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## Tuberous sclerosis complex with oral manifestations: A case report and literature review

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### Abstract

**Introduction:** Tuberous sclerosis complex (TSC) is a neurocutaneous syndrome produced by a number of genetic mutations. The disease is characterized by the development of benign tumors affecting different body systems. The most common oral manifestations of TSC are fibromas, gingival hyperplasia and enamel hypoplasia.

**Clinical Case:** A 35-year-old woman diagnosed with TSC presented with a reactive fibroma of considerable size and rapid growth in the region of the right lower third molar.

**Discussion:** In the present case the association of TSC with dental malpositioning gave rise to a rapidly evolving reactive fibroma of considerable diameter. Few similar cases can be found in the literature. Patients with TSC present mutations of the TSC1 and TSC2 genes, which intervene in cell cycle regulation and are important for avoiding neoplastic processes. No studies have been found associating TSC with an increased risk of oral cancer, though it has been shown that the over-expression of TSC2 could exert an antitumor effect. Careful oral and dental hygiene, together with regular visits to the dentist, are needed for the prevention and early detection of any type of oral lesion. The renal, pulmonary and cardiac alterations often seen in TSC must be taken into account for the correct management of these patients.

**Key words:** Tuberous sclerosis, reactive fibroma, oral manifestations.

## Introduction

Tuberous sclerosis complex (TSC) is a neurocutaneous syndrome characterized by the development of benign tumors such as neurofibromas and angiofibromas located anywhere in the body (skin, central nervous system, heart, kidneys, etc.).

Patients with TSC present mutations of the TSC1 and TSC2 genes, which intervene in cell cycle regulation. This is a dominant autosomal hereditary disease, though 60-70% of all cases are the result of spontaneous mutations (1,2). The prevalence of TSC ranges from 1:6,000 to 1:10,000 individuals, and the diagnosis is usually established between 4-10 years of age or in puberty (3).

TSC manifests with variable signs and symptoms together with angiofibromas distributed in a characteristic "butterfly" pattern on the face and forehead. The most important neurological problems are mental retardation, seizures, autism and learning difficulties. The diagnostic criteria of TSC have been divided into major and minor features (Table 1). The presence of two major characteristics or of one major criterion and two minor criteria confirms the diagnosis. A molecular diagnosis is advised in patients at risk, in order to diagnose the disease before the actual symptoms appear (1,3,4).

The cerebral manifestations and renal complications of TSC exert an important influence upon patient prognosis (4).

The most common oral manifestations of TSC are fibromas, gingival hyperplasia and enamel hypoplasia (5). Other less frequent findings in the oral cavity are a high arched palate, bifid uvula, harelip and/or cleft palate, delayed dental eruption and the presence of diastemas (6).

**Table 1.** Diagnostic criteria of tuberous sclerosis complex (TSC).

<p><b>Major criteria</b></p> <ul style="list-style-type: none"> <li>- Facial angiofibromas</li> <li>- Multiple ungual fibromas (Koenen tumors)</li> <li>- Cortical tubercle</li> <li>- Subependymal nodule</li> <li>- Multiple astrocytomas</li> <li>- Renal angioliomas</li> <li>- Hypomelanocytic maculae (3 or more)</li> <li>- Cardiorhabdomyomas</li> </ul>
<p><b>Minor criteria</b></p> <ul style="list-style-type: none"> <li>- Cerebral tubercles</li> <li>- Non-calcified subependymal nodules</li> <li>- Hamartomatous rectal polyps</li> <li>- Gingival fibromas</li> <li>- Non-renal hamartomas</li> <li>- Multiple renal cysts</li> <li>- Retinal hamartomas</li> <li>- Enamel hypoplasia</li> </ul>

## Clinical Case

A 35-year-old woman was seen in the Service of Oral Surgery (Dental Clinic of the University of Barcelona, Spain) in March 2009 for the evaluation of continuous, intense pain for the past two days, located in the right hemimandibular region. The patient explained that she noticed the appearance of an asymptomatic mass in the right lower third molar region a few months ago, and that the lesion had gradually grown since then.

TSC had been diagnosed at age 23 years as a result of the presence of Koenen tumors on the face, fingers and toes, lumbar connective tissue nevus, parascapular hypomelanocytic macula, and enamel hypoplasia of the left upper central incisor. Magnetic resonance imaging, funduscopy and abdominal ultrasound were also performed, revealing the presence of renal alterations. In 1999 the patient underwent kidney transplantation due to chronic renal failure secondary to angiomyolipomas, and two years later bilateral breast fibroadenomas were removed and a simple total hysterectomy was performed due to multiple uterine fibromatosis. On several occasions she underwent surgery for the removal of Koenen tumors, angiofibromas and epidermoid cysts in the facial region. Posteriorly, in 2005, right and left radical nephrectomy was carried out.

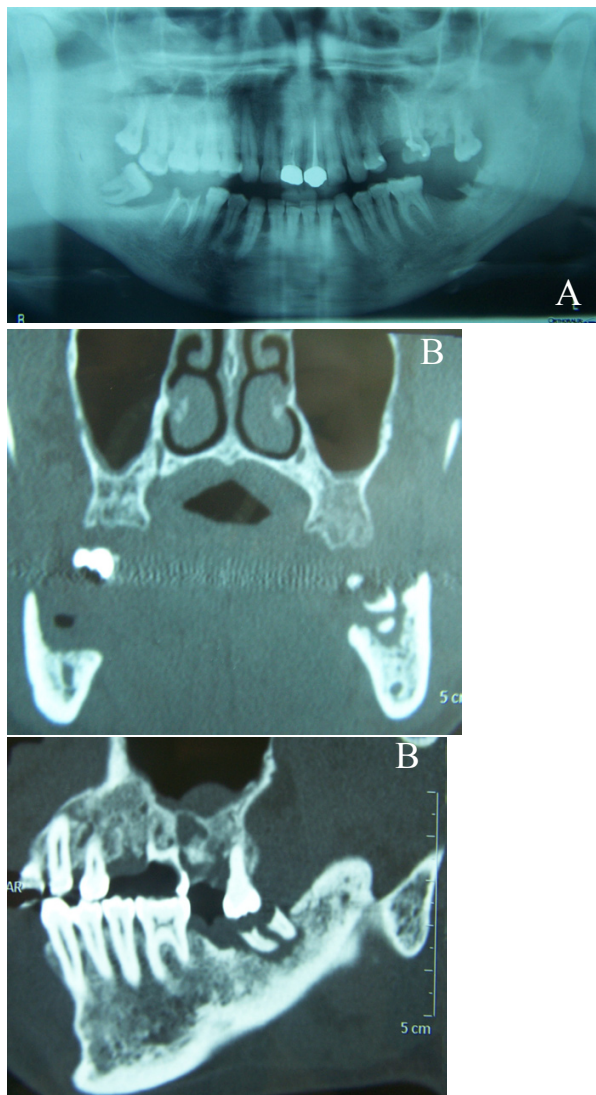
At the time of her visit to our Service, the patient was taking the following medication: 5 mg of glucocorticoids daily via the oral route (Dacortin® 5 mg; Merck, Madrid, Spain), 250 mg of cyclosporine daily via the oral route (Sandimmun neural® 50 mg; Novartis, Barcelona, Spain), and 20 mg of enalapril maleate daily via the oral route (Renitec® 5 mg; Merck, Madrid, Spain).

Oral and dental exploration revealed the presence of a papillomatous tumor of the same color as the oral mucosa and measuring 2.5 cm in diameter, enveloping the right lower third molar, which in turn showed grade 3 mobility (Fig. 1A). A lesion of similar characteristics but smaller size (1 cm) was identified in association to the root fragments of the left lower third molar (Fig. 1B). The lesions were asymptomatic, but percussion of the right lower third molar caused pain.

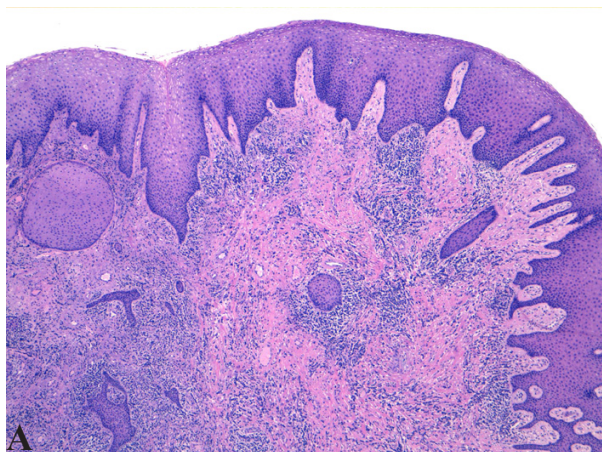
A panoramic radiography and a computed tomography scan of the mandible and upper maxilla (Fig. 2A-B) showed well defined radiotransparencies with regular margins in the region of the lower third molars. The lower third molars were removed and the associated lesions were resected. The histopathological study of the tumor tissue confirmed the presence of reactive fibroma (Fig. 3A-B).



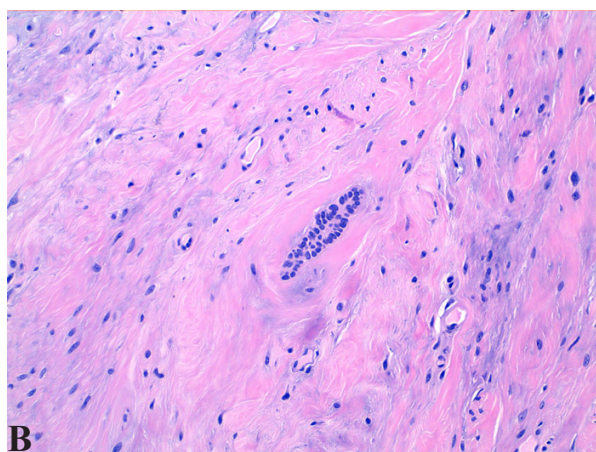
**Fig. 1.** Clinical examination. A. Lesion associated to the right lower third molar. B. Lesion related to the root remains of the left lower third molar.



**Fig. 2.** Radiological study. A. Panoramic radiography (March 2009). B. Sagittal and coronal views of the computed tomography scan (April 2009).



**Fig. 3.** Histological study (hematoxylin-eosin stain). A. Chronic inflammation with epithelial hyperplasia is observed (x100).



B. Collagen-containing fibrous tissue fragments are seen, with few cells, enveloping remains of odontogenic epithelium (x200).

## Discussion

Tuberous sclerosis complex (TSC) is often associated with mental retardation (in 70% of cases) and epilepsy (90%). Koenen tumors and angiofibromas in turn are observed in 15-20% and 70% of all cases, respectively. Renal angiomyolipomas and cysts affect one-half of patients with TSC and are the cause of chronic renal failure that may prove fatal. Cardiac rhabdomyomas are normally observed before age 25 years in 30-50% of all cases, and are also a cause of early death (4,7). Our patient presented Koenen tumors, renal oncocytomas and angiomyolipomas, angiofibromas and enamel hypoplasia, but no mental retardation or epilepsy.

The most common oral manifestations of TSC are fibrous hyperplasias and enamel hypoplasia (7). The former are more often found in the gingival zones of the anterior sector, though involvement of the lips, tongue and palate is not unusual. According to some authors, these hyperplasias may be secondary to the medication usually taken by these patients (8). The incidence of oral fibromas in TSC varies according to the different literature sources between 50-69%, with an average diameter of 5 mm (9-12). The aggressivity of the lesions depends on the severity of the local factors. Our patient presented a rapidly evolving reactive fibroma measuring 2.5 cm in diameter, associated to a malpositioned lower third molar. The literature offers no evidence of similar oral fibromas.

It should be noted that these patients present mutations of the TSC1 and TSC2 genes. These genes intervene in cell cycle regulation and are important for avoiding neoplastic processes (13). No studies have been found associating TSC with an increased risk of oral cancer, though according to Kawaguchi et al. (14), TSC2 overexpression could exert an antitumor effect in oral cancer, since it is an oncosuppressor gene. Fleury et al. (15) published a case of undifferentiated pleomorphic sarcoma located in the mandible of a patient with TSC.

Enamel hypoplasia is present in the permanent dentition of almost 100% of these patients, and is associated with an increased risk of caries. This anomaly typically affects the vestibular surfaces of several teeth. No specific studies have been published on the oral hard tissue manifestations of TSC. According to Barron et al. (16), mesenchymal tumors such as myxoma, desmoplastic fibroma and odontogenic fibroma can be found in the maxillas of patients diagnosed with this disease. A correct differential diagnosis of these lesions must be established in order to apply adequate treatment (15,16).

Patients with TSC must adopt measures for careful oral and dental hygiene, with regular visits to the dentist, in order to eliminate potential irritative factors and ensure the early diagnosis of any possible lesions. The oral healthcare professional in turn must always request a detailed medical report on the condition of the patient.

Due to the frequent renal, cardiac and pulmonary alterations, general anesthesia, intravenous sedation and pre- and postoperative medication must be administered with caution.

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