Evidence-based protocol-led management of renal angiomyolipoma: A review of literature

Sophie Vaggers[1], Patrick Rice[1], Bhaskar K. Somani[1], Rajan Veeratterapillay[2], Bhavan P. Rai[2]

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ABSTRACT

Renal angiomyolipomas (R-AMLs) are rare benign tumors, which occur sporadically and in association with genetic conditions such as tuberous sclerosis complex (TSC) and lymphangioleiomyomatosis (LAM). The key clinical concern is life-threatening hemorrhage. There is uncertainty about the optimal management strategy for patients with R-AMLs. We aim to review the evidence and provide a protocolled approach for the management of R-AMLs. A literature search of R-AML was conducted using MEDLINE and EMBASE for articles published between January 1990 and March 2020. Patient with TSC and sporadic cases were included. Treatment strategies, including active surveillance, surgery, selective arterial embolization (SAE), ablation, and systemic therapies, were reviewed. Outcomes from contemporary case series of active surveillance, surgery, and SAE were collated. There were no randomized controlled trials on this topic. The retrospective case series reviewed showed that many R-AMLs can be managed safely with active surveillance. Tumor size is the most important predictor of bleeding, and other factors such as rate of growth, women of child-bearing age, aneurysm size, and symptoms should be considered when deciding on prophylactic treatment. There is limited evidence for the traditional 4-cm cutoff for treatment, which may lead to overtreatment. The primary intervention options are SAE and surgery; whereas SAE is a less invasive option, nephron sparing surgery offers a lower risk of recurrence. Both appear to have similar morbidity, and the current evidence does not recommend one over the other in most cases. Thermal ablation has promising results but has only been trialed in small case series. Patients with TSC can be offered mammalian target of rapamycin inhibitors of which everolimus appears to cause the greatest shrinkage of tumors with an acceptable side-effect profile. R-AMLs should be assessed for their risk of bleeding. Low-risk tumors should be treated with active surveillance. High-risk tumors should be treated with SAE or surgery. Systemic treatments are the first-line of treatment for patients with TSC to preserve renal parenchyma.

Keywords: Active surveillance; angiomyolipoma; arterial embolization; haemorrhage; kidney; nephron sparing surgery; renal.

[1]Urological Surgery Department, University Hospital Southampton NHS Trust, Southampton, UK
[2]Department of Urology, The Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK

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Corresponding Author: Sophie Vaggers
E-mail: sophie.vaggers@doctors.org.uk

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Introduction

Renal angiomyolipomas (R-AML) are rare benign renal tumors with an overall prevalence of approximately 0.13%–0.44% and a females to males ratio of 2:1.[1-3] Angiomyolipomas (AMLs) occur sporadically in 80% of cases, and the remaining 20% are associated with genetic mutations causing tuberous sclerosis complex (TSC) or lymphangioleiomyomatosis (LAM).[4-6] They are composed of blood vessels, smooth muscle cells, and adipose tissue.[7] R-AMLs classically present symptomatically with hemorrhage or pain[8] but are more likely to be discovered incidentally, especially with an increasing rate of abdominal scans. AMLs have a characteristic hyperechoic appearance on ultrasound (US) scans owing to their high lipid content. US can misdiagnose these tumors in up to one-third of cases with occasional renal cell carcinomas (RCC) being missed.[9] Most R-AMLs can be diagnosed with computed tomography (CT) scans; however, some fat-poor tumors, which mimic RCC, may need magnetic resonance imaging (MRI) scans and potentially a biopsy to confirm the diagnosis.[10,11]

The key clinical concerns for R-AMLs is hemorrhage, which may be life-threatening.[12] Historically, for patients considered at high risk of hemorrhage, the primary treatment option would be nephrectomy.[1] With advances in

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technology, the management is now more targeted. Low-risk R-AMLs can be managed with active surveillance.[8,13] High-risk R-AMLs are managed with less invasive treatments such as nephron sparing surgery (NSS), selective arterial embolization (SAE), or mammalian target of rapamycin (mTOR) inhibitors.[14]

The lack of prospective trials in this field and a limited number of large retrospective case series have created difficulties for clinicians in choosing the best approach for their patient. We provide an up-to-date review on the management of R-AMLs with an evidence-based protocolled approach (Figure 1) to treatment options.

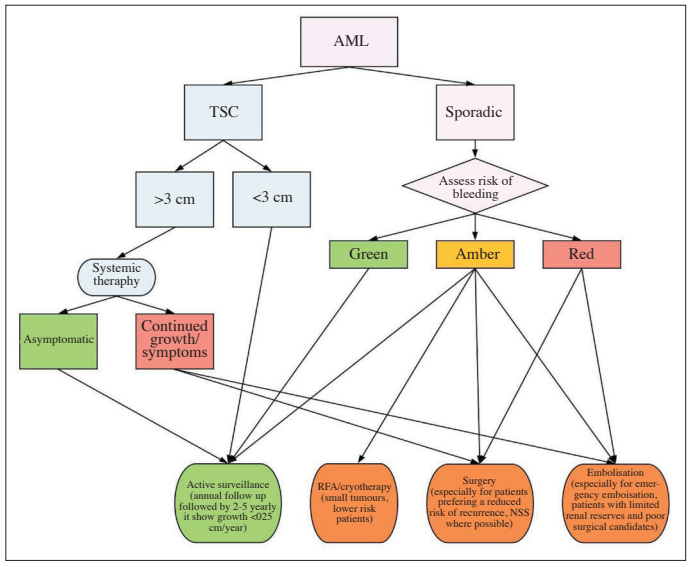

Figure 1. An evidence-based protocolled approach for management of renal angiomyolipomas

Main Points:

- Renal angiomyolipomas (R-AMLs) are rare benign tumors—some remain asymptomatic, whereas some present with life-threatening hemorrhage.
- Treatment options include active surveillance, surgical management, embolization, or systemic therapy; however, there is uncertainty about the optimal management strategy for these patients.
- There are no randomized controlled trials on this topic, but retrospective case series show that many R-AMLs can be managed safely with active surveillance.
- Tumor size is the most important predictor of bleeding, and other factors such as rate of growth, women of child-bearing age, aneurysm size, and symptoms should be considered when deciding on prophylactic treatment.
- New systemic therapies are currently being offered to patients with tuberous sclerosis to help shrink the angiomyolipomas.

Methods

A literature search of R-AMLs was conducted using MEDLINE and EMBASE for articles published between January 1990 and March 2020. The results were filtered for English language articles and human studies. Search terms included but were not limited to "renal angiomyolipoma," "kidney," "AML," "embolization," "nephrectomy," "partial nephrectomy," "nephron sparing surgery," "ablation," and "mTOR." Further sources were identified in the reference lists of the identified articles. Case series including >10 patients relating to surgical management, selective transarterial embolization and ablative therapies, and clinical trials of mTOR inhibitors (including sufficient data on selected patients and outcomes) were specifically reviewed. A management protocol was devised on the basis of the evidence in these studies.

Active Surveillance and Risk of Hemorrhage

Patients who are asymptomatic with small tumors and at low risk of rupture may be managed conservatively. Table 1 shows the categorization of patients into low, medium, and high risk on the basis of the available evidence outlined below. A R-AML of >4 cm has long been considered as high risk. This approach was initiated by Oesterling et al.[1] in their literature review and small case series in 1986. They found that 82% of R-AMLs of >4 cm were symptomatic with hemorrhage or pain compared with only 23% of the tumors of <4 cm. Since this study was published, AMLs have often been intensively imaged and treated prophylactically when they reach this size.[15] There have been concerns that there was significant selection bias of symptomatic patients in these early studies.[8] More recent studies suggest that the risk bleeding only increases with much larger tumors.[16,17] There has been no definitive size recommended for intervention; however, a pooled analysis by Kuusk[17] reported a significantly increased risk of bleeding in tumors of > 6 cm, and Lee et al.[18] suggested that tumors of >7.35 cm had a higher risk of bleeding. In the selection of recent case studies, we observed that in patients on active surveillance, the rate of spontaneous hemorrhage was low at 0.0%–3.1% (Table 2). Approximately 78.5%–90% of these patients had tumors, which were found incidentally, and most tumors were smaller than 4 cm.

Size is not the only factor to consider when selecting which patients can be safely managed with active surveillance and which patients are at risk of hemorrhage; intralesional aneurysms might also be a factor that predicts hemorrhage. In a study of 23 patients, Yamakado et al.[19] found that all 8 patients with a ruptured R-AML had aneurysms of >5 mm in diameter. A multivariable regression analysis of factors predictive of rupture found that aneurysm size was the sole predictor of rupture ($p<0.001$) and that the size of tumor was not a predictive factor. Rimon et al.[20] created a grading system for the vascularity of R-AMLs on the basis of dig-

Table 1. Categorization of R-AMLs into low, medium, and high risk of hemorrhage and need for treatment

Risk level		Low	Medium	High
Size of tumor		<4 cm	4–6 cm	>6 cm
Symptoms		Asymptomatic No bleeding	Moderate symptoms, e.g. mild flank pain	Severe symptoms, e.g. hemorrhage, significant pain or mass effect
Growth rate		<0.25 cm/year	>0.25 cm/year	>0.25 cm/year
Imaging results	Aneurysms	Aneurysms <2.5 mm	Aneurysm >5 mm	Aneurysm >5 mm
	Vascularity	Minimal vascularity	Moderate vascularity	Significant vascularity
Patient factors			Good compliance with follow-up	Patients of child-bearing age. Unable to access follow-up/ emergency treatment.

R-AML: renal angiomyolipoma.

Table 2. Selected representative case series for active management of AMLs

Paper	Number patients	FU time (months)	Initial size	Patients with TSC (%)	Growth Rate (cm/year)	Incidental presentation (%)	Spontaneous bleeding (%)	Active treatment (%)
Bhatt et al., 2016[8]	447	43	88% ≤4 cm; 12% >4 cm	3.8	0.02	90.8	2.7	5.6
Chan et al. 2018[23]	217	24	Median: 0.9 cm (0.3–8.6)	0	0.1	NR	0.0	2.8
Maclean et al. 2014[22]	135	21.8	<2 cm	4.4	0.015	NR	2.2	2.2
Ouzaid et al. 2014[16]	130	49	70.8% <4 cm; 29.2% ≥4 cm	7.7	NR	78.5	3.1	13.1
Mues et al. 2010[13]	45	54.8	Mean: 1.7 cm (0.7–13)	0	0.08	83.9	2.3	6.7
Total	974			3.6			2.1	10.1

NR: not recorded; FU: follow-up; AML: angiomyolipoma; TSC: tuberous sclerosis complex

ital subtraction angiography and CT scan. Tumors with minimal vascularity were less likely to bleed. The European Association of Urology has suggested treatment for patients with persistent pain or acute or repeated bleeding episodes, women of child-bearing age, patients with limited access to follow-up or emergency interventions, and suspicion of malignancy.[21]

There is no consensus on the frequency of imaging in active surveillance; the frequency can be decided on a case-by-case basis on the basis of the initial size of tumor, rate of growth, age of presentation, and TSC status. Periodic imaging is important to determine the growth rate of tumor. In a retrospective review by Bhatt et al.,[8] a subset of patients with a higher growth rate of >0.25 cm/year were at an increased risk of hemorrhage. Most R-AMLs grow at a very slow rate of 0.015–0.1 cm/year, and these R-AMLs do not need frequent reimaging. Some studies suggest that small AMLs of <2 cm may not need follow-up at all because their risk of significant growth is around 1%.[22] After evaluating the growth of their sporadic AML cases, Chan et al.[23] suggested a surveillance policy of 5 US/year for patients with AMLs between 2.1 cm and 29 cm and 2 US/year for those with tumors between 3 cm and 3.9 cm. Surveillance was stopped if there was no growth. Some studies report an increased growth rate in larger tumors,[22] but others report no difference in the rate of growth between small and large AMLs.[8,23]

Patients with TSC, studied by Seyam at el.,[24] were found to have a significantly higher growth rate of 1.25 cm/year compared with 0.19 cm/year for sporadic AMLs. The International Tuberous Sclerosis Complex Consensus conference recommends an abdominal MRI every 1–3 years to monitor disease progression. Furthermore, AMLs diagnosed at a younger age have been found to have an increased growth rate, possibly because of undiagnosed TSC.[22]

Surgical Management

Surgical management of AMLs have progressed from nephrectomies to open NSS and to minimally invasive NSS.[25-27] Given

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Table 3. Characteristics of selected NSS series for AML

Study	N	FU time (months)	Mean initial size, cm (range)	Patients with TSC (%)	Incidental presentation/ asymptomatic (%)	Surgical procedure
Heidenreich et al. 2002[25]	28	57.6	5.5 (2.7–27)	NR	82.2	Open NSS
Minervini et al. 2007[27]	37	56.4	4.8 (1.5–15.0)	22	44	Simple enucleation/RN
Boorjian et al. 2007[31]	58	96	3.9 (0.8–12.5)	0	54.7	Open NSS
Msezane et al. 2010[29]	14	28.8	2 (IQR: 2–7.5)	NR	NR	LPN
Golan et al. 2017[32]	40	8	7.5 (IQR: 5–8.5)	15	75	RAPN

NSS: nephron sparing surgery; RN: radical nephrectomy, RAPN: robot-assisted partial nephrectomy; LPN: laparoscopic partial nephrectomy; NR: not recorded; IQR: interquartile range; FU: follow-up; AML: angiomyolipoma; TSC: tuberous sclerosis complex

Table 4. Outcomes of selected NSS series for AML

Study	Postoperative renal function	Recurrence rate	Resolution of symptoms	Postoperative complications		
				Mortality	CD 1/2	CD 3/4
Heidenreich et al. 2002[25]	0.5	0%	100%	0%	NR	10.7% Fistula (3)
Minervini et al. 2007[27]	4.2% (p=0.063)	5.9%	NR	0%	8.1% AF (1) Infection (2)	2.7% Wound infection with drain (1)
Boorjian et al. 2007[31]	0.1	3.4%	100%	0%§	12.1% Ileus (5) Infection (1) Urine leak (1)	13.5% Hemorrhage (1) Urine leak (requiring intervention) (2) Pneumothorax (1) Dialysis (1)
Msezane et al. 2010[29]	preoperative eGFR 99.2, postoperative eGRFR 84	0%	NR	0%	14.2 NR (2)	7.1% Hemorrhage (1)
Golan et al. 2017[33]	-5% (IQR-14, 0)	0%	100%	0%	2.5% Urine leak (1)	2.5% Infection (drain) (1)

eGFR: estimated glomerular filtration rate;§: disease specific; CD: Clavien Dindo; AF, atrial fibrillation; NR: not recorded; NSS: nephron sparing surgery; AML: angiomyolipoma.

the benign nature of these lesions, renal-preserving treatments are favored. Outcomes from large studies for the treatment of RCC demonstrate that NSS delivers better renal function and improved survival than nephrectomy.[28] However, there are indications where nephrectomy may be necessary, for example, R-AMLs that have replaced most renal parenchyma and cases with a strong suspicion of malignancy.

NSS is an effective treatment for R-AML with low rates of recurrence of 0%–5.9% across our selected case series (Tables 3 and 4) with 100% resolution of symptoms reported. The complication rate was moderately low and was no different from NSS for other renal tumors.[29,30] As would be expected, increasing tumor size significantly correlated with higher intraoperative blood loss, longer warm ischemic time, and duration of hospital stay.[27] The most common complications were ileus, urine leak, and hemorrhage. Postoperative transfusions were not included in the complication rate. Of 117 cases reviewed, there were 2 (1.1%) reported cases of patients requiring embolization for hemorrhage postoperatively.[29,31] Moreover, 5 (2.8%) patients developed urine leaks requiring intervention-4 were treated with ureteric stents and 1 with reconstructive surgery. Several studies showed a small decrease in renal function, although this was rarely significant.[25,27,29] No patients developed new renal insufficiency. In Boorjian et al.'s[31] study of 58 patients, only 1 patient had a significant worsening of their pre-existing chronic renal impairment after being treated with NSS for AML and RCC of the ipsilateral kidney. The patient ultimately required hemodialysis during follow-up. A small number of patients with NSS of a solitary kidney had no long-term increase in creatinine (CN).[27]

Table 5. Characteristics of select contemporary embolization series for AML

Study	N	FU time (months)	Mean initial size, cm (range)	Patients with TSC (%)	Incidental presentation/ asymptomatic	Emergency procedure
Anis et al. (2020)[44]	71	121	9.8 (IQR: 7–12)	17.60%	45.9%	0%
Wang et al. (2017)[45]	79	35.9	8.4 (SD 3.5)	27.8%	39.2%	0%
Planché et al. (2011)[47]	30	20.5	8.2 (0.3–17.3)	60%	76.7%	0%
Ramon et al. (2009)[46]	41	57.6	10.3 (2.5–25.0)	19.5	51.2%	0%
Chan et al. (2011)[48]	27	85.2	10.9 (4–30)	3.70%	46.4%	33.3%

SD: standard deviation; IQR: interquartile range; FU: follow-up; AML: angiomyolipoma; TSC: tuberous sclerosis complex.

Table 6. Outcomes of select contemporary embolization series for AML

Study	Post-procedure renal function	Size reduction	Repeat procedure	Post-procedure complications			
				Mortality	PES	CD 1/2	CD 3/4
Anis et al. (2020)[44]	eGFR: 81.97	27%	41.1% re-embolization, 5.9% surgery***	0§	NR	1.4% Abscess (requiring nephrectomy) (1)	1.4% Abscess (requiring nephrectomy) (1)
Wang et al. (2017)[45]	NR	1.7 cm±1.3; 20.7%±16.0†	43.0% planned, 6.3% unplanned	NR	86.1%	NR	2.5% Dialysis (1) Pleural effusion (1)
Planché et al. (2009)[47]	CN: pre=83 μmol/L post=82 μmol/L	43%±32	16.7% re-embolization*	NR	NR	20% Renal infarction (4) Acute pain syndrome (2)	6.7% Abscess (1) Liquefaction necrosis (1)
Ramon et al. (2009)[46]	CN: pre=0.89 ng% post=0.87 ng%	NR	61.4% re-embolization, 6.3% surgery***	0%§	12.2%	11% NR	0%
Chan et al. (2011)[48]	NR	9.9 cm (SD: 3.9) to 7.4 cm (SD: 3.4)†	14.3% re-embolization, 14.3% surgery*	0%	34.4%**	NR	NR

PES: postembolization syndrome; eGFR: estimated glomerular filtration rate; CN: creatinine; §: disease specific; CD: Clavien Dindo; AML: angiomyolipoma; NR: not recorded.

*AMLs, **SAEs, ***Kidney units, †statistically significant, ‡3 months for AMLs followed for 1–6 months after embolization.

Several techniques have been suggested in the literature. AMLs are surrounded by a distinct pseudocapsule that allows enucleation through an avascular plane. A case series of simple enucleation of 37 AMLs was successful in all but 3 patients where sharp dissection was used because of difficulties in defining the plane of the tumor.[27] Robot-assisted partial nephrectomy has been shown to be a safe and effective alternative.[32] In a small case series, Golan et al.[32] showed that patients who received NSS after failed embolization of an AML had no significant difference in operative time, blood loss, or postoperative complications.

Surgery is not the first-line of treatment in patients with TSC.[33] The bilateral nature of the condition and multiple tumors mean that repeated surgical interventions with loss of renal tissue may hasten the need for renal replacement therapy.[34] If surgery is necessary, NSS is vital because saving the nephrons is a priority, although embolization may be the preferred option to preserve the renal tissue.

Embolization

SAE is used to devascularize the AMLs, which combines the aims to preserve maximal renal tissue and reduce the risk of further

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bleeding.[35,36] SAE can be performed with a variety of embolic agents, including metallic coils, trisacryl gelatin microspheres, and polyvinyl alcohol, with larger embolic agents being associated with a better long-term efficacy than smaller agents.[37,38]

SAE allows the treatment of AMLs present in difficult-to-access locations, for example, hilar tumors, which are not amenable to partial nephrectomy. SAE is also particularly well suited to stabilizing a patient with acute hemorrhage[39] and is frequently chosen over surgical management, which would in most cases lead to a total nephrectomy. Patients who are high-risk surgical candidates should be offered SAE as a first-line of treatment. With large AMLs, SAE can also be used before surgery to reduce the size of tumors and the likely procedural difficulties. In a retrospective analysis of 36 patients, SAE before NSS decreased the operating time, intraoperative blood loss, and warm ischemia time ($p<0.05$) and improved postoperative renal function ($p<0.001$).[40]

SAE is considered to be a relatively safe procedure, with a recent systematic review summarizing 524 cases of SAE for AMLs, which found a low level morbidity of 6.9% (not including postembolization syndrome [PES]) and technical success rate of 93.3%. However, SAE has a high reintervention rate of 20.9% over an average follow-up of 39 months[36] because of regrowth or rebleeding of the tumor. Young patients with TSC are particularly at risk, with a greater rebound growth after SAE than that in patients with sporadic AMLs.[41,42] Tumors with multiple feeders also have a higher risk of recurrence than the tumors fed by a distinct arterial branch.[43] Furthermore, patients who present with acutely bleeding AMLs and treated with embolization are at a higher risk of needing retreatment.[44]

In this review, outcomes were mixed for embolization with high re-embolization rates of 16.7%–61.4%, potentially because of the variation in the proportion of patients with TSC (3.7%–60%) and follow-up times (20.5–121 months) (Tables 5 and 6).[44-48] The mean initial size ranged from 8.2 cm to 10.9 cm. Symptomatic R-AMLs were treated in 23.3%–60.7% patients, and asymptomatic R-AMLs, with treatment as a prophylactic measure, were treated in 39.2%–76.7% patients. The high re-embolization rates (16.7%–61.4%) indicate that embolization is not always a one-off procedure, and either planned or unplanned future embolization is likely to be needed. In the studies reviewed, there was a low conversion to requiring surgery (5.9%–14.3%).

A significant number of patients suffer from PES (12.2%–86.1%). PES is a self-limiting condition characterized by low-grade fever, pain, fatigue, nausea, and vomiting with symptoms peaking at around 48 hours after the procedure and resolving within a week. Other minor complications (Clavien Dindo [CD] 1/2) ranged from 11.2% to 20.0%. Major complications were much less frequent, with CD 3/4 complications ranging from 2.5% to 6.7%, with zero procedural complications, indicating a high overall safety of embolization.

Overall, SAE provides a safe and effective technique for targeting and reduction of R-AMLs and confers both a low rate of major complications and conversion to surgery. However, this comes at a cost of a high rate of needing re-embolization.

Ablation

Radiofrequency ablation (RFA) and cryotherapy have been proposed as alternatives to embolization after their widespread use to treat renal malignancies. It is hypothesized that they may cause less damage to the surrounding tissues. A small study included 15 patients with R-AMLs who were successfully treated with RFA with a minor decrease in CN level and no recurrences during a mean follow-up of 21 months.[49] The procedure-specific complication rate was 13.3%, with hematuria and intercostal nerve transection reported with it. The largest cryotherapy study reported 19 cases with no major complications and no recurrence with a 25-month follow-up.[50] These studies appear to show a lower rate of reintervention than embolization, but larger and prospective studies are required to confirm these initial findings.

Systemic Therapies

Systemic oral therapies, everolimus and sirolimus, inhibit the mTOR pathway. Mutations in the *TSC1* and *TSC2* genes occur in most patients with TSC and result in hyperactivation of mTOR signaling pathway and subsequent unregulated proliferation of cells.[52] mTOR inhibitors treat multiple manifestations of TSC, including AMLs, respiratory, dermatological, and neurological conditions.[52,53]

Davies et al.[54] investigated sirolimus for the treatment of R-AMLs in 16 patients with TSC or LAM in a phase 2 nonrandomized open-label trial. All AMLs reduced in size, and 50% had a formal partial response by the Response Evaluation Criteria in Solid Tumors criteria of at least a 30% reduction in the sum of the longest diameters of the tumor. The mean longest diameter of the tumors was similar at 12 and 24 months suggesting that the tumor response is maintained by further treatment, but the maximal response was attained in the first 12 months. The most common side effects were oral mucositis (37.5%), respiratory infections (31.3%), and proteinuria (31.3%). There were 3 serious adverse events possibly related to sirolimus-1 patient with severe sporadic LAM died after a respiratory infection, and 2 other patients were hospitalized with infections.

Everolimus was tested in a double-blind placebo-controlled phase 3 trial, Examining everolimus In a Study of Tuberous sclerosis complex (EXIST-2).[55] The trial showed that 42% of patients with

TSC or LAM and AMLs of >3 cm benefited from >50% reduction in tumor after 6 months. After these results, the patients were then recruited to a long-term open label everolimus trial in an extension phase. After a median follow-up of 47.2 months, the patients showed a good response, with 58% of them having >50% reduction in tumor.[56] The most common adverse events that were suspected to be treatment-related were stomatitis, hypercholesterolemia (30.4%), acne (25.9%), aphthous stomatitis, and nasopharyngitis. There was a reasonably high rate of CD 3/4 adverse events at 26.8%, most commonly grade 3 amenorrhea (4.2% of the at-risk female population) and decreased blood phosphorous (3.6%). In the initial EIXST-2 trial, there was no decrease in the renal function, although renal function decreased in the extension phase, but this was less than the decrease observed in placebo patients in the earlier trial. No patients experienced spontaneous bleeding of their AMLs. Everolimus appeared to be better tolerated and provided more reduction in tumor volume. This was corroborated by a retrospective analysis of 18 patients receiving either everolimus or sirolimus, which demonstrated a mean volume reduction of AML of 55.6% or 30.5%, respectively.[57]

There is a concern about the side effects of these medications; however, it is mostly argued that the side effects are preferable to renal damage or hemorrhage caused by AML progression.[53,54] The side effects are often reversed by stopping the treatment.[56,58] However, there is a rebound effect when stopping the treatment, wherein the AMLs often start to regrow. Intermittent everolimus administration was tested by Hatano et al.[58]. In total, 8 patients did not have any tumor growth after everolimus withdrawal. The other 18 patients who experienced regrowth to >70% of the pretreatment tumor volume restarted everolimus. The average size reduction in the retreatment group was 61%, equivalent to the initial reduction of 61%. Intermittent treatment may be a preferred option because long-term administration of everolimus for chemotherapy has shown to increase the risk of developing gonadal dysfunction,[56] interstitial lung disease,[59] and immune–suppression-related complications.[60]

Guidelines from the 2012 TSC consensus conference recommended mTOR inhibitors as the first-line of treatment with lesions >3 cm.[33] After mTOR inhibitors, SAE or NSS were recommended as possible second-line of therapies for AMLs, but nephrectomy should be avoided if possible.[33] Renal failure is a common feature of TSC and a significant cause of morbidity and mortality.[61,62] Overtreatment with SAE and NSS can exacerbate premature loss of kidney function.[61]

Pregnancy

AMLs are at risk of rapidly increasing in size during pregnancy because of an increase in the circulating blood volume, increase in pressure owing to uterine growth,[63] and hormonal sensitivity to estrogen and progesterone.[64] A handful of case studies report AML rupture during pregnancy, with a range of management options of early delivery, emergency/prophylactic embolization, or active surveillance.[65] There is no evidence to conclude the best approach; however, AMLs in women of child-bearing age are often prophylactically treated because of the concerns of rupture during pregnancy causing maternal or fetal harm.[66]

Limitations

The quality of evidence in the literature regarding the management of R-AMLs is inadequate, predominately level 4. There are no prospective randomized trials, and there are a very limited number of studies comparing different treatment modalities. This is understandable because R-AMLs are a rare condition, and collaboration between multiple organizations would be necessary to provide sufficient patients for large study. Ideally, prospective randomized trials are needed to clarify the risk of hemorrhage, indications for intervention, and the best treatment modality for different patient groups. There is significant heterogeneity of the data; therefore, we were unable to directly compare the surgical and SAE series. Many of the studies conducted to date combine the data from patients with TSC and sporadic cases. These patient groups act differently in their risk of hemorrhage, growth, and recurrence and should be treated as separate groups.

Conclusion

Many R-AMLs have a low risk of bleeding and are slow-growing and asymptomatic. These tumors can be managed with active surveillance. Larger tumors have an increased risk of bleeding, but the cutoff for treatment appears to be 6–7 cm rather than 4 cm, which has long been adhered to. Other factors such as rate of growth, women of child-bearing age, aneurysm size, symptoms, and risk of malignancy should be considered when deciding on prophylactic treatment.

The primary intervention options are SAE and NSS; whereas SAE is a less invasive treatment, NSS offers a lower risk of recurrence and retreatment. Both appear to have a similar morbidity, and the current evidence does not recommend one over the other in the average patient. However, SAE is particularly well suited for treating acute hemorrhage in tumors with a distinct arterial feeder or in patients with multiple comorbidities. Total nephrectomy should only be used as the last resort or with significant risk of malignancy. mTOR inhibitors are the first-line of treatment for TSC, and embolization may be the preferred second-line of treatment to prevent the loss of normal renal parenchyma.

The management strategy provided here is limited by the quality of evidence it is based on. When deciding a management plan, urologists should also consider each individual clinical scenario and patient and surgeon preference and match it up to the resources available to manage these patients.

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