

Unilateral Papules on the Face

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An 18-year-old woman presented with a progressive appearance of firm, red-brown, asymptomatic, 1- to 3-mm, dome-shaped papules on the right cheek that developed over the course of 2 years. She had 10 lesions that covered a 2×4-cm area on the right medial cheek. No similar-appearing lesions were detectable on a full-body skin examination, and no periungual tumors, café au lait macules, or shagreen patches were noted. A full-body skin examination using a Wood lamp revealed 1 small hypopigmented macule on the right second finger. The patient had a history of treatment-refractory migraines; magnetic resonance imaging 5 years prior to the current presentation revealed a nonspecific lesion in the left parietal gyrus. There was no personal or family history of seizures, cognitive delay, kidney disease, or ocular disease. Punch biopsy of a facial lesion was performed for histopathologic correlation.

WHAT'S THE DIAGNOSIS?

- agminated melanocytic nevus
- agminated Spitz nevus
- benign cephalic histiocytosis
- fibrofolliculoma
- mosaic tuberous sclerosis

PLEASE TURN TO **PAGE E4** FOR THE DIAGNOSIS

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The authors report no conflict of interest.

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THE DIAGNOSIS: Mosaic Tuberous Sclerosis

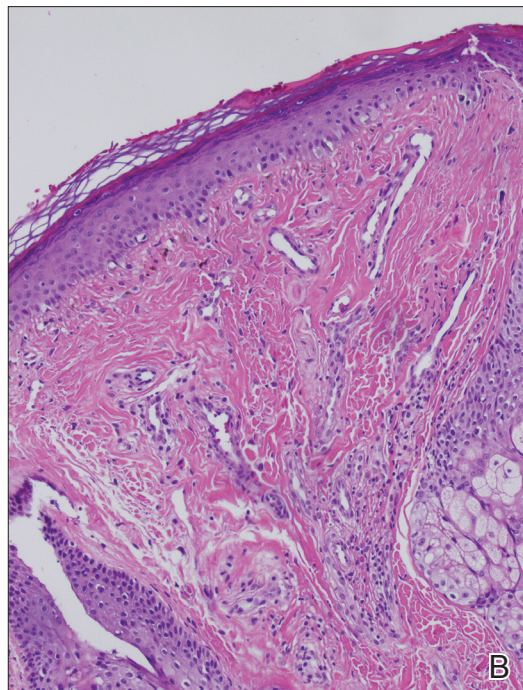
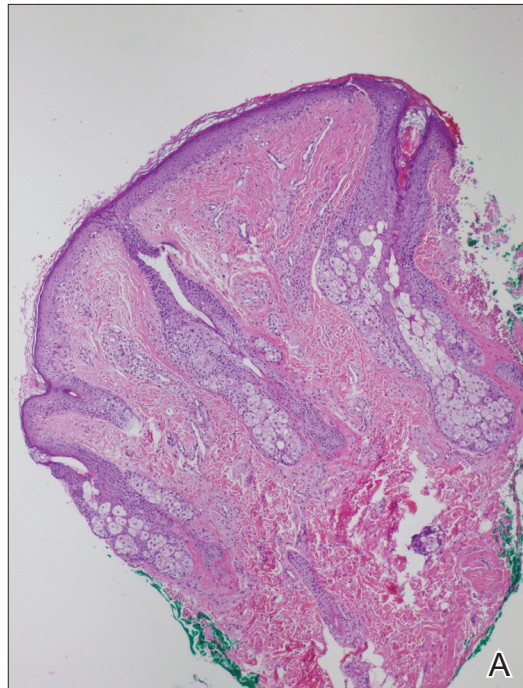
A punch biopsy of the facial lesion was stained with hematoxylin and eosin, which demonstrated spindled and stellate fibroblasts with dilated blood vessels (Figure), consistent with an angiofibroma. Given the clinical presentation and histologic findings, there was concern for a diagnosis of tuberous sclerosis (TSC). The patient was referred for genetic workup but tested negative for mutations of the TSC genes in the blood. Because the patient had only unilateral facial lesions, a possible cortical tuber, no other symptoms, and tested negative for TSC gene mutations, mosaic TSC was considered a likely diagnosis. Her facial lesions were treated with pulsed dye vascular laser therapy.

Tuberous sclerosis is an autosomal-dominant neurocutaneous disorder caused by inactivation of the genes *TSC1* (encoding hamartin) and *TSC2* (encoding tuberin). Mutation results in overactivation of the downstream mTOR (mammalian target of rapamycin) pathway, resulting in abnormal cellular proliferation and hamartomas. These benign tumors can be found in nearly every organ, most often in the central nervous system and skin, and they provide for a highly variable presentation of the disease.¹

Tuberous sclerosis affects 1 in 6000 to 10,000 live births and has a prevalence of 1 in 20,000 individuals. Of these individuals, 75% carry sporadic mutations, and 75% to 90% eventually test positive for a TSC gene mutation.² Genetic mosaicism has been reported in 28% of cases affected by large deletions¹ and as few as 1% of cases involving small mutations.³

The dermatologic manifestation of mosaic TSC most often includes unilateral angiofibromas, whereas in non-mosaic cases, angiofibromas cover both cheeks, the forehead, and the eyelids. The other skin lesions of TSC—shagreen patches, forehead plaques, hypomelanotic macules, and ungual fibromas—are seen less frequently.⁴⁻⁶ Additionally, neurologic disease in mosaic patients is notably milder, with 57% of mosaic patients found to have epilepsy compared to 91% of nonmosaic patients.⁷ Our patient had both unilateral facial angiofibromas and a cortical lesion suspicious for a tuber, prompting a suspected diagnosis of mosaic TSC.

The methods of diagnosis outlined by the International Tuberous Sclerosis Complex Consensus Group pose a challenge in diagnosing mosaic TSC. The clinical criteria require 2 major (eg, multiple angiofibromas, angiomyolipomas, a shagreen patch) and 1 minor feature (eg, dental enamel pit, renal cyst).² However, case reports detailing unilateral facial angiofibromas have described patients with isolated dermatologic findings.^{5,6} Further, it has been demonstrated that genetic studies in mosaic TSC can be unreliable depending on the tissue sampled.⁸ Thus, for



A and B, A punch biopsy of a facial lesion demonstrated spindled and stellate fibroblasts with dilated blood vessels (H&E, original magnifications $\times 4$ and $\times 10$).

patients who have mosaic TSC, establishing a definitive diagnosis is not always possible and may rely solely on the clinical picture.

Considering the differential diagnosis, benign cephalic histiocytosis usually would present with small red-brown macules and papules symmetrically located on the head and neck. The lesions occur at a younger age, usually in the first year or two of life. Fibrofolliculomas present as multiple whitish, slightly larger papules found on the central face. They are a marker for Birt-Hogg-Dubé syndrome, which also is associated with spontaneous pneumothorax.

Agminated means clustering or grouping of lesions. Agminated melanocytic nevi and agminated Spitz nevi are clusters of nevi. These lesions can vary in size and color. They may be elevated or flat. Melanocytic nevi usually are tan-brown or black. Spitz nevi may be pink or pigmented brown or black. To definitively differentiate between these 2 diagnoses and this patient's diagnosis of angiofibroma, a biopsy is needed.

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