Renal epithelioid angiomyolipoma: A case report

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Abstract. Epithelioid angiomyolipoma (EAML) of the kidney is an uncommon neoplasm with malignant potential. It can occur sporadically or be associated with tuberous sclerosis. EAML is a monotypic variant of angiomyolipoma (AML), which is classified as neoplasm of the perivascular epithelioid cell or perivascular epithelioid cell tumor. Due to its epithelioid nature and paucity of fat components, unlike classic AML, which has abundant adipose tissue with characteristic features on CT scans, it is difficult to distinguish EAML from renal cell carcinoma and fat-poor AML on CT or MRI preoperatively, which may lead to misdiagnosis and unnecessary nephrectomy. The present report describes two cases of renal EAML, which were successfully treated by laparoscopic surgery. Preoperative diagnosis had not been achieved until surgery was performed and histological analysis was accomplished. No local recurrence or distal metastasis was observed during follow-up. Although the differential diagnosis was challenging preoperatively, a diagnosis of EAML should be considered and surgical excision was the preferred treatment strategy for the patients with localized tumors.

Introduction

Epithelioid angiomyolipoma (EAML), which was first described by Mai *et al* (1) in 1996, is a rare variant of angiomyolipoma (AML). AMLs are the most common mesenchymal neoplasms of the kidney with an incidence of 0.1-0.3% in healthy adults (2). AMLs are classified as neoplasms of the perivascular epithelioid cell or perivascular epithelioid cell tumor 'PEComa', which also includes lymphangioleiomyomatosis, and pulmonary and extrapulmonary clear cell sugar tumors (3). Renal EAMLs can occur sporadically or be associated with tuberous sclerosis (TSC) (4). Approximately one-third of EAMLs have been found to present with malignant biological behavior (5). According to a Japanese cohort study, the percentage of EAML cases among non-classical AML cases, which included EAML and fat-poor AML, was 17.9% (6). Although most cases of EAML follow a benign course, approximately one third of EAML cases are characterized by aggressive biological behavior, such as local recurrence after excision, enlarged lymph nodes, extension into the venous system and distant metastases (3,4,7).

Unlike classical AML, which is a benign renal entity composed of dysmorphic blood vessels, smooth muscle and adipose tissue, EAML is characterized by minimal fat content and an abundance of epithelioid cells (7). Atypia within the epithelioid cells, the presence of mitotic figures and necrosis are common and are associated with a more aggressive course of disease (8). Thus, EAML exhibits similar findings compared with renal cell carcinoma (RCC) and fat-poor AML on standard CT scans, making preoperative diagnosis challenging (9,10). However, surgery is the treatment of choice and is curative in most cases of EAMLs (3,6). The present report describes two cases of renal EAML, which were treated successfully by laparoscopic surgery. Although preoperative diagnosis was difficult to achieve, EAML should be included in the differential diagnosis when a renal lesion is found and correct histological diagnosis of this subtype of renal AML is crucial. Erroneous diagnosis of simple renal AML instead of EAML may lead to insufficient postoperative management.

Case report

Case 1. A 34-year-old female patient complaining of acute left flank pain was referred to The First Affiliated Hospital of Shandong First Medical University and Shandong Provincial Qianfoshan Hospital (Jinan, China) in November 2021. The patient had no previous illnesses or family history of TSC, and no gross hematouria was recorded. CT scans revealed a large hyperdense left renal mass arising from the renal sinus on non-contrast imaging (Fig. 1A). After contrast medium was administrated, the mass was enhanced and

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heterogeneous (Fig. 1B). These findings were similar to those of RCC in standard CT imaging (hypodense or isodense mass in plain scans and hyperdense mass in contrast-enhanced imaging) (9,10). The tumor was hypointense in gadolinium enhanced T1-weighted MRI (Fig. 1C), and also hypointense in fat-saturated T2-weighted imaging (Fig. 1D).

In the differential diagnosis of the patient, three types of disease were considered: RCC, renal pelvic carcinoma and AML with acute hemorrhage. Due to its location in proximity to the renal pedicle, biopsy of the tumor was not performed. Retrograde ureteroscopy was conducted and no pelvic mass was found during the procedure. After a negative metastatic workup, the patient underwent a left radical nephrectomy using the retroperitoneal laparoscopic technique.

Histologic examination revealed a 47x45-mm tumor with hemorrhage, which could explain the onset of acute pain of the patient, and the protocol for histopathological staining was as follows: After appropriate tissue sampling, tumor blocks were fixed in solution consisting of 10% formaldehyde in 0.01 M phosphate-buffered saline (PBS) for 2 h at room temperature. Subsequently, tissue blocks were loaded into the Tissue-Tek VIP® 6 AI Tissue Processor (Sakura Finetek USA, Inc.) and then embedded in paraffin. The paraffin blocks were cut into sections with 5-μm thickness, dewaxed with xylene, and rehydrated in a descending ethanol series (95, 90, 80 and 75%) and water. Slices were immersed in Harris hematoxylin staining solution for 5 min at room temperature and then differentiated with 0.3% acid alcohol, followed by incubation with 0.6% ammonia for 5 sec at room temperature. Subsequently, samples were incubated with eosin staining solution for 1-3 min at room temperature and then dehydrated with ethanol and xylene at room temperature, and finally, slides were mounted with neutral gum and observed under a light microscope (LEICA DM2000; Leica Microsystems GmbH). Histologically, spindle epithelioid cells, which were clustered around blood vessels, could be observed in the tumor of the patient. The tumor cells were mostly composed of eosinophilic epithelioid cells. The cytoplasm of tumor cells was clear or granular with vesicular chromatin and prominent nucleoli (Fig. 2A).

For immunohistochemistry (IHC), 5-μm-thick tumor sections from a paraffin block were deparaffinized and rehydrated as previously described (11). For quenching of endogenous peroxidase activity, the slides were incubated with 3% hydrogen peroxide solution in methanol for 30 min at room temperature in the dark. Heat-induced epitope retrieval was adopted; slides were rinsed three times with 0.01 M PBS, then treated with antigen retrieval reagent (0.01 M citrate buffer solution; pH 6.0) in a pressure cooker for 10 min. Slides were washed three times with 0.01 M PBS (pH 7.4; 5 min/wash) at room temperature, and were then blocked with 10% goat non-immune serum (SP KIT-B3; Fuzhuo Maixin Biotech Co., Ltd.) for 30 min at room temperature to prevent non-specific binding. Sections were rinsed three times with 0.01 M PBS (pH 7.4; 5 min/wash), and were then incubated with monoclonal primary anti-HMB45 (1:200; ab190913; Abcam), anti-melan A (1:200; ab187369; Abcam) and anti-α-smooth muscle actin (α-SMA; 1:500; ab247685; Abcam) antibodies at 4˚C for 12 h. Primary antibodies were diluted with PBS. Slides were washed three times with 0.01 M PBS (5 min/wash), then incubated with Peroxidase-AffiniPure Goat Anti-Rabbit IgG (ready to use; cat. no. KIT-9706; Fuzhou Maixin Biotech Co., Ltd,) for 30 min at 37˚C. Peroxidase-conjugated streptavidin (Invitrogen; Thermo Fisher Scientific, Inc.) was applied, diaminobenzidine was used as the chromogen and sections were counterstained with Mayer's hematoxylin for 2 min at room temperature. Subsequently, slides were sealed with Permount Mounting Medium and observed under a light microscope (LEICA DM2000; Leica Microsystems GmbH). Images were captured with Digital Pathology Scanner (PRECICE series 510; UNic medical Corp.). The tumor cells were strongly positive for HMB-45 (Fig. 2B), weakly positive for melan A (Fig. 2C) and diffusely positive for α-SMA (Fig. 2D). The pathologic diagnosis was most consistent with EAML, which was defined as an epithelioid component ≥80% according to the 2016 World Health Organization (WHO) Classification of Renal Neoplasms (12).

The patient recovered well and was discharged 8 days after surgery, and no local recurrence or remote metastasis was observed during 3-monthly follow-up with clinical evaluation and CT scans of the chest, abdomen and pelvis. The follow-up would continue for 2 years, then biannual follow-up up to 5 years must be carried out, followed by annual follow-up in the future. At present, the patient has undergone routine clinical evaluation and CT scans of the chest, abdomen and pelvis at the outpatient clinic (The First Affiliated Hospital of Shandong First Medical University and Shandong Provincial Qianfoshan Hospital, Jinan, China), and no recurrence or metastasis have been observed. Written informed consent was obtained from the patient for publication of the present report.

Case 2. A 20-year-old male patient presenting with right flank pain for 7 h and hematouria for 2 h was admitted to The First Affiliated Hospital of Shandong First Medical University and Shandong Provincial Qianfoshan Hospital (Jinan, China) in October 2018. Past medical and family histories were unremarkable. CT scans demonstrated a hyperdense mass of the right kidney, measuring 58x52 mm (Fig. 3A). After contrast medium was administrated, the tumor was slightly enhanced and the renal pelvis was invaded (Fig. 3B). AML with hemorrhage was considered, which might lead to the flank pain and hematouria of the patient. Since it was hard to distinguish AML with hemorrhage from RCC, which might be treated by radical nephrectomy, on CT imaging, a fine-needle biopsy was conducted subsequently, but no tumor tissue was found, potentially due to necrosis or hemorrhage of the mass (13). The patient underwent a partial right nephrectomy using the retroperitoneal laparoscopic approach.

Similar to patient 1, gross examination also revealed hemorrhage of the tumor, which led to presentation of flank pain of the patient. The same protocol as described for patient 1 was used for histopathological staining and IHC. Histologic analysis of the tumor revealed that sheets of round and polygonal epithelioid cells were arranged in close nests, which were interspersed with stroma consisting of abundant blood vessels (Fig. 4A). IHC staining revealed that the tumor cells were strongly positive for HMB-45 (Fig. 4B), and diffusely positive for melan A (Fig. 4C) and α-SMA (Fig. 4D). Histologically, both cases exhibited mainly epithelial cells interspersed with smooth muscle cells in two distinct patterns. A diffuse growth pattern was more evident in case 1, with epithelial cells and

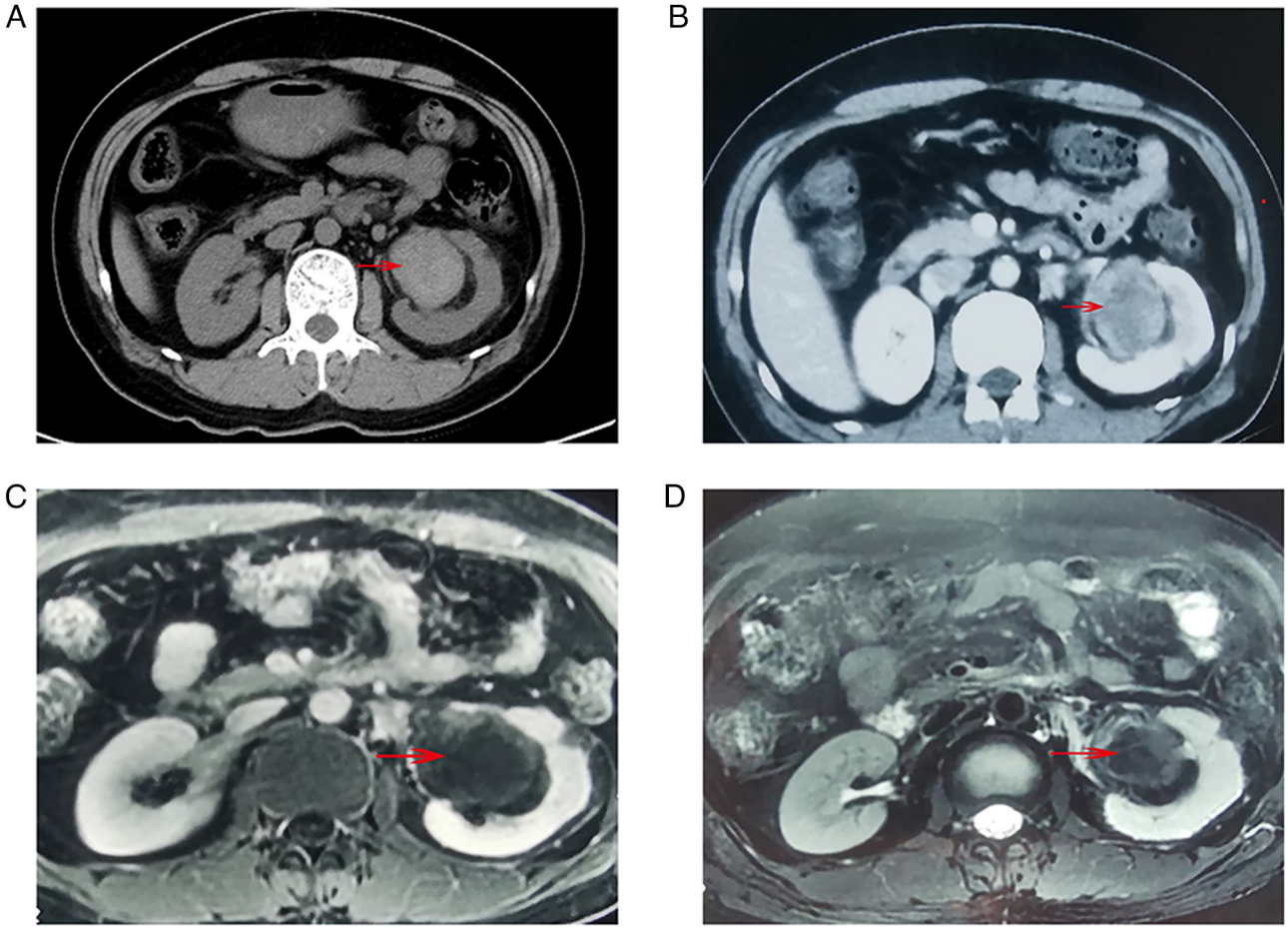

Figure 1. Radiographic images of the tumor in patient 1. (A) Non-contrast CT scan showing a large hyperdense left renal mass arising from the renal sinus (arrow). (B) Enhanced CT scan showing that the mass was enhanced and heterogeneous (arrow). (C) The tumor was hypointense on gadolinium enhanced T1-weighted MRI (arrow). (D) The tumor was also hypointense on fat-saturated T2-weighted imaging (arrow).

plump spindle-shaped cells arranged in diffuse sheets. The cytoplasm of tumor cells was clear to granular or feathery with vesicular chromatin and prominent nucleoli (Fig. 2A). A carcinoma-like growth pattern was observed in case 2, in which large polygonal cells with dense cytoplasm and atypical nuclei with prominent nucleoli were arranged in cohesive nests with wide alveoli (Fig. 4A). Immunohistochemically, the epithelial cells expressed the melanocyte maker HMB-45 and melanin A. The two cases were diagnosed as EAML according to the WHO classification of tumors (12).

There was no evidence of recurrence or metastasis 4 years postoperatively (Fig. 3C). The protocol for follow-up was the same as that for patient 1. The present patient also had a favorable course of disease with routine clinical evaluation and CT scans. At present, the right kidney of the patient appears to be a normal size compared with the left kidney and no atrophy has been observed. Written informed consent was obtained from the patient for publication of the present report.

Discussion

Classic renal AML is a benign mesenchymal tumor composed of dysmorphic blood vessels, smooth muscle and adipose tissue (14). Pathologically, AMLs are considered to arise from perivascular epithelioid cells and are often grouped together with other PEComas (15). EAML is a rare subtype of AML, accounting for 4.6% of all AMLs (16), and is composed of epithelioid cells arranged in sheets with a lack of abnormal vessels and adipocytes (1). The 2016 World Health Organization Classification of Renal Neoplasms defined EAML as a potentially malignant mesenchymal neoplasm (12). Metastatic disease has been reported in one-third of reported cases of EAML, including sporadic and TSC-associated EAMLs (3,14,17).

Genetically, TSC is a group of autosomal dominant genetic disorders caused by germline mutations in the TSC complex subunit 1 (*TSC1*) or TSC complex subunit 2 (*TSC2*) genes (18). The proteins hamartin and tuberin are encoded by the *TSC1* and *TSC2* genes, respectively (18). Among patients with TSC, the prevalence of AML has been reported as 55-90%, with an earlier presentation than sporadic cases (19,20). Steiner *et al* (21) reported that patients with TSC presented with AML at a mean age of 31.5 years (range, 17-62 years), while patients without TSC presented with AML at a mean age of 53.6 years (range, 19-74 years). TSC-associated AMLs typically present with multiple, bilateral and symptomatic tumors of the kidney (20). As well as AMLs, patients with TSC may develop renal cysts, RCC, oncocytoma, perirenal cysts and polycystic kidney disease (20).

Histologically, EAML can resemble and be misdiagnosed as sarcomatoid or high-grade RCC (22). However, EAML

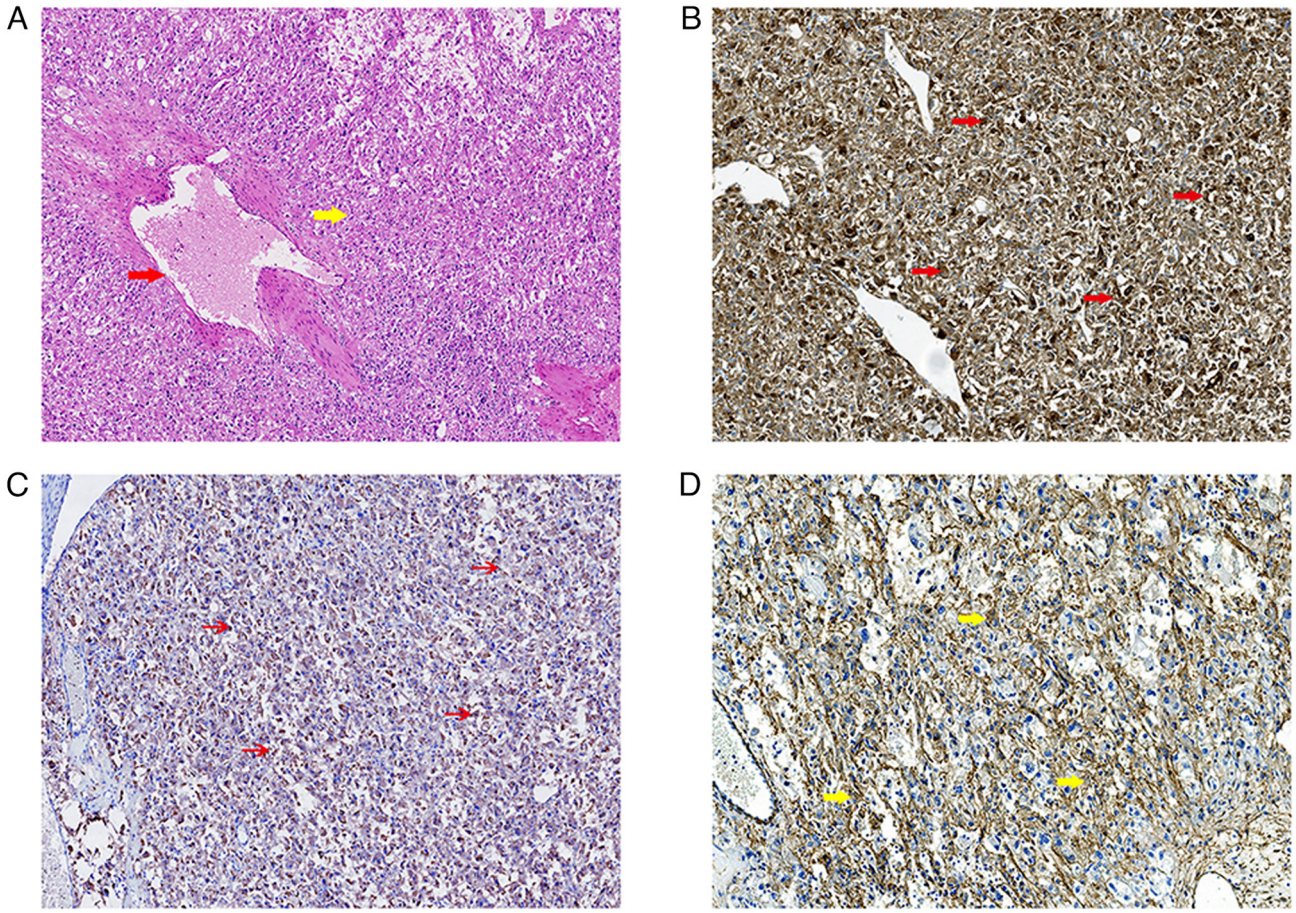

Figure 2. Histopathological findings of the tumor in patient 1. (A) Epithelial cells and plump spindle-shaped cells were arranged in dense and diffuse sheets. The cytoplasm of tumor cells was clear or granular with vesicular chromatin and prominent nucleoli (yellow arrow). Pleomorphic epithelioid cells with abundant eosinophilic cytoplasm clustered around blood vessels (red arrow). Magnification, x20. The tumor cells were (B) strongly positive for HMB-45, (C) weakly positive for melan A and (D) diffusely positive for α-smooth muscle actin (arrows). Magnification, x100.

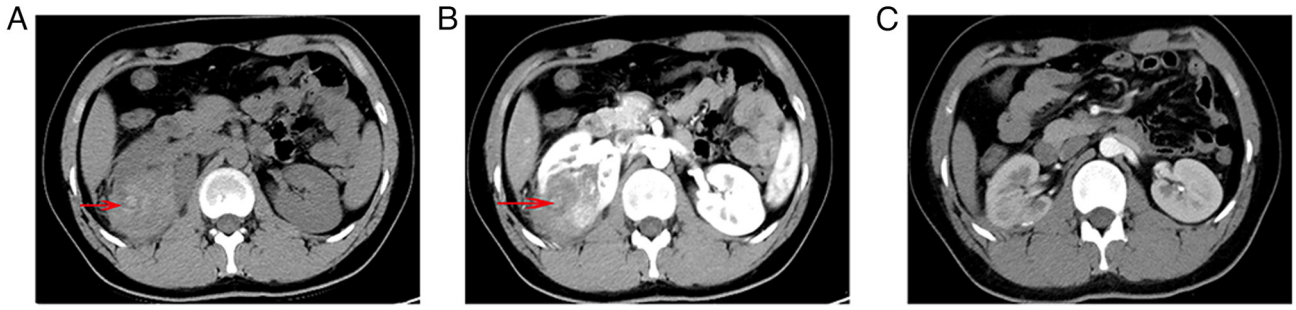

Figure 3. CT scan of patient 2. (A) Non-contrast CT scans demonstrated a hyperdense mass of the right kidney, measuring 58x52 mm (arrow). (B) After contrast medium was administrated, the tumor was slightly enhanced and the renal pelvis was invaded (arrow). (C) No recurrence was observed after 4 years of follow-up.

can be differentiated from RCC by the presence of immunohistochemistry markers such as melanosome-associated proteins (HMB-45 antigen and melan A) and smooth muscle markers [actin monoclonal antibody (HHF-35), α-SMA and caldesmon] (22,23). The presence of malignant potential in EAML has been attributed to the following parameters: TSC and/or concurrent AML, tumor size >7 cm, tumor necrosis, extrarenal extension and/or involvement of the renal vein, and carcinoma-like growth pattern. These parameters were used to stratify patients into groups with low, intermediate and high risk for disease progression, which had a risk of disease progression of 15, 64 and 100%, respectively (24). Brimo *et al* (8) studied several features that increased the likelihood of malignancy in renal EAML with atypia. Based on these features, the authors developed a predictive model of four atypical features that included ≥70% atypical epithelioid cells, ≥2 mitotic figures per 10 high-power fields, atypical mitotic figures and necrosis. The presence of three or all of the features was predictive of malignant behavior. This model accurately categorized 78% of clinically malignant EAMLs

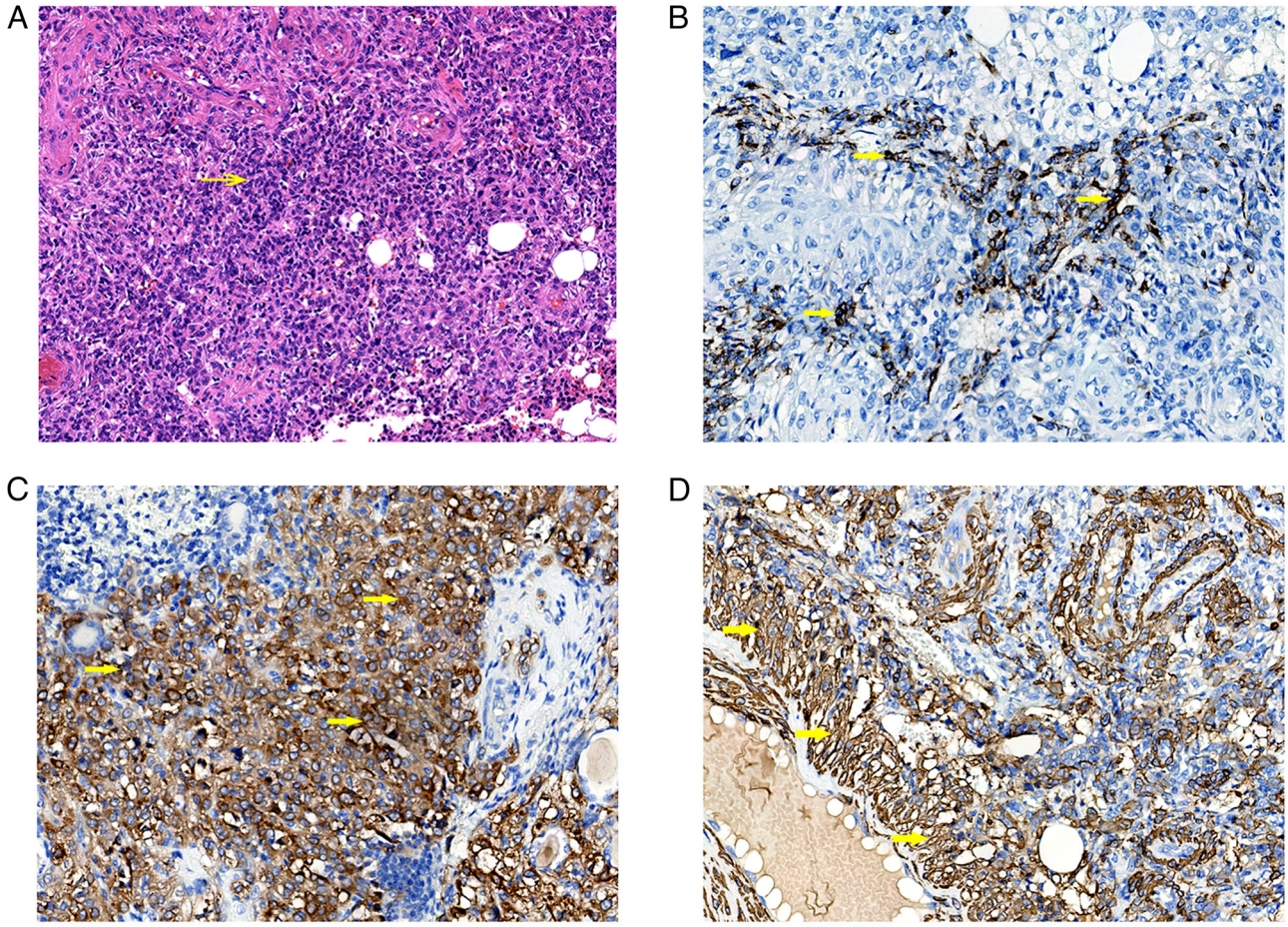

Figure 4. Histopathological findings of the tumor in patient 2. (A) Sheets of round and polygonal epithelioid cells (arrow) were arranged in close nests, which were interspersed with stroma consisting of abundant blood vessels. Magnification, x100. The tumor cells were strongly positive for (B) HMB-45, and diffusely positive for (C) melan A and (D) α-smooth muscle actin (arrows). Magnification, x200.

with atypia and 100% of clinically benign EAMLs with atypia (8).

It is difficult to distinguish EAMLs and fat-poor AMLs from RCC based on CT scans since they do not contain radiographically identifiable fat (9,25). Radiologically, EAML typically presents as a large mass with intratumoral hemorrhage and necrosis (26). Most EAMLs exhibit hyperattenuation on unenhanced CT (typically >45 Hounsfield units) and T2 hypointensity due to their epithelioid muscle component (26). These findings cannot accurately identify EAMLs preoperatively and differentiate them from RCC, as seen in the present cases. Although the presence of necrosis or cystic changes and the absence of fat have been found to be independent predictors of EAML on CT imaging (10), most patients are treated as having a presumed RCC (23). There are also a few studies that have reported positron emission tomography (PET) findings of AMLs (27-29). Fat-poor AMLs might mimic RCC on ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET because of increased FDG uptake (27). Increased tracer accumulation on ^{18}F-FDG PET/CT imaging was also observed in pure EAML (28) and local recurrence of EAML after nephrectomy (29). Although it is difficult to differentiate EAML from RCC on CT scans, these radiographic findings may prompt the urologist to consider a percutaneous biopsy if the suspicion of EAML is raised by CT imaging (13). Percutaneous biopsy may serve an important role in diagnosis in these cases, because a core biopsy should be highly accurate in the diagnosis of AML with minimal fat (30).

AML is the most common renal neoplasm associated with spontaneous perirenal hemorrhage, closely followed by RCC (31). In the two present cases, the first presentation of the tumors was hemorrhage, leading to acute flank pain. A previous study reported that hemorrhage was one of the potential causes of heterogeneity on CT (32). From a pathological point of view, both AML and EAML consist of thick-walled poorly organized blood vessels without elastic fibers that can be observed under the microscope, and thus, have a tendency to bleed, particularly in large tumors (24). In the two present cases, hemorrhage of the tumors might be the potential causes of hyperattenuation on unenhanced CT, making them undistinguishable from RCC. In both cases, spontaneous hemorrhage of the tumor was suspected before surgeries, so AML with hemorrhage was first considered, which should be treated by nephron-sparing surgery (NSS) when technical feasible. In case 1, the tumor arose from the renal sinus, where partial nephrectomy was challenging with possible postoperative complications, so radical nephrectomy was performed. In case 2, although percutaneous biopsy was carried out, no tumor tissue was found, potentially due to necrosis or hemorrhage of the mass. Subsequently, the patient was treated by NSS to maximally preserve renal

function. Definitive diagnosis of EAML was confirmed by histologic analysis. Both cases exhibited mainly epithelial cells in two distinct patterns, where a diffuse growth pattern was more evident in case 1 and a carcinoma-like growth pattern was more evident in case 2. Although preoperative diagnosis was difficult to achieve, EAML should be included in the differential diagnosis when a renal lesion is found and correct histological diagnosis of this subtype of renal AML is crucial because erroneous diagnosis of simple renal AML instead of EAML may lead to insufficient postoperative management. If the tumors described in the present case report were preoperatively considered to be benign AMLs, they may have been treated conservatively, which could have led to progression of the disease. At present, both cases appear to have had a benign course of disease after surgery, supporting the fact that the incidence of malignant behavior of EAMLs is quite low (5.0%) (16); however, close follow-up should be maintained due to the malignant potential of EAML.

The management of EAML is controversial due to uncertainty regarding the natural history of the condition. However, because EAML has the potential for malignancy, it is often managed as RCC. Surgery is the treatment of choice and curative in most cases (33,34). Since CT imaging is seldom sufficient to rule out RCC, resection is both diagnostic and therapeutic (34). Treatment should be tailored to the patient with the goal of renal function preservation (34). When resection is chosen, nephron-sparing approaches should be performed due to improved renal function and decreased overall mortality when technically feasible (35). Furthermore, in patients with TSC, where multifocal, bilateral and recurring lesions are almost universal, nephron sparing is paramount (19). Since TSC is associated with mutations that result in activation of the mTOR signaling pathway, mTOR inhibitors have also been explored as systemic therapeutic agents for managing this disease in patients with TSC (3). Everolimus has been assessed in a phase III study of TSC- and lymphangioleiomyomatosis-associated AML. In the study, the authors identified a response rate of 42%, with 80% of patients achieving at least a 30% reduction in size. Furthermore, no patient who had a tumor response exhibited progression during follow-up (36). Based on these results, everolimus was approved by the US Food and Drug Administration for the treatment of AML in the setting of TSC (37). There has also been a case report of successful treatment of a patient with pulmonary metastasis from EAML using everolimus. The authors concluded that by identifying EAML and recognizing its high-risk features, which have been described by Nese *et al* (24), the administration of mTOR inhibitors might lead to improved clinical outcomes in patients with recurrent metastatic EAMLs (3).

The preoperative distinction between EAML and RCC may not be critical as both lesions are treated with surgical resection. However, among consecutive resected EAMLs, the incidence of malignant behavior is quite low (5.0%) (16), and some studies have reported that mTOR inhibitors, such as sirolimus or temsirolimus, may represent an improved treatment option for patients with EAML (38,39). Therefore, the correct diagnosis of renal EAML can potentially direct clinicians to a more effective chemotherapy, particularly in patients with extensive disease. Therefore, the CT imaging-based pre-operative diagnosis of this type of AML or biopsy may become important in the future (25).

Although most reported cases of EAML, including the two present cases, are unilateral, bilateral EAMLs have also been reported in a patient with TSC, and metastatic lesions were identified in the right lung, liver, diaphragm and mesentery of the patient by autopsy (40). Recurrence and metastasis have been reported in 17.2 and 48.5%, respectively, of patients with EAMLs (24). Local recurrence was found after prior renal surgeries (3,41,42), so close follow-up was required (3,34). Saoud *et al* (3) reported that a large retroperitoneal mass was detected as a recurrence 9 months after left radical nephrectomy. Varma *et al* (41) reported local renal fossa recurrence extending to the vena cava 9 years after right nephrectomy, with metastasis to the liver, colon and lung. Late local, peritoneal and systemic recurrence have also been reported 12 years after left nephrectomy (42). Thus, a vigorous follow-up even after curative surgery and complete remission is warranted.

Mahajan *et al* (34) recommended that a 3-monthly follow-up with clinical evaluation and relevant radiological investigations for 2 years was imperative for EAML. Biannual follow-up up to 5 years must be undertaken, followed by annual follow-up (34). Others have recommended treating EAML using the National Comprehensive Cancer Network guidelines currently in place for the treatment of RCC (43), and implementing similar follow-up protocols compared with those for RCC (44,45).

In summary, the present study reported two cases of EAML, which were successfully treated by laparoscopic surgery. Preoperative diagnosis was challenging. Definitive diagnosis was not accomplished until histological analysis was performed. Due to the malignant potential of EAML, surgical resection is the gold standard treatment strategy for this neoplasm when technically feasible (32). Although the present cases had a favorable course of disease, it was considered appropriate to continue close follow-up, similar to the follow-up for RCC, due to approximately one third of EAMLs having been found to present with malignant biological behavior (3-5,7). Thus, long-term follow-up is required to detect any recurrence or metastasis of the present patients. It is also recommended that all similar cases should be subject to a similar, longer follow-up period.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

SH was the principal person responsible for the study, and contributed to the conception and the design of the study. HL,

XZ and QZ obtained and analyzed the patient information, and contributed to manuscript drafting and critical revisions of the intellectual content, while JW performed analysis and interpretation of CT imaging and MRI data. XY performed the histological examination of the tumor. HL, XZ, QZ, JW, XY and SH confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

All procedures were approved by the ethics committee of The First Affiliated Hospital of Shandong First Medical University (approval no. 2023S348; Jinan, China). Closely adhering to the principles of careful pre-, intra- and postoperative preparation and management, the whole treatment procedure for the two patients complied with our institutional standards. Written informed consent for participation was obtained from the patients.

Patient consent for publication

Written informed consent for publication of the article was obtained from the patients.

Competing interests

The authors declare that they have no competing interests.

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