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Case Report

Tuberous Sclerosis Complex- A Clinico-Imaging Illustrative Case Report

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Abstract

Tuberous sclerosis complex (TSC) is a fascinating neurocutaneous syndrome, characterized by the formation of hamartomatous lesions in multiple organ systems. Patients develop hamartomas of the brain, kidneys, heart, lungs, skin and eyes. The important oral manifestations include oral mucosal angiofibromas and dental enamel pits. This report attempts to document oro-cutaneous manifestations along with imaging characteristics of central nervous system in a patient with TSC.

Keywords: Tuberous Sclerosis; Angiofibromas; Dental Enamel Pits; Ash Leaf Macules; Shagreen Patches

Abbreviations

TSC: Tuberous Sclerosis Complex; AMLs: Angiomyolipomas; CNS: Central Nervous System; MENS: Multiple Endocrine Neoplasia; MRI: Magnetic Resonance Imaging; SENs: Subependymal Nodules; SEGAs: Subependymal Giant Cell Astrocytomas; DTI: Diffusion Tensor Imaging; PET: Positron Emission Tomography

Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutaneous syndrome with complete penetrance and high phenotypic variability [1]. The name is due to growth resembling potatoes occurring in the brain. The clinical picture traditionally associated with TSC is Vogt's triad i.e. epilepsy, mental retardation and facial angiofibromas. This classic triad is seen in only 30 - 40% of affected individuals [2]. This disorder was earlier known as Epiloia or Bourneville's disease and was first reported by Freidrich Von Recklinghausenin1862 [3]. Gomez., *et al*. described the full spectrum of the disease [3].

The prevalence of TSC is 1 in 6000 newborns with no gender predilection and ethnic clustering [4]. The disease is caused by a mutation in either the TSC1 or TSC2 gene, located on chromosome 9p and16q respectively (TSC1-MIM1191100, TSC2-MIM 191092). Hamartin and tuberin are the proteins encoded by TSC1 and TSC2 respectively [5]. The heterodimer formed by hamartin and tuberin functions as a tumor suppressor by inhibiting mTOR kinase cascade [6]. Dysfunctional gene products from altered TSC1 or TSC2 gene loci lead to disorganized cellular overgrowth and abnormal differentiation. Most of the TSC mutations are spontaneous involving TSC2 gene and lead to a more severe phenotype. The familial cases account for 50% of cases and are mostly due to TSC1 gene mutation [7]. Some individuals acquire TSC through a process called gonadal mosaicism. Forme Fruste, a variant of TSC is due to somatic mosaicism [8]. Apart from the cutaneous stigmata, TSC patients develop multiple brain lesions, angiomyolipomas (AMLs), lymphangiomyomatosis of lungs, cardiac rhabdomyomas and very rarely skeletal and vascular abnormalities [9].

Although there have been many case reports published so far, our case report is rare, as there have been extremely few reports describing the central nervous system (CNS) features. The present case is an effort to present the most classical CNS features for the dental fraternity, as these are difficult to comprehend by dentists. This report illustrates the oral, cutaneous and CNS manifestations in a 32 year old female, who presented to dental outpatient department with multiple growths in the oral cavity.

Case Report

A 32 year old female presented to the department of Oral Medicine and Radiology, with chief complaint of multiple growths on her gums since 15 years. On further history taking, it was revealed that the oral growths increased in number since 5 years and occasionally bleed while brushing. The family history revealed that her father and elder brother had similar oral growths and both suffered from seizures. The patient was non-epileptic and was not on any medications. The patient presented with multiple dark brown to black papules, which measured 1 - 7 mm, concentrated more on the malar region around the ala of the nose and periorbital area (angiofibromas) (Figure 1a). The papules on the right malar region clustered to form raised hyperpigmented plaque (shagreen patch) (Figure 1b). Multiple skin tags and raised darkly pigmented papules were also seen on the neck and around the axillae (Figure 1c). The skin in the lumbosacral area presented with multiple hypopigmented leaf like spots (Ash leaf spots) (Figure 1d). Few sessile and firm nodular growths were noted on the digits of left foot, suggestive of periungual fibromas or Köenen tumors (Figure 2). Intraoral examination revealed multiple dome shaped papules on the gingival and alveolar mucosa anterior to first molars. The papules measured 2 - 5 mm in size, formed dense aggregates on the gingival and alveolar mucosa of maxillary anteriors. A single growth on the mucosa with respect to 12 tooth was pedunculated and measured 1 cm x 1 cm (Figure 2a). Some papules were the extensions of the interdental papillae (Figure 3b). The buccal mucosa also revealed multiple small hyperpigmented papules resembling melanotic macules (Figure 3c). Examination of dental tissues revealed multiple chalky white hypoplastic areas and enamel pits (Figure 3b and 3d). These oral and skin manifestations suggested a diagnosis of TSC. Differential diagnosis included Cowden syndrome, Birt-Hogg- Dube syndrome and multiple endocrine neoplasia (MENS) type 1. Informed consent from the patient and institutional ethical board was obtained to carry out further investigations. Panoramic radiograph and skull radiographs were non-contributory. A magnetic resonance imaging (MRI) scan for the brain demonstrated multiple cortical and sub cortical tubers, sub-ependymal

nodules (SENs), sub-ependymal giant cell astrocytomas and radial glial bands (Figure 4a-4d). Histopathological examination of the excisional biopsy revealed a hyperplastic epithelium overlying a dense connective tissue containing dilated capillaries and scattered inflammatory cell in filtrate consistent with a diagnosis of angiofibroma. Investigations for lungs, heart, kidneys were not performed due to financial constraints. Following the revised diagnostic criteria by National Institutes of Health published in 1998, the diagnosis of TSC was confirmed [10].

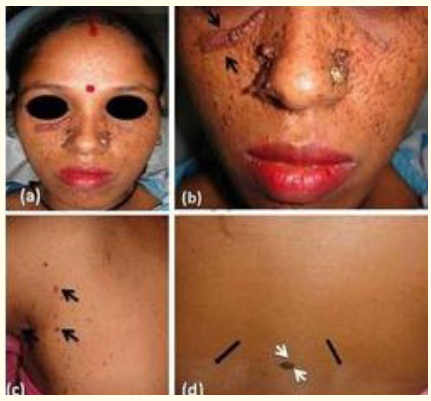

Figure 1: (a): Facial Profile Photograph showing multiple dark brown to black papules on the malar region, concentrated around the ala of nose and periorbital area. (b): Papules on the right malar region clustered to form raised hyperpigmented plaque (shagreen patch) (black arrows). (c): Multiple skin tags and raised darkly pigmented around the axillae (black arrows). (d): Lumbosacral area showing hypopigmented leaf like spots (Ash leaf macules) [long black arrows]and raised connective tissue nevi (white arrows).

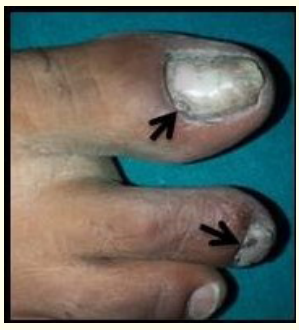

Figure 2: Periungual fibroma present around the nail bed in the toe and middle finger of foot.

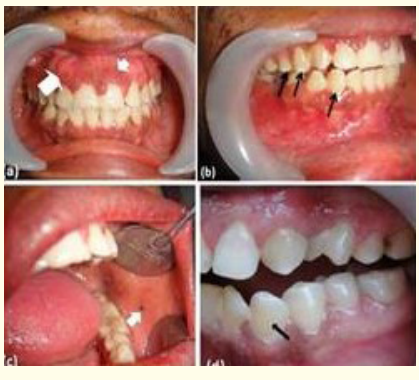

Figure 3: (a): Photograph showing multiple dome shaped papules on the gingivae and alveolar mucosa (white arrows). (b): Examination of dental tissues showing chalky white hypoplastic enamel (black arrows). (c): Buccal mucosa showing small hyperpigmented papules resembling melanotic macules (white arrows). (d): Examination of dental tissues showing enamel pits (black arrow).

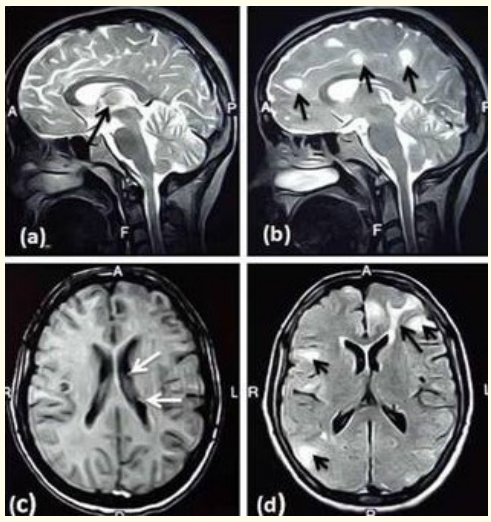

Figure 4: (a): Magnetic resonance imaging's can for the brain revealed giant cell astrocytomas in the right foramen of munro (black arrow). (b): Sagittal view of MRI showing dominant hyperintense lesion in the frontal cortex and subcortical region (black arrows). (c): Coronal view of MRI scan demonstrated multiple small subependymal nodules identified along the walls of lateral ventricle on left side (white arrows). (d): Coronal MRI scan revealed dominant hyperintense lesion in the left frontal cortex and subcortical region consistent with cortical tubers (small black arrows). Abnormal increasing signal extending from subependymal surface of ventricle through the left white matter of left side of frontal lobe which is continuous with the subcortical tuber of frontal lobe suggestive of radial glial band (long black arrow).

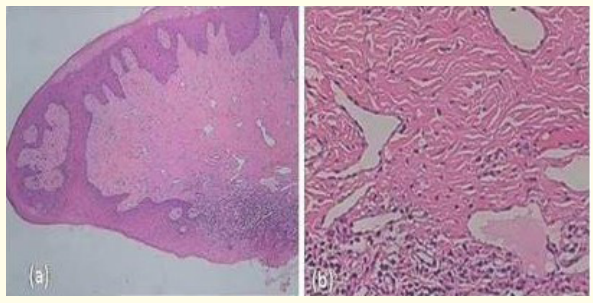

Figure 5 a and b: Haematoxylin and eosin staining revealed hyperplastic epithelium, dense connective tissue, dilated capillaries and inflammatory cells.

Discussion

Tuberous sclerosis complex was earlier known as Epiloia (epilepsy, low intelligence and adenoma sebaceum) and was proposed by Sherlock [11]. The classic triad of epiloia is seen in only 30% of affected patients [12]. The term adenoma sebaceum is a misnomer and is better understood as angiofibroma, as it contains connective and vascular elements [13]. All the currently reported oral and CNS features in patients with Tuberous sclerosis have been reviewed and compiled in table 1.

The most common and earliest cutaneous stigmata in TSC is multiple hypopigmented macules (Ash leaf spots) seen in more than 90% of patients at a very young age [14]. Angiofibromas form discrete pink papules on the malar region of the face in 70% of TSC patients. Shagreen patches are localized thick, rubbery plaques with a pebbly texture, resembling pig skin commonly seen on the face and lumbo sacral area. They are seen in 20 - 50% of TSC cases [15]. Both these findings were presenting our case.

Koenen's tumors are periungual and subungual fibromas which are firm and flesh colored growths arising from the nail folds, and are seen in 15 - 20% of cases [16]. In our case periungual fibromas were present ion the digits of left foot. The common intraoral manifestations are fibrous over growths found on gingival and other sites. The non-gingival sites affected include buccal mucosa, labial mucosa, superior labial frenulum, palate and tongue in descending order of frequency [17]. The true prevalence of these gingival overgrowths is not well documented. Different studies have been published, stating a varying prevalence ranging from 36 - 69% [18]. These oral fibromas are similar to sporadic oral irritation fibromas, but are multiple [17]. Similar gingival growths were present in our case affecting gingival, alveolar mucosa and buccal mucosa in descending order of frequency. Dental pits are observed in 100% of TSC patients, which become more apparent by applying disclosing agents [18]. Our case presented with multiple enamel pits and hypoplastic enamel areas. Cowdens syndrome, Birt-Hogg-Dube syndrome and MENS type1 present with similar oral fibrous overgrowths, but there is absence of dental pitting [19].

Gingival overgrowths can worsen if the patient is on enzyme inducing antiepileptic drugs. The dental specialists should recommend the neurophysicians to prescribe non-enzyme inducing antiepileptic drugs which do not cause gingival enlargement [20]. The neurological manifestations include cortical and subcortical tubers, radial glial bands, subependymal nodules (SENs) and subependymal giant cell astrocytomas (SEGAs). The tubers are seizure inducing hamartomas seen in 90% of TSC patients. These tubers have low T1 signal and high T2 or FLAIR signal and on calcification significant signal loss is seen. Diffusion tensor imaging (DTI) and positron emission tomography (PET) have been promising techniques in localizing more epileptogenic tubers [9]. SENs are hamartomas that do the ependymal surface of lateral ventricles. They are difficult to see on MRI, as they are isointense to gray matter. SEGAs are low grade neoplasms that are found at foramen of Munro [21].

All these CNS features were demonstrated in our patient. Radial glial bands present in over 80% of TSC patients, represent heterotopic neuronal and glial elements that arrested during cortical migration. They extend from the ependymal surface of the ventricle to the cortex, sometimes terminating in a subcortical tuber. Such glial bands were present in our case too. The dental surgeons should be aware of seizures in TSC patients. Epilepsy contraindicates the use of removable dentures. Rubber dam clamps should be ligated due to the potential of aspiration during a seizure. Mental retardation is present in 50% of TSC cases, usually associated with seizures [22]. Our case subject presented with mild autistic behavior but without seizures.

The abdominal manifestations include renal cysts, angiomyolipomas in kidneys and other abdominal organs. These patients are at increased risk of renal cell carcinoma. The proximity of TSC2 gene with polycystic kidney disease gene (PKD1) accounts for the renal complications associated with TSC [9]. Kidney function impairment contraindicates the use of erythromycin in these patients as the blood levels may rise to toxic levels [18]. The cardiac rhabdomyomas and pulmonary lymphangiomyomatosis can cause dyspnoea, pneumothorax. The pulmonary pneumothorax contraindicates any dental procedure [23]. Also, multi organ assessment should be done before anesthesia. The presence of mental retardation mandates the use of deep sedation and general anesthesia for better patient management. A combination thiopentone, vecuronium and nitrous oxide with isoflurane is preferred during general anesthesia in dental surgeries [25].

S. No.	Authors and Year	Oral findings	CNS findings
	Lopez E., *et al*. 2003 [25]	Angiofibromas of upper lip	Seizures
2.	Binitha MP., *et al*. 2006 [26]	Multiple, randomly and uniformly distributed, small, irregular, hyperpigmented and hypopigmented macules without atrophy on oral mucosa. Multiple angiofibromas on the face, gingival fibromas, and pitting of dental enamel.	Neurodevelopmental testing demonstrated mild mental retardation and learning disability. Electroencephalography was normal. Computed tomography of the head demonstrated periventricular subependymal calcified tubers. Magnetic resonance imaging examination of the head and brain was normal.
3.	Rama Rao GR., *et al*. 2008 [27]	Facial angiofibromas: 14/15 patients Forehead plaque-7/15 patients	CNS involvement-8/15patients Subependymalnodules-8/15 patients Subependymal giant cell astrocytomas-2/15 patients Cortical tubers-2/15 patients
4.	Gallaghar A., *et al*. 2010 [28]		Right frontal cortical tuber characterized by a calcified component
5.	Martelli H., *et al*. 2010 [29]	Nodular lesions in the gingival of the Left upper and lower lateral incisors, and dental enamel pits in the lower canines. Few nodular lesions in nasal and perinasal area	Normal CNS findings
6.	Truchuelo T., *et al*. 2011 [30]	Numerous firm erythematous papules consistent with facial angiofibromas, with a telangiectatic surface located on cheeks, ash leaf-like hypopigmented macules	None mentioned
7.	Jahagirdhar P B., *et al*. 2011 [31]	Multiple papules on the nose and Malar region exhibiting a butterfly fashion, enamel pitting and gingival growths	None mentioned
8.	Harutunian K., *et al*. 2011 [32]	Koenen tumors, angiofibromas and epidermoid cysts on the face, enamel hypoplasia of right lower third molar tooth	None mentioned
9.	Gontijo GM., *et al*. 2013 [33]	Angiofibromas on malar region and chin	Multiple amorphous Subependimary calcifications

10	Sarkar S., *et al*. 2016 [34]	Multiple well-defined, reddish-brown sessile nodular growths on the forehead, nose, and cheeks in a characteristic "butterfly pattern," Shagreen patch, and periungual fibromas. Multiple gingival growths and hypoplastic enamel pits	Subependymal regions of both ventricles indicating multiple calcified tuberous lesions (subependymal nodules)
	Cao Y *et al*. 2017 [35]	Angiofibromas scattered on face, and neck, obviously on face	Multiple calcifications along the wall of the lateral ventricle

Table 1: Literature review of oral and CNS features in Tuberous Sclerosis Complex reported till date.

Conclusion

This case report describes the fascinating nature of TSC and the dynamic role played by the dental surgeons in diagnosing such a multi-organ disease based on oral manifestations and thereby reducing the mortality. Also, the dental surgeons should be mindful about the dental considerations in TSC.

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