The Ochsner Journal 10:200–204, 2010

Cutaneous Manifestations of Tuberous Sclerosis

Sue Hake, DPM, FACFAS

Department of Podiatry, Ochsner Medical Center–North Shore, Ochsner Clinic Foundation, Covington, LA

ABSTRACT

Purpose: To describe a case of periungual masses probably related to tuberous sclerosis and to review the literature regarding tuberous sclerosis, including the historical, clinical, and diagnostic aspects. Also discussed is the long-term follow-up of the disease.

Methods: Report of a case of periungual masses secondary to tuberous sclerosis and review of the literature from 1999 to 2009, with the use of MEDLINE (National Library of Medicine).

Results: I describe a case of periungual masses occurring as a result of tuberous sclerosis. A literature review confirms periungual masses associated with tuberous sclerosis in most cases. Also, the observance of cutaneous manifestations is most helpful in the diagnosis of this disorder.

Conclusion: Tuberous sclerosis is an uncommon disorder, which has a variable clinical presentation. Tuberous sclerosis is associated with seizures and mental retardation. In the absence of these 2 signs/symptoms, physicians should still consider the diagnosis when presented with varied dermatologic conditions.

INTRODUCTION

Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutaneous syndrome. It is characterized by a widely variable phenotype and the development of multiple hamartomas distributed at various sites throughout the body, especially the brain, skin, retina, kidney, heart, and lung.[1–4] The prevalence is not well defined, with reported incidence of from 1:6,000 to more than 1:100,000.[1–13] This is perhaps due to undiagnosed or mildly affected symptomatic individuals.[1] There appear to be 2 major loci where mutations can cause TSC: TSC1 9q34 and TSC2 at 16p13.3.[5,7,14] Also, 50% to 84% of cases are sporadic as new mutations.[4–7] Although the classic triad of TSC is seizures, mental retardation, and angiofibromas, this triad occurs in only 29% of patients.[1,14] However, skin involvement is cardinal for suspecting the diagnosis of TSC.[5,8,9] In the following case, periungual fibromas are a major criterion for diagnosing TSC.

Address correspondence to:
Sue Hake, DPM, FACFAS
Department of Podiatry
Ochsner Medical Center–North Shore
Ochsner Clinic Foundation
1000 Ochsner Blvd.
Covington, LA 70433
Tel: 985-875-2828
Fax: 985-875-2771
Email: shake@ochsner.org

Key Words: Feet, fibroma, subungual, tuberous sclerosis

CASE

A 56-year-old white woman presented with multiple growths on every digit of both feet. She related a history of having had them since her early twenties. The mass on the second toe of the right foot impeded her wearing shoes comfortably. She had not shown these masses to anyone, including her primary physician. She related a past history of seizures as a very young child for which she continues to receive medication. She also has had 3 miscarriages, which were associated with a ''malfunctioning kidney.'' No records were attainable for review. The rest of the history was negative, and she appeared to have normal cognitive function. There was no family history of tuberous sclerosis.

The examination revealed pedal digits displaying multiple lobulated fibromas. The largest mass measured 3 $\times$ 2.5 cm (Figure 1).

Results from the neurovascular examination of the lower extremity were normal. The orthopedic examination demonstrated bilateral hallux abductovalgus deformities. Radiographs revealed bone cysts in multiple digits. Surgical intervention with sharp excision was performed owing to the size and severity of the lesions.

The lesions were histologically identified as consistent with tuberous sclerosis by both Ochsner Clinic Foundation and Mayo Clinic (Figure 2).

The postoperative period was uneventful. The patient developed a small reoccurrence of the lesion on 1 digit of her left foot 4 months postoperatively. She is pain free and able to wear shoes.

DISCUSSION

Tuberous sclerosis syndrome has been referred to in the literature as Bourneville disease, Pringle disease, and epiloia.[15] These all refer to the entity of TSC that is highly variable even within families.[14] To

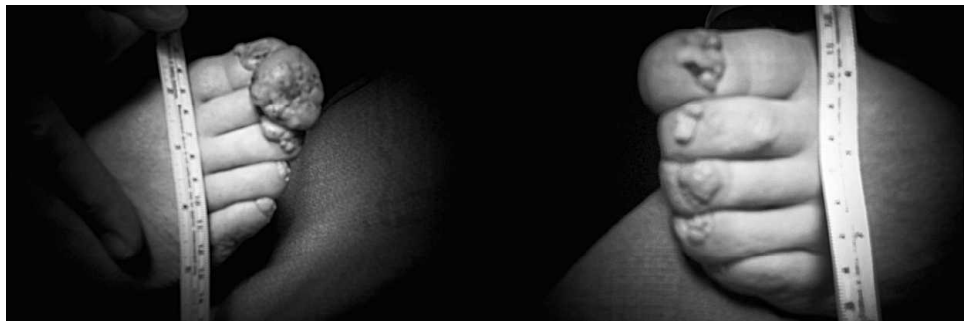

Figure 1. Clinical appearance of periungual fibromas. Left: right foot; right: left foot.

aid with the diagnosis of this disorder, criteria for major and minor features have been devised. A definite diagnosis requires 2 major features or 1 major and 2 minor features.[4] A probable diagnosis of TSC requires 1 major and 1 minor feature.[1]

Major features:

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

Minor features:

1. Multiple randomly distributed pits in dental enamel
2. Hamartomatous rectal polyps
3. Bone cysts
4. Cerebral white matter radial migration lines

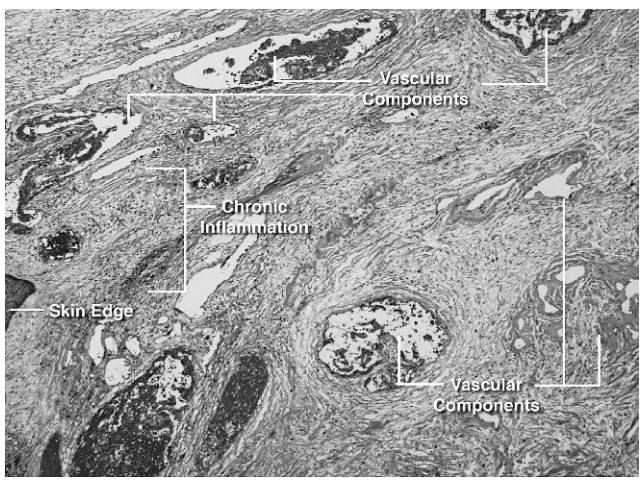

Figure 2. Photomicrograph showing histopathology of the lesions.

5. Gingival fibromas
6. Nonrenal hamartomas
7. Retinal achromic patch

DNA testing is useful for diagnosis and for determining the causative mutation. However, approximately 30% of patients with TSC have negative results for genetic testing of TSC1 and TSC2.[3] Therefore, a careful skin examination for patients at risk for TSC is the easiest and most accessible method to establish a diagnosis. One must be aware that all diagnostic features are age dependent.[1,3]

The most common skin lesions are hypomelanotic macules (ash-leaf spots) that occur in more than 90% of patients with TSC. They are best visualized by Wood light.[1,3] Other cutaneous clinical features include forehead plaques, shagreen patch, and facial angiofibromas.[5,16] Koenen fibromas develop in up to 50% of cases of TSC, with onset occurring around puberty.[1,4,5,17,18] These tumors range in size and can involve every digit. The feet are more commonly involved than the hands. The nodules are usually skin colored or reddish, arising from the nail bed. Histologically, they are fibromas or angiofibromas similar to fibrous forehead plaques and facial anigiofibromas.[1,3,17] The presence of periungual fibromas is a major criterion in the diagnosis of TSC and, as in facial angiofibromas, it is nearly always pathognomonic for TSC (Table).

TSC has many extracutaneous manifestations. Neurologic manifestations are the leading cause of morbidity and mortality in TSC. Brain hamartomas are often responsible for intractable seizures most commonly seen as infantile spasms. Approximately 90% to 96% of patients with TSC suffer from seizures.[1] Many patients with TSC experience mental retardation, autism, and increased intracranial pressure.[3] Renal and pulmonary manifestations are strongly associated with TSC. Angiomyolipoma is the most common renal lesion (up to 80%) found in patients with TSC. Pulmonary involvement is relatively rare. Cardiovascular features are often the earliest diagnostic finding.[1] The lesions are usually asymptomatic unless they cause obstruction of flow.[3] Ocular findings of TSC are retinal hamartomas and occur in 40% to 50% of

Table. Cutaneous Manifestations of Tuberous Sclerosis

Cutaneous Lesions	Descriptions	Age of Onset	Prevalence, %	Diagnostic Classification
Hypomelanotic macules ''ash leaf'' or Fitzpatrick patches	Leaf-shaped or polygonal white spots enhanced by a Wood lamp	Earliest cutaneous lesion; usually present at birth or infancy	97.2	Major
Facial angiomas	Red to pink papules with a smooth surface, symmetrically distributed over the centrofacial areas, sparing the upper lips	Second to fifth year of life; become more prominent with age	74.5	Major
Shagreen patches	Slightly elevated patch or plaque, 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	Major
Molluscum pendulum	Multiple soft pedunculated skin growths on neck, rarely in axilla or groin	More common during first decade of life, rarely during infancy	22.6	___
Forehead fibrous plaque	Yellowish brown or skin-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*	**Shin-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, 1–2 mm, white spots symmetrically distributed over extremities	Second decade of life or adulthood	2.8	Minor

* These were the lesions presented by the patient discussed in this report.

patients.[1] These most often do not cause visual dysfunction. Numerous other findings include tooth pitting and radiographic abnormalities. TSC often presents with bone abnormalities that do not limit motion. All bones may show osteoclastic lesions; the characteristic changes are patches of osteosclerosis. The bones of the hand and feet may show cystlike areas, particularly in the distal phalanges.[19] However, these rarely attract medical attention.[1,3]

With the variable expression of TSC, it is often difficult to diagnose this entity. As in the case presented, all the pieces of the puzzle may not come together until later in life. A diagnostic work-up should include a careful history and skin examination. If infantile spasms or autism are present, magnetic resonance imaging (MRI) of the brain is indicated. If these investigations are inadequate for diagnosis of TSC, an ophthalmologic examination for retinal hamartomas or renal ultrasonography may provide confirmatory evidence. Echocardiography is usually not helpful beyond the age of 2 years because cardiac rhabdomyomas regress with advancing age.[3]

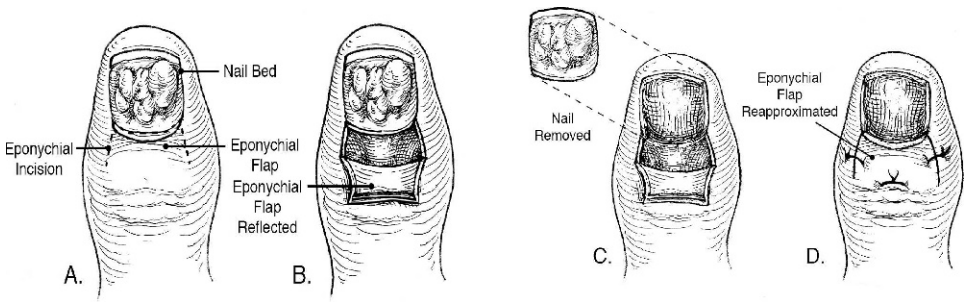

Figure 3. Procedure for excision of lesions.

Follow-up testing after the diagnosis puts focus on treatment or prevention of problems. If there are no seizures, an electroencephalogram is not needed. Neurodevelopment testing is done upon school entry. Giant cell astrocytomas of the brain typically do not grow after the second decade of life, whereas renal angiomyolipomas often enlarge during early adulthood. Therefore, MRI of the brain is repeated every 1 to 3 years during childhood and adolescence. Renal ultrasonography is repeated every 1 to 3 years.[3]

TREATMENT

The cutaneous lesions, as identified in this case, were sharply excised as demonstrated (Figure 3).

Treatment options included using a CO_2 laser, which provides efficient and bloodless extraction of the lesions,[4,8] or phenolization that allows for a better cosmetic result.[5,8,9,15] However, in this case, the severity and penetration of the lesion into bone led to the decision to perform a sharp excision of the mass. The nail bed was not salvageable. The reoccurrence rate of Koenen tumors is high. Complete excision is required to achieve a permanent cure.[20]

Recent discoveries have led to the use of oral rapamycin to induce regression of tumors associated with TSC. This may represent a major advance in therapy.[1,20–22]

CONCLUSION

TSC is a multisystem disorder with variable clinical manifestations. To decrease the morbidity from seizures, an early diagnosis of TSC is essential. The appropriate diagnosis requires a multidisciplinary approach to properly treat affected individuals. This case met the criteria, set forth in this article, for diagnosis as tuberous sclerosis. It demonstrates the need for awareness of the cutaneous manifestations of the disease and of the correlation of these manifestations with other body systems.

REFERENCES

1. Schwartz RA, Fernández G, Kotulska K, Jóźwiak S. Tuberous sclerosis complex: advances in diagnosis, genetics, and management. *J Am Acad Dermatol*. 2007;57(2):189-202.
2. Jozwiak J, Jozwiak S, Wlodarski P. Possible mechanism of disease development in tuberous sclerosis. *Lancet Oncol*. 2008;9(1):73-79.
3. Kandt RS. Tuberous sclerosis complex and neurofibromatosis type 1: the two most common neurocutaneous diseases. *Neurol Clin*. 2002;20(4):941-964.
4. Berlin AL, Billick RC. Use of CO2 laser in the treatment of periungual fibromas associated with tuberous sclerosis. *Dermatol Surg*. 2002;28(5):434-436.
5. Mazaira M, del Pozo Losada J, Fernández-Jorge B, Fernández-Torres R, Martínez W, Fonseca E. Shave and phenolization of periungual fibromas, Koenen's tumors, in a patient with tuberous sclerosis. *Dermatol Surg*. 2007;34(1):111-113.
6. Iscan A, Kurul S, Dirik E. Clinical findings in tuberous sclerosis in Turkish children. *J Pediatr Neurol*. 2005;3(2):95-102.
7. Schnur RE. Tuberous sclerosis: the persistent challenge of clinical diagnosis. *Arch Dermatol*. 1995;131(12):1460-1462.
8. Kwiatkowski DJ, Short MP. Tuberous sclerosis. *Arch Dermatol*. 1994;130(3):348-354.
9. Harris-Smith R, Elston DM. Tuberous sclerosis. *Cutis*. 2002;69:103-169.
10. Tashiro M, Hirose W, Hanabusa H, et al. Pancytopenia in tuberous sclerosis. *Med Sci Monit*. 2001;7(3):444-447.
11. Roach ES, Smith M, Huttenlocher P, Bhat M, Alcorn D, Hawley L. Diagnostic criteria: tuberous sclerosis complex—report of the Diagnostic Criteria Committee of the National Tuberous Sclerosis Association. *J Child Neurol*. 1992;7(2):221-224.
12. Roach ES, Gomez MR, Northrup H. Tuberous sclerosis complex consensus conference: revised clinical diagnostic criteria. *J Child Neurol*. 1998;13(12):624-628.
13. Danden JW, Teeslink R, Parrish A. Hamartoma of the spleen: a manifestation of tuberous sclerosis. *Am Surg*. 1975;41(9):564-566.
14. Ruiz-Villaverde R, Blasco-Melguizo J, Hernández-Jurado I, Naranjo-Sintes R, Gutierrez Salmerón MT. Bilateral and multiple periungual fibromas as an oligosymptomatic form of tuberous sclerosis. *Dermatology*. 2004;209(2):160-161.
15. Feinstein MH. Foot pathology associated with tuberous sclerosis and neurofibromatosis. *J Am Podiatry Assoc*. 1972;62(9):336-350.
16. Webb D, Osborne JP. Tuberous sclerosis. *Arch Dis Child*. 1995;72:471-474.
17. Baran R, Richert B. Common nail tumors. *Dermatol Clin*. 2006;24(3):297-311.

18. Aste N, Pau M, Aste N, Biggio P. Tuberous sclerosis with unusual giant ungual fibromas. *J Eur Acad Dermatol Venereol*. 2003;17(1):100-101.
19. Radó JP, Haris A. Metabolic bone disease (anticonvulsant osteomalacia) and renal tubular acidosis in tuberous sclerosis. *Intern Med*. 1993;32(7):574-579.
20. Ward PE, McCarthy DJ. Periungual fibroma. *Cutis*. 1990;46:118-124.
21. Lee N, Woodrum CL, Nobil AM, Rauktys AE, Messina MP, Dabora SL. Rapamycin weekly maintenance dosing and the potential efficacy of combination sorafenib plus rapamycin but not atorvastatin or doxycycline in tuberous sclerosis preclinical models. *BMC Pharmacol*. 2009;9:8.
22. Sampson JR. Therapeutic targeting of mTOR in tuberous sclerosis. *Biochem Soc Trans*. 2009;37(pt 1):259-264.