

Series Editor: Camila K. Janniger, MD

Unilateral Facial Angiofibromas Without Other Evidence of Tuberous Sclerosis: Case Report and Review of the Literature

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Bilateral facial angiofibromas are common cutaneous manifestations of tuberous sclerosis, an autosomal-dominant disease characterized by hamartomas of multiple organs. Papules in patients with tuberous sclerosis typically appear between 4 and 10 years of age, becoming more extensive during puberty before stabilizing. We present a 28-year-old man with unilateral facial angiofibromas, which may represent a segmental form of tuberous sclerosis.

Cutis. 2007;80:284-288.

Tuberous sclerosis is an autosomal-dominant disorder affecting multiple organs, with hamartomas developing in the brain, skin, kidneys, heart, and eyes. Cutaneous manifestations include hypomelanotic macules, subungual fibromas, facial angiofibromas (adenoma sebaceum), fibrous plaques of the forehead, and connective tissue nevi (shagreen patches). More than 90% of patients with tuberous sclerosis have at least one cutaneous manifestation, though none are pathognomonic.¹ Facial angiofibromas, which occur in approximately 75% of cases of tuberous sclerosis, can be important indicators of the disease.

Facial angiofibromas most commonly occur in a bilateral distribution, though there have been rare occurrences of unilateral facial angiofibromas (Table). We present a patient with unilateral facial angiofibromas but no other manifestations of tuberous sclerosis.

Case Report

A 28-year-old white man presented for evaluation of multiple papules on the right side of the nose and perialar cheek, which first appeared at approximately 14 years of age. The largest papule recently had become irritated and pruritic and bled with trauma.

The patient's past medical history was notable for a motor vehicle accident at the age of 23 years, at which time a noncontrasted computed tomographic scan of the head revealed no abnormalities. He denied any history of seizures, headaches, visual or auditory disturbances, kidney disease, or lung disease. There was no family history of cutaneous or neurologic disorders.

Results of a physical examination revealed approximately 30 flesh-colored and erythematous papules measuring 0.2 to 0.4 cm on the right nasal ala, right nasal bridge, and right perialar cheek (Figure 1). The forehead and chin were not affected. Results of a complete cutaneous examination, including use of a Wood lamp, revealed no hyperpigmented or hypomelanotic macules, shagreen patches, or subungual fibromas.

The clinical differential diagnosis included angiofibromas, fibrofolliculomas, and trichoepitheliomas. A shave biopsy was performed on a 0.4-cm pink papule that recently had bled with trauma. Histologic evaluation revealed multiple ectatic dermal blood vessels within a fibrous stroma with stellate fibroblasts, concentric collagen fibers, and an inflammatory infiltrate consistent with an inflamed

Accepted for publication April 18, 2007.

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Reported Cases of Unilateral Facial Angiofibromas*†

Reference (Year)	Age of Onset	Sex	Location of Angiofibromas	Associated Findings	Family History of Tuberos Sclerosis	Treatment
Audrey ^{†2} (1903)	N/A	N/A	N/A	N/A	N/A	N/A
Dowling ³ (1925)	N/A (19 y at presentation)	Male	Unilateral face	N/A	N/A	Electrocauterization
Whitehouse ⁴ (1926)	7 y	Male	Unilateral cheeks, nasal bridge, ear	N/A	N/A	N/A
McGrae and Hashimoto ⁵ (1996)	3 y	Female	Left nose and cheek	None	N/A	None
Anliker et al ⁶ (1997)	18 y	Male	Left nose and cheek	None	No	CO ₂ laser therapy
Garcia Muret et al ⁷ (1998); Muret and Vallverdu ⁸ (2004); Garcia-Muret and Pujol ⁹ (2000)	N/A	N/A	Primarily unilateral face with minimal contralateral involvement	Bilateral renal angiomyolipomas later detected	N/A	N/A
Garcia-Muret et al ⁷ (1998)	N/A	N/A	N/A	N/A	N/A	N/A
Silvestre et al ¹⁰ (2000)	2 y	Male	Right cheek, nasogenial sulcus	None	No	Electrocauterization
	5 y	Male	Left cheek	Hypopigmented macule on abdomen	No	None
Del Pozo et al ¹¹ (2002)	N/A (59 y at presentation)	Female	Left nose and cheek	None	No	N/A
Trauner et al ¹² (2003)	5 y	Male	Left nose and cheek	Poliosis on left occipital scalp	No	Cryotherapy

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Table. (continued)

Reference (Year)	Age of Onset	Sex	Location of Angiofibromas	Associated Findings	Family History of Tuberous Sclerosis	Treatment
Sharma et al ¹³ (2004)	8 mo	Female	Left nasal bridge, nasolabial sulcus, medial cheek	Hypopigmented macule, café au lait spot on left back	No	Pulsed dye laser
Mashhood and Amjad ¹⁴ (2004)	7 y	Male	Right face	Periungual fibromas on right second and third fingers and right second toe, hypopigmented patches on right trunk and buttocks, right retinal phacomias, right-sided paraventricular intracranial calcifications	No	Electrocauterization
Current report	14 y	Male	Right nasal ala, right nasal bridge, right perialar cheek	None	No	None

*N/A indicates not applicable.

[†]Early reports did not use modern imaging studies; thus, it is difficult to exclude the possibility of occult systemic manifestations.

[‡]Article published in French; thus, the details of the patient are not presented.

[§]Original article published in French. The information presented is obtained from the English translation of the abstract and from a subsequent article commenting on 1 of 2 patients from the original article.

angiofibroma (Figure 2). Results of a physical examination by a geneticist, including a neurologic examination, failed to reveal other signs or symptoms of tuberous sclerosis. Further imaging studies were not recommended. Treatment of the angiofibromas with CO₂ laser ablation was recommended, but the patient declined therapy.

Comment

Tuberous sclerosis is an autosomal-dominant neurocutaneous disorder that is characterized by hamartomas of multiple organs, including the brain, skin,

kidneys, heart, and eyes. Up to two thirds of cases occur without a known family history of the disorder, suggesting the possibility of spontaneous mutations or gene mosaicism. Although tuberous sclerosis exhibits complete penetrance, there is variable expression both between and within families.^{15,16}

Two genes have been implicated in the pathogenesis of tuberous sclerosis: (1) *TSC1* (tuberous sclerosis 1), which encodes the protein hamartin, and (2) *TSC2* (tuberous sclerosis 2), which encodes the protein tuberin. Hamartin and tuberin directly interact with each other and are thought to affect

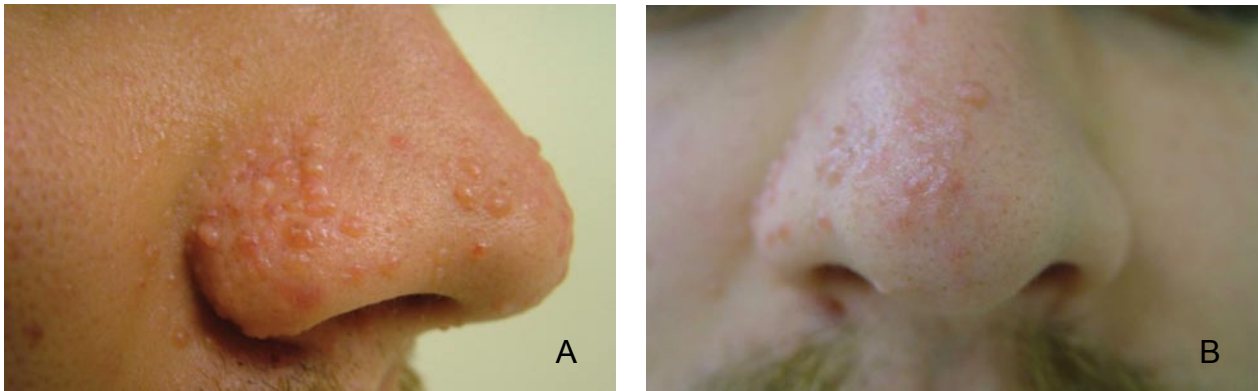


Figure 1. Flesh-colored and erythematous papules on the right nasal ala, right nasal bridge, and right perialar cheek (A and B).

cell growth and proliferation and perhaps cellular adhesion and migration.¹⁷⁻¹⁹ Because they inhibit cellular proliferation, hamartin and tuberlin have been suggested to function as tumor suppressors.¹⁷

There is evidence that loss of heterozygosity, in which the remaining normal copy of *TSC1* or *TSC2* is mutated, occurs in angiomyolipomas, facial angiofibromas, and cardiac rhabdomyomas in patients with tuberous sclerosis.²⁰⁻²² Several cases of unilateral facial angiofibromas previously have been reported, perhaps representing segmental cutaneous forms of tuberous sclerosis because of gene mosaicism. It has been postulated that the occurrence of unilateral facial angiofibromas may be analogous to segmental neurofibromatosis, another autosomal-dominant neurocutaneous disorder that can present in a unilateral distribution.²³ Although unilateral facial angiofibromas may represent a segmental expression of tuberous sclerosis, they also have been suggested to represent a distinct clinical disorder or perhaps a segmental manifestation of another disorder in which angiofibromas are found, such as multiple endocrine neoplasia

type 1.¹² Other authors maintain that unilateral facial angiofibromas can be a manifestation of non-mosaic tuberous sclerosis, supported by the report of a patient with angiofibromas found predominantly on one side of the face,⁷ with minimal contralateral involvement, who later developed additional bilateral noncutaneous manifestations of tuberous sclerosis.^{8,9} A patient in whom unilateral facial angiofibromas occurred in association with other ipsilateral cutaneous and noncutaneous manifestations of tuberous sclerosis also has been described, highlighting the importance of considering systemic involvement in patients with this presentation.¹⁴ An additional consideration is the potential for a concomitant gonadal mutation in the presence of segmental cutaneous involvement, thus allowing possible transmission of generalized tuberous sclerosis to offspring. This phenomenon has been observed in other autosomal-dominant disorders, such as neurofibromatosis and epidermolytic hyperkeratosis.^{24,25}

Although our patient first noted the appearance of facial papules at 14 years of age, they typically

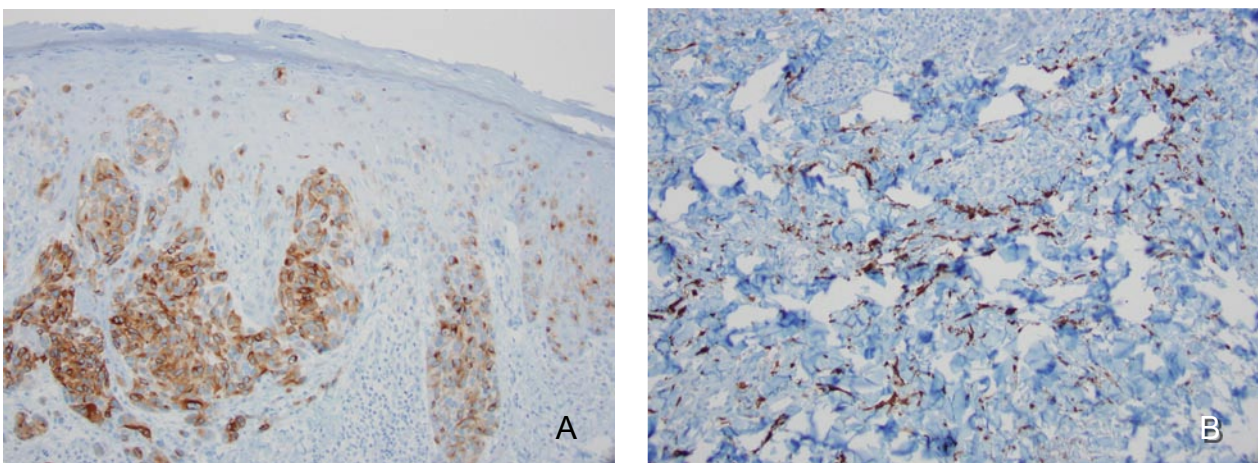


Figure 2. Pedunculated papule with prominent fibrous stroma and ectatic dermal blood vessels (H&E, original magnification $\times 10$)(A). Concentric fibrosis and thin-walled blood vessels (H&E, original magnification $\times 40$)(B).

appear at an earlier age in patients with tuberous sclerosis, often between 4 and 10 years of age, becoming more extensive during puberty before stabilizing. Age of onset of unilateral facial angiofibromas in previously reported cases ranged from 8 months to 18 years (Table). Fibrous plaques of the forehead and periungual fibromas, or Koenen tumors, are variations of angiofibromas that can be seen in tuberous sclerosis but were not present in our patient.

The underlying cause of our patient's unilateral facial angiofibromas is not clear but may include a postzygotic mutation in one of the causative genes for tuberous sclerosis or another genetic syndrome, a localized cutaneous expression of generalized tuberous sclerosis, homeobox gene abnormalities, a local nonhereditary phenomenon, or a distinct syndrome. Treatment of facial angiofibromas has included surgical excision, cryosurgery, dermabrasion, electrocauterization, and ablative or vascular laser therapy.

Conclusion

Unilateral facial angiofibromas may represent uncommon manifestations of segmental tuberous sclerosis. Patients with this presentation should be examined closely for other findings, and the patient and his/her family members should be educated regarding the genetic nature of tuberous sclerosis and its manifestations. Imaging studies and periodic monitoring for development of additional signs of tuberous sclerosis may be appropriate.

At the time the manuscript was accepted for publication, only 13 other cases of unilateral facial angiofibromas had been reported.

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