Update on the Diagnosis and Management of Renal Angiomyolipoma

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Purpose: Advances in minimally invasive therapies and novel targeted chemotherapeutics have provided a breadth of options for the management of renal masses. Management of renal angiomyolipoma has not been reviewed in a comprehensive fashion in more than a decade. We provide an updated review of the current diagnosis and management strategies for renal angiomyolipoma.

Materials and Methods: We conducted a PubMed® search of all available literature for renal or kidney angiomyolipoma. Further sources were identified in the reference lists of identified articles. We specifically reviewed case series of partial nephrectomy, selective arterial embolization and ablative therapies, including trials of mTOR inhibitors for angiomyolipoma from 1999 to 2014.

Results: Renal angiomyolipoma is an uncommon benign renal tumor. Although associated with tuberous sclerosis complex, these tumors occur sporadically. Risk of life threatening hemorrhage is the main clinical concern. Due to the fat content, angiomyolipomas are generally readily identifiable on computerized tomography and magnetic resonance imaging. However, fat poor angiomyolipomas can present a diagnostic challenge. Novel research suggests that various strategies using magnetic resonance imaging, including chemical shift magnetic resonance imaging, have the potential to differentiate fat poor angiomyolipoma from renal cell carcinoma. Active surveillance is the accepted management for small asymptomatic masses. Generally, symptomatic masses and masses greater than 4 cm should be treated. However, other relative indications may apply. Options for treatment have traditionally included radical and partial nephrectomy, selective arterial embolization and ablative therapies, including cryoablation and radio frequency ablation, all of which we review and update. We also review recent advances in the medical treatment of patients with tuberous sclerosis complex associated angiomyolipomas with mTOR inhibitors. Specifically trials of everolimus for patients with tuberous sclerosis complex suggest that this agent may be safe and effective in treating angiomyolipoma tumor burden. A schema for the suggested management of renal angiomyolipoma is provided.

Conclusions: Appropriately selected cases of renal angiomyolipoma can be managed by active surveillance. For those patients requiring treatment nephron sparing approaches, including partial nephrectomy and selective arterial embolization, are preferred options. For those with tuberous sclerosis complex mTOR inhibitors may represent a viable approach to control tumor burden while conserving renal parenchyma.
RENAL angiomyolipoma is an uncommon tumor that, although benign, in most cases can involve difficult management decisions. This entity was first referenced in 1900, and in 1911 Fischer first described the histopathology as including 3 components, ie dysmorphic blood vessels, smooth muscle and mature adipose tissue, from which the tumor derives its name. However, the term angiomyolipoma did not come into wide use until the middle of the 20th century. These tumors can occur sporadically or in association with tuberous sclerosis complex or, more rarely, sporadic lymphangioleiomyomatosis.

Diagnosis and management of renal AML have not been reviewed in a comprehensive fashion in more than a decade. In that time advances in minimally invasive therapies and novel targeted chemotherapeutics have increased the options for management of AML. We provide an up-to-date review of the current diagnosis and management of renal AML, including a management algorithm, which should be of value to the practicing urologist.

METHODS

A PubMed search of all available literature for renal or kidney angiomyolipoma was conducted. Further sources were identified in the reference lists of identified articles. Case series (including at least 10 cases and most followup data) of partial nephrectomy, SAE and ablative therapies as well as trials of mTOR inhibitors for the treatment of AML from 1999 to 2014 were specifically reviewed. A management algorithm was constructed using the available data.

EPIDEMIOLOGY

Renal AMLs occur uncommonly in the general population, with females more commonly affected than males. A screening study for renal neoplasms using ultrasound in 17,941 Japanese adults revealed an overall rate of renal AML of 0.13%, with 0.22% of females affected and 0.1% of males. Historical series demonstrate a female-to-male ratio of 2:1. The proportion of AML cases involving TSC is about 20%. TSC is an autosomal dominant disease with an estimated prevalence of 1 in 10,000. A reported rate of renal AML in association with TSC range from 55% to 90%. Renal AML also occurs in 30% to 50% of patients with sporadic LAM, a much rarer condition than TSC that is almost exclusively seen in women. Age at presentation varies, with patients with TSC more likely to present by their 20s or 30s, and patients with sporadic AML in their 40s or 50s.

PATHOPHYSIOLOGY

Renal AML can occur as part of TSC sporadically or, less commonly, in association with sporadic LAM. The molecular genetics of TSC have been well characterized, with mutations to TSC1 at chromosomal location 9q34 and TSC2 at 16p13.3 identified. Although generally considered an autosomal dominant condition, up to two-thirds of patients have sporadic mutations to TSC1 and TSC2. TSC1 and TSC2 encode proteins carrying the same names, also known as hamartin and tuberin, respectively. These proteins interact with each other to form heterodimers, whose most important role is inhibition of the mTOR pathway.

Loss of TSC1 or TSC2 leads to unchecked activation of mTOR, which leads to unregulated protein synthesis, increased cell growth and proliferation, increased angiogenesis, and changes in cell orientation and migration. These downstream effects of unchecked mTOR activation lead to a variety of clinical manifestations associated with TSC. The most common of these manifestations are seen in the central nervous system, with more than 90% of affected individuals having some combination of epilepsy, neurocognitive impairment and autism due to cortical tubers, subependymal nodules and giant cell astrocytomas. The majority of patients with TSC will also have some combination of cutaneous manifestations, which can include hypomelanotic macules, facial angiofibromas, ungual fibromas and shagreen patches.

The prevalence of renal AML in individuals with TSC is high (55% to 90% of cases), and these cases are generally multifocal and bilateral. Of women with TSC 40% will manifest some degree of pulmonary LAM, leading to pneumothorax, chylous pleural effusions and cystic lung disease. Other major features of TSC can include cardiac rhabdomyomas and retinal hamartomas. To establish a diagnosis of TSC, patients generally must have 2 major features of the syndrome or 1 major and 2 minor features. Genetic testing serves to confirm the diagnosis and the specific mutation involved in those who meet criteria, and can be useful in screening other family members in the case of a sporadic mutation.
DIAGNOSIS

Clinical Presentation

With the increased use of cross-sectional imaging, more than 80% of AMLs are now discovered incidentally, with hemorrhage at presentation (Wunderlich syndrome) seen in less than 15% of cases and shock in less than 10% in contemporary series.7,8 The classic triad of symptoms associated with renal masses of flank pain, palpable mass and hematuria was historically found in 37% to 41%, 11% to 35% and 11% to 24% of patients with AML, respectively.1,2 More recent series show generally lower rates of these symptoms, although Seyam7 and Sooriakumaran8 et al found that 50% and 22% of their cohorts, respectively, presented with pain and hematuria. Tumors are more likely to be large, multifocal and bilateral at presentation in patients with TSC, with current series revealing mean tumor sizes of 3.5 to 19.3 cm in patients with TSC vs 1 to 4 cm in those with sporadic AML.7,8

Imaging

Renal AML can be diagnosed reliably based on CT or MRI findings.9 The presence of fat is the hallmark finding, with the incidence of fat containing RCCs low enough that differentiating them from AMLs is rarely difficult.10,11 On ultrasound AMLs are almost always hyperechoic compared to renal parenchyma due to the presence of macroscopic fat. However, RCC also appears hyperechoic on US in approximately a third of cases.12 While AML has relatively characteristic findings on US, the overall diagnostic reliability of US is not high enough to allow it to be used confidently to distinguish AMLs. However, once a definitive diagnosis of AML has been made (ie via CT), US may be used to follow patients with AML.12

CT has excellent sensitivity, specificity, and positive and negative predictive values regarding AML and renal masses in general.13 Moreover, CT is rapid, cost effective and widely available in clinical practice. Even in small masses (less than 2 cm) macroscopic fat is often conspicuous enough to diagnose AML (fig. 1). Areas within a lesion of –15 HU or less are generally considered diagnostic of macroscopic fat. In 4% to 5% of AMLs intralesional fat cannot be detected on CT due to the small amount of fat within the lesion. These lesions are hyperdense on CT and enhance after administration of contrast medium. These AMLs represent a diagnostic challenge since they can closely mimic RCC.14 Fat may also be obscured by hemorrhage within an

Figure 1. a, axial image from contrast enhanced CT shows exophytic, primarily fat containing lesion arising off anterior mid right kidney. b, axial image from MRI of same lesion seen on CT. Note marked T2 hypointensity of exophytic right renal lesion, which is due to fibrotic elements within lesion. c, axial noncontrast enhanced T1 image of same lesion seen on CT. Note T1 hyperintensity of lesion secondary to macroscopic fat within lesion, typical of classic AML. d, axial, post-contrast, fat suppressed T1 images of same lesion reveal signal dropout of mainly fat containing lesion, again consistent with classic AML.
AML. In these instances phase contrast MRI may be helpful. Lesions that contain fat (macroscopic or microscopic) and calcification indicate a diagnosis of RCC since AMLs rarely contain calcifications. Like CT, MRI is accurate and specific for AML, is essentially equivalent in accuracy to CT in the diagnosis of AML and can be particularly helpful in diagnosing fat poor AMLs (fig. 1). Unlike CT, MRI does not expose the patient to ionizing radiation. Moreover, the diagnosis of AML can be made via noncontrast enhanced MRI, which is of particular usefulness in patients with compromised renal function. The disadvantages of MRI are cost, time to complete the scan and decreased availability compared to CT in daily clinical practice. On MRI comparing T1-weighted images with and without frequency selective fat suppression allows for detection of macroscopic fat within an AML. Masses that appear T1 hyperintense without fat suppression and T1 hypointense after frequency selective fat suppression are consistent with AML.

Another set of MRI sequences that is useful in diagnosing AML is in phase vs opposed phase chemical shift sequencing. Chemical shift imaging results in a sharp black boundary (india ink artifact) at the interface of macroscopic fat (contained in cells of AML) and water (contained in the renal parenchyma) on the opposed phase images (fig. 2). This sign is particularly useful in fat poor AMLs and in lesions smaller than 3 cm, in which the aforementioned typical T1 findings of AMLs may not be readily apparent. Another imaging clue suggestive of fat poor AML over RCC is relative T2 hypointensity of the lesion, which is the result of the predominance of the smooth muscle component and paucity of fat in the AML.

**Histopathology**
Renal AML is a mesenchymal neoplasm made up of 3 components in varying proportions, ie abnormal blood vessels, special spindle cells and mature adipocytes. AML is believed to be derived from perivascular epithelioid cells. Therefore, it is also called a pure epithelioid renal AML, or PECOMA, or is at least considered part of the PECOMA family.

Grossly AMLs are located in the renal parenchyma (fig. 3, a), rather than the capsule or perinephric tissue. The tumor is typically a well...
circumscribed mass with a tan-white, pink or yellow cut surface, depending on the lipid content (fig. 3, b). Hemorrhage can be seen with a red cut surface but necrosis is uncommon. Histologically a typical angiomyolipoma is a tumor made up of 3 components (fig. 4, a), namely vessels (angio), spindle cells (myo) and adipose tissue (lipo). The vessels are typically eccentric and thick walled. Spindle tumor cells may grow around a vessel (fig. 4, b) and have the features of smooth muscle and melanocytes. They range from mature appearing smooth muscle cells or immature spindle cells (fig. 4, c) to epithelioid cells. Adipocytes, which are intermingled with spindle cells, are mature without cytological atypia. Immunohistochemically HMB-45 and Melan-A, melanocytic markers, are often positive in the AML spindle cell component (fig. 4, d). Smooth muscle markers such as smooth muscle actin are also positive. Keratins and other epithelial markers are negative.

AML may display a wide range of histological variations that can make pathological diagnosis difficult. Focal degenerative cytological atypia (fig. 5, a) or epithelial appearance (fig. 5, b) in an AML can be seen, which can be mistaken for renal cell carcinoma or sarcoma. However, these atypical features usually are not associated with malignant behavior. Hyalinization (fig. 5, c), cystic changes or calcification can also be present in an AML. The lipomatous component can be minimal or absent (fig. 5, d) but these tumors are usually HMB-45 positive. AMLs may coexist with renal cell carcinoma. However, a true malignant AML is rare. There is some controversy over the diagnosis and behavior of epithelioid angiomyolipoma. Based on our experience and published studies, the majority of renal AMLs with focal epithelioid features are benign. Only pure epithelioid renal AMLs (PECOMAs) are potentially aggressive. Risk factors for malignant AML include size greater than 7 cm, tumor necrosis and epithelioid carcinoma-like pattern (fig. 6).

MANAGEMENT

Active Surveillance and Indications for Intervention

Historically the criteria for intervention in cases of renal AML have been symptomatic lesions larger than 4 cm, suspected malignancy and presence in women of childbearing age. Some authors have also suggested associated aneurysm larger than 5 mm, concomitant TSC and poor access to followup or emergency care as additional considerations for treatment. Figure 7 demonstrates an updated management schema based on the following discussion.

There have been no prospective randomized trials comparing surveillance and treatment for AML. Most series including cases of renal AML managed by active surveillance have been relatively small, the majority of which have sporadic nonTSC associated AMLs. These sporadic AMLs tend to exhibit a much slower growth rate through time compared to AMLs in patients with TSC. In comparing growth rates between sporadic and TSC associated lesions Seyam et al found an interval growth rate of 0.19 cm/yearly for sporadic AMLs and 1.25 cm/yearly for AMLs in patients with TSC at a mean followup of more than 3 years (p <0.05). There are no criteria currently for how frequently cases should be imaged when managed by surveillance. In the absence of guidelines the individual clinical scenario, including size of the lesion and
whether the patient has TSC, should guide surveillance imaging protocols. The recommendation historically has been that patients with AMLs larger than 4 cm undergo intervention, especially in the setting of TSC. This size threshold is based on retrospective series showing that patients with tumors larger than 4 cm more often experienced hemorrhage and other symptoms, had interval growth and required intervention more often than those with AMLs smaller than 4 cm.\textsuperscript{1,2,12,24}

However, the historically quoted threshold of 4 cm for intervention has recently been questioned. Ouzaid et al published the largest series of AMLs managed by active surveillance, which included 130 individuals, almost 80% of whom were asymptomatic and 29% of whom had masses larger than 4 cm.\textsuperscript{25} After a mean followup of 4 years only 13% of patients had discontinued surveillance and undergone treatment, while 34% of those with lesions larger than 4 cm had undergone treatment. Main indications were flank pain and interval tumor growth, although 35% of those with failed surveillance had a retroperitoneal hemorrhage or gross hematuria. Predictors of failing surveillance were symptoms at presentation and AML larger than 4 cm. However, the authors argue that 67% of symptomatic patients and 66% with tumors larger than 4 cm could be maintained on surveillance, suggesting that following the historical criteria can result in overtreatment.\textsuperscript{25} Importantly no patient surveilled who ultimately underwent surgical resection had a malignancy on pathological examination.

The size of intrallesional aneurysms associated with the AML is reportedly predictive of hemorrhage. Yamakado et al examined tumor and aneurysm size on CT and angiography of 23 patients treated for sporadic and TSC associated AMLs.\textsuperscript{23} They found that increasing aneurysm size (p < 0.05) and tumor size (p < 0.01) were associated with rupture, and that aneurysm size was positively correlated with tumor size (p < 0.003). Furthermore, in a multivariable regression analysis of factors predictive of rupture using tumor size 4 cm or larger and aneurysm size 5 mm or larger the aneurysm size was the sole predictor of rupture (p < 0.001).\textsuperscript{23}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig4.png}
\caption{Typical histological features of angiomyolipoma. \textit{a}, all 3 components (vessels, spindle cells, adipocytes) can be seen. H&E, reduced from ×100. \textit{b}, spindle tumor cells appear to radiate from vessel wall. H&E, reduced from ×100. \textit{c}, immature spindle cells in AML. H&E, reduced from ×200. \textit{d}, spindle cells stain positive for HMB-45. Reduced from ×200.}
\end{figure}
Finally, although bleeding AML during pregnancy is a rare event described only in case reports, this condition has potentially devastating consequences of significant maternal and/or fetal morbidity and/or mortality. Boorjian et al observed ubiquitous estrogen receptor expression and a subset of tumors with progesterone and androgen receptor expression, suggesting AMLs to be hormonally sensitive. This finding would support the observation that AMLs tend to enlarge and rupture during pregnancy, and, therefore, prophylactic treatment of AMLs should be discussed with women of childbearing age.

Surgery

For those patients in whom intervention is indicated surgical options remain the most well characterized form of treatment. Mirroring the evolution of surgical management for renal malignancies, surgery for AML has progressed from nephrectomy to open NSS to minimally invasive NSS. An attempt at NSS should be made in all patients when feasible, as it has been reported in the RCC literature that partial nephrectomy yields superior renal functional outcomes and potentially improved overall mortality compared to nephrectomy. Use of NSS is even more critical in patients with TSC, as the multifocal and bilateral disease pattern with a higher rate of recurrence makes renal parenchymal preservation a key concern.

The contemporary NSS series for AML are listed in table 1. Most series present data on open NSS approaches and include predominantly patients with sporadic AML. Overall these series reveal that NSS is effective for renal AMLs, with low rates of recurrence and complications. One of the largest series of NSS for AML, by Boorjian et al, included 58 patients with sporadic AMLs (4 with solitary kidneys) and demonstrated a 3.4% recurrence rate and a 12% complication rate at a median followup of 8 years, with no de novo chronic renal insufficiency. Lesion size is an obvious consideration. In a series of 34 AMLs treated with open NSS Minervini et al found that increased tumor size correlated with increased intraoperative EBL (p < 0.001), ischemia time (p < 0.001) and duration of hospital stay (p = 0.034). Expectedly the most commonly encountered complications overall

Figure 5. H&E staining shows histological variants of AML. a, degenerative nuclear atypia. Reduced from ×400. b, epithelioid appearance. Reduced from ×400. c, hyalinization (sclerosing). Reduced from ×100. d, spindle-cell-only (lipid poor) patterns can also be seen in AMLs. Reduced from ×40.
following NSS for AML are urinary leak/fistula (4%), hemorrhage (3%) and ileus (3%).

Many of the data for laparoscopic NSS for AML come from LPN series for small renal masses, where AML was first identified on surgical pathology. Expectedly most AMLs resected were smaller than 4 cm, although Simmons et al successfully performed LPN in 12 AMLs larger than 4 cm. That group, in comparing perioperative outcomes in patients with AMLs and those with malignant tumors, found no difference in operative time, EBL, warm ischemia time, positive margin rate or complication rate. Msezane et al retrospectively compared 14 LPNs for AMLs (2 cm median size) to 170 LPNs for malignancy and likewise found no difference in EBL, ischemia time or complication rate. These data may suggest that the laparoscopic NSS data for RCC are likely generalizable to at least small AMLs.

**Figure 6.** a, large (17 cm) epithelioid AML. b, perivascular patterns. H&E, reduced from ×100. c, necrosis. H&E, reduced from ×200. d, carcinoma-like patterns. H&E, reduced from ×400. e, sample stains positive for HMB-45. Reduced from ×400. f, sample stains positive for Melan-A. Reduced from ×400. Tumor has all risk factors for malignancy and is likely to behave aggressively.
In those patients in whom NSS is not feasible due to extent or location of tumor burden, nephrectomy and embolization remain treatment options. For patients with TSC, medical therapy with mTOR inhibitors is an emerging strategy that could be used in the presence of unresectable disease or limited renal parenchymal reserve.

**Embolization**

Historically there was a greater trend toward surgery over embolization for renal AMLs. However, this pattern has shifted, with SAE emerging as a first-line management option for AMLs, especially in cases of acute hemorrhage and refractory hemodynamic instability (fig. 8). The contemporary SAE series for AML are listed in table 2. Numerous agents can be used for embolization, including absolute ethanol, polyvinyl alcohol and trisacryl gelatin microspheres. To date, no study has shown the superiority of any embolic agent over another regarding actively treating patients with hemorrhaging AMLs, preventing hemorrhage or treating symptoms.

**Table 1. Results of select contemporary nephron sparing surgery series for AML**

<table>
<thead>
<tr>
<th>References</th>
<th>No. pts</th>
<th>Surgical approach</th>
<th>Cm tumor size</th>
<th>Cm no. complications (%)</th>
<th>MI EBL</th>
<th>Mean change in creatinine (mg/dl)</th>
<th>No. recurrence (%)</th>
<th>Mean followup (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yip et al33</td>
<td>16</td>
<td>Open NSS</td>
<td>Smaller than 4 in 4 pts, larger than 20 in 5 pts</td>
<td>2 (12.5)</td>
<td>Not available</td>
<td>Not available</td>
<td>0 (0)</td>
<td>26.4</td>
</tr>
<tr>
<td>Heidenreich et al29</td>
<td>28</td>
<td>Open NSS</td>
<td>Mean 5.5 (range 2.5–17.0)</td>
<td>3 (10.7)</td>
<td>Mean 320 (range 50–1,200)</td>
<td>0.3</td>
<td>0 (0)</td>
<td>57.6</td>
</tr>
<tr>
<td>Boorjian et al28</td>
<td>58</td>
<td>Open NSS</td>
<td>Mean 3.9 (range 0.8–12.5)</td>
<td>7 (12.1)</td>
<td>Mean 350 (range 50–1,200)</td>
<td>0.1</td>
<td>2 (3.4)</td>
<td>96.0</td>
</tr>
<tr>
<td>Minervini et al30</td>
<td>34</td>
<td>Open NSS</td>
<td>Mean 4.8 (range 0.8–15.0)</td>
<td>4 (11.8)</td>
<td>Mean 170 (range 70–650)</td>
<td>0.04</td>
<td>2 (5.9)</td>
<td>56.4</td>
</tr>
<tr>
<td>Simmons et al32</td>
<td>35</td>
<td>LPN</td>
<td>Smaller than 2 in 9 pts, larger than 4 in 12 pts</td>
<td>4 (11.4)</td>
<td>Mean 250</td>
<td>Not available</td>
<td>Not available</td>
<td>Not available</td>
</tr>
<tr>
<td>Msezane et al31</td>
<td>14</td>
<td>LPN</td>
<td>Median 2.0 (IQR 1.6–3.4)</td>
<td>3 (21.4)</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>251 ± 213</td>
</tr>
</tbody>
</table>

**Figure 7. Proposed updated management algorithm for renal AML.** While options are suggested, specific treatment decisions should take into consideration individual clinical scenario, and patient and surgeon preference. RFA, radio frequency ablation.
Recurrence of AML after SAE is variable and depends on the etiology of the AML (eg sporadic vs TSC). Recurrence rates are highly variable, ranging from approximately 11% to 40%. As expected, the postoperative recurrence rate is low. Hospital stays can be less than 24 hours but may be prolonged by post-embolization syndrome. Moreover, blood loss for SAE is minimal. Complications from SAE include post-embolization syndrome, vascular injury, renal infarction with abscess formation and nontarget embolization. Post-embolization syndrome, characterized by fever, flank pain and leukocytosis, is the most common complication, reportedly occurring in up to 80% of cases, and is managed conservatively. Other complications are infrequent. However, given the high rate of recurrence, particularly in patients with TSC, lifelong surveillance is required.39

Ablation
Reports of the use of laparoscopic and percutaneous ablative therapies for AML are mainly restricted to small, asymptomatic tumors, with few data available on use in large or symptomatic tumors. The radio frequency ablation data available for AML largely consist of 2 series of small renal masses that were suspicious for RCC and observed to be AML on biopsy at laparoscopic or percutaneous radio frequency ablation. Overall these series reveal good efficacy with few to no repeat treatments, minimal complications and no recurrences at median followup of up to 45 months. The data on laparoscopic or percutaneous cryoablation of AML are even more limited, with the largest series including just 7 patients. Overall ablative techniques have demonstrated some promise in the

Table 2. Results of select contemporary selective arterial embolization series for AML

<table>
<thead>
<tr>
<th>References</th>
<th>No. pts</th>
<th>Tumor size</th>
<th>No. complications (%)</th>
<th>No. recurrent hemorrhage, symptoms or growth (%)</th>
<th>No. repeat embolization (%)</th>
<th>No. surgery (%)</th>
<th>Mos followup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al38</td>
<td>11</td>
<td>Mean ± SD</td>
<td>1 (9.1)</td>
<td>2 (18.2)</td>
<td>1 (9.1)</td>
<td>1 (9.1)</td>
<td>Mean 28.2</td>
</tr>
<tr>
<td>Ramon et al39</td>
<td>41</td>
<td>Mean 10.3 cm (range 2.5—20.0)</td>
<td>8 (19.5)</td>
<td>16 (39.0)</td>
<td>15 (36.6)</td>
<td>15 (36.6)</td>
<td>Mean 57.6</td>
</tr>
<tr>
<td>Bishay et al34</td>
<td>16</td>
<td>Mean 15.0 cm (range 10.0—25.0)</td>
<td>2 (12.0)</td>
<td>3 (18.8)</td>
<td>9 (56.3)</td>
<td>3 (7.3)</td>
<td>Mean 29.0</td>
</tr>
<tr>
<td>Chick et al35</td>
<td>34</td>
<td>Mean 11.9 cm (range 2.9—24.4)</td>
<td>1 (2.9)</td>
<td>5 (14.7)</td>
<td>2 (5.9)</td>
<td>0 (0)</td>
<td>Mean 44.2</td>
</tr>
<tr>
<td>Chan et al35</td>
<td>27</td>
<td>Mean 10.9 cm (range 4.0—30.0)</td>
<td>0 (0)</td>
<td>6 (22.2)</td>
<td>4 (14.8)</td>
<td>2 (5.9)</td>
<td>Mean 85.2</td>
</tr>
<tr>
<td>Villalta et al40</td>
<td>48</td>
<td>Mean ± SD</td>
<td>5 (10.4)</td>
<td>14 (29.2)</td>
<td>14 (29.2)</td>
<td>14 (29.2)</td>
<td>Mean 14.0 (small particles), 29.0 (large particles)</td>
</tr>
<tr>
<td>Hocquelet et al37</td>
<td>19</td>
<td>Mean ± SD</td>
<td>2 (10.5)</td>
<td>2 (10.5)</td>
<td>2 (10.5)</td>
<td>0 (0)</td>
<td>Median 28.0</td>
</tr>
</tbody>
</table>

No. pts mean ± SD. Data exclude post-embolization syndrome.

Figure 8. a, axial contrast enhanced CT of large right retroperitoneal hematoma arising from right kidney in patient who presented with flank pain and hypotension. Large area of low density at anterolateral aspect of lesion is consistent with fat. Findings are characteristic of AML with hemorrhage. b, digital subtraction angiography obtained at embolization for lesion. Multilobulated aneurysm is seen arising from segmental branch of right renal artery, which was source of bleeding for AML. c, digital subtraction angiography obtained after embolization with combination of particles and coils reveals occlusion of aneurysm. Hypotension resolved with embolization therapy.
treatment of a subgroup of AMLs that some would argue should be managed by surveillance.

**mTOR Inhibitors**

The most novel strategy for treating AML tumor burden in patients with TSC or sporadic LAM uses targeted therapeutics focused on inhibition of the mTOR pathway, with the goal of halting further tumor progression and promoting regression of existing tumors. Sirolimus was the first mTOR inhibitor studied in managing renal angiomyolipoma in the setting of TSC or sporadic LAM. Also known as rapamycin, sirolimus was initially developed as an immunosuppressive agent for use in solid organ transplantation. The 4 phase II trials of sirolimus for AML included a total of 94 patients with TSC or sporadic LAM and renal AMLs treated for up to 24 months.\(^44-48\) Overall using the RECIST (Response Evaluation Criteria in Solid Tumors) definition of partial response as at least a 50% reduction in volume or 30% reduction in longest diameter, there was a 46.8% response rate to sirolimus at 12 months but no complete responses.\(^44-48\)

In the 2 trials where patients were treated continuously for 24 months no significant difference was found in decrease in AML volume or longest diameter between 12 and 24 months, suggesting that these patients attain a maximal response within the first 12 months of treatment.\(^45,47\)

These trials suggest that responses in patients with AMLs treated with sirolimus are unlikely to be durable, and patients will require maintenance therapy to continue to derive benefit. Overall sirolimus was well tolerated, with stomatitis (52%), hyperlipidemia (40%), skin lesions (30%), respiratory infections (29%) and proteinuria (18%) being the most commonly encountered adverse events.\(^44-48\) There was 1 death reported secondary to a severe respiratory infection.\(^47\)

Everolimus, another rapamycin derivative, has been studied most extensively, with data from 2 randomized controlled trials to date suggesting efficacy and safety.\(^49,50\) This agent now carries Food and Drug Administration approval for treatment of AML in the setting of TSC, as well as TSC related subependymal giant cell astrocytoma and advanced renal cell carcinoma after failed treatment with tyrosine kinase inhibitors. The EXIST-2 (Everolimus for Angiomyolipoma Associated with Tuberous Sclerosis Complex or Sporadic Lymphangioleiomyomatosis) study was a double-blind, randomized, controlled trial that included 118 patients with a 3 cm or larger AML in the setting of TSC or sporadic LAM randomized 2:1 to receive everolimus or placebo.\(^49\) At a median interval of 38 weeks there was a 42% response rate (95% CI 31%–53%) for the everolimus group vs 0% (95% CI 0%–9%) for placebo (42% difference, 95% CI 24%–58%, p < 0.0001), with response defined as a 50% or greater volume reduction in total AML burden. Median time to response was 2.9 months, and 80% of the everolimus group had at least a 30% response. Progression-free rates at 12 months were 92% (95% CI 89%–100%) for everolimus and 25% (95% CI 1%–64%) for placebo, with everolimus superior to placebo in time to progression (hazard ratio 0.08, 95% CI 0.02–0.37, p < 0.0001). No patient who achieved a response in AML volume reduction had progression. The most common observed adverse events were stomatitis (48%), nasopharyngitis (24%), acne-like skin lesions (22%), headache (22%), cough (20%) and hypercholesterolemia (20%).\(^49\)

Although these trials suggest efficacy and safety of everolimus in decreasing AML tumor burden and preventing progression in individuals with TSC, it is still unclear what the role of everolimus ultimately will entail. There certainly is a use for mTOR inhibitors in patients with TSC with bulky tumors not amenable to other treatments and in patients with less remaining renal reserve. However, questions regarding the durability of responses, duration of treatment and impact of toxicity from chronic therapy remain. Additionally the role of mTOR inhibitors in the treatment of patients with non-TSC associated AMLs remains to be determined.

**CONCLUSIONS**

Renal AML is an uncommon benign tumor that can occur sporadically or as a manifestation of TSC or sporadic LAM. Unlike in historical series, the majority of AMLs are now found incidentally, with hemorrhagic presentation being less common. Intralesional fat on CT or MRI is diagnostic of AML. However, in the small subset of tumors in which fat is difficult to detect the chemical shift sequences may allow a diagnosis. For management of AML active surveillance remains the first-line option in properly selected asymptomatic cases involving small AMLs. NSS and selective arterial embolization are preferred management strategies in cases involving symptomatic or large tumors due to increased risk of hemorrhage. Each option may have benefits, depending on the clinical situation. However, the level of evidence in the current literature does not allow a recommendation of a particular option over another. The recent literature suggests that mTOR inhibitors are efficacious and safe in controlling AML tumor burden in patients with TSC, while preserving the renal parenchyma. Further clarifications regarding which patients with TSC need treatment, duration of therapy and impact of long-term treatment remain as areas of future study.
REFERENCES


