



Case report of everolimus-induced sustained partial response in metastatic renal epithelioid angiomyolipoma

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ABSTRACT

Epithelioid variant of angiomyolipoma (EAML) is a newly defined entity and a close mimicker of renal cell carcinoma. There is a growing body of evidence to suggest its aggressive behavior in terms of local recurrence, metastasis and death. The treatment for this subset of patients has posed challenges for the experts. Chemotherapy plays little active role and so molecular profiling to identify genomic alterations amenable to targeted therapies has paved the way. Recently, tyrosine kinase inhibitors and mTOR inhibitors have been utilised both in adjuvant and neoadjuvant settings and have shown promising results in terms of survival. We present a case of a metastatic epithelioid angiomyolipoma treated sequentially with imatinib, crizotinib and now maintaining a sustained partial response with everolimus.

Keywords: Angiomyolipoma; epithelioid; everolimus; mTOR inhibitors; renal cell carcinoma.

Introduction

Angiomyolipoma is a benign clonal mesenchymal neoplasm. It is a triphasic tumor comprising of thick walled blood vessels, smooth muscle cells and adipose tissue. Histologically two variants have been reported-Classic and epithelioid. The classic variant follows an indolent course however, epithelioid angiomyolipoma is considered as the malignant counterpart with aggressive behaviour. A literature search in the PubMed revealed approximately 200 cases of epithelioid variant of angiomyolipoma (EAML) so far. However, the true incidence is likely to be higher as it is a close histological mimicker of classic Acute Myeloid Leukemia (AML), Renal Cell Carcinoma (RCC) and hence misdiagnosed.^[1,2] Ideal treatment strategies remain undefined. Radical tumor resection could be an important in the treatment of early stage disease and adjuvant radio-chemotherapy may be beneficial, however there have been very few randomized control trials to corroborate these findings.^[3] Targeted therapies including imatinib, crizotinib

and mammalian target of rapamycin (mTOR) inhibitors are being investigated for patients with advanced disease.^[4] Clinicians should be aware of this new treatment paradigm to design better treatment protocols.

Case presentation

A healthy 63- year-old hypertensive lady, presented to our facility in September 2015. She was a diagnosed case of malignant renal epithelioid angiomyolipoma in the year 2010 and now came with complaints of dry cough of short duration, loss of weight, appetite, occasional evening rise of temperature and an X- ray chest revealing multiple bilateral ill-defined round opacities suggestive of metastases. Preliminary workup included hematological investigations, renal and liver function tests and a positron emission tomography CT (PET-CT). Her hematological and biochemical parameters were within normal limits. PET- CT (Figure 1) was suggestive of mildly metabolically active disease in right renal fossa, bilateral pleural and parenchymal lung lesions, liver, bone,

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and paraaortic lymph node lesions. Further on, an ultrasound-guided fine needle aspiration cytology (FNAC) and biopsy from the liver lesion were performed. The FNAC was suggestive of a metastatic lesion involving the liver. Liver biopsy showed singly scattered and cohesive clusters of neoplastic cells having large nuclei with fine chromatin, conspicuous nucleoli and moderate to abundant eosinophilic cytoplasm (Figure 2, 3). Occasional mitosis was noted and necrosis was absent. Immunohistochemical analysis showed neoplastic cells expressing Melan A (Figure 4a), Human melanoma black 45 (HMB 45) (Figure 4b) and negative expression for CK (Figure 4c), S-100, synaptophysin, Thyroid Transcription Factor (TTF1), Paired box gene 8 (PAX-8), Hepatocyte paraffin 1 (Heppar 1) (Figure 4d). So, diagnosis of EAML was confirmed. Treatment decisions in patients pre-

senting with metastatic EAML is challenging as chemotherapy has a limited role. Hence in pursuant to the above protocol next generation sequencing (NGS) was performed using a cancer hot spot panel of 50 oncogenes and tumor suppressor genes to identify any mutations amenable for Food and Drug Administration (FDA) approved targeted therapies. Genomic alterations detected in the tumor block included missense mutations in Kit gene (KIT) (145C>T), FMS like tyrosine kinase 3 (FLT 3) (1812G>T), Kinase insert domain receptor (KDR) (1416A>T) and Tyrosine protein kinase met (MET) (2967 C>T) genes. The patient was started on tyrosine kinase inhibitor, oral imatinib in October 2015. In January 2016 patient presented with symptoms of weakness, weight loss and increased episodes of cough with expectoration. A PET- CT evaluation showed progressive disease in lung /liver, renal fossa and soft tissue. A trial of another multikinase inhibitor crizotinib (200 mg/day) was then advised starting from February 2016. Patient showed symptomatic relief for the next 4 months. A reevaluation with PET-CT performed in June 2016 showed further disease progression in lungs with interval changes in other lesions. She was then started on oral everolimus, an mTOR inhibitor at a dosage of 5 mg initially with escalation to 10 mg. Subsequently due to poor tolerance due to development of oral ulcers and GI toxicity, the dose was then reduced to 5 mg. An interim evaluation three months after treatment with oral everolimus in October 2016 revealed partial response, with decrease both in the extent and metabolic activity in the right renal fossa, liver and lung lesions and left paracolic lymph node. Oral everolimus treatment was maintained for 3

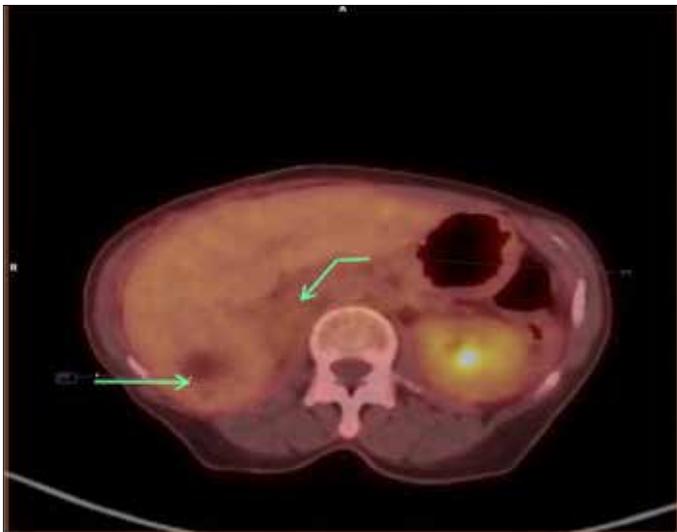


Figure 1. Axial view showing metabolically active disease in the right renal fossa and liver lesion in September 2015 (green arrows)

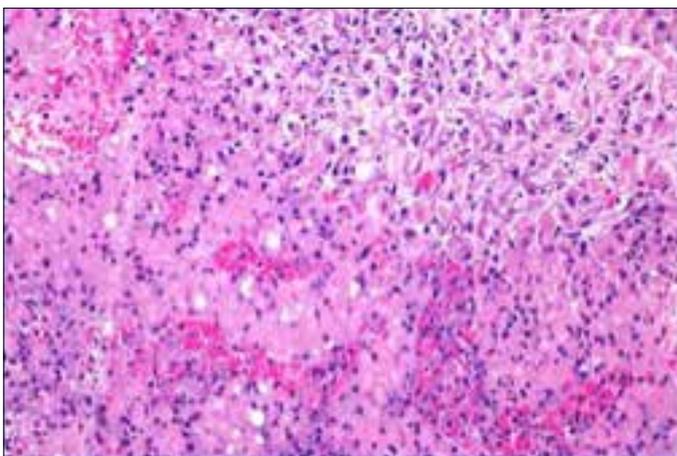


Figure 2. H&E stained sections show tumor cells infiltrating the liver parenchyma (X10 magnification)

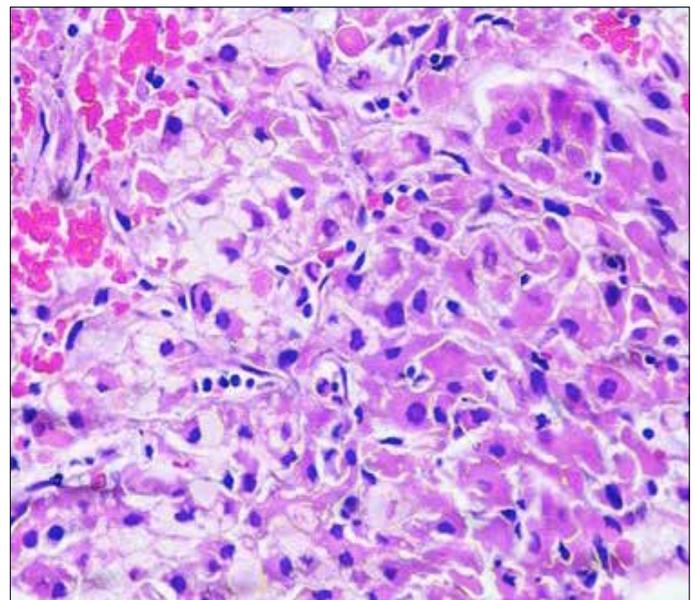


Figure 3. H&E stained sections show cohesive clusters of neoplastic cells having moderate to abundant eosinophilic cytoplasm, large nuclei with fine chromatin and conspicuous nucleoli (X40 magnification)

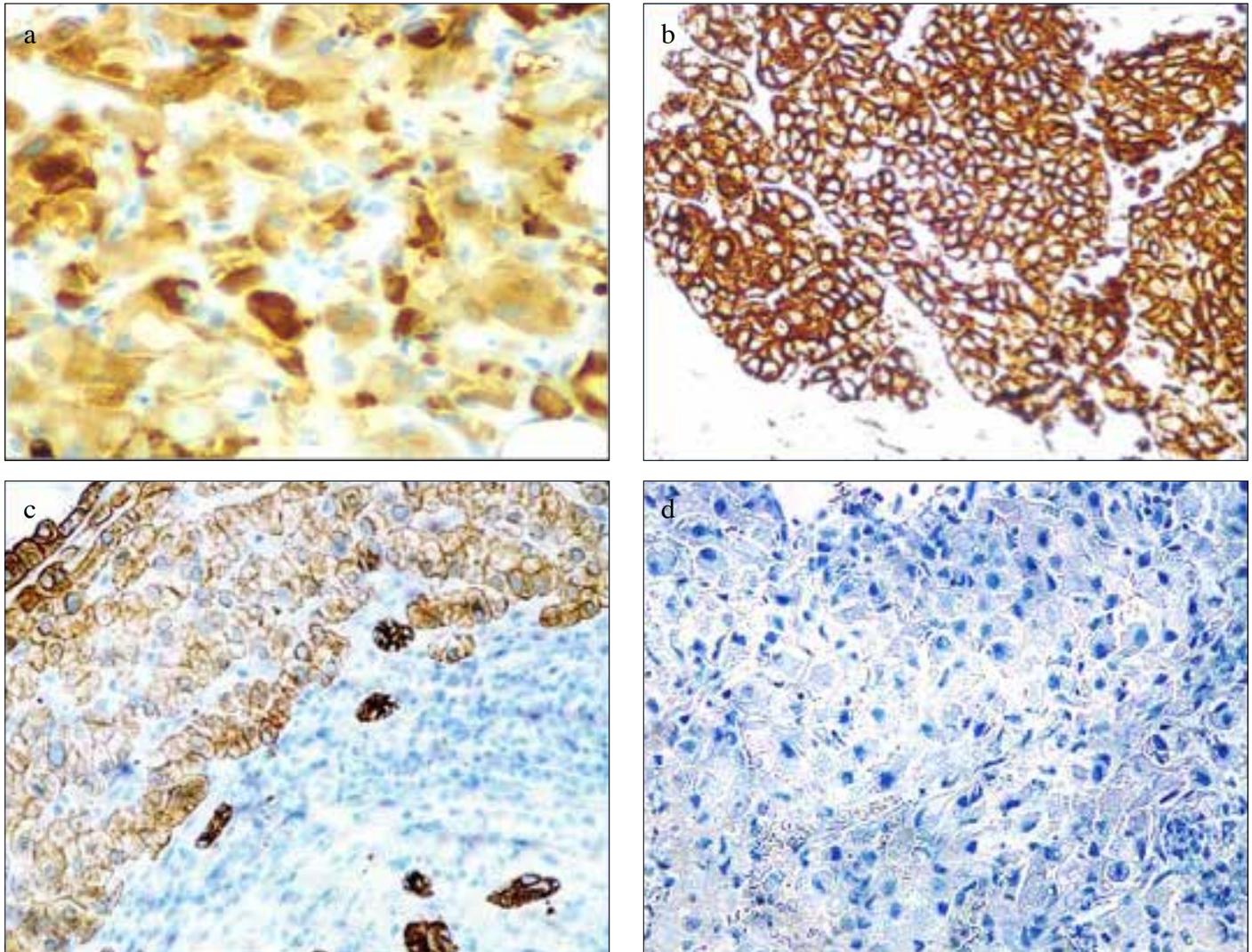


Figure 4. a-d. (a) Melan A. IHC demonstrates strong cytoplasmic immunopositivity in tumor cells with Melan A. (b) HMB45. IHC demonstrates cytoplasmic immunopositivity in tumor cells with HMB45. (c) CK. IHC with CK demonstrates cytoplasmic immunopositivity in normal hepatocytes and immunonegativity in tumor cells. (d) Heppar 1: IHC with Heppar 1 shows tumor cells with negative immunostaining

more months. She tolerated the treatment fairly well except for the complaints of anorexia and weight loss (grade 2) which were constant features. A PET- CT performed in July 2017 has continued to show a partial response (Figure 5). Presently, the patient is on 5mg oral everolimus treatment for more than a year while maintaining a good performance status. This case represents a rare entity of multiple genomic alterations treated with multiple targeted therapies showing good response to everolimus. Patient is alive with disease at 2nd year of her disease.

Discussion

Epithelioid variant of angiomyolipoma belongs to the PEComa (perivascular epithelioid cell) family of tumors. This group en-

compasses related mesenchymal tumors like renal and extrarenal angiomyolipoma, lymphangiomyomatosis, clear cell “sugar tumor” of the lung (CSST), extrapulmonary ‘sugar’ tumor, clear cell myomelanocytic tumor of the falciform ligament, and other “unusual clear cell tumors”. According to Amin MB et al. 2004 World Health Organization (WHO) has now classified EAML as a distinct tumor entity in its tumor classification of the urinary system and male genital organs.^[1] Although the most preferred site for AML’s is kidneys, other sites such as lungs, livers, lymph nodes, retroperitoneum, female genital organs and adrenal glands are not spared. Immunophenotypically these lesions show positivity with both smooth muscle (actin, desmin) and melanosome markers (HMB-45, Melan A).^[1,5] Genetically PEComas are linked to the tuberous sclerosis genes TSC1 , TSC2 and EAML known to oc-



Figure 5. Axial view demonstrating reduced FDG uptake in the right renal fossa and increased necrosis in the liver lesion in July 2017 (green arrows)

cur as a part of the tuberous sclerosis complex. Sporadic forms or non-tuberous sclerosis related AML's have also shown activation of mammalian targets of rapamycin (mTOR) signalling pathways paving way for the development of therapeutics involving mTOR inhibitors like everolimus and temsirolimus.^[6] Furthermore, at the molecular level, the TSC1 and TSC2 genes encode proteins that form a protein complex (TSC1/TSC2) that negatively regulates mammalian target of rapamycin complex 1 (mTORC1). Thus, when the TSC1/TSC2 complex is disrupted, mTORC1 is inappropriately activated leading to disruption of downstream pathways which regulates protein translation and cell growth. Wolff et al.^[7] has reported that there were significant histological and clinical differences between AML and EAML, the latter being more aggressive presenting with metastases and resistant to conventional chemotherapies. According to Shitara et al.^[8] cited enthralling case reports in 2011 and highlighted a dramatic tumor response with everolimus in a recurrent EAML over 7 months. The author also alluded about that several other reports suggesting disappointing results with conventional cytotoxic agents and that everolimus was an oral drug much convenient relative to the infusional temsirolimus.

Bissler et al.^[9] has recently published results of a Phase IIIB randomized trial wherein 112 patients with sporadic EAML and tuberous sclerosis-associated EAML were enrolled. They were treated with 10 mg everolimus daily and titrated based on tolerability. The tumor reduction with 28.9 months of therapy was 54%, further corroborating with our findings.

With the information currently available, it is our opinion that mTOR inhibitors represent the best treatment option for patients with unresectable EAML. The present study shows a rational way forward to treat this aggressive disease in a conservative manner.

Informed Consent: Written informed consent was obtained from the patient for publication of his clinical details.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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