Tuberous sclerosis complex (TSC) is an autosomal dominant disorder in which benign tumors develop in various organ systems, including the kidney (angiomyolipomas and cysts), brain (subependymal giant cell astrocytomas [SEGAs] and epipto- genic tubers), skin (facial angiofibromas), lung (lymphangioliomyomatosis [LAM]), heart (rhabdomyomas), and retina. Although benign, all TSC tumors have the potential to severely affect organ function; for example, lesions in the brain are associated with hydrocephalus, seizures, mental retardation, and autism. TSC has an estimated incidence of 1 in 5,800 births and a global prevalence approaching 1 million individuals.

HISTORICAL OVERVIEW OF THE EVOLVING CHARACTERIZATION AND UNDERSTANDING OF TSC

The first clinical observation of a patient with TSC was published during the 19th century, in which an infant who died several days after birth was described as having cardiac rhabdomyomas and sclerotic brain lesions. In the late 1880s, the French neurologist Désiré Bourneville described a patient with neurologic symptoms and brain lesions resembling “hard potatoes” or “tubers.” A few years later, the Scottish dermatologist John Pringle gave the first English description of facial angiofibromas as “adenoma seba- ceum.” Accordingly, the disease was called “adenoma sebaceous,” “Bourneville’s disease,” “Pringle’s disease,” or “Bourneville-Pringle disease” in different countries. Around 1900, it was recognized that epilepsy, cognitive retardation, and facial angiofibroma are manifestations of the same disease. Subsequently, other manifestations involving the kidneys, eyes, heart, and lungs were discovered. To better describe the complex and variable disease manifestations, the disease later was called TSC. TSC was recognized as having a hereditary component as early as 1913, although the genes responsible, TSC1 (chromosome 9q) and TSC2 (chromosome 16p), were not identified until much later. Interestingly, a contiguous gene defect of a family with TSC and polycystic kidney disease helped identify the first gene for adult polycystic kidney disease (PKD1).

It was not until the last 25 years of major advances in molecular biology and genetics that the pathophysiologic process underlying TSC was elucidated. Both TSC1 and TSC2 are tumor suppressor genes, requiring a second “hit” in addition to a germline mutation to inactivate both alleles of either gene for tumor development. Approximately 70%-80% of patients with TSC have no family history and presumably have...
sporadic mutations.\textsuperscript{9} \textit{TSC2} mutations are more common than \textit{TSC1} mutations and are associated with a more severe phenotype.\textsuperscript{10} Both mutations are autosomal dominant and have a penetrance of almost 100\%,\textsuperscript{11} meaning that all affected individuals eventually will develop symptoms of the disease. However, individuals present with a large variability in disease burden and symptoms. Knowledge of the complex molecular pathophysiologic process underlying TSC is assisting our efforts to better understand this phenomenon.

By 2003, the role of the \textit{TSC1} gene product hamartin and the \textit{TSC2} gene product tuberin in regulating the mammalian target of rapamycin (mTOR) pathway was becoming well described.\textsuperscript{12} Hamartin and tuberin form a complex to inhibit mTOR through inactivation of Rheb, a homolog of the signal transduction protein Ras.\textsuperscript{13} mTOR can form one of 2 complexes: the rapamycin-sensitive mTOR complex 1 or the rapamycin-insensitive mTOR complex 2.\textsuperscript{14} The mTOR pathway through mTOR complex 1 has a key role in regulating protein production while influencing cell growth, cell proliferation, and angiogenesis (Fig 1).\textsuperscript{15-17} In addition, Notch, a signaling protein that keeps cells in an undifferentiated proliferative state, is inactivated by the TSC complex.\textsuperscript{18,19}

In physiologically normal cells, Akt-mediated inactivation of tuberin results in proteosomal degradation of the hamartin/tuberin complex, thereby permitting mTOR signaling.\textsuperscript{20,21} In patients with TSC, the second unaffected \textit{TSC} allele can be sufficient for maintaining normal function despite the underlying germline mutation. However, if the unaffected \textit{TSC} allele is hit by a second mutation during the patient’s lifetime, the result is loss of adequate functioning gene product. Thus, mutations in either \textit{TSC1} or \textit{TSC2} that result in loss of hamartin or tuberin, respectively, allow for an unregulated increase in mTOR activity.\textsuperscript{2,20} Evidence of this increased mTOR activation has been observed in TSC patient–derived cell lines and tumors.\textsuperscript{22,23} It is hypothesized that this dysregulated mTOR signaling increases tumor cell growth, proliferation, and metabolism, thus promoting the progression of TSC lesions.

**CLINICAL PRESENTATION AND DIAGNOSIS OF TSC**

Examining the pathophysiologic characteristics of the genetic TSC defect, it becomes clear that the same germline mutation may result in a highly variable phenotype, depending on the time and location of the second-hit mutation. As a consequence, the clinical presentation of TSC is highly variable (Table 1), with a wide diversity of symptoms across patients.\textsuperscript{3,4} Thus, some patients are severely mentally disabled due to the development of SEGAs or tubers, resulting in variable degrees of seizures or hydrocephalus, depending on the developmental timing and site of the mutation. Others have no signs of cerebral manifestations and have completely normal mental status.\textsuperscript{26} Others have retinal or cardiac hamartomas; facial angiofibromas, which can be very discrete and do not always have a typical presentation\textsuperscript{27}; other types of skin tumors (including Koenen tumors, confetti skin lesions, and gingival fibromas [Fig 2]); lung involvement; or frequently, angiomyolipomas in the kidneys. Diagnostic tests thus should include dermatologic, neurologic, and ocular examination; echocardiogram; computed tomography/magnetic resonance imaging (MRI) or ultrasound of the kidneys, lungs, and brain; and, if needed, pulmonary function tests.\textsuperscript{3,26}

Currently, diagnosis of TSC is based on clinical observations because it is simple and highly reliable. The clinical diagnostic criteria for TSC are divided
into major and minor features (Box 1). At least 2 major features or 1 major feature and 2 minor features are required for a definite diagnosis; patients with 1 major and 1 minor feature have a probable diagnosis, and those with 1 major or 2 minor features have a possible diagnosis. Molecular genetic testing of the TSC1 and TSC2 genes is available, but is not recommended as a diagnostic tool for all patients with TSC because of the complexity introduced by the large size of the 2 genes, the wide variety of mutations, and the

<table>
<thead>
<tr>
<th>Affected System and Lesion</th>
<th>Characteristics</th>
<th>Incidence $^{3,24,25}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Lesions include hypopigmented macules, ungual fibromas, facial angiofibromas</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Renal</td>
<td>Composed of abnormal blood vessels, smooth muscle cells, adipocytes</td>
<td>55%-75%</td>
</tr>
<tr>
<td>Angiomyolipoma</td>
<td>Associated with spontaneous life-threatening hemorrhage as a result of aneurysms forming in the abnormal vasculature</td>
<td></td>
</tr>
<tr>
<td>Epithelial cysts</td>
<td>Generally asymptomatic but associated with hypertension and kidney failure</td>
<td>45%</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>Incidence similar to general population but affects patients at a younger age</td>
<td>2%-3%</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Diffuse proliferation of abnormal smooth muscle cells and cystic changes in lung</td>
<td>26%-39%</td>
</tr>
<tr>
<td>Lymphangioleiomyomatosis</td>
<td>Affects women almost exclusively</td>
<td></td>
</tr>
<tr>
<td>Neurologic</td>
<td>All seizure subtypes have been observed, often refractory to medical treatment</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>Cortical tubers</td>
<td>Growth can result in cognitive disability and neurobehavioral disabilities</td>
<td>70%-80%</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Cortical tubers often found in same region in which seizures originate</td>
<td></td>
</tr>
<tr>
<td>Subependymal giant cell</td>
<td>Often protrude into ventricles of the brain</td>
<td>10%-20%</td>
</tr>
<tr>
<td>Paleomicrophalystomas</td>
<td>Can cause obstruction of cerebrospinal fluid flow, hydrocephalus, increased intracranial pressure, death</td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td>Develop within the cardiac cavities prenatally and regress spontaneously with age</td>
<td>50%-70%</td>
</tr>
<tr>
<td>Rhabdomyomas</td>
<td>Associated with cardiac arrhythmias</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. Images of notable dermatologic lesions associated with tuberous sclerosis complex. Facial angiofibromas, (A) mild, (B) intermediate, and (C) severe; (D) hypomelanotic macule >3 cm; periungual fibromas (Koenen tumors), (E) mild and (F) severe; (G) gingival fibromas and multiple dental enamel pits; (H) confetti skin lesions; (I) shagreen patch; (J) skin tags; (K) soft fibromas; and (L) forehead fibrous plaque. Panel I: ©Elsevier, Inc. ElsevierImages.com.
For example, the presence of cardiac rhabdomyomas is useful in confirming the diagnosis. However, in young patients with vague clinical features suggestive of TSC, identification of a genetic diagnosis may not confirm or rule out TSC in some cases.

**Box 1. Diagnostic Criteria for Tuberous Sclerosis Complex**

**Major Criteria**
- Facial angiofibroma (infancy to adulthood)
- Ungual fibroma (adolescence to adulthood)
- Shagreen patch (childhood)
- Hypomelanotic macule (infancy to childhood)
- Cortical tuber (fetal life)
- Subependymal nodule (childhood to adolescence)
- Subependymal giant cell tumor (childhood to adolescence)
- Retinal hamartoma (infancy)
- Cardiac rhabdomyoma (fetal life)
- Renal angiomyolipoma (childhood to adulthood)
- Lymphangioleiomyomatosis (adolescence to adulthood)

**Minor Criteria**
- Multiple pits in dental enamel
- Hamartomatous rectal polyps
- Bone cysts
- Cerebral white-matter radial migration lines
- Gingival fibromas
- Retinal achromic patch
- "Confetti" skin lesions, ie, groups of small, lightly pigmented spots
- Multiple renal cysts

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**Note:** When available, age of onset is indicated in parentheses.

Two major features or 1 major feature plus 2 minor features are required for a definite diagnosis of tuberous sclerosis complex (TSC); for a probable diagnosis of TSC, 1 major and 1 minor feature are required; for a possible diagnosis of TSC, 1 major or 2 or more minor features are needed. Cerebral cortical dysplasia and cerebral white-matter radial migration lines are counted together as 1 feature of TSC; when both lymphangioleiomyomatosis and renal angiomyolipomas are present, other features of tuberous sclerosis must be present before TSC is diagnosed. Data were modified from Roach et al.

In addition to major diagnostic features, minor features affect the teeth (dental pits), gums (gingival fibroma), digestive tract (hamartomatous rectal polyps), blood vessels (aneurysms), and bony skeleton (bone cysts or sclerosis). Data are not available to list typical age at onset.

**KIDNEY LESIONS**

From the nephrologist’s perspective, clinical presentation may be characterized by the presence of angiomyolipomas or cysts in the kidneys, as well as evidence of mental disability or dermatologic features (eg, facial angiofibromas or gingival fibromas). However, sporadic asymptomatic angiomyolipomas found on routine ultrasound or computed tomography/MRI are not necessarily a defining diagnostic feature of TSC in the absence of other characteristics. Because nearly all patients with TSC have some form of angiomyolipoma or neurologic involvement, a complete medical history and physical examination of patients with angiomyolipomas should be used to rule out or confirm a diagnosis of TSC. Only in rare cases are additional diagnostics needed.

Cysts in the kidneys are common in patients with TSC, occurring in 30%-34. Although cysts rarely cause symptoms, they can compromise kidney function and often are associated with kidney failure and hypertension. Some patients with TSC have a contiguous deletion of regions in both the TSC2 gene and PKD1 gene, resulting in a more severe degree of kidney cysts. Renal cell carcinomas (RCCs), including clear cell, chromophobe, and papillary types, also occur in patients with TSC. The risk of RCC in patients with TSC is similar to that in the general population (2%-3% lifetime risk); however, RCC typically is diagnosed in patients with TSC in their 30s, whereas RCC typically is diagnosed in the general population in their 50s or 60s. Angiomyolipomas commonly occur in up to 80% of patients with TSC and represent the most common cause of TSC-related mortality in adults. Angiomyolipomas manifest as multiple and bilateral benign kidney tumors that are rich in blood vessels, adipose tissue, and smooth muscle. Histologically, angiomyolipomas can be divided into 2 variants: (1) a classic form containing abnormal vascular smooth muscle that may show atypical nuclei and mitotic figures and adipose tissue and (2) an epithelioid form with a large component of epithelioid cells that may be atypical or variable in size and have significant mitotic activity. Although angiomyolipomas exhibit cells with atypical nuclei with high mitotic activity, these lesions are not malignant. Although often asymptomatic, angiomyolipomas can be associated with life-threatening hemorrhage as a result of aneurysms forming in the abnormal vasculature. Patients with angiomyolipomas >4 cm in diameter have a higher risk of hemorrhage. Furthermore, although benign, larger angiomyolipomas may compress normal kidney tissue or encroach into normal tissue, with the potential to culminate in kidney failure.
In addition to the impact of angiomyolipomas on the kidneys, angiomyolipomas are hypothesized to underlie the pathogenesis of LAM, a devastating pulmonary disease occurring exclusively in women that results from smooth muscle cell proliferation in the lungs and leads to interstitial lung disease, cystic lung destruction, recurrent spontaneous pneumothorax, and chylous effusions. Approximately 60% of patients with sporadic LAM also have kidney angiomyolipomas. Somatic mutations in TSC2 were found in both LAM patient-derived angiomyolipomas and LAM tissues, supporting a direct role of TSC2 in LAM pathogenesis. Moreover, in 4 patients for whom both tissues were available, the same TSC2 mutation was found in both LAM and angiomyolipomas but not normal kidney or lung, suggesting that the tumor cells were genetically identical and arose from a common progenitor. This led Carsillo et al to propose a “benign metastasis” model for LAM pathogenesis in which angiomyolipomas cells migrate from the kidneys and metastasize to the lungs. This model was supported by an analysis of a patient with recurrent LAM after a lung transplant, in which the same TSC2 mutation was present in both the original LAM cells and the recurrent LAM cells after the lung transplant, suggesting that the recurrent LAM was derived from the patient.

**TREATMENT OPTIONS FOR ANGIOMYOLIPOMAS**

Current management strategies for angiomyolipomas emphasize the importance of monitoring angiomyolipoma growth, preferably by ultrasound or MRI. Historically, the primary treatment modalities for patients with TSC-associated angiomyolipomas have included angiographic catheter embolization and surgery. Angiomyolipomas >4 cm in diameter are at risk of bleeding and should be treated by embolization or, if embolization is impossible, nephron-sparing resection. Not all angiomyolipomas can be resected or embolized easily, especially if multiple lesions are present and have encroached on normal tissue, because any surgery or embolization may lead to the loss of healthy nephrons and compromise kidney function. Finally, new angiomyolipomas may develop after local treatment in other places. It is important to note that in an emergency setting with a life-threatening bleed, especially in the case of very large angiomyolipomas, the lesion may be mistaken intraoperatively for RCC and therefore incorrectly result in total nephrectomy surgery. In the event of repeated severe life-threatening bleeding, definitive treatment with nephrectomy and kidney transplant may be considered. These methods treat only the manifestations of kidney angiomyolipomas; however, there currently...
are no approved systemic therapies to treat the principal biochemical abnormality (ie, unregulated mTOR activation) caused by the mutations in TSC-associated angiomyolipomas.

Newer systemic treatment options that directly target mTOR currently are under investigation. In preclinical studies, mTOR inhibitors have been shown to decrease the phosphorylation of downstream effectors of mTOR, resulting in decreased DNA synthesis and cellular proliferation in TSC patient-derived tumor cell lines, including angiomyolipomas (Fig 1).22,42 In a mouse model of TSC in which cystadenomas spontaneously develop in the kidneys, mTOR inhibition significantly decreased tumor burden and kidney cyst severity and improved overall survival.43

Initial observations have noted clinical improvement in patients with angiomyolipomas treated with the mTOR inhibitor sirolimus.44,45 In a patient case study of a 38-year-old woman with TSC and large bilateral angiomyolipomas, a dramatic decrease in angiomyolipoma volume was seen after 1 year of sirolimus treatment and persisted 6 months after the 2-year treatment course. Moreover, a substantial size reduction of both kidneys occurred during the first year of treatment.44 Consistent with this finding, a multicenter phase 2 study conducted in the United Kingdom (TESSTAL [Trial of Efficacy and Safety of Sirolimus in Tuberous Sclerosis and LAM]; ClinicalTrials.gov identifier NCT00490789) in 16 patients with TSC- or LAM-associated angiomyolipomas showed decreases in angiomyolipomas with sirolimus treatment (mean decrease in the longest diameter at 12 months, 25%) and an overall response rate of 50%.46 Treatment-related adverse events were mostly mild and included mouth ulcers, infections, metabolic abnormalities, fatigue, and peripheral edema.46 In addition, a number of case reports describe improvements in symptoms with sirolimus treatment, including regression of facial angiofibroma,47 LAM,45,48 and SEGA.49,50

A 24-month phase 1/2 open-label study by Bissler et al45 evaluated the potential of sirolimus to decrease angiomyolipoma volume in 25 patients with TSC or sporadic LAM. Sirolimus was administered for the first 12 months of the study. Angiomyolipoma volume decreased by a mean of 53.2% ($P < 0.001$) from baseline to month 12; 80% (16/20) of evaluable patients experienced a ≥30% decrease in angiomyolipoma volume (Fig 4).45 Mean angiomyolipoma volume increased after sirolimus therapy was stopped, yet remained significantly less than baseline volume; 6 months after the end of sirolimus treatment, mean volume had reached 76.8% of its baseline value ($P < 0.001$), and at 24 months, it was 85.9% of baseline ($P = 0.005$).45 The most common adverse events were stomatitis (aphthous ulcers or mucositis; n = 22), diarrhea (n = 12), and upper respiratory tract infections (n = 18); 6 of 10 serious adverse events were considered possibly related to or worsened by sirolimus (diarrhea with dehydration, community-acquired pneumonia, pyelonephritis, cellulitis, stomatitis, and one case of angiomyolipomas-related hemorrhage that occurred 2 days after the start of sirolimus treatment).45

A phase 2 study described the successful treatment of SEGAs with the mTOR inhibitor everolimus.49 In this open-label study, 28 patients (mostly children; median age, 11 years) with growing SEGAs were treated with low doses of everolimus (median trough levels, 4.2 ng/mL at 3 months and 5.0 ng/mL at 6 months). Within 6 months of treatment, a clinically meaningful decrease in SEGAs was noted in 75% of patients, accompanied by a significant decrease in neurologic symptoms, such as seizures. The convincing...
ing results of this small phase 2 study led to US Food and Drug Administration approval of everolimus in TSC patients with SEGAs that cannot be treated with surgery. The phase 3 EXIST-1 (Examining Everolimus in a Study of TSC; NCT00789828) currently is evaluating the response rate of TSC-associated SEGAs to everolimus therapy more thoroughly.

Based on these promising results, additional clinical trials are investigating the efficacy of sirolimus and everolimus in patients with TSC-associated angiomyolipomas. Currently ongoing clinical trials include an open-label phase 1/2 trial of everolimus (RAD001 Therapy of Angiomyolipomata in Patients With TSC and Sporadic LAM; NCT00457964) and an open-label phase 2 study of sirolimus (Sirolimus in Treating Patients With Angiomyolipoma of the Kidney; NCT00126672) in patients with TSC- or LAM-associated angiomyolipomas. In addition, the phase 3 EXIST-2 (NCT00790400) trial is a randomized double-blind placebo-controlled study of everolimus in 99 patients with TSC- or LAM-associated angiomyolipomas. The primary end point is angiomyolipoma response rate. Because accumulating evidence collectively supports the ability of mTOR inhibitors to reduce or stabilize other TSC-associated conditions, secondary and exploratory end points of EXIST-2 include changes in other TSC-associated lesions (eg, SEGAs volume and skin lesions), neuropsychological assessments, and cognitive function, seizure severity, and pulmonary function analyses.

CONCLUSIONS

Although the clinical presentation of TSC is highly variable, the diagnosis can be relatively straightforward when guided by clinical observation and medical history, except in a few atypical cases. Nephrologists should carefully screen patients who present with angiomyolipomas or kidney cysts plus evidence of neurologic compromise or characteristic dermatologic features for TSC. Current treatment options, surgery and angiographic catheter embolization, are focused on conserving kidney function and limiting the risk of potentially fatal hemorrhage. mTOR inhibitors have shown promise as a new type of therapy for reducing the size of TSC-associated angiomyolipomas and represent the first systemic therapeutic approach to treat the underlying cause of TSC (ie, targeting unregulated mTOR activation). Results from currently ongoing phase 2/3 clinical trials of the mTOR inhibitors sirolimus and everolimus in patients with TSC- or LAM-associated angiomyolipomas will continue to define the treatment landscape for this patient population.

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