Case - Genetic mosaicism of TSC2 gene in a patient with multifocal renal epithelioid angiomyolipomas

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INTRODUCTION

Renal angiomyolipomas (AML) are benign tumors of the kidney and present in approximately 0.2–0.3% of adults.[1] Approximately 20% of AML are associated with hereditary syndromes, most notably tuberous sclerosis complex (TSC), which is characterized by germline variants in either the TSC complex subunit 1 gene (*TSC1*) or TSC complex subunit 2 gene (*TSC2*).[2] AML in TSC have biallelic inactivation of either the *TSC1* or *TSC2*, dependent upon which gene carried the germline alteration, and somatic loss of either of these genes has been shown to promote pathogenesis in sporadic AML.[3]

Although TSC is traditionally recognized as an autosomal-dominant genetic disorder secondary to germline pathogenic variants, approximately 10–15% of patients do not have identifiable germline mutations by standard testing. A majority of these patients without conventionally detected germline alterations harbor factors such as mosaicism and intronic splice site variations in TSC, and their presence can pose significant challenges for both diagnosis and genetic counseling.[4,5]

Epithelioid AML (eAML) represents 2.7–5.8% of all resected AML and can be associated with TSC,[6] and has been shown to have malignant potential, with the capacity to develop metastatic disease or tumor involvement of the renal vein and inferior vena cava.[7] On histologic assessment, eAML exhibits hyperplasia of epithelioid cells and a low content of mature fat cells. Additional features unique to eAML may include mitotic figures, hemorrhage, necrosis, and foamy macrophages.[8] On imaging, eAML presents similarly to AML, although intratumoral hemorrhage and necrosis may be more prominent.[9]

Herein, we present an exceptionally rare case of a patient without a germline pathogenic variant indicative of TSC who developed multifocal renal tumors and underwent robotic-assisted partial nephrectomy for three tumors. All tumors were histologically eAML and demonstrated biallelic mutation of *TSC2* with one shared mutation in *TSC2* that could not be detected in germline testing, suggesting genetic mosaicism.

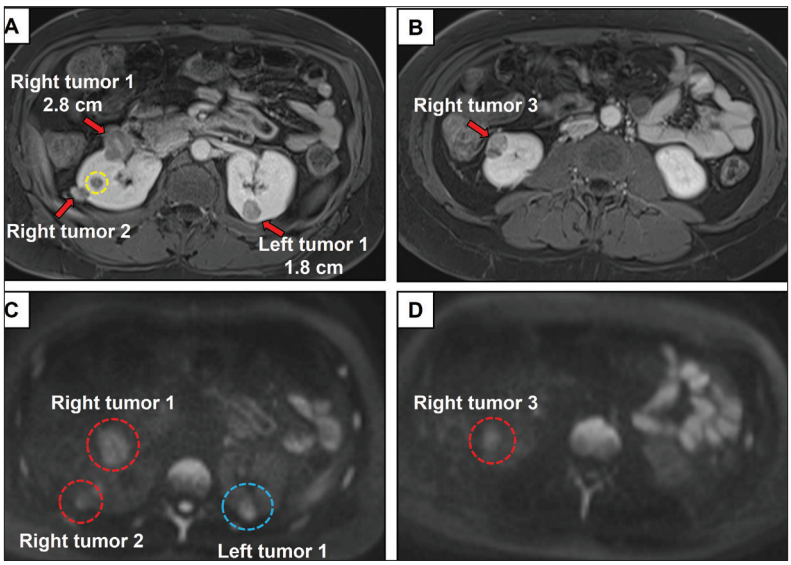

Figure 1. Preoperative MRI axial images showing the three right renal masses that were subsequently removed with partial nephrectomy, and a left renal tumor that is undergoing active surveillance. (A) MRI T2 FS images, right tumors 1 and 2 were in the anterior and posterior midportions of the right kidney, respectively. The yellow dashed circle indicates the small, stable endophytic AML that was not resected, and the arrow points to the left renal tumor that the patient will be undergoing active surveillance. (B) MRI T2 FS image showing right tumor 3 was in the anterior lower pole of the right kidney. (C) MRI showing restricted diffusion is most prominent on right tumor 1 (b=2000 s/mm2 on 3T MRI) as compared to the right tumor 2, which prompted partial nephrectomy, the light blue dashed circle indicates the small left renal tumor with restricted diffusion. (D) MRI showing restricted diffusion of right tumor #3, which prompted partial nephrectomy. MRI: magnetic resonance imaging.

CASE REPORT

A 33-year-old, African-American female with no significant past medical history and no family history suggestive of TSC was found to have bilateral multifocal renal masses during workup for infertility. Initial magnetic resonance imaging (MRI) demonstrated bilateral multifocal renal masses suggestive of AML (right kidney lesions measuring at 1.3 cm, 0.3 cm, and 0.4 cm; left

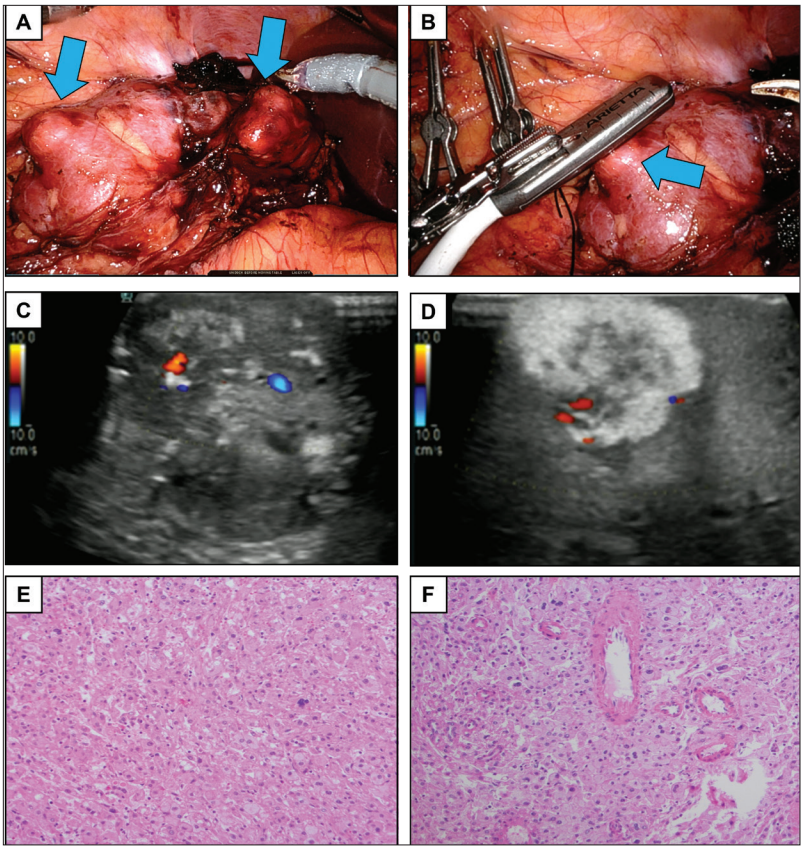

Figure 2. Intraoperative images, intraoperative ultrasound of the right renal masses, and tumor histology. (A) Intraoperative images at the time of tumor resection and (B) intraoperative renal ultrasound (blue arrow pointing at the tumors). (C) Tumor #1 demonstrated a complex pattern of hyper- and hypoechoic regions with intratumoral vascularity and poorly-defined borders. (D) Tumor #3 demonstrated hyper-echogenicity and demarcated borders with mild intratumoral complexity. Tumor #2 appeared similar to tumor #3 on intraoperative ultrasound. (E) Low power of a cellular epithelioid angiomyolipoma (H&E 150X). (F) Prominent vascular structures surrounded by smooth muscle (H&E 150X).

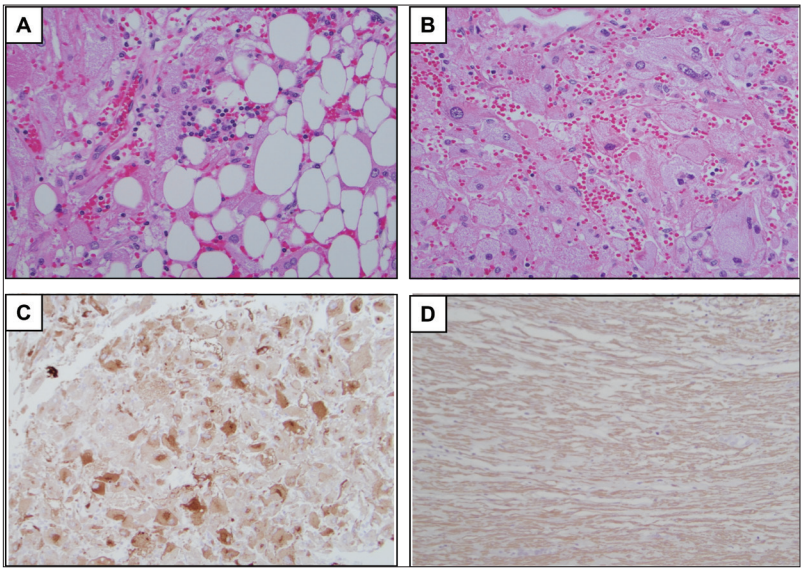

Figure 3. Histological images. (A) Fibroadipose tissue surrounded by muscle with atypical cells (H&E 200X). (B) Epithelioid cells with a prominent atypical nucleus and abundant eosinophilic cytoplasm (H&E 200X). (C) Special stains for Melan A. (D) Special stains for smooth muscle actin.

kidney measuring 1.4 cm, 1.0 cm, 0.4 cm, and 0.4 cm). The patient did not fulfill the criteria for TSC. Germline genetic testing was negative for pathogenic variants in *TSC1* or *TSC2*. Thirty months later, MRI showed four right renal masses, with growth of the index lesion on the right kidney to 2.3 cm. Subsequently, the patient underwent percutaneous renal ultrasound-guided biopsy of the right renal mass, which demonstrated AML with positive staining for SMA, HMB-45, and Melan-A.

At the age of 42 years, MRI showed growth of the right renal masses, with the largest being 2.8 cm, and growth of the left renal masses, with the largest being 1.8 cm (Figures 1A, 1B). The anteromedial mass (tumor #1) in the right kidney showed concerning features of being lipid-poor and highly restricted on diffusion-weighted MRI, and the decision was made to resect the right-sided lesions (Figures 1C, 1D). She underwent a right robotic-assisted partial nephrectomy (Figures 1A, 1B).

Intraoperative ultrasound was performed. The stable mass in the same kidney was not resected given its small size and endophytic nature; three tumors were removed (3.9 cm, 1.8 cm, and 1.6 cm) (Figures 2A, 2B). All tumors were confirmed to be eAML on histopathology, with moderate atypia (Figures 2C–F, Figures 3A–D), and demonstrated a significant epithelioid component (epithelioid cells with large eosinophilic cytoplasm, large nuclei, multinucleation, with moderate atypia and nucleoli). No necrosis or mitotic features were identified. The patient convalesced well after surgery.

At the three-month followup, MRI of the abdomen revealed surgical beds free of tumors. New baseline estimated glomerular filtration rate (eGFR) was 92 ml/min/1.73m^2 (preoperative: 88 ml/min/1.73m^2). The patient remains on active surveillance and all renal masses are stable.

In relation to genetic analysis, initial genomic testing (TruSight Oncology 500 Gene Panel v3, DNA) of tumor #3 identified two *TSC2* variants, a known pathogenic nonsense alteration (c.2251C>T, p.Arg751*),[2,10,11] and a likely pathogenic frameshift alteration (c.1693_1699delCTGGGGC, p.Leu565fs*131). Further whole exome sequencing demonstrated that the p.Arg751**TSC2* variant was shared between all tumors (Figure 4A), while unique additional *TSC2* variants were observed in each lesion (p.His1727Glnfs*47 in tumor #1, p.Met2761lefs*57 in tumor #2, and p.Leu565Phefs*131 in tumor #3. All variants were confirmed by Sanger sequencing (Figure 4B–D).

DISCUSSION

Given the rarity of renal eAML and its malignant potential, characterization of the genomic features and clinical behavior of eAML remains an important area of research. Herein, we present the first reported case of primary multifocal eAML to our knowledge. A germline pathogenic variant suggestive of TSC was absent, and although the three ipsilateral renal eAML had a shared mutation in *TSC2*, each had a separate, distinct second *TSC2* mutation. The common *TSC2* pathogenic variant suggests genetic mosaicism, in which a de novo *TSC2* alteration has occurred early in development, allowing it to be shared by multiple renal cells but not be detected throughout the kidney or within the blood DNA. The unique *TSC2* variants indicate that the three eAML tumors arose independently rather than via metastatic intra-renal spread.

TSC is an autosomal-dominant genetic disorder most frequently associated with a germline mutation in *TSC1* or *TSC2*, with reported sporadic cases and somatic mutations.[2,3] The abnormal function of those genes leads to persistent activation of the mammalian target of rapamycin (mTOR) signaling pathway, resulting in aberrant cell growth and proliferation, which subsequently gives rise to tumors such as hamartomatous lesions, renal AML, and renal eAML, among others.[1,2]

This report expands upon prior case studies suggesting that pathogenic variants in *TSC2* may be associated with eAML.[13,14] While the *TSC2* (c.2251C>T, p.Arg751*) genomic variant has been shown to occur in TSC, the present case uniquely suggests that the *TSC2* (c.2251C>T, p.Arg751*) genomic alteration may be associated with the occurrence of eAML.[10,11] Additionally, the identification of biallelic mutations in the *TSC2* of each eAML suggests that the development of eAML follows the 'two-hit hypothesis,' similar to other TSC related lesions. It is important to note that other genes that have been associated with eAML include *TP53* and *ATRX*.[15]

In patients with renal masses suspicious of eAML, genetic testing of *TSC1/TSC2* alterations associated with this malignancy can provide physicians with a better framework to decide on early surgical intervention. Further genetic and molecular characterization of patients with eAML and their potential pathogenic genomic variants is essential, as this could potentially aid in differentiating between those patients with potential renal AML and those at risk for eAML. This genetic knowledge would assist urologists and genetic counselors in deciding on the need for more frequent surveillance or earlier surgical intervention for individuals with identified pathogenic variants.

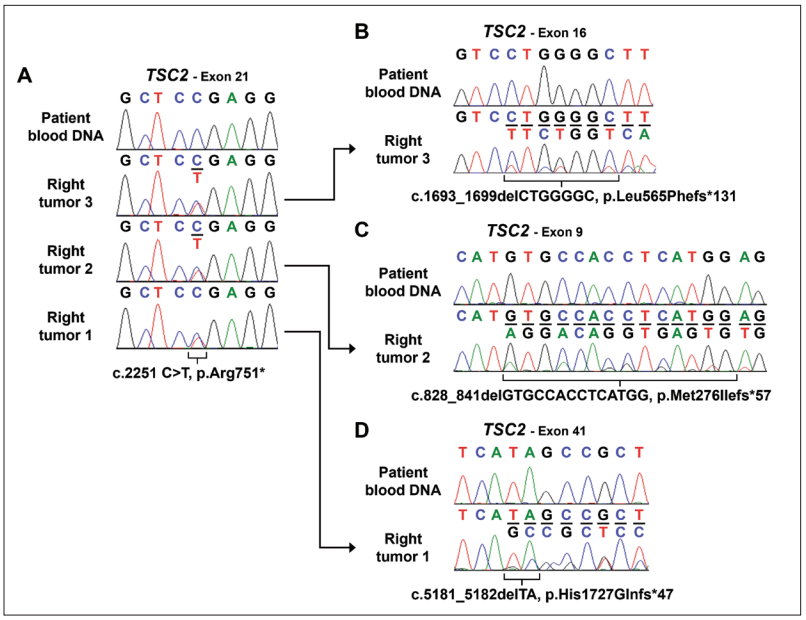

Figure 4. Sequence chromatograms of TSC2 exons harboring pathogenic variants across the three eAML tumor samples. (A) The p.Arg751* pathogenic variant (c.2251C>T) was observed in all three eAML tumor samples, but not in the blood sample. (B) The p.Leu565Phefs*131 variant (c.1693_1699delCTGGGGC) is seen only in tumor 3. (C) The p.Met276Ilefs*57 variant (c.828_841delGTGCCACCTCATGG) is seen only in tumor 2. (D) The p.His1727Glnfs*47 (c.5181_5182delTA variant) is seen only in tumor 1.

CONCLUSIONS

This case highlights the presence of *TSC2* genetic mosaicism in a patient with multifocal renal eAML without a germline pathogenic variant indicative of TSC. We identified a pathogenic *TSC2* variant (c.2251C>T, p.Arg751*) as a potential driver for eAML development. Further genetic characterization of eAML might inform clinical decisions regarding surveillance and early surgical intervention, ultimately improving patient management and outcomes.

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