Case Report

Renal epithelioid aggressive angiomyolipoma in a patient with tuberous sclerosis and past contralateral benign renal angiomyolipoma

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Abstract

Twenty-five percent of all aggressive angiomyolipomas (AMLs) are related to tuberous sclerosis. Our patient was a 42-year-old man with tuberous sclerosis and a medical history of a benign AML in the left kidney. Presently, an epithelioid AML was detected in his right kidney and, despite our conducting extensive surgery, a large pulmonary metastasis with mediastinal lymph node involvement followed 20 months later. Close follow-up of the patient is advised when epithelioid cells are observed in angiomyolipoma. Immunohistochemistry for mismatch repair proteins showed that PMS2, MSH2, and MSH6 were absent in both the tumor and normal kidney. Microsatellite instability may contribute along with a mutation of *TSC* gene to the oncogenic events leading to AML.

Keywords:
CD68, lung metastases, microsatellite instability, PAX8, renal angiomyolipoma

Introduction

Classic, triphasic, renal angiomyolipoma (R-AML)—composing of dysmorphic and thick blood vessels, smooth muscle cells, and mature adipose tissues—is the most common benign mesenchymal tumor of the kidney. It derives from the proliferation of perivascular epithelioid cells with melanocytic and myoid differentiation and usually displays benign features. The kidney is the most common primary organ for AML. AMLs are sporadic in 80% of cases, with the remaining occurring in association with tuberous sclerosis complex (TSC) or lymphangioleiomyomatosis, where they can be bilateral and multiple. TSC-associated AML can be seen in children and adults. Biallelic loss of the tuberous complex genes *TSC1*/*TSC2* have been found to drive R-AML development.[1]

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A sporadic variety is typically seen in middle-aged female patients (female-to-male ratio of 4:1), with a mean age of 43 years.[2] At times, R-AML may exhibit capsular invasion and perinephric extension. On rare occasions, the tumor may show invasion into the renal vein and the inferior vena cava, indicating an aggressive behavior. Lymph nodal involvement is also described. Approximately 75% of all reported cases of aggressive AML occur as sporadic isolated cases, with only 25% related to TSC.[3]

Herein, we describe a TSC-related R-AML exhibiting malignant behavior.

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Case Report

A 42-year-old man with a history of TSC presented with complaint of a persistent mild pain in the right lumbar region. Past medical history was notable for the excision of a benign AML in the left kidney. Urinalysis showed no blood, leukocytes, or protein. A renal ultrasound revealed a 12-cm hypoechoic mass within the upper right kidney. No renal vein involvement was observed. It also showed an infiltration of the perirenal fat and of the para aortic-lumbar-lymphnodes-aortic nodes with no nodules in the liver nor in the lung. The patient underwent a radical right nephrectomy. Gross examination revealed an enlarged right kidney of 14 × 8 × 7 cm entirely replaced by a whitish, non-encapsulated mass with foci of necrosis and hemorrhage. The mass invaded through the capsule into the perirenal fat tissue and extended into the renal sinus. No tumor thrombus in the renal vein was noted. Histology revealed a triphasic AML, with characteristically thick-walled blood vessel, scarce fat tissue, and myoid differentiation [Figure 1a]. Additionally, large areas (30%) of atypical epithelioid round pleomorphic and, occasionally, giant multinucleated tumor cells with abundant eosinophilic or pale cytoplasm and macronucleoli could be observed [Figure 1b]. In these areas, the tumor exhibited infiltrative growth and showed abundant necrosis. The mitotic rate of the tumor cells was low (1/10 HPF) in AML with classical features, while Ki67 immunopositivity was high in epithelioid areas (48%) [Figure 2a]. The epithelioid cells failed to immunostain with epithelial membrane antigen (EMA), pancytokeratin AE1/AE3, PAX8, p53 and, like the usual AML component, were labelled with HMB45 [Figure 2b], smooth muscle actin [Figure 2c], CD99 (focally), and CD68R (membranous). Other positive stains included focal membranous CD10 and PDL1 in the epithelioid cell areas. CD117, which is said to be expressed in AML, was negative in both components. Immunohistochemistry for mismatch repair (MMR) proteins was used to identify MMR status. Our results showed that PMS2, MSH2, and MSH6 were absent in both the tumor and the normal kidney. MLH1 was positive in the kidney parenchyma and only focally and weakly expressed in AML. The tumor was multifocal in the kidney, and metastases in 7 out of 13 lumbo-aortic lymph nodes were detected. The final diagnosis was aggressive R-AML with epithelioid component, pT3a, pN1.

Twenty months later, a pulmonary metastasis measuring 13 × 9 × 7 cm and with mediastinal lymph node metastasis was detected. Microscopically, it showed epithelioid features with large necrotic areas and invasion of lymphovascular spaces. The immunoprofile was the same as that of the renal primary.

The patient gave his consent for publication.

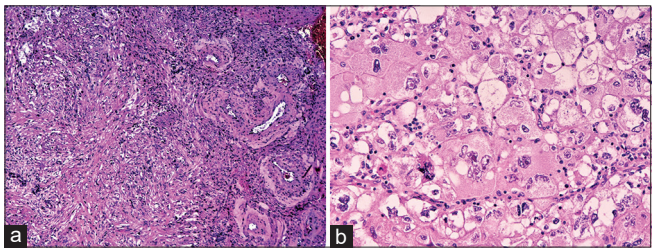

Figure 1: (a) The classic AML component shows variable mixture of mature adipose tissue, thick-walled vessels, and smooth muscle cells with fascicular growth pattern. (b) The epithelioid cells present clear or eosinophilic cytoplasm, round-to-oval enlarged, vesicular, nuclei, prominent nucleoli and varying degrees of nuclear atypia. (Hematoxylin and eosin, ×100 and × 400, respectively)

Discussion

Our patient showed the classical TSC-related kidney involvement, with bilateral and multifocal R-AML. Only the first lesion showed a benign behavior and was cured with surgical removal, while the second lesion displayed epithelioid features, lymph node involvement, and malignant behavior with subsequent lung metastasis. There are no conclusive histological criteria for malignancy in AML, despite lymphovascular invasion, lymph node, or distant metastases being generally considered as signs of aggressive behavior. Entirely benign R-AML may show extension into the inferior vena cava and even involvement of regional lymph nodes, which are seldom followed by distant

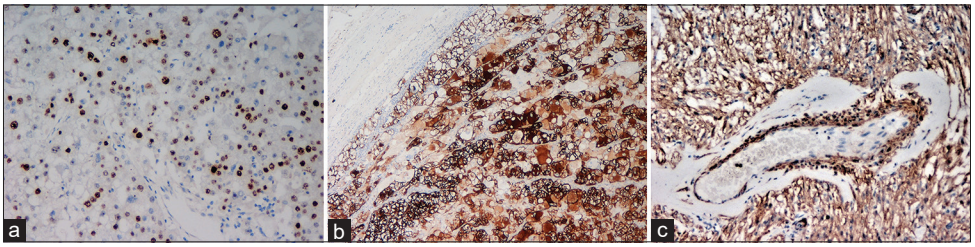

Figure 2: (a) In the epithelioid component, the Ki67 proliferation index was 48%. AML classically immunoreacts with HMB45 (b, epithelioid component) and actin smooth muscle (c, classic component with abnormal blood vessel), due to myomelanocytic differentiation (PEComa). (Avidin-biotin-DAB, ×100, ×200, and × 200, respectively)

metastases. Therefore, some authors believe that nodal involvement is just a multicentric growth pattern rather than metastasis.[4] Neoplastic thrombosis of the vena cava is most often associated with the tumor's large size and central right side location, as the right renal vein is short and displays a straight course.[5] Presently, it is recognized that renal and lymph node AML show a clonal origin,[6] but the significance of such discovery is yet to be elucidated.

The epithelioid variant of R-AML (R-EAML) is more prone to be at risk of developing metastatic behavior, and as much as one third of them develop distant lesions,[7] mainly in the liver and lung, with a mortality rate of 35%–40%.[8] Among the other parameters predictive of malignant behavior, a high percentage of epithelioid cells appears to be important, as well as marked atypia, higher mitotic activity,[9] and large mass diameter.[10] R-EAML has been recognized in the 2016 World Health Organization (WHO) classification of renal tumors. It contains polygonal, atypical epithelioid cells with abundant cytoplasm, vesicular nuclei, and prominent nucleoli. Its occurrence in association with TSC is higher than classic AML. The five adverse prognostic parameters of pure R-EAML are TSC, necrosis, tumor size >5–7 cm, extra-renal spread, and/or renal vein involvement and carcinoma-like growth pattern.[10] Also increased mitotic activity and nuclear anaplasia should raise significant concern for malignant outcome.[11] Recent studies also suggest that Ki67 index exceeding 10% and p53 overexpression in R-EAML may indicate the malignant behavior of the tumor.[12] Malignant R-EAMLs are treated as a clear cell carcinoma.[7] The present case contained epithelioid cells, and this component appeared rather atypical, showing large size, nucleoli, necrosis and intratumoral hemorrhage. While AML in lymph nodes showed microscopically the usual spindled features, lung metastases were composed exclusively of epithelioid cells.

There is no agreement as to the amount of epithelioid cells that are necessary to qualify R-EAML. According to some authors, at least 5% of cells must exhibit epithelioid features,[13] while others believe that the histological criteria should include the absence of fat tissue and of thick-walled blood vessel.[7] The pure epithelioid form is extremely rare, occurring in 1% of AML, but its association with TSC is higher than classic AML.[7] At any rate, a close follow-up of the patient is advised when epithelioid cells are observed in AML.

R-EAML should be differentiated from t (6;11) renal cell carcinoma, due to the overlapping immunohistochemical expression of melanocytic markers, such as HMB45 and Melan-A. PAX8 is the most reliable tool in this respect, showing negative results in R-EAML and vice versa,[14] as it was in the present case. Also, CD68R has been demonstrated to be consistently positive in AML[14] and was expressed in the present case.

The molecular profile of AML has rarely been investigated. Kattar *et al*.[15] evaluated chromosomal imbalances by comparative genomic hybridization and found that these were, by far, more frequent in sporadic AML, and often involved whole chromosomal or partial deletions of the 5q33-q34 region. No microsatellite instability was found in a study on benign sporadic liver AML using microsatellite markers selected to cover chromosomal regions commonly deleted in hepatocellular carcinoma (HCC) and many other human tumors.[16] We tested non-epithelioid and epithelioid AML areas, as well as the neighboring normal kidney tissue of this patient for microsatellite instability (MSI), as it has never been investigated in R-EAML. In humans, seven DNA mismatch repair proteins (MLH1, MLH3, MSH2, MSH3, MSH6, PMS1 and PMS2) work coordinately in sequential steps to initiate repair of DNA mismatches. PMS2/MLH1 complex coordinates the activities of other proteins that repair errors made during DNA replication. According to Vogelstein *et al*.,[17] more than half of somatic mutations identified in tumors occur in a pre-neoplastic phase (in a field defect), during the growth of apparently normal cells. This could explain why PMS2, MSH2, and MSH6 deficiencies were present in the histologically normal kidney of our patient and may account for the estimated risk of kidney cancer of about 4% in TSC patients. Our results should prompt wider investigations in TSC-associated AML, as high-frequency MSI and mutation of tumor suppressor gene TSC may contribute to the oncogenic events leading to AML and/or kidney cancer occurrence.

In conclusion, AML with malignant character is extremely rare. The presence of an epithelioid component should raise suspicion for a malignant behavior and should, therefore, not be overlooked.

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Conflicts of interest
There are no conflicts of interest.

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