Adult-onset tuberous sclerosis complex with florid Koenen's tumors, facial angiofibromas, and asymptomatic cortical tubers

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Tuberous sclerosis complex (TSC) is an autosomal dominant disorder characterized by the development of hamartomatous tumors in multiple organs, including the skin. Most patients present early in life with seizures, intellectual disability, and cutaneous angiofibromas. However, patients may often not present these features until late adulthood. A 55-year-old female presented with complaints of sudden and florid appearance of multiple fibrokeratomas around all twenty of her nails, along with multiple hyperpigmented papules on her face. On examination, she also had gingival fibromas and a single skin-colored plaque on her lower back. Histopathology of lesions over the face, back, and fingernails were compatible with the diagnoses of angiofibroma, shagreen patch, and fibrokeratoma, respectively. She was advised laser ablation of the facial lesions and excision of the nail fibrokeratomas. MRI of the brain showed multiple cortical tubers and subependymal nodules. Late presentation of TSC during adulthood may delay the diagnosis and prevent the screening of early tumor formation, potentially increasing morbidity. This was exemplified in our clinical case, where asymptomatic cortical tubers were discovered on MRI only after the appearance of skin lesions and fibrokeratomas around the nails.

Keywords: tuberous sclerosis, angiofibroma, nails, brain neoplasms

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INTRODUCTION

Tuberous sclerosis complex is an autosomal dominant genodermatosis presenting with facial angiofibromas, shagreen patch, periungual fibromas, ash leaf macules, and various internal organs hamartomas involving the eye, kidney, lung, heart, and brain [1]. Mutation in either tumor suppressor genes TSC1 or TSC2 may lead to tumor predisposition [2]. However, no mutation has been identified in approximately 15% of patients who fulfill diagnostic criteria for TSC [3]. Prevalence of tuberous sclerosis is around 1 in 15000–30000 persons. The classical triad of seizures, intellectual disability, and cutaneous angiofibromas is observed in less than 30% of patients, mostly early in life. However, some patients may not present these features until late adulthood [4]. Morbidity and mortality from TSC-related pulmonary and renal disease predominate in adults, so these patients should undergo regular monitoring [5,6]. Here, we report the clinical features of a case of TSC manifesting in adult life.

CASE REPORT

A 55-year-old homemaker presented with a five-year history of the sudden and florid appearance of multiple asymptomatic, flesh-colored, rounded to clove-shaped papules and plaques ranging from

3×3 mm to 10×10 mm with a smooth surface on and around all twenty of her nails (Figure 1). The proximal and lateral nail folds could not be delineated, though cuticle loss and nail plate irregularities were observed. One year prior to presentation, the patient also had multiple asymptomatic, deep brown 2 mm×2 mm papules over her bilateral malar area, nose, and chin (Figure 2). A single, asymptomatic, non-tender, skin-colored plaque of size 4×12 mm was also noted in the right lumbar area. Oral examination exhibited diffuse gingival enlargement and dental pits in the left mandibular canine and first premolar. There was no history of similar lesions in any first-degree relative, nor did the patient provide any history of seizures or behavioral abnormalities. The patient's general condition was stable, and a systemic examination revealed no abnormalities. No remarkable abnormalities were seen in the baseline blood and urine investigations, chest X-ray, abdominal ultrasonography, electrocardiogram (ECG), electroencephalography (EEG), and computerized tomography (CT) of the thorax and abdomen. However, magnetic resonance imaging (MRI) of the brain revealed multiple small subependymal nodules and cortical tubers (Figure 3). Histopathologic evaluations of the plaque over the nail, papule over the face,

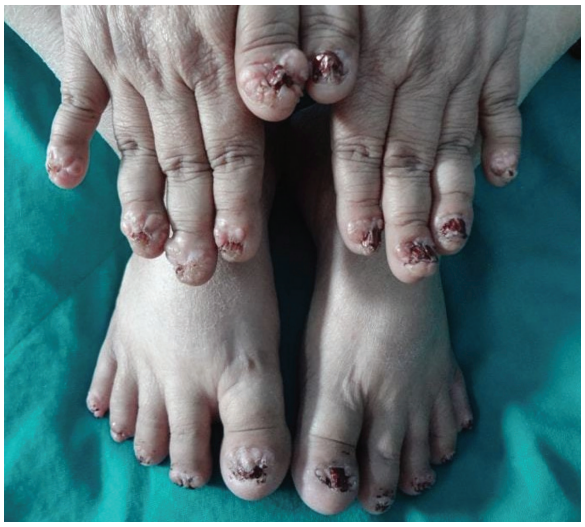

Figure 1. Multiple digital fibrokeratomas on and around all twenty nails.

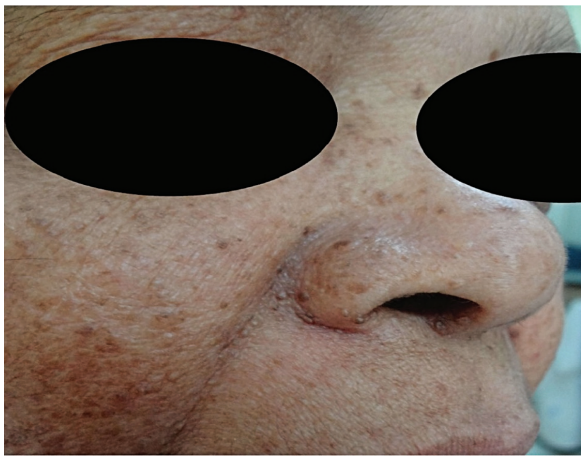

Figure 2. Facial angiofibromas.

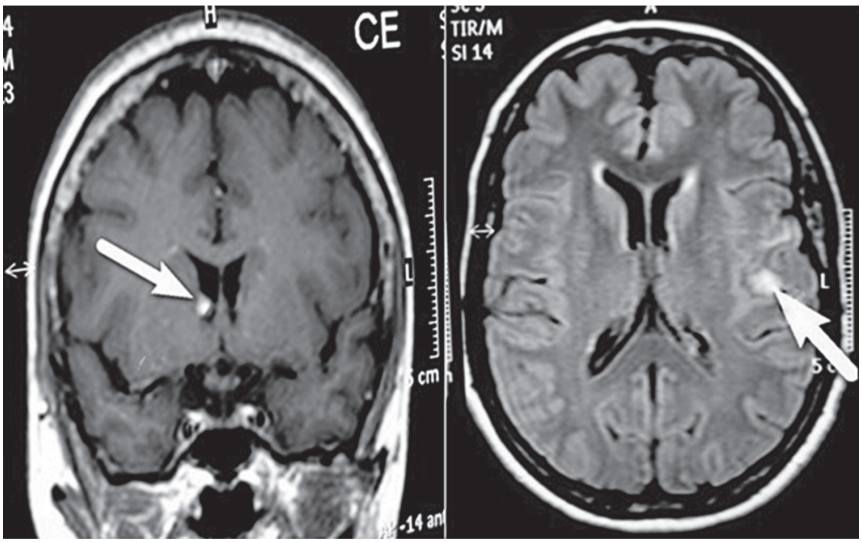

Figure 3. Brain magnetic resonance imaging (MRI) showing a small subependymal nodule and cortical tuber.

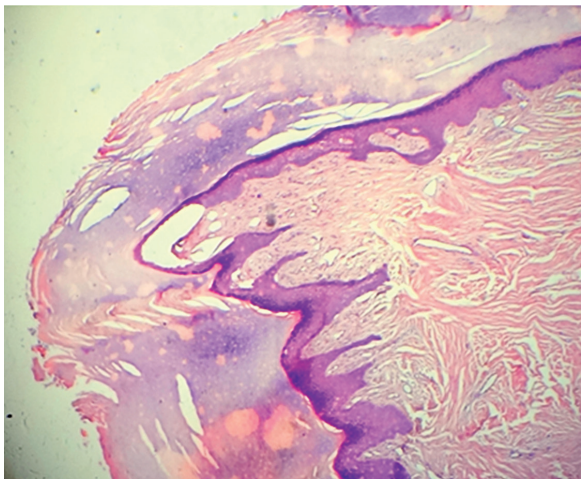

Figure 4. Biopsy from nail consistent with features of fibrokeratoma showing hyperkeratosis and acanthosis with thickened and branched rete ridges. Vertically oriented, thick, interwoven bundles of collagen were noted within the dermis (H & E, ×40).

and plaque over the back were consistent with diagnoses of fibrokeratoma, angiofibroma, and collagenoma, respectively (Figure 4). A definite diagnosis of tuberous sclerosis was made according to the revised diagnostic criteria for tuberous sclerosis (based on 6 major and 2 minor criteria). The patient was advised surgical excision of the digital fibrokeratomas and laser ablation of facial angiofibromas. She was also advised regular yearly follow-ups. Genetic testing was advised, which the patient refused due to financial reasons. Her five children were counseled to undergo clinical evaluations to rule out any features of genetically acquired tuberous sclerosis.

DISCUSSION

Tuberous sclerosis complex (TSC) is an inherited and occasionally sporadic disease characterized by hamartomas in the brain, skin, eyes, heart, lungs, and kidneys. Patients often present with epilepsy, mental retardation, and low IQ during early life [7]. Genetic studies have revealed that parents may not be affected in two out of three cases. The disease results from a new dominant mutation either in the TSC1 gene on chromosome 9q34 [8] or the TSC2 gene on chromosome 16p13.3. [9], with the latter accounting for nearly 78% of cases [10]. Adult patients with mutations in TSC2 may be at a higher risk of developing subependymal tumors [11]. Nearly one in four pathogenic mutations in the TSC2 gene result from missense mutations [12]. In addition, somatic mosaicism is also responsible for a mild phenotype of TSC [13]. It has previously been shown that individuals with adult penetrance tend to have relatively fewer skin manifestations and are less likely to have seizures [14]. Although our patient presented no history of seizure, headache, or blurred vision, she did have prominent skin lesions of TSC and asymptomatic cortical tubers, and subependymal nodules were discovered after a brain MRI was done. The onset of angiofibromas may be delayed due to late disease penetrance [15]. In a recently published study with a large patient population, 27.4% (220/803) of patients with TSC had a history of subependymal nodules [11].

In a previous case report, a 59-year-old woman with normal intelligence presented with late-onset TSC, mainly having neurological signs but no dermatological lesions [16]. In our patient, no neurological symptoms were observed. However, different dermatological lesions suggested the diagnosis of TSC, and her cortical tubers and subependymal nodules were discovered on MRI of the brain. A prospective study of 86 patients with TSC over a period of two years suggested central nervous system involvement to be the most common clinical presentation at diagnosis, followed by dermatological manifestations [17].

A bioactive substance like Basic Fibroblast Growth Factor (BFGF) may be responsible for the soft tissue growth [18]. Many tissues potentially respond to BFGF, and high circulating BFGF could have diverse effects. In our patient, the sudden appearance of angiofibromas and digital fibrokeratomas might have been because of elevated BFGF, although this could not be confirmed. A study conducted by Seibert *et al.* in adult women diagnosed with adult-onset TSC showed that skin lesions appear late in this patient population compared with childhood TSC patients. It was also observed that patients with adult-onset TSC were more likely to present with pulmonary and renalcomplications [15]. However, in our patient, ultrasonography of abdomen, ECG, EEG, and CT of thorax and abdomen were normal and no tumor was detected.

Patients diagnosed with adult-onset TSC may be asymptomatic during childhood. Nevertheless, the risk of serious morbidity may persist. Hence,

in these patients, a detailed evaluation of organ involvement is necessary, and it is vital to establish a baseline for organs that could be affected by disease progression [19]. Delayed and sudden appearance of tuberous sclerosis lesions along with digital fibrokeratomas may warrant an investigation for cortical tubers and subependymal nodules.

Conflict of Interest: None declared.

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