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EDUCATIONAL REVIEW

Renal tumors in tuberous sclerosis complex

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Abstract

Tuberous sclerosis complex (TSC) is a multisystem hereditary disorder characterized by the growth of benign tumors (hamartomas) in multiple organs, including the kidneys. Renal angiomyolipomas (AML) are a major diagnostic feature of TSC and are present in the majority of patients by adulthood. However, AML are usually asymptomatic during childhood when neurological and developmental manifestations are the main source of morbidity. Kidney manifestations of TSC have historically been the main cause of morbidity and mortality of adults with TSC. The recognition that the complications of TSC are caused by dysregulation of the mammalian target of rapamycin (mTOR) pathway has led to an enormous progress in the management of patients with TSC in the last two decades, the establishment of diagnostic guidelines, and trials which have shown the therapeutic benefit of mTOR inhibitors. Kidney surveillance of children with TSC now provides the opportunity for timely interventions to reduce the impact of TSC in adulthood. In this review, we discuss the current management of kidney tumors associated with TSC, including the diagnosis, surveillance, and treatment options for these lesions. We also present outcome data from international registries demonstrating the effectiveness of the current management strategies. With clear management guidelines and efficient treatment of kidney tumors, we envisage that the long-term outcomes of patients with TSC will further improve in the future.

Keywords Tuberous sclerosis complex · Renal angiomyolipoma · Renal cell carcinoma · mTOR inhibitor

Introduction

Tuberous sclerosis complex (TSC) is a multisystem hereditary disorder affecting over 1 million people worldwide with an incidence of approximately 1:6000 live births [1, 2]. The clinical manifestations of TSC are the consequence of loss-of-function mutations in one of the two TSC genes leading to the overactivity of the mammalian target of rapamycin (mTOR) pathway. The main manifestation of TSC is the growth of benign tumors (hamartomas) in multiple organs, including the skin, the brain, the heart, the lungs, and the kidneys.

In this educational review, we present the new information published over the last decade with an emphasis on the diagnosis, management, and follow-up data of the kidney tumors associated with TSC.

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Genetics

There are two genes associated with TSC: *TSC1* gene localized to 9q24 chromosome and *TSC2* gene localized to 16p13 chromosome [3]. The products of these genes are proteins called hamartin and tuberin, respectively. These proteins together form the TSC complex that acts as a growth/tumor suppressor as part of the mTOR pathway [4].

TSC is an autosomal dominant condition with complete penetrance but variable expressivity which explains the variability of clinical manifestations even within the families. About two-thirds of new TSC cases are due to de novo mutations in one of the TSC genes. Disease-causing mutations are

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identified in approximately 85–90% of individuals with clinical diagnosis of TSC by genetic testing. Approximately, 70% of these are mutations involving the *TSC2* gene. Apart from being more common, *TSC2* mutations are also more severe as the majority of these are loss of function mutations [5].

Diagnosis of TSC

The diagnosis of TSC is either clinical or genetic [6, 7]. Clinical diagnosis is based on a constellation of clinical signs that have been grouped into major (11) and minor (6) criteria. A definitive TSC diagnosis requires the presence of either two major or one major and two minor criteria, while the presence of one major or two or more minor criteria suggests possible TSC diagnosis. Renal angiomyolipomas (AML) (at least 2) are one of the major features, and multiple kidney cysts are one of the minor features of TSC. Of note, a combination of the two major features (lymphangioleiomyomatosis ([LAM)] and AML) without other features does not meet criteria for a definitive diagnosis of TSC. The identification of a pathogenic mutation in either *TSC1* or *TSC2* from DNA obtained from normal tissue is sufficient to make definite diagnosis of TSC [7]. For the purpose of this diagnosis, a pathogenic mutation is defined as a mutation that clearly inactivates the function of the TSC1 or TSC2 proteins (out-of-frame indel or nonsense mutation), prevents protein synthesis (large genomic deletion), or a missense mutation whose effect on protein function has been established by functional assessment [8, 9].

Clinical manifestations of TSC

While in the past, the clinical diagnosis of TSC was delayed, and based on the investigations of patients presenting with epilepsy, these days most patients with TSC are diagnosed in infancy or early childhood [10]. With the advances in prenatal imaging, many cases of TSC are recognized antenatally based on the finding of cardiac or brain lesions [11, 12]. Timely referral to centers with TSC expertise allows for appropriate investigations (brain imaging, EEG recording) to confirm the diagnosis of TSC before these children develop seizures. As part of TSC surveillance, we perform kidney imaging on all newborns with suspected TSC, even though the kidney imaging is normal in a majority of infants.

Kidney manifestation of TSC

The most common kidney manifestations of TSC are angiomyolipomas and cysts. Other tumors, such as renal cell carcinoma or renal oncocytoma, are less common, especially in children.

Angiomyolipomas

AML are benign tumors (hamartomas) of the kidney and, as their names indicates, comprise immature vessels, muscle, and fat cells (Fig. 1). The cell of origin of AML is unknown but studies suggest that AML most likely derive from pericytes (perivascular epithelial cells) [13]. Renal pericytes have the ability to differentiate into various cell lines (plasticity) and can accumulate lipids and support angiogenesis—the characteristics of AML precursors. Genetic analyses have shown that a second-hit (somatic) mutation in *TSC1* or *TSC2* genes leads to the loss of heterozygosity of these precursor cells, leading to unregulated mTOR pathway activity and eventually proliferation of the renal pericytes into immature vessels, muscle, and fat cells [14].

AML start developing in patients with TSC early in life, and by the age of 10 years, the majority of children will have AML detectable on kidney imaging. AML are usually multiple and bilateral, and their numbers and sizes increase with increasing age [15]. Approximately 80% of adult patients with TSC have AML in their kidneys. Children with AML are usually asymptomatic but bleeding, pain, elevated blood pressure, or even kidney impairment have been reported in children with TSC.

The major complication associated with AML is spontaneous hemorrhage. Data collected in case series suggest that hemorrhage is very rare in AML smaller than 3 cm in maximum diameter. Other factors that have been associated with hemorrhage are the speed of growth and the size of intralesional aneurysms [16, 17].

As most children with AML are asymptomatic and the potential for complications increases with increasing size of

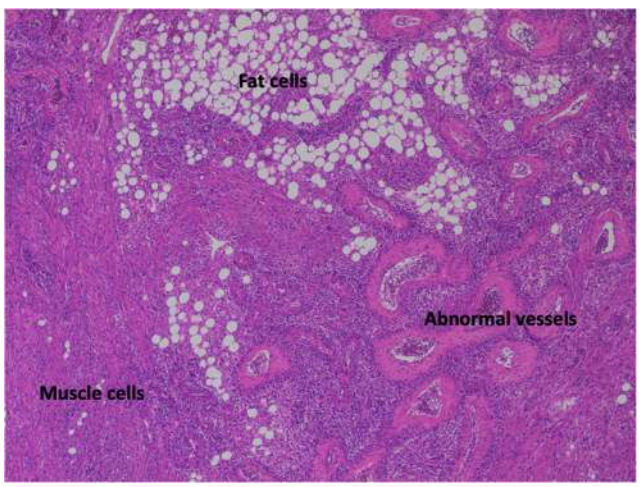

Fig. 1 Histopathology of angiomyolipoma. The tissue obtained by kidney biopsy shows characteristic features of angiomyolipoma: immature vessels of various calibers with abnormal vessel wall that are prone to aneurysm development; areas of disorganized muscle cells and fat cells (haematoxillin and eosin staining × 40 magnification); courtesy of Dr Leo Francis, Pathology, Queensland

these tumors, kidney surveillance is warranted. Recommendations by the International Tuberous Sclerosis Complex Consensus Conference are to image kidneys at diagnosis of TSC and then every 1–3 years throughout lifetime [18]. The preferred modality is magnetic resonance imaging (MRI) because of the better structural assessment of the lesions, including the ability to identify lipid-poor lesions, the ability to detect aneurysms in the feeding vessels, and the ability to detect extrarenal hamartomas (Fig. 2). The drawback of MRI is the requirement for general anesthetic in small children and children who are unable to remain still during the procedure. Kidney ultrasound is an acceptable alternative if the tumors on initial MRI have typical appearance of AML (Fig. 3). Any lipid-poor lesions should be subsequently imaged by MRI (see the "Lipid-poor AML" section).

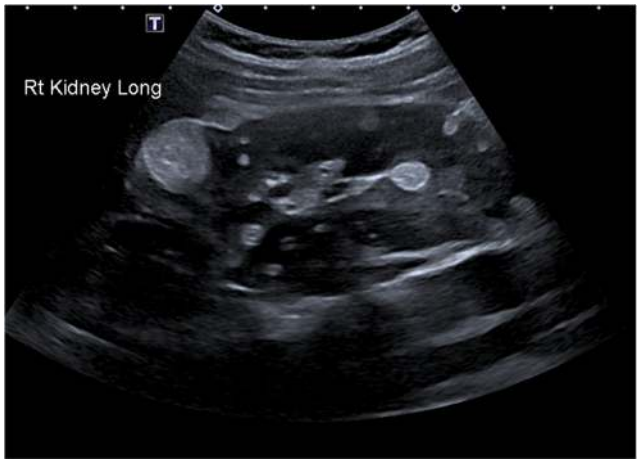

Fig. 3 Angiomyolipoma on kidney ultrasound. Kidney ultrasound of the right kidney demonstrates multiple angiomylipomas of various sizes. Echogenicity of the lesions is typical and reflects high lipid content of the lesions

Treatment of AML

With increasing size of AML, the risk of bleeding—the major complication of a large AML—is significantly increased. In the past, the only treatment options were either embolization or surgical resection of AML. With the introduction of mTOR inhibitors into clinical practice, the growth of these tumors can be controlled and the use of invasive and potentially nephron harmful procedures can be limited.

mTOR pathway inhibitors

The mTOR pathway, consisting of two complexes (mTOR complex 1 and mTOR complex 2), is a constitutively active pathway involved in normal cell growth and differentiation [19]. mTOR complex 1 (mTORC1) activates protein translation, nucleotide, and lipid synthesis and is involved in angiogenesis and lymphangiogenesis. mTOR complex 2 (mTORC2) controls glucose metabolism and is involved in cell migration and cytoskeletal re-arrangement. In short, mTORC1 controls "how much the cells grow" and mTORC2 "where the cells grow." The activity of mTORC1 is tightly controlled by TSC complex, comprising hamartin (product of *TSC1* gene), tuberin (product of *TSC2* gene), and TBC1D7 proteins. The TSC complex receives multiple signals from other growth factors and pathways about the availability of energy and oxygen required for growth. In this tightly regulated and complex process, the TSC complex acts as a "brake" on the mTORC1 complex preventing normal cell overgrowth and growth of tumors (Fig. 4). In patients with

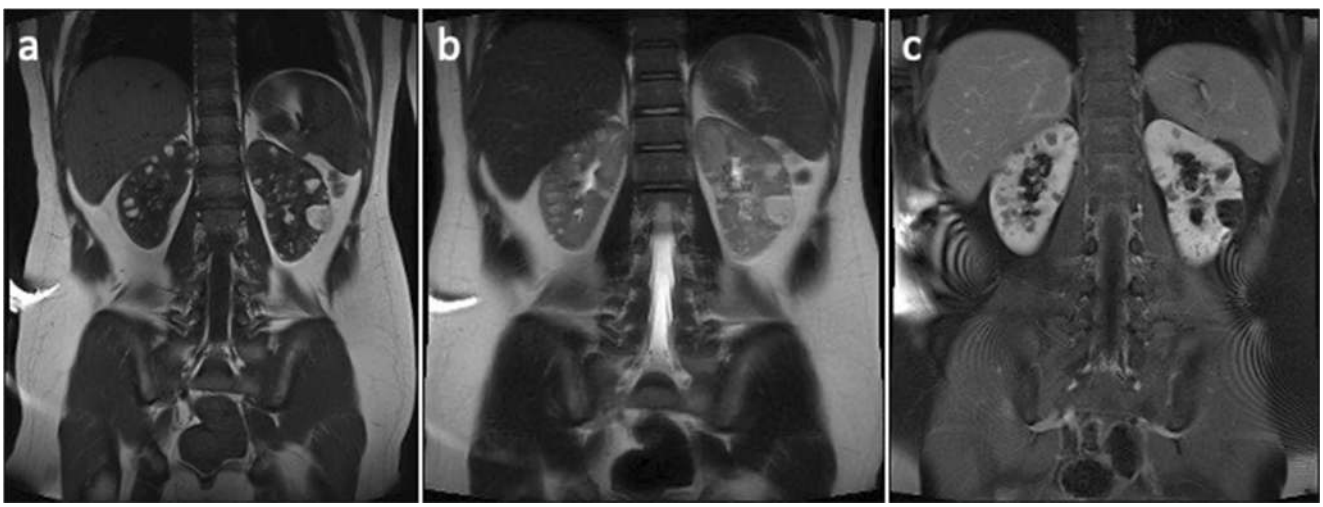

Fig. 2 Magnetic resonance imaging of angiolipomas. MRI demonstrates multiple lesions in both kidneys, consistent with angiomyolipomas. T1 (**a**), T2 (**b**), and T1 fat-saturated post contrast (**c**) MRI sequences allow for confirmation of composition of the lesions, including intralesional fat content, helping in differentiation between angiomyolipoma and renal cell carcinoma

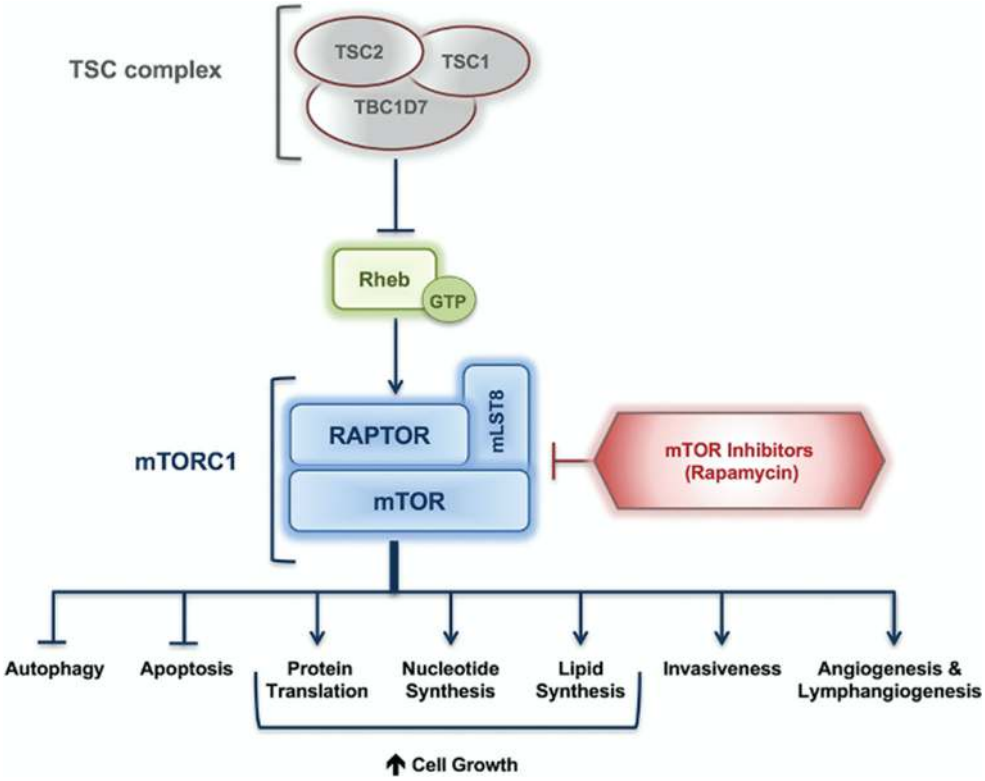

Fig. 4 TSC and mTORC1 signaling pathway. TSC complex controls the activity of mTORC1, preventing cell overgrowth. In patients with TSC gene mutations, this control is lost, leading to the growth of hamartomas. mTOR inhibitors block mTORC1 directly. Reproduced from [13], used with permission

mutations in one of the TSC genes, mTORC1 is not regulated in a usual way, becoming overactive with subsequent growth of hamartomas. mTOR inhibitors are able to block the mTOR pathway directly at the level of mTORC1.

After a few published case reports of the effectiveness of mTOR inhibitors to decrease the growth of AML in TSC patients, the landmark study on treatment of AML with sirolimus was published in 2008 [20]. In this non-randomized, open label, proof of concept trial, adults with TSC and AML and/or LAM of the lungs ($n = 20$) received sirolimus with dose adjustments based on the imaging response (decrease in size of AML) and sirolimus target blood levels (up to 15 ng/mL). The participants were treated for 12 months and followed for a further 12 months after stopping sirolimus. The primary outcome was the size of AML at 12 and 24 months. There was at least a 30% decrease in size of AML in 80% of patients in the first 12 months of treatment. The average size of AML decreased by 47% at 12 months but increased after stopping sirolimus to 86% of pre-treatment size at 24 months. This study confirmed the clinical observation that mTOR inhibitors are able to stop or decrease the growth of AML in patients with TSC but also that ongoing treatment is necessary for sustained effect.

Following the successful treatment of subependymal giant cell astrocytomas (SEGA) in patients with TSC by mTOR inhibitor everolimus (EXIST-1 trial), the EXIST-2 trial investigated whether this treatment can successfully control the growth of AML and pulmonary LAM [21]. EXIST-2 was a double-blind, placebo-controlled study in adults with TSC and AML (at least 3 cm in diameter) or spontaneous LAM. The patients were enrolled in a 2:1 fashion to receive either placebo or everolimus (fixed dose of 10 mg once a day; dose adjustments allowed based on the basis of safety findings) for at least 6 months. The primary outcome was the proportion of patients with at least 50% reduction in tumor volume in the absence of new AML, significant increase of kidney volume, and significant AML-related bleeding. Of 118 enrolled patients (79 everolimus and 39 placebo), 42% receiving everolimus and 0% receiving placebo achieved the primary outcomes with a median time to response of 2.9 months. At 24 weeks, 55% and 80% of patient in the everolimus group had at least 50% and 30% reduction of the size of AML, respectively, vs. 0% (50% reduction) and 3% (30% reduction) in patients in the placebo group. The adverse effects of everolimus treatment were generally mild with the most common side effect being stomatitis and mouth ulcers. Thus, the results of this study showed that everolimus is able to reduce the size of AML in adult patients with TSC with an acceptable safety profile. Positive results of this trial led to the approval of everolimus for the treatment of AML in TSC patients in many countries.

Following the favorable results in the EXIST-2 trial, participants were offered to switch to open-label everolimus treatment in an extension phase of this study. Four-year follow-up of these patients has been reported [22]. The primary outcomes of at least 50% reduction in AML size in the absence

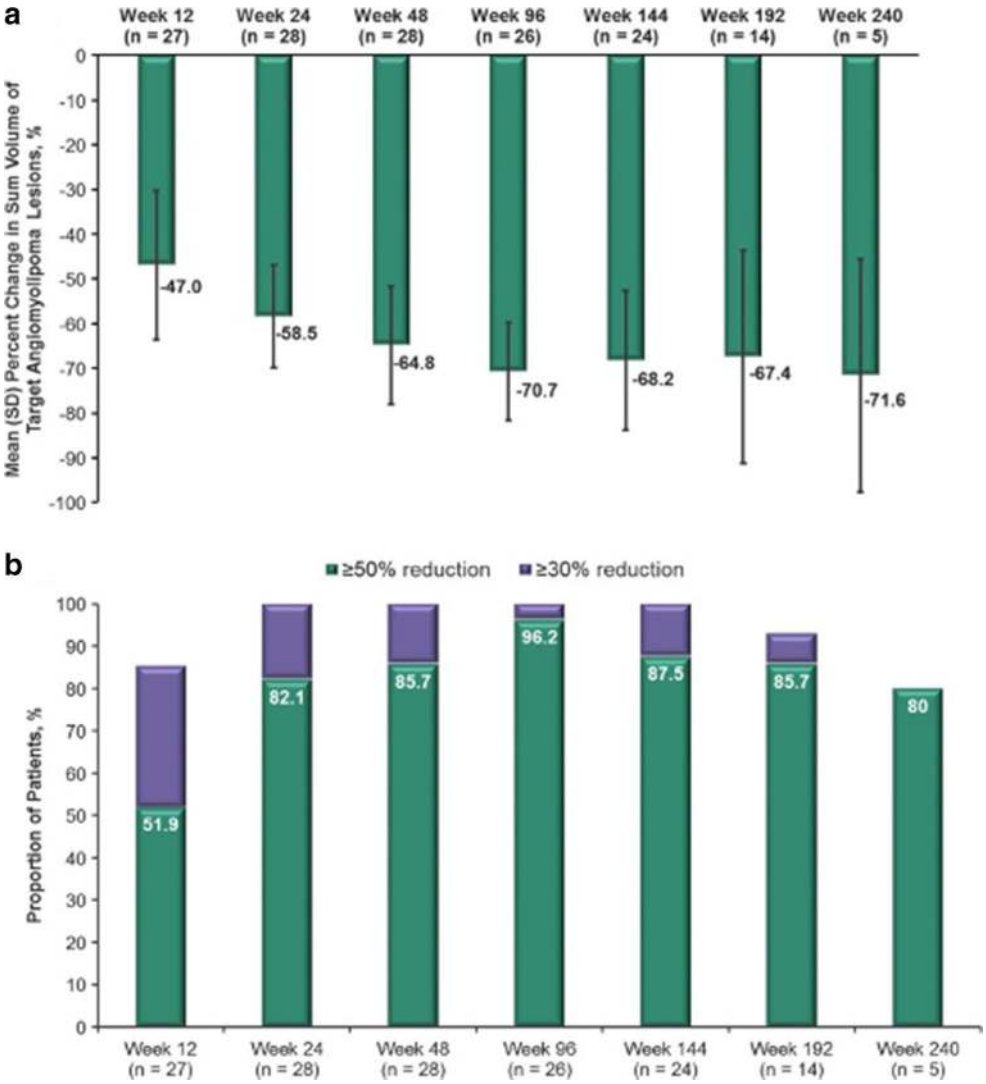

Fig. 5 Effect of everolimus on angiomyolipoma size in children with TSC. **a** Mean (standard deviation) reductions in the sum of volume of target angiomyolipoma lesions over time, and **b** the proportions of patients achieving an angiomyolipoma volume reduction of ≥ 50% or ≥ 30% over time. Reprinted with permission under Creative Commons license (http://creativecommons.org/licenses/by/4.0/) from [24]

of new AML, significant increase of kidney volume, and significant AML-related bleeding were the same as in the original EXIST-2 trial. Of the 112 patients, 58% had a reduction of AML, with 97% of patients achieving the response at some point in the study. Two-thirds of participants showed at least 50% reduction and 80% at least 30% reduction in the size of AML at the end of the study. This study thus showed a sustained reduction of AML in adult TSC patients with AML and sporadic LAM over the long term with minimal and acceptable side effects. A further analysis of the EXIST-2 cohort tracked AML re-growth in 16 patients who had discontinued everolimus [23]. This study showed AML re-growth in 31% of patients over 48 weeks; however, re-growth rates were not rapid.

These studies have demonstrated the effective and safe use of everolimus in adults with TSC. A study published in 2018 reported on the use of everolimus in children with TSC and AML [24]. This was a post hoc analysis of the EXIST-1 trial in which patients (including children) with TSC and SEGA were treated with everolimus. The response rate was the same as in the EXIST-2 trial. Of 33 children (< 18 years) enrolled in the study, 23 finished the study as per protocol. AML response rate was achieved in 75.8% of patients with sustained reduction in the size of AML over the 4-year period. At the end of the study, over 80% of children had sustained at least 50% reduction and over 90% sustained at least 30% reduction of the AML volume (Fig. 5). Similar to the adult study, the side effects were minimal and improved with time. This analysis showed for the first time that everolimus is effective and well tolerated in children with TSC and AML with sustained reduction of the AML size.

Long-term effects of everolimus on kidney function have been studied in extension phases of EXIST-1 and EXIST-2 trials [25]. A total of 111 patients from the EXIST-1 trial (including children) and 112 patients from the EXIST-2 trial were analyzed. After approximately 4 years of treatment, the mean estimated glomerular filtration rate (GFR) remained stable in both studies with, as expected, higher GFR in the EXIST-1 trial with pediatric patients when compared with

the EXIST-2 trial (115 vs. 88 ml/min/1.73 m^2, respectively). The decline of kidney function was predominantly confined to patients with decreased kidney function at the start of the trials. The authors also monitored the development of proteinuria (one of the potential side effects of mTOR inhibitor treatment). The incidence of proteinuria increased with the use of everolimus (more evident again in the EXIST-2 trial) but was mainly mild. The conclusion of this study was that the use of everolimus in TSC patients does not appear to be nephrotoxic and may preserve kidney function.

We have used everolimus in patients with TSC and AML over the last 5 years. This medication is fully funded by the Australian government for the indication of large SEGA or visceral tumors associated with TSC. The initial approval is for 3 months. For ongoing supply beyond 3 months, the response to treatment (decrease in size of AML) must be demonstrated. We treat large AML (3 cm or more in diameter). The starting dose is usually 2.5 mg or 5 mg once daily (depending on the size of the patient), and the dose is adjusted depending on the trough blood level. We aim for the level of 5 ng/mL or higher. Many children with TSC are receiving treatment with enzyme-inducing antiepileptic drugs and may require higher daily doses of everolimus to achieve desired therapeutic levels. Response to therapy can be monitored by reduction in size of AML or stabilization of growth of smaller lesions. The medication is usually well tolerated. Mouth ulcers are the most common side effect, and these improve with temporary decrease of the dose of everolimus and with time. Topical therapies, such as sucralfate, triamcinolone, and benzocaine, may be used for symptom control and to hasten the healing [26]. We advise the patients and families to stop medication during the intercurrent infections and surgeries. We monitor urine for proteinuria on early morning samples using protein/creatinine ratio.

Other treatment options for AML

Before the availability of mTOR inhibitors, large AML with potential to bleed were electively treated with embolization to decrease the size and prevent this complication (Fig. 6). This treatment option is still the modality of choice in many countries that do not have access to mTOR inhibitors. The risk of bleeding from AML increases with the increasing size of these tumors (by definition, large AML at risk of bleeding is defined as > 4 cm in diameter) and if large aneurysm (> 5 mm) is present in feeding arteries. Embolization is performed by an interventional radiologist and is generally followed by administration of corticosteroids to minimize post-embolization syndrome (pain and fever post procedure) and sometimes antibiotics [27]. Embolization is also a procedure of choice for already-bleeding AML. If surgical treatment of AML is required, nephron-sparing surgery (partial nephrectomy) is preferred [28]. Repeated embolization and any surgical procedure might lead to the damage of the functioning kidney tissue and should be avoided, if possible [18]. This treatment should always be discussed with a surgeon experienced in the treatment of kidney tumors.

Lipid-poor AML

Lipid-poor AML are characterized by minimal fat content, which makes them more difficult to assess by kidney ultrasound. MRI is the imaging modality of choice for these lesions that may be large and characterized by progressive growth. Differentiation from renal cell carcinoma (RCC) is important. There are various imaging techniques used for differentiation between AML and RCC [29]. In- and out-of-phase MRI imaging is used commonly with fat content that is present on in-phase images disappearing on out-of-phase images (Fig. 7), the characteristic feature of AML. Sometimes, the results of these studies are inconclusive, and biopsy of the lesion is required. In our experience, the majority of biopsied lesions in children with TSC are lipid-poor AML.

Cystic kidney disease in TSC

Cystic kidney disease is the second most common kidney manifestation in patients with TSC after AML. Commonly, cysts are detected early in life and are present in approximately half of the patients with TSC [30, 19]. The most severe cystic disease is associated with *TSC2/PKD1* contiguous gene deletion syndrome in which deletion of both of these genes on chromosome 16 predisposes patients to cyst development, usually in early childhood [31] (Fig 8). Patients with *TSC2/PKD1* mutation often have a severe phenotype with urine concentration defects, hypertension, and diminished kidney function with the risk of developing kidney failure during the second or third decade of life [32]. Otherwise, there is little evidence that small cysts seen in young children with isolated *TSC2* or *TSC1* mutations lead to any clinical consequences. Although there is some data that mTOR inhibitors may reduce cyst number and size in patients with TSC [33], there is a lack of evidence that mTOR inhibitors preserve kidney function in patients with *TSC2/PKD1* contiguous gene deletion syndrome.

TSC-associated renal cell carcinoma

The reported incidence of RCC in TSC patients is 2–4% [34]. This incidence is above the general population risk of 1%. TSC-associated RCC develops at a younger age when compared with the general population (~ 30 vs. ~ 55 years, respectively). RCC is rare in childhood but has been reported [35], even at a very young age [36, 37]. There is a higher risk of this

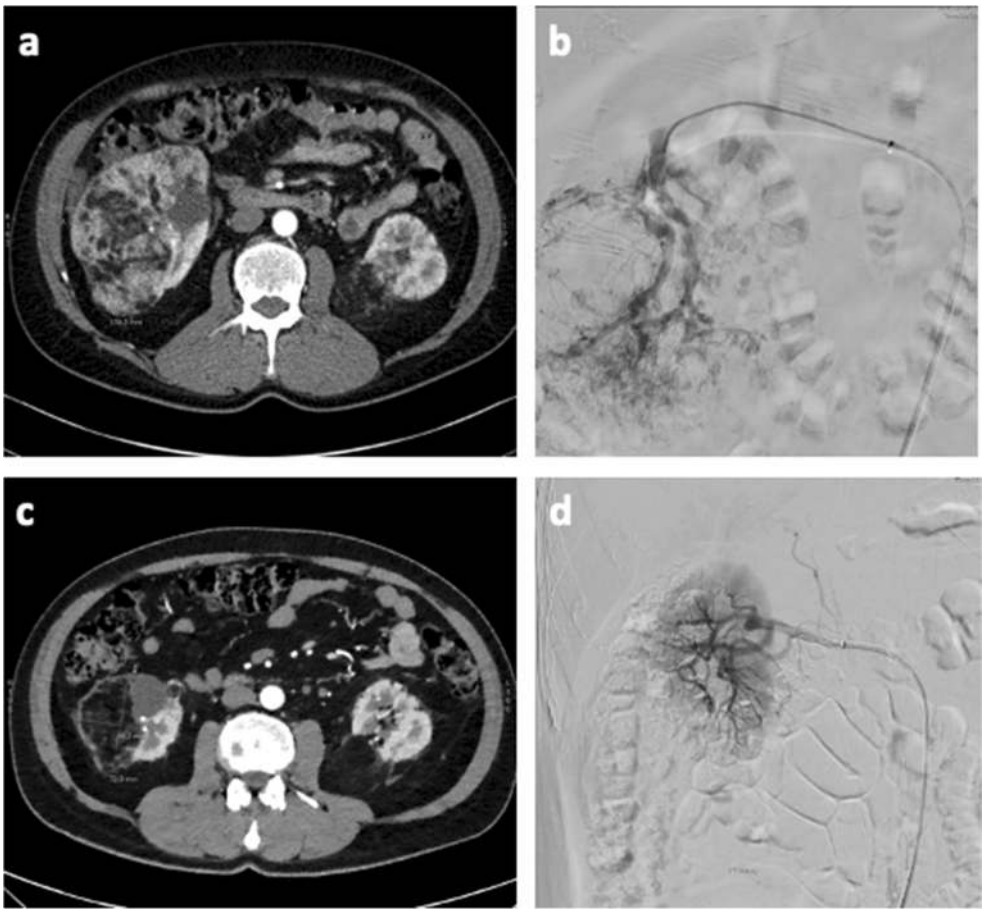

Fig. 6 Elective embolization of large angiomyolipoma. Large (14 cm in diameter) angiomyolipoma (AML) of the right kidney on CT scan (**a**); elective embolization of the AML (**b**); follow-up CT scan demonstrates significant decrease in the size (7 cm in diameter) of AML (**c**), confirmed on post-embolization angiography (**d**)

cancer in patients with *TSC2* mutations, with presumed mechanism of loss of heterozygosity of the tumor cells (second hit mutation) leading to malignant transformation of the cells [38]. TSC-associated RCC are often multiple and bilateral; they generally grow faster than AMLs and usually have no lipid content. Various histological types of RCC have been reported in TSC patients with papillary, clear cell, and chromophobe histological types being the most common [34]. The histological distinction between RCC and AML is based on positive staining for either cytokeratin (positive in RCC) or HMB-45 (positive in AML). The treatment of RCC is based on the staging of the tumor and includes various combinations of surgical resection, radiotherapy, and immunotherapy and/or molecularly targeted therapy [39].

Renal oncocytoma

Renal oncocytoma is a very rare benign tumor of the kidney that has been described in TSC patients [40, 41]. Despite the

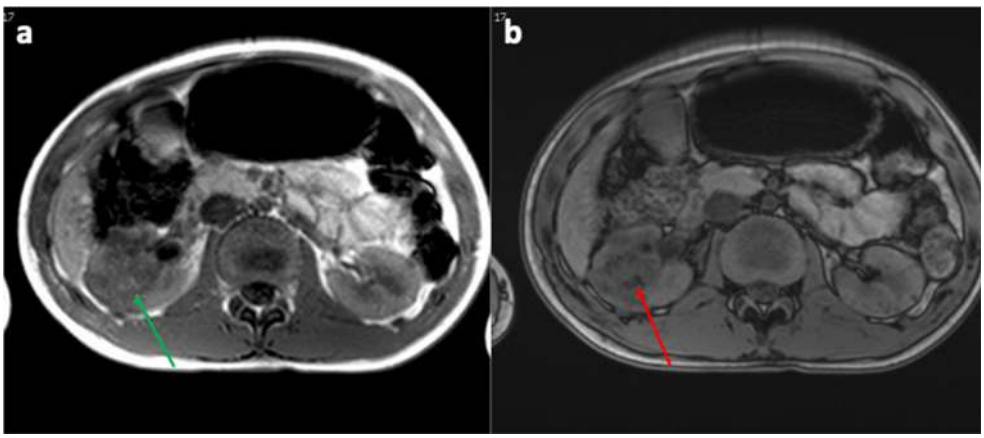

Fig. 7 In- and out-of-phase MRI imaging of lipid-poor angiomyolipoma. T1 in-phase and T1 out-of-phase sequences. T1 in-phase sequence (**a**) does not show typical high fat content of the lesion (arrow); T2 out-of-phase sequence (**b**) shows small areas of signal drop out (arrow) confirming microscopic areas of fat in the lesion, suggestive of lipid-poor angiolipoma

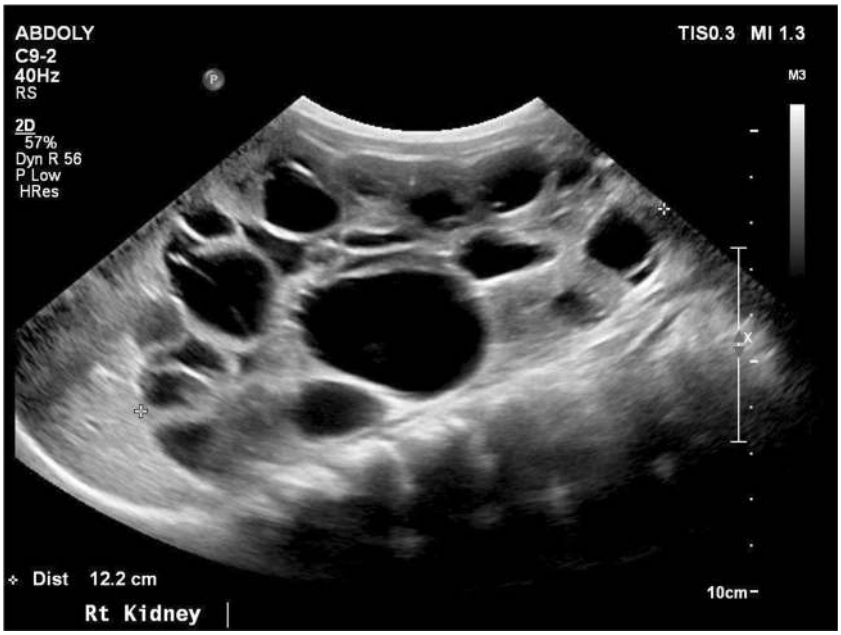

Fig. 8 Cystic kidney disease in TSC. Ultrasound of the right kidney in a 1-year-old child with *TSC* and *TSC2/PKD1* contiguous gene deletion syndrome showing massively enlarged kidney containing multiple large cysts

fast growth similar to RCC and often large size of this tumor, it is never invasive. In contrast to RCC, renal oncocytomas are usually solitary and unilateral tumors. The histological diagnosis of oncocytoma is based on intensely eosinophilic granular staining of the cells of the tumor, reflecting large numbers of mitochondria [42]. The treatment of choice for oncocytoma is surgical resection.

Long-term kidney outcomes in TSC

Lifetime risk of kidney failure in patients with TSC is probably ~ 1% [43, 44]. The risk factors for kidney failure are AML and cyst burden, prior surgeries and embolizations, uncontrolled hypertension, and underlying chronic kidney disease. A small number of patients with *TSC2* mutations may have a contiguous deletion involving the *PKD1* gene and present with a severe polycystic kidney phenotype. Patients with a contiguous gene mutation may develop hypertension in early childhood and progress to kidney failure by early adulthood.

The long-term renal follow-up of patients with TSC is therefore essential. The data on long-term management and outcomes of these patients have historically been sparse, especially in children, but in recent years, international collaboration has yielded important information in this field. One of the most successful collaborations has been TuberOus SClerosis registry to increase disease Awareness (TOSCA) Registry [45]. TOSCA is a multicenter, international disease registry that aims to assess manifestations, interventions, and outcomes in patients with TSC. The TOSCA registry core dataset includes data on epidemiology, genetics, and clinical presentation, including organ-specific data. The kidney dataset includes the characteristics of AML (bilateral, multiple, size, and growth), clinical symptoms and signs, management of AML, and effects of age, gender, and genotype on these tumors. The first results of this important collaboration have recently been published [15]. Over 2000 patients (including children) with TSC from 170 sites in 31 countries have been enrolled. The median age at diagnosis of TSC was 1 year (range < 1 to 69 years) with 52% female predominance. Of approximately half of the patients who had been genetically tested, the majority had *TSC2* mutation (64.4%), followed by *TSC1* mutation (19.7%). Six patients (0.6%) had both *TSC1* and *TSC2* mutations, while no mutation was identified in 14.4% of patients. As expected, the presence of AML increased with age of patients (Fig. 9). Less than 10% of patients 2 years old or younger had AML, while approximately half of the patients had AML detected on imaging by the age of 10 years. By adulthood, ~ 80% of patients had AML in their kidneys. In the whole cohort, AML were present in the majority of patients (51.8%), more commonly in females (57.8%). Median age at diagnosis of AML was 12 years.

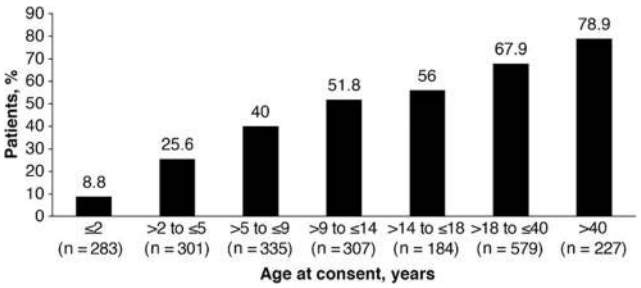

Fig. 9 Prevalence of renal angiomyolipomas across age groups. Reprinted with permission under Creative Commons license (http://creativecommons.org/licenses/by/4.0/) from [41]

The prevalence of AMLs was higher in patients with *TSC2* mutations. The majority of AML were multiple (88.4%) and bilateral (83.9%). Larger AML (> 3 cm in diameter) were present in 34.3% of patients. Most patients were asymptomatic (82%) but if they developed clinical problems, the most common symptoms and signs were bleeding, pain, elevated blood pressure, and impaired kidney function. The most common modality of treatment was embolization followed by mTOR inhibitors. The TOSCA registry provides a valuable insight into the burden, clinical characteristics, complications, and treatment of AML in patients with TSC.

Conclusions

Kidney tumors, mainly AML, are an important feature of TSC. Most children with TSC will have AML diagnosed by medical imaging by adult age. Large AML have a potential to bleed and are therefore an important source of morbidity in TSC patients. The majority of AML, however, remain small and clinically asymptomatic. It is therefore important to continue surveillance for these tumors throughout the lifetime of TSC patients. We now have well-defined guidelines for the surveillance and the management of AML. With the addition of mTOR inhibitors to our armamentarium of TSC treatments, there is a hope that the need for invasive procedures, such as embolization or surgical resection, will decrease with time, with better preservation of functioning kidney tissue of TSC patients. There is evolving evidence that the kidney outcomes of TSC patients with AML have improved in recent decades as a result of medical rather that surgical management of the tumors, as highlighted by the data from the TOSCA trial demonstrating decreasing rates of invasive surgical interventions and low accumulative prevalence of bleeding from AML [45]. As kidney complications are currently the main cause of morbidity/mortality of adult patients with TSC, we hope that we will be able to change the future of these patients.

Key summary points

1) Renal angiomyolipomas (AML) develop in 80% of people with tuberous sclerosis complex (TSC) by adulthood. The risk of hemorrhage increases as AML increase in size above 3 cm in diameter.

2) All children with TSC should undergo regular surveillance with kidney imaging.

3) Randomized controlled trials have shown that mTOR inhibitors are effective in reducing growth and size of AML in patients with TSC.

4) Early initiation of mTOR inhibitors may reduce the need for embolization and/or nephrectomies and lead to preservation of kidney function.

5) Renal cell carcinoma occurs rarely in TSC but needs to be differentiated from lipid-poor AML.

Multiple-choice questions (answers follow reference list)

1 Which of the following statements about the genetics of tuberous sclerosis complex (TSC) is correct?

- A TSC is inherited in an autosomal recessive fashion.
- B If a family has a child with TSC, there is at least a 50% chance their next child will have TSC.
- C The expression of TSC within affected families is very variable.
- D Most children with TSC have a mutation affecting the *TSC1* gene.
- E A positive genetic test is required to make the diagnosis of TSC.

2 Which one of the following statements about the renal manifestations of TSC is correct?

- A Angiomyolipomas are visible on kidney imaging in 50% of newborns with TSC.
- B Kidney cysts are an uncommon finding in TSC except when there is a contiguous gene mutation of *TSC2* and *PKD1*.
- C Lipid-poor renal lesions are typically malignant.
- D The prevalence of renal cell carcinoma is higher in children with TSC than in the general age-matched population.
- E Hypoplastic kidneys are a cardinal feature of TSC.

3 Which one of the following statements about mTOR inhibitors in TSC is correct?

- A Angiomyolipomas may regrow if treatment with an mTOR inhibitor is withdrawn.
- B Everolimus has been shown to be more effective than sirolimus in management of renal angiomyolipomas.
- C Low-dose tacrolimus has a synergistic effect with everolimus to prevent growth of renal angiomyolipomas in TSC.

D Antiepileptic drugs typically inhibit the cytochrome P450 pathway.
E Oral mTOR inhibitors have not been approved for use in children with TSC.

4 Which of the following statements about kidney screening in TSC best represents the current international consensus guidelines?

A An abdominal CT scan should be performed when TSC is suspected.
B Kidney MRI should be performed every 5 years during childhood.
C Kidney imaging should occur every 1 to 3 years throughout life.
D Serum creatinine should be measured annually.
E DMSA kidney scan should be used if a lipid poor lesion is suspected.

5 A kidney ultrasound has been performed in a 15-year-old girl with TSC. The ultrasound shows an echogenic lesion in the upper pole of the right kidney measuring 6.5 × 4 cm. The patient has not had flank pain or hematuria. Which of the following statements is most correct?

A Spontaneous hemorrhage occurs in more than 60% of renal angiomyolipomas that are greater than 3 cm in diameter.
B Therapy with everolimus would be expected to lead to a reduction in size of the lesion over 6 to 12 months.
C A CT angiogram is indicated to screen for intralesional aneurysms.
D A biopsy of the lesion is indicated to exclude a renal cell carcinoma.
E Intervention is not indicated as there is a low risk that this lesion will continue to grow.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Peron A, Northrup H (2018) Tuberous sclerosis complex. Am J Med Genet C: Semin Med Genet 178:274–277. https://doi.org/10.1002/ajmg.c.31657
2. Hong CH, Tu HP, Lin JR, Lee CH (2016) An estimation of the incidence of tuberous sclerosis complex in a nationwide retrospective cohort study (1997-2010). Br J Dermatol 174:1282–1289. https://doi.org/10.1111/bjd.14415
3. Peron A, Au KS, Northrup H (2018) Genetics, genomics, and genotype-phenotype correlations of TSC: insights for clinical practice. Am J Med Genet C: Semin Med Genet 178:281–290. https://doi.org/10.1002/ajmg.c.31651
4. Curatolo P, Bombardieri R, Jozwiak S (2008) Tuberous sclerosis. Lancet 372:657–668. https://doi.org/10.1016/s0140-6736(08)61279-9
5. Au KS, Williams AT, Roach ES, Batchelor L, Sparagana SP, Delgado MR, Wheless JW, Baumgartner JE, Roa BB, Wilson CM, Smith-Knuppel TK, Cheung MY, Whittemore VH, King TM, Northrup H (2007) Genotype/phenotype correlation in 325 individuals referred for a diagnosis of tuberous sclerosis complex in the United States. Genet Med 9:88–100. https://doi.org/10.1097/gim.0b013e31803068c7
6. Roach ES, Sparagana SP (2004) Diagnosis of tuberous sclerosis complex. J Child Neurol 19:643–649. https://doi.org/10.1177/08830738040190090301
7. Northrup H, Krueger DA, International Tuberous Sclerosis Complex Consensus Group (2013) Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol 49:243–254. https://doi.org/10.1016/j.pediatrneurol.2013.08.001
8. Hoogeveen-Westerveld M, Ekong R, Povey S, Karbassi I, Batish SD, den Dunnen JT, van Eeghen A, Thiele E, Mayer K, Dies K, Wen L, Thompson C, Sparagana SP, Davies P, Aalfs C, van den Ouweland A, Halley D, Nellist M (2012) Functional assessment of TSC1 missense variants identified in individuals with tuberous sclerosis complex. Hum Mutat 33:476–479. https://doi.org/10.1002/humu.22007
9. Hoogeveen-Westerveld M, Ekong R, Povey S, Mayer K, Lannoy N, Elmslie F, Bebin M, Dies K, Thompson C, Sparagana SP, Davies P, van Eeghen AM, Thiele EA, van den Ouweland A, Halley D, Nellist M (2013) Functional assessment of TSC2 variants identified in individuals with tuberous sclerosis complex. Hum Mutat 34:167–175. https://doi.org/10.1002/humu.22202
10. Chung CWT, Lawson JA, Sarkozy V, Riney K, Wargon O, Shand AW, Cooper S, King H, Kennedy SE, Mowat D (2017) Early detection of tuberous sclerosis complex: an opportunity for improved neurodevelopmental outcome. Pediatr Neurol 76:20–26. https://doi.org/10.1016/j.pediatrneurol.2017.05.014
11. Dragoumi P, O'Callaghan F, Zafeiriou DI (2018) Diagnosis of tuberous sclerosis complex in the fetus. Eur J Paediatr Neurol 22:1027–1034. https://doi.org/10.1016/j.ejpn.2018.08.005
12. Gu X, Han L, Chen J, Wang J, Hao X, Zhang Y, Zhang J, Ge S, He Y (2018) Antenatal screening and diagnosis of tuberous sclerosis complex by fetal echocardiography and targeted genomic sequencing. Medicine (Baltimore) 97:e0112. https://doi.org/10.1097/MD.0000000000010112
13. Lam HC, Nijmeh J, Henske EP (2017) New developments in the genetics and pathogenesis of tumours in tuberous sclerosis complex. J Pathol 241:219–225. https://doi.org/10.1002/path.4827
14. Sepp T, Yates JR, Green AJ (1996) Loss of heterozygosity in tuberous sclerosis hamartomas. J Med Genet 33:962–964. https://doi.org/10.1136/jmg.33.11.962
15. Kingswood JC, Belousova E, Benedik MP, Carter T, Cottin V, Curatolo P, Dahlin M, L DA, d'Augeres GB, de Vries PJ, Ferreira JC, Feucht M, Fladrowski C, Hertzberg C, Jozwiak S, Lawson JA, Macaya A, Marques R, Nabbout R, O'Callaghan F, Qin J, Sander V, Sauter M, Shah S, Takahashi Y, Touraine R, Youroukos S, Zonnenberg B, Jansen AC (2019) Renal angiomyolipoma in patients with tuberous sclerosis complex: findings from the TuberOus SClerosis registry to increase disease Awareness. Nephrol Dial Transplant 34:502–508. https://doi.org/10.1093/ndt/gfy063

16. O'Callaghan FJ, Noakes MJ, Martyn CN, Osborne JP (2004) An epidemiological study of renal pathology in tuberous sclerosis complex. BJU Int 94:853–857. https://doi.org/10.1111/j.1464-410X.2004.05046.x
17. Yamakado K, Tanaka N, Nakagawa T, Kobayashi S, Yanagawa M, Takeda K (2002) Renal angiomyolipoma: relationships between tumor size, aneurysm formation, and rupture. Radiology 225:78–82. https://doi.org/10.1148/radiol.2251011477
18. Krueger DA, Northrup H, International Tuberous Sclerosis Complex Consensus G (2013) Tuberous sclerosis complex surveillance and management: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol 49:255–265. https://doi.org/10.1016/j.pediatrneurol.2013.08.002
19. Lam HC, Siroky BJ, Henske EP (2018) Renal disease in tuberous sclerosis complex: pathogenesis and therapy. Nat Rev Nephrol 14:704–716. https://doi.org/10.1038/s41581-018-0059-6
20. Bissler JJ, McCormack FX, Young LR, Elwing JM, Chuck G, Leonard JM, Schmithorst VJ, Laor T, Brody AS, Bean J, Salisbury S, Franz DN (2008) Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangioleiomyomatosis. N Engl J Med 358:140–151. https://doi.org/10.1056/NEJMoa063564
21. Bissler JJ, Kingswood JC, Radzikowska E, Zonnenberg BA, Frost M, Belousova E, Sauter M, Nonomura N, Brakemeier S, de Vries PJ, Whittemore VH, Chen D, Sahmoud T, Shah G, Lincy J, Lebwohl D, Budde K (2013) Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet 381:817–824. https://doi.org/10.1016/s0140-6736(12)61767-x
22. Bissler JJ, Kingswood JC, Radzikowska E, Zonnenberg BA, Belousova E, Frost MD, Sauter M, Brakemeier S, de Vries PJ, Berkowitz N, Voi M, Peyrard S, Budde K (2017) Everolimus long-term use in patients with tuberous sclerosis complex: Four-year update of the EXIST-2 study. PLoS One 12:e0180939. https://doi.org/10.1371/journal.pone.0180939
23. Bissler JJ, Nonomura N, Budde K, Zonnenberg BA, Fischereder M, Voi M, Louveau AL, Herbst F, Bebin EM, Curatolo P, Zonta A, Belousova E (2018) Angiomyolipoma rebound tumor growth after discontinuation of everolimus in patients with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis. PLoS One 13:e0201005. https://doi.org/10.1371/journal.pone.0201005
24. Bissler JJ, Franz DN, Frost MD, Belousova E, Bebin EM, Sparagana S, Berkowitz N, Ridolfi A, Kingswood JC (2018) The effect of everolimus on renal angiomyolipoma in pediatric patients with tuberous sclerosis being treated for subependymal giant cell astrocytoma. Pediatr Nephrol 33:101–109. https://doi.org/10.1007/s00467-017-3806-1
25. Bissler JJ, Budde K, Sauter M, Franz DN, Zonnenberg BA, Frost MD, Belousova E, Berkowitz N, Ridolfi A, Christopher Kingswood J (2019) Effect of everolimus on renal function in patients with tuberous sclerosis complex: evidence from EXIST-1 and EXIST-2. Nephrol Dial Transplant 34:1000–1008. https://doi.org/10.1093/ndt/gfy132
26. Davies M, Saxena A, Kingswood JC (2017) Management of everolimus-associated adverse events in patients with tuberous sclerosis complex: a practical guide. Orphanet J Rare Dis 12:35. https://doi.org/10.1186/s13023-017-0581-9
27. Bissler JJ, Racadio J, Donnelly LF, Johnson ND (2002) Reduction of postembolization syndrome after ablation of renal angiomyolipoma. Am J Kidney Dis 39:966–971. https://doi.org/10.1053/ajkd.2002.32770
28. Nelson CP, Sanda MG (2002) Contemporary diagnosis and management of renal angiomyolipoma. J Urol 168:1315–1325. https://doi.org/10.1097/01.ju.0000028200.86216.b2
29. Razik A, Das CJ, Sharma S (2019) Angiomyolipoma of the kidneys: current perspectives and challenges in diagnostic imaging and image-guided therapy. Curr Probl Diagn Radiol 48:251–261. https://doi.org/10.1067/j.cpradiol.2018.03.006
30. Rakowski SK, Winterkorn EB, Paul E, Steele DJR, Halpern EF, Thiele EA (2006) Renal manifestations of tuberous sclerosis complex: incidence, prognosis, and predictive factors. Kidney Int 70:1777–1782. https://doi.org/10.1038/sj.ki.5001853
31. Brook-Carter PT, Peral B, Ward CJ, Thompson P, Hughes J, Maheshwar MM, Nellist M, Gamble V, Harris PC, Sampson JR (1994) Deletion of the TSC2 and PKD1 genes associated with severe infantile polycystic kidney disease — a contiguous gene syndrome. Nat Genet 8:328–332. https://doi.org/10.1038/ng1294-328
32. Sampson JR, Maheshwar MM, Aspinwall R, Thompson P, Cheadle JP, Ravine D, Roy S, Haan E, Bernstein J, Harris PC (1997) Renal cystic disease in tuberous sclerosis: role of the polycystic kidney disease 1 gene. Am J Hum Genet 61:843–851. https://doi.org/10.1086/514888
33. Siroky BJ, Towbin AJ, Trout AT, Schäfer H, Thamann AR, Agricola KD, Tudor C, Capal J, Dixon BP, Krueger DA, Franz DN (2017) Improvement in renal cystic disease of tuberous sclerosis complex after treatment with mammalian target of rapamycin inhibitor. J Pediatr 187:318–322.e312. https://doi.org/10.1016/j.jpeds.2017.05.015
34. Yang P, Cornejo KM, Sadow PM, Cheng L, Wang M, Xiao Y, Jiang Z, Oliva E, Jozwiak S, Nussbaum RL, Feldman AS, Paul E, Thiele EA, Yu JJ, Henske EP, Kwiatkowski DJ, Young RH, Wu CL (2014) Renal cell carcinoma in tuberous sclerosis complex. Am J Surg Pathol 38:895–909. https://doi.org/10.1097/PAS.0000000000000237
35. Al-Saleem T, Wessner LL, Scheithauer BW, Patterson K, Roach ES, Dreyer SJ, Fujikawa K, Bjornsson J, Bernstein J, Henske EP (1998) Malignant tumors of the kidney, brain, and soft tissues in children and young adults with the tuberous sclerosis complex. Cancer 83:2208–2216
36. Breysem L, Nijs E, Proesmans W, Smet MH (2002) Tuberous sclerosis with cystic renal disease and multifocal renal cell carcinoma in a baby girl. Pediatr Radiol 32:677–680. https://doi.org/10.1007/s00247-002-0765-9
37. Lendvay TS, Broecker B, Smith EA (2002) Renal cell carcinoma in a 2-year-old child with tuberous sclerosis. J Urol 168:1131–1132. https://doi.org/10.1097/01.ju.0000023872.96719.39
38. Tyburczy ME, Jozwiak S, Malinowska IA, Chekaluk Y, Pugh TJ, Wu CL, Nussbaum RL, Seepo S, Dzik T, Kotulska K, Kwiatkowski DJ (2015) A shower of second hit events as the cause of multifocal renal cell carcinoma in tuberous sclerosis complex. Hum Mol Genet 24:1836–1842. https://doi.org/10.1093/hmg/ddu597
39. Ambalavanan M, Geller JI (2019) Treatment of advanced pediatric renal cell carcinoma. Pediatr Blood Cancer 66:e27766. https://doi.org/10.1002/pbc.27766
40. Jimenez RE, Eble JN, Reuter VE, Epstein JI, Folpe AL, de Peralta-Venturina M, Tamboli P, Ansell ID, Grignon DJ, Young RH, Amin MB (2001) Concurrent angiomyolipoma and renal cell neoplasia: a study of 36 cases. Mod Pathol 14:157–163. https://doi.org/10.1038/modpathol.3880275
41. Elsamaloty H, Abdullah A, Elzawawi M (2010) Multiple bilateral renal oncocytoms in a known case of tuberous sclerosis: a case report. Abdom Imaging 35:115–117. https://doi.org/10.1007/s00261-008-9486-3
42. Williams GM, Lynch DT (2020) Renal oncocytoma. In: StatPearls. StatPearls Publishing LLC, Treasure Island

43. Bissler JJ, Kingswood JC (2004) Renal angiomyolipomata. Kidney Int 66:924–934. https://doi.org/10.1111/j.1523-1755.2004.00838.x
44. Eijkemans MJ, van der Wal W, Reijnders LJ, Roes KC, van Waalwijk, van Doorn-Khosrovani SB, Pelletier C, Magestro M, Zonnenberg B (2015) Long-term follow-up assessing renal angiomyolipoma treatment patterns, morbidity, and mortality: an observational study in tuberous sclerosis complex patients in the Netherlands. Am J Kidney Dis 66:638–645. https://doi.org/10.1053/j.ajkd.2015.05.016
45. Kingswood JC, Bruzzi P, Curatolo P, de Vries PJ, Fladrowski C, Hertzberg C, Jansen AC, Jozwiak S, Nabbout R, Sauter M, Touraine R, O'Callaghan F, Zonnenberg B, Crippa S, Comis S, d'Augeres GB, Belousova E, Carter T, Cottin V, Dahlin M, Ferreira JC, Macaya A, Benedik MP, Sander V, Youroukos S, Castellana R, Ulker B, Feucht M (2014) TOSCA - first international registry to address knowledge gaps in the natural history and management of tuberous sclerosis complex. Orphanet J Rare Dis 9:182. https://doi.org/10.1186/s13023-014-0182-9

Answers to multiple-choice questions:

1. C 2. D 3. A 4. C 5. B