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Tuberous Sclerosis: A Unique Case Report

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Abstract **Case Report**

Tuberous sclerosis is a neurocutaneous syndrome with an autosomal dominant inheritance. Tuberous sclerosis has an approximate incidence of one in ten thousand to fifty thousand. Tuberous sclerosis complex Syndrome (TSCs) is a dominantly inherited disorder affecting multiple organs; caused by mutations of either the *TSC1* or *TSC2* gene encoding hamartin and tuber in respectively. It is characterized by the development of benign tumors affecting different body systems. The most common oral manifestations of TSC are fibromas (angiofibromas), gingival hyperplasia and enamel hypoplasia and the formation of hamartomas in multiple organ systems leading to morbidity and mortality. It is important to make an early diagnosis of TSC so that lifelong monitoring, early recognition of complications and proactive treatment can lower the morbidity and mortality rates.

Keywords: Tuberous sclerosis, Tuberous sclerosis complex Syndrome, seizures, hamartomas, "confetti" lesions, periungual fibroma.

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INTRODUCTION

Tuberous sclerosis complex (tsc) is a multisystemic neurocutaneous genetic condition with autosomal dominant inheritance, characterized by hamartomas that affect multiple organs, including skin, central nervous system, heart, lungs, and kidney. It is also known as epiloia or pringle-bourneville phacomatosis, and was initially described in the 19th century by virchow and von recklinghausen, who identified hamartomas in the brain and heart during the necropsy of patients with seizures and mental retardation. However, the correlation between the cutaneous manifestations with other clinical symptoms and the description of the syndrome were made by bourneville in the beginning of the 20th century. Years after, campbell in 1905 and vogt three years later established the triad that characterizes tsc, which is mental retardation, epilepsy and pringle type of sebaceous adenoma (angiofibroma) [1, 2].

Diagnostic criteria for tuberous sclerosis were firstly established in 1998 in 2012, in the second international tuberous sclerosis complex consensus conference held in Washington, these criteria were reviewed with the aim of presenting recommendations for the diagnosis, surveillance and management of tsc patients [3].The condition affects one in every 6,000 to 10,000 individuals and can affect both sexes and all ethnic groups equally. It has a great phenotypical variability, which can sometimes make its recognition difficult [4,5].

CASE REPORT

A 40 year old female patient presented with multiple growths in the upper gums since 6 years. The patient noticed the growth for the past 6 years, which gradually increased in size to attain the present size. There was no history of pain or blood/purulent discharge associated with the growth. Past dental history and family history were in significant. On general physical examination, multiple well‑defined, reddish brown sessile nodular growths were noted on the nose, cheeks, around eyes and chin. Vital signs were found to be within satisfactory limits. On intraoral examination, similar well defined, sessile, firm, and nodular growths were seen in the marginal and attached gingiva in the upper anterior region of varying sizes. Multiple hypoplastic enamel pits were noted in the occlusal aspect of posterior teeth and labial surface of anterior teeth. The most typical dermatological finding was the hypopigmented macules known as "confetti" lesions present on the back of the patient. Ungual fibroma or koenen tumor were tumors observed later, and progressively increase in size and caused longitudinal ridging on the nails as they affected the ungual matrix. Based on the history and clinical

findings, a provisional diagnosis tuberous sclerosis was made.

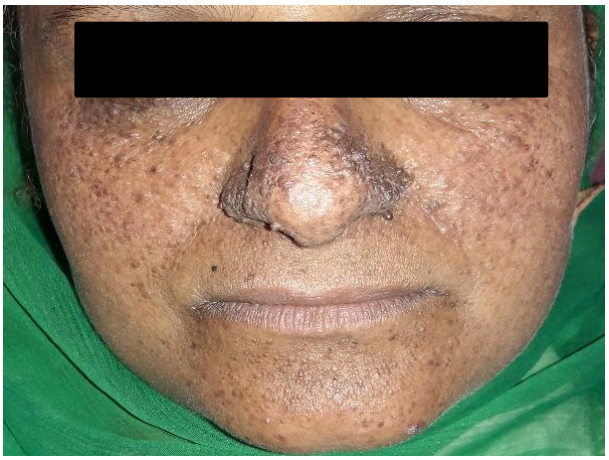

Fig-1:Showing multiple hamartomatous fibromas on face

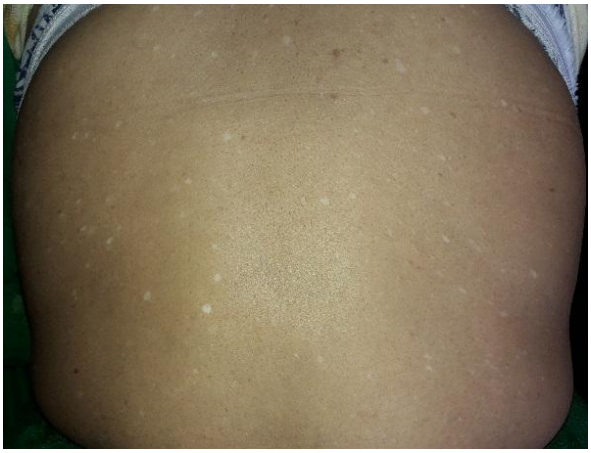

Fig-2:Hypopigmented macules "confetti" lesions on back

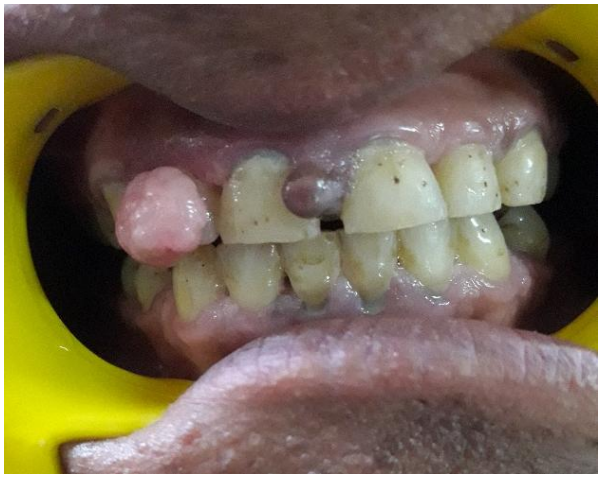

Fig-3: Multiple gingival growths and hypoplastic enamel pits

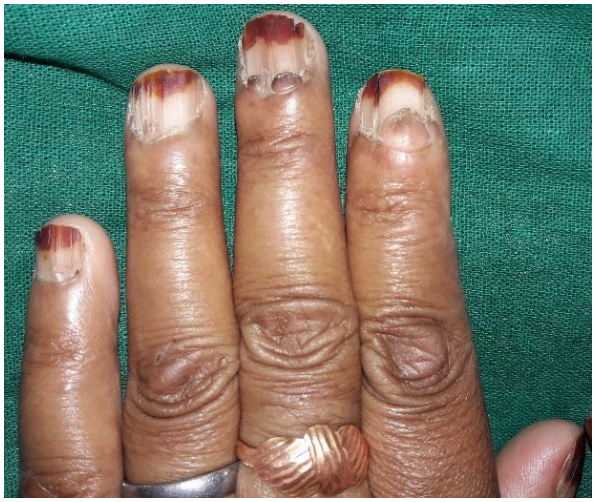

Fig-4: Periungual fibroma (Koenen tumor)

DISSCUSSION

Tsc is characterized by the development of unusual tumor like growths (hamartomas) in brain, skin, retina, and viscera. The term "tuberous sclerosis" refers specifically to the presence of multiple sclerotic masses scattered throughout the cerebrum. The diagnosis of tsc is based on the identification of hamartomas in more than one organ system [6]. Tsc is an autosomal dominant disorder with nearly complete penetrance but variable expressivity. The abnormal genes have been localized to one of two sites, the long arm of chromosome 9 (9q34), designated as tsc 1 (encoding hamartin), and the short arm of chromosome 16 (16p 13.3) designated as tsc 2 (encoding tuberin). These gene products form a tumor suppressor complex which drives rheb (rashomolog enriched in brain) a member of ras superfamily into the inactive guanosine diphosphate bound state. When Rheb is in the guanosine triphosphate bound active state, it stimulates the mammalian target of rapamycin (mtor),an evolutionarily conserved protein kinase and a major effector of cell growth. The mutations in these genes result in constitutive mtor activation leading to the formation of various growths and hamartomas in various organs of thebody[7]. In a study conducted on 325 tsc individuals, 17% of the mutations were found in the tsc1 gene, 50% in the tsc2gene, 4% unclassified variants, and 29% with no identifiable mutations[8].

At the tuberous sclerosis consensus conference of 1998, the clinical diagnostic criteria of tsc were revised and a new classification system based on major and minor findings was established. The presence of two major features or one major and two minor features was considered sufficient for a definitive diagnosis.

The majorfeatures include (a) hypomelanotic macules (≥3, at least 5 mm diameter), (b) angiofibromas (≥3) or fibrous cephalic plaque, (c) ungual fibromas (≥2), and (d) shagreen patch.

The minor features include (1) "confetti" skin lesions, (2) dental enamel pits (≥3), and (3) intraoral fibromas (≥2) [9].

The most common oral manifestations of tsc are fibromas, gingival hyperplasia, and enamel hypoplasia (in almost 100% of these patients and is associated with an increased risk of caries). The other features include hamartomatous rectal polyps, nonrenal hamartomas, multiple renal and bone cysts, high arched palate, bifid uvula, cleft palate, delayed dental eruption, and presence of diastemas. Our case presented with three major features– facial angiofibromas, köenen tumors and hypomelanotic macules and two minor features – gingival fibromas and enamel hypoplasia [10,11].There are no specific symptoms for the diagnosis of tsc. However, there are clinical presentations that can occur in the context of tsc that require further investigation. Moreover, if the patient under investigation has one of the biological parents with tsc, there is a 50% chance that the patient under investigation has the condition. This 50% risk remains unchanged when multiple siblings are affected.

Diagnostic suspicion of tsc comes from the antenatal detection of cardiac rhabdomyomas; the post-natal identification of hypopigmented macules on the skin; seizures in childhood, particularly with spasms; and presence or absence of cognitive impairment during autism assessment. The international tuberous sclerosis complex consensus recommends yearly screening for neuropsychiatric disorders and when clinically indicated [12].

From the dermatologist point of view, a full dermatological examination is recommended. Family history of at least three generations should be obtained, and genetic testing should be considered in cases where there is suspicion of the diagnosis or for family-planning. Dental and ophthalmological evaluations are also recommended, including fundoscopy, to all individuals with the diagnosis of tsc in search of hamartomas and retinal hypopigmented lesions. Complementary investigations should be considered in children at the time of diagnosis and include brain magnetic resonance, to evaluate tubercles, subependymal nodules or other intracranial lesions; electroencephalogram, to evaluate the activity of subclinical seizure; transthoracic echocardiogram, to investigate rhabdomyomas (particularly in patients younger than three years of age) and electrocardiogram, to evaluate underlying conduction defects. Imaging studies, including abdominal ultrasound, computed tomography or magnetic resonance should be performed at the time of diagnosis, regardless of age, to evaluate angiomyolipomas or renal cysts, being the abdominal magnetic resonance the preferred method since many angiomyolipomas can be poor in fat tissue and not visualized by the other methods. Pulmonary function tests and high-resolution chest computed tomography for the investigation of lymphangioleiomyomatosis are indicated for women with 18 years old or older and in symptomatic men [13].

CONCLUSION

TSC is a lifelong condition, therefore individuals should be regularly monitored by an experienced clinician. It is not uncommon for patients with TSC to have symptoms or signs that do not lead to immediate diagnosis. In some cases, diagnosis is delayed for prolonged periods of time. Clinicians including child and adult neurologists, dermatologists, nephrologists and cardiologists should be aware of the myriad potential presenting symptoms and signs of TSC. Early diagnosis is very important for thorough clinical and radiological evaluation, continuous monitoring of symptoms, family planning, genetic counseling and reduction in morbidity and mortality rate.

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