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Malignant Epithelioid Angiomyolipoma: Tumor and Metabolic Response to Everolimus as Evaluated With Positron Emission Tomography

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Keywords

Angiomyolipoma; Imaging; Kidney tumors; Lymphoma; Mammalian target of rapamycin

Introduction

Renal angiomyolipoma (AML) is a benign mesenchymal neoplasm with a classic triphasic histology, adipose tissue, epithelioid smooth-muscle—like cells, and abnormally thick-walled blood vessels.^{1–3} Although most AMLs occur in the kidneys, they also occur in other sites, such as the liver, lungs, uterus, vagina, ovaries, colon, lymph nodes, skin, bone, nasal and/or oral cavities, retroperitoneum, and adrenal glands.^{2,3} Epithelioid AML (eAML) is a rare, recently recognized subtype with a natural history of malignancy. There is little knowledge about the origin, treatment options, clinical course, and imaging evaluation for these aggressive tumors.^{2,4–6}

Inhibitors of the mammalian target of rapamycin (mTOR) protein were recently approved by the US Food and Drug Administration for various tuberous sclerosis—related lesions, including AML.⁷ Genetic analyses also reported mTOR activity in non—tuberous sclerosis-related AMLs. These studies provide functional evidence that mTOR activation is common to sporadic, non—tuberous sclerosis-related AMLs,⁸ which suggests the possibility that mTOR inhibitors such as everolimus and temsirolimus may be therapeutic for this class of disease.

This article focuses on 3 aims: (1) to highlight the fluorine-18 fluorodeoxyglucose (FDG) avidity of these tumors on positron emission tomography (PET) computed tomography (CT), which, to our knowledge, has not been previously reported, (2) to demonstrate the response of eAML to mTOR inhibitors, as suggested by other case reports, and (3) to show the concomitant occurrence of peripheral T-cell lymphoma (PTCL) in association with recurrent eAML.

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Disclosure

The authors have stated that they have no conflicts of interest.

Case Report

A 58-year-old man had a 3-cm AML monitored for the past 14 years. The AML remained stable on surveillance. Recent imaging showed a new enhancing mass with central extension and possible early renal vein tumor thrombus suspicious for renal cell carcinoma (Figure 1) associated with spontaneous left subcapsular hematoma. The patient had no evidence of metastatic or local regional disease, and no significant medical history except for hypercholesterolemia. He smoked (12 pack-years) but had quit smoking 25 years previously. There was no supraclavicular, cervical, or occipital adenopathy, and no abdominal tenderness or intrathoracic disease. The patient underwent a successful left laparoscopic radical nephrectomy without adrenalectomy 2 days after referral to our center.

Pathology findings revealed a 5-cm eAML and an additional smaller triphasic renal AML of the kidney (3.5 cm), with negative surgical resection margins. The eAML was composed predominantly of pleomorphic tumor cells with a rhabdoid appearance (Figure 2). Focally, spindle cell and adipocytic components were also noted. The smaller tumor had classic findings for a triphasic AML. Both tumors were diffusely positive for a panmelanoma cocktail (HMB-45 and MART-1) and negative for epithelial markers.

The patient was monitored every 3 months thereafter with CT of the abdomen and chest, which showed no abnormalities. Within 13 months of his initial surgery, he developed palpable adenopathy, worsening macular rash, and constitutional symptoms. Biopsy of a cervical lymph node, forearm skin punch, and bone marrow aspirate confirmed peripheral T-cell lymphoma (PTCL). On repeated scans, a large recurrence was noted in the left renal bed as well as worsening splenomegaly likely due to the lymphoma (Figure 3). The mass was bilobed and measured 4.6 by 8 cm. CHOP (cyclophosphamide, hydroxydaunomycin (doxorubicin), vincristine, and prednisone) chemotherapy was initiated with excellent symptomatic response in the first cycle. A percutaneous biopsy confirmed recurrent eAML.

An FDG PET-CT performed 14 months after the patient's initial surgery and after initiation of CHOP showed that the lymph nodes had regressed in size and metabolic activity, and that an FDG-avid mass had enlarged in the left nephrectomy bed. On the basis of previous reports,^{9,10} everolimus was added to his regimen when starting on cycle 2 of CHOP. The patient continued to improve clinically. Repeated imaging after initiation of everolimus showed a dramatic reduction in size and metabolic activity in the eAML (Figure 3).

The patient experienced myelotoxicity, which required dose reduction of CHOP, and he was unable to continue beyond cycle 6, but his PTCL appeared to be in complete remission. After he received four 15-day courses of everolimus therapy, plans were made for surgical resection of the residual mass. Shortly before the surgery, however, the patient developed rapidly worsening systemic symptoms, and recurrent PTCL was diagnosed. His clinical condition deteriorated rapidly over the next 2 months with fever, progression of lymphoma, and failure to respond to salvage chemotherapy with 1 cycle of ifosfamide, carboplatin, and etoposide. The patient's prognosis was deemed to be very poor due to the refractory lymphoma, and 20 months after onset of his original nephrectomy, the patient was admitted to hospice.

Discussion

We report a case of eAML by highlighting the role of FDG PET-CT as a useful imaging tool, the use of everolimus as effective therapy, and the concomitant occurrence of eAML and PTCL. Unfortunately, our patient died of refractory PTCL before he could reap the full benefit of the everolimus therapy coupled with surgical consolidation for the eAML. We

believe that the PET response was a result of the everolimus, based on the biopsy of the area that underwent changes with FDG uptake on PET and the timing of therapy (Figure 4).

One of the first reports of eAML was made by Delgado et al,¹¹ in which they reported 5 renal tumors initially misdiagnosed as renal cell carcinoma, adrenocortical carcinoma, or sarcoma, and that were later discovered to have common morphologic and immunohistochemical features; all were composed of epithelioid cells and stained positive for melanocytic markers. Several reports of identical tumors have been published, which showed local recurrence, distant metastases, and death from disease in a subset of patients.^{4,12}

The term “epithelioid angiomyolipoma” was used and subsequently adopted as a distinct entity by the World Health Organization Classification of Tumors as a form of AML with malignant potential.¹ A recent study of eAML showed local recurrence and/or distant metastases in one-third of cases.⁴ Martignoni et al⁵ described eAML as a distinct clinicopathologic variant of AML and histologically described it as an unusual renal tumor composed exclusively of large, atypical, densely packed, clear to eosinophilic epithelioid cells.^{1,5,6} Aydin et al² identified eAML with a mean epithelioid component of 51% in 8% of cases. Only 1% of their series represented pure eAML composed of 100% epithelioid component.

Immunohistochemical features indicative of eAML include the positive combination of HMB-45 and Melan-A.^{2,6} In a recent meta-analysis of 69 well-documented cases of eAML, the malignancy rate was 38%.¹³ Brimo et al⁴ described 34 patients with eAML, 9 (26%) showed signs of recurrence and/or distant metastases, and 4 died of their disease; of them, 2 had distant metastases at diagnosis.⁴

AMLs comprise approximately 1% of renal tumors removed and occur in the setting of tuberous sclerosis or sporadically.^{2,12,14,15} The kidney is the most common organ of classic AML and eAML.⁴ Our patient did not have diagnostic criteria for tuberous sclerosis.¹⁶ Although there is no standard therapy for eAML, the mTORC1 pathway was shown to be activated in eAML.¹⁷ The potential efficacy in this setting was shown in previously reported cases.^{9,10} There is a lack of clinical trials for eAML; therefore, the net sum of data supports use of mTOR inhibitors when surgery is not indicated.^{9,10}

Few studies have been published about FDG PET in the diagnosis of AML.¹⁸ Most published descriptions have documented AML as metabolically active on FDG PET.^{19–21} Another group found that patients with AML did not have increased FDG uptake but did have increased 11C-acetate metabolism.²² Although the CT appearance of renal AML is a major criterion in its assessment due to its fat content,¹⁸ eAML does not display the same characteristic imaging. Thus, this information could be helpful in the diagnosis, staging, and treatment response of these lesions. Furthermore, FDG PET is shown to be an effective measure and marker of disrupted glycolytic metabolism triggered by mTOR inhibitors as a major player in the regulation of signaling pathway cascade in glucose metabolism. In fact, increased FDG had previously been shown to be mTOR-dependent in kidney cancer.²³ More recently, FDG PET was shown to be a surrogate marker of drug efficacy in non—small-cell lung cancer, glioblastoma, an ovarian cancer model, or a drug dosing tool in preclinical studies during mTOR inhibition by using everolimus.^{24–27} Our case further contributes and reinforces this concept in the literature that FDG PET can be a valid marker of metabolic response to mTOR inhibitors independently from the type of tumor.

Prior data showed mTOR activity in AMLs that supported the use of mTOR inhibitors,^{8,28} and recent clinical trials led to approved use of everolimus for the treatment of tuberous sclerosis—related AML.²⁹ Relevant to our particular patient, there may also be an

abnormality in the mTOR pathway supported by the experimental use of everolimus in the treatment of lymphoma.³⁰

The short follow-up of this patient is one of the limitations of this report, due to the patient's coexistent PTCL being the ultimate cause of his death. Contamination of clinical and radiographic data from the 2 coexistent cancers was possible. However, we histologically documented this case of recurrent eAML, its progression during the first cycle of CHOP chemotherapy, which resulted in regression of the lymphoma, and the subsequent response of the eAML with the addition of everolimus.

Conclusion

This case illustrates the possible role of PET-CT on follow-up of known eAML, supports other case reports on the utility of mTOR inhibitors as an effective treatment option for recurrent or metastatic eAML, and demonstrates the unusual copresentation of PTCL with recurrent eAML. These data may prove useful in future clinical and research endeavors for this rare disease.

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Clinical Practice Points

- Epithelioid angiomyolipoma is a rare disease and a recently recognized subtype with a natural history of malignant behavior. There is a lack of knowledge about the origin, treatment options, clinical course, and imaging evaluation for these aggressive tumors.
- We present this case of a concomitant occurrence of peripheral T-cell lymphoma with local recurrence of an epithelioid angiomyolipoma, which showed significant avidity on fluorine-18 fluorodeoxyglucose positron emission tomography—computed tomography as well as a significant and evident response to everolimus that supports the utility of mammalian target of rapamycin inhibitors as an effective treatment option for advanced epithelioid angiomyolipoma.

Figure 1.
Computed Tomography, Showing a Left Renal Mass With Perinephric Hemorrhage (Left Panel) and a Known Renal Angiomyolipoma That had Been Observed and Unchanged for 14 Years (Right Panel)

Figure 2.

(A) Epithelioid Angiomyolipoma, Showing Diffuse Growth Pattern (H&E, Original Magnification $\times 10$). Inset: Tumor is Composed of Pleomorphic Cells With Rhabdoid Features and Nuclear Pleomorphism (H&E, Original Magnification $\times 20$). (B) Immunohistochemical Stain for Panmelanoma Antigen, Showing Diffuse Staining in Tumor Cells (HMB-45—MART-1, Original Magnification $\times 10$). (C) Another Tumor From the Same Patient Demonstrated Classic Triphasic Histology, Including Fat, Smooth Muscle, and Large-caliber Blood Vessels Within the Tumor (H&E, Original Magnification $\times 10$). (D) Immunohistochemical Stain for Panmelanoma Antigen, Showing Positive Staining, Concentrated Primarily in the Perivascular Areas and in the Smooth Muscle Component, Which is Typical for this Entity (HMB-45—MART-1, Original Magnification $\times 10$)

Figure 3.
(A) Top row, Positron Emission Tomography (PET) and Computed Tomography (CT) Before Everolimus (Maximum Standardized Uptake Value of 9.3 Measured in the Cranial Part of the Mass). (B) Bottom Row, PET-CT After Everolimus (Maximum SUV of 4.1 Measured at the Residual Mass)

Figure 4.

Diagnostic and Treatment Timeline

Abbreviations: CHOP = cyclophosphamide/hydroxydaunomycin (doxorubicin)/vincristine/prednisone; eAML = epithelioid angiosarcoma.