

Fibrous Forehead Plaque

What's the diagnosis?



A 30-year-old woman presented to our dermatology clinic for evaluation and treatment options of a large 4×2-cm, firm, flesh-colored plaque on the superior aspect of the mid forehead. The plaque initially presented at 10 years of age and had grown since then. She reported no prior treatment of this nontender lesion and denied a family history of skin problems. She also had numerous skin tags all over the face, neck, and upper back that had increased in number for most of her adult life. In reviewing her medical history, she reported experiencing her first seizure at 15 months of age. She was evaluated by the neurology department at that time and was diagnosed with epilepsy.

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The Diagnosis: Tuberous Sclerosis Complex

Tuberous sclerosis complex (TSC) is an autosomal-dominant neurocutaneous syndrome characterized by multiple hamartomas distributed in multiple organs of the body, most commonly the skin, brain, eyes, heart, kidneys, liver, and lungs. In 1908, Vogt¹ elucidated the classic diagnostic triad of seizures, mental retardation, and facial angiofibromas (formerly termed *adenoma sebaceum*). However, the full triad is evident in only 29% of cases; 6% of TSC patients have none of these 3 findings.² The disease is caused by alterations in 2 TSC genes, *TSC1* and *TSC2*, on chromosomes 9 and 16, respectively. Both are tumor suppressor genes and mutations in either can be responsible for all the complications seen in the disease.³ The gene products of the 2 genes, hamartin and tuberlin, appear to act together in the regulation of cell growth by inhibiting a substance known as the mechanistic target of rapamycin.^{4,5} Up to two-thirds of cases may occur from spontaneous mutations.^{2,6} The disease is extremely variable in its manifestations, particularly the skin manifestations. This discussion will review the many cutaneous manifestations of TSC, most of them documented in our patient, and their frequency of occurrence.

Early recognition of TSC is vital because prompt implementation of the recommended diagnostic evaluation (eg, neuroimaging studies, electroencephalogram, electrocardiography, renal ultrasonography, chest computed tomography) may prevent serious clinical consequences.⁷ Neurologic manifestations are the leading cause of morbidity and mortality in patients with TSC.^{2,8,9} Brain hamartomas in the form of cortical tubers, subependymal nodules, and subependymal giant cell astrocytomas often are responsible for intractable seizures, most commonly as infantile spasms. Approximately 90% to 96% of TSC patients have seizures.⁶ Renal manifestations are strongly associated with TSC. Angiomyolipoma is the most common renal lesion found in TSC patients.^{4,9,10} Up to 80% of patients have renal angiomyolipomas. Their incidence increases with age.^{4,11,12} Tuberous sclerosis complex is known as a cause of epilepsy and mental retardation, but renal disease is a major cause of morbidity.¹³ Cardiovascular manifestations often are the earliest diagnostic findings in patients with TSC. Rhabdomyoma is the most common primary cardiac tumor in infants and children.^{11,13,14} The most common ocular findings in TSC are retinal hamartomas, appearing in 40% to 50% of patients.¹⁵

Cutaneous features frequently occur and are the most clinically apparent findings of TSC; if

overlooked, diagnosis could be delayed, which ultimately increases mortality. The diagnosis of TSC continues to be based primarily on clinical grounds because most patients older than 5 years demonstrate multiple skin lesions.⁶ In 1992, specific diagnostic clinical criteria were created for TSC, which stratified the clinical features of TSC into 3 tiers—primary, secondary, and tertiary—based on their specificity.¹⁶ In subsequent years, some of the classic clinical signs once regarded as pathognomonic for TSC, such as single ungual fibroma or multiple renal angiomyolipomas, were questioned. New modifications to the original diagnostic criteria were necessary given the advances in both TSC clinical information and molecular genetics. In the summer of 1998, a consensus conference held in Annapolis, Maryland, was assembled by the Tuberous Sclerosis Alliance for the purpose of reevaluating and updating the clinical diagnostic criteria.⁷ The revised criteria were simplified into 2 main categories—major and minor features—based on the diagnostic importance and degree of specificity for TSC of each clinical and radiographic feature (Table 1). There are a number of considerations that merit close attention when applying these clinical criteria. Despite the large number of clinical features delineated, the diagnosis of TSC may be challenging early in life, particularly in patients younger than 2 years. The value of the clinical criteria for early diagnosis and prompt management of TSC is limited by the fact that many stigmata become apparent only in late childhood or adulthood. The lack of pathognomonic signs of TSC can add to the challenge of diagnosing subtle or atypical cases.⁶

A careful skin examination of individuals at risk for TSC is the best and the easiest method of establishing the diagnosis in most cases. According to Gomez,¹⁷ 96% of patients with TSC have one or more main skin lesions of the disease, including facial angiofibromas, ungual fibromas, shagreen patches, or hypomelanotic macules. However, the diagnosis is more difficult in small children because many skin lesions become obvious with age; in fact, the full dermatological spectrum may never develop.¹⁷

Facial angiofibromas, also known as sebaceous adenomas, are the most visible and unsightly cutaneous manifestations of TSC, often resulting in stigmatization for both the affected individuals and their family members. These facial lesions often do not appear until late childhood or adulthood. In this case, the initial diagnosis often is made by the dermatologist who appreciates the significance of the white macules in a neonate. However, these hypomelanotic macules

cannot be detected by the unaided eye, thus a physician would be wise to examine an infant with infantile spasms or mental retardation with a Wood lamp, which accentuates the lesions.²

Table 1.

Revised Diagnostic Criteria for TSC^a**Major Features**

1. Facial angiofibromas or forehead plaque
2. Nontraumatic ungual or periungual fibroma
3. Hypomelanotic macule (≥ 3)
4. Shagreen patch (connective tissue nevus)
5. Multiple retinal nodular hamartomas
6. Cortical tuber^b
7. Subependymal nodule
8. Subependymal giant cell astrocytoma
9. Cardiac rhabdomyoma (single or multiple)
10. Lymphangiomyomatosis^c
11. Renal angiomyolipoma^c

Minor Features

1. Multiple, randomly distributed pits in dental enamel
2. Hamartomatous rectal polyps^d
3. Bone cysts^e
4. Cerebral white matter radial migration lines^{d,e}
5. Gingival fibromas
6. Nonrenal hamartomas^d
7. Retinal achromic patch
8. "Confetti" skin lesions
9. Multiple renal cysts^d

Abbreviation: TSC, tuberous sclerosis complex.

^aDefinite TSC: either 2 major features or 1 major feature plus 2 minor features; probable TSC: 1 major plus 1 minor feature; possible TSC: either 1 major feature or 2 or more minor features.

^bWhen cerebral cortical dysplasia and cerebral white matter migration tracts occur together, they should be counted as 1 rather than 2 features of TSC.

^cWhen both lymphangiomyomatosis and renal angiomyolipomas are present, other features of TSC should be present before a definite diagnosis is assigned.

^dHistologic confirmation is suggested.

^eRadiographic confirmation is suggested.

Data from Schwartz⁵ and Roach et al.⁶

Hypomelanotic macules were the overwhelmingly most common early findings in TSC. Infants with seizures or other possible stigmata of TSC should be carefully evaluated for these hypomelanotic macules as well as for other associated findings. Hypomelanotic macules can appear anywhere on the body, except the hands, feet, and genitalia; they are most commonly found on the lower extremities. Wood lamp examination reveals an accentuation of the hypopigmentation, which is a decrease in but not an absence of pigmentation. Lance ovate hypomelanotic macules are pathognomonic for TSC, thus the presence of 3 or more macules in an infant seriously suggests the diagnosis of TSC and echocardiography should be performed. The combination of white macules and seizures also increases the likelihood of TSC.¹⁸

Angiofibromas typically are found in the butterfly region of the face. Nico et al¹⁹ reported 2 patients with the complete syndrome of TSC who had multiple papules on the genital area in addition to classic facial lesions. Thus, it is important to examine the genital region of TSC patients and not misdiagnose these lesions as genital warts.

Jóźwiak et al¹⁸ screened 106 children with TSC and listed the prevalence of the most common cutaneous lesions. The results are presented in Table 2.

In a study by Webb et al,² 131 patients with TSC were examined and 126 (96%) exhibited skin signs. Although there was considerable variation in the age of expression of all the skin lesions, there was a trend toward the earlier expression of hypomelanotic macules and forehead fibrous plaques compared with facial angiofibromas and ungual fibromas. Shagreen patches usually were present by puberty. Ungual fibromas appeared for the first time as late as the fifth decade of life and were the only clinical feature in 3 patients. Ungual fibromas were present in 36% (47/131). Ten patients (8%) presented because of the skin manifestations and 21% (28/131) received treatment of symptomatic skin lesions. Two patients had large hamartomas at unusual sites, the occiput and forearm.²

Our 30-year-old patient presented to our clinic accompanied by her grandmother who served as legal guardian and historian for the patient. The patient experienced her first seizure at 15 months of age. She was evaluated by the neurology department at that time and was diagnosed with epilepsy. In the months following, she developed strabismus of the eyes and was examined by the ophthalmology department. Retinal hamartomas were discovered and she was diagnosed with TSC. Her seizure disorder was managed by a neurologist with the use of topiramate. In her 20s, she had renal and cardiac workups, which were negative, and she continued to be free of any genitourinary

Table 2.

Cutaneous Manifestations Associated With TSC

Cutaneous Lesions	Description	Age of Onset^a	Prevalence^a	Diagnostic Classification
Hypomelanotic “ash leaf” macules or Fitzpatrick patches	Leaf-shaped or polygonal white spots, enhanced by Wood lamp examination; more common on the trunk and buttocks	Earliest cutaneous lesion; usually present at birth or infancy	97.2%	Major ^b
Facial angiofibromas	Red to pink papules with a smooth surface; symmetrically distributed over the centropalpebral areas, sparing the upper lips	Second to fifth year of life; become more prominent with age	74.5%	Major
Shagreen patches	Slightly elevated patches or plaques, usually found on the dorsal body surfaces, especially the lumbosacral area; its rough surface resembles an orange peel; represents a connective tissue nevus, sometimes called collagenoma	Rare during infancy; tend to increase in size and number with age	48.1%	Major
Molluscum pendulum	Multiple soft pedunculated skin growths on neck, rarely in axilla or groin	More common during first decade of life; rare during infancy	22.6%	Major ^c
Forehead fibrous plaque	Yellowish brown or flesh-colored plaques of variable size and shape, usually located on the forehead or scalp	Common at any age and can be seen at birth or early infancy	18.9%	Major
Periungual fibromas	Flesh-colored or reddish nodules seen on the lateral nail groove, nail plate, or along the proximal nail folds; more commonly found on the toes than on the fingers	Present at puberty or soon after; become more common with age	15.1%	Major
“Confetti-like” macules	Multiple 1- to 2-mm white spots symmetrically distributed over extremities	Second decade of life or adulthood	2.8%	Minor

Abbreviation: TSC, tuberous sclerosis complex.

^aData from Jóźwiak et al.¹⁸

^bRequires 3 or more.

^cNot included as part of TSC diagnostic criteria.

or cardiac concerns. One year prior to presentation she underwent a brain computed tomography scan after a bicycle accident and was informed that she had “scarlike” lesions within the cerebral cortex. There was no known history of TSC in other family

members. On physical examination, she was noted to be delayed in mental development and intelligence. She stated her first notable skin lesions appeared at 10 years of age and were skin tags of the upper back and neck and over the face. Soon after, the cheeks

and nose developed numerous shiny brownish pink papules (Figure 1). Over the course of the next 20 years she developed other skin findings noted on our present skin examination. The superior aspect of the mid forehead revealed a 4×2-cm, raised, flesh-colored, firm tumorous plaque. The neck and upper back had multiple 2- to 5-mm, soft, pedunculated, polypoid, brownish pink papules. Her mid back revealed ill-defined, slightly elevated, rosy plaques and macules with a roughened speckled appearance (Figure 2). Several of the toenails and fingernails showed firm, fleshy, spiculelike papules around and under the nail bed (Figure 3). The lower anterior tibia revealed several oval-shaped, flat, well-demarcated, hypopigmented macules (Figure 4). Lesions on the face and mid back were biopsied and histopathology confirmed angiofibroma and shagreen patch, or connective tissue nevus, respectively. Our patient did not undergo treatment of any of these skin lesions, particularly the facial angiofibromas. Cosmetic

treatment options such as laser or surgical removal were presented to her, but she declined.

A brief review of the literature for treatment options of facial angiofibromas and the fibrous forehead plaque indicated that current treatments include but are not limited to cryotherapy, electrocautery, electrosurgery, shave excision, chemical peels, argon laser, CO₂ laser, and radiofrequency equipment.²⁰ For the best outcome, these treatments have to be repeated throughout childhood and teenage years. Rapamycin, also known as sirolimus, and its analogs are new therapeutic options for TSC. Rapamycin is an inhibitor of the mechanistic target of rapamycin and can normalize this unregulated pathway in a TSC patient. Various preclinical models have shown that rapamycin treatment reduces TSC-related tumors, including brain, skin, and kidney tumors.²¹ A pilot study by Foster et al²² revealed improvement in the facial angiofibromas of 4 children treated with 2 topical preparations of



Figure 1. Angiofibromas of the nose and cheeks.



Figure 2. Shagreen patches on the lower back.



Figure 3. Periungual fibromas.



Figure 4. Hypomelanotic café au lait macules on the anterior aspect of the lower leg.

rapamycin. The study revealed that younger patients with smaller angiofibromas had the best response with near-complete clearance. Rapamycin topical preparations were more cost effective than pulsed dye laser under general anesthesia.²²

Tuberous sclerosis complex is not the only syndrome that can present with facial angiofibromas or numerous skin tag-type lesions such as those in our patient. It is important to also consider Birt-Hogg-Dubé syndrome and multiple endocrine neoplasia type 1 in the differential diagnosis of multiple facial angiofibromas, particularly with adult onset.²³

Our case was presented to review the cutaneous manifestations of TSC and their presentation frequency, with the intent to enable the dermatologist to make a more accurate and earlier diagnosis of TSC. In doing so, morbidity of TSC patients could be decreased and quality of life increased.

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