

## Sirolimus and Temsirolimus for Epithelioid Angiomyolipoma

A 24-year-old man with familial tuberous sclerosis complex (TSC) presented to University of Texas Southwestern (Dallas, TX) in February 2009 with abdominal pain, vomiting, and generalized weakness. Five months previously, at another institution, he had undergone a right radical nephrectomy of a 24-cm epithelioid angio-

myolipoma (EAML) that ruptured during surgery. Pathologic examination of the tumor at our institution showed sheets of epithelioid cells surrounding haphazardly shaped vessels embedded in a hyalinized stroma with focal myxoid change (Fig 1A; H&E, hematoxylin and eosin). The neoplastic cells were large, round or oval, with eccentric round nuclei, prominent nucleoli, and eosinophilic cytoplasm. They resembled ganglion cells and rare mitoses were appreciated (one in ten high-power fields). Immunohistochemical studies showed that the neoplastic cells expressed, as is characteristic of this tumor type,

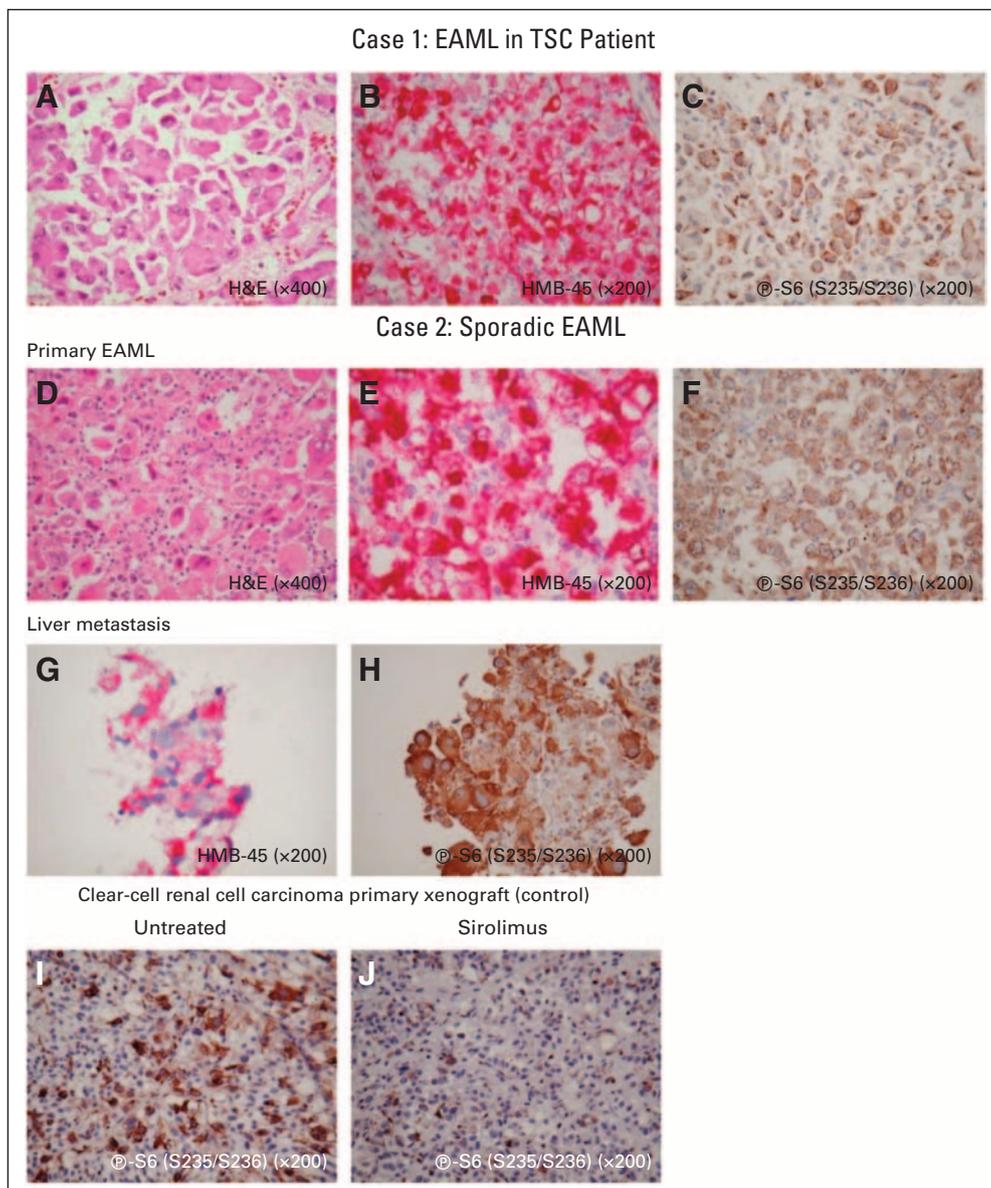


Fig 1.

the melanocytic markers HMB-45 and Melan-A/MART-1 (Fig 1B and data not shown). At presentation to our institution, the patient appeared debilitated and pale, he was tachycardic to 140 bpm but not hypotensive, and his abdomen was markedly distended and diffusely tender. Laboratory studies showed a hemoglobin level of 3.8 g/dL. After transfusion with seven units of packed RBCs (PRBCs), a magnetic resonance imaging of the abdomen was performed and it demonstrated displacement of retroperitoneal and intra-abdominal contents by a 20-cm complex mass arising in the right renal fossa, which exhibited mixed signal intensity consistent with prior hemorrhage. The study could not be completed due to severe nausea, and an enhanced computed tomography (CT) study was subsequently obtained (Fig 2A). An angiogram was performed and showed the mass to be extensively vascularized by branches of the right hepatic artery, a residual right adrenal artery, right T11-T12 intercostal and L1-L4 lumbar branches, as well as the superior mesenteric artery. Supplying branches from the hepatic and adrenal arteries, as well as the L1-L4 arteries, were successfully embolized, but bleeding continued, and to maintain a hemoglobin level over 8 g/dL, eight units of PRBC had to be transfused over the course of the following week. Not surprisingly given bowel compression by the mass, the patient was unable to take food orally, and he was started on total parenteral nutrition. Several core biopsies were obtained and showed sheets and nests of epithelioid cells resembling those from the original EAML amid extensive hem-

orrhage and necrosis. On the third week after admission, bleeding continued, and seven additional units of PRBC were administered. Surgery was considered, but surgical mortality was deemed prohibitively high. Medical therapy was similarly considered, but there is no standard therapy for EAML, and chemotherapy has limited benefit.<sup>1,2</sup> A discussion was held with the patient about empirical treatment with sirolimus, and towards the end of February, he started sirolimus at 6 mg daily. Soon after the initiation of sirolimus, the patient's hemoglobin stabilized, and no further transfusions were required. Already in March, a CT scan showed the mass to be decreased in size with a markedly reduced area of peripheral enhancement (Fig 2B). Of note, 3 weeks after the initiation of sirolimus, blood cultures grew *Candida albicans*. A previously placed peripherally inserted central line was removed; a transthoracic echocardiogram showed no vegetations; and the patient was treated with antifungals according to sensitivities, with multiple subsequent blood cultures being negative. Two and a half months after admission, the patient was discharged to a rehabilitation facility, and 1.5 months later, at the end of May, a CT scan showed the mass to be markedly decreased in size and predominantly necrotic, with a thin ring of peripheral enhancement (Fig 2C), and these findings remained stable (Fig 2D).

The second case is that of a 78-year-old man with no family history of TSC or other manifestations of the disease who presented in September 2006 to North Shore University Hospital (Manhasset, NY)

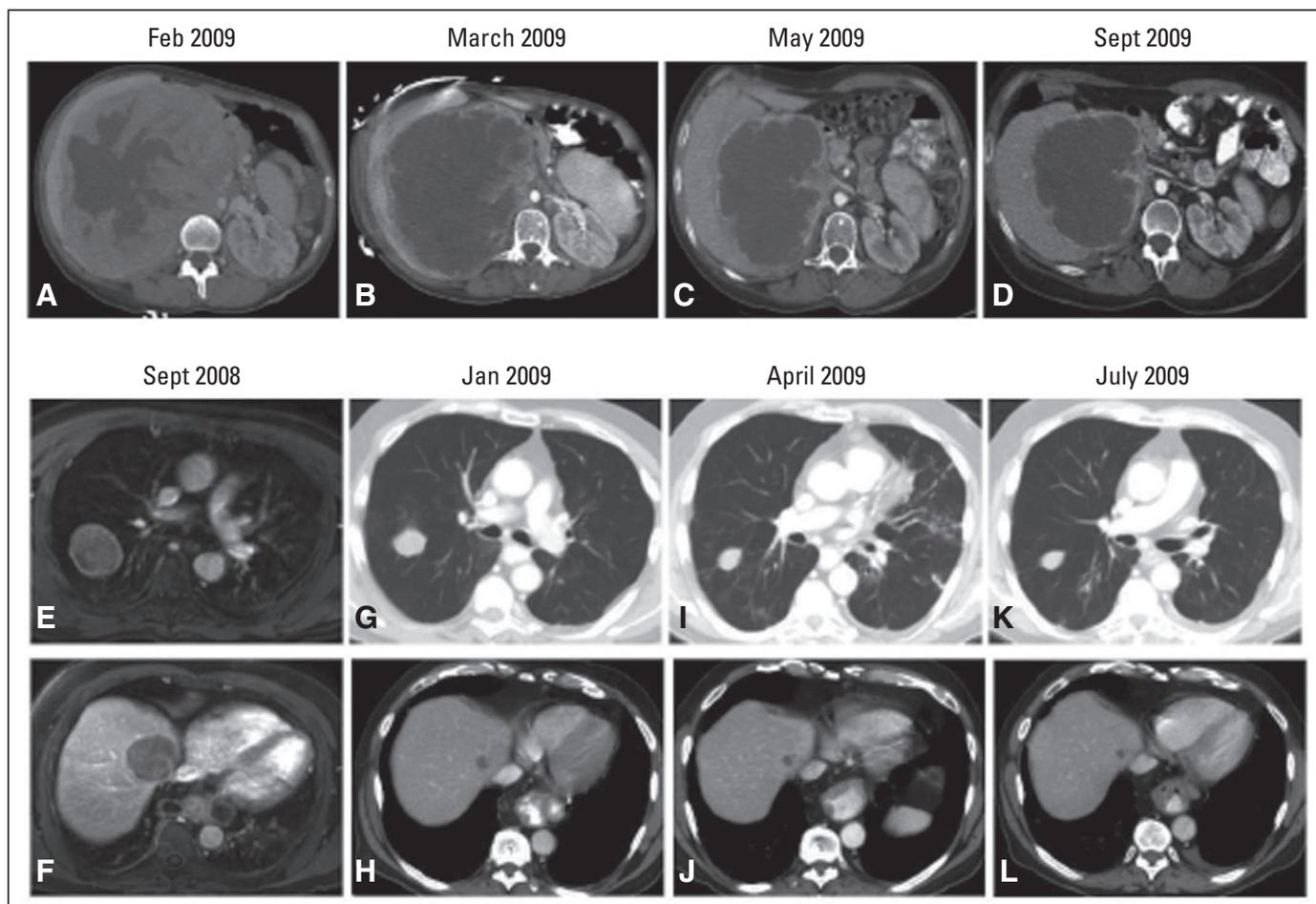


Fig 2.

with weight loss and was found to have a 14-cm left renal mass, which was resected and turned out to be an EAML. Pathological slides were reviewed at University of Texas Southwestern, and except for a lymphoplasmacytic stromal reaction, the findings were similar to those of the first case (compare Figs 1D and 1A). In addition, the epithelioid cells similarly expressed HMB-45 (Fig 1E) and Melan-A/MART-1 (data not shown). The patient did well until approximately 1 year later, when he was found to have a 6-cm mass in the liver, and a 1.7-cm mass in the renal bed. Percutaneous liver biopsy showed epithelioid cells undistinguishable from the original renal mass with strong expression of HMB-45 (Fig 1G). In November, the liver mass, which by that time had reached 14 cm, was resected. While the renal mass was initially stable, it subsequently grew and in May 2008 was resected and similarly showed EAML. Multiple additional metastasis developed subsequently and a magnetic resonance imaging in September of 2008 showed, among others, a 5-cm right lung mass (Fig 2E), a new 5.4-cm lesion in the dome of the liver (Fig 2F), and a 4-cm renal bed mass. At that time, the patient was started on temsirolimus. Serial CT scans since then showed steady reduction in the size of masses (Figs 2G to 2L), with the most recent scan in July 2009 showing complete resolution of the nephrectomy bed mass, and persistent reduction of the lung and liver masses (Figs 2K and 2L). A dose reduction was required for thrombocytopenia, and treatment was intermittently discontinued because of interstitial pneumonitis.

Herein, we report two patients with EAML treated with either sirolimus or temsirolimus, which is largely a sirolimus prodrug.<sup>3,4</sup> In the first patient, the EAML developed in the context of TSC, and in the second it arose in the absence of TSC manifestations. While little is known about EAML, an uncommon malignancy, substantially more is known about its benign counterpart, angiomyolipoma (AML), in the context of which EAMLs sometimes arise. AML is a benign mesenchymal tumor composed of abnormal blood vessels, smooth muscle cells, and adipose tissue. While most AMLs are sporadic, the incidence of AMLs in patients with TSC is quite high (55% to 75%).<sup>5</sup> The increased predisposition to AML development in TSC patients suggests that the genes disrupted in TSC, the tuberous sclerosis complex 1 (*TSC1*) and 2 (*TSC2*) genes, may contribute to the pathogenesis also of sporadic AML. Indeed, the *TSC2* gene has also been found to be mutated in sporadic AML.<sup>6</sup> At the molecular level, the *TSC1* and *TSC2* genes encode proteins that form a protein complex (TSC1/TSC2) that functions to negatively regulate mammalian target of rapamycin complex 1 (mTORC1).<sup>7</sup> Thus, when the TSC1/TSC2 complex is disrupted, mTORC1 is inappropriately activated, and this has been observed in AML, in the context of both TSC,<sup>8</sup> as well as in the sporadic setting.<sup>9</sup> mTORC1 functions as a serine/threonine kinase, and it plays a critical role in regulating protein translation and cell growth.<sup>10</sup> In addition, we have previously shown that TSC1/TSC2 disruption results in an mTORC1-dependent activation of the hypoxia-inducible factor and a concomitant increase in vascular endothelial growth factor,<sup>11</sup> which may contribute to the prominent vascularization observed in AMLs. Importantly, there exists a specific inhibitor of mTORC1—sirolimus.<sup>12</sup> In a sirolimus discontinuation phase I/II trial enrolling AML patients, the size of AML lesions decreased by approximately 50% after 12 months on sirolimus, and after its discontinuation, AML lesions increased in size.<sup>13</sup> While a definitive trial has not been conducted, the data suggest that sirolimus may have some activity against benign AML. While EAML shares some features with AML, such as reactivity with melanocytic markers,<sup>2,14</sup> EAML differs signifi-

cantly from AML both histologically and clinically. Histologically, EAML is composed almost exclusively of sheets of epithelioid cells that exhibit features characteristic of aggressive disease including marked nuclear atypia and occasionally increased mitoses, which may be abnormal.<sup>2</sup> In addition, as in the second patient, unlike AML, EAML metastasizes.<sup>1,2</sup> There is no standard therapy for EAML, and anecdotal reports of various chemotherapy regimens show overall poor outcomes.<sup>1</sup> Importantly, the mTORC1 pathway was recently shown to be activated in EAML,<sup>15</sup> and this is consistent with our results. In both patients, the epithelioid cells exhibited high levels of phosphorylated ribosomal S6 (S235/236) protein, which is an indicator of mTORC1 activity (Figs 1C, 1F, and 1H). In fact, as shown in primary clear-cell renal cell carcinoma xenografts (shown as a control), sirolimus effectively inhibits mTORC1 signaling and S6 phosphorylation (compare Figs 1I and 1J). Both patients were treated empirically with mTORC1 inhibitors, and in both cases we observed significant tumor responses and substantial clinical improvement. Our cases also illustrate some of the most serious, albeit uncommon, adverse effects of mTORC1 inhibitors including interstitial pneumonitis and a predisposition to opportunistic infections. These two cases suggest that mTORC1 inhibitors may be effective against EAML. While the role of mTORC1 inhibitors in AML is being explored in clinical trials, there are no studies we are aware of evaluating mTORC1 inhibitors specifically in malignant EAML. EAMLs are uncommon, and this question may not be addressed in the foreseeable future. With the information currently available, it is our opinion that mTORC1 inhibitors represent the best treatment option for patients with unresectable EAML.

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#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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