CT imaging and histopathological features of renal epithelioid angiomyolipomas

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AIM: To describe computed tomography (CT) imaging and histopathological manifestations of renal epithelioid angiomyolipomas (EAMLs) for better understanding and cognition in the diagnosis of this new category of renal tumours.

MATERIALS AND METHODS: Clinical data and CT images from 10 cases of EAML were retrospectively analysed. All patients underwent CT with and without contrast medium administration, with multiplanar reconstruction (MPR) when needed.

RESULTS: Plain CT manifestations of EAMLs were a higher density of mass (10–25 HU) than renal parenchyma, bulging contour of the involved kidney, absence of fat, distinct edges without a lobulate appearance. Contrast-enhanced CT features were markedly heterogeneous enhancement (from rapid wash-in to slow wash-out), large tumour size without lobular appearance, complete capsule with distinct margins and frequent mild necrotic areas. Histopathological features were epithelioid cells with eosinophilic cytoplasm, large and deeply stained nuclei, and dense arrangement of tumour cells with patchy necrosis; diffuse sheets of epithelioid cells were positive for HMB-45 (melanoma-associated antigen) and negative for epithelial membrane antigen (EMA) staining.

CONCLUSION: Multiple specific CT features correlated well with the histopathology and may play an important role in the primary diagnosis of EAMLs.

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Introduction

Renal angiomyolipomas (AMLs) are a common benign tumour with relatively characteristic imaging findings.1 Epithelioid angiomyolipoma (EAML) of the kidney is a rare mesenchymal neoplasm, which was recently categorized as a distinct entity, and which has been gradually gaining recognition and acceptance by more and more experts in this field.2,3 In contradistinction to typical AMLs, EAMLs often mimic renal cell carcinoma (RCC), renal sarcoma, or AML with minimal or absent fat on imaging evaluation, which may lead to incorrect diagnosis. EAML presents a significant diagnostic challenge,2 as misdiagnosis may result in negative impact on clinical care. To date, only a few cases of EAML have been reported all over the world with limited clinical and histopathological descriptions.3,5 EAML imaging and histopathological features have not been comprehensively described in the literature so far. Herein, the imaging features of EAMLs were compared with the corresponding histopathological characteristics, analysed and summarized as a part of a retrospective study. Greater
understanding of EAMLs may lead to improved management and diagnosis of this new category of renal tumour.

Materials and methods

Clinical data

Ten cases of confirmed EAML were collected from three hospitals from May 2005 to November 2011. All medical records including the history of the disease, imaging studies, and surgical and pathological data were retrieved for the 10 cases. The imaging features were retrospectively compared with the corresponding histopathology. Unenhanced computed tomography (CT) and tri-phase contrast-enhanced CT were performed in all cases. The cases included six men and four women aged 26–47 years old with the average age of 35.6 years old. Results of routine laboratory tests including complete blood count, serum glucose, electrolytes, and tests of hepati and renal function revealed no significant abnormalities in these cases. Subsequently routine pathological and immunohistochemical examinations were performed after radical resection of the whole kidney.

Imaging methods

CT was carried out using helical CT machine (Somatom Sensations 64, Siemens, Erlangon, Germany). Images were obtained from the top of the kidneys to pubis, using 1–1.8 pitch at 120 kV (mA was adjusted automatically). The conventional reconstruction interval and thickness were 5 mm for the arterial, venous, and delayed phase images, for unenhanced CT images as well. If needed, raw images reconstructed at 1 mm section thickness were transferred to an independent workstation (Syngo, Siemens Medical Solutions). Multiplanar reconstruction (MPR) or curved planar reconstruction (CPR) was obtained so as to clearly demonstrate the lesions. For contrast-enhanced studies, 80–100 ml non-ionic iodine contrast material (Iohexol, Omnipaque, GE company, Shanghai, China) at a concentration of 300 mg iodine/ml was injected into the antecubital vein at a rate of 3 ml/s using a mechanical injector (Ulrich, Ulm city, Germany). Arterial, venous and delayed-phase CT was performed after initiation of intravenous contrast medium injection, acquired with delay of 30–45, 60–70, and 120–180 s, respectively. The degree and pattern of enhancement after intravenous contrast media injection with identification of tumour-spreading patterns (including nephric and perinephric changes) were evaluated by two senior radiologists specializing in diagnostic imaging of the abdomen.

The institutional Ethics Committee approved this retrospective study and waived the need for informed consent.

Results

Unenhanced CT

The median tumour diameter was 14 cm in the 10 cases, ranging from a minimum diameter of 5 cm to maximum diameter of 28 cm. All the masses demonstrated associated bulging contour of the kidney, so the maximum diameter of the tumour was beyond the expected kidney contour, and the edges of the tumour were distinct, without a lobulate appearance. The tumour density was higher than the normal renal parenchyma (about 10–25 HU higher); however, irregular areas of slightly patchy low attenuation suggestive of mild necrosis in the tumour were seen in eight cases (Fig 1).

Contrast-enhanced CT

The mass showed moderately inhomogeneous enhancement in eight cases, and relatively homogeneous enhancement accompanied by a thickened artery within the tumour in the other two cases as visualized on contrast-enhanced CT, particularly on the venous and delayed-phase images. Evaluation of the pattern of dynamic enhancement revealed that all of the lesions demonstrated the pattern of “rapid wash-in and slow wash-out” (Figs 1 and 2). The border between the tumour and normal kidney was distinct in nine cases, whereas the tumour margin in one case was indistinct and infiltrative accompanied by retroperitoneal lymphadenopathy. Preoperatively, only one case was diagnosed as “atypical AML, RCC cannot be excluded”. Eight cases were misdiagnosed as RCC; the remaining one case was misdiagnosed as a renal sarcoma.

Postoperative pathological evaluation

Gross pathological specimens were obtained. Nine cases had a complete capsule and the capsule was partly damaged in one case, with tumours weighed approximately 0.4–4.5 kg. The gross cut surface showed a fleshy texture with regions of grey–yellow and grey–red appearance. Patchy necrosis with no cystic areas was noted and haemorrhage was seen in one case. The pathological evaluation revealed epithelioid, short spindle cells with eosinophilic cytoplasm, large and deeply stained nuclei, and dense arrangement of tumour cells with patchy necrosis (Figs 1e and 2b). Immunohistochemical studies demonstrated that the tumour cells were positive for CD10 (acute lymphoblastic leukaemia antigen), S-100 (acidic calcium-binding protein), and HMB-45 (melanoma-associated antigen; Fig 1f), but negative for CK7 (cytokeratin 7), CK18 (cytokeratin 18), and EMA (epithelial membrane antigen). Histopathological diagnosis of renal EAML was made in all the 10 cases, and one case demonstrated retroperitoneal lymphadenopathy (Fig 1). All patients were followed-up after surgery for 2–3 years and no obvious signs of recurrence or metastasis was found at CT examination.

Discussion

Overview and histopathological features of EAML

EAML, which was first reported by Mai et al. in 1996, is a rare mesenchymal tumour which has been gradually gaining recognition and acceptance in recent years.1–35
So far, only a small number of cases have been reported, with EAML described in case reports or in small multi-institutional series. EAML has been misclassified as AML for a long time. In 2004, the International Agency for Research on Cancer (IARC) of WHO classified EAML as a distinct entity (as opposed to typical or classical AML) and defined it as a mesenchymal tumour with malignant potential. The tumour primarily consists of epithelioid cells, and a focus of typical AML-like area may be observed in some cases. EAML primarily occurs in the kidney, with rare reports of EAML in the liver, pancreas, and bone. As opposed to typical AML, EAML is composed of single-core or multi-core epithelioid cells with none or few vessels or adipocytes typical for AML, and is nearly always confused with typical AML.

**Figure 1** A 47-year-old man suffering dull pain in the left upper abdomen for 1 year. Unenhanced CT images (a, b) showing a very large tumour in the left kidney with heterogeneous density and indistinct margins with normal renal parenchyma (long white arrows), measuring 21 × 28.2 × 12.4 cm in size. The densities in the higher attenuation portion of the tumour and in the normal renal parenchyma were 60 and 36 HU, respectively. Irregular, patchy low attenuation, suggestive of necrosis, was noted within the mass. An enlarged lymph node, about 7.2 cm in diameter, was also found (short black arrows). The contrast-enhanced CT images (c, d) demonstrated moderately inhomogeneous enhancement within the mass. Additionally, there were two small masses (about 3.5 cm in diameter) in the right kidney, which demonstrated grossly homogeneous enhancement (short white arrows). (e) The tumour was composed of diffuse sheets of epithelioid cells and only scattered thick-walled blood vessels, but without adipocytes (haematoxylin and eosin stain, ×200). (f) Neoplastic cells showed strong immunoreactivity to HMB-45 (immunohistochemical stain with HMB-45, original magnification ×100).
other neoplasms,\textsuperscript{4,5} such as RCC, sarcomas, or atypical AML due to the lack of grossly visible fat on imaging. Characteristic immunohistochemical phenotypes of EAML include positive testing for markers of melanocytes (HMB45, Melan-A) and markers of smooth muscle cells (SMA, MSA), with negative testing for specific markers of epithelium (CK, EMA), which is conclusive for the diagnosis of EAML.\textsuperscript{4,6,8,9} Although the growth pattern of EAML may be similar to AML, this tumour may show an invasive pattern of growth including degeneration, necrosis, and haemorrhage. Occasionally, lymph metastasis may be seen. However, true cystic areas, and peripheral vascular and renal sinus invasion are rarely seen. It is reported that the male: female ratio is 1:3, and that the average age at diagnosis of EAML is 44 years old\textsuperscript{10}; however, in another study the male: female ratio and average age of at diagnosis were reported as 1:1 and 40 years old, respectively.\textsuperscript{10} Furthermore, about one-quarter of the patients were less than 30 years old, and one-third of the patients were less than 36 years old in the present study. Approximately 26% cases of EAML were associated with tuberous sclerosis (none were found in the present series). The mean age of diagnosis for this study was 36 years, slightly younger than in reports listed the above. However, the differences in the reported mean age of diagnosis in these studies are likely due to the small number of cases reviewed in these series.

\textbf{CT image interpretation}

Prospectively, it is difficult to determine the correct diagnosis using imaging alone due to poor understanding of this new category of renal tumours. The cases in the present study were misdiagnosed on preoperative evaluation. The imaging features of EAML are different from RCC, sarcomas, and typical AML. After a thorough review of the current literature, notwithstanding the small number of reports on the imaging findings of EAML,\textsuperscript{11} the imaging manifestations of these renal tumours may suggest the correct diagnosis. The characteristic imaging features of EAML include higher density (than normal renal parenchyma) at unenhanced CT,
lack of fat density, bulging contour of the affected kidney, markedly heterogeneous enhancement (rapid wash-in and slow wash-out), large lesion size without a lobular appearance, complete capsule with distinct margin and frequent presence of mild necrotic areas, occasional regional lymph node metastases without peripheral vascular and renal sinus invasion. These findings are occasionally similar to findings of atypical AML, i.e., AML with minimal fat. The higher density at unenhanced CT has been ascribed to multiple factors. The reasons for this phenomenon are thought due to the densely packed cells, mainly in a pattern of epithelioid cells; the relative hyper-vascularity; positivity to markers for melanocytes and smooth muscle cells by immunohistochemistry; the absence of fat and stroma; and regional haemorrhage. The pattern of dynamic enhancement seen as “rapid wash-in and slow wash-out” to the authors’ knowledge has not been described prior to this study and is thought to correlate with known pathological descriptions: abundance of abnormal vessels, higher cellular density and decreased tumour stroma, presence of complete capsule, and lack of draining vessels. Radiologically, it may be more reasonable to suggest mesenchymal tumour as the preliminary diagnosis if EAML is suspected due to the low incidence of this tumour. However, when EAML is considered by the radiologist, a HMB-45-related immunohistochemical examination should be advised for further evaluation, especially if the patient is younger than 30 years presenting with a solid renal tumour with most of the above imaging characteristics. The final diagnosis will depend on the histopathological examination, especially immunohistochemistry. Awareness of these radiological findings and histopathological features may help improve the diagnostic evaluation and understanding of EAML and provide better guidance for clinical management.

Differential diagnosis

EAML should be distinguished from tumours such as RCC, fat poor AML, and sarcomas. RCC is often centred in the renal parenchyma, showing a lobulate contour, irregular and indistinct edges, with obvious necrosis, cystic changes, with haemorrhage and/or calcification inside of the tumour. It demonstrates moderately to markedly heterogeneous enhancement with “rapid wash-in and wash-out” pattern of dynamic enhancement. In addition, metastases and vessel invasion are more common in RCCs. Regarding malignant AML or fat-poor AML, to date, there are only a few reports and no reported diagnostic criteria of the aggressive AML diagnosed by histopathology. Although fat-poor AMLs had been reported recently, there is no information regarding the immunohistochemistry characteristics, and it has not been pathologically defined as a category. Hence, this description, i.e., fat-poor AML, provides few guidelines for specific clinical treatment. Most EAMLs demonstrate no macroscopic fat and have the same morphological characters as AML. Therefore, when considering the diagnosis of fat-poor AML or malignant AML on imaging evaluation, correlation should be made with pathological and immunohistochemical examination in order to exclude the possibility of EAML. Regarding renal sarcomas, there is no imaging feature specific for renal sarcoma reported in the literature; therefore, it is relatively difficult to make the definite diagnosis of renal sarcoma based only on imaging. With the possible exception of liposarcomas, which may have identifiable characteristic fat attenuation, it is very difficult to differentiate the other different types of renal sarcoma due to their similar imaging and histopathological manifestations. However, renal sarcomas most likely share some common features including relatively large size, grossly heterogeneous attenuation, lobulate contour, irregular or indistinct edges, and moderate to extensive heterogeneous enhancement. The markers for HMB45 and Melan-A are negative, and markers for CK and EMA are positive in renal sarcomas, allowing for differentiation from EAMLs.

Treatment, prognosis, and prospect

Most of EAMLs were preoperatively misdiagnosed as RCCs or sarcomas, so radical nephrectomy was usually adopted in the reported literature. Although EAMLs are potentially malignant, with occasional adjacent tissue invasion and metastases, the prognosis is overwhelmingly positive according to multiple studies showing no recurrence or metastasis in several years follow-up after surgery. However, other studies showed that EAML demonstrates malignant potential and should be regarded clinically as similar to other malignant renal tumours rather than to the typical AML in terms of behaviour and treatment.

In summary, EAML is a new entity in pathological classification proposed by the WHO in recent years, with imaging features resembling or overlapping those of so-called malignant AML, fat-poor AML, or atypical AML. With increased understanding and recognition of EAMLs, this entity should be considered as a primary differential diagnostic possibility when atypical AML imaging features, such as those listed above, are identified. Multiple specific CT features correlated well with the histopathology and may play an important role in the primary diagnosis of EAMLs. More imaging studies are required to elucidate and confirm the relationship between EAMLs and atypical AMLs.

References


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