Fatal malignant metastastic epithelioid angiomyolipoma presenting in a young woman: case report and review of the literature

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Abstract

Epithelioid angiomyolipomas (EAMLs) are rare mesenchymal tumors whose malignant variant is extremely uncommon and highly aggressive. Treatment strategies include chemoradiation, transcatheter arterial embol - ization and surgical resection, which has remained the mainstay treatment. Targeted therapies including mammalian target of rapamycin (mTOR) inhibitors such as Temsirolimus may offer some hope for progressive malignant EAMLs that are not amenable to other treatment modalities. We report a fatal case in a young female who presented with rapidly progressive metastatic EAML that did not respond to mTOR therapy. The literature has shown reduction in tumor burden with the use of mTOR inhibitors, but unfortunately due to the rarity of malignant EAML, a meaningful approach to treatment remains challenging.

Introduction

Angiomyolipomas, including epithelioid angiomyolipoma (EAML) are a sub type of Perivascular Epithelioid Cell tumors (PEComas) a family of mesenchymal tumors with a strong association with tuberous sclerosis.[1] The malignant variant of EAML is extremely uncommon and highly aggressive.[2] Treatment strategies including chemoradiation and transcatheter arterial embolization (TAE) have demonstrated some efficacy in localized and differentiated, progressive disease. Surgical resection has remained the mainstay treatment.[3] Targeted therapies including mammalian target of rapamycin (mTOR) inhibitors such as Temsirolimus may offer some hope for cases of progressive malignant EAMLs that are not amenable to surgical resection or other treatment modalities. We report a fatal case in a young female who presented with rapidly progressive metastatic EAML.

Case Report

This female patient was diagnosed on nephrectomy, at age 31, as having an epithelioid angiomyolipoma of the left kidney. Metastatic disease presented in the mediastinum 7 years later, at age 38. The tumor was characterized by nests of cells with abundant, clear to eosinophilic, polygonal cytoplasm (epithelioid features). There was marked nuclear pleomorphism with nuclear enlargement, irregularity, and eosinophilic macronucleoli. Multinucleated tumor cells were present. Histologic features of aggressive growth included mitoses and necrosis. Immunophenotyping of the original and metastatic tumors was characteristic of EAML, with positive staining for at least one melanocytic marker (Figure 1A-D).

One month prior to her last admission she presented with epigastric pain, intractable nausea and vomiting and was hospitalized for pancreatitis. Abdominal/pelvic computerized tomography scan showed in addition to pancreatitis findings, partial thrombosis of the superior mesenteric vein (SMV) with a lobulated soft tissue mass at the right cardiophrenic angle. The patient was treated for pancreatitis, stabilized and discharged home on oral anticoagulation. Repeat imaging on readmission revealed new hypodensities throughout the liver and lungs; new masses in the pancreas and uterus; enlargement of the right cardiophrenic mass; near-complete occlusion of the portal vein, IVC, and SMV; and a focal hypodensity in the right atrium suggestive of extension of a SVC thrombus (Figure 2), despite being on Warfarin with documented therapeutic INRs.

Fine needle aspiration biopsy of several lesions including the liver, pancreas, and cardio-phrenic mass all showed metastatic epithelioid angiomyolipoma. Debulking procedures to reduce tumor burden were not considered given the extensive intravascular involvement. The patient was started on temsirolimus and completed a total of 12 cycles but continued to show progression of metastatic disease. Five months later, she succumbed to the disease due to tumor burden with a complication of uncontrollable retroperitoneal bleeding.

Discussion

PEComa is a family of mesenchymal tumors, with a strong association with tuberous sclerosis, which includes angiomyolipomas (AML), clear cell sugar tumors (CCST) and pulmonary lymphangioleiomyomatosis.[4] A subtype of AML is the epithelioid angiomyolipoma (EAML). EAML is a rare tumor usually presenting during the fourth decade of life,[5] whose malignant variant is extremely uncommon and rather aggressive. In its malignant form the most common primary site is the kidney.[5] It has been reported that one third, of these primary tumors of the kidney have led to metastases and probable mortality.[2]

Most recently, clinicopathologic prognostic indicators have been reported. In one of the largest studies of atypical EAMLs (40 cases) Brimo *et al.* found that larger tumor size, older age, lymphovascular and renal vein invasion were seen more commonly in malignant EAMLs. They concluded that histological findings including an increased mitotic count (2> per 10 hpf), necrosis, atypical mitotic figures and nuclear atypia in greater than 70% of cells were predictive of malignant behavior. A tumor that displays three or more of these findings has an increased risk of malignancy.[6] Our patient was found to have recurrent, metastatic disease, with large tumor burden and histologic findings including necrosis, nuclear atypia (>70%), and atypical mitotic figures, meeting 3 out of 4 of Brimo's criteria for a bad prognosis. Also of note, pathologic features including tumor size greater than 7 cm, involvement of the renal vein and or perinephric fat tissue

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as well as the presence of TSC portend to poor prognosis in EAML.[7]

Individual cases of patients undergoing chemotherapy and or radiation treatment for malignant EAML have been reported. Doxorubicin did show a 50% reduction in tumor burden in a single individual.[8] But there have been reported poor responses to dacarbazine, carboplatin, cyclophosphamide as well as dacarbazine, ifostamide and mesna and no response reported for a patient receiving radiation.[9,10] There has been scant published data in regard to chemoradiation treatment likely due to the rarity of the disease as well as due to the emergence of other modes of treatment.

Treatment strategies for EAMLs are aimed at reducing tumor burden and delaying the progression of disease, they encompass chemoradiation, transcatheter arterial embolization (TAE), surgical resection and targeted therapies with mammalian target of rapamycin (mTOR) inhibitors. TAE treatments to localized tumors have shown significant reduction in tumor burden and control of bleeding.[11] Lee *et al.* demonstrated that TAE may be used as adjunct therapy to systemic treatment in progressive, metastatic EAMLs. Radiofrequency ablation (RFA) also has been shown to decrease tumor burden with a less complicated side effect profile in renal AML.[12] Surgical resection can be curative in localized disease but in metastatic or advanced disease it is performed for palliative effect only.

Therapy using Mammalian target of rapamycin (mTOR) inhibitors, such as temsirolimus and Everolimus have shown favorable responses in a few case reports with patients diagnosed with malignant EAMLs that are not amenable to surgical resection. In a report from Shitara *et al.,* a 52 year old male with recurrent EAML was treated with mTOR inhibitor everolimus. Two month CT follow up showed marked decrease in tumor size and no progression of disease over the next 7 months.[13] Along with a favorable side effect profile, Everolimus and other mtor inhibitors have at times shown a modest tumor burden reduction in the few case reports published of EAML. This was seen in which sirolimus and temsirolimus were single agents given to two different patients with EAML, resulting in overall decreased size and enhancement of malignant lesions.[14] Unfortunately, for the patient reported in our case study temsirolimus had no significant impact in controlling her progression of disease.

Similarly poor responses have been documented in other patients who have received mTOR inhibitors. Higa *et al.* reported a poor clinical response with rapid tumor growth after initiating a patient on sirolimus.[15] This result along with the poor clinical response from the patient presented in this report, lead one to postulate that inhibiting the mTOR pathway

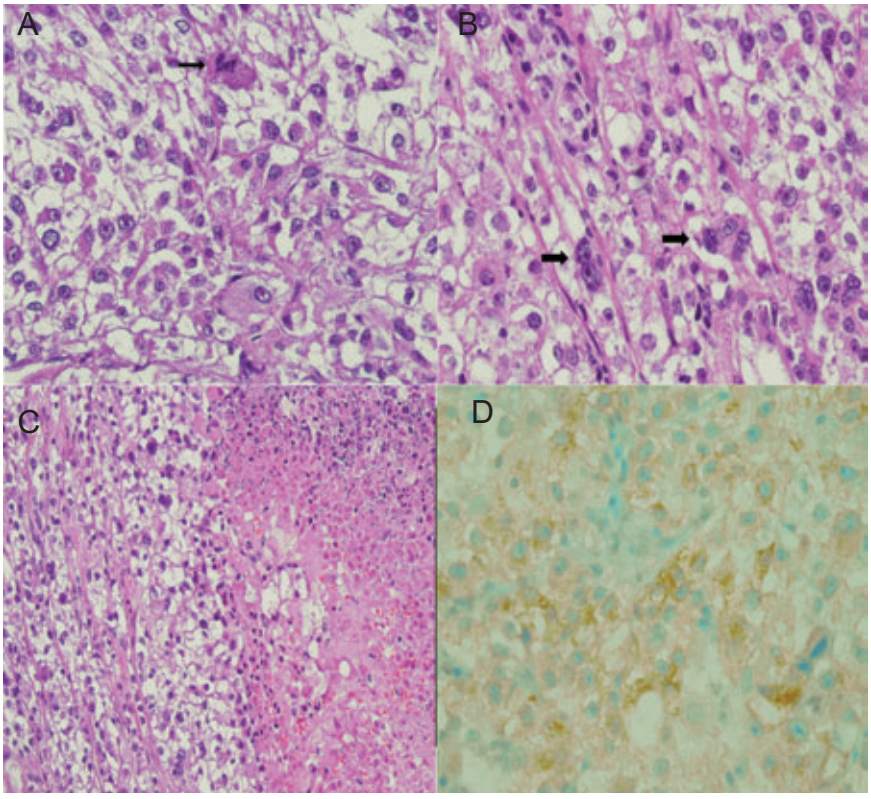

Figure 1. A) Nests of cells with abundant eosinophilic to clear cytoplasm and marked nuclear pleomorphism. Note atypical mitotic figure (arrow) [Hematoxylin and eosin, x500]; B) multinucleated tumor cells (arrows) [Hematoxylin and eosin, x500]; C) geographic necrosis (right) [Hematoxylin and eosin, x250]; D) positive immunoreactivity for Melan-A [x500].

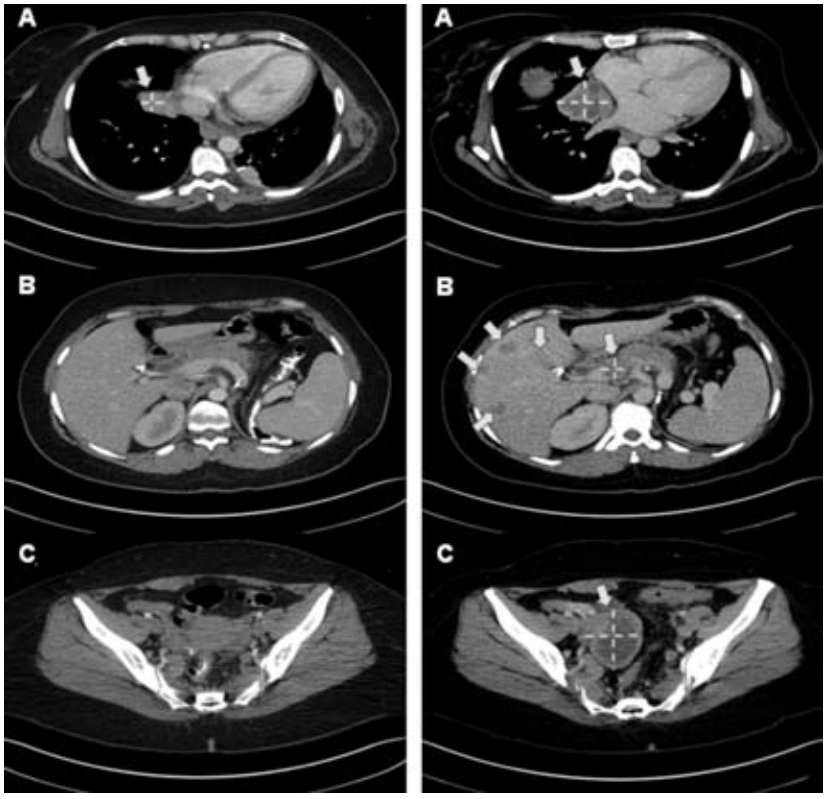

Figure 2. Computed tomography scan of abdomen and pelvis showing diffuse metastases involving the liver (B), pancreas (B) as well as a cardiophrenic mass (A) and right ovarian mass (C).

may at times only provide mild relief it at all in the progression of aggressive malignant EAML. The malignancy may feature a different pathway or is more heterogeneic in nature, possibly involving multiple genes and pathways leading to its proliferation.

Due to the rarity of EAML an overall meaningful approach to the treatment of these malignancies remains challenging. In order to advance in the treatment and overall understanding of EAML, further insight into targeted regiments, genetics and continuing reporting is needed to aid in prognosis, diagnosis and treatment of this rare and potentially fatal condition.

Conclusions

Reduction in tumor burden with the use of mTOR inhibitors has been demonstrated in isolated cases of malignant EAML but unfortunately due to the rarity of this entity a meaningful approach to the treatment of these tumors remain challenging. Our case represented a therapeutic challenge and did not show a favorable response to mTOR therapy with consequent mortality.

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