

## Oral Manifestations of Tuberous Sclerosis Complex in a Young Patient during Orthodontic Treatment

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### Abstract

Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutaneous disorder in which patients may develop hamartomas in multiple organs and presents with variable clinical expression. It may present with a triad of epilepsy, intellectual deficiencies, and facial angiofibromas. Oral manifestations are common in the form of gingival enlargement, fibromas, and sporadic enamel pitting. This is a case study of a 17-year old male with a medical history significant for TSC. The patient was referred by his orthodontist to a periodontist for treatment of gingival enlargement that was impeding orthodontic therapy and proper oral hygiene

**Keywords:** Tuberous sclerosis, Angiofibromas, Gingival overgrowth, Orthodontic therapy

## Introduction

Tuberous sclerosis complex (TSC), also known as Bourneville's disease, is a rare autosomal-dominant neurocutaneous syndrome with a high incidence of spontaneous mutations [1-4]. The phenotypic expression of TSC is highly variable and includes seizures, intellectual deficiency, facial angiofibromas distributed in a butterfly pattern around the nose, cheek, and chin [5,6], as well as non-dermatological manifestations in the heart, kidneys, lungs, abdominal organs, gingiva, retina or bones[7,8].

It is estimated that the prevalence of TSC is 1:6,000 individuals [1,3,9]. TSC is caused by loss-of-function mutations to the TSC1 and TSC2 tumor suppressor genes located on chromosomes 9q34 and 16p13, respectively [8]. The TSC1 gene produces a protein called hamartin, and the TSC2 gene has protein product of tuberin. This tumor-suppressor hamartin-tuberin protein complex is involved in cell growth and differentiation [10]. Thus, the inactivating mutations of TSC1 and TSC2 leads to a loss of these proteins resulting in cellular hyperproliferation and hamartoma formation in various organs [5,8,11]. Due to the large variation of clinical symptoms of TSC, the diagnostic criteria are categorized into major and minor features as shown in Table 1 [12,13]. A definitive diagnosis of TSC is confirmed by the presence of two major features, or one major feature with two or more minor features [1,12,13]. A possible diagnosis of TSC is characterized by having either one major feature or two or more minor features [12,13].

Oral-facial manifestations observed in TSC are common. It includes sporadic enamel pitting on surface of anterior permanent teeth, and fibrous hyperplasia (angiofibromas) located predominately on the anterior gingival mucosa (presenting as gingival enlargement), but can also be found on the lips, buccal mucosa, palate, and tongue [1, 3,14-16]. Less common oral manifestations include hemangiomas, facial asymmetry, high arched palate, bifid uvula, cleft lip/palate, delayed eruption and diastemas [16-18]. Gingival enlargement secondary to anticonvulsant medication is also highly prevalent [17].

## Clinical Presentation

A 17-year-old male was referred by his orthodontist to the Department of Periodontology at the University of Illinois in Chicago College of Dentistry for management of gingival enlargement. The patient was diagnosed with TSC by his physician and reported no family history of the disease. The patient was not taking any medication and denied any history of seizures or any other clinical symptoms of TSC besides skin and oral lesions. Extra-oral examination revealed multiple angiofibromas spreading across his cheeks and nose in a butterfly pattern (Figure.1). Intraoral examination revealed gingival overgrowth in the maxillary and mandibular anterior regions, including interdental papilla that extended as much

as two-thirds of the crown length in some locations (Figure 2, Figure. 3 and Figure.4). A few areas of fibrotic plaques were identified on the keratinized gingiva and the lower labial mucosa (Figure. 5). The periodontal evaluation revealed pocket depths ranging from 3mm to 6 mm with minimal bleeding on probing and localized areas of marginal gingival redness. Oral hygiene was fair and the gingival swelling was fibrotic in nature. The teeth exhibited no mobility. Radiographic evaluation demonstrated no significant findings related to TSC (Figure. 6). A biopsy was planned but was not completed due to the patient's scheduling conflict, therefore no histological examination was performed.

The main goal of periodontal treatment for this patient was to reduce the gingival enlargement in order to facilitate orthodontic treatment and proper oral hygiene. The patient was planned for phase I therapy which including oral hygiene instructions and scaling and root planing, followed by a reevaluation in 6 weeks. Phase II therapy included gingivectomies to facilitate orthodontic therapy as needed.

## Discussion

This case report demonstrates TSC presenting with oral manifestations of gingival fibromas located on keratinized gingiva, as well as on the oral mucosa. The gingival fibromas were impeding proper oral hygiene and orthodontic therapy. Although TSC is an inherited in the autosomal dominant manner the patient presented in this case has no family history of the disorder. This is not unusual as over 70% of TSC cases are the result of spontaneous mutations [12]. The clinical expression is highly variable, making a definitive diagnosis difficult at times and often it goes undiagnosed. The symptoms can range from mild dermatologic lesions with normal life expectancy to severe neurological involvement, including persistent epilepsy and intellectual disability [12]. This patient has a milder expression of the syndrome exhibiting only dermatologic and oral symptoms. He has multiple bilateral facial angiofibromas, which are hamartomatous nodules of vascular and connective tissue that present on the nasolabial folds, cheeks, and chin in a butterfly wing pattern [8,12]. Facial angiofibromas are considered a major feature of TSC and occur in approximately 75% of patients, with their size and number increasing during adolescence and can result in a disfiguring appearance [12,19].

Developmental enamel pitting can occur in as many as 50% to 100% of patients [5,16, 20, 21]. However, enamel pitting is not pathognomonic of TSC as it is also observed in other disorders such as amelogenesis imperfecta, pseudo-hypoparathyroidism and tricho-dento-osseous syndrome [16,22]. As our patient was in active orthodontic therapy, inspection of the teeth in its entirety could not be thoroughly completed due to bracket placement on the facial surface. It is possible that the patient has sporadic enamel pitting under his orthodontic brackets and will need to be evaluated upon completion of his orthodontic treatment. Multiple fibrous papules, presenting as gingival enlargement is the second most common oral finding of TSC and can be observed in 11% to

<b>DIAGNOSTIC CRITERIA FOR TSC:</b>	
<b>Definitive Diagnosis:</b> Two major features with two or more minor features	
<b>Possible Diagnosis:</b> One major feature or two or more minor features	
<b>Major Diagnostic Criteria</b>	<b>Minor Diagnostic Criteria</b>
Facial angiofibromas or fibrous cephalic plaque	Dental enamel pits, randomly distributed
Nontraumatic ungula or periungual fibroma	Intraoral fibromas (gingival fibromas/oral fibrous papules)
Hypermelanotic macules	“Confetti” skin lesions
Shagreen patch	Bone “cysts”
Multiple retinal nodular hamartomas	Retinal achromic patch
Cortical dysplasias (includes tubers and cerebral white matter radial migration lines)	Nonrenal hamartomas
Subependymal nodules	Multiple renal cysts
Subependymal giant cell astrocytoma	Hamartomatous rectal polyps
Cardiac rhabdomyomas	
Lymphangiomyomatosis	
Renal angiomyolipoma	

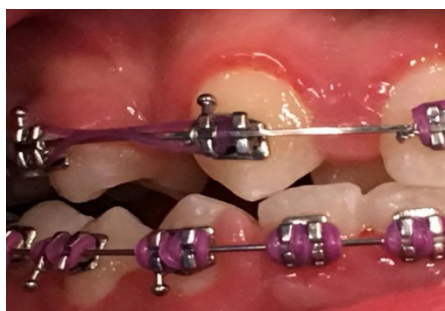
**Table 1:** Major and Minor Diagnostic Criteria for TSC (12,13)



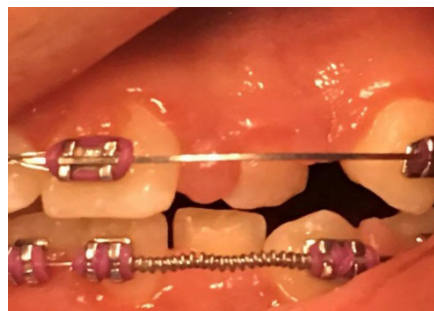
**Figure 1:** Angiofibromas presenting in a butterfly



**Figure 2:** Gingival enlargement surrounding maxillary



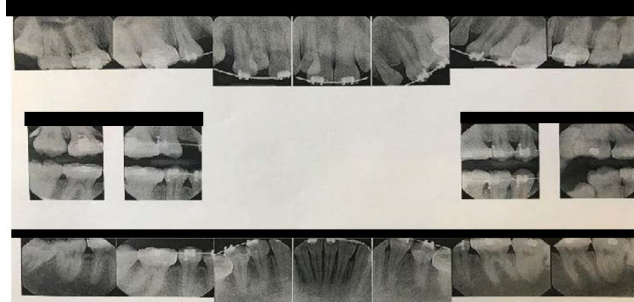
**Figure 3:** Gingival enlargement surround maxillary and



**Figure 4:** Extensive gingival overgrowth around maxillary



**Figure 5:** Intraoral fibromas on labial mucosa and fibrotic plaques on gingiva and lower lip (arrows)



**Figure 6:** FMX at the time of the diagnostic clinic. No pathological anomalies detected

56% of patients [16]. Medication-induced gingival enlargement should be considered as part of the differential diagnoses since seizures are seen in approximately 90% of patients with TSC [11,16,24]. Anticonvulsant medication, such as Phenytoin, is known to potentially contribute to and exacerbate gingival enlargement [16,23]. In this case, the patient did not have any history of seizures and was not taking any medication, thus the gingival enlargement was a result of TSC as opposed to being a side effect of the anticonvulsant medication. Additionally, the gingival enlargement that is induced by medication typically presents as a generalized gingival enlargement, as opposed to localized areas as observed in this case. Another differential diagnosis for the gingival enlargement in this patient is the presence of the fixed orthodontic appliances, which can create a challenge for maintaining proper oral hygiene. However, overall the patient had fairly good oral hygiene and his plaque control was adequate. The enlarged gingivae had a fibrotic appearance, which is consistent with angiofibromas due to TSC, rather than the soft friable enlarged tissue resulting from inflammation. Although angiofibromas are most commonly seen on the gingiva they are also found in other intraoral areas, such as buccal mucosa, lips, tongue, and palate, as was seen in this patient.

## Conclusion

This is a case report of a mild expression of TSC illustrating oral manifestations of the disease that may be overlooked. Due to the highly variable clinical expression of TSC it often goes undiagnosed. It is important for dentists to be familiar with the oral signs of TSC in order to help the patient achieve an early diagnosis, genetic counseling, provide better management in collaboration with the medical team and enhance quality of life.

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