

Isolated Unilateral Facial Angiofibroma or Segmental Tuberous Sclerosis Complex?

Sir,

Tuberous sclerosis complex (TSC) is an autosomal-dominant neuro-cutaneous disorder affecting multiple organs, with hamartomas developing in the brain, skin, kidneys, heart, and eyes. Cutaneous manifestations include hypomelanotic macules, subungual fibromas, facial angiofibromas, fibrous plaques of the forehead, and shagreen patches. More than 90% of patients with TSC have at least one cutaneous manifestation, though none are pathognomonic.^[1] They commonly occur in bilateral distribution, but rarely they can be unilateral.^[2] We report a case of unilateral isolated facial angiofibromas manifesting as segmental TSC, which can be explained on the basis of loss of heterozygosity and abnormality of the homeobox gene.

A 24-year-old male born of the non-consanguineous marriage presented to us with asymptomatic skin to red-colored raised lesions over nose since 15 years. The lesions first appeared at 9 years of age, which progressively increased in number and size over the last 15 years. There was no history of seizures, headache, visual or auditory disturbances, mental retardation, or early puberty. None of the family members had similar complaints. Cutaneous examination revealed multiple, firm, well-defined, dome-shaped, reddish-brown papules present on the right side of the nose area [Figure 1a and b]. There were no periungual fibromas, shagreen patches, café-au-lait macules, forehead plaques, or hypopigmented patches. The rest of the cutaneous and systemic examination was unremarkable. Based on history and clinical examination, differential diagnoses of unilateral facial angiofibroma (UFAs), trichoepithelioma (TEs), fibrofolliculoma (FFs), syringoma, and sebaceous hyperplasia

were considered [Table 1]. Dermoscopy of facial lesions was performed using 3Gen Dermlite DL4 (CA, USA) 10× polarized mode. Dermoscopy revealed multiple yellowish-white dots distributed over a pinkish-gray background, suggestive of angiofibroma [Figure 2]. Histopathological examination of papule over nose revealed the presence of concentric arrangement of collagen bundles around multiple hair follicles and dilated blood vessels in the upper dermis suggestive of angiofibroma [Figure 3a and b]. Extracutaneous involvement was excluded by carrying out appropriate investigations such as computed tomography of the brain, chest X-ray, abdominal sonography, echocardiography, and fundus examination. Genetic mutation analysis was not done due to a lack of resources. Based on history, examination, dermoscopy, and histopathology, a diagnosis of unilateral facial angiofibromas (UFAs) with no other features of TSC was reached. The patient was treated with cryosurgery and showed moderate improvement at the end of 2 months of treatment [Figure 4]. The patient was asked to follow up regularly to rule out extracutaneous manifestations of TSC.

Adenoma sebaceum was first described as a distinct feature of TSC by Balzer and Menetrier^[3] in 1885 and Pringle^[4] in 1890. However, adenoma sebaceum is a misnomer as these lesions are neither adenomatous nor sebaceous. The histopathologic evaluation has proven these lesions to be angiofibromas.^[5] The classical triad of mental retardation, convulsions, and angiofibromas occur in 29% of TSC patients and 6% of them lack all manifestations.^[6] Facial angiofibromas occur in 80%–90% of TSC patients, typically presenting after 5 years of age.

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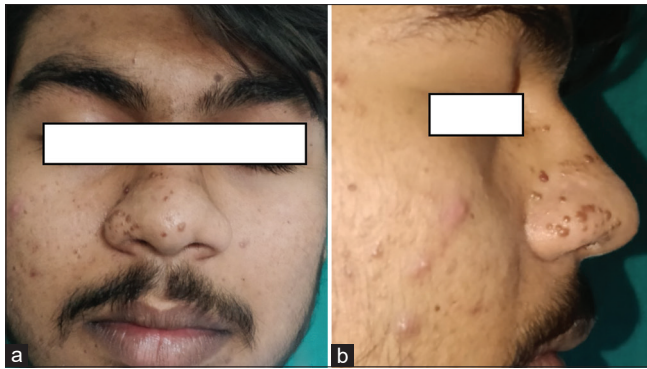


Figure 1: (a and b) Multiple, firm, well-defined dome-shaped, reddish-brown papules present on the right side of nose

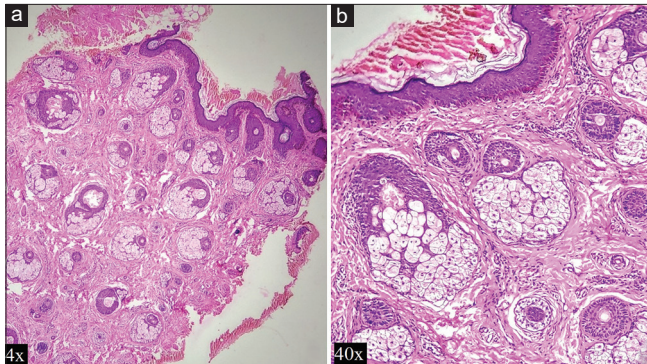


Figure 3: (a and b) Histopathological examination of papule over nose revealed the presence of concentric arrangement of collagen bundles around multiple hair follicles and dilated blood vessels in upper dermis suggestive of angiofibroma (H and E 4x: a, 40x: b)

They commonly occur as bilateral symmetrical small tan to erythematous telangiectatic papules over cheek, chin, and nose. These lesions have also been reported in patients with multiple endocrine neoplasia type 1 and neurofibromatosis (NF). UFAs with or without poliosis, as the only clinical manifestation of TSC is rare.^[5] Rarely, these lesions occur unilaterally, as seen in our case. UFA may be analogous to segmental NF and considered as segmental TSC.^[7] This may arise from postzygotic mutations or loss of heterozygosity (LOH), where the abnormal phenotypical expression only occurs in affected segments of the body. It has been postulated that an abnormality in the homeobox gene and genetic mosaicism may reflect the segmental distribution of lesions.^[8] It has been reported that LOH in which the remaining normal copy of TSC1 and TSC 2 is mutated, occur in angiomyolipoma, cardiac rhabdomyoma, and FAs. Some authors suggested that patients with isolated UFAs need to follow up to look for the development of other extracutaneous manifestations of TSC. The dermoscopic features of FA were described by Bahera in 2017 as multiple yellowish-white dots distributed over a pinkish-gray background and crypts in few lesions, as seen in our case.^[9] Histologically, the yellowish-white dots correspond to the follicular hyperkeratosis along

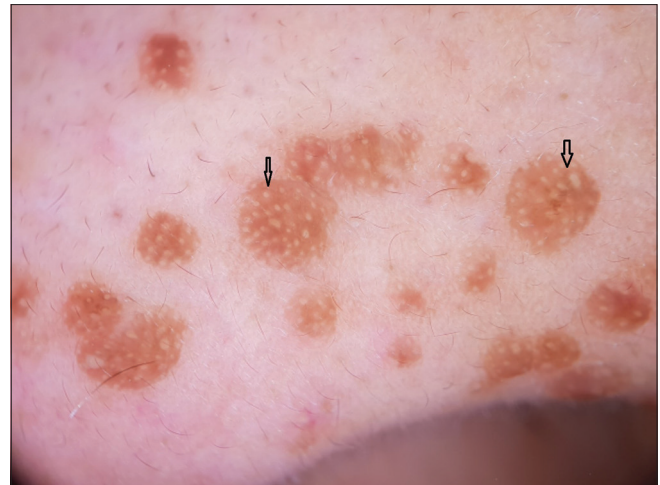


Figure 2: Dermoscopy of facial papule showing multiple yellowish-white dots (black arrow) distributed over a pinkish-gray background, suggestive of angiofibromas (3Gen DermLite DL4 (CA, USA) 10x polarized mode)

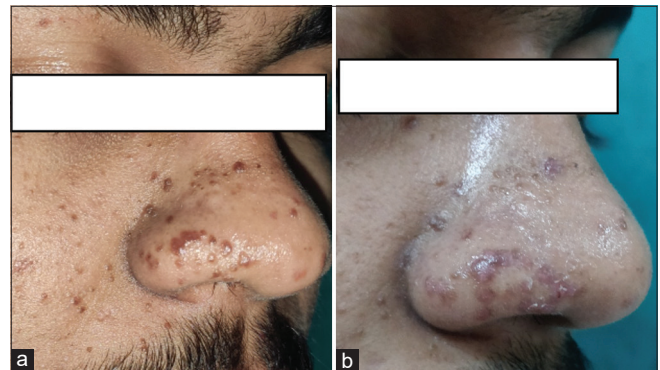


Figure 4: (a and b) Pretreatment (a) and posttreatment (b) of unilateral facial angiofibromas

with the presence of sebum, the pinkish-gray color to the proliferating blood vessels along with pigmentary incontinence, dermal melanophages while crypts to the pseudofollicular opening. Isolated FAs without any other evidence, as in our case, are very rarely reported in the literature [Table 2].^[6,8,10-16] Invasive procedures such as cryotherapy, radiofrequency ablation, dermabrasion, excision, chemical peeling, and lasers, have been tried but all these procedures carry a risk of permanent scarring, the requirement of sedation, and incomplete removal. Recently, topical sirolimus has shown significant improvement of adenoma sebaceum.^[17] In our case, he was treated with cryotherapy, and there was a moderate improvement of lesions without any sequelae.

We report this case because of its rarity to create awareness among dermatologists and to emphasize the need to follow up in such patients for the development of extracutaneous manifestations of TSC.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have

Table 1: Differential diagnoses for facial angiofibroma

Differential diagnosis	Clinical Features	Histopathology	Dermoscopy
Facial angiofibromas	Bilateral symmetrical small tan to erythematous telangiectic papules	Irregular dermal proliferation of fibrous tissue and blood vessels	Multiple yellowish-white dots distributed over pinkish-gray background
Trichoepitheliomas	Numerous skin-colored firm papulo-nodules	Branching nests of basaloid cells, horn cysts with abortive hair papillae	Thin pearly white background, arborizing vessels and milia-like cysts
Fibrofolliculoma	Single or multiple yellow-white smooth dome-shaped papules.	Central distorted hair follicle, surrounded by mantle of basophilic, fibrous stroma	Well demarcated areas of pallor with central follicular plugging
Syringoma	Solitary or multiple skin-colored or slightly yellow soft papules	Numerous tubular structures embedded in dense collagenous stroma	Homogenous light brownish area, with partial delicate light brown pigment network
Sebaceous Hyperplasia	Small, soft, yellow slightly umbilicated papules	Enlarged sebaceous gland lying in proximity to the epidermis	Yellow lobules with crown vessels

Table 2: Review of literature of isolated UFAs in absence of other cutaneous or extracutaneous features of TSC

Case reports	Age/sex	Site
McGrae and Hashimoto (1996) ^[8]	23/M	Left cheek
Anliker <i>et al.</i> (1997) ^[10]	26/M	Left cheek
Silvestre <i>et al.</i> (2000) ^[6]	5/M ; 12/M	Right cheek
Del Pozo <i>et al.</i> (2002) ^[11]	59/F	Left cheek
Trauner <i>et al.</i> (2003) ^[12]	52/M	Left cheek
Camprubi <i>et al.</i> (2006) ^[13]	13/M	Left cheek
Hall <i>et al.</i> (2007) ^[14]	28/M	Left cheek
Bordel Gomez <i>et al.</i> (2008) ^[15]	28/M	Right cheek
Gutte and Khopkar (2013) ^[16]	30/M	Right cheek
Our case	24/M	Right cheek

given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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