

Epithelial and Fibrous Hyperplasia: An Oral Manifestation of Tuberous Sclerosis Complex

A Case Study

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ABSTRACT

The authors present a case study of a 13-year-old female with a past medical history of tuberous sclerosis complex (TSC), an autosomal dominant disorder. It usually presents with a triad of epilepsy, mental deficiency and facial angiofibromas that are often distributed around the nose, cheek and chin, and are frequently shaped like butterfly wings. In addition, oral manifestations include gingival enlargement and developmental enamel pitting on the facial aspect of the anterior permanent dentition in 50% to 100% of patients. The patient's chief complaint was gingival enlargement and gingival bleeding. The histology of the excised gingival tissue revealed epithelial and fibrous hyperplasia, consistent with TSC.

Tuberous sclerosis complex (TSC), also known as Bourneville's disease or epiloia, is an autosomal dominant disorder with a neurological manifestation. It was first documented in 1862 by Von Recklinghausen in a brief report and then more thoroughly described in 1880 by Desire-Magloire Bourneville, who observed that the disease was only suspected in patients that presented with "mental retardation and fits."^{1,2}

In 1908, Vogt described TSC as a disorder that presents with a triad of epilepsy, mental deficiency and facial angiofibromas that are often distributed around the nose, cheek and chin, and are

frequently shaped like butterfly wings.^{2,3} With the advent of new techniques for genetic studies, it is currently understood that TSC is an autosomal dominant disease with high penetrance, and that males and females have a 50% chance of passing the affected gene to their offspring.⁴ It is caused by inactivating mutations of TS1 and TS2 tumor suppressor genes located on chromosomes 9q34 and 16p13.3, respectively, leading to cellular hyperproliferation and hamartoma formation in different organs of the body, most commonly, the kidneys, heart, eyes, gingiva, skin and brain.^{2,5,6} No single organ is affected in every patient diagnosed with TSC; and there is no proof that any single clinical or radiographic sign present in one organ is absolutely specific for TSC.⁶

Diagnosis is usually made by clinical, pathologic and/or radiographic findings. Because of the variation in symptoms of TSC disorder, the diagnosis of TSC has been divided into major and minor criteria. A patient is said to "definitely" have TSC if he or she presents with two major features or one major feature and two or more minor features.⁷⁻¹⁰ "Probable" TSC diagnosis is reached if a patient presents with one major and one minor feature, while a diagnosis of "possible" TSC is made if the patient presents with one major feature or two or more minor features (Table 1).⁷⁻¹⁰ However, patients should be considered for the syndrome if they present with a history of seizures and hypomelanotic lesions, as 90% of patients present with seizures and up to 98% present with skin lesions.^{7,10}

Oral manifestations of TSC include developmental enamel pitting on the facial aspect of the anterior permanent dentition in 50% to 100% of patients.^{2,11,12} The pathogenesis of pitted enamel hypoplasia in TSC is not understood. Previous studies suggest that the pits extend to the dentoenamel junction. The pits appear to

TABLE 1

Tuberous Sclerosis (TS) Diagnostic Criteria⁹

Major Features

1. Facial angiofibromas or forehead plaque.
2. Non-traumatic unguial or periungual fibroma.
3. Hypomelanotic macules (more than three).
4. Shagreen patch (connective tissue nevus).
5. Multiple retinal nodular hamartomas.
6. Cortical tuber.
7. Subependymal nodule.
8. Subependymal giant cell astrocytoma.
9. Cardiac rhabdomyoma, single or multiple.
10. Lymphangiomyomatosis.
11. Renal angiomyolipoma.

Minor Features

1. Multiple randomly distributed pits in dental enamel.
2. Hamartomatous rectal polyps.
3. Bone cysts.
4. Cerebral white matter migration lines.
5. Gingival fibromas.
6. Non-renal hamartoma.
7. Retinal achromic patch.
8. Confetti skin lesions.
9. Multiple renal cysts.

Definite TSC: Either two major features or one major feature with two minor features.

Probable TSC: One major feature and one minor feature.

Possible TSC: Either one major feature or two or more minor features.



Figure 1. Reveals facial angiofibromas consisting of blood vessels and fibrous tissue, and Shagreen's patch on the back, Periungual fibromas (Koenen's tumor) on thumb.



Figure 2. Gingival overgrowth between #23 and #24 showing low smile line.

result from a reduction in the amount of enamel matrix formed. This may be because of a primary defect in odontoblasts, or in ameloblasts, or may be the result of defective interaction between odontoblasts and ameloblasts.¹³

However, enamel pitting is not unique to TSC; it is also associated with other abnormalities of amelogenesis, including pitted amelogenesis imperfecta, vitamin D-dependent rickets, epidermolysis-bullosa-dystrophica, pseudo-hypoparathyroidism and tricho-dento-osseous syndrome.¹ Since enamel pits might be the most common oral manifestation of TSC, they may be a helpful marker in the diagnosis of this disorder.¹³

Multiple fibrous papules that present clinically as gingival enlargement are the second most common oral finding of TSC, affecting 11% to 56% of patients. The fibrous papules are seen predominantly on the anterior gingival mucosa, although the lips, buccal mucosa, palate and tongue may be involved.^{11,12} Less common oral manifestations include hemangiomas, facial asymmetry, high arched palate, bifid uvula, lip/palate, delayed eruption and diastemas.^{11,12,14}

Because of the varying clinical manifestations, the prevalence and incidence of TSC differs among epidemiological studies. Incidence of TSC varies from 1:10000 to 1:100000, depending upon the study.⁵ A study showed that 1:8000 newborns and 1:6000 adults have the disorder.^{4,6} Differences in data may be explained by diagnostic criteria and partial forms of presentation of the disorder.⁴ Both sexes are affected in a similar frequency, but women may show more prominent signs. There are no reports showing disproportionate involvement in a particular ethnic group.⁶

Case Report

A 13-year-old female presented to Brookdale University Hospital dental clinic for comprehensive dental care and gingival bleeding from the areas of overgrowth. She had been an inconsistent patient since 2004. A medical clearance from her primary care physician, dated June 2008, described her past medical history as “tuberous sclerosis with skin lesions/seizure disorder and learning issues and two small rhabdomyomas in the left ventricle with good heart function, and shagreen's patch on her back.” She is on Keppra (levetiracetam) 250 mg two times a day and has no known drug allergies. Extraoral exam shows facial angiofibromas; no swelling, no lymphadenopathy and no temporomandibular disorder were observed (Figure 1).

The intraoral exam showed missing permanent first molars (#3, #14, #19, #30), which were extracted in 2006. Notes from her clinic chart stated the first molars were extracted “due to dysmorphic and abnormal development”; hypoplastic maxillary central incisors (#8 and #9), gingival enlargement about 2 cm by 1 cm on facial gingival papilla between #23 and #24; gingival enlargement also observed between facial papilla of #7,#8, #9 and lingual of #6 and #7; ankylosed and over-retained primary tooth #K, edge-to-edge incisal occlusion, and rotated #28 (Figures 2-4).

Methods

On Sept. 25, 2012, the patient presented for a gingivectomy on the maxillary anterior region; a gingivectomy was achieved previously on the mandibular anterior region. Her medical history was reviewed. She was administered 72 mg 2% lidocaine with 0.034 mg epinephrine for local infiltration of the buccal and palatal gingiva, from tooth #6 to #11. Using an 11- and 15-blade scalpel, a gingivectomy was performed on the lingual and facial gingival of teeth #6 to #11; crown lengthening was performed on tooth #9; and an enameloplasty, to reduce bulbous enamel, on facial cervical third of #8 and #9 (Figure 5). Tissue from the papillary overgrowth from the palatal area between teeth #6 and #7 was sent to the laboratory for biopsy. Hemostasis was achieved with gauze, and a Coe-pak was placed in incised areas. The patient was advised to take ibuprofen every four to six hours when needed for pain and to return in two weeks for postop and again at two months (Figure 6).

The pathology report, dated 10/01/2012, of gingival tissue fixated in formalin, measuring 1.5 cm x 0.7 cm x 0.3 cm, showed “keratotic, stratified squamous epithelium covering a core of dense and cellular fibrous connective tissue. Numerous enlarged stellate-shaped fibroblasts, some containing multiple nuclei, were seen in the lesional stroma. Scattered lymphocytes and plasma cells were also seen. The diagnosis was epithelial and fibrous hyperplasia” (Figure 7).

Discussion

TSC is an autosomal dominant neuro-cutaneous disorder characterized by the development of multiple hamartomas distributed throughout the body, skin, brain, heart, kidneys, liver and lungs.¹⁵ Two-thirds of the patients report sporadic mutations. It is usually associated with the classic triad of mental retardation (in 70% of cases), seizures (in 90% of cases) and angiofibromas (95% of cases). However, this classic triad is only present in 29% of patients with the disorder; 6% of these patients lack all three.^{2,16} Oral manifestations such as enamel pitting and fibromatous growth of the gingiva are also seen in patients with TSC, and are considered minor features of the disorder.^{7,16,17}

In the case presented here, the patient appeared with the classic triad of history of seizure disorder, “learning issues” and angiofibromas, with a butterfly-like pattern on the face;^{18,19} In addition, a consultation with her primary care physician revealed she had cardio-rhabdomyomas, facial angiofibromas and periungual fibromas (Koenen’s tumor); these are all major features of the disorder. Thus, her diagnosis of TSC is definite.

Her chief complaint was gingival overgrowth that bleeds when she brushes, which affects her home care and negatively affects her quality of life. She was not concerned about her esthetics but, rather, difficulty brushing and flossing. We decided on minimal gingival reduction and restorative treatment until she was older. Her treatment plan included oral hygiene instructions,



Figure 3. Gingival overgrowth of facial papilla and gingival margins of #6 through #11.



Figure 4. Panoramic radiograph.



Figure 5. Anatomical crown exposure and gingivectomy.



Figure 6. Two-month postsurgery.

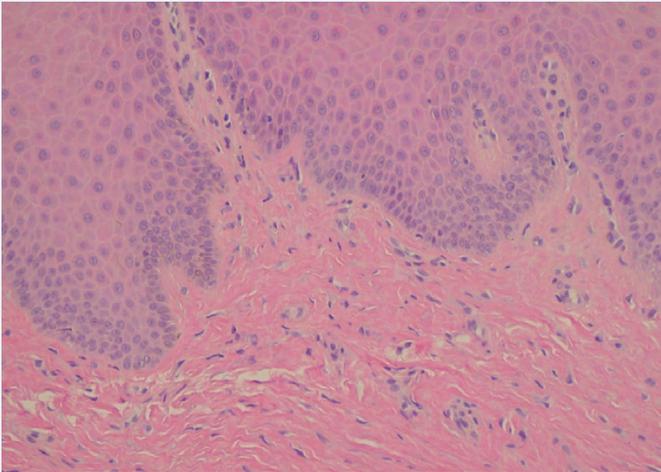


Figure 7. Dense fibrous connective tissue is noted subjacent to surface mucosa (hematoxylin and eosin, 10x).

mechanical debridement and periodontal re-evaluation, at which time a gingivectomy was recommended and completed to provide improved function, esthetics and, thus, improved quality of life.⁸

The differential diagnosis of these gingival lesions includes the gingival overgrowth induced by medications such as calcium channel blockers, phenytoin (Dilantin), or cyclosporine. The patient in this case is on Keppra (levetiracetam), which is one of the new antiepileptic drugs that pose less of a chronic risk of gingival enlargement.²⁰ It is noteworthy that uniform and generalized gingival enlargement, the common pattern of gingival enlargement induced by other epileptic drugs, was not observed in this case;¹⁴ thus, Keppra was least likely the cause of the sporadic gingival enlargements observed.

Also, in the literature, gingival enlargement due to familial or medication causes are histologically described as showing elongated, narrow rete ridges, which was also not observed histologically in this case.⁸

Excised tissue from a gingivectomy submitted to the lab was diagnosed as epithelial and fibrous hyperplasia. In the literature, histology of the enlarged gingiva of TSC has been described as showing keratotic stratified squamous epithelium overlying dense fibrous connective tissue, surrounded by abundant distinctive pleomorphic stellate-shaped cells with multiple nuclei present,^{8,14}

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which we saw in this case. Thus, we can deduce that the gingival overgrowth in this case was most likely primarily a result of the TSC disorder. However, some literature also observes numerous dilated capillaries histologically;^{8,14} but these were not observed in this case.

The recurrence of these lesions in the gingival tissue after gingivectomy and periodontal care is rare, probably because of the effectiveness of the treatment.¹⁴ However, there can be possible rebound of gingival enlargement with anti-seizure medications; thus, routine recall and plaque control are strongly advised after gingivectomy.^{8,11}

Conclusion

Signs and symptoms of TSC vary, with many cases going undiagnosed.¹⁵ Dentists should be aware of the oral clinical manifestations of TSC, which include enamel pits and gingival overgrowth. The 2012 International Tuberous Sclerosis Complex Clinical Consensus Conference concluded that skin and oral lesions are common in TSC and that early intervention, including genetic counseling, may help to increase the quality of life of these patients.¹⁰ //

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