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Case report

Renal epithelioid angiomyolipoma presenting clinically as renal cell carcinoma – A case report

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Abstract
We describe a 22-year old female who presented with a 5-year history of a palpable, painless mass in the right flank. Computerized tomography demonstrated a solid renal mass measuring 18 cm × 13 cm with peripheral calcification, areas of vascularity and necrosis. The appearance suggested renal cell carcinoma or nephroblastoma, but percutaneous renal biopsy suggested an adrenal origin. At right radical nephrectomy, the adrenal gland was completely normal. Histology showed sheets and nests of epithelioid cells with abundant eosinophilic to clear cytoplasm, confirming a diagnosis of epithelioid angiomyolipoma (EAML), a rare mesenchymal tumor belonging to the perivascular epithelioid cell tumor family (PEComas). At 33 months followup, there was no evidence of recurrence or metastases.

Background

Perivascular epithelioid cell tumors (PEComas) represent a small family of rare tumors, which includes both classic angiomyolipoma (AML) and its potentially malignant variant epithelioid angiomyolipoma (EAML). PEComas are associated with the tuberous sclerosis complex and characterized by the World Health Organization as a "proliferation of perivascular epithelioid cells (PECs)" [1]. EAML is often confused with renal cell carcinoma (RCC) given similar presenting symptoms and lack of macroscopic fat on radiographic imaging [2]. Herein, we report a case of renal epithelioid angiomyolipoma.

Case report

A 22-year old female was referred to our facility from an outside institution with a 5-year history of being aware of a palpable mass in

Abbreviations: PEComa, perivascular epithelioid cell tumor; EAML, epithelioid angiomyolipoma; AML, angiomyolipoma; RCC, renal cell carcinoma; CT, computerized topography; IVC, inferior vena cava; TSC, tuberous sclerosis complex.

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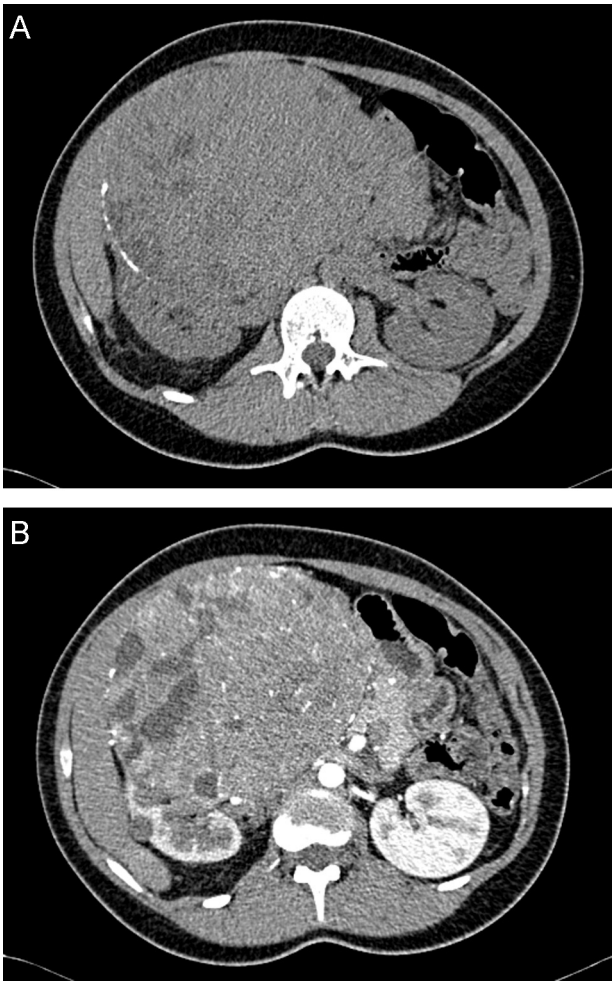

Figure 1 (A) Non-contrasted CT showing solid mass in right flank with linear peripheral calcification. (B) Contrast-enhanced CT (arterial phase) showing areas of necrosis in tumor arising from right kidney.

the right upper quadrant of her abdomen. She denied any associated symptoms, including pain, hematuria or weight loss. Her past medical history was unremarkable, specifically no history of epilepsy or mental retardation, and there was no family history of renal malignancy or tuberous sclerosis. On physical examination, there were no cutaneous or other stigmata of tuberous sclerosis. A large (>10 cm) non-tender, mobile mass was palpable in her right upper quadrant.

Laboratory results demonstrated normal hemoglobin (13.3 g/dl) and creatinine (40 μmol/l), as well as a negative urinalysis. Electrolytes were within normal range, and she was non-reactive on HIV testing. Computerized topography (CT) of the abdomen with intravenous contrast identified an 18 cm × 13 cm mass with linear peripheral calcification, areas of vascularity and necrosis, arising from the right kidney, which contained a few small cysts (Fig. 1A and B). No visceral metastases or involvement of the right renal vein or IVC were noted. Chest X-ray was normal.

The patient underwent a percutaneous right renal biopsy to determine whether the renal mass was a Wilms' tumor (nephroblastoma), which could be treated with chemotherapy prior to surgery. The histology showed cells with predominantly clear cell cytoplasm, and some cells with eosinophilic/granular cytoplasm. It was positive for Melan A on immunohistochemistry. Diagnosis was made of "a clear-cell lesion most likely of adrenal origin". Further endocrine studies revealed a normal serum cortisol (193 nmol/l) and normal 24-h urine cortisol (487 nmol/24 h), as well as normal urine metanephrines (metadrenaline/metnoradrenaline at 118/165 nmol/L).

She was scheduled for a radical right nephrectomy and adrenalectomy. Intraoperatively, the right adrenal was found to be uninvolved, as the tumor grossly originated solely from the right kidney. It was noted to be well encapsulated and mobile. The right adrenal was normal and was not removed. The postoperative course was uncomplicated, and she was discharged on post-surgical day 5.

Macroscopically, the mass was solid, tan in color and measured 17.9 cm × 19 cm × 12 cm with a weight of 2000 g. It was situated in the pelvis of the kidney and bulging into the surrounding soft tissue. Cysts were noted along the periphery.

Microscopically, different growth patterns were encountered including solid sheets, nests and papillary structures. The tumor cells were epithelioid with abundant eosinophilic to clear cytoplasm (Fig. 2A). Incipient tumor necrosis was noted (<10%). One mitotic figure or less per 50 high power fields was identified. Invasion into the renal parenchyma was evident but lymphovascular invasion was not demonstrated. The peripheral tumor free margin was less than 1 mm.

Immunohistochemically, the tumor cells stained strongly positive for Melan A and HMB-45 (Fig. 2B and C). Smooth muscle actin was focally positive. CD-10, S100, and chromogranin staining were negative. Final diagnosis was pure epithelioid angiomyolipoma.

The patient was seen in follow-up at 33 months after surgery. She was asymptomatic, and on examination and CT imaging there was no evidence of local tumor recurrence or metastases.

Discussion

Renal epithelioid angiomyolipoma (EAML) is a rare mesenchymal tumor belonging to the perivascular epithelioid cell tumor family (PEComas) [1,2]. Other PEComa members include pulmonary and extrapulmonary clear cell "sugar" tumors, lymphangiomyomatosis, and clear cell myomelanotic tumors of the falciform ligament, ligamentum teres, and common bile duct [3]. EAML is closely related to the classical, triphasic angiomyolipoma (AML), and also demonstrates loss of the 16p chromosome and tumor suppressor gene TSC2 (16p13) [4]. Both tumors are strongly associated with the tuberous sclerosis complex (TSC).

Unlike its typically benign counterpart, EAML has well documented malignant potential with approximately one third of reported cases developing metastatic disease [1,3–6]. Tumor suppressor p53 (TP53) mutation is detected in epithelioid, but not classic AML, suggesting that it may play a role in malignant transformation [1]. While both neoplasms have a strong association with TSC, a nearly 4-fold greater prevalence of TSC has been demonstrated amongst EAML patients [7].

While its triphasic pattern easily identifies AML, pure EAML is typically devoid of microscopic fat and abnormal vessels [8]. Histologically, it appears as a proliferation of epithelioid cells with abundant granular cytoplasm. The tumor cells are round to

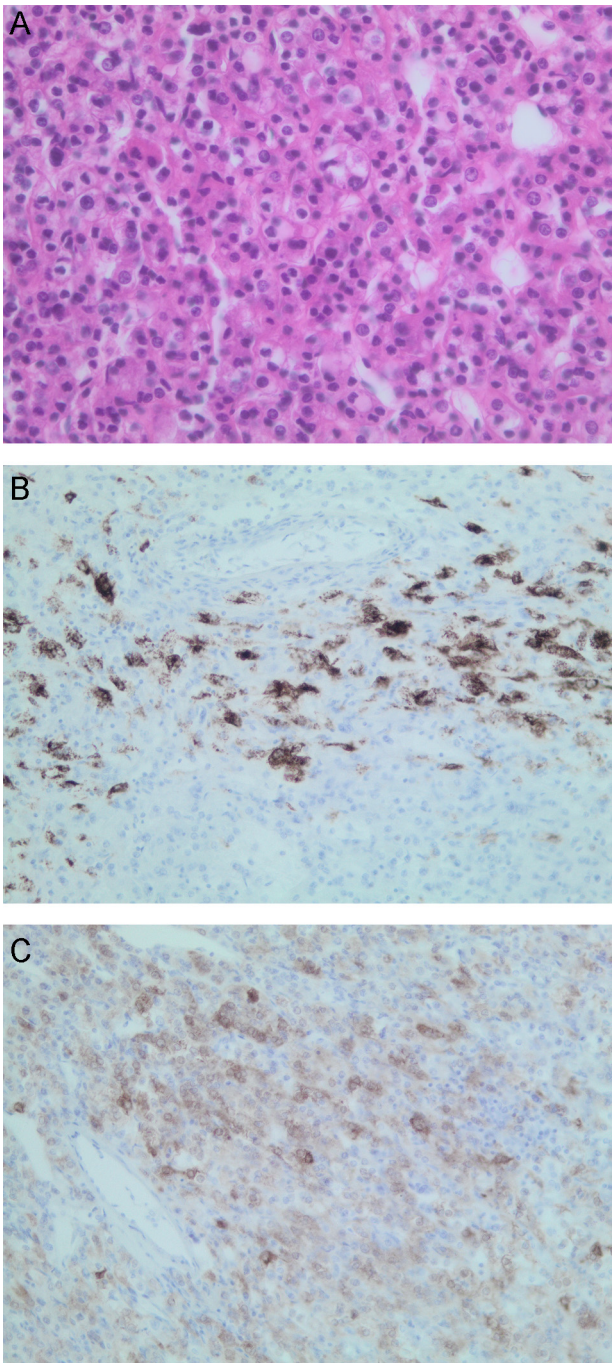

Figure 2 (A) Photomicrograph showing sheets and nests of epithelioid cells, many with abundant eosinophilic cytoplasm and some with clear cytoplasm (hematoxylin and eosin stain 200×). (B) Melan A immunohistochemical stain showing cytoplasmic positivity in many tumor cells. (C) HMB 45 immunohistochemical stain displaying positivity in the cytoplasm of tumor cells.

polygonal with enlarged vesicular nuclei and prominent nucleoli [1]. Giant multinucleated cells and hemorrhage are common [3].

EAML is often confused with RCC, especially on contrasted radiographic studies as it appears as an enhancing mass without a visible adipose component [2]. The frequent presence of necrosis, infiltrative growth, and extension into the inferior vena cava/renal vein typically results in a RCC diagnosis, metastatic evaluation, and radical nephrectomy [9]. On histology, it may also be misdiagnosed as RCC, sarcoma, or medullary carcinoma based upon its dominant epithelioid appearance [5]. Accurate diagnosis requires immunohistochemical analysis. EAML expresses typical AML staining patterns with positive HMB-45, smooth muscle actin, Melan A, and occasionally CD68 [10]. In contrast, RCC demonstrates immunostaining positive for cytokeratin (CK) and epithelial membrane antigen (EMA) [2].

Initial management of EAML consists of surgical excision. There is no standard algorithm for long term surveillance following surgical cure, however, it is highly recommended, as disease recurrence has been documented more than 5 years after surgical excision [11]. Bleeker et al. recently introduced a modified Folpe criteria for the risk stratification of PEComas [12]. Tumors defined as 'malignant' exhibit two or more of the following features: size >5 cm, infiltrative growth pattern, high nuclear grade and cellularity, mitotic rate >1/50 HPG, necrosis, or vascular invasion.

For disease recurrence and metastasis, recent studies have demonstrated success with mTOR inhibitors [6,13,14]. This therapy targets the mTOR cell signaling pathway involved in RNA translation, a member of which includes the TSC2 gene product tuberin [4].

Our patient's tumor was risk classified as 'malignant' secondary to its high nuclear grade, large size, and presence of necrosis. However, her preoperative metastatic evaluation was negative. She was seen at our clinic at 33 months postoperatively without evidence of recurrence, but has subsequently been lost to follow up.

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