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An unusual appearance of renal epithelioid angiomyolipoma

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ABSTRACT Epithelioid angiomyolipoma is a recently described rare variant of renal angiomyolipoma. It can occur in patients with or without tuberous sclerosis. We report the imaging findings of a case of epithelioid angiomyolipoma that showed the presence of fatty tissue undifferentiated from the typical angiomyolipoma at the beginning. After partial nephrectomy, tumour recurrence occurred two years later, presenting as completely solid tumours with no adipose tissue, and with invasion into the psoas muscle and left adrenal gland. Differentiation of this tumour from renal cell carcinoma is difficult. Both the radiologist and surgeon should be aware of the existence of this tumour and its potentially malignant behaviour.

Keywords: diagnosis, kidney, neoplasm, perivascular epithelioid cell, spiral CT
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INTRODUCTION

Angiomyolipoma (AML) is a histologically complex mesenchymal tumour composed of thick-walled blood vessels, adipose tissue and smooth muscle cells. Although it has been reported to occur in other extra-renal sites such as the liver and the retroperitoneum, the kidney remains the most common site of involvement. Long believed to be a benign hamartoma, AML is now deemed to belong to a family of neoplasms known as perivascular epithelioid cell tumours. These tumours are characterised by the proliferation of unique epithelioid cells distributed around blood vessels.[1] Epithelioid angiomyolipoma (EAML), a variant of AML, is a histologically benign tumour with aggressive clinical behaviour that may mimic renal cell carcinoma (RCC) in imaging studies. We report a case of EAML that recurred with tumour multiplicity, which invaded the psoas muscle and left adrenal gland after tumour resection.

CASE REPORT

A 68-year-old female patient complained of months of left flank soreness. There was no history of haematuria and tuberous sclerosis. Sonography showed a bulging mass that consisted of a hypoechoic upper portion and a hyperechoic lower portion located at the left kidney (Fig. 1). Computed tomography (CT) showed an 8 cm × 7.5 cm × 6.4 cm lobulated, exophytic mass arising from the upper pole of the left kidney. In addition to fatty tissue, soft tissue components, which were enhanced after the administration of a contrast agent, were found to be embedded within the mass (Fig. 2). Under the impression of AML, the patient underwent retroperitoneoscopic partial nephrectomy. Pathology revealed a well-defined tumour composed of sheets of epithelioid cells in nesting and trabecular patterns, supported by rich vasculature. These tumour cells showed abundant

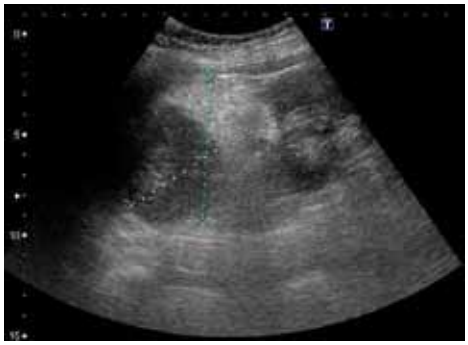

Fig. 1 Sonographic image shows a 7 cm × 8.4 cm heterogeneous bulging mass with a hypoechoic upper portion and a hyperechoic lower portion at the left kidney.

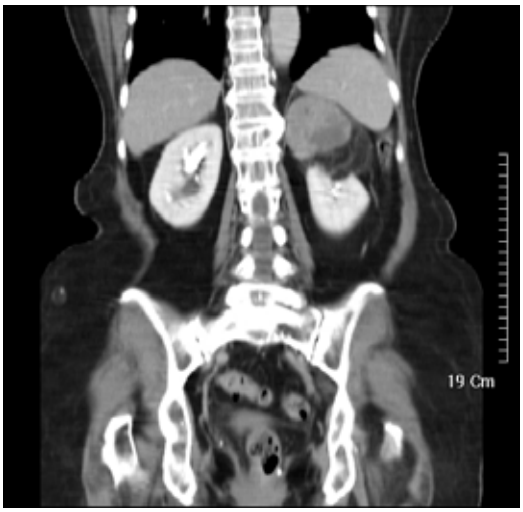

Fig. 2 Reconstructed contrast-enhanced CT image shows a tumour composed of fatty tissue and soft tissue occupying the upper pole of the left kidney.

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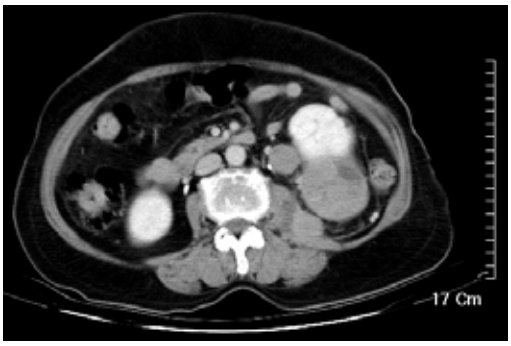

Fig. 3 CT performed 2 years after partial nephrectomy. Contrast-enhanced CT image shows the presence of soft tissue nodules at the left renal hilum and lower pole of the left kidney, with tumour invasion into the left psoas muscle. No obvious fatty component is seen in these lesions.

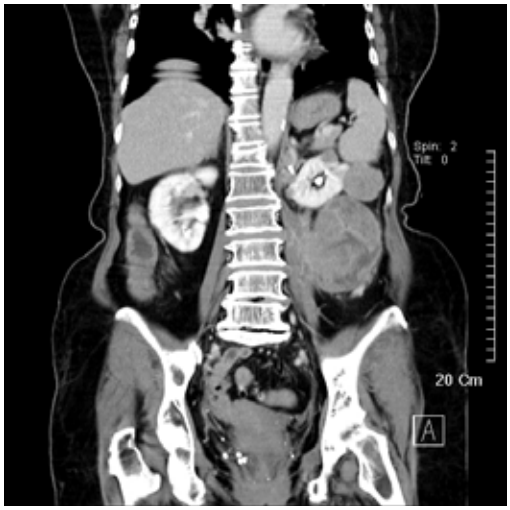

Fig. 4 CT performed at 6-month follow-up. Contrast-enhanced CT image in reconstructed coronal section shows multiple heterogeneous soft tissue masses at the left suprarenal fossa, left kidney, perirenal space and retroperitoneum. Tumour invasion into the left adrenal gland and psoas muscle is observed.

eosinophilic cytoplasm and mildly pleomorphic nuclei with no obvious mitotic activity. Very limited foci of adipose tissue with thick-walled blood vessels surrounded by slender spindle cells were also discernible. Immunohistochemically, the epithelioid and spindle tumour cells were positive for human melanoma black-45 (HMB-45) and smooth muscle actin, and very focally positive for epithelial membrane antigen, but not cytokeratin AE1/AE3 and CD117, thus confirming the diagnosis of EAML.

Postoperatively, the patient remained well for about two years until she complained of left abdominal pain. Sonography performed revealed the presence of left renal masses. CT showed several nodules and masses devoid of fatty components present in the renal hilum, psoas muscle, perirenal space and left adrenal region, with the largest one measuring 5.7 cm × 6.8 cm in size (Fig. 3). The patient refused operation and opted to keep close observation on these tumours. Six months later, the patient was admitted to our hospital due to progressive enlargement of the aforementioned masses, with the largest one measuring 8.2 cm × 7.3 cm × 8.9 cm in size (Fig. 4). Radical nephrectomy, excision of the retroperitoneal tumour and left lymphadenectomies were performed. Intraoperatively, three large tumours with necrotic tissue were found; one tumour measuring 5 cm × 5 cm in size was seen arising from the lower pole of the left kidney while the other two, measuring 5 cm × 5 cm and 7 cm × 7 cm, were found to originate from the renal capsule with invasion into the left psoas muscle. Pathology and immunohistochemical stain confirmed that these masses were EAMLs. Eight months after the radical nephrectomy, a 4 cm × 1.5 cm soft tissue mass, which was most likely a recurrent EAML, developed at the left psoas muscle. The patient, however, refused any further treatment.

DISCUSSION

Renal AML is a mesenchymal tumour composed of variable proportions of dysmorphic blood vessels, smooth muscle and fatty tissue. It consists of two distinct histological subtypes, classic triphasic AML and monophasic EAML. Classical AML is benign and contains all three of its namesake components. EAML, on the other hand, is composed of sheets of round to polygonal epithelioid cells, with granular eosinophilic cytoplasm admixed in most cases with varying amounts of the typical components of classic triphasic AML.[2] The nuclei of this neoplasm may show varying degrees of nuclear atypia; hence, it can be erroneously diagnosed as a sarcoma or RCC, particularly when other components of AML are obscure and atypia is prominent.[3,4] Positive immunostain with HMB-45 can confirm the diagnosis.

In 2009, Aydin et al[5] reported that none of their EAML patients (15 out of 194 AML patients) had local recurrence or metastasis after a mean follow-up period of 5.1 years. In contrast, Nese et al[6] reported in 2011 that half of their 41 cases had metastasis and a third of these died due to the disease, indicating that metastatic EAML has a poor prognosis. Although metastasis is one of the hallmarks of malignancy, it is still difficult to predict the malignant behaviour of EAML. Some researchers have proposed that necrosis, nuclear atypia and mitotic activity are useful for predicting metastatic behaviour, but this is still inconclusive, as necrosis, nuclear atypia and mitotic activity have also been reported in EAML cases without metastases.[7] The five adverse prognostic parameters for EAML proposed by Nese et al include: (a) association with tuberous sclerosis complex (TSC); (b) necrosis size greater than 7 cm; (c) extra-renal extension; (d) renal vein involvement; and (e) carcinoma growth pattern.[6] These five parameters are associated with disease progression, including recurrence, metastasis or death due to the disease. In any case, when encountering EAML in a patient, one should be aware of its aggressive clinical behaviour and the need for close follow-up for recurrence and metastasis. The mean time to developing metastatic disease during follow-up is 17–31 months, with the liver, lung and peritoneum/mesentery being the most common sites of metastases.[6]

About 80% of AMLs are sporadic. The remaining 20% are associated with TSC,[8] a multi-organ system disease with renal

manifestation as a significant cause of morbidity and mortality. Classical AMLs occur predominantly in females, with a ratio of 4:1 in both sporadic and TSC cases, while the ratio of occurrence of EAML in females vs. males is 6.5:1,[5] with nearly half of the cases associated with tuberous sclerosis.[2,5] According to Aydin et al, the mean size of an EAML is larger than that of a classical AML, and patients with EAML are also younger than classical AML patients (38.6 years vs. 52.3 years).[5]

Although the imaging features of classical AMLs have been well described in radiology literature, few case reports have described the imaging features of EAMLs.[9,10] CT or magnetic resonance (MR) imaging is frequently used to detect foci of fat, the presence of which suggests AML. However, it is difficult to diagnose EAML, as the mature adipose cells and abnormal blood vessels that are characteristic of classical AML are usually not evident in EAML. Furthermore, EAMLs usually appear as hyperattenuating masses with variable enhancement on CT,[9] thus making it more difficult to differentiate RCC from EAML. This is particularly important in tuberous sclerosis patients, as they have a higher risk of developing both RCC and AML. On MR imaging, EAML also demonstrates a high cellular content with no evidence of fat – a feature that should raise suspicion of RCC – making differentiation between these two kinds of tumour very challenging. Therefore, in a patient with tuberous sclerosis, any renal mass that is not a simple cyst and does not contain fat should be considered suspicious for malignancy.[9]

Luo et al stated in 2011 that they were unable to find any reports of EAML with fat densities noted on CT or MR imaging.[10] In our case, fat was seen in the tumour during the first admission, although a large amount of soft tissue was also present. After excision of the fat-containing tumour, recurring tumours detected in subsequent imaging studies were devoid of fat content. Therefore, we suggest that even for a fat-containing renal tumour, the possibility of an EAML should be considered whenever a large amount of soft tissue is present or if the presence of fat makes it impossible to exclude an EAML.

In fact, a considerable number of EAML cases have been misdiagnosed as RCC in the past, particularly when the epithelioid component is the major component of an AML. Fine needle aspiration has proven to be a relatively useful and inexpensive technique in establishing the diagnosis in renal neoplasms. It has been established to be accurate for subtyping variants of RCC, with discrepancies usually made when papillary or sarcomatoid RCC is mistaken for clear cell RCC.[8] Cytologically, EAML bears striking similarities to classical RCC, and to a lesser degree, clear cell RCC and oncocytoma. When epithelioid cells are present in an aspirate from the kidney, EAML should be included in the differential diagnosis. The presence of HMB-45 immunoreactivity, and the absence of cytokeratin and vimentin immunoreactivity in these tumour cells would confirm the diagnosis.[11]

It has been well established that the management of renal AML depends on the size of the tumour, the radiological features and the histological appearance, and this includes observation, embolisation and surgical excision. The decision-making process is relatively easy in most cases due to its classical features on CT. However, in the case of EAML, as the tumour mimics RCC on imaging studies, most patients with EAML are treated with surgical excision, which is the gold standard treatment for RCC. We should consider surgical excision of EAML, as in the case of RCC, due to its malignant potential. Partial nephrectomy should be reserved for tumours < 4 cm in size, and it should be considered in all settings of localised malignancies that would otherwise render the patient anephric and with a subsequent need for renal replacement therapy. For tumours > 4 cm, radical nephrectomy should be performed.

Currently, there is no known effective therapy for EAML other than surgery. Doxorubicin has been favourably reported, with Cibas et al having successfully reduced the size of recurrent EAML by 50% after two cycles of chemotherapy with doxorubicin.[12] Kenerson et al discovered that EAMLs uniformly exhibit the activation of the mTOR cascade, which contributes to tumour growth and progression.[13] This suggests that mTOR inhibitors, such as rapamycin or temsirolimus, may provide therapeutic benefits in the treatment of EAML.[14] These recent reports indicate that adjuvant therapy might be beneficial to EAML patients. However, the long-term efficacy of these agents and the most effective agent remains to be determined. Further studies in this aspect and long-term follow-up of patients after surgery will help to establish a standard for treatment and follow-up.

In summary, EAML is a recently described rare variant of renal AML, which may occur in patients with or without tuberous sclerosis. These potentially malignant tumours resemble RCC, both radiographically and histologically, and can be locally aggressive and metastatic. Histologically, they can be distinguished from RCC not only by identifying the epithelioid cells within the tumour, but also by immunostain (positive for HMB-45 and negative for cytokeratin and S100). Although previous studies have reported the absence of fat in EAML, our case showed the presence of both soft tissue component and fat within the tumour during the first admission. Thus, we conclude that whenever a fatty renal mass contains large amounts of soft tissue, the possibility of EAML should be included in the differential diagnosis. It is also crucial for both the clinician and radiologist to be aware of this potentially malignant disease.

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