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Renal angiomyolipoma – a short review of the literature

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Abstract: *Renal angiomyolipomas (AML) are the most common benign renal tumors. By containing an important amount of fat tissue they are easily identifiable on CT and MRI images, thus no biopsy should be needed for a diagnosis. However there is a small percentage of AMLs that have very little fat tissue and are very difficult to differentiate from renal cell carcinoma. Along fat tissue, they also contain smooth muscle and blood vessels. Renal AMLs can occur as a sporadic finding, or more frequently in association with tuberous sclerosis complex (TSC) or pulmonary lymphangioleiomyomatosis (LAM). These tumors are usually an incidental finding on imaging tools, but sometimes a serious presentation is rupture and hemorrhage, which can easily evolve to shock. Therapeutical management vary from active surveillance to surgical removal, and it needs to be individualized for every patient and according to the clinical presentation.*

Keywords: *renal angiomyolipoma, tuberous sclerosis, therapeutical management*

INTRODUCTION

Renal AMLs are the most common benign renal tumors, having a reported prevalence of 0.2-0.6%, with a female to male ratio in favor of females. Because of the increase use of imaging tools and the advances in imaging methods the frequency of detection in the general population is increasing. AMLs are more frequently associated with patients with tuberous sclerosis complex (TSC), having been reported in 75-85% of cases with renal lesions and in 49-60% in TSC patients overall [1-2]. In cases of lymphangioleiomyomatosis (LAM), aproximately 45-60% of patients tend to have renal AMLs, usually being multiple and bilateral [3-4]. Even though the prevalence of AMLs is low among patients who do not have TSC or LAM, combined with the fact that the prevalance of sporadic AML exceeds the estimated birth incidence of TSC or LAM, it makes it more common [5]. AMLs are a member of a group of tumors called neoplasms with perivascular epithelioid differentiation, arising by clonal proliferation of epithelioid cells distributed around blood vessels [6, 7].

Histological findings

Renal AMLs are made of smooth-muscle-like cells, adipocyte-like cells, and epithelioid cells, with the three types of cells appearing to be derived from pericytes, fact suggested by the fact that these cells express perycite markers [8].

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AMLs are classified in two major histological groups. The most common histological variant is the classic one, having abnormally thick-walled vessels that lack a well-developed internal elastic lamina and varying amounts of spindle smooth-muscle-like cells and adipose tissue. However, some tumors consist solely of one component, while the other elements are present in very small amounts. In the classic variant epitheliod cells are rare, making up less than 10% of cells in this type of AML [9]. Classic AMLs are bening but, there are cases with local invasion into the perirenal fat, and in very rare ocasions into the collecting system, renal vein, or inferior vena cava and right atrium. The epithelioid variant, unlike the classic one can undergo malignant transformation. There is no consensus on the percentage of epithelioid cells that is required to make a diagnosis of the epithelioid variant, but studies sugest that a percent higher than 70% of epithelioid cells, a tumor size >7 cm, vascular invasion, ≥2 mitotic figures per 10 high-power fields, atypical mitotic figures and necrosis suggest an increased risk for malignant transformation [10].

Epithelioid cells are differentiated by their abundant eosinophilic and granular cytoplasm.

Epithelioid AML has less fat tissue than the classic variant, making it more difficult to diagnose by imaging, frequently resembling and be misdiagnosed as renal cell carcinoma.

In addition to these two major histological groups, there is a rare variant, characterized by solid and cystic areas, called angiomyolipoma with epithelial cysts. It is a benign lesion with no evidence of metastasis or recurrence following surgical excision [11]. The three variants are differentiated from each other only after biopsy.

DIAGNOSIS

Clinical presentation

Commonly patients are asymptomatic at the time of diagnosis, AMLs being an incidental finding. This is explained by the increasing use of imaging tools and the advances in imaging technology [12].

Among symptomatic patients, the most common sign is flank pain, followed by a palpable mass, haematuria, anaemia, urinary tract infection, or an impaired renal function. In a study conducted by Koo et al on 129 patients, 75% of them were asymptomatic [13]. Regarding symptomatic patients, Bissler et al found that out of the 32 sypmtomatic patients included into their study 20 had flank pain, 7 had hematuria and 2 had spontaneous rupture [14].

A serious form of presentation, seen in less than 15% of cases, is spontaneous retroperitoneal haemorrhage, which can lead in one third of patients to shock. Therefore, risk of a life-threatening bleeding is the main clinical concern in a patient diagnosed with AML [12].

The epithelioid variant of AMLs can undego malignant transformation. Though rare, it is characterized by local aggressivness, lymphadenopathy, and distal metastases. The larger the tumour, the more likely it is to spread, acting like a veritable retroperitoneal tumor [15-19] and can produce secondary hydronephrosis that must be drained with a double J stent [20, 21].

AMLs tend to be more aggressive in patients with TSC or LAM, thus symptomatic patients are more commonly found in these cases. It is important to screen patients diagnosed with AML for TSC and LAM. Patients with multiple, bilateral, or larger (≥4 cm) are at higher risk for TSC and the tumors are usually diagnosed at an early age.

Imaging features

By containing fat tissue AMLs are very easily diagnosed using imaging tools. However, in cases of hemorrhage, calcification, necrosis or low fat content the diagnosis becomes a challenge. A recent article classified renal AMLs as fat-rich, fat-poor, or fat-invisible, based on the amount of fat detected on imaging studies [22].

A hyperechoic lesion, resulting from a combination of fat, blood vessel, and muscle contents, with a posterior acoustic shadow, due to the multiple tissue interfaces is the classical appearance of an AML rich in fat tissue on ultrasound [23]. The echogenity of the tumor depends on the percentage of fat tissue in the AML, usually being the same as or greater than that of

the renal sinus, but as the amount of fat gets lower, the echogenity decreases.

AML low in fat content are usually a mixture of hyperechoic and isoechoic lesions compared with the renal parenchyma, while a fat-invisible AML is homogenously isoechoic with it. In these cases it is hard to differentiate renal cell carcinoma from an AML on ultrasound [22, 24].

Computed tomography (CT) scan is recommended when hyperechoic lesion is found by ultrasound, having excellent sensitivity, specificity, and reproducibility regarding renal masses. Computed tomography can identify macroscopic fat in AML as low-density area of −10 HU or lower. Fat-poor AMLs are heterogeneously isoattenuating or hyper-attenuating, but on the other hand, fat-invisible AMLs appear homogenously hyperattenuating. Contrast-enhanced CT is not necessary for diagnosing fat-rich AML but shoud be performed where there is a risk for tumor bleeding, to identify the tortuous vessels, before therapeutic embolization can be scheduled [22, 25].

Kidney AML can be very similar with renal cell carcinomas and hemorrhagic cysts on the MRI images, thus fat suppression techniques may be helpful in differentiate them from each other [23]. As in computed tomography imaging, contrast enhanced MRI has a limited role in the diagnosis of AML.

In some cases, especially in fat-invisible AMLs, when both CT and MRI images are inconclusive and we cannot differentiate AMLs from renal cell carcinomas on imaging alone, percutaneous renal biopsy is recommended to avoid unnecessary treatment.

TREATMENT

AMLs being an incidental finding on imaging tools in asymptomatic patients, implies that a small percentage of cases requires active treatment.

The current guidelines regarding AMLs recommend active treatment in well-selected cases, such as: symptomatic tumours, the presence in women of childbearing age, poor access to follow-up or emergency care and large masses, but a size threshold remains controversial (historically a size greater than 4 cm was considered an indication for surgery).

Active surveillance

If the indication for active treatment are not present, all patients with AML should undergo routine monitoring by imaging to assess stability [26]. Patients with tumors less than 2 cm should do renal ultrasound every 3 to 4 years and those with masses measuring 2 to 4 cm should undergo ultrasound monitorisation every year. Patients with masses larger than 4 cm in diameter, who do not undergo surgery should be assesed, by ultrasound or CT every 6 months, and if stable, anually. The same with patients with epithelioid variants. Patients who have had surgical removal of an epithelioid AML, at high-risk for malignant transformation, should have whole-body CT six months after surgery and yearly thereafter for at least five years [27].

Embolization

Selective embolization of the renal artery is the preferred treatment for patients with life-threatening retroperitoneal hemorrhage. Embolization can be performed preoperatively to reduce the difficulty and complications of the surgical removal. It has a relatively high percentage of side effects including: fever, flank pain, leucocytosis, nausea, and vomiting within the first three days after the procedure, but nothing that cannot be managed conservatively. Other rare complications include non-target embolization of normal parenchyma or renal infarction [28,29]. Altough it is a generally well-tolerated procedure, it has a risk of regrowth and repeated haemorrhage after embolization [30].

Surgical excision

Partial or radical nephrectomy can be used to treat renal AMLs, being the only treatment that completely removes the renal mass. Current guidliness recommend that nephron-sparing surgery should always be performed whenever possible, being even more important in patients with TSC or LAM, because of the multifocality of the disease in this group of patients and the higher risk of recurrence. Radical nephrectomy should be used only in selected cases,

with large masses and a high risk of malignant transformation, or when other treatment options are not viable. Sometimes, in an emergency setting, a radical nephrectomy can be a life-saver [18].

Minimal invasion techniques

Cryoablation and percutaneous radiofrequency ablation can be used as an alternative to embolization or surgery. Different studies show good efficacy with minimal complications, very few therapy sessions and no recurrences, but these minimal invasion techniques should be used on small (1-3 cm in diameter) and asymptomatic lesions [31].

Medical treatment

mTOR inhibitors, such as Sirolimus or Everolimus, decreases the risk of tumor progression and reduces the size of the tumor, especially in patients with TSC or LAM., but the use of these drugs in sporadic LAMs is still debatable. Recent guidelines recommend the use of mTOR inhibitors in patients with progressive renal LAMs greater than 3 cm in asymptomatic patients with TSC or LAM as the first line of treatment. Other treatments are required in case of secondary complications, such as cardiovascular diseases [32-36] or infections [37, 38].

DISCUSSIONS

A Japanese study, using a population-based ultrasound screening, included 18,000 healthy adults, and found that 0.1 percent of men and 0.2 percent of women had renal AML [39]. Rule et al stated that renal AMLs are more common seen in middle aged women, compared to men, findings supported by Koo and his team in their research on a group of 117 patients with sporadic AML, that found that 92% of patients were women with a mean age of 52 years old [16, 40].

Ewalt et al in their longitudinal study on 60 children with TSC found that renal AMLs were present in 48% of boys and 60% of girls at a mean age of 7 years old and in 76% of boys and 83% of girls at a follow-up age of 10 years old, suggesting that the prevalence of renal AMLs in patients with TSC is increasing with age [41].

In their paper on diagnosis and management of renal angiomyolipoma, Seyam and his colleagues included 60 patients with renal AMLs with a median age of 45 years old, from which 43 were females. Half the patients presented with flank pain and only 13 had hematuria. They screened patients for TSC and found this disease in 14 patients. More than half the patients were followed up expectantly, the mean size of the tumor being 4 cm in diameter, suggesting that the majority of patients with AMLs should undergo routine monitoring to assess stability. 29 patients needed active treatment to control bleeding and relieve pain or because of the risk of malignant transformation. Tumors that are larger in size have a higher risk of bleeding, the mean size of masses in which retroperitoneal hemorrhage was discovered was approximately 11 cm. Patients were followed up for a mean of 4 years and the lesions grew an average of 5 cm for TSC patients and less than 1 cm for the sporadic group, suggesting that patients with TSC are at a higher risk of progression. Furthermore, patients whom had TSC compared with the sporadic group were younger at presentation (26 versus 49 years old), had bigger renal masses (19 cm compared with a mean of 4 cm) and had multiple or bilateral lesions [42]. Similar findings were stated in a smaller group study conducted by Nelson et al (336 patients with 19% having TSC). The patients within the sporadic renal AMLs group were older (mean 52 years old compared with 30 years old), had smaller AMLs (mean 5 compared 9 cm), and were much less likely to have both multiple lesions (13% compared with 97%) and acute hemorrhage (14% compared with 44%) [43].

Some authors recommend that renal AMLs measuring 4 to 8 cm in diameter should be observed, if asymptomatic and close follow-up can be achieved [44, 45].

Bissler and his colleagues in their paper on mTOR inhibitors included 118 patients with AMLs, 5 of which were sporadic, the rest being in correlation with TSC. The target of at least 50 percent reduction in the total volume of the mass was achieved in 42% of the patients treated with everolimus compared with none of the patients treated with placebo, with a median response time of 3 months. Progression of AMLs was significantly more common in the placebo group (21%

compared with 4% in the mTOR inhibitors treated group) [46].

mTOR inhibitors treatment can be used to reduce the volume of tumors so the patients can benefit from a nephron-sparing surgery, fact stated in Staehler's paper on „Nephron-sparing resection of angiomyolipoma after sirolimus pretreatment in patients with tuberous sclerosis". Patients treated with Sirolimus had a 38 to 95% reduction in AML volume [47].

The efficacy of selective renal artery embolization was demonstrated in a study conducted on 30 patients with large renal AMLs (mean size of 8 cm). In 83% of AMLs that were embolized, the procedure was complete after a single sesion. The median reduction volume was 43% at a follow-up of 6 months and 81% at 12 months. They found that the response was poor for fat-rich AMLs compared with fat-poor tumors [48].

De Luca stated that sporadic AMLs smaller than 1.5 cm showed no growth over 5 year follow-up in 92% of cases [49]. Furthermore, Oesterling et al said that AMLs greater than 4 cm in diameter grow more rapidly and other authors found that younger patients compared with older individuals had a higher risk of progression [50, 51]. On the other hand, epithelioid variants of AMLs have a poorer prognosis. In one study conducted on 40 patients with renal epithelioid AMLs and atypia detected on histologic examination, local recurrence or distant metastases were present in 26% of cases [52]. Nese et al had the same results in their study on 41 patients with pure epithelioid AML, out of which 36% had a metastatic disease at the time of presentation, and 16% developed metastatic disease during follow-up [53].

CONCLUSION

AMLs are a benign group of renal tumors, commonly associated with TSC and LAM, but can also appear sporadically in the population. The detection of AMLs is increasing because of an increase in the use of imaging and advances in imaging technology. The diagnosis of AML is generally made by imaging in asymptomatic patients, although a biopsy may be required to diagnose fat-poor lesions. In terms of therapeutical management, several treatment option are available, though a small percentage of patients require it and the treatment should be individualized for every patient. Most of the AMLs can be managed by active surveillance. Pure epithelioid variants of AMLs have a poor prognosis comapared with the clasic variant.

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