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CASE REPORT

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Orofacial manifestations and dental treatment considerations in patients with tuberous sclerosis complex: a case report

Yen-Cheng Chen[1], Chia-Ling Tsai[2,*]

[1]Department of dentistry, Kaohsiung Armed Forces General Hospital, 802301 Kaohsiung, Taiwan
[2]Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, 833401 Kaohsiung, Taiwan

***Correspondence**
tsaicl@cgmh.org.tw
(Chia-Ling Tsai)

Abstract

Background: Tuberous sclerosis complex (TSC1/TSC2, Online Mendelian Inheritance in Man (OMIM) # 191100/613254) is a rare autosomal dominant genetic disorder characterized by the development of benign tumors in multiple organs, and its diagnosis is based on both genetic testing and clinical evaluation. The severity of TSC varies significantly, from being asymptomatic to posing potential life-threatening risks. **Case**: This study reports a case of TSC exhibiting all orofacial diagnostic features, illustrates detailed characteristics of these features clinically and histologically, and discusses the additional considerations or pitfalls for diagnosing TSC based solely on orofacial manifestations. The case also inspires the importance of detecting and managing the central cusp in TSC patients, showcasing its potential to spark new research directions in TSC within dentistry. **Conclusions**: By promptly and accurately identifying the orofacial diagnostic features of TSC, dental practitioners can offer effective dental treatment planning for such patients and potentially aid in the early diagnosis of TSC, thereby enhancing the patient's overall prognosis.

Keywords

Tuberous sclerosis complex; Orofacial manifestation; Early diagnosis; Dental treatment; Central cusp

1. Introduction

Tuberous sclerosis complex (TSC1/TSC2, Online Mendelian Inheritance in Man (OMIM) # 191100/613254) is a rare genetic disorder caused by mutations in two genes, *TSC1* and *TSC2* [1]. Approximately 30% of TSC cases follow an autosomal dominant inheritance pattern, while the remaining 70% result from spontaneous mutations, with *TSC2* gene mutations being four times more prevalent in de novo cases [1, 2]. The *TSC1* and *TSC2* genes were found to encode hamartin and tuberin proteins, respectively, which are important in regulating the mammalian target of rapamycin (mTOR) pathway, which regulates cell growth, size and proliferation. Mutations in these genes lead to disinhibition of the mTOR signaling pathway, resulting in tissue overgrowth and the development of benign tumors in organs such as the brain, kidneys, heart, skin and oral cavity [3]. The severity of TSC varies widely, ranging from asymptomatic to potentially life-threatening, with *TSC2* gene mutations generally associated with more severe phenotypes [4].

The incidence of TSC is estimated to range between 1:6000 and 1:10,000 in live births [5, 6]. Early diagnosis and intervention are essential for improving patient prognosis as symptoms may remain latent until later stages [7]. Presently, the diagnosis of TSC can be achieved through genetic testing or clinical evaluation, although approximately 10% to 15% of patients may lack identifiable mutations [5]. The clinical diagnostic criteria encompass major and minor features, with a definitive diagnosis requiring at least two major features or one major and two or more minor features [5] (Table 1, Ref. [5]).

While there is presently no cure for TSC, there are some treatment options to manage its symptoms. Research into the function of *TSC1*/*TSC2* genes has led to the utilization of rapamycin (mTOR) inhibitors and related drugs to address certain TSC manifestations [8]. Antiepileptic drugs, particularly medications such as Vigabatrin, are commonly used to manage seizures [9]. Surgical intervention may be required to excise tumors from affected organs, especially if they impede normal function. Given TSC's impact on multiple organ systems, a multidisciplinary team of medical professionals is essential for comprehensive care. Symptoms and complications of TSC may manifest at various life stages, necessitating ongoing surveillance and adjustments to treatment plans.

This study reports a case of TSC that met all orofacial diagnostic features, examines the diagnostic significance of orofacial features and discusses dental treatment considerations for affected patients.

TABLE 1. Diagnostic criteria of tuberous sclerosis complex and medical conditions relevant to our patient.

Types	Diagnostic criteria	Relevant medical conditions of our patient	Current treatment of our patient
Genetic diagnosis	A pathogenic variant in *TSC1* gene or *TSC2* gene	V (*TSC2* gene)	X
Major Criteria			
	Hypomelanotic macules (≥3; at least 5 mm diameter)	X	X
	Angiofibroma (≥3) or fibrous cephalic plaque	V	Topical mTORi treatment (Rapamycin ointment)
	Ungual fibromas (≥2)	X	X
	Shagreen patch	V	Topical mTORi treatment (Rapamycin ointment)
	Multiple retinal hamartomas	V	Annual ophthalmic evaluation
	Multiple cortical tubers and/or radial migration lines	V	Annual brain MRI
	Subependymal nodule (≥2)	V	
	Subependymal giant cell astrocytoma	V	
	Cardiac rhabdomyoma	V	Annual echocardiography
	Lymphangiomyomatosis (LAM)	X	X
	Angiomyolipomas (≥2)	V (several in bilateral kidneys)	MRI of the abdomen every 1–3 years
Minor Criteria			
	"Confetti" skin lesions	X	X
	Dental enamel pits (≥3)	Has not been diagnosed yet	X
	Intraoral fibromas (≥2)	History of one fibroma in lower lip	Status post excision
	Retinal achromic patch	V	Annual ophthalmic evaluation
	Multiple renal cysts	V	MRI of the abdomen every 1–3 years
	Nonrenal hamartomas	X	X
	Sclerotic bone lesions	X	X

Definite diagnosis of TSC: Two major features or one major feature with two minor features.
Possible TSC diagnosis: Either one major feature or more than two minor features.
A combination of the two major clinical features, Lymphangiomyomatosis and angiomyolipomas, without additional features that do not fulfill the criteria for a definitive diagnosis.
Adapted from Northrup et al. [5], 2021.
TSC: tuberous sclerosis complex; mTORi: mammalian target of rapamycin inhibitor; MRI: magnetic resonance imaging; V: The relevant medical conditions of our patient meet the diagnostic criteria; X: No relevant medical condition/current treatment in our patient.

2. Case report

An 11-year-old boy presented at the Pediatric Dental Clinic with intermittent pain in his lower left posterior tooth for the past week. He had epilepsy since he was 1.5 years of age. After recurrent seizure episodes, he underwent comprehensive diagnostic evaluations, including a whole-body screening and genetic testing, which confirmed the diagnosis of TSC with *TSC2* gene mutation. However, there was no family history of TSC or other hereditary diseases across three generations. Apart from TSC, the patient denied any other systemic illness. The epilepsy was effectively managed with Vigabatrin (500 mg/tab) and Lamotrigine (50 mg/tab) twice daily. Table 1 outlines the relevant diagnosed medical conditions and ongoing treatment. Notably, the patient exhibited no obvious neuropsychological issues and cooperated well during dental procedures.

2.1 Extraoral findings (Fig. 1A)

The patient exhibited typical facial features associated with TSC, including facial angiofibromas (Fig. 1A).

2.2 Intraoral (Figs. 1B,C,2) and radiographic (Fig. 3) findings

The patient presented with a chronic apical abscess over the lower left buccal gingivae and a small nodular lesion over the interdental papillae between the upper central incisors (Fig. 1B). No caries was detected, but multiple dental enamel pits were observed on the surface of the teeth (Fig. 1C). Both bilateral lower second premolars exhibited a central cusp, while Tooth 35 was diagnosed with an open apex and pulp necrosis due to a central cusp fracture.

2.3 Treatment and follow-up

We performed regenerative endodontic procedures on Tooth 35 in response to the patient's chief complaint. Additionally, we re-evaluated Tooth 45, which had previously undergone protective resin restoration around the central cusp, to determine the necessity for occlusal adjustment. The nodular lesion observed over the interdental papillae between the upper central incisors was managed through enhanced oral hygiene instruction, with regular monitoring of the lesion's size initially. Following the six-month follow-up visit, the patient reported uncomfortable sensations while brushing around the

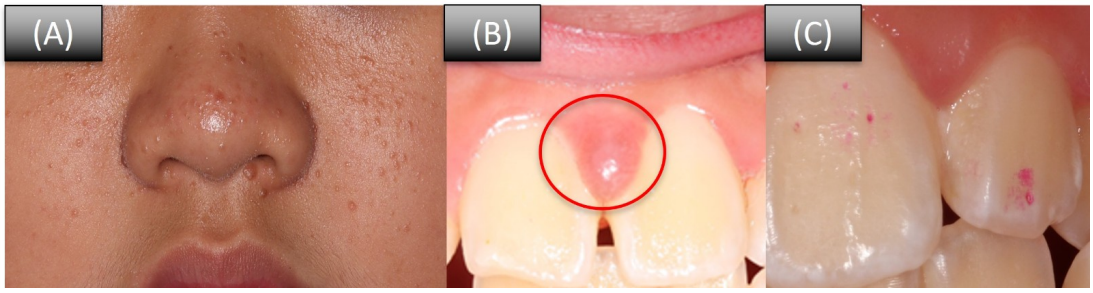

FIGURE 1. Clinical manifestations of orofacial features in our patient with tuberous sclerosis complex. (A) Extraoral photograph revealing angiofibromas in the mid-face region. (B) The nodular lesion circled over the interdental papillae between the upper central incisors. (C) Dental enamel pits visualized using a disclosing agent.

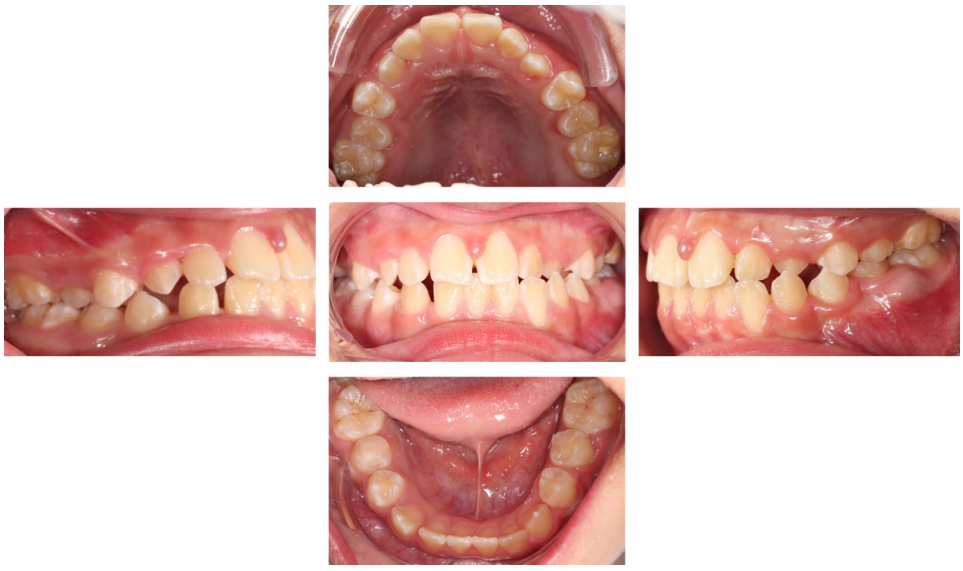

FIGURE 2. Comprehensive dental arch photos of our patient with tuberous sclerosis complex at the first clinical appointment. The patient presented with intermittent pain in the lower left posterior tooth for one week, accompanied by abscess formation over the buccal gingivae of Tooth 35.

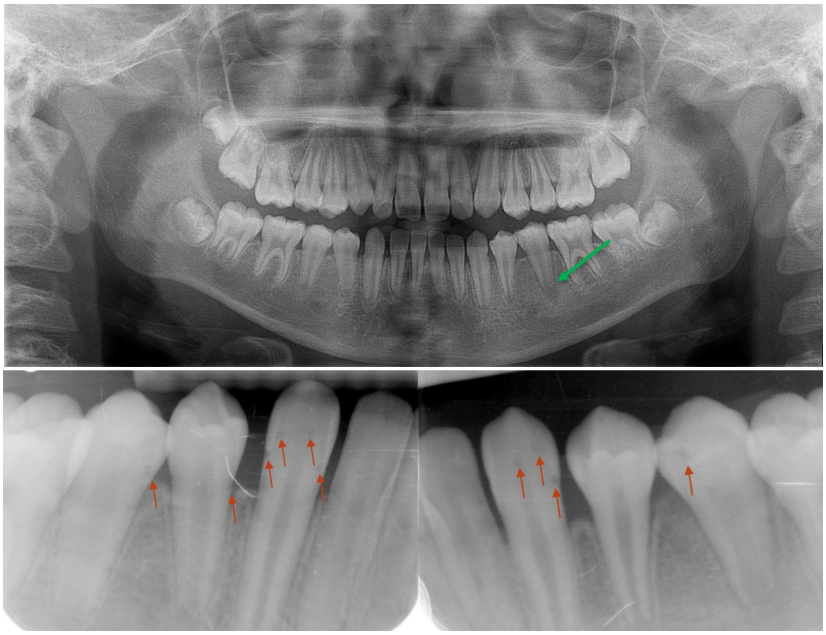

FIGURE 3. Radiographic images obtained during the initial clinical assessment of our patient with tuberous sclerosis complex. Tooth 35 demonstrates an open apex and radiolucent apical lesion (green arrow), while periapical films reveal multiple radiolucent images corresponding to dental enamel pits (red arrows).

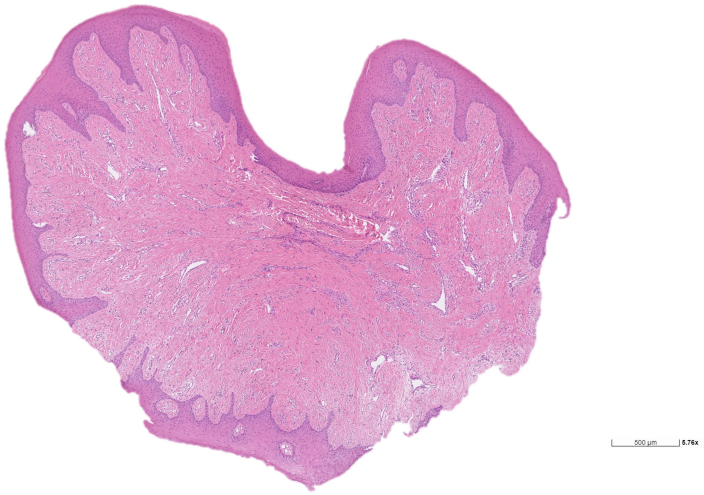

FIGURE 4. Histopathological image of the nodular lesion located over the interdental papillae between the upper central incisors. The pathology report sections demonstrate polypoid cutaneous mucosa with hyperplastic squamous epithelium and dense fibrous tissue stroma. No malignancy was observed.

lesion. After a discussion with the patient and his parents, an excisional biopsy of the lesion was performed, and the pathology report confirmed it to be a fibroepithelial polyp, clinically recognized as an oral fibroma [10] (Fig. 4). For the multiple dental enamel pits, we implemented oral hygiene instructions, active surveillance, and professional topical fluoridation every three months to prevent caries. The patient remained asymptomatic and reported no complaints following the excisional biopsy of the oral fibroma up to the 18-month follow-up visit (Figs. 5,6).

3. Discussion

3.1 Early diagnosis through orofacial features of TSC

The extraoral manifestations of TSC commonly include angiofibromas or fibrous cephalic plaques. Angiofibromas, observed in approximately 70% to 75% of TSC cases [11–13], typically emerge within the first decade of life. Their numbers may increase during adolescence, evolving from vascular macules to fibrous, dome-shaped growths. These lesions typically appear symmetrically on areas such as the malar region, nasal dorsum, nasolabial fold, forehead and chin. They can cause aesthetic distortion and, in some instances, result in bleeding and visual impairment. Fibrous cephalic plaques, found in approximately 18% to 25% of individuals with TSC [11–13], share histological similarities with angiofibromas. These

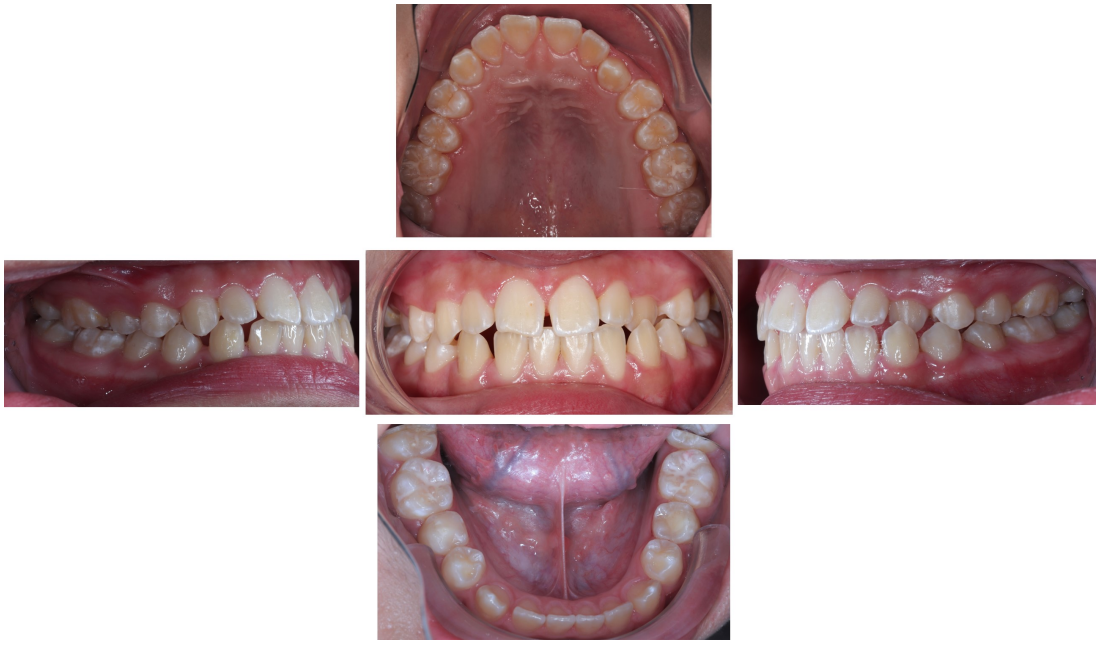

FIGURE 5. Comprehensive dental arch photos of our patient with tuberous sclerosis complex at the 18-month follow-up visit. The patient presented with good oral hygiene and was free from any pathological lesions.

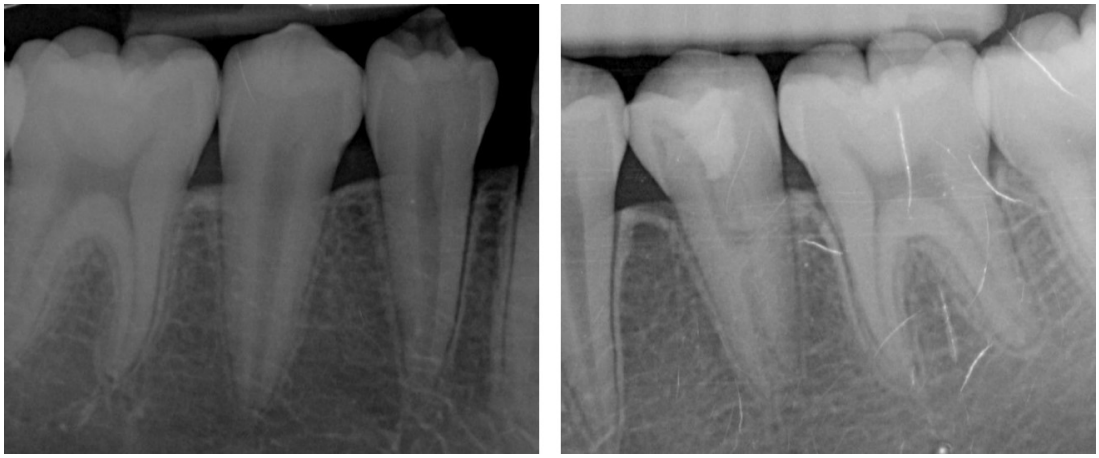

FIGURE 6. Periapical films of teeth 35 and 45 at the 18-month follow-up visit. The radiolucent apical lesion of tooth 35 had healed, and there were increases in root length and root wall thickness observed in both teeth 35 and 45.

patches, characterized by yellow-brown or flesh-colored raised skin, often manifest in infancy and may represent the initial cutaneous signs of TSC. These extraoral features, commonly emerging in childhood, serve as important diagnostic indicators for TSC.

The intraoral features of TSC include dental enamel pits and intraoral fibromas. Dental enamel pits, observed in over 70% of TSC patients [14, 15], usually vary in size, from pinpoint to larger indentations up to 3 mm in diameter. These pits can be clinically detected or identified through radiography as radiolucent images. Despite their significance as a diagnostic indicator in TSC, the occurrence of pits in healthy individuals and other conditions, such as pitted hypoplastic amelogenesis imperfecta, limits their specificity as a diagnostic criterion, thereby categorizing them as a minor feature. Intraoral fibromas represent the second most common manifestation of TSC, with an incidence of 11% to 69% [11, 14, 16]. Although it predominantly appears on the maxillary anterior gingiva, it can also occur at other intraoral sites. Fibromas observed on the attached gingiva present as dome-shaped papules, often matching the color of the gingiva or slightly whitish. Interdental fibromas protrude from the interdental papillae, sometimes with irregular small papules on the surface. Nongingival oral fibromas on the buccal and labial mucosa vary in color, appearing yellowish or bluish in some cases. These lesions are typically asymptomatic, with patients often unaware of their presence. The differential diagnosis for oral fibromas includes various oral lesions. Thus, differentiating intraoral fibromas associated with TSC from other oral lesions involves considering various factors such as etiopathogenesis, location, size and extent [17] and can be used to guide clinicians in making an accurate diagnosis.

A summary of the orofacial diagnostic criteria is shown in Table 2 (Ref. [5]). Dental enamel pits and oral fibromas, categorized as minor features of TSC, lack specificity for diagnosing TSC due to their occurrence in isolation within the general

TABLE 2. Orofacial diagnostic criteria of tuberous sclerosis complex.

Types of features	Diagnostic criteria
Extraoral features	
Major features	Angiofibromas (≥3) or Fibrous cephalic plaque
Intraoral features	
Minor features	Dental enamel pits (≥3)
	Intraoral fibromas (≥2)

Definite diagnosis of TSC: Two major features or one major feature with two minor features.
Possible TSC diagnosis: Either one major feature or more than two minor features.
Adapted from Northrup H et al. [5], 2021.

population or in association with other conditions. Therefore, relying only on these minor features to diagnose TSC is not advisable. Additionally, these features must surpass a certain threshold (dental enamel pits, n ≥ 3; intraoral fibromas, n ≥ 2) to meet diagnostic criteria. In contrast, among the orofacial diagnostic features, the extraoral features such as angiofibroma (n ≥ 3) or fibrous cephalic plaque, classified as major features of TSC, hold significant importance as they have the potential to independently establish a possible diagnosis and contribute to a definite diagnosis when combined with two other intraoral minor features. Thus, detecting and diagnosing the disease through orofacial diagnostic features is essential for pediatric dentists. Once a possible diagnosis has been established, initiating interdisciplinary collaboration with other healthcare providers is necessary to conduct a comprehensive examination and manage TSC patients promptly.

3.2 Dental treatment considerations in patients with TSC

Before providing dental care for patients with TSC, it is necessary to obtain their medical history. TSC patients commonly exhibit impaired organ functions, such as compromised kidney function or heart conduction disorders, which can impact medication dosages or the risk associated with receiving general anesthesia during dental procedures. In addition to assessing physical health, careful evaluation of the patient's neuropsychiatric status is essential [18]. This assessment influences the patient's ability to cooperate with dental treatment and maintain oral hygiene.

Since dental enamel pits and intraoral fibromas are prevalent oral features in patients with TSC [14], establishing oral hygiene instruction and ensuring regular follow-up are essential for preventing these lesions from advancing to more severe oral condition. Dental enamel pits can be treated through restorative treatment, either to prevent caries or for aesthetic purposes [11]. The removal of intraoral fibromas is recommended in case where functional or aesthetic concerns arise due to excessive tumor size [19].

Systemic medication and treatment for TSC can sometimes affect oral health. mTOR inhibitors are essential for managing TSC symptoms; however, a common adverse event associated with these drugs is mTOR inhibitor-associated stomatitis (mIAS), which is typically characterized by mouth ulcers that usually develop around ten days after the start of medication. While they often heal spontaneously within 2–3 weeks, patients often experience severe pain during the course of the disease. For such cases, local or systemic corticosteroid treatment is generally effective in alleviating this discomfort [20, 21]. Additionally, many TSC patients suffer from epilepsy, necessitating the use of antiepileptic medications for seizure control. However, individuals taking antiepileptic drugs like phenytoin may experience gingival overgrowth, affecting up to 50% of patients. In mild cases, non-surgical methods such as improved oral hygiene or antiseptic mouthwashes can help reduce inflammation in the gingival tissues and avoid the need for surgery. However, severe cases often require surgical intervention for effective management [22]. Although changing the medications may significantly impact the condition, this can be challenging due to medical or financial constraints.

In regard to this present case report, the patient's chief complaint was due to a central cusp fracture of Tooth 35. Central cusps are anomalies that occur during the bell stage of tooth development. Altered proliferation and folding of the inner enamel epithelium, along with adjacent ectomesenchymal cells of the dental papilla, result in the formation of a tubercle on the occlusal surface of the teeth [23, 24]. Mutations in the *TSC1* or *TSC2* genes can disrupt the function of the mTOR complex, which is known to play an important role in enamel organ development [25]. This disruption may be associated with the formation of the central cusp. Taga H *et al.* [26] reported a prevalence of central cusps in TSC of 16.7%, significantly higher than the 4% reported in healthy individuals. The study also revealed a significantly higher incidence of neurological issues in the group with central cusps, based on the correlation between intraoral manifestations and associated diseases affecting other organs. In managing central cusps, the significant proportion of dental pulp within the tubercle makes it susceptible to pulp exposure, necrosis and apical infection if the structure fractures due to external force or occlusal wear. It is crucial to carefully monitor the structural integrity, pulp status, and root development of teeth containing such structures. Collectively, it is recommended to identify the presence of these tooth structures in patients with TSC and implement appropriate management strategies accordingly.

Patients with TSC require regular dental visits and radiographic examinations. Table 3 (Ref. [10, 27]) presents a summary of dental considerations that could be used as a reference for practitioners to formulate treatment strategies.

TABLE 3. Dental Treatment considerations in patients with tuberous sclerosis complex.

Characteristics		Treatment considerations/options
Medical History		
Physical condition	Impaired organ function	Medication dosage adjustment; Risk of accepting sedation or general anesthesia
Neuropsychiatric condition	Dental cooperative ability	Sedation or general anesthesia may be required
Adverse event of systemic medication/treatment	mTOR inhibitor-associated stomatitis	Pain control by local or systemic corticosteroid treatment.
	Drug-induced gingival overgrowth	Non-surgical method for reducing inflammation in the gingival tissues; Surgical excision
Dental enamel pits		
	Caries risk	Conservative caries prevention protocols; Restoration treatment
	Aesthetic consideration	
Intraoral fibroma	Functional or aesthetic impact due to excessive tumor size	Oral hygiene instruction; Eradication of the irritation factors [10]; Excision
Central cusp		
	Structural integrity	Occlusal adjustment; Protective resin restoration; Endodontic treatments
	Pulp status and root development assessment	

Conservative caries prevention protocols include oral hygiene instruction, sealants and fluoride [27].
Regular dental visits and radiographic examinations are necessary, with the dental follow-up period depending on the patient's general condition and caries risk assessment.
mTOR: mammalian target of rapamycin.

4. Conclusions

Orofacial characteristics in individuals with TSC can serve as valuable indicators for diagnosis by dental professionals. Suspected cases of TSC necessitate comprehensive whole-body screening, interdisciplinary evaluation, and treatment, as early diagnosis and collaborative efforts among medical specialists can improve the prognosis and quality of life of TSC patients. The unique dental attributes of TSC patients highlight the need for a more thorough examination and comprehensive management approach. The presence of the central cusp in TSC patients deserves increased attention in both diagnosis and dental care. Further statistical investigations and research efforts are warranted to confirm its diagnostic significance.

ABBREVIATIONS

TSC: tuberous sclerosis complex; OMIM: the Online Mendelian Inheritance in Man; mTOR: mammalian target of rapamycin; mIAS: mTOR inhibitor-associated stomatitis.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

YCC—completed the treatment and began writing the manuscript. CLT—provided consultation on treatment, contributed to the manuscript, and revised it. Both authors assessed the patient. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by The Chang Gung Medical Foundation Institutional Review Board (IRB No: 202301971B0). Informed consent signed by the patient and his parents.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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