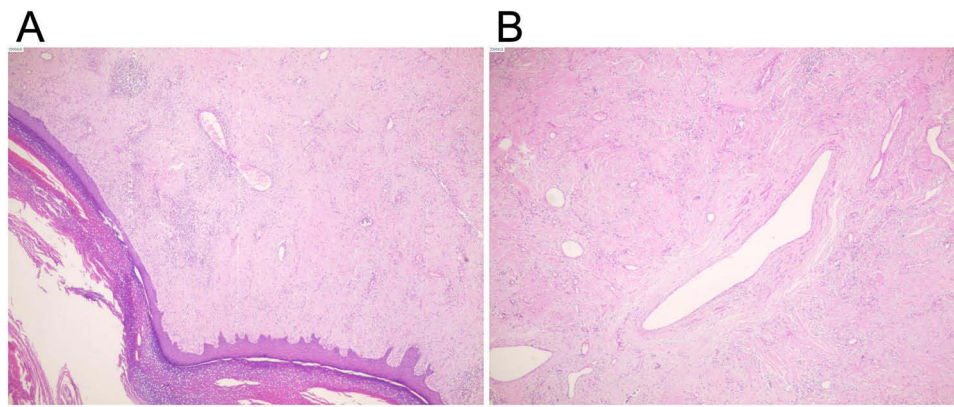
A 67-year-old gentleman presented to our department due to recurrence of multiple periungual polypoid tumors on all the toes of the right foot. He reported a polypoid tumor history for at least 30 years. Seven year ago, he showed seizure once, and then no recurrence was reported afterwards. On physical examination, there were polypoid and verrucous protrusions on the nail fold side of the proximal toe (Figure 1). He showed no clinical manifestations in the musculoskeletal tissues. The concentrations of carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), neuron-specific enolase (NSE), Carbohydrate antigen 19–9 (CA19-9), CA724 and prostate-specific antigen (PSA) were in their normal ranges. Computed tomography (CT) scan indicated multiple subependymal nodules (Figure 2A and B), together with renal cyst (Figure 2C). Pathological analysis indicated fibroepithelial-like lesions, epidermal hyperkeratosis, and acanthosis. Besides, this was accompanied by thickened branched spinous processes, fibroblasts and dense collagen tissue in the center, and multiple dilated vascular components (Figure 3). Therefore, the patient was diagnosed with TSC presenting as PF. For the treatment, the patient merely received a local resection to remove the tumor in toes. In the recent follow-up, the patient showed no recurrence. The study protocol was consistent with the ethical principles of the Helsinki and was approved by the Ethics Committee of the Sanya Central Hospital (The Third People's Hospital of Hainan Province). Written informed consent was obtained from the patient.



**Figure 1** A 67-year old gentleman showed skin-colored tumors and nail dystrophy in the toes of right foot, which were consistent with periungual fibroma. (A). The overall condition of the right foot. (B). The nail development was disrupted by the tumor. (C). Polypoid on one finger.



**Figure 2** Multiple high-density nodules were observed under the cerebral ependymium, which were consistent with the features of subependymal nodules. (A and B). Multiple high-density subependymal nodules with clear boundary. (C). Renal cyst was considered as there was a low-intensity nodule protruding the renal profile, with a diameter of 12 mm. The red color represented the upper pole of right kidney. The green color represented the small cyst.



**Figure 3** Pathological findings of the skin tumors. (A). The epidermis of the tumor was hyperkeratinized, and the epidermal protrusions were reduced, together with presence of multiple dilated blood vessels under the epithelium. (B). Dilated blood vessels and surrounding proliferation of fibroblasts.

## Discussion and Conclusions

TSC is a relatively rare autosomal dominant genetic disorder with an incidence of 1:6000–1:10,000.<sup>7</sup> Patients with TSC could show hamartomas in any organ. The classic triad of TSC includes facial angiofibromas, mental retardation, and intractable epilepsy, which usually presents in childhood.<sup>8</sup> In fact, merely 30% of patients show all the three characteristics, and multisystem manifestations vary substantially, which makes it a challenge for the diagnosis.<sup>9</sup> TSC patients show increased risks of developing multiple benign or malignant tumors in various organs. As one of the tumors that cause nail deformities of the digits adjacent to the proximal or lateral nail folds, PF in TSC patients are presenting as multiple slowly growing, elongated or oval, flesh-colored lesions with distal hyperkeratosis.<sup>10</sup> These patients usually show distortion of the nail plate, involving both fingers and toes. In this case report, we reported a TSC patient with PF involving the toes, and summarized the clinical and genetic features based on a literature review.

In 2021, the International Tuberous Sclerosis Consensus Conference proposed diagnostic criteria for tuberous sclerosis, including clinical and genetic diagnostic criteria.<sup>5</sup> The clinical diagnostic standards were divided into primary and secondary standards. The major criteria were as follows: hypomelanotic macules, angiofibroma or fibrous cephalic plaque, ungual fibromas, shagreen patch, multiple retinal hamartomas, multiple cortical tubers and/or radial migration lines, subependymal nodule, subependymal giant cell astrocytoma, cardiac rhabdomyoma, lymphangiomyomatosis, and angio-myolipomas (AML). The minor criteria were as follows: “Confetti” skin lesions, dental enamel pits, intraoral fibromas, retinal achromic patch, multiple renal cysts, nonrenal hamartomas, and sclerotic bone lesions.<sup>5</sup> The genetic criteria for the TSC diagnosis was based on the pathogenic mutations of *TSC1* or *TSC2*. However, approximately 10–25% of TSC patients showed no pathogenic mutations in *TSC1* or *TSC2*. *TSC1* and *TSC2* variants whose effect on protein synthesis or function were not definitely pathogenic, and would not be considered diagnostic unless supported by additional ACMG criteria for pathogenicity.<sup>11</sup> In this study, the patient did not receive genetic test due to financial causes; however, this would not affect the final diagnosis of TSC as the patient showed presence of PF ( $\geq 2$ ) and subependymal nodule.

TSC patients often show central nervous system (CNS) involvement, with epileptic seizures as the most commonly reported symptoms.<sup>12</sup> About 63% of TSC patients experienced at least one epileptic seizure.<sup>13,14</sup> For those with CNS involvement, the subependymal nodules, cortical dysplasia, and subependymal giant cell astrocytomas are the most common symptoms.<sup>6</sup> In this case, the patient merely showed an epileptic seizure 7 years ago, with no recurrence afterwards. CT examination revealed that the patient had multiple subependymal nodules. This implied that imaging was critical for the diagnosis of TSC.

Renal manifestations are the second most common findings associated with TSC, with AML occurring in 80% and renal cystic disease in 50% of patients.<sup>12</sup> Most of the patients with AML are asymptomatic. However, the AML progression may lead to hematuria and renal failure, which is considered as the main cause of TSC-related death.<sup>15</sup> An AML diameter of 30 mm or more would lead to increased risk of renal or hepatic hemorrhage and rupture.<sup>16–18</sup> The treatment of TSC-related renal angioleiomyoma is mainly based on the principle of preserving renal function and

**Table 1** A Literature Review for the TSC Patients Presenting as PF

Patient	Age	Gender	Clinical Symptoms	Major Features of TSC	Minor Features of TSC	TSC1/ TSC2 Mutations	PF Involvement	Reference
No. 1	18 years	Male	Seizure at postpartum 6, with delayed development	Angiofibromas, PF, Shagreen patch, multiple retinal hamartomas, cortical dysplasias.	Dental enamel pits.	None	Two fingers	Kabi et al <sup>22</sup>
No. 2	26 years	Male	Multiple growths in the upper and lower gums at age 5.	Angiofibromas, ungual fibromas, Shagreen patch, subependymal nodules	Dental enamel pits, intraoral fibromas.	None	One finger and two toes	Sarkar et al <sup>23</sup>
No. 3	38 years	Female	Skin lesions (eg forehead plaques) at an infant, facial angiofibromas in her childhood, periungual fibromas on her foot in adulthood.	Angiofibromas, ungual fibromas, Shagreen patch, multiple retinal hamartomas, cortical dysplasias, subependymal nodules	Confetti skin lesions, dental enamel pits.	None	Foot	Gipson et al <sup>21</sup>
No. 4	67 years	Female	Seizure	Angiofibromas, ungual fibromas, cortical dysplasias, lymphangioleiomyomatosis, angiomyolipomas.	Nonrenal hamartomas	None	Two fingers	Comninou et al <sup>20</sup>
No. 5	37 years	Female	Seizure before 8 years	Hypomelanotic macules, ungual fibromas, Shagreen patch, and Cortical dysplasias.	None	TSC1 and family history	On left hand	Zhao et al <sup>24</sup>
No. 6	25 years	Female	Abdominal pain and hypertension	Hypomelanotic macules, angiofibromas, ungual fibromas, Shagreen patch, cortical dysplasias, subependymal nodules, angiomyolipomas.	None	None	Toes	El Aoud et al <sup>26</sup>
No. 7	28 years	Male	Nail lesions, epilepsy at 1 age	Hypomelanotic macules, ungual fibromas, Shagreen patch, subependymal nodules, subependymal giant cell astrocytoma.	Multiple renal cysts	None	Pink papules at the proximal nail fold of several toes	Balak et al <sup>25</sup>
No. 8	38 years	Female	Multiple hypo pigmented lesions all over her skin and small periungual fibromas	Hypomelanotic macules, Ungual fibromas, and Cortical dysplasias.	None	TSC2	Site not mentioned	Pannu et al <sup>28</sup>
No. 9	66 years	Female	TSC with skin symptoms diagnosed at age 20	Hypomelanotic macules, angiofibromas, ungual fibromas, subependymal nodules, angiomyolipomas.	None	None	All fingers and toes	Han et al <sup>27</sup>
No. 10	52 years	Female	Progressively enlarging skin-coloured excrescences on several fingers, long-standing history of well-controlled seizures.	Hypomelanotic macules, ungual fibromas	None	Sporadic mutation of TSC1 gene	Fingers	Ortega-Quijano et al <sup>9</sup>
This case	67 years	Male	Recurrence of multiple periungual polypoid tumors on both toes	Ungual fibromas and subependymal nodules.	Renal cyst	None	Toes	This case report

prolonging the quality of life mainly including selective renal artery embolization, surgical resection, and radiofrequency ablation. Our case showed cystic lesions in the right kidney, and no additional management was required during the hospitalization. In the future, more attention should be paid to the renal function.

TSC is also accompanied by various skin symptoms, including skin depigmentation spots, angiofibromas, connective tissue nevus, PF, as well as gingival tumors. The tumors originated from the nail fold area on the proximal side of the foot, which were nodular and verrucous in appearance. The development of the nail plate was disrupted and partially resulted in the absence of the nail plate. Ma et al<sup>19</sup> reported that the histological changes of PF were mainly composed of different proportions of fibroblasts, collagen fibers and blood vessels. The epidermal changes were characterized by keratinization, hyperacanthosis, granular cell thickening and other changes. In this study, we reported a rare case of TSC presenting as PF, with multiple PF on both feet. Actually, it is still a challenge to define the proportion of subungual fibroma who would be eventually confirmed with TSC, as individuals with subungual fibroma were recommended but not necessary to undergo TSC screening. To further illustrate the clinical and genetic features of TSC, we performed a comprehensive literature research to the published articles in PubMed until January 2024. Case reports were collected by conducting a PubMed search with the term “tuberous sclerosis complex”, “periungual fibromas” or “ungual fibromas”, and “case reports”. Eventually, we found a total of 11 TSC patients presenting PF, including 10 published case reports<sup>9,20–28</sup> and our case (Table 1). According to the literature review, the TSC could involve almost all organs, with no racial or gender preferences. Although great advances have been made in the management of TSC, its prognosis remains poor with the median patient age at death of approximately 33 years.<sup>6</sup> In this case report, our patient was aged 67 years upon diagnosis, and the seizure only onset once. He was diagnosed based on the presence of major features of TSC (ie ungual fibromas and subependymal nodules) and minor features (ie renal cyst).

In summary, we reported a rare case report of TSC presenting PF at the age of 67. The patient initially presented with multiple PF on the toes, and then TSC was highly suspected. Then, CT scan was performed, which showed subependymal nodules and renal cyst. Finally, the patient was diagnosed with TSC, and he merely received surgery for the treatment. No recurrence was reported in the follow-up.

## Abbreviations

TSC, tuberous sclerosis complex; PF, periungual fibromas; CEA, carcinoembryonic antigen; AFP, alpha-fetoprotein; NSE, neuron-specific enolase; CA19-9, carbohydrate antigen 19-9; PSA, prostate-specific antigen; AML, angiomyolipomas; CNS, central nervous system; CT, computed tomography.

## Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

## Ethics Approval and Consent to Participate

The study protocol was consistent with the ethical principles of the Helsinki and was approved by the Ethics Committee of the Sanya Central Hospital (The Third People's Hospital of Hainan Province). Written informed consent was obtained from the patient.

## Consent for Publication

Informed consent for publication and publication consent of accompanying images were obtained from the patient.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no competing interests.

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