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

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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 3 mm 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 gingivectomy 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 impedng 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% to100%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, pseudohypoparathyroidism 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
**Table 1: Major and Minor Diagnostic Criteria for TSC (12,13)**

| Major Diagnostic Criteria | Minor Diagnostic Criteria |
|----------------------------|----------------------------|
| Facial angiofibromas or fibrous cephalic plaque | Dental enamel pits, randomly distributed |
| Neutromatric ungula or periungual fibroma | Intraoral fibromas (gingival fibromas/oral fibrous papules) |
| Hypomelanotic macules | “Confetti” skin lesions |
| Shagreen patch | Bola cysts |
| Multiple retinal nodular hamartomas | Retinal achromatic patch |
| Cortical dysplasias (includes tubers and cerebral white matter radial migration lines) | Neuronal hamartomas |
| Subependymal nodules | Multiple renal cysts |
| Subependymal giant cell astrocytoma | Hamartomatic rectal polyps |
| Cardiac rhabdomyomas | |
| Lymphangiomyomatosis | |
| Renal angiomyolipoma | |

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

**Figure 2:** Gingival enlargement surrounding maxillary teeth

**Figure 3:** Gingival enlargement surrounding maxillary teeth

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

**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 was 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.

References

1. De Jesus Araújo L, Braga Muniz G, Santos E, et al. (2013) Tuberous sclerosis complex diagnosed from oral lesions. Sao Paulo Med J. 131:351-355.

2. Roach ES (2004) Miller VS. Neurocutaneous disorders. Cambridge University Press.

3. De Jesus Araújo L, Yamamoto De Almeida L, Santos Lima J, Martellilún J, et al. (2011) Evaluation of MMP-1, MMP-10, TIMP-1, a-SMA and TGF-b1 in angiofibromas of tuberous sclerosis. Minerva Stomatol 60:25-33.

4. Araujo L de J, Lima LS, Alvarenga TM, et al. (2011) Oral and neurocutaneous phenotypes of familial tuberous sclerosis. Oral Surg Oral Med Oral Pathol Oral RadiolEndod 111:87-94.

5. Stalker HJ, Zori RT (2005) Tuberous Sclerosis. R. C. Phillips Units Newsletter XVII (1).

6. Osborne JP (1998) Diagnosis of tuberous sclerosis. Arch Dis Child 63:1423-1425.

7. Mann L, Ebrahimi-Fakhari D, Heinrich B, et al. (2017) [ESPED- Survey: TSC-disease in children and adolescents: preliminary results from a German epidemiological survey]. Wien Med Wochenschr 167:271-275.

8. Curatolo P, Bombardieri R, Jozwaik S (2008) Tuberous sclerosis. Lancet 372:657-68.

9. Osborne JP, Fryer A, Webb D (1991) Epidemiology of tuberous sclerosis. Ann N Y Acad Sci. 615:125-127.

10. Apak A, Haliloglu G, Kose G, et al. (2003) Mutation analysis of the TSC2 gene in 33 Turkish familial cases with tuberous sclerosis. Turk J Pediatr 45:1-5.

11. Rodrigues DA, Gomes CM, Costa IM (2012) Tuberous sclerosis complex. An Bras Dermatol87:184-196.

12. Ebrahimi-Fakhari D, Meyer S, Vogt T, et al. (2017) Dermatological manifestations of tuberous sclerosis complex (TSC). J Dtsch DermatolGes 15:695-700.

13. Northrup H, Krueger DA (2013) International Tuberous Sclerosis Complex Consensus G. Tuberous sclerosis complex diagnostic criteria update recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatric Neurol 49:243-254.

14. Scully C (1997) Orofacial manifestations in tuberous sclerosis. Oral Surg Oral Med Oral Pathol 44:706-716.

15. Sparling JD, Hong CH, Brahim JS, et al. (2007) Oral findings in 58 adults with tuberous sclerosis complex. J Am AcadDermatol 56:786-790.
16. Mbibi SU, Segelnick SL, Weinberg MA (2015) Epithelia and Fibrous Hyperplasia: An oral Manifestation of Tuberous Sclerosis Complex. A Case Study. NY State Dent J 81:37-41.

17. Damm DD, Tomich CE, White DK (1999) Drummond JF. Intraosseous fibrous lesions of the jaws: a manifestation of tuberous sclerosis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 87: 334-340.

18. Scully C (1997) Orofacial manifestations in tuberous sclerosis. Oral Surg Oral Med Oral Pathol 44:706-716.

19. Muzykewicz DA, Newberry P, Danforth N, et al. (2007) Psychiatric comorbid conditions in a clinic population of 241 patients with tuberous sclerosis complex. Epilepsy Behav 11:506-513.

20. Lopez-Lopez J, Rodriguez-de-Rivera-Campillo E, Marques-Soares MS, et al. (2004) Tuberous sclerosis and its oral manifestations. A clinical case. Med Oral 9:216-223.

21. Devlin LA, Shepherd CH, Crawford H, Morrison PJ (2006) Tuberous sclerosis complex: clinical features, diagnosis, and prevalence within Northern Ireland. Dev Med Child Neurol 48:495-499.

22. Flanagan N, O'Connor WJ, McCartan B, Miller S, et al. (1997) Developmental enamel defects in tuberous sclerosis: a clinical genetic marker? Jr Med Gene 34:637-639.

23. Asconape JJ (2002) Some common issues in the use of antiepileptic drugs. SeminNeurol 22:27-39.

24. Samir H, Ghaffer HA, Nasr M (2011) Seizures and intellectual outcome: Clinico-radiological study of 30 Egyptian cases of tuberous sclerosis complex. Eur J Paediatr Neurol 15:131-137.