CME

Tuberous sclerosis complex: A multisystem disorder

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ABSTRACT

Tuberous sclerosis complex (TSC) is a genetic disorder that affects multiple organ systems but often goes unrecognized, and a delay in diagnosis can lead to multiple complications. Healthcare professionals should be educated on the many signs and symptoms associated with the disorder, know how to treat them symptomatically, and recommend routine screening to assess for complications. Correctly identifying, diagnosing, and treating TSC can give patients a better quality of life and prevent further complications associated with the disorder.

Keywords: tuberous sclerosis complex, familial tumor syndrome, renal failure, skin lesions, genetic disorder, neurocognitive disorder

Learning objectives

- Identify the signs and symptoms of TSC.
- Understand the diagnostic criteria for TSC.
- Recognize the complications associated with TSC and how best to use a multidisciplinary approach to management.

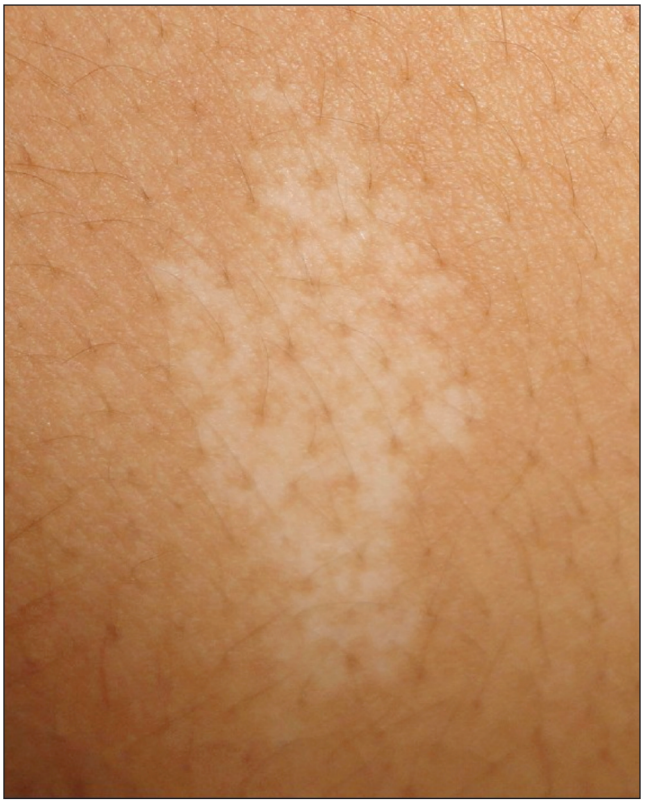
CASE

A 19-year-old woman presented to the ED with a chief complaint of heaviness in the chest.

History Her past medical history was significant for tuberous sclerosis complex (TSC) that was diagnosed when she was 10 years old, after her younger brother was found to have the disease. The patient had characteristic shagreen patches (**Figure 1**) and had been undergoing routine surveillance for TSC-related manifestations since her diagnosis with no clinically significant complications until now.

Physical examination The patient's vital signs were BP, 118/74 mm Hg; heart rate, 78 beats/minute; respirations, 16; oral temperature of 98.7° F (37.1° C); and an Spo_2 of 95% on room air. She was 65.5 in (166 cm) tall and weighed 117 lb (53.1 kg). Workup revealed no emergency causes of her chest heaviness, which was felt to be secondary to anxiety. Her laboratory evaluation revealed abnormalities with her kidney function tests: creatinine of 3.2 mg/dL (normal range, 0.50–1.10 mg/dL), blood urea nitrogen (BUN) of 36 mg/dL (normal range, 8–20 mg/dL), and an estimated glomerular filtration rate (eGFR) of 20 mL/minute (normal range, greater than 60 mL/min). A urinalysis revealed no abnormalities. She was asymptomatic with regards to genitourinary or other related system complaints and had not started any new medications.

Given the asymptomatic nature of the kidney disease, she was discharged and instructed to follow up with a nephrologist. The nephrologist performed a renal ultra-



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Key points

- TSC is a multifaceted, often underdiagnosed genetic neurocutaneous disorder affecting multiple organ systems.
- The condition is characterized by a variety of benign tumors of the central nervous system, kidneys, skin, heart, eyes, lung, and liver.
- Common manifestations include epilepsy, cognitive deficits and learning disabilities, autism, pulmonary disease, and kidney dysfunction.
- Early recognition and diagnosis is essential to managing and treating patients with TSC, particularly with regards to screening and preventing complications.

sound and ultrasound-guided biopsy and diagnosed the patient with focal segmental glomerular sclerosis (FSGS) and stage 4 chronic kidney disease (CKD), both felt to be secondary to TSC. Although the patient does not require dialysis, she is on the kidney transplant list and has regular follow-ups with her nephrologist.

DISCUSSION

TSC is a genetic, neurocutaneous disorder affecting multiple organ systems including the central nervous system, kidneys, skin, heart, eyes, lung, and liver. The disease was first described by the French neurologist Bourneville in the 1880s and is characterized by the appearance of multiple benign, noninvasive lesions called hamartomas in multiple organs.[1,2] TSC is an autosomal dominant disorder, but as many as two-thirds of patients can have multiple sporadic mutations that cause the disorder.[2,3] The genes that are affected are found on the tumor suppressor genes TSC1 9p34 and TSC2 16p13. The TSC1 gene encodes for hamartin, and the TSC2 gene encodes for the tuberin protein; both are responsible for inhibiting cell signaling from the mammalian target of rapamycin (mTOR), a protein kinase signaling pathway that controls cell growth and proliferation.[2-4] The distribution, size, number, and location of the mutations that can cause symptoms vary widely even within a family, as was noted to be the case with our patient.[2]

EPIDEMIOLOGY

TSC is estimated to affect 1 in 6,000 newborns in the United States.[5] The disease prevalence is 40,000 to 80,000 people in the United States, and about 1 million people worldwide; however, this number is likely greater due to many cases going undiagnosed.[5,6] TSC has been shown to affect ethnicities and sexes equally.[5,6]

CLINICAL MANIFESTATIONS

The classic manifestations associated with TSC are adenoma sebaceum, seizures, and intellectual disability. Other common manifestations include central nervous system (CNS) involvement, angiomyolipomas, shagreen patches, hypomelanotic macules (ash leaf spots), and cardiac rhabdomyomas.[4] Although these are some of the common manifestations, many other serious conditions and symptoms can occur with TSC and will be discussed based on the organ system affected.

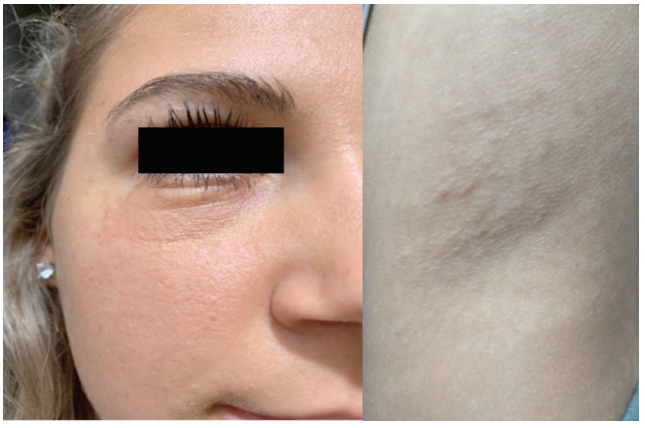

FIGURE 1. Shagreen patches on the patient's face and lower back

Neurologic manifestations Epilepsy is one of the most frequent features of TSC, occurring in about 85% of patients.[7] Infantile spasms are a common initial presentation and one of the most common seizures associated with the disease. Another frequent seizure type encountered in these patients is focal seizure with or without secondary generalization. Patients with seizures are more likely to experience neurocognitive deficits such as autism spectrum disorder, intellectual disability, and mood disturbances.[3] The term TSC-associated neuropsychiatric disorders (TAND) is used to describe the collective psychiatric, intellectual, academic, neurophysiologic, and psychosocial abnormalities associated with the disorder.[5]

Three types of tumors often are found in the CNS of patients with TSC, including cortical tubers, subependymal nodules, and giant cell astrocytomas. Cortical tubers are a disorganized collection of abnormal but benign cells. Given their cortical localization, tubers can cause seizures. Subependymal nodules are located just below (superficial to) the ependyma of the lateral ventricles. These nodules often contain calcium, which makes them easily seen on CT scan (**Figure 2**). Subependymal giant cell astrocytomas (SEGA, **Figure 3**) occur in 5% to 15% of patients with TSC and can lead to complications including obstructive hydrocephalus.[5] Cortical dysplasia, a defect of neuronal migration, also frequently is seen in patients with TSC. Other, usually asymptomatic, brain lesions that may be associated with TSC are arachnoid cysts (**Figure 3**). One study estimated the prevalence of arachnoid cysts in the general population at 1% compared with 5% of patients with TSC; these cysts should be considered a part of the spectrum of TSC.[8]

Dermatologic manifestations Some of the dermatologic findings in patients with TSC are hypomelanotic macules,

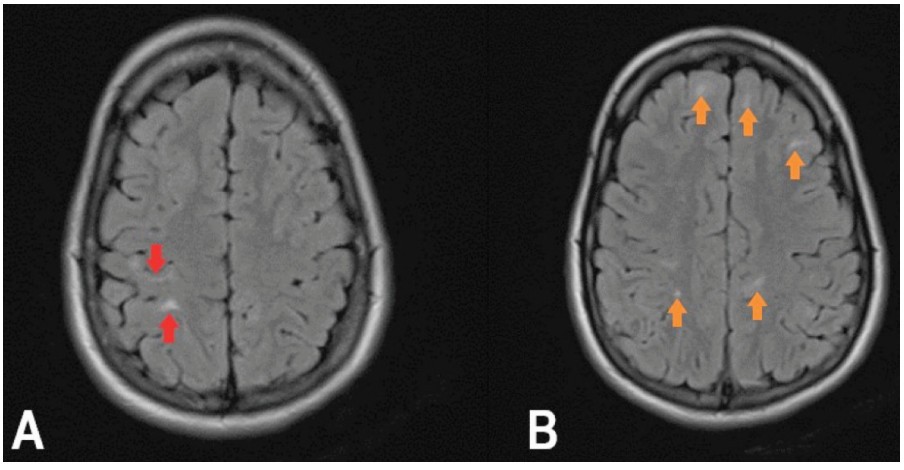

FIGURE 2. Cortical tubers (A) and subependymal nodules (B) on CT scan

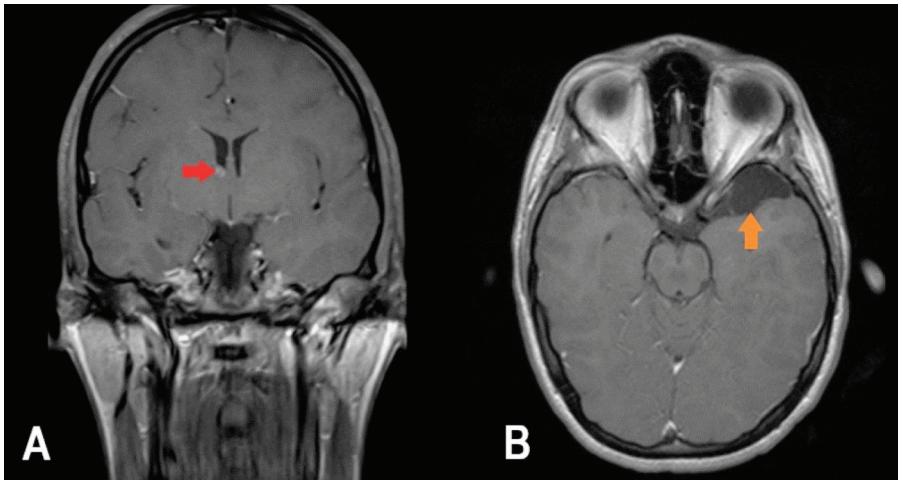

FIGURE 3. A subependymal giant cell astrocytoma (A) and left temporal arachnoid cyst (B)

shagreen patches, and facial angiofibromas. Hypomelanotic macules are white patches on the skin that can occur at birth or in early infancy (**Figure 4**). They can be found prominently on the trunk, arms, and legs.[5] They vary in size and shape but are important because about 90% of patients with TSC have these lesions.[5,9] Shagreen patches (**Figure 1**) appear as large plaques and have a rough surface. They typically are found on the lower back but occur in other locations and are observed in about 50% of patients.[9] Angiofibromas occur in about 75% of patients and are a type of vascular red tumor found on the face in a typical butterfly pattern around the nasal folds and malar eminences (**Figure 4**). They typically appear in children after age 5 years and over time can develop a cobblestone appearance.[2] Many patients have several facial angiofibromas, but uncommonly they can present as an isolated lesion.[9] Other less common lesions include "confetti" lesions, which are hypopigmented macules that can be found on the arms and legs, and ungual fibromas, which are flesh-colored papules that can be found under the nailfolds.[2]

Cardiac manifestations Cardiac rhabdomyomas are benign tumors of the heart that occur in about 50% of patients with TSC.[6] They are commonly found in the ventricles and are associated with cardiac dysrhythmias such as Wolff-Parkinson-White (WPW) syndrome. The tumors can compromise ventricular and valvular function, resulting in outflow obstruction. Tumors frequently are found in early fetal life on prenatal ultrasound and often are one of the first noted manifestations of the disease, making them one of the major diagnostic criteria (**Table 1**).[9]

Renal manifestations Renal cysts, angiomyolipomas, impaired kidney function, and renal cell carcinoma are among the renal manifestations of TSC. Renal cysts are associated with kidney failure and hypertension and occur in about 40% of patients.[10] Renal cysts commonly present as single to multiple lesions that are uniform in size. They are rarely symptomatic; however, less commonly, renal cysts can coexist with polycystic kidney disease.[10] Cystic disease of the kidneys is most commonly found in patients with TSC2 and PKD1 gene deletions and is associated with early renal failure.[10] Renal cysts usually remain asymptomatic, but for patients with these specific gene deletions the cysts become multiple, large, and can lead to end-stage renal failure early in life.[2]

Angiomyolipomas are benign tumors composed of smooth muscle, vascular, and adipose tissue that can be found in multiple organs but are mostly found in the kidney. They are relatively specific to TSC and are found in 80% of patients.[9,11] Angiomyolipomas can bleed, putting patients at an increased risk of CKD. Usually they grow slowly and are monitored with ultrasound throughout the patient's life. Unfortunately, renal-related disease is the most common cause of TSC-related death in adults, making identification of these tumors at an early age essential.[9,11]

The case patient did not have angiomyolipomas but had polycystic kidneys, which likely contributed to the development of her CKD. An ultrasound of her kidneys was performed and showed small echogenic kidneys with renal biopsy revealing FSGS. Although FSGS is not commonly associated with TSC, research done with mouse models has found a link between knockout of TSC2 and develop-

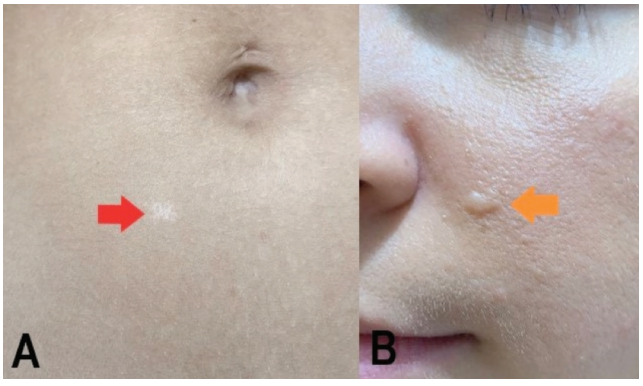

FIGURE 4. A hypomelanotic macule (A) and a facial angiofibroma (B)

ment of FSGS.[12] More research is needed to clarify this potential link in humans.

Ophthalmologic manifestations Retinal hamartomas and achromic patches are some of the ophthalmologic findings associated with TSC. Retinal hamartomas are of similar histology to cortical tubers. They usually do not cause vision disturbances, can be multiple, and often are found in younger children who do not have other features of TSC.[9] They occur in 30% to 50% of patients.[9] Retinal achromic patches are described as areas of hypopigmentation on the retina and are found in about 40% of patients.[9]

TABLE 1. Diagnostic criteria for TSC[6,9]

Patients with two major features or one major feature and two or more minor features have a definite diagnosis of TSC. Patients with one major feature or two or more minor features have a possible diagnosis of TSC. A TSC1 or TSC2 pathogenic mutation in DNA from normal tissue is enough to make the diagnosis of TSC via genetic testing. A pathogenic mutation is defined as one that clearly inactivates the function of the TSC1 or TSC2 proteins, prevents protein synthesis, or is a missense mutation whose effect on protein function has been established by functional assessment. Other TSC1 and TSC2 variants that are not as clear or certain do not meet these criteria and do not meet the diagnosis of TSC.

Major features
- Hypomelanotic macules (3 or more, at least 5 mm in diameter)
- Angiofibromas (3 or more) or fibrous cephalic plaque
- Ungual fibromas (2 or more)
- Shagreen patch
- Multiple retinal hamartomas
- Cortical dysplasias
- Subependymal nodules
- Subependymal giant cell astrocytoma
- Cardiac rhabdomyoma
- LAM
- Angiomyolipomas (2 or more)

Minor features
- "Confetti" skin lesions
- Dental enamel pits (3 or more)
- Retinal achromic patch
- Multiple renal cysts
- Nonrenal hamartomas

Pulmonary manifestations Lymphangioleiomyomatosis (LAM) is a major criterion for the diagnosis of TSC, and is associated with benign-appearing smooth muscle cells that infiltrate lung structures. Cystic pulmonary parenchymal changes are associated with LAM, with LAM occurring in 30% to 40% of women with TSC and 12% of men with TSC.[9] Some of the symptoms of LAM are progressive dyspnea on exertion and recurrent pneumothoracies.[9] LAM is difficult to treat and holds a poor prognosis.[1]

Other rare manifestations of TSC include multifocal micronodular pneumocyte hyperplasia (multiple benign alveolar type II pulmonary nodules scattered through the lungs) and clear-cell tumors of the lung, a benign, rare condition consisting of mesenchymal tumors found in the lungs.[9]

Dental manifestations Dental enamel pits often are multiple and are considered a minor diagnostic feature of TSC. Intraoral fibromas can be found on the gingiva, buccal and labial mucosa, and tongue. These fibromas are found in 20% to 50% of patients with TSC and were previously considered a minor criterion, but were removed from the current guidelines.[9]

Other manifestations Other conditions that can be found in patients with TSC include bone cysts and hamartomas found in other areas including the adrenal gland, liver, thyroid, pancreas, pituitary, and the gonads.[9]

DIAGNOSTIC CRITERIA

The diagnostic criteria for TSC can be found in **Table 1**. The diagnosis of TSC requires two major features, or one major and two minor features. The genetic criteria diagnosis is separate from the diagnostic criteria.

Diagnostic imaging studies that can be useful to diagnose TSC include CT and MRI to evaluate the brain and surrounding structures for the presence of TSC-related tumors. MRI also is useful for evaluating the liver and kidneys for angiomyolipomas and other tumors. Ultrasound also can be used for evaluation of the liver and kidneys. Serum blood tests are primarily used to evaluate kidney function, with BUN, creatinine, and eGFR. An electroencephalogram (EEG) can be used to evaluate for seizure activity. High-resolution CT is useful to evaluate the lungs for evidence of LAM or multifocal micronodular pneumocyte hyperplasia; pulmonary function testing also is recommended for evaluating LAM.[6] An echocardiogram and an ECG can be used to evaluate for rhabdomyomas. In some instances, cardiac rhabdomyomas can be detected prenatally by ultrasound.[3,5,6] A full dermatologic examination is recommended, as well as dental and ophthalmologic evaluations, including a fundoscopic examination to search for hamartomas and retinal hypopigmented lesions.[3] Laboratory and diagnostic testing guidelines are discussed in **Table 2**.

Genetic testing can confirm the diagnosis of TSC by detecting alterations in either TSC1 or TSC2, which are the basis for TSC.[5] Genetic evaluation is important because it can give a definite genetic diagnosis to those who may

TABLE 2. Treatment guidelines for TSC[15]

Adapted with permission from the Tuberous Sclerosis Alliance guidelines.

Organ system	Procedure	Newly diagnosed TSC	Previously diagnosed TSC
Brain	Brain MRI with and without gadolinium	Yes	Every 1-3 years up to age 35 years; periodically as adults if SEGAs are present in childhood
	EEG	Yes; if abnormal, follow up with 24-hour video EEG	Routine EEG determined by clinician; video EEG when seizure occurrence is unclear or unexplained behavioral or neurologic change occurs
	TAND checklist	Yes	Annually at each clinical visit
	Comprehensive evaluation for TAND	If warranted by TAND checklist analysis	At key developmental time points (years): 0-3 months, 6-9 months, 12-16 months, 28-35 months, and as needed thereafter
	Counsel parents of infants	Educate parents to recognize infantile spasms*	N/A
Skin, teeth, eyes	Complete eye examination with dilated fundoscopy	Yes	Annually if lesions or symptoms are identified at baseline
	Detailed skin examination	Yes	Annually
	Detailed dental examination	Yes	Every 6 months
	Panoramic radiographs of teeth	At age 7 years and older	At age 7 years if not done previously
Heart	Fetal echocardiography	Only if rhabdomyomas are identified by prenatal ultrasound	N/A
	Echocardiogram	Yes	Every 1-3 years if rhabdomyoma is present in asymptomatic children; more frequently in symptomatic adults
	ECG	Yes	Every 3-5 years; more frequently if symptomatic
Kidneys	BP	Yes	Annually
	Abdominal MRI	Yes	Every 1-3 years
	GFR test	Yes	Annually
Lungs	Clinical screening for LAM symptoms**	Yes	At each clinical visit
	Pulmonary function testing and 6-minute walk test	In all females age 18 years and older; males only if symptomatic	Annually if lung cysts detected by high-resolution CT
	High-resolution CT of the chest	Yes	Every 2-3 years if lung cysts detected on high-resolution CT; otherwise every 5-10 years
	Counsel on risks of smoking and estrogen use	In adolescent and adult females	At each clinical visit for those at risk of LAM
Genetics	Genetic consultation	Obtain three-generation family history	Offer genetic testing for TSC1 and TSC2 and counseling if not done previously in patients of reproductive age

* Treat infantile spasms with vigabatrin as first-line therapy. Adrenocorticotropic hormone can be used as a second-line therapy if vigabatrin treatment is unsuccessful.
** Evaluate for LAM when the patient has symptoms such as unexplained chronic cough, chest pain, or breathing difficulties (including exertional dyspnea and shortness of breath).

not yet exhibit any signs or symptoms of TSC and also can help guide testing for family members. Knowledge of the specific gene mutation can also help family members determine if the cause is a sporadic or familial inherited gene.[6] Genetic testing is also useful for family planning.[13] When evaluating a family history for the disease, the closest three generations to the patient should be screened with the diagnostic criteria. Genetic counseling should be recommended to all TSC patients and their families.[14]

TREATMENT AND FOLLOW-UP

Treatment guidelines for TSC can be found in **Table 2**. A multispecialty approach, with neurologists, pediatricians, dermatologists, ophthalmologists, internists, cardiologists, dental specialists, and psychiatrists working together, is needed to control and treat symptoms.[5] Patients should follow up regularly with these specialists to monitor for symptoms.

Anticonvulsants can be used to control seizures; the specific drug used depends on the type of seizure the patient

is having, patient age, and possible adverse reactions. These drugs have many potential adverse reactions and should be prescribed and monitored by a clinician well versed in the use of anticonvulsants.

More specifically, vigabatrin was approved in 2009 to treat infantile spasms in patients ages 1 month to 2 years and should be used as first-line therapy for patients with this seizure type.[5,15] Corticotrophin injection gel also has been approved and should be used as second-line therapy.[5,15] In some instances, multiple anticonvulsants may be necessary, or surgery may be required to control seizures that are not controlled by medications. Neurosurgical input may be needed for patients with hydrocephalus and mass lesion.

Everolimus, an mTOR inhibitor, can be used to treat subependymal giant cell astrocytomas and renal angiomyolipomas.[5] The medication is FDA-approved for treating TSC-related subependymal giant cell tumors in adults and children. Everolimus and surgical resection are the two main treatments for TSC-related subependymal giant cell tumors, with the selection of treatment based on patient circumstances. Common adverse reactions associated with everolimus include stomatitis, diarrhea, vomiting, nasopharyngitis, upper respiratory infections, pyrexia, cough, and rash.[16,17] Angiomyolipomas and renal cysts may need to be treated or removed surgically in some cases. Arterial embolization can be used to cut off the blood supply and shrink the tumor before it is removed or ablated.[5]

Rhabdomyomas may only need to be treated if they are causing symptoms, but should be frequently monitored. In some cases, they can be treated with mTOR inhibitors, such as everolimus. Antiarrhythmics also can be used for these tumors.[5]

Patients taking mTOR inhibitors for angiomyolipomas or SEGAs may notice improvement in skin lesions. Topical mTOR inhibitors can treat facial angiofibromas. Otherwise, treatment of facial angiofibromas is mainly cosmetic, and can be handled with laser, dermabrasion, or surgical removal.[5,17]

mTOR inhibitors also are approved to treat LAM. Theories that mTOR inhibitors have a connection with female hormones have not been proven; however, clinicians should consider discontinuing estrogen-containing products in patients with LAM, because estrogen may have negative effects on LAM.[5,17] Oxygen therapy and bronchodilators also can be used to help treat symptoms in patients with impaired lung function.[5,17]

CONCLUSION

TSC is a rare autosomal-dominant genetic disorder affecting multiple organ systems and can be debilitating if not diagnosed early and treated symptomatically. Clinicians need to be aware of the findings and symptoms that can accompany TSC in order to arrive at a timely diagnosis. Ultimately, treatment of TSC requires a team of clinicians monitoring for disease-related complications and symptoms; however, early detection and management can improve the outcome of patients with this rare disease. **JAAPA**

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