


## Case Report

# Metastatic epithelioid angiomyolipoma treated with everolimus in a patient receiving hemodialysis: A case report

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### Abbreviations & Acronyms

AML = angiomyolipoma  
 CT = computed tomography  
 EAML = epithelioid AML  
 HD = hemodialysis  
 HE = hematoxylin and eosin  
 HMB = human melanin black  
 MRI = magnetic resonance imaging  
 mTOR = mammalian target of rapamycin  
 PEComa = perivascular epithelioid cell tumor  
 PET = positron emission tomography  
 TAE = trans-arterial embolization  
 TSC = tuberous sclerosis complex

**Introduction:** A patient undergoing hemodialysis and being treated with everolimus for metastatic epithelioid angiomyolipoma has never been described in the literature, to our knowledge.

**Case presentation:** A 53-year-old woman who had undergone trans-arterial embolization for epithelioid angiomyolipoma was referred with a chief complaint about right knee pain. Hemodialysis had been started after the embolization. Needle biopsy specimens of tumors obtained from behind the right kidney and in the right femur were diagnosed as epithelioid angiomyolipoma metastases. The patient underwent treatment with everolimus and achieved a partial response after 6 months of treatment without serious adverse events.

**Conclusion:** Everolimus might be effective for patients with metastatic epithelioid angiomyolipoma who are undergoing hemodialysis.

**Key words:** epithelioid angiomyolipoma, everolimus, hemodialysis, mammalian target of rapamycin inhibitors, tuberous sclerosis.

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## Keynote message

We report a rare case of metastasis of EAML in bone that was treated with everolimus. It is important to note that everolimus may offer clinical benefit for patients with metastatic EAML who are undergoing HD.

## Introduction

EAML is an infrequently seen variation of AML with aggressive features similar to those of a malignant tumor. We report our rare experience of metastatic EAML in a patient undergoing HD who was treated with everolimus and review the available literature.

## Case presentation

A 53-year-old woman complaining primarily of right knee pain was referred to our hospital. She had been examined for convulsive attack in early childhood and diagnosed as having TSC complicated by subependymal nodules and lymphangiomyomatosis. She underwent selective TAE for hemorrhage from AML in 2011 and had begun HD. Later, because of bleeding from a residual aneurysm of AML, TAE of both renal arteries was performed. In 2015, the patient experienced right low back pain, and CT revealed two tumors of 2 cm in size behind the right kidney. Resection of these tumors after TAE had been judged as high risk in a previous hospital. Thus, TAE of the residual feeding artery and needle biopsies of the tumors were conducted. The specimen had shown sheet-like hyperplasia comprised of epithelioid cells. Immunohistochemically, the tumor cells had stained positive for Melan-A, smooth muscle actin, c-kit and vimentin, and negative for cytokeratin and HMB-45. Based on these results, the tumors had been diagnosed as an EAML (Fig. 1). After TAE, the tumor did not show significant changes. The patient then presented with right knee pain in 2017, at

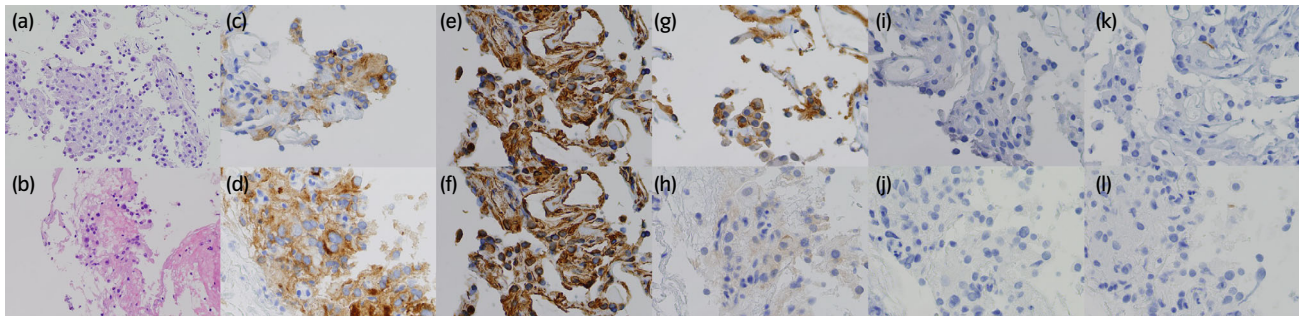
which time CT scans and PET-CT revealed a bone tumor in the distal right femur (Figs 2,3). Needle biopsies of the bone tumor performed for histological confirmation showed epithelioid cells with relatively large nuclei. Immunohistochemically, the tumor cells were positive for Melan-A and vimentin, weakly positive for c-kit, and negative for cytokeratin and HMB-45. As these features resembled those of the retroperitoneal EAML, the bone tumor was diagnosed as a metastasis of the EAML (Fig. 1). She was subsequently referred to our hospital for treatment with the mTOR inhibitor everolimus.

Considering the HD and her previous complications, we treated her with 5 mg everolimus per day. The patient tolerated the everolimus well with no serious adverse events. A PET-CT scan obtained 3 months later showed reduced accumulation in the two tumors behind the right kidney and in the bone metastasis (Fig. 3). On CT scan, the tumors behind the right kidney showed a significant reduction in tumor size, from 83 to 56 mm, resulting a partial response according to

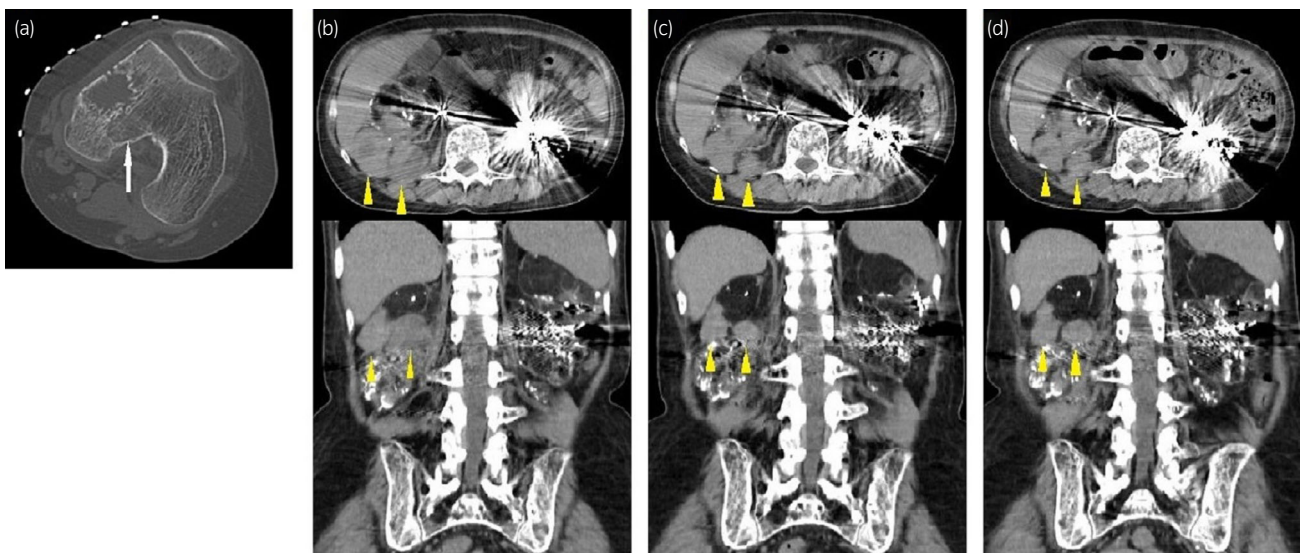
the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) after 6 months of treatment with everolimus (Fig. 2). Although tumor size and accumulation were reduced in the bone metastasis, on CT scan, the tumor behind the kidney had enlarged slightly after 9 months of treatment and showed increased accumulation on PET-CT after 1 year of treatment (Figs 2,3). We therefore increased the everolimus dose to 10 mg, which is continuing without signs of rapid disease progression.

## Discussion

EAML belongs to the PEComa family, which comprises tumors with perivascular epithelioid cell differentiation, advocated by the World Health Organization classification in 2002. Most PEComas are benign, but they can occasionally behave in a malignant manner, either as invasive tumors recurring locally or by developing distant metastases.<sup>1</sup> Histologically, EAML is characterized by the presence of diffuse



**Fig. 1** Histology and immunohistochemical staining of the retroperitoneal tumor and femoral tumor biopsy specimens: (a) primary tumor, HE ( $\times 20$ ), (b) bone tumor, HE ( $\times 20$ ), (c) primary tumor, Melan-A ( $\times 40$ ), (d) bone tumor, Melan-A ( $\times 40$ ), (e) primary tumor, vimentin ( $\times 40$ ), (f) bone tumor, vimentin ( $\times 40$ ), (g) primary tumor, c-kit ( $\times 40$ ), (h) bone tumor, c-kit ( $\times 40$ ), (i) primary tumor, cytokeratin ( $\times 40$ ), (j) bone tumor, cytokeratin ( $\times 40$ ), (k) primary tumor, HMB-45 ( $\times 40$ ), and (l) bone tumor, HMB-45 ( $\times 40$ ).



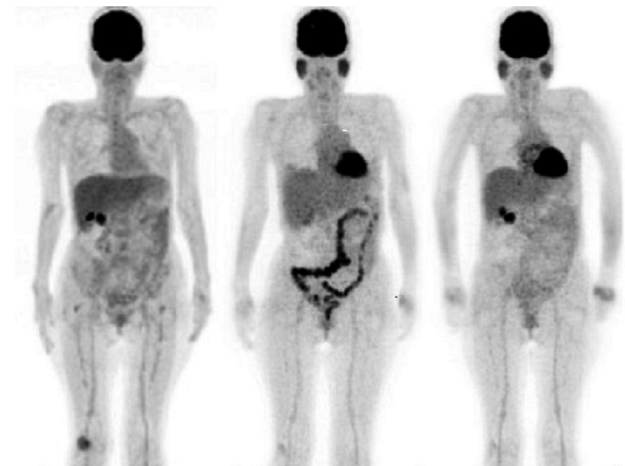
**Fig. 2** (a) CT scan showed the tumor in the right femur (arrow). (b) Abdominal CT scan showed EAML (arrow) behind the right kidney before treatment. (c) CT scan showed a reduction in tumor size (arrow) after everolimus administration for 6 months. (d) CT scan showed slight enlargement of the tumor (arrow) after everolimus administration for 9 months.

proliferation of atypical epithelioid cells and nuclear cells and nuclear atypia. In immunohistochemical staining, EAML is generally positive for HMB-45, Melan-A, smooth muscle actin, c-kit, and vimentin and negative for epithelial markers such as cytokeratin,<sup>2</sup> but HMB-45 and Melan-A can be negative in some patients.<sup>3</sup> In our patient, as the tumors had these characteristics, the final diagnosis was EAML. Brimo *et al.*<sup>4</sup> uncovered recurrences and Faraji *et al.*<sup>5</sup> observed metastasis in about 60% of the reported EAML cases. Cong *et al.* reported that the presence of hypointensity on T2 weighted image, restricted diffusion on diffusion-weighted image, round tumor-kidney interface, reticular, and marked enhancement (rapid wash-in and wash-out) should further raise suspicion for renal EAML on MRI.<sup>6</sup>

EXIST-2 is a randomized, double-blind, phase 3 trial that showed a significant reduction in AML volume compared with a placebo in TSC patients.<sup>7</sup> To our best knowledge, there are only five reported cases of malignant EAML treated with everolimus. As in our case, these other EAML cases all showed a strong response to everolimus, although the treatment periods were shorter than that in our patient (Table 1).<sup>8–12</sup> Citak *et al.*<sup>8</sup> reported a case of local recurrence after nephrectomy using everolimus as second-line therapy. After 3 months of

treatment, CT revealed almost complete remission, but after 8 months of treatment, progression of the tumor had occurred. Lattanzi *et al.*<sup>9</sup> reported a case of recurrence and metastasis of EAML in which everolimus was effective for 8 months. Reports of the other three cases similarly noted that EAMLs responded to everolimus for 2–7 months. Everolimus was administered in these five cases exhibiting local recurrence or development of distant metastases after nephrectomy. The above results suggest that everolimus may have exerted a beneficial effect in patients with metastatic EAML.

Reports on treatment of renal cell carcinoma in patients receiving HD have become common. Although the efficacy of mTOR inhibitors such as everolimus in patients receiving HD is not well documented in the literature, neither temsirolimus nor everolimus concentrations were significantly affected by HD in patients with renal cell carcinoma in comparison with those not receiving HD.<sup>13,14</sup> No serious side effects were observed with normal 10 mg/day administration in some reports, and none recommended a special administration schedule. However, everolimus 5 mg/day was administered in the present patient in consideration of social factors such as not being able to hospitalize the patient. In addition,



**Fig. 3** Radiographic tumor activity on PET over time indicating (left-to-right): baseline pre-everolimus scan, best response to everolimus after 3 months, progression on everolimus after 12 months.

SUVmax	Retroperitoneum	10.17	3.43	10.14
	bone	4.51	1.62	1.33

SUVmax = maximum standardized uptake value.

**Table 1** Reported cases of EAML treated with everolimus

Case no.	Age (years)	Sex	Line of therapy	Metastatic lesion	Duration (months)	Response	HD	TSC	Reference no.
1	12	Male	2nd	Retroperitoneum	8	+	–	+	8
2	38	Male	1st	Retroperitoneum, mesentery	8	+	–	–	9
3	58	Male	1st	Retroperitoneum	2	+	–	–	10
4	52	Male	1st	Liver, spleen, pelvis	7	+	–	–	11
5	50	Female	1st	Lung, liver, pelvis	6	+	–	–	12
6	53	Female	1st	Retroperitoneum, bone	12	+	+	+	Present case

patients can still take an increased dose of 10 mg of everolimus without major side effects. For patients on long-term maintenance HD, it is desirable to adjust the dose on the basis of the complications each patient suffers. The dose and scheduling of molecular targeted therapy for a patient receiving HD remain a major challenge. We look forward to standard guidelines for patients receiving HD.

Although one report of EAML showed limited efficacy of doxorubicin, other therapies were ineffective.<sup>15</sup> As mentioned above, although an mTOR inhibitor may appear to be effective in the treatment of EAML, the long-term effects of this therapy are unknown. Thus, standard therapy for metastatic EAML remains to be clarified. Lattanzi *et al.*<sup>9</sup> reported treatment of a patient with metastasized EAML with anti-PD-1 immune checkpoint inhibitor nivolumab in the second-line setting. The patient achieved near-complete response that has continued for 2 years after treatment. We hope immune checkpoint inhibitors such as nivolumab will become a treatment option for malignant EAML. Due to rareness of metastases of EAML, no consensus has been reached on how to use these drugs and to select surgical resection in clinical practice. Going forward, further case reports and studies will be required to establish a standard therapy for metastatic EAML.

## Conflict of interest

The authors declare no conflict of interest.

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