Renal angiomyolipomas

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INTRODUCTION

Angiomyolipomas (AMLs) belong to a family of tumors collectively referred to as neoplasms with perivascular epithelioid differentiation (or PEComas) [1]. These tumors arise by clonal proliferation of epithelioid cells distributed around blood vessels [2].

Renal AMLs may occur in association with tuberous sclerosis complex (TSC) or pulmonary lymphangioleiomyomatosis (LAM) or occur as a sporadic finding among patients who have neither TSC nor pulmonary LAM.

This topic reviews sporadic renal AMLs that occur among patients who do not have TSC and renal AMLS that occur among patients with sporadic pulmonary LAM. Renal AMLs that occur in association with TSC are discussed elsewhere. (See "Renal manifestations of tuberous sclerosis complex", section on 'Angiomyolipomas'.)

PATHOLOGY

Pathogenesis of AMLs and disease associations — AMLs are lesions of the kidney comprised of smooth-muscle-like cells, adipocyte-like cells, and epithelioid cells. The three cell types appear to be derived from pericytes. This is suggested by the fact that they all express pericyte markers (angiotensin II type 1 receptor, platelet-derived growth factor receptor-beta, desmin, alpha-smooth muscle actin, and vascular endothelial growth factor [VEGF] receptor 2) but not the endothelial cell marker CD31 or the adipocyte marker S-100 [3].

AMLs may be sporadic or associated with tuberous sclerosis complex (TSC) or, less commonly, sporadic pulmonary lymphangioleiomyomatosis (LAM). (See 'Epidemiology' below and "Renal manifestations of tuberous sclerosis complex" and "Sporadic lymphangioleiomyomatosis: Clinical presentation and diagnostic evaluation".)

There are two major histologic variants of AMLs: classic and epithelioid (picture 1) [4-6]. (See 'Classic variant' below and 'Epithelioid variant' below.)

In addition, there is a rare cystic variant, called angiomyolipoma with epithelial cysts (AMLEC), which is characterized by solid and cystic areas. (See 'Angiomyolipoma with epithelial cysts' below.)

Variants are distinguished from each other only by biopsy.

Classic variant — Most AML are classic variants [7]. The major features of the classic variant include abnormally thick-walled vessels that lack a well-developed internal elastic lamina and varying amounts of spindle smooth-muscle-like cells and adipose tissue (picture 1). Any one of the three cell types (ie, smooth-muscle-like cells, adipocyte-like cells, and epithelioid cells) may predominate or be virtually absent. In general, epithelioid cells are sparse and make up fewer than 10 percent of cells in the classic variant [7].

Classic AMLs are benign but can be locally invasive, extending into the perirenal fat or, rarely, the collecting system, renal vein, or inferior vena cava and right atrium. Involvement of lymph nodes and/or the spleen is thought to represent multicentricity of origin rather than metastases since long-term follow-up in patients with these manifestations has not demonstrated evidence of further disease progression [8,9]. (See 'Prognosis' below.)

Epithelioid variant — In contrast to the classic variant, the epithelioid variant always has an epithelioid cell component (picture 1) [10]. There is no consensus on the percentage of epithelioid cells that is required to make a diagnosis of the epithelioid variant, with values ranging from 10 to 100 percent in published studies [7,11]. Epithelioid cells are distinguished by an abundant eosinophilic and granular cytoplasm (picture 1) [10]. Epithelioid AMLs are often fat poor, which makes them more difficult to diagnose by imaging. (See 'Diagnosis and evaluation' below.)

Unlike the classic AML, the epithelial variant may undergo malignant transformation and require prophylactic surgery or at least close follow-up. Histologic features that suggest an increased risk for malignant transformation include ≥70 percent epithelioid cells, tumor size >7 cm, vascular invasion, ≥2 mitotic figures per 10 high-power fields, atypical mitotic figures, and necrosis [12]. (See 'Treatment and monitoring' below.)

Angiomyolipoma with epithelial cysts — AMLEC is a rare cystic variant of AML characterized by solid and cystic areas. AMLEC is a benign lesion with no evidence of metastasis or recurrence following surgical excision [13].

This variant is characterized by immunohistochemical positivity of the subepithelial stroma for melanocytic markers (HMB45 and melan-A) [13]. These markers help to differentiate this lesion from other renal cystic renal neoplasms such as multilocular cystic renal cell carcinoma, cystic nephroma, and mixed epithelial and stromal tumor of the kidney. (See 'Differential diagnosis' below.)

EPIDEMIOLOGY

Renal AMLs are found in approximately 0.3 to 2.1 percent of kidneys at routine autopsy [14]. The frequency of detection in the general population is increasing because of an increase in the use of imaging and advances in imaging technology [4,6,15-18]. Using population-based ultrasound screening, a Japanese study of almost 18,000 healthy adults identified renal AMLs in 0.1 percent of men and 0.2 percent of women [17]. A later study using multidetector contrast-enhanced computed tomography (CT) reported AMLs in 2.2 percent of 1948 potential kidney donors (mean age 43 years) [18].

Renal AMLs are more common in women than men and are typically discovered in middle age [18]. In one study including 117 patients with sporadic AML, 92 percent of patients were women, and the mean age was 52 years [19].

AMLs are much more common among patients with tuberous sclerosis complex (TSC) or lymphangioleiomyomatosis (LAM). In various series, AML have been reported in 75 to 85 percent of TSC patients with kidney lesions and in 49 to 60 percent of TSC patients overall [20-22]. (See "Renal manifestations of tuberous sclerosis complex", section on 'Epidemiology'.)

Approximately 45 to 60 percent of patients with sporadic pulmonary LAM have renal AMLs that tend to be multiple and bilateral [23-26]. (See "Sporadic lymphangioleiomyomatosis: Clinical presentation and diagnostic evaluation", section on 'Non pulmonary'.)

However, TSC is very uncommon, and LAM is rare. Thus, although the prevalence of AMLs is low among patients who do not have TSC or LAM, the prevalence of sporadic AML markedly exceeds the estimated birth incidence of TSC or LAM [27]. (See "Tuberous sclerosis complex: Genetics, clinical features, and diagnosis", section on 'Genetics' and "Tuberous sclerosis complex associated lymphangioleiomyomatosis in adults", section on 'Epidemiology'.)

Thus, among patients who present with AML, the chances are high that the lesion is sporadic AML and not TSC- or LAM-associated AML.

CLINICAL FEATURES

Most patients with sporadic AML are asymptomatic and have normal kidney function [4,19]. The AMLs are usually incidentally detected on kidney ultrasound or computed tomography (CT) that is obtained for an unrelated reason [4,6,15-18].

However, some patients present with flank pain, retroperitoneal hemorrhage, or recurrent episodes of gross hematuria. Occasionally, patients present with impaired kidney function due to slow, chronic impingement of the AMLs on normal tissue.

Among symptomatic patients, flank pain is probably most commonly described. In a retrospective analysis of 129 patients, 75 percent were asymptomatic [19]. Among 32 symptomatic patients, symptoms included flank pain in 20, gross hematuria in 7, and spontaneous rupture in only 2 patients [15]. However, when it occurs, retroperitoneal hemorrhage may be severe, resulting in serious pain or shock [28]. (See "Overview of the diagnosis and initial management of traumatic retroperitoneal injury", section on 'Clinical evaluation' and "Evaluation of and initial approach to the adult patient with undifferentiated hypotension and shock", section on 'Hypovolemic shock'.)

Symptoms are more likely in larger AML. In one study, symptoms at presentation were more likely with an AML size ≥4 cm (86 versus 54 percent with smaller lesions) [4].

DIAGNOSIS AND EVALUATION

Establishing diagnosis — The diagnosis of sporadic AML is usually made by imaging studies (usually ultrasound, computed tomography [CT], or magnetic resonance imaging [MRI]). In most cases, ultrasound can suggest the diagnosis. However, we obtain CT or MRI for a definitive diagnosis in all patients who have possible AML detected by ultrasound. If the diagnosis cannot be made with certainty by CT or MRI, we obtain needle-guided biopsy.

The critical diagnostic features for all imaging modalities rely on the presence of fat in the AML lesion, and the diagnostic accuracy depends upon the amount of fat tissue in the tumor. Diagnostic features for each imaging modality are discussed at length elsewhere. (See "Renal manifestations of tuberous sclerosis complex", section on 'Radiographic diagnosis'.)

However, approximately 5 percent of AMLs contain no fat detectable by imaging studies (minimal fat or fat-poor AMLs [29]). Epithelioid AMLs are often fat poor.

For minimal fat or fat-poor lesions, image-guided percutaneous needle biopsy should be performed since the diagnosis cannot be made with certainty by imaging [30]. However, if the lesion is highly suspicious for malignancy because of intratumoral necrosis or calcifications, many clinicians would elect to surgically remove the lesion rather than perform diagnostic biopsy [31]. Additional details regarding the biopsy and histopathologic findings are discussed at length elsewhere. (See "Renal manifestations of tuberous sclerosis complex", section on 'Biopsy'.)

Differential diagnosis — The differential diagnoses of AML include other kidney masses detected by imaging, including renal cell carcinoma and oncocytoma and metastatic lesions from primary tumors elsewhere. In addition, retroperitoneal liposarcomas and adrenal myelolipomas, especially when developing adjacent to the kidney, can mimic the appearance of AML. (See "Renal manifestations of tuberous sclerosis complex", section on 'Renal cell carcinoma' and "Renal manifestations of tuberous sclerosis complex", section on 'Oncocytoma'.)

These entities are usually distinguished from each other by characteristic radiographic features (see "Renal manifestations of tuberous sclerosis complex", section on 'Radiographic diagnosis'). Patients in whom a definitive diagnosis cannot be made by imaging may require biopsy with analysis of tissue using specific immunohistochemical techniques.

Alternatively, the rate of growth of the lesion may help to differentiate a slowly growing, benign AML from a more rapidly growing renal cell carcinoma. The diagnostic approach to kidney masses, including surveillance, is discussed at length elsewhere. (See "Diagnostic approach, differential diagnosis, and management of a small renal mass".)

Identification of patients with tuberous sclerosis complex — We screen all patients with newly diagnosed AML for possible undiagnosed or subclinical tuberous sclerosis complex (TSC) (table 1). In one study, approximately 10 percent of patients who had symptomatic AML had underlying TSC [15].

The extent of the evaluation depends on the index of suspicion for TSC:

- Asymptomatic adult patients who have one or two small (ie, <4 cm) AML are low risk for TSC. Among such patients, it is sufficient to obtain family history and perform a careful review of systems and physical exam. The clinician, however, should be familiar with the characteristic features of TSC. (See "Tuberous sclerosis complex: Genetics, clinical features, and diagnosis", section on 'Diagnostic criteria'.)

- Patients with multiple (>2), bilateral, or larger (ie, ≥4 cm) AMLs are at higher risk for TSC. Among such patients, we perform a full evaluation for TSC. The diagnostic criteria for TSC are based upon specific clinical features that are discussed elsewhere. (See "Tuberous sclerosis complex: Genetics, clinical features, and diagnosis", section on 'Diagnostic criteria'.)

Sporadic renal AMLs, compared with TSC-associated AMLs, are generally detected at an older age, are solitary rather than multiple, are less likely to cause spontaneous hemorrhage and symptoms, and grow at a slower rate [4,7,32]. In a study of 60 adults with renal AMLs, 14 of whom had TSC, patients with sporadic renal AMLs were older at presentation (mean 49 versus 26 years), had much smaller AMLs (mean size 4 versus 19 cm), and were much less likely to have multiple and bilateral AMLs (13 versus 100 percent) [32].

Similar findings were noted in a much larger review of 336 patients (19 percent with TSC) who underwent surgery for renal AMLs [4]. The patients with sporadic renal AMLs were older (mean 52 versus 30 years), had smaller AMLs (mean 5.4 versus 8.9 cm), and were much less likely to have both multiple lesions (13 versus 97 percent) and acute hemorrhage (14 versus 44 percent).

A potential limitation to these observations is that the data come from urology centers and are therefore somewhat biased for inclusion of symptomatic patients with more progressive disease.

Among patients who undergo biopsy, histologic features may also help to distinguish sporadic from TSC-related AML. In a single-institution study of 194 renal AMLs in 185 patients, three histologic markers were observed more frequently in patients with TSC: epithelioid-variant AMLs, epithelial kidney cysts, and microscopic AML foci [7]. However, the utility of such markers in identifying patients with TSC has not been proven.

Identification of patients with pulmonary lymphangioleiomyomatosis — We do not screen patients who present with sporadic AML for sporadic pulmonary lymphangioleiomyomatosis (LAM). Only a very small percentage of patients presenting with sporadic AML have LAM. (See "Sporadic lymphangioleiomyomatosis: Epidemiology and pathogenesis".)

Conversely, patients who have LAM should be screened for AML. Approximately 45 to 60 percent of patients with sporadic pulmonary LAM have renal AMLs that tend to be multiple and bilateral [23-26]. The clinical manifestations, diagnosis, and treatment of renal AMLs associated with sporadic pulmonary LAM are similar to those described for renal AMLs associated with TSC. (See "Renal manifestations of tuberous sclerosis complex", section on 'Angiomyolipomas'.)

Potential issues in women — Several clinical observations suggest that female sex hormones promote the growth of renal AMLs. These observations include increased frequency and size of renal AMLs in women, hemorrhagic complications during pregnancy, and reports of renal AML growth during pregnancy [33-36] or after treatment with exogenous hormone therapy [37].

Thus, women with known renal AMLs should be cautioned about the potential risks of pregnancy and estrogen administration, and the frequency of imaging surveillance should be increased, at least initially.

TREATMENT AND MONITORING

Treatment — Treatment is required in a minority of patients with AML [20]. Our approach depends on the clinical presentation.

Acute life-threatening hemorrhage — For patients with acute life-threatening hemorrhage, the preferred therapy is selective renal artery embolization since it stabilizes the patient's condition and often eliminates the need for additional, more invasive therapy.

Non-life-threatening signs or symptoms — Treatment may be required to prevent bleeding or to address symptoms (usually pain and recurrent gross hematuria).

Interventions include nephron-sparing surgery, selective renal artery embolization, complete or radical nephrectomy, and radiofrequency or thermal ablation.

There is a role for mammalian (mechanistic) target of rapamycin (mTOR) inhibitors for selected patients with AML, but mTOR inhibitors are more commonly used among patients with tuberous sclerosis complex (TSC)-associated rather than sporadic AML.

Our approach is determined by the size and number of lesions and the comorbidities of the patient [31].

We suggest prophylactic surgery or embolization to prevent hemorrhage among patients with renal AMLs >4 cm in diameter, particularly those with high vascularity and/or an aneurysm measuring ≥5 mm in diameter [38]. These tumors are more likely to cause hemorrhage [4,38].

However, some authors have recommended observation of asymptomatic renal AMLs 4 to 8 cm in diameter if close follow-up (at six months and then yearly, if stable) is feasible [39,40]. In such cases, the patient should be instructed to seek prompt medical attention if symptoms develop and to avoid contact activities in which flank or abdominal impact is likely to occur. Nephron-sparing surgery or selective renal artery embolization are preferred approaches.

We administer the mTOR inhibitor, everolimus, to patients who have multiple large angiolipomas that show evidence of growth (ie, ≥5 mm per year) and to patients who have had prior nephrectomy or embolization. Patients with multiple angiomyolipomas, particularly if they are large or bilateral, and patients who have undergone prior embolization or nephrectomy are not good candidates for embolization [41]. Multiple large lesions often require extensive or repeat embolization, which is associated with a risk of chronic kidney disease (CKD). Similarly, surgical interventions for bilateral lesions markedly increase the risk of CKD.

mTOR inhibitors reduce tumor volume and decrease the risk of progression of lesions [42-46]. The best data are provided by the double-blind, randomized Examining Everolimus in a Study of TSC (EXIST)-II trial of 118 patients (113 with TSC and 5 with sporadic LAM) [47]. The entry criteria were age ≥18 years, a definite diagnosis of TSC or sporadic LAM, and at least one renal AML ≥3 cm in its largest diameter. The primary endpoint of at least a 50 percent reduction in the total volume of all target AMLs identified at baseline was achieved in 42 percent of the patients treated with everolimus compared with none of the patients treated with placebo. The median time to response to everolimus was 2.9 months. Progression of AMLs was significantly more common in the placebo group (21 versus 4 percent). The median time to progression was 11.4 months with placebo and was not reached with everolimus.

We require evidence of growth (ie, ≥5 mm per year) prior to committing to long-term treatment with mTOR inhibitors since many AMLs may stop growing or grow very slowly in older adults [48].

Caution should be used among patients who have reduced kidney function with estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2. Such patients are at risk for further reductions in clearance, particularly if they also have proteinuria. If mTOR inhibitors are used for such patients, the eGFR should be rechecked within one month of starting treatment and every four months thereafter.

Benefits and risks of treatment with mTOR inhibitors should be discussed prior to initiation of treatment. Appropriate immunizations should be arranged (live vaccines cannot be given once treatment has started). Adverse events associated with the administration of mTOR inhibitors include stomatitis, diarrhea, aphthous ulcers, nasopharyngitis, acne-like lesions, hypercholesterolemia, hypophosphatemia, amenorrhea, noninfectious pneumonitis, and increased susceptibility to infections. A practical guide for the management of these adverse events has been published [49].

Selection of surgical approach — Among such patients who are selected for surgery because of tumor size or persistent (but non-life-threatening) signs or symptoms, we recommend

nephron-sparing approaches rather than complete nephrectomy, even for large (>7 to 10 cm) and/or multiple AMLs [50]. Selective renal artery embolization may be used when the size or location precludes nephron-sparing surgery.

Among patients in whom a partial nephrectomy cannot be safely performed without a significant risk of hemorrhage or urinary fistula, a nephrectomy may be required.

Complete nephrectomy plus tumor thrombectomy is usually indicated to treat AMLs associated with tumor thrombus in the renal vein, inferior vena cava, and the right atrium, with cardiopulmonary bypass when the tumor extends to the right atrium.

Nephron-sparing surgery — Nephron-sparing surgery for large AMLs, such as enucleation or partial nephrectomy, may be effective in patients with exophytic or well-demarcated tumors.

In a small number of patients, preoperative treatment with sirolimus, an mTOR inhibitor, has been used to reduce the tumor volume and facilitate the surgery. In a study of three patients with renal AMLs that were not amenable to nephron-sparing surgery, sirolimus therapy resulted in a 38 to 95 percent reduction in AML volume that permitted nephron-sparing surgery to be performed [42].

Selective renal artery embolization — Selective renal artery embolization is most commonly used in patients in whom the size or central location of the tumor precludes nephron-sparing surgery [51-56]. The presence of one or more large hypertrophic feeding vessels facilitates the procedure. Potential problems, which are not rare, include incomplete embolization, complications (postembolization syndrome, acute respiratory distress, and abscess formation), and recurrence of symptoms or AML growth [51-56].

The efficacy of selective renal artery embolization was illustrated in a report of 30 patients (mean age 44 years) with large renal AMLs (mean diameter 8.2 cm), 18 of whom had TSC [56]. The embolization protocol combined three agents (pure alcohol for capillary occlusion, 500 to 700 micrometer microspheres for arteriole occlusion, and coils for proximal occlusion of the feeding pedicles). There were four technical failures. Among the AMLs that were embolized, embolization was complete after a single procedure in 83 percent. The mean reduction in AML volume was 43 percent at one to six months and 81 percent in the 12 AMLs followed for more than one year. The response was significantly **smaller** in fat-rich compared with fat-poor AMLs.

In addition to producing a persistent reduction in the size of large renal AMLs, selective renal artery embolization is also the preferred initial therapy in patients with acute life-threatening hemorrhage since it stabilizes the patient's condition and often eliminates the need for

additional, more invasive therapy. In contrast, hydration and bed rest may be sufficient for less severe episodes of gross hematuria, which often resolve within a few days.

Complete nephrectomy — Selected patients with renal AMLs require complete nephrectomy. Complete nephrectomy is considered when it is determined, either prior to or during surgery, that a partial nephrectomy cannot be safely performed without significant risk of hemorrhage or urinary fistula.

Complete nephrectomy plus tumor thrombectomy is usually indicated to treat AMLs associated with tumor thrombus in the renal vein, inferior vena cava, and the right atrium, with cardiopulmonary bypass when the tumor extends into the right atrium.

Radiofrequency ablation and cryoablation — Percutaneous radiofrequency ablation and cryoablation have been effective therapies for solid kidney masses measuring 1 to 3 cm in diameter, including renal cell carcinoma and fat-poor AMLs, with a low rate of complications [57]. These techniques have also been successful in the treatment of renal AMLs <4 cm in diameter without bleeding complications [31,58,59].

However, as mentioned above, intervention is primarily performed for renal AMLs >4 cm in diameter (see 'Treatment' above). The efficacy and safety of percutaneous radiofrequency ablation and cryoablation for larger AMLs are not known.

Surveillance — All patients with AML should undergo routine monitoring by imaging to assess stability. The frequency and imaging modality depend on AML size and, if it is known, the variant.

Patients with AML <2 cm — Every three to four years by kidney ultrasound. Small AMLs grow very slowly [60]. We use kidney ultrasound rather than computed tomography (CT) or magnetic resonance imaging (MRI) as it is safer, and there are no data to suggest screening by CT or MRI confers benefit.

Patients with AML 2 to 4 cm — Every year by kidney ultrasound.

Patients with AML >4 cm who do not undergo surgery — As noted above, we resect most lesions that are >4 cm. However, if an AML >4 cm is not resected, then it should be reimaged by kidney ultrasound in six months and then yearly, if stable [39,40,61].

Epithelioid variants that are not surgically resected — Patients with epithelioid lesions demonstrated by biopsy, which have not been surgically resected, should be reimaged with kidney ultrasound in six months to confirm stability and yearly thereafter.

After surgical resection of epithelioid AML at high risk of malignant transformation — Patients who have had surgical resection of epithelioid AML, which had high-risk histologic features for malignant transformation, should have a whole-body CT and with additional imaging of the abdomen by MRI, if needed, six months after surgery and yearly thereafter for at least five years. Metastatic disease has been reported years after resection of epithelioid AMLs with high-risk features for malignant transformation [12]. Histologic features that suggest an increased risk for malignant transformation include ≥70 percent epithelioid cells, tumor size >7 cm, vascular invasion, ≥2 mitotic figures per 10 high-power fields, atypical mitotic figures, and necrosis [12].

Women who are pregnant or on estrogen therapy — Women who are pregnant or receiving estrogen therapy should have imaging by kidney ultrasound at six months and, if the renal AML is stable, at one-year intervals thereafter. Female sex hormones promote the growth of renal AMLs, and hemorrhagic complications tend to occur during pregnancy [33-36] or after treatment with exogenous hormone therapy [37].

PROGNOSIS

The long-term prognosis depends on the variant and the size.

Classic variant — Most classic AMLs are slow growing, particularly if <4 cm [4,32,48,62]. In one study of 35 patients with sporadic AML (not biopsied) with mean diameter <1.5 cm, 92 percent showed no growth over five years of follow-up [62].

AMLs ≥4 cm may grow more rapidly [38]. AMLs grow faster in younger than in older individuals [60].

Loss of kidney function is uncommon with sporadic AML. In one study that compared outcomes of tuberous sclerosis complex (TSC)-associated and sporadic AML, patients with sporadic AMLs did not develop a reduction in kidney function at a mean follow-up of 3.3 years [4].

Epithelioid variants — Epithelioid variants may undergo malignant transformation. However, this is infrequent, and the magnitude of risk depends on the histologic features. In one study of 40 consecutive patients with renal epithelioid AMLs and atypia detected on histologic examination, local recurrence or distant metastases were present in nine (26 percent) [63]. In another report including 41 patients with pure (monotypic) epithelioid renal AMLs, metastatic disease was present in 36 percent at diagnosis, and 16 percent who were without metastases at diagnosis had new metastatic disease at follow-up [11]. (See "Renal manifestations of tuberous sclerosis complex", section on 'Malignant renal epithelioid angiomyolipomas'.)

A model based on histologic features predicts the risk of malignant transformation [63]. Features include ≥70 percent atypical epithelioid cells, two or more mitotic figures per 10 high-power fields, atypical mitotic figures, and necrosis. The presence of three or all four of these features was highly predictive of malignancy. In one study, the model accurately identified 78 percent of patients who developed malignant epithelioid AMLs and 100 percent of patients with benign lesions [63].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Chronic kidney disease in adults".)

SUMMARY AND RECOMMENDATIONS

- Angiomyolipomas (AMLs) are lesions of the kidney comprised of smooth-muscle-like cells, adipocyte-like cells, and epithelioid cells. AMLs may be sporadic or associated with tuberous sclerosis (TSC) or sporadic pulmonary lymphangioleiomyomatosis (LAM). Renal AMLs are uncommon in the general population, although the frequency of detection is increasing because of an increase in the use of imaging and advances in imaging technology. AMLs are much more common among patients with TSC or LAM. (See 'Introduction' above and 'Pathogenesis of AMLs and disease associations' above.)

- The two major histologic types of AML include classic and epithelioid variants. Most patients with sporadic AML have the classic type. Classic AMLs are benign but can be locally invasive, whereas the epithelioid variant occasionally undergoes malignant transformation as manifested by local recurrence and/or distal metastases. (See 'Classic variant' above and 'Epithelioid variant' above.)

- The diagnosis of AML is generally made by imaging, although a biopsy may be required to diagnose fat-poor lesions. (See 'Establishing diagnosis' above.)

- Treatment is required in a minority of patients with renal AML. Our approach depends on the clinical presentation.

    - For patients with acute life-threatening hemorrhage, we perform selective renal artery embolization. Renal embolization stabilizes the patient's condition and often eliminates the need for additional, more invasive therapy.

- For patients without acute hemorrhage who have renal AMLs larger than 4 cm in diameter, particularly with high vascularity and/or an aneurysm measuring ≥5 mm in diameter, we suggest nephron-sparing surgery or selective embolization, providing the AMLs are not multiple, very large, or bilateral (**Grade 2C**). These tumors are more likely to hemorrhage.

- For patients without acute hemorrhage who have multiple bilateral AMLs larger than 4 cm in diameter that show evidence of growth (ie, ≥5 mm per year), we administer the mammalian (mechanistic) target of rapamycin (mTOR) inhibitor, everolimus. (See 'Treatment' above.)

- AMLs require ongoing surveillance by imaging. Our approach is defined. (See 'Surveillance' above.)

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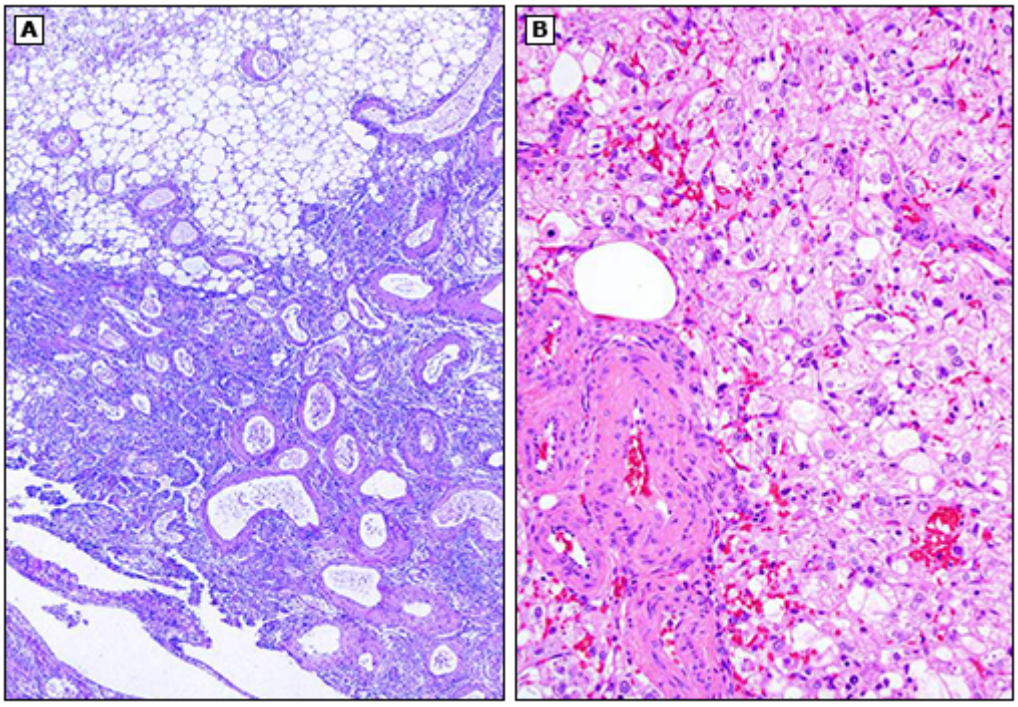
GRAPHICS

Histologic features of AML



(A) Classic AML containing adipose tissue, abnormal blood vessels with thickened walls, and spindle smooth muscle-like cells.

(B) Epithelioid AML containing round-to-polygonal epithelioid cells with round nucleoli and abundant granular cytoplasm.

AML: angiomyolipoma.

Graphic 90669 Version 1.0

Diagnostic criteria for tuberous sclerosis complex

Genetic diagnostic criteria
The identification of either a *TSC1* or *TSC2* pathogenic mutation in DNA from normal tissue is sufficient to make a definite diagnosis of TSC. A pathogenic mutation is defined as a mutation that clearly inactivates the function of the TSC1 or TSC2 proteins (eg, nonsense mutation), prevents protein synthesis (eg, large deletion), or is a missense mutation whose effect on protein function has been established by functional assessment.
Note that 10 to 25% of patients with TSC have no mutation identified by conventional genetic testing, and a normal result does not exclude TSC, or have any effect on the use of clinical diagnostic criteria to diagnose TSC.
Clinical diagnostic criteria
Major clinical features:
Hypomelanotic macules (≥3, at least 5 mm diameter)
Angiofibromas (≥3) or fibrous cephalic plaque
Ungual fibromas (≥2)
Shagreen patch (connective tissue nevus)
Multiple retinal hamartomas
Cortical dysplasias (includes tubers and cerebral white matter radial migration lines)
Subependymal nodules
Subependymal giant cell astrocytoma
Cardiac rhabdomyoma
Lymphangioleiomyomatosis (LAM)*
Angiomyolipomas (≥2)*
Minor clinical features:
"Confetti" skin lesions (1 to 2 mm hypomelanotic macules)
Dental enamel pits (≥3)
Intraoral fibromas (≥2)
Retinal achromic patch
Multiple renal cysts
Nonrenal hamartomas
Definite TSC:
Two major clinical features, or one major and two or more minor clinical features

Possible TSC:
Either one major clinical feature or two or more minor clinical features

TSC: tuberous sclerosis complex.

* A combination of LAM and angiomyolipomas without other features does not meet criteria for a definite diagnosis.

For most recent version of diagnostic criteria, please visit: Northrup H, Aronow ME, Bebin EM, et al. Updated International Tuberous Sclerosis Complex Diagnostic Criteria and Surveillance and Management Recommendations. Pediatr Neurol 2021; 123:50.

Original figure modified for this publication. Northrup H, Krueger DA, International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 international tuberous sclerosis complex consensus conference. Pediatr Neurol 2013; 49:243. Table used with the permission of Elsevier Inc. All rights reserved.

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