RETROPERITONEAL TUMOR: DIFFERENTIAL DIAGNOSIS BEYOND "THE USUALLY SUSPECTED"

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ABSTRACT

We present a case of 33-year old woman who complained of dull pain in right lumbar area. Image studies reviewed tumor mass in right retroperitoneal space without clear evidence of connection to the kidney that was surgically removed *en bloc*. Histologically, tumor tissue was found to contain mature fat, unevenly dispersed abnormal blood vessels of variable thickness and spindle cell component that seemed to irradiate from vessel walls. On closer examination, multiple small foci appeared to contain larger polygonal cells with abundant clear cytoplasm, imparting epithelioid outlook. Only a few of these cells demonstrated increased nuclear atypia; almost no mitotic figures were seen. Based on the high fat content, presence of spindle and epithelioid cells with mildly atypical nuclei and rare whirling pattern of spindle cell growth the initial diagnosis was Liposarcoma. This led to seeking of second opinion which resulted in additional diagnostic evaluation by immunohistochemistry. Cytokeratin AE1-AE3 and S100-protein tested negative; HMB-45 showed positivity in scattered majority of cells with synchronous strong expression of Smooth Muscle Actin. Morphology, supplemented with data from immunohistochemical investigation favored Angiomyolipoma (AML). The authors discuss details about the histological diagnosis of AMLs, terminology related to localization in retroperitoneum and relevant issues concerning the origin, biology and treatment of these rare neoplasms.

Key words: *angiomyolipoma, retroperitoneal tumor, histological diagnosis.*

INTRODUCTION

The majority of the retroperitoneal tumors tend to present in advanced clinical stage due to relative scarcity of vital organs and abundance of loose connective tissue, thus offering enough space for tumors to grow and remain clinically silent. Malignant tumors of the retroperitoneum are roughly four times more frequent than benign lesions, in contrast to neoplastic disease occurring elsewhere in the body, where benign disease predominates (9). In infancy, nephroblastoma (Wilms' tumour), neuroblastoma and germ cell tumours are overrepresented, while in adults the majority of retroperitoneal neoplasms are primary lymphoproliferative, parenchymatous epithelial tumours (renal, adrenal, pancreatic), or represent metastatic disease from known or unknown primary sites elsewhere. Soft tissue (mesenchymal) tumours of the retroperitoneum are less common. The range of frequently encountered retroperitoneal mesenchymal neoplasms is more limited, with the usually suspected lesions being of a lipomatous, smooth muscle or neural nature. Beyond these three histogenetic types, only rarely in practice some tumors with uncertain origin and biological behavior are encountered.

CASE PRESENTATION

33-year old women with no significant past medical history, except for two Cesarean deliveries, was admitted in our hospital for diagnostic evaluation. She reportedly complained of dull pain in right lumbar area. Image studies reviewed tumor mass in right retroperitoneal space without clear evidence of connection to the kidney. Laboratory values were with in normal range and she was suitable for operative intervention. During surgery an ill defined tumor mass was found to encase the right kidney and *en bloc* resection followed. The specimen was submitted for histologic evaluation. Grossly, the sample consisted of obviously intact kidney measuring 10x6 cm, surrounded by multinodular, yellowish soft tumor that added roughly 6 cm to each side of the kidney (**Fig. 1A**). Histologically, tumor tissue was found to contain mature fat, unevenly dispersed abnormal blood vessels of variable thickness and spindle cell component that seemed to irradiate from vessel walls, occasionally fusing into solid areas with hyperchromatic nuclei. Neoplastic nests with the same appearance were found within superficial part of kidney cortex (**Fig. 1B**). On closer examination, multiple small foci appeared to contain larger polygonal cells with abundant clear cytoplasm, imparting epithelioid outlook (**Fig. 1C**). Only a few of these cells demonstrated increased nuclear atypia (**Fig. 1D**); almost no mitotic figures were seen. Based on the high fat content, presence of spindle and epithelioid cells with mildly atypical nuclei and rare whirling pattern of spindle cell growth the initial diagnosis was Liposarcoma. This led to seeking of second opinion which resulted in additional diagnostic evaluation by immunohistochemistry. Cytokeratin AE1-AE3 and S100-protein tested negative; HMB-45 showed positivity in scattered majority of cells (**Fig. 1E**) with synchronous strong expression of Smooth Muscle Actin (**Fig. 1F**). Morphology, supplemented with data from immunohistochemical investigation favored Angiomyolipoma (AML).

DISCUSSION

AMLs are rare clonal tumors of enigmatic origin, heterogeneos histological presentation and diverse clinical outcome. The most popular localization is kidney and renal AMLs account for 1% of renal tumors, occurring exclusively in females, with an overall incidence in the general population of 0.07-0.3% (7). Extrarenal occurrences are well documented, liver being the first among other organs to frequently harbor AMLs followed by retroperitoneum (6). Some authors further classify retroperitoneal AMLs as renal end extrarenal depending on how obvious a connection with renal parenchyma exists (6, 7). In our experience, such connection is hard to establish, is a function of quantity and quality of materials submitted for examination and probably represent a single entity.

AMLs are often found incidentally when the kidneys are imaged for other reasons. Symptomatic presentation is most frequently with spontaneous retroperitoneal haemorrhage; the risk of bleeding being proportional to the size of the lesion (> 4 cm diameter) (4). Shock due to severe haemorrhage from rupture is described as Wünderlich syndrome (1). Patients may present with numerous other symptoms: palpable mass, dull pain, haematuria, hypertension, urinary tract infections, renal failure.

AMLs are currently believed to belong to a family of neoplasms called perivascular epithelioid cell tumors (PEComas). PEComas (tumors showing perivascular epithelioid cell differentiation) are a family of mesenchymal neoplasms that include AML, clear cell "sugar" tumor of the lung, lymphangiomyomatosis, and a group of uncommon lesions that arise in soft tissue, visceral organs, and skin. All these tumors share a distinctive cell type, the perivascular epithelioid cell or “PEC” – cells that so far have never been recognized in normal human tissue. The PEC is an unusual cell type showing morphologic, immunohistochemical, ultrastructural, and genetical distinctive features. Most commonly this is consistent with epithelioid appearance with a clear to granular cytoplasm, a round to oval, centrally located nucleus and an inconspicuous nucleolus with clear cut tendency for perivascular residency. Immunohistochemically, PECs express cross-lineage

melanocytic and myogenic markers, such as HMB- 45, Melan-A/Mart1, smooth muscle actin and, less commonly, desmin (4). Though criteria to recognize PECs (and AMLs in particular) seem rather straightforward their origin is still debated. One current hypothesis is that the neoplasm derives from undifferentiated cells of the neural crest with smooth muscle and melanocytic phenotype. A second hypothesis is that PEC has a myoblastic origin with a molecular alteration that leads to the expression of melanogenesis and melanocytic markers; a third hypothesis is that PEC has a pericytic origin (4).

Two main histological types of AMLs are currently recognized: classical and epithelioid variant. Both these variants seem quite different in terms of histology and biological behavior. Classical AML is typically defined by triphasic morphology, is almost never reported to have local recurrences and distant metastases and has an overall indolent clinical course. Contrary to this, epithelioid AMLs (EAMLs) are often characterized by aggressive clinical events in approximately 30% of cases diagnosed, though minimal threshold has never been establish as to define EAMLs (2). Varying amount of epithelioid component is occasionally seen in an otherwise classical AMLs and the prognostic significance of the epithelioid component is uncertain in such setting. EAML is described as having polygonal cells with clear to eosinophilic cytoplasm and round to oval nuclei that may show varying degree of nuclear atypia, sometimes posing a differential with renal cell carcinoma or sarcoma. Therefore, in 2010, Brimo et al. proposed the concept of atypical EAMLs, and suggested that certain atypical morphological features may be correlated with malignant behavior (3). Those features include: $\geq$ 70% atypical epithelioid cells; $\geq$ 2 mitotic figures per 10 HPF; atypical mitotic figures; and necrosis. Additionally, these authors concluded that the presence of three or more of the above features predicts an increased risk of clinically malignant behavior.

Management of AMLs localized in retroperitoneum often coincides with measures in cases of renal AMLs: angioembolisation, nephron-sparing or radical nephrectomy. Clinical decision depends on tumor size, mode of spread – singular versus multiple foci, performance status of the patient etc.

AMLs are known to occur in two distinct clinical settings: the more common sporadic form and in association with tuberous sclerosis complex (TSC), which itself raises the probability of having AML of any part of the body by 60-80 %. Explanation of this phenomenon is rooted in genetic abnormalities in *TSC1* and *TSC2* genes, with loss of function mutations in *TSC2* gene occurring predominantly in sporadic AMLs (8). This gene mutation is often manifested by specific deregulation of a cell signaling pathway promoting neoplastic growth and survival via mammalian target of rapamycin (mTOR), (5). At the edge of targeted therapy, current insights into molecular mechanisms represent a rationale for employing mTOR inhibitors for successful control of distinct AML groups (10).

IN SUMMARY, we present a case of AML which appears to be the last expected in the long differential list of retroperitoneal tumors. Combining the detailed morphological and phenotypic studies the diagnosis is usually easy to achieve, but nonetheless straightforward and unequivocal. In our case the quantity and quality of epithelioid component did not suffice the requirements for EAML, least atypical EAML, and therefore is proper to be classified as classical AML. This, however, is not predictive for neither benign nor malignant biological behavior and close clinical follow-up is strongly recommended.

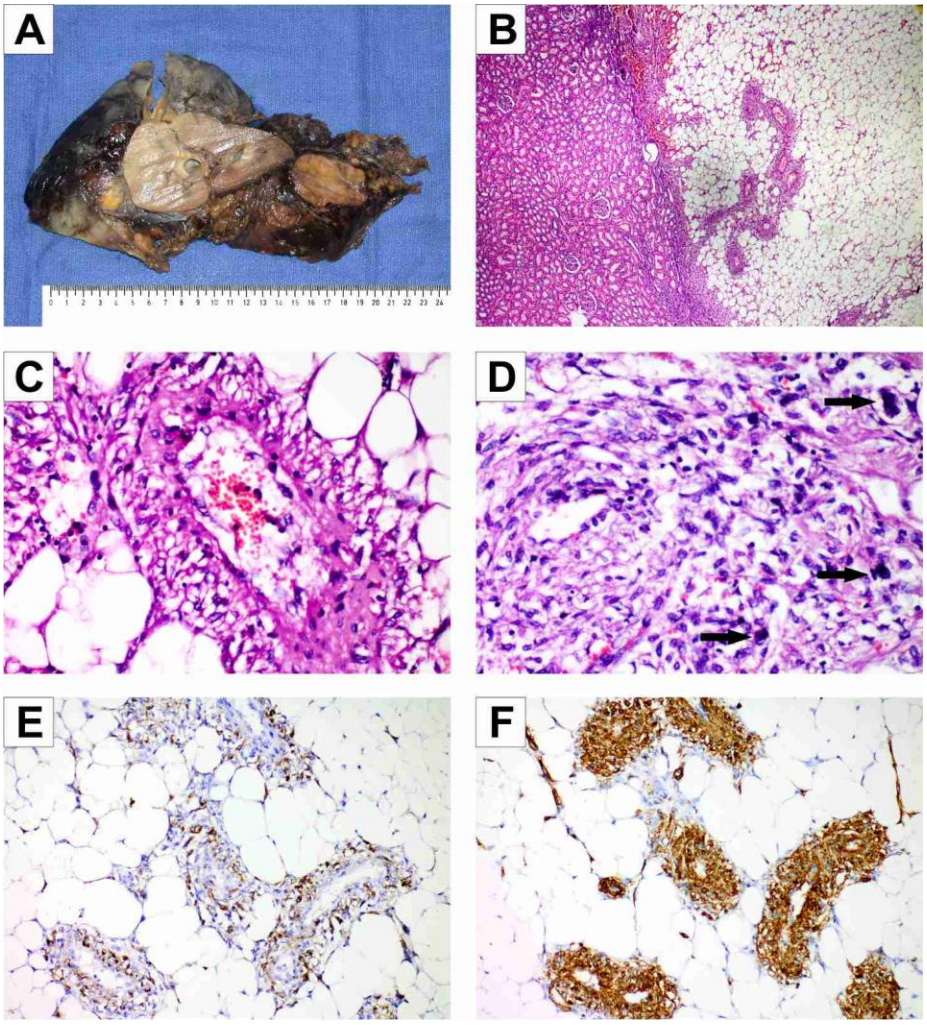

Fig. 1. A – gross specimen. **B** (H&E) - AML nests within superficial part of kidney cortex. **C** (H&E) - epithelioid component of AML. **D** (H&E) - epithelioid cells with nuclear atypia. **E** - synchronous immunohistochemical expression of HMB-45 with Smooth Muscle Actin – **F**.

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