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An Extremely Rare Case of Tuberous Sclerosis Coexistent with Acanthosis Nigricans

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Abstract

Tuberous sclerosis complex is a rare genetic condition characterized by benign tumors in several organs. Acanthosis nigricans is a skin condition characterized by dark velvety skin in body folds and skin creases; this condition is associated with obesity or diabetes. The concurrent occurrence of both is extremely rare. We report the second case of tuberous sclerosis complex coexistent with acanthosis nigricans in a 13-year-old Yemeni girl.

Keywords: Acanthosis Nigricans, Cutaneous Disorder, Insulin Resistance, Molluscum Fibrosum, Skin Tags, Tuberous Sclerosis Complex

Introduction

Tuberous sclerosis complex (TSC) is a rare autosomal-dominant multisystem genodermatosis. The TSC diagnostic criteria, including major and minor criteria, were updated in 2021 (Table1) [1]. Acanthosis nigricans (AN) is a cutaneous disorder that is mostly associated with obesity and insulin resistance and rarely with internal malignancy; it manifests as a brown velvety thickening of the skin, mostly on the neck and axilla [2]. Both TSC and AN are characterized by skin tags, which are mainly observed on the neck, axillae, and groin. Molluscum fibrosum pendulum is the name given to skin tags seen in patients with TSC, where they are larger, numerous, and with early onset, compared to those seen in patients with AN [3].

Case report

A 13-year-old obese girl with epilepsy and mental deficiencies presented with thick, hyperpigmented skin, mainly on the neck, and less pronounced on the axillae, along with numerous skin tags. A cutaneous examination revealed skin-colored firm papules (angiofibromas) almost completely covering the central face, and larger papules and plaques on the left outer eye angle and forehead (fibrous cephalic plaques) (Figure 1a,1b). The patient's neck was covered with a brown velvety skin superimposed by several soft compressible growths extending to the upper back (molluscum fibrosum pendulum) (Figure 1c,1d). A cauliflower-like brown nodule was observed at the base of the 4th left toenail (epiungual fibroma) (Figure 1e). Brain magnetic resonance imaging revealed multiple cortical tubers, along with several subependymal nodules, and abdominal ultrasonography revealed renal angiomyolipomas; cardiac echocardiography failed to detect any cardiac rhabdomyomas. An oral examination revealed multiple gingival fibromas and dental enamel pits (Figure 1a). Striae dystensae were observed on the patient's abdomen (Figure 1f). Her body mass index was 34, and laboratory investigations revealed a homeostatic model assessment of insulin resistance value of 6.8 and glycated hemoglobin value of 9.7, confirming the diagnosis of insulin resistance associated AN. The TSC diagnostic criteria, including major and minor criteria, were updated in 2021.1 A definitive TSC diagnosis requires that two major criteria or one major and two minor criteria be satisfied. As the patient satisfied five major and two minor criteria for TSC, she was diagnosed with TSC in association with AN based on clinical findings (Table 1). The present case is the second reported association of TSC and AN. Further studies are needed to study the extent of this association, and other conditions associated with TSC.

Discussion

Hamartin (TSC1) and tuberin (TSC2) form a tumor suppressor complex in TSC that inhibits the mammalian target of rapamycin complex 1 (mTORC1) signaling pathway; both proteins are required for the complex to function. Inhibition of mTORC1 prevents excessive cell growth and proliferation [4]. However, as the pathway is active in several physiological processes, its dysregulation is implicated in numerous diseases, including metabolic disorders and cancer. TSC is caused by the mutation of either TSC1 or TSC2, which results in the constitutive activation of mTORC1 instead of inhibition, and accordingly, a predisposition to the development of benign and malignant tumors in many organs.

DIAGNOSTIC CRITERIA FOR TUBEROUS SCLEROSIS COMPLEX (TSC)	
Major features	**Minor features**
Cutaneous	
1. Hypomelanotic macules (≥3, diameter ≥5 mm)	1. "Confetti" skin lesions
2. Facial angiofibromas (≥3) or fibrous cephalic plaque +	
3. Ungual fibromas (≥2) +	
4. Shagreen patch	
Extracutaneous	
5. Multiple retinal hamartomas	2. Dental enamel pits (≥3) +
6. Multiple cortical tubers and/or radial migration lines +	3. Intraoral fibromas (≥2) +
7. Subependymal nodules (≥2)+	4. Retinal achromic patch
8. Subependymal giant cell astrocytoma	5. Multiple renal cysts
9. Cardiac rhabdomyoma	6. Non-renal hamartomas
10. Lymphangioleiomyomatosis	7. Sclerotic bone lesions
11. Angiomyolipomas (≥2; renal - other organs, e.g., liver) +	

Table 1. Revised diagnostic criteria for tuberous sclerosis complex (TSC) (2021)[1]

+: present in our patient

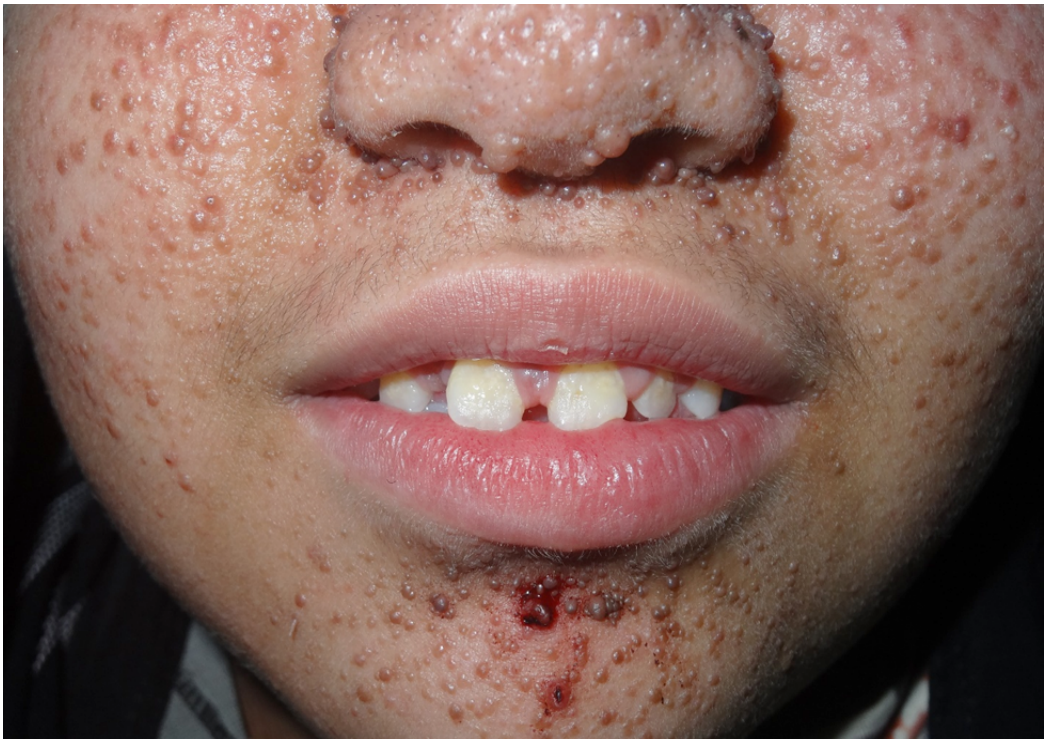

Figure 1A. Multiple angiofibromas on the face, along with gingival fibromas and dental enamel pits.

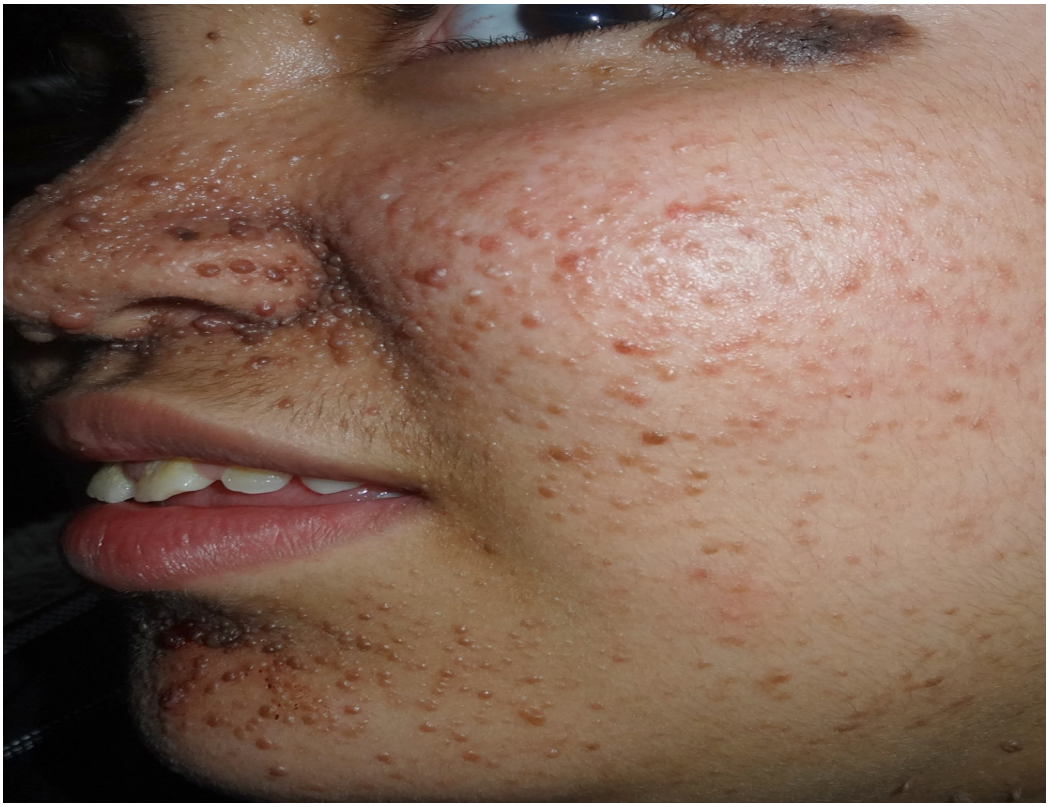

Figure 1B. Left lateral view of the face. Multiple angiofibromas and one cephalic fibrous plaque at the lateral left eye angle.

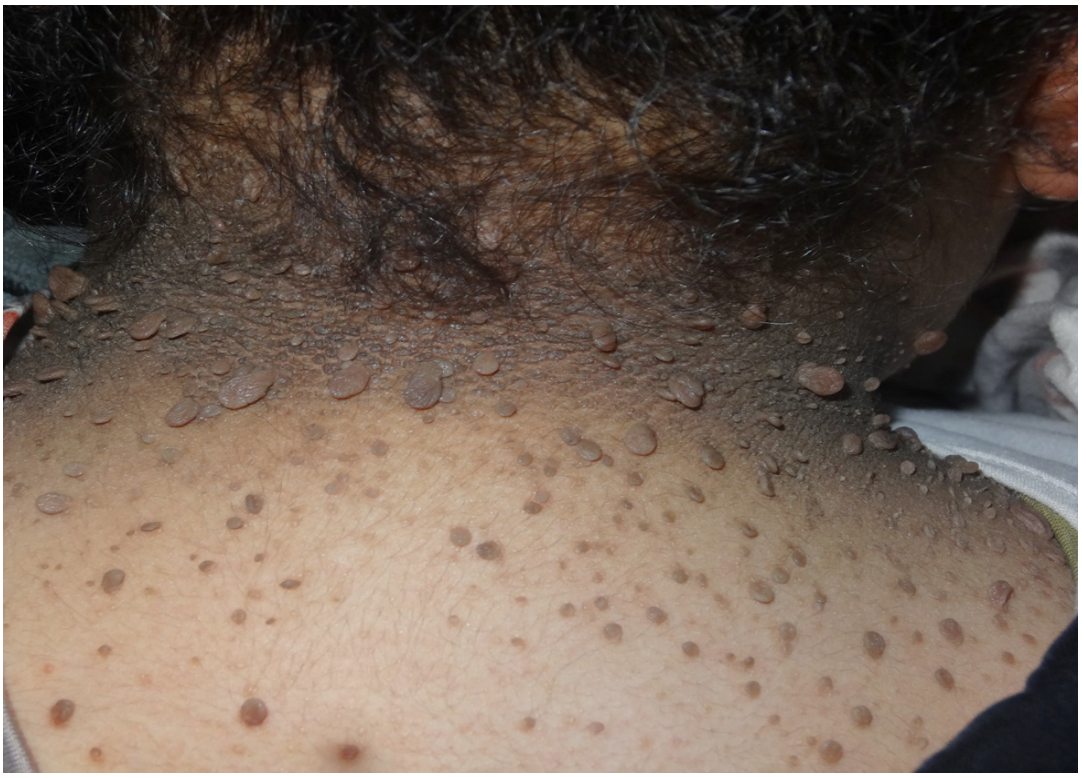

Figure 1C. Dorsal view. Acanthosis nigricans on the neck and upper back with multiple skin tags.

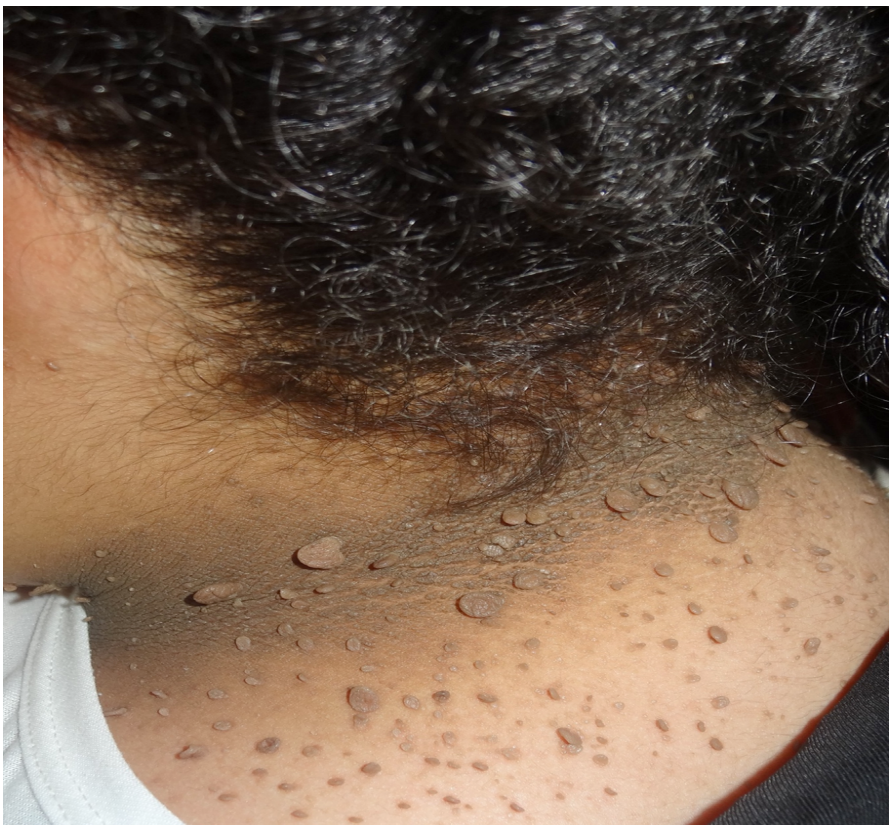

Figure 1D. Left lateral view of the neck. Velvety brown skin and several unusually large skin tags extending to the upper back.

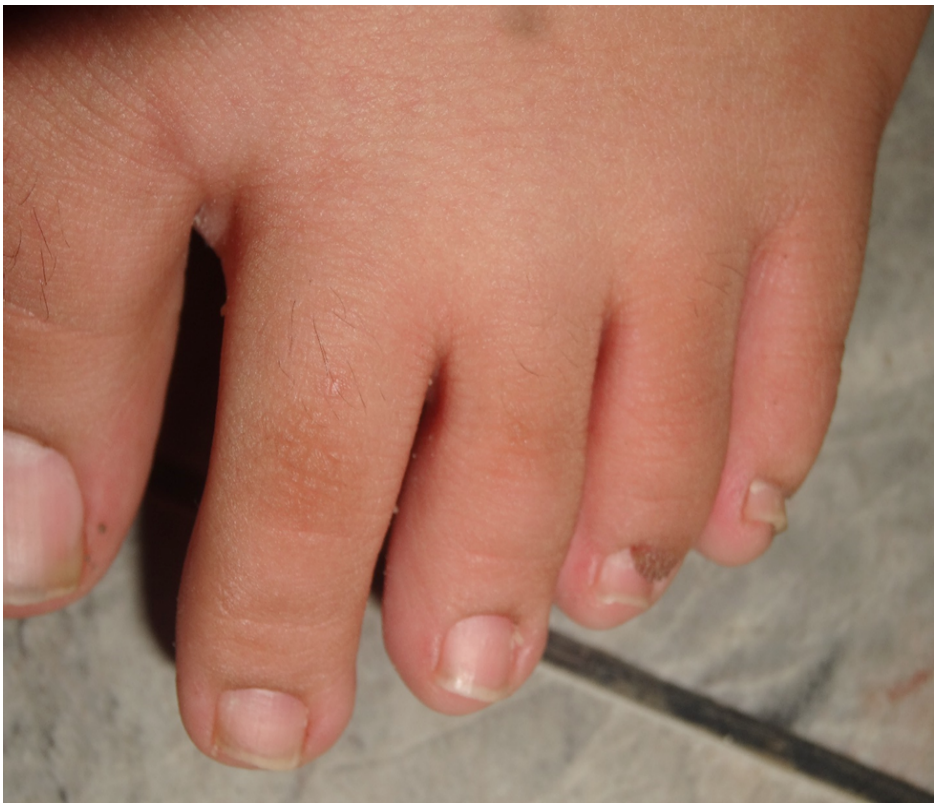

Figure 1E. Dorsal view of the left foot with acanthosis nigricans and a mamillated epiungual fibroma on the 4th toe nail.

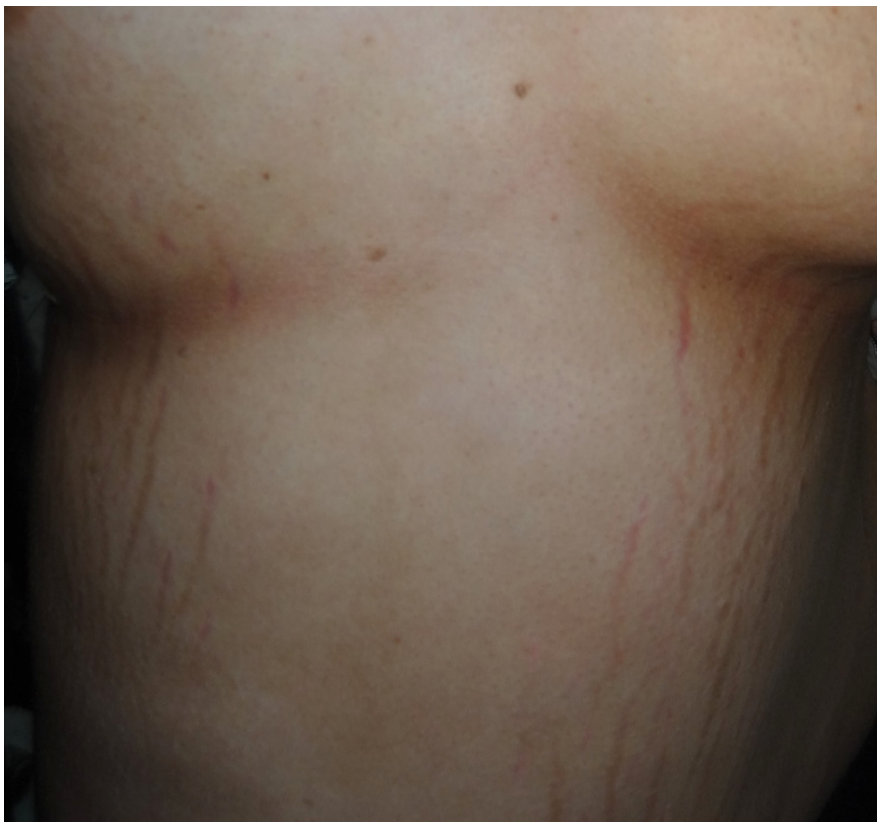

Figure 1F. Multiple striae dystensae bilaterally on the flank

TSC in association with AN has been previously reported only once by Scotvold et al. in a 13-year-old girl in 1976.5 The present case represents the second case. This rare association between the two conditions can be explained by the role of TSC1 and TSC2 in controlling food intake (the mTORC1 pathway promotes anabolic processes) and inducing insulin resistance, which is the most common condition associated with AN [6].

Both TSC and AN can be difficult to diagnose owing to varied symptoms and disease severity. Dark, thickened flexural lesions of AN should be differentiated from confluent reticulated papillomatosis, pityriasis versicolor, x-linked ichthyosis, retention hyperkeratosis, and nicotinic acid ingestion. Angiofibromas of TSC should be differentiated from tricholemmomas, syringomas, skin-colored papules on the face, and dermal nevi; they can also be mistaken for acne vulgaris or rosacea. Periungual fibromas of TSC may be mistaken for periungual warts.

Cutaneous manifestations of TSC such as skin tags, angiofibromas, ungual fibromas, or mollusca fibrosa are treated by electrocoagulation. AN is treated by chemical peels or ablative CO_2 laser. Oral sirolimus is effective in improving TSC cutaneous and internal tumors as well as obesity and AN [7, 8]. Patients with AN will benefit from restrictive food intake, and oral antidiabetic drugs.

Abbreviations:

TSC, Tuberous sclerosis complex

AN, Acanthosis nigricans

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Conflict of interest: None

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