



(RESEARCH ARTICLE)



## Hemorrhagic renal angiomyolipoma: An analysis of 6 cases with review of the literature

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### Abstract

Renal angiomyolipoma is the most common benign solid tumor of the kidney. It can occur sporadically or in association with tuberous sclerosis, which is an autosomal dominant inherited disease. Hemorrhagic rupture of renal angiomyolipoma with retroperitoneal hematoma is the most serious complication that can be life-threatening and requires urgent management. The aim of this study is to review, through 6 cases and by means of a review of the literature, the diagnostic criteria of renal angiomyolipoma and the particularities of management of hemorrhagic renal angiomyolipoma. We carried out a retrospective study which concerned 6 patients with hemorrhagic renal angiomyolipoma, unilateral or bilateral, during the period between January 2019 and August 2021, in the Urology Department of the Hassan II University Hospital in Fez. The average age of our patients was 53 years with an F/M sex ratio of 2. Bourneville's tuberous sclerosis was diagnosed in 3 patients. The circumstances of discovery of renal angiomyolipoma were: acute flank pain associated with anemic syndrome in 3 patients, incidental discovery in 1 patient, clot hematuria in 1 patient and abdominal mass in 1 patient. Clinical examination revealed hemodynamic instability in 1 patient, flank defense in 2 patients, lumbar mass in 1 patient and lumbar tenderness in 1 patient. The abdominal CT angiogram allowed us to retain the diagnosis of renal angiomyolipoma in all the patients, with a bilateral form in the 3 patients with tuberous sclerosis of Bourneville. Renal embolization was performed in 5 patients, while total nephrectomy was performed in 1 patient. Renal angiomyolipoma is a rare tumor in daily urological practice. Its hemorrhagic risk requires a good knowledge of diagnostic, therapeutic and monitoring methods.

**Keywords:** Renal angiomyolipoma; Bourneville tuberous sclerosis; Retroperitoneal hematoma; Renal embolization

### 1. Introduction

Renal angiomyolipoma (AML) is a rare tumor which, although benign in most cases, can present difficult management decisions. It accounts for 0.3% of all kidney tumors [1-2]. It was first described histologically by Fisher in 1911 as comprising three components: dysmorphic blood vessels, smooth muscle and adipose tissue, from which the term tumor is derived [3-4]. This tumor can occur sporadically or in association with tuberous sclerosis Bourneville (TBS) or more rarely sporadic lymphangioleiomyomatosis (ALL). Renal angiomyolipomas are classified into three types: Classical angiomyolipoma, low-fat angiomyolipoma and epithelioid angiomyolipoma: aggressive, potentially malignant form [5]. Although there is an increasing tendency to diagnose this tumor incidentally using imaging means, hemorrhagic rupture of renal AML remains a frequent and potentially fatal clinical presentation requiring renal embolization or nephrectomy hemostasis [6].

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## 2. Material and methods

A retrospective study was carried out including 6 cases of hemorrhagic renal angiomyolipoma, whether or not associated with TSC, during the period between January 2019 and August 2021, in the Urology Department of the Hassan II University Hospital in Fez.

Our analysis was based on the evaluation of the epidemiological, clinical and radiological characteristics of renal angiomyolipoma, as well as the modalities of its management, in particular hemorrhagic renal AML.

These data were collected from medical files archived in the Urology Department of the Hassan II University Hospital in Fez, as well as data archived in the "Hosixnet" computerized hospital system.

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## 3. Results

### 3.1. Description of cases

#### 3.1.1. Age

The average age was 53, with extremes ranging from 31 to 68.

Bourneville tuberous sclerosis was associated in 3 cases, with an average age of 47 years, compared to an average age of 60 years observed in the 3 cases with sporadic renal AML.

#### 3.1.2. Gender

Among the 6 cases in our study, 4 were female, thus determining a F / M sex ratio of 2/1.

For the 3 patients with associated TSC, 2 of them were male.

### 3.2. Circumstances of discovery (Figure1)

Anemic syndrome and acute flank pain were the main symptoms revealing the disease in 3 patients. The other modes of revelation were: clotting hematuria in one case, an abdominal mass in one case and an accidental discovery during an abdominal CT scan performed in the context of acute pancreatitis in one case.

### 3.3. Clinical examination

The general examination revealed hemorrhagic shock in a single case, requiring its management in intensive care.



**Figures 1** Facial angiofibromas and "sore skin" plaques in a patient with TSC.

The physical examination objectified lumbar fossa defense in 2 cases, lumbar tenderness in 2 cases and lumbar contact in 1 case. The physical examination was normal in the incidentally discovered renal AML case.

Dermatological examination of patients with TSC revealed: facial angiofibromas in all patients, “painful skin” plaques in 2 patients, nail fibroids in one patient and hypochromic macules in 2 patients (Figures1).

### 3.4. Paraclinical examinations

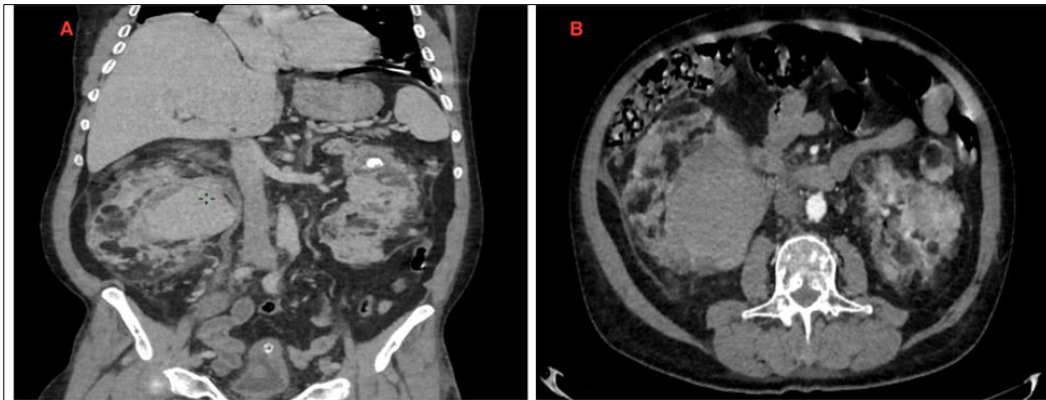
#### 3.4.1. Biology

Anemia was diagnosed in 4 patients with varying hemoglobin values between 6 -10g / dl, 2 of whom had TBS.

Renal failure was demonstrated in only 1 patient with TBS, with a creatinine clearance of 40ml / min according to the MDRD formula.

#### 3.4.2. Imaging

Renal ultrasound was performed in 3 patients, showing heterogeneous hyperechoic lesions in all patients and polycystic kidneys in a single patient.



**Figure 2** CT images of bilateral renal AML in cross section (B) and coronal reconstruction (A) in a patient with TSC, showing polycystic kidney disease with a large right hemorrhagic cyst.



**Figure 3** CT scan showing hepatic angiofibroma in a patient with TSC



**Figure 4** Brain CT image showing subependymal nodules in a patient with TSC.

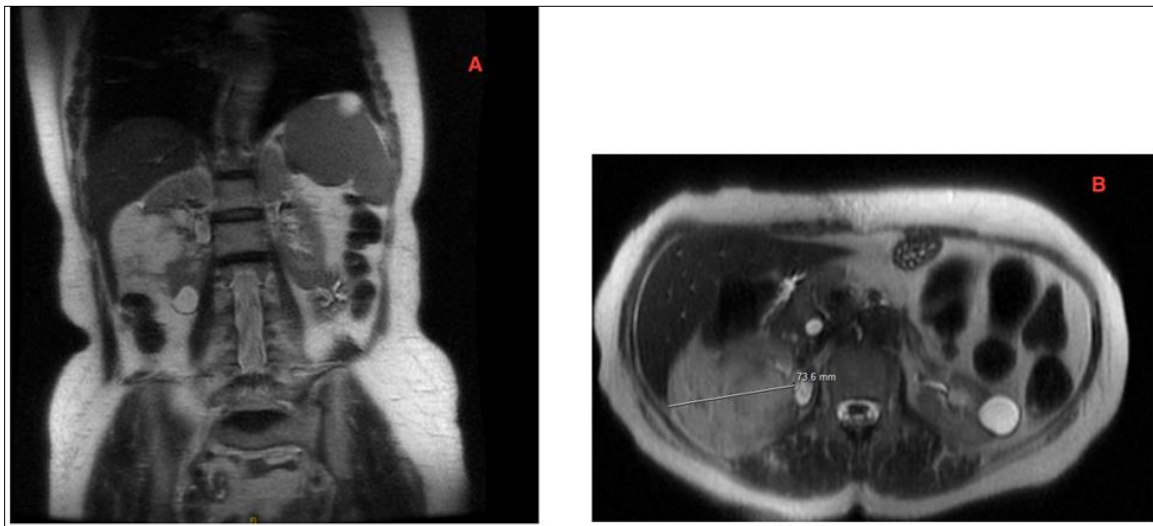
Abdominal C- / C + CT scan was performed in all patients, allowing a positive diagnosis of renal angiomyolipoma by detecting its fatty component (Figure 2). AML was bilateral in the 3 patients with TSC and unilateral in the 3 sporadic

cases. The fatty component was predominant in all patients. The tumor size varied between 6 cm and 17 cm with an average of 11 cm. Tumor rupture with retroperitoneal hematoma has been described in 3 patients, aneurysm dystrophy with intratumoral rupture has been described in 2 patients, while aneurysm rupture in the excretory tract has been described in a single patient. Polycystic kidney disease was observed in only 1 patient with TSC, associated with right pyelocalicel dilation in the same patient. A hepatic angiofibroma was detected in a single patient during TSC (Figure 3).

A brain scan was performed in 3 patients objectifying subependymal nodules and cortical tubers in all patients and a giant cell astrocytoma in one patient, thus making it possible to retain the diagnosis of TBS in these patients (figure 4).

A chest scan was performed in 3 patients showing multiple bilateral cystic lesions in one patient.

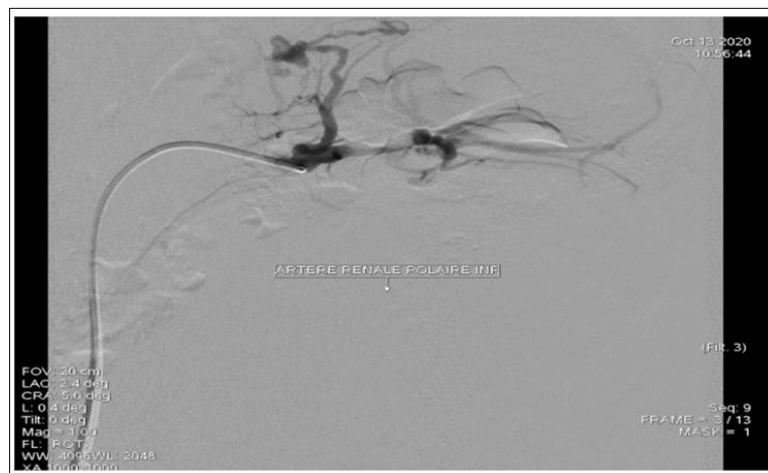
Abdominal MRI was performed in a case demonstrating a tumor lesion by hypersignal in the T1, T2 sequences (figure 5) and by hypointense in the T1 sequence with suppression of the fat signal.



**Figure 5** MRI images in T2 sequence of a right renal AML in cross section (B) and coronal (A) showing the tumor in hypersignal.

### 3.5. Therapeutic care

For the 6 patients in our series, 5 were treated in the urological surgery department while only one patient was admitted to the intensive care unit for management of his hemorrhagic shock. The length of the hospital stay varied between 6 days and 20 days.



**Figure 6** Arteriographic image in renal pre-embolization showing an aneurysmal inferior polar artery

Regarding blood transfusion, 4 patients received a red blood cell transfusion. No post-transfusion complications have been reported.

Unilateral renal embolization was performed in 5 patients (Figure 6), while total hemostatic nephrectomy was performed in a single patient.

The postoperative outcome was good in all patients, no case of death was reported in our series.

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## 4. Discussion

### 4.1. Epidemiology

Renal AML rarely occurs in the general population, with women being more affected than men. Its prevalence is estimated at 0.28% in men and 0.6% in women with a sex ratio of 2/1 [7]. The prevalence of AML associated with TSC is approximately 20% [3].

Bourneville tuberous sclerosis (TBS) is an autosomal dominant disease with an estimated prevalence of 1/12000 with a birth rate as high as 1/1600 [8]. In patients with this disease, the rate of occurrence of renal AML in the literature varies within a range of 55% to 90% [9].

Renal AML can also occur in 30-50% of subjects with sporadic lymphangioleiomyomatosis (AML), a much rarer condition than TBS, occurring exclusively in women [10].

Sporadic renal AML most commonly occurs after the age of 40, most often single and unilateral, while renal AML associated with TBS occurs at a younger age (20-30 years), most often multiple and bilateral [11-12].

In our series, of the 6 cases with renal AML, 3 had TSC with an average age of 47 years compared to 60 years in the sporadic cases. The sex ratio was 2:1.

### 4.2. Pathophysiology

Renal AML may occur as part of TSC, sporadically or less frequently in association with AML. TSC is genetically characterized by mutations in the TSC 1 and TSC 2 genes located respectively at the 9q34 and 16p3.3 loci [8-9].

These two genes code for two proteins: hamartin and tuberin which interact to form the hamartin-tuberin complex which is fundamental in inhibiting the mammalian target of rapamycin (mTOR) signaling pathway [8-9]. Loss of TSC 1 and TSC 2 function induces loss of control over activation of the mTOR pathway, which creates uncontrolled cell growth and proliferation [9].

The loss of control of the activation of the mTOR pathway induces other clinical manifestations associated with TBS, this is the example of the neurological manifestations resulting from the involvement of the central nervous system: epilepsy, neurocognitive disorders and autism, due to cortical tubercles, subependymal nodules and astrocytomas [8-9].

### 4.3. Clinical presentation

With the increasing use of sectional imaging, more than 80% of renal AML are discovered incidentally, with Wunderlich syndrome (spontaneous retroperitoneal hematoma) observed in less than 15% of cases associated with hemorrhagic shock in less than 10% of cases [12-13].

The classic renal tumor triad of flank pain, hematuria and a palpable mass has been observed in the literature in 11-24% of patients with renal AML [3-4]. The more modern series generally show lower rates of these symptoms, although Seyam et al. found in their cohort that pain and hematuria were present in 50% and 22% of cases, respectively [12-13].

In our series, renal AML was discovered in a hemorrhagic situation in 3 patients (Wunderlich syndrome) with hemorrhagic shock in 1 patient, hematuria in 1 patient, a palpable mass in 1 patient, and an incidental discovery during an imaging performed for another pathology in 1 patient.

#### 4.4. Imaging

The diagnosis of renal AML can be reliably made on computed tomography (CT) or magnetic resonance imaging (MRI) [14]. Ultrasound is not sensitive for renal AML, it usually shows a hyperechoic lesion with shadow cone, which cannot be distinguished from other renal tumors [15]. However, once the diagnosis of renal AML has been established, ultrasound may be useful for its follow-up [16].

##### 4.4.1. Computed tomography (CT)

CT has excellent sensitivity and specificity for diagnosing renal AML and renal masses in general [17]. In addition, it is a fast and accessible means of imaging in everyday practice. Even for small tumors <2cm, the presence of gross fat is often visible allowing the diagnosis of AML. Areas of density <10-15 HU are generally considered a diagnosis of gross fat [17]. In 4 to 5% of cases, the fat cannot be detected on the CT scan because of its small amount within the tumor (AML low in fat): These lesions generally appear hyperdense > 45 HU and are evenly enhanced afterwards. Injection, which can mimic renal cell carcinoma [18]. Fat may also be masked by intratumoral hemorrhage, in which case phase contrast MRI (PC-MRI) may be useful [18].

##### 4.4.2. Magnetic resonance imaging (MRI)

Like CT, MRI has high sensitivity and specificity for diagnosing renal AML equally in terms of precision. It may be particularly useful for the diagnosis of low-fat AML [18]. Unlike CT, MRI does not expose you to the risk of radiation. In addition, the diagnosis of renal AML can be established by MRI without injection of contrast medium, which is indicated in renal failure. The disadvantages of this review are the high cost and the accessibility problem in everyday practice.

Classical renal AML appears in T1 and T2 hypersignal, and in T1 hypointense with suppression of the fat signal [19]. When renal AML is low in fat, chemical shift sequences may be useful [20], it appears in T1 and T2 hypointense and shows no loss of signal with selective fat suppression or in chemical shift sequences. [21].

In our series, the positive diagnosis of renal AML was retained thanks to the tomodensitometry which objectified the classic aspect of AML by highlighting its fatty component.

#### 4.5. Therapeutic care

##### 4.5.1. Observation and active surveillance

Sporadic renal AML: frequently asymptomatic with slow growth [22]. Active surveillance is indicated for asymptomatic patients with a tumor <4cm.

Renal AML associated with TBS: Occurs at an earlier age, it grows faster than that of sporadic AML. Indeed, Seyam et al reported that the growth rate of renal AML associated with TBS was significantly higher than that of sporadic AML (annual growth rate: 1.25cm vs 0.19cm) [23]. Active surveillance is indicated for patients with asymptomatic tumor <3cm.

Currently, there is no consensus on the pace of monitoring. According to the recommendations of the ITSCCC (International Tuberosus Sclerosis Complex Consensus Conference) for monitoring renal AML associated with TBS, abdominal MRI or ultrasound should be performed every 1-3 years to monitor disease progression for throughout the life of the patient [24].

##### 4.5.2. Embolization

The most feared complication of renal AML is intra-tumor or retroperitoneal hemorrhage following tumor rupture, which can be life-threatening. In this case, renal artery embolization is an effective treatment option. In addition to its effect on reducing tumor size, renal embolization has a hemostatic effect by preserving the renal parenchyma. It can be done with absolute alcohol, metal coils, Trisacryl gelatin microspheres, and n-butyl-2-cyanocrylates.

Renal embolization is indicated as a first-line treatment for hemorrhagic renal AML, and in intra-tumoral aneurysms greater than or equal to 5 mm, considered to be at very high risk of rupture [25].

Over surgery, embolization has several advantages including low complication rate, preservation of renal function, and satisfactory short-term (<5years) results [26]. However, it has several drawbacks: Unlike sporadic renal AML, TBS-associated AML tends to increase after embolization [27]. Indeed, Ewalt et al reported that, among 16 patients who

underwent renal embolization for AML associated with TBS, 9 presented tumor growth [27]. Likewise, Boorijian et al reported that renal embolization, in patients with renal AML associated with TSC, was associated with a high risk of recurrence and re-bleeding compared to partial nephrectomy [28].

Post-embolization syndrome is the most common complication occurring in 80% of cases. Symptoms include fever, nausea, flank pain, and leukocytosis. It requires symptomatic treatment [29].

In our series, renal embolization was performed in 5 patients whose indication was hemorrhagic renal AML.

#### 4.5.3. Surgery

Surgery is not recommended as a first-line treatment for renal AML [24]. Surgical treatment is considered if there is suspicion of malignancy, presence of symptoms or risk of bleeding. In these cases, partial nephrectomy is accepted as the optimal procedure based on its feasibility, its low rate of complications and the preservation of renal function [28], regardless of the approach used (open surgery, laparoscopic or robot-assisted) who have objectified similar results [6]. Total nephrectomy should be discussed with caution due to the increased risk of secondary renal failure [31].

Renal AML associated with TSC is often bilateral and multifocal with a high risk of recurrence, which warrants medical treatment combined with surgery. Indeed, the preoperative administration of mTOR inhibitors may reduce the rate of recurrence and facilitate the difficulty of partial nephrectomy [30].

In our series, surgery was performed in a single patient who underwent total nephrectomy for hemorrhagic AML.

#### 4.5.4. mTOR inhibitors

Everolimus is indicated for the treatment of renal AML associated with TBS and locally advanced renal cell carcinoma after failure of tyrosine kinase inhibitors. The ITSCC recommends mTOR inhibitors as first-line therapy for renal AMLs associated with TBS of a size greater than or equal to 3 cm, even asymptomatic [24]. Ni et al. retrospectively studied the short-term effect of everolimus on renal AML associated with TSC. In their study, the tumor volume reduction rate was 56.5% at 12 weeks after the start of treatment [32]. Wang et al. compared in their study the efficacy of everolimus and sirolimus, they concluded that everolimus at a dosage of 10 mg / d was more effective than sirolimus at 2 mg / d for the treatment of renal AML associated with the STB [33].

The main side effects of mTOR inhibitors include: yeast infection, irregular menstrual cycle, abdominal pain, and proteinuria.

In our series, no patient received treatment with mTOR inhibitors.

#### 4.5.5. Ablative treatments

They include radiofrequency ablation, microwave ablation, and cryoablation. Their indications are limited to symptomatic small tumors and in patients with a single anatomical or functional kidney [34].

f-Indications: [35] (figure7):

Asymptomatic renal AML

\* Associated with the STB: -Tumor> = 3cm: 1st line mTOR inhibitors

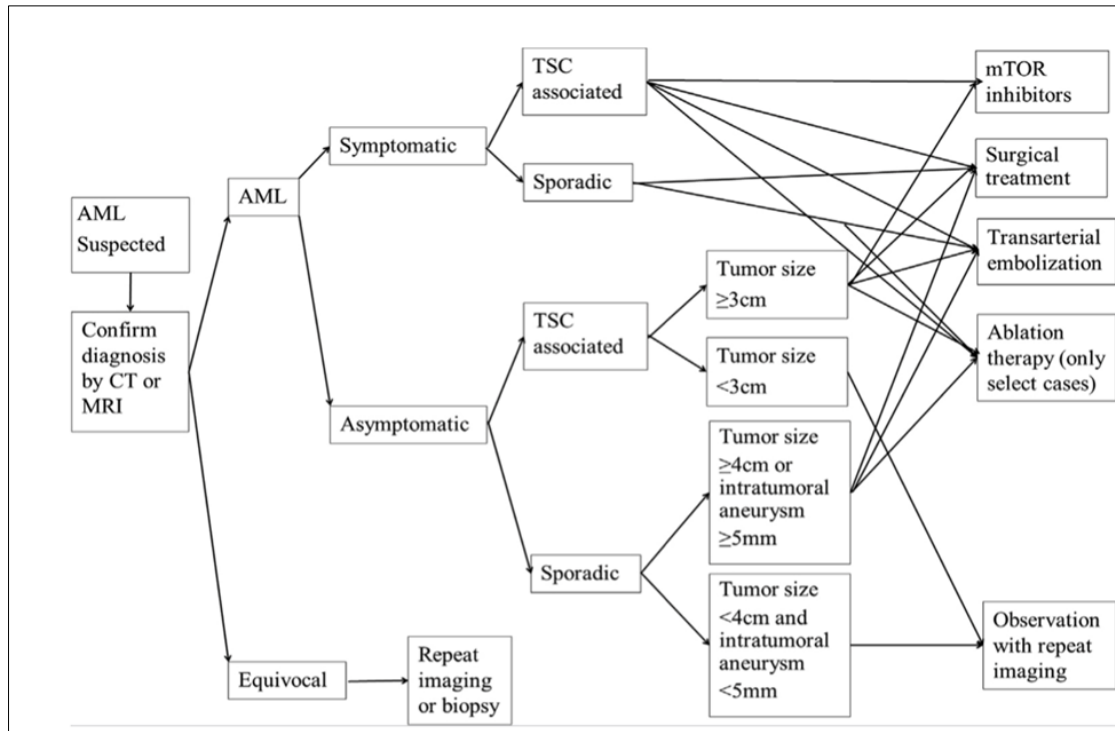
Second-line renal embolization or nephrectomy

-Tumor <3cm: active surveillance (ultrasound or MRI) every 1-3 years for life.

\* Sporadic

-Tumor> = 4cm and / or intratumoral aneurysm> = 5mm: Renal embolization or nephrectomy.

-Tumor <4cm, intratumoral aneurysm <5mm: active surveillance.



**Figure 7** Updated algorithm for the management of renal AML [35]

Symptomatic renal AML

\*Associated with TBS: Renal embolization or nephrectomy +/- mTOR inhibitors or ablative treatment (single kidney and / or small tumor)

\* Sporadic: Renal embolization or nephrectomy.

**5. Conclusion**

Renal AML is a benign tumor that can occur sporadically or as a manifestation of TBS. Unlike the older series, the majority of AMLs are currently discovered in an insidious fashion with often a hemorrhagic presentation which can be life-threatening, so correct diagnosis, careful monitoring and appropriate treatment are necessary in management. Positive diagnosis is based on CT scan or MRI by detecting the fatty component of AML, except in low fat subtypes requiring chemical shift sequences. Renal embolization is indicated as first-line treatment for hemorrhagic renal AML. Larger scale studies are desirable to determine when embolization cannot be substituted for surgery.

**Compliance with ethical standards**

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*Disclosure of conflict of interest*

The authors declare no conflict of interest.

*Statement of informed consent*

Informed consent was obtained from all individual participants included in the study.



*Statement of ethical approval*

Ethical approval to report these cases was obtained from CHU Hassan II ethics committee HASSAN II FEZ, MORROCO UROLOGY DIVISION.

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