

## Renal angiomyolipomata

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**Renal angiomyolipomata.** Renal angiomyolipomata can exist as an imaging curiosity or represent a life-threatening condition. There are likely over 10 million people world-wide who have a renal angiomyolipomata and approximately one tenth of these people also have tuberous sclerosis complex. The optimum treatment of angiomyolipomata is focused on sparing renal tissue and has included no intervention, both total and partial nephrectomy, and embolization. As basic science investigation into the biology of angiomyolipomata progresses, there is even hope for successful drug therapy. Because these renal lesions can be associated with other organ system dysfunction, a number of medical specialists become involved in the care of affected patients. The purpose of this article is to update the nephrologist on the molecular understanding of renal angiomyolipomata and for the possibilities of pharmacologic therapy in the future.

Renal angiomyolipomata exhibit an extremely broad disease spectrum, from merely an imaging curiosity to a life-threatening condition. Using the estimated world population of over six billion individuals [1], the gender distribution and frequency of angiomyolipomata [2], there are over 10 million people world-wide with renal angiomyolipomata and approximately one tenth of these also have tuberous sclerosis complex. The optimum treatment of angiomyolipomata has logically focused on sparing renal tissue. It has included no intervention, both total and partial nephrectomy, and embolization. As basic science investigation into the biology of angiomyolipomata progresses, there is even hope for successful drug therapy, at least in tuberous sclerosis complex and lymphangiomyomatosis. Because these renal lesions can be associated with other organ system dysfunction, a number of medical specialists become involved in the care of affected patients. The purpose of this article is to update the nephrologist on the clinical and pathologic features of

this lesion, with special emphasis on the molecular understanding of renal angiomyolipomata in tuberous sclerosis and lymphangiomyomatosis. Recent basic science discoveries in these diseases offer hope for pharmacologic therapy in the future.

### DISEASE FREQUENCY AND ASSOCIATED CONDITIONS

Grawitz [3], in 1900, first used the term renal angiomyolipoma to describe a large renal tumor comprised of fat, muscle, and blood vessels. In a study of 8501 autopsies in which there were no stigmata of tuberous sclerosis complex recognized, Hajdu and Foote [4] found two males and 25 females with angiomyolipomata, resulting in frequencies of 0.02% and 0.29% of the total population, respectively. These data compare favorably to the imaging studies by Fujii et al [2] involving 12,970 male and 4971 female Japanese that identified angiomyolipomata in 13 (0.1%) males and 11 (0.22%) females. The difference in frequency in males in these two studies likely reflects the small numbers of males in each. The consistent increased frequency in females may be due in part to hormonal differences. Angiomyolipomata often express receptors for both estrogen and progesterone [5].

### ASSOCIATED CONDITIONS

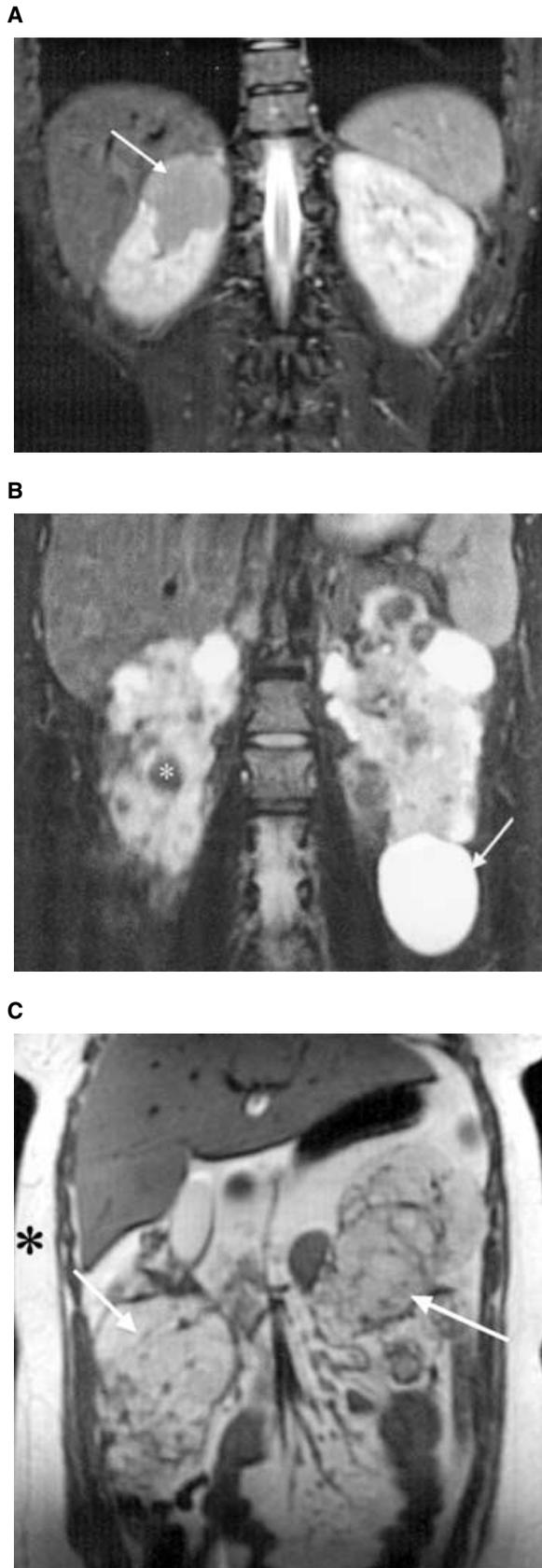
Although often found incidentally, renal angiomyolipomata can be associated with two conditions affecting other organ systems: tuberous sclerosis complex (TSC) and sporadic lymphangiomyomatosis (LAM). This review focuses on the angiomyolipomata in these diseases. Twenty years after Bourneville [6] described TSC, he and Brissaud [7] noted renal angiomyolipoma in patients with TSC. TSC actually has three renal phenotypes, including angiomyolipomata, cysts, and carcinoma. These lesions may occur individually or coexist (Fig. 1). Growth of angiomyolipomata in patients with TSC is often first detected during childhood [8] and continues into adulthood [9, 10]. An autopsy study found that 67% of TSC patients have angiomyolipomata [11]. The frequency of

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**Key words:** angiomyolipomata, tuberous sclerosis complex, lymphangiomyomatosis, oncocytoma, epithelioid, PEComa.

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angiomyolipoma varies with the age of the population being studied; the frequency is higher in older subjects.

There are two morbidities associated with renal angiomyolipomata. The first and more dramatic is Wunderlich syndrome [12], retroperitoneal hemorrhage originating in the angiomyolipoma. Angiomyolipomata, as they enlarge, frequently develop both micro- and macroaneurysms which can rupture [13, 14]. Patients with this sudden, painful, and often life-threatening event are most often first seen in the emergency department. Up to 20% of patients with such hemorrhages present in shock [15]. With such a presentation, the treatment may be a total nephrectomy. This approach complicates the patient's long-term care. Angiomyolipomata associated with TSC are bilateral and a nephrectomy would result in a significant loss of functional renal tissue, thus hastening the need for renal replacement therapy. The risk of hemorrhage from renal angiomyolipomata has been reported to be between 25% and 50% [16]. A population study suggests that the cumulative risk of a hemorrhage is 18% for females and 8% for males [17]. However, among a clinic population of approximately 310 adult and pediatric tuberous sclerosis complex patients in Cincinnati, we have seen only nine cases of hemorrhage (~3%). This difference may be, at least in part, due to our aggressive embolization program, population age differences or length of follow-up. Although angiomyolipomata appear to grow over time, and there is an association between lesion size and hemorrhage [10, 18], bleeding is in fact much more strongly associated with aneurysm formation [19]. This, in part, explains why modest lesions and young patients can still have substantial hemorrhages. The likely scenario is that the larger aneurysms rupture and decompress into the retroperitoneal space or renal pelvis (Fig. 2).

The second morbidity of renal angiomyolipomata is the insidious encroachment of the angiomyolipoma on normal renal tissue, which may lead to renal failure [20, 21]. The precise incidence of end-stage renal disease (ESRD) in the tuberous sclerosis population has not been well defined, but European surveys suggest that approximately 1% of the TSC patient population with normal intellect is receiving dialytic renal replacement therapy [20, 21], leading to an estimate that over 30,000 TSC patients are

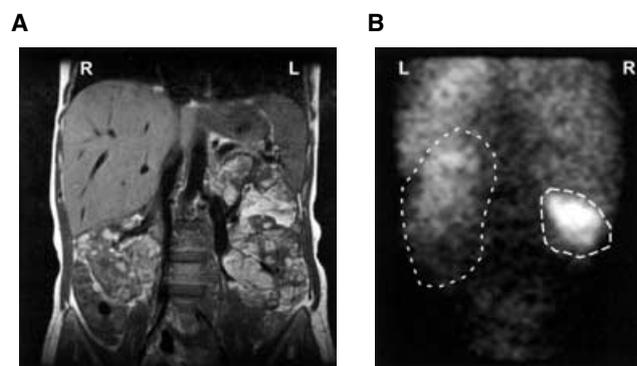
**Fig. 1. Magnetic resonance (MR) imaging of the renal lesions of three adult tuberous sclerosis complex (TSC) patients.** (A) Fast spin echo inversion recovery image demonstrates the lesion in the upper pole of the right kidney by the contrast with the normal kidney. (B) Fast spin echo T2-weighted image demonstrating the bright signal intensity of lesions compatible with a cyst (see arrow) and dark signal intensity lesion compatible with fat (asterisk). Both cystic and angiomyolipomata can be identified in both kidneys. (C) T1-weighted image with two lesions with increased signal intensity (arrows) similar to subcutaneous fat (asterisk), compatible with large angiomyolipoma.



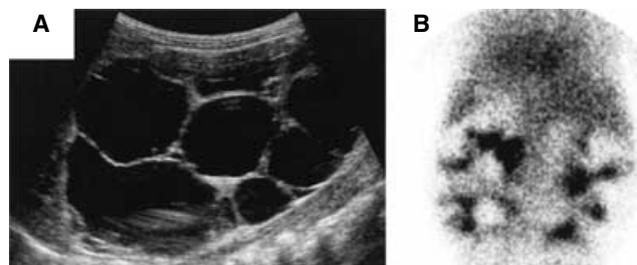
**Fig. 2. Angiography of the right kidney revealing angiomyolipoma of the upper pole with aneurysms.** The largest is marked with the arrow.

on dialysis worldwide. Shepherd et al [22] examined death certificates for patients in their TSC clinic and found that of 355 patients, 40 died as a result of their TSC, most commonly due to renal failure. These studies are helpful to understand the scope of disease, though the actual number of patients with renal insufficiency and comorbidities is unknown. The percentage of TSC patients developing ESRD because of polycystic kidney disease, multiple interventions for hemorrhage, or replacement of renal tissue by angiomyolipomata is unclear. Renal function is often normal even in patients with apparently bilateral confluent angiomyolipomata. Kidneys with a large angiomyolipoma burden can still contribute significantly to total renal function and the decision to undergo a nephrectomy should be carefully balanced against the loss of function (Fig. 3).

Approximately 35% of patients with TSC will have renal cysts [23]. Although these lesions may be large, they usually are not numerous and rarely cause problems. One exception is the polycystic kidney disease phenotype, or disease manifestation, of TSC, in which patients are at risk for the same morbidities as patients with autosomal polycystic kidney disease (Fig. 4). This phenotype is due to joint disruption of the *TSC2* gene and the very closely adjacent *PKD1* gene resulting in both TSC and polycystic kidney disease [24, 25]. Even patients with the polycystic phenotype can develop angiomyolipomata.



**Fig. 3. Demonstration of preserved function despite large angiomyolipoma burden in an adult.** (A) Magnetic resonance imaging (MRI) scan demonstrating significant involvement in the both kidneys. (B) Despite a large angiomyolipoma burden, the  $^{99m}\text{Tc}$ -diethylene-triamine pentaacetic acid ( $^{99m}\text{Tc}$ -DTPA) scan demonstrates function in both kidneys. The glomerular filtration rate for this patient was approximately  $95 \text{ mL/min/1.73 m}^2$ , and the right kidney contributed 44% of the total function. The functional kidney tissue is circled using a dotted line.

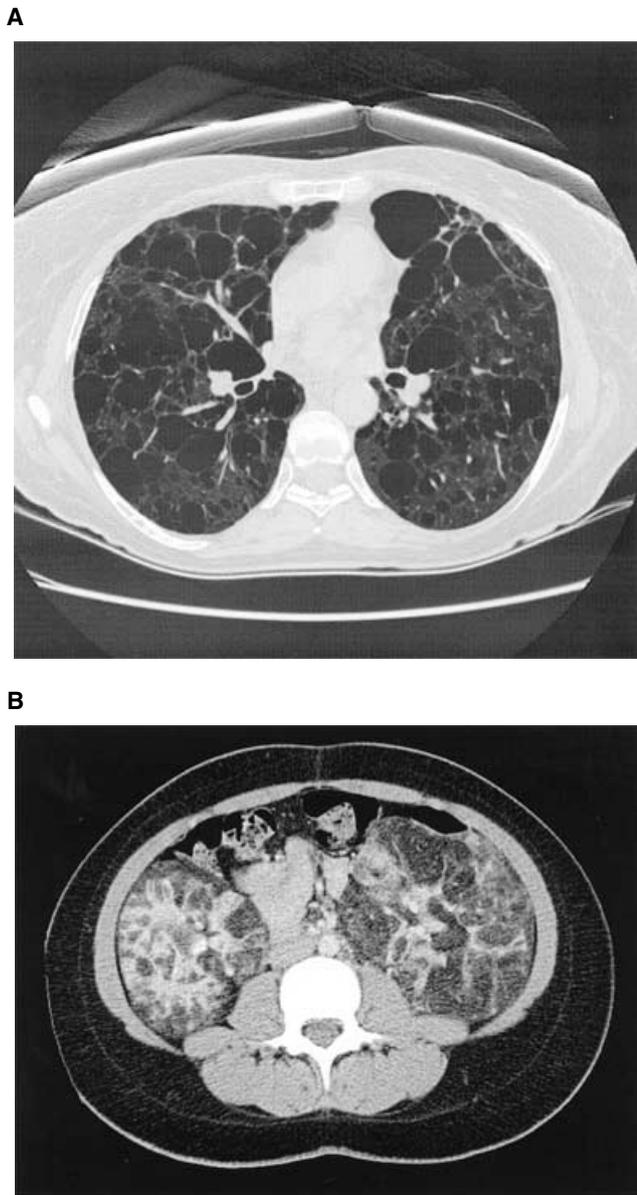


**Fig. 4. Polycystic renal variety of tuberous sclerosis complex (TSC) in a child.** (A) Renal ultrasound revealing significant polycystic disease. (B) Renal scan revealing functional renal tissue between the cysts. The child had a normal glomerular filtration rate and well-controlled hypertension.

Angiomyolipomata are also associated with LAM (Fig. 5), a disease involving the pulmonary interstitium which occurs almost exclusively in young females [26], though its presence in a male has been reported [27]. Approximately 40% of female patients with TSC also develop a cystic pulmonary disease consistent with LAM [28–30]. However, the disease progression may be different from the sporadic form of the disease and only approximately 1% of women with TSC develop clinical symptoms [31].

LAM also occurs in patients without TSC (denoted as sporadic LAM). This sporadic form is rare, less than 1000 affected women have been identified world-wide [32], and 60% of these patients also have an angiomyolipoma [11]. The angiomyolipoma histopathologic features seen in sporadic LAM are identical with those found in TSC [33].

Both TSC associated and sporadic LAM is characterized by smooth muscle infiltration into the walls of the alveoli and small airways. This can lead to cystic



**Fig. 5. Utility of computed tomography (CT) in lymphangiomyomatosis (LAM).** (A) High resolution CT scan revealing cystic parenchymal changes of LAM. (B) Renal CT scan demonstrating multiple lesions of  $-15$  to  $-100$  Hounsfield units, characteristic of fat.

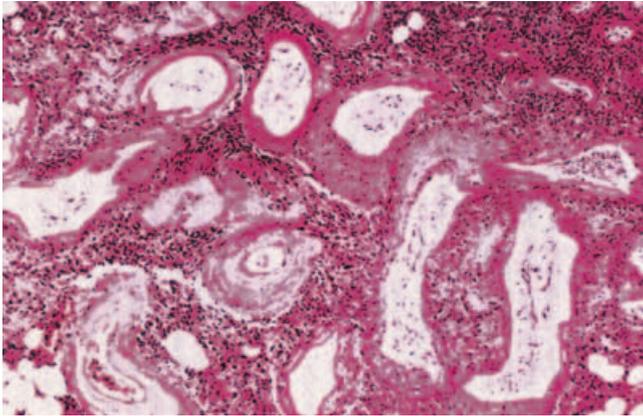
degeneration of lung tissue, impaired gas exchange, respiratory failure, and death. Progressive symptomatic lung disease may occur in patients diagnosed with sporadic LAM and such progression likewise would be predicted to occur in women with TSC-associated LAM. There is recent evidence that LAM may be caused by metastases of angiomyolipoma cells to the lung [34, 35]. These cells express estrogen receptors [36], and this finding has been used to help explain the gender bias in sporadic LAM as well as a rationale for a therapeutic trial of progesterone [37].

## CLASSIFICATION OF RENAL ANGIOMYOLIPOMATA

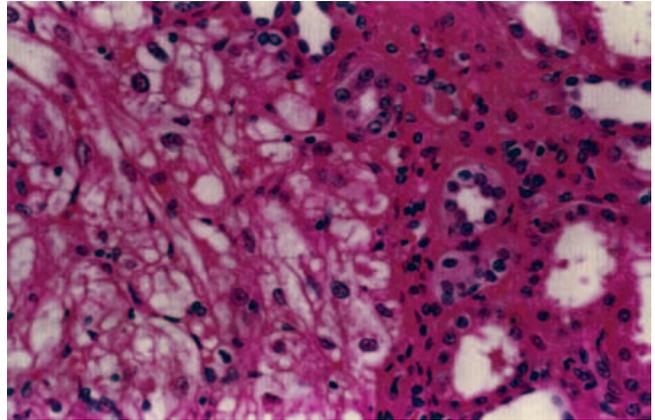
Angiomyolipomata were originally thought by Fischer [38] to be an abnormal proliferation of the tissues that are normally present in the kidney, and hence, he classified them as hamartomata. Dickinson et al [18] noted that fat and smooth muscle are not normally found in the renal parenchyma, and classified angiomyolipomata as choristomata. As basic science investigation has better defined these lesions, angiomyolipomata are best classified as neoplasia. This classification is supported by the finding that these lesions arise from clonal expansion based on nonrandom X chromosome inactivation [39] and exhibit lymph node invasion [40, 41]. The perivascular epithelioid cell has been implicated as the progenitor for a family of neoplasms, including angiomyolipoma, lymphangiomyoma, and clear cell tumors of the lung and pancreas [42, 43]. These cells have been proposed to differentiate into spindle-shaped cells with features of adipose, smooth muscle, and eosinophilic and clear epithelioid cells. A feature of these perivascular epithelioid cell-derived lesions is HMB-45 immunoreactivity; the spindle and epithelioid cells often stain with anti-smooth muscle actin while the fat cells stain with S-100 antibodies. While most often described in the kidneys, angiomyolipomata also have been identified in the liver [44], ovary [45], fallopian tube [46], spermatic cord [47], palate [48], and colon [49].

There are two basic types of angiomyolipoma. The classic form contains vascular, smooth muscle, and adipose tissue (Fig. 6). The contribution of each of these components can vary from lesion to lesion in the same kidney. The vascular component may be scant or may dominate the lesion [50]. Five different types of vessels within angiomyolipomata have recently been recognized [51], some of which are deficient in elastic fibers [52]. The smooth muscle component can be limited to a small amount cuffing the vasculature [53], or may be so extensive that imaging detects a solid mass devoid of fat [54]. In classic angiomyolipomata, there can be patches of smooth muscle cells that exhibit nuclear atypia with mitotic figures; despite these findings, such lesions typically do not behave as a malignant lesion. There are only a few case reports of sarcoma arising from an angiomyolipoma, which has been termed malignant angiomyolipoma [55, 56]. Like the smooth muscle and vascular component, the adipose element of angiomyolipomata can be variable. Most often the fat component is made up of mature fat tissue. Very rarely, renal angiomyolipomata can infiltrate surrounding tissue [57].

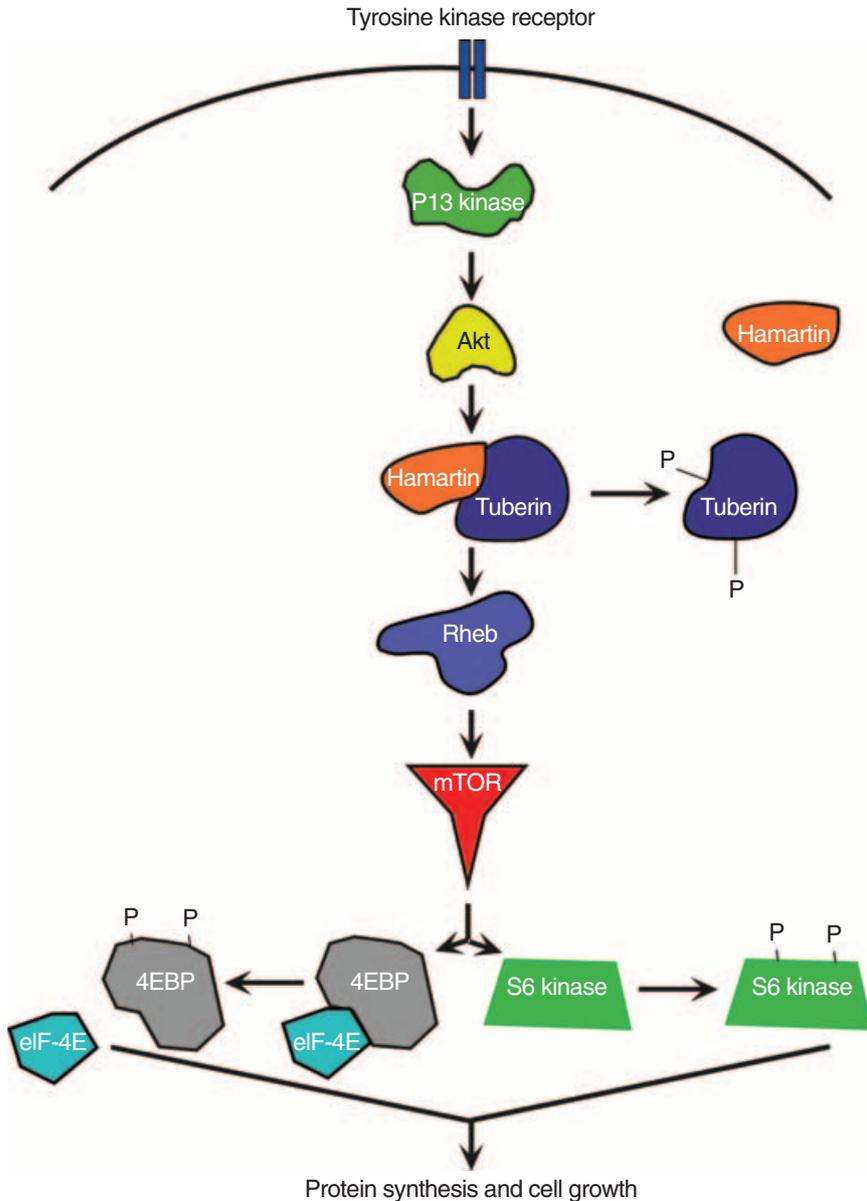
The epithelioid variant of angiomyolipomata has recently been described [58, 59]. These lesions have a large component of epithelioid cells (Fig. 7). The epithelioid cells may be polygonal with a slight degree of nuclear atypia, or atypical and variable in size; these lesions may



**Fig. 6. Classic renal angiomyolipoma histology using hematoxylin and eosin stain.** Note the multiple thick-walled blood vessels, smooth muscle cells, and fat cells.



**Fig. 7. Epithelioid renal angiomyolipoma histology using hematoxylin and eosin stain.** Note clear demarcation of normal renal tissue and the polygonal epithelioid cells.



**Fig. 8. Model for how tuberlin and hamartin regulate cell growth.** Binding of ligands (such as insulin) to cell surface tyrosine kinase receptors results in autophosphorylation of the receptor, and docking of adaptor proteins and phosphatidylinositol 3'-kinase (PI3K). Protein kinase B (PKB), also known as Akt, is phosphorylated and activated, which in turn phosphorylates tuberlin. Tuberlin dissociates from hamartin, permitting phosphorylation and activation of mammalian target of rapamycin, or mTOR, by way of Rheb. Activated mTOR phosphorylates S6K and initiation factor 4E binding protein (4E-BP), and the kinase activity and release of the kinase activity and release of translation initiation factor eIF-4E promote protein synthesis and cell growth. Absence of tuberlin permits constitutive activation of S6K and 4E-BP, which provides a persistent and inappropriate stimulus for growth (adapted in part from McManus and Alessi [113]).

exhibit significant mitotic activity. There are few or no abnormal vessels or fat cells in these lesions. Very aggressive epithelioid angiomyolipomata have been reported, sometimes as HMB-45 antibody–positive malignant angiomyolipomata, and these lesions can recur after resection and can be fatal [59–61]. Based on further analysis of these cases as well as other studies, Eble [62] postulates that the epithelioid renal angiomyolipomata are more aggressive than the more typical angiomyolipoma.

### ASSOCIATION WITH CANCER

Other neoplasms appear to be associated with angiomyolipomata. These include oncocytomas and renal cell carcinomas. Oncocytoma, a benign, renal epithelial cell neoplasm, consists of polygonal cells with abundant, finely granular cytoplasm filled with mitochondria. These lesions make up about 5% of surgically resected renal neoplasms [63], and may be more common in TSC [64]. The lesions histochemically label with epithelial cell markers but fail to express vimentin and are HMB-45 nonreactive [63, 65]. Another lesion, which histologically appears to be an oncocytoma, but lacking epithelial cell markers and is HMB-45–positive, has been described as an oncocytoma-like angiomyolipoma [63].

The concurrence of renal cell carcinoma and angiomyolipoma appears to be rare. Jimenez et al [64] identified only 52 cases in the literature, and was the uncertain whether patients with TSC were at increased risk for a renal cell neoplasm compared to the general population. Pea et al [66] note that the epithelioid variant of angiomyolipoma closely simulates renal cell carcinoma, making it difficult to determine the real frequency of authentic renal cell carcinomas among the reported cases in the literature. The epithelioid variety can also exhibit a clear cell histologic appearance [67]. A distinction between renal cell carcinoma and angiomyolipomata has been made in part based on the immunohistochemical findings. Renal cell carcinoma exhibit keratin but lack HMB-45 staining, while the epithelioid variety will demonstrate the reverse [66]. Tello et al [68] have performed a meta-analysis and failed to find a statistical relationship between TSC and renal cell carcinoma. However, the occurrence of renal cell carcinoma in children and young adults with TSC [69], including several reports of multifocal renal cell carcinoma in children with TSC under the age of 10 years, would indicate that an association does exist.

Two interesting observations may offer insight into the link between cancer and angiomyolipomata. First is that renal carcinoma in TSC has been seen in association with renal cystic disease [69], analogous to carcinoma associated with other (non-TSC) renal cystic diseases [70]. Perhaps the carcinoma risk is linked to the renal cystic disease and not to the angiomyolipomata. The second observation is that angiomyolipoma have been

noted to have other chromosomal abnormalities, suggesting the possibility that, in some lesions, the specific secondary chromosomal rearrangement may contribute to malignant progression [69]. Although the relationship of tuberous sclerosis and renal cell carcinoma is uncertain, angiomyolipoma can act aggressively, and can rarely undergo malignant transformation. Therefore, angiomyolipoma should be closely monitored to avoid undue patient risk [71].

### GENETICS OF ANGIOMYOLIPOMATA

Angiomyolipomata develop from clonal expansion of a cell that has acquired proliferative autonomy [39, 72, 73]. Genetic linkage analyses of families with TSC have led to the discovery of two genes that are associated with angiomyolipomata. These genes are *TSC1*, found at chromosome 9q34, and *TSC2* found at 16p13 [74]. Analysis of sporadic angiomyolipomata has likewise revealed an association with *TSC2* [75]. In a study of 130 sporadic (i.e., nonfamilial) TSC cases, 68% had germline *TSC2* mutations, 22% had no identifiable mutation, and 10% had germline *TSC1* mutations [76, 77].

Angiomyolipomata, TSC, and LAM related as well as at least some unrelated lesions, appear to be the consequence of somatic mutagenesis. The molecular pathogenesis of an angiomyolipoma associated with TSC involves the inheritance of a mutant allele compounded by a somatic mutation that results in a loss of heterozygosity (LOH). Patients with TSC have a germline mutation in the copy of the *TSC1* or *TSC2* gene that either arose sporadically or was inherited from the affected parent. Cells are heterozygous with one abnormal and one functional gene. The single normal allele is sufficient to ensure normal cell proliferation and organ development. However, sporadic somatic mutations of the wild-type allele in vulnerable tissues lead to a variable number of tumors. The cells of the lesion appear to be either homozygous or hemizygous for the mutant allele because they exhibit LOH at the involve TSC locus. The role of somatic mutagenesis in TSC has been clearly established [75, 78–80]. LOH of *TSC2* was also noted by Smolarek et al [81] in 7 of 13 angiomyolipomata from women with sporadic LAM, and specific *TSC2* mutations were identified [82]. In this sporadic form of disease, approximately half of the women also have renal angiomyolipomata. Angiomyolipomata not associated with sporadic LAM or TSC have also been reported to exhibit LOH at chromosome 16p13. Martignoni et al [83] studied epithelioid angiomyolipoma tissue from three patients without TSC or LAM, and found LOH at chromosome 16p13 in one of these patients. These findings raise the possibility that least some of the angiomyolipomata not associated with LAM or TSC also may be associated with mutations in the *TSC2* gene. These germline and somatic mutations

silence the locus and are an example of the two-hit hypothesis Knudson [84] proposed for retinoblastoma.

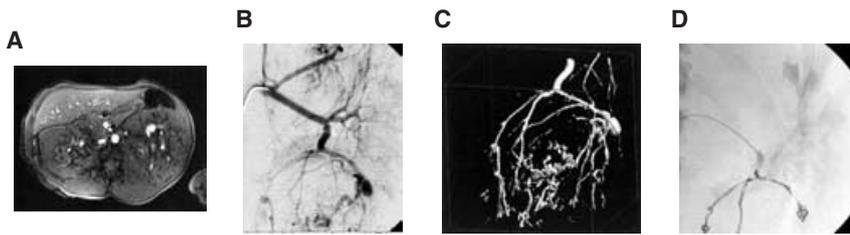
The origin of LAM cells is also controversial, but three lines of evidence suggest that angiomyolipoma smooth muscle cells metastasize to the lung, where they proliferate and progressively replace the normal lung tissue. First, TSC mutations in LAM cells and angiomyolipoma cells from sporadic LAM patients, who do not have germ line mutations in TSC genes, are identical, suggesting a common origin [82]. Second, TSC patients with LAM are more likely to have large or problematic angiomyolipomata, which are potentially more likely to seed the lung [28]. Studies from the University of Cincinnati and elsewhere have revealed that pulmonary cystic changes consistent with LAM are present in up to 40% of women with TSC [28–30]. Third, a recent genetic analysis of recurrent LAM lesions in a lung allograft after lung transplantation proved the recipient origin of smooth muscle cells in the lesion [34]. LAM cells isolated from the lung and angiomyolipomata cells share many genotypic and phenotypic characteristics, including genetic mutations in TSC genes and staining with specific markers, including the melanocyte-derived monoclonal antibody HMB-45 and to smooth muscle actin. Because of their biologic similarities and growing evidence that the lung lesion in TSC may arise from angiomyolipomata, we postulate that strategies that effectively control the growth of angiomyolipoma cells in the kidney may also control the growth of LAM cells in the lung. As explained above, an important feature of the cells in LAM and angiomyolipomata is that, in addition to an inherited mutation in one copy of their *TSC1* or *TSC2* genes, they have undergone a second somatic mutation that has disabled the wild-type gene. This second mutation produces a deficiency of either hamartin or tuberin, respectively. Insight into how this genetic difference between angiomyolipoma and normal cells leads to disease expression has only recently become available (for review, see [85]). Genetic analysis of *Drosophila* homologues *Tsc1* and *Tsc2* helped identify a role for hamartin and tuberin in cell organ morphology. Initially described by Farrus and Garcia-Bellido in 1976, the fruit fly *gigas* was found to have a mutation in the human homologue for *Tsc2* by Ito and Rubin [86]. Further work in this experimental system revealed that the *Tsc1* and *Tsc2* loci played a role in the regulation of cell and organ size. Homozygous inactivation of either *Tsc1* or *Tsc2* had identical phenotypic result, an increase in organ size that was due to an increase in cell size. Conversely, a simultaneous increase in the expression from both the *Tsc1* and *Tsc2* loci resulted in the opposite phenotype. Because cell size regulation had been associated with the PI3K-Akt-S6K pathway, genetic studies designed to elucidate the possible position of the *Tsc1* and *Tsc2* gene product in the pathway have been undertaken by several investigators.

Cultured mammalian cells lacking tuberin or hamartin constitutively produce a high level of S6K and 4EBP1 [87–89]. Treatment of these cells with rapamycin results in a rapid dephosphorylation and these treated cells become resistant to amino acid starvation [90]. These findings are consistent with the activation of the mammalian phosphatidylinositol 3'-kinase (PI3K)-Akt-S6K pathway and the pivotal role for mTOR in the absence of hamartin or tuberin (Fig. 8).

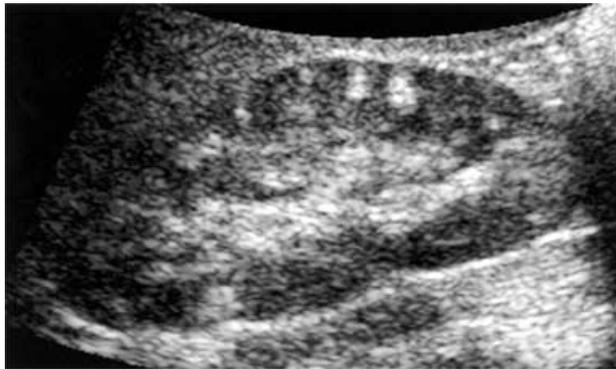
## CLINICAL MANAGEMENT

Angiomyolipomata are most often identified by imaging studies done to work up suspected disease, including hemorrhage, or as an incidental finding. Although these lesions can be quite large when identified, they typically are rather slow growing, and their large size attained over a longer time. Such predictable growth allows the clinician to identify a malignant lesion by a sudden increase in size, and underscores the value of periodic imaging. Large nonmalignant lesions can arise because of slow, continuous growth, or by the coalescence of multiple adjacent lesions. Lesions typically contain variable amounts of vascular, smooth muscle, and adipose elements. The composition is quite variable and they may also be composed of mostly solid elements such as smooth muscle. The epithelioid variety also contains very little or no fat nor the typical dysplastic vascular elements. The decision to biopsy such lesions is based on unusual growth and imaging characteristics. The risk of spontaneous hemorrhage, associated with aneurismal rupture [19] does not, by itself, increase the risk of bleeding following biopsy. The bleeding risk with biopsy is likely to be somewhat increased based on the dysplastic nature of the angiomyolipomata vasculature, but such is rarely the case in the epithelioid variety, and the vascular portion of the lesion can be crudely assessed by the degree of enhancement on imaging studies. In cases where the diagnosis is not clear, biopsy can guide therapy [91].

The primary reason to intervene in patients with renal angiomyolipomata has been to alleviate symptoms such as pain or hemorrhage, or to establish a diagnosis when the lesion has a low fat content that raises the suspicion of a carcinoma. Factors that affect the decision to intervene, as well as the method include the presence of symptoms, lesion size, visible aneurysms, renal reserve, pregnancy plans, patient occupation, activity, and compliance. The recent urological literature has embraced a renal sparing approach for angiomyolipomata [92]. Key to the long-term outcome of patients with multiple renal angiomyolipomata is the preservation of renal function. Current clinical measurements of renal function fail to measure renal reserve. This concept is critical because many case reports regarding nephron-sparing surgeries use normal serum creatinine values to indicate the



**Fig. 9. Renal aneurysm in an angiomyolipoma.** (A) Single proton gradient resonance (SPGR) sequence magnetic resonance imaging (MRI) revealing a 1.1 cm bright signal intensity in the lower pole of the left kidney compatible with a dilated or ectatic vessel or an aneurysm. (B) Angiography clearly showing the large aneurysm. (C) Three-dimensional reconstruction of vasculature to aid in embolization procedure. (D) Postembolization angiography showing the lack of blood flow to the vasculature, and the coils in place.



**Fig. 10. Renal ultrasound revealing multiple angiomyolipomata in a child.** Because these lesions typically contain a significant amount of adipose tissue, they are bright on ultrasound.

absence of renal damage [93, 94]. Because renal angiomyolipomata continue to grow, albeit slowly, indications for a total nephrectomy are limited and include a nonfunctioning kidney resulting in uncontrolled hypertension, local tissue invasion [95], tumor in the renal vein [96, 97], or very strong evidence of malignancy.

Partial or nephron-sparing nephrectomies run the risk of significant hemorrhage, and therefore should be undertaken only if unequivocally indicated. A suitable alternative to such invasive procedures is embolization (Fig. 9). Embolization, first used to treat angiomyolipomata approximately 20 years ago, obliterates the blood supply to the angiomyolipomata and thus reduces the risk of hemorrhage [98]. Embolization also has significant side effects. Following embolization, approximately 85% of patients develop post-embolization syndrome, including significant fever and pain [16, 98–109]. The use of glucocorticoids can ameliorate this complication [14]. Embolization is the preferred therapy and appears to be the most successful nephron-sparing procedure [92].

Although embolization and surgical therapies can successfully treat solitary lesions, the much more vexing clinical problem of coalescent renal angiomyolipomata that replace renal parenchyma has remained largely undressed (Fig. 10). When bleeding occurs in this circumstance, it can be impossible to identify which lesion is the source.

## ANIMAL MODELS OF ANGIOMYOLIPOMATA

Data from experimental animals and humans confirm the *in vivo* relevance of the Akt signaling pathways in tuberous sclerosis. Although not perfect mimics of the human disease, tuberin and hamartin heterozygous null mice develop several renal and hepatic neoplasms that are thought to be potential models for tuberous sclerosis [88, 110]. The hepatic tumors are rich in smooth muscle and are HMB-45–positive, consistent with the histological and immunohistochemical characteristics of LAM and angiomyolipoma lesions from patients. Female mice die from fatal hemorrhage into the liver lesion after 1 year of age, suggesting an influence of estrogen that also mimics human LAM. Most encouraging is that S6K is constitutively activated in the lesions of the TSC1+/- mice, and rapamycin quenches both the S6K phosphorylation and inappropriate cell growth in murine embryonic fibroblasts isolated from the animals [88]. Several investigators have demonstrated that rapamycin causes shrinkage of renal tumors in mouse [111] and rat [112] TSC models. The shrinkage was associated with inhibition of S6K phosphorylation and abundant apoptosis. S6K is constitutively active in LAM lesions, angiomyolipomata [51], and LAM cell models derived from humans and the Eker rat, and rapamycin can suppress inappropriate cell growth and S6K activation [87].

## CONCLUSIONS AND FUTURE DIRECTIONS

Renal angiomyolipomata are far from uncommon, and a great deal of progress has been made in understanding the genetics and biochemistry of this lesion, especially as it pertains to diseases like TSC and LAM. The optimum treatment of angiomyolipomata continues to be focused on sparing renal tissue. Initial published preclinical experimentation as well as ongoing work support the possibility that pharmacologic therapies may become available. Human trials to evaluate the utility of rapamycin in the treatment of renal angiomyolipoma associated with TSC and LAM are already underway. Should such therapies have efficacy, the discipline of nephrology that already has experience with drugs like rapamycin will likely play a dominant role in the care of these patients.

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