Scientific Research

Tumor Response to Temsirolimus for Epithelioid Angiomyolipoma and Novel Mutation of *SMARCB*1/*INI*1 Tumor Suppressor Gene

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Abstract

Epithelioid angiomyolipoma (EAML) is a rare morphologic variant of classic angiomyolipoma (AML), showing potentially malignant phenotype. AML is a benign mesenchymal tumor, which shows frequent inactivating mutations of *TSC*1 (encodes harmartin) or *TSC*2 (encodes tuberin) genes. Disruption of harmatin-tuberin complex and subsequent inappropriate activation of mTOR pathway is a distinct feature of AML. Thus, mTOR pathway inhibitors have shown significant clinical response in AML. Compared to the great success of mTOR inhibitors in AML, there is no standard therapy for EAML yet. Here, we present a patient with EAML who responded well to mTOR inhibitor (temsirolimus) but suffered rapid disease progression after cessation of temsirolimus. In addition, we performed Cancer Hotspot Panel (Ion AmpliSeq™) analysis to identify novel tumorigenic properties of EAML. Of note, Cancer Hotspot Panel analysis revealed novel missense mutation in *SMARCB*1 (c.1119-41G > A) tumor suppressor gene and subsequent immunohistochemistry analysis also revealed weak and partial losses of *SMARCB*1/*INI*1 protein in nuclei of tumor cells. In this study, we suggest that mTOR inhibitors also can be effective against EAML. However, the

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long-term efficacy of mTOR inhibitors in EAML needs to be supported in further studies. Furthermore, we speculate that the newly found missense mutation of *SMARCB*1/*INI*1 gene can be the possible novel tumorigenic properties of EAML and highlights the possibility of further novel targeted therapy beyond mTOR inhibitors in EAML.

Keywords

Epithelioid Angiomyolipoma, Temsirolimus, *SMARCB*1/*INI*1

1. Introduction

Angiomyolipoma (AML) is a benign mesenchymal tumor, which occurs most commonly in kidney. AML has strong association with tuberous sclerosis complex (TSC), caused by mutations that inactivate either *TSC*1 (encodes harmartin) or *TSC*2 (encodes tuberin) [1] [2]. The harmatin-tuberin complex functions to regulate the activity of the mammalian target of rapamycin complex 1 (mTORC1) negatively [3]-[5]. Actually, disruption of harmatin-tuberin complex and subsequent inappropriate activation of mTOR pathway has been observed in TSC-associated AML, as well as in the sporadic AML [6] [7]. Recent clinical trials have confirmed significant benefit of mTOR pathway inhibitors (sirolimus and everolimus) in patients with AML, showing a volume reduction of nearly 50% and response rate of 42% [8] [9].

Epithelioid angiomyolipoma (EAML) is a rare morphologic variant of classic AML. Pathologically, EAML is characterized by predominant proliferation of epithelioid cells showing nuclear atypia and increased mitoses [10] [11]. Clinically, EAML is classified as potentially malignant neoplasm, in contrast to benign nature of AML [12]. Compared to the great success of mTOR inhibitors in AML, there is no standard therapy for EAML yet. One report showed disappointing results of cytotoxic chemotherapy and only a few case reports showed effectiveness of mTOR inhibitors in EAML [10] [13] [14]. Furthermore, there has been no known possible mechanism explaining its clinically aggressive character, beyond *TSC*1/*TSC*2 mutation with mTOR pathway activation.

Here, we report a patient with EAML who showed dramatic response to mTOR inhibitor (temsirolimus) but suffered from rapid disease progression after cessation of treatment. Furthermore, for the first time, we report a novel mutation of *SMARCB*1/*INI*1 tumor suppressor gene in EAML.

2. Materials and Methods

2.1. Ethics Statement

The protocol was approved by the Samsung Medical Center Institutional Review Board (SMC IRB), and the study was conducted in accordance with the 1996 Declaration of Helsinki. Written informed consent was obtained from the patient for use of the sample in the research.

2.2. DNA Preparation

DNA was extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. Unstained 4-µm-thick tissue sections were deparaffinized, and tumor tissue was manually microdissected using as a guide an H&E-stained slide from the same block. DNA was extracted using DNA extraction kit (Qiagen, CA, USA). A Qubit DNA high-sensitivity assay kit (Life Technologies) was used to quantify purified DNA.

2.3. Cancer Hotspot Panel (Ion AmpliSeq™) Analysis

Library preparation for each sample was performed using the IT AmpliSeq 2.0 Beta kit and IT AmpliSeq cancer panel primers (Life Technologies) following the manufacturer's instructions. Briefly, 10 ng of DNA was amplified by polymerase chain reaction (PCR) with the Ion AmpliSeq Cancer Panel Primer Pool and Ion AmpliSeq HiFi Master Mix with the protocol recommended by the manufacturer. The 46 genes included in this panel are *ABL*1, *EZH*2, *JAK*3, *PTEN*, *AKT*1, *FBXW*7, *IDH*2, *PTPN*11, *ALK*, *FGFR*1, *KDR*, *RB*1, *APC*, *FGFR*2, *KIT*, *RET*, *ATM*, *FGFR*3, *KRAS*, *SMAD*4, *BRAF*, *FLT*3, *MET*, *CDH*1, *GNA*11, *MLH*1, *SMO*, *CDKN*2A, *GNAS*, *MPL*, *SRC*,

*CSF*1*R, GNAQ, NOTCH*1, *STK*11, *CTNNB*1, *HNF*1*A, NPM*1, *TP*53, *EGFR, HRAS, NRAS, VHL, ERBB*2, *IDH*1, *PDGFRA, ERBB*4, *JAK*2, *PIK*3*CA* and *SMARCB*1. Library concentration was determined with an Agilent High Sensitivity DNA Kit (Agilent Technologies, Inc). Sequencing was performed using the Ion PGM (Personal Genome Machine) 200 Sequencing Kit according to the manufacturer's instructions on Ion 316 Chips. For bioinformatics analysis, Ion Torrent platform-specific pipeline software (Torrent Suite version 2.0; Life Technologies Corporation) was used.

2.4. Immunohistochemistry

Immunohistochemical analyses were performed using a streptavidin-biotin-peroxidase method (Histofine; Nichirei, Tokyo, Japan). The primary monoclonal antibody used in this patient was BAF47, an antibody to the *INI*1 gene product (clone 25; 1:250; 20 min microwave; BD transduction Laboratories, San Diego, CA, USA). Non-tumor tissue, including entrapped normal tissue, inflammatory cells, and endothelial cell tissue, were used as a positive control.

3. Results

3.1. Case History

A 58-year-old man was referred to medical oncology clinic at Samsung Medical Center with multiple intraabdominal masses. He had been diagnosed with malignant monotypic epithelioid angiomyolipoma that had formed left renal mass eleven years ago, which had been subsequently surgically resected. During the past ten years, the disease has recurred six times at multiple sites, including previous operation site, omentum, retroperitoneum, left psoas muscle, and liver. The patient had received a number of surgical resection, radiotherapy, and radiofrequency ablation for the relapsed disease and treatment history after relapse was summarized in **Table 1**. Pathology specimen obtained from surgery on the 6th relapse re-confirmed the malignant monotypic epithelioid angiomyolipoma with predominant large epithelioid cells with clear cytoplasm, large hyperchromatic nuclei and multinucleation. The tumor cells were positive for Human Melanoma Black-45 (HMB-45). However, follow-up abdominopelvic computed tomography (CT) after 12 months showed multiple recurrent intraabdominal masses with largest one located in anteroinferior aspect of pancreas head (**Figure 1(a)**). The patient already had received repeated surgery due to relapsed disease and palliative chemotherapy was considered preferentially rather than prompt further surgical resection.

Accordingly, we started temsirolimus therapy at a dose of 25 mg intravenously once per day on day 1 and 8, every 4 weeks. After 4 cycles of treatment, follow-up abdominopelvic CT showed a volume reduction with dramatic cystic degeneration of the peripancreatic mass, indicating significant response to temsirolimus (**Figure 1(b)**). However, 4 months later, follow-up abdominopelvic CT showed a volume increase with a newly developed enhancing soft-tissue portion in the previous degenerated cystic peripancreatic mass (**Figure 1(c)**). At this time of disease progression, after obtaining written informed consent (using the form approved by the SMC Institutional Review Board), we performed Cancer Hotspot Panel (Ion AmpliSeq™) analysis. At the same time, we started everolimus therapy (7.5 mg orally once daily) for 3 weeks followed by a 1-week rest period. Treatment was repeated every 4 weeks. The patient has received 2 cycles of everolimus treatment and the patient is now stable in partial response.

Table 1. Treatment history after relapse of EAML.

| Disease status	Sites of release	Treatment
1st relapse	Previous nephrectomy site	Resection
2nd relapse	Retroperitonum with extension to omentum and transverse colon	Resection
3rd relapse	Retroperitoneum with extension to stomach	Resection followed by radiotherapy
4th relapse	Liver	Radiofrequency ablation
5th relapse	Left psoas muscle	Resection followed by radiotherapy
6th relapse	Peritoneum	Resection
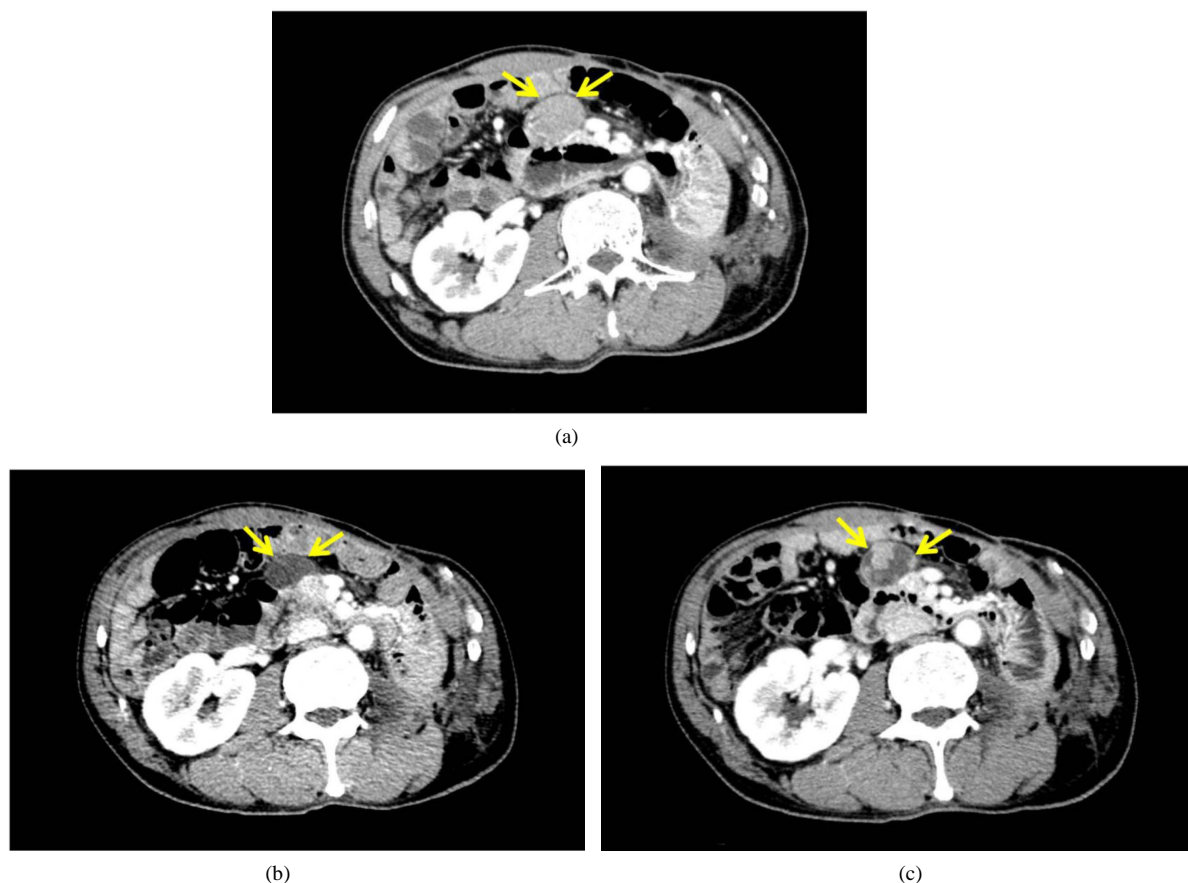
Figure 1. A 58-year-old man with recurrent EAML at anteroinferior aspect of pancreas head. Abdominopelvic CT was taken. (a) Before initiation of treatment with temsirolimus; (b) After 4 cycles treatment with temsirolimus; (c) At the time of disease progression, further 4 months later after cessation of temsirolimus.

3.2. Cancer Hotspot Panel (Ion AmpliSeq™) Analysis

Cancer Hotspot Panel (Ion AmpliSeq™) analysis of this patient revealed missense mutation in *SMARCB*1 (c.1119-41G > A) tumor suppressor gene. No mutations are detected in other oncogenes or tumor suppressor genes (ABL1 EZH2 JAK3 PTEN AKT1 FBXW7 IDH2 PTPN11 ALK FGFR1 KDR RB1 APC FGFR2 KIT RET ATM FGFR3 KRAS SMAD4 BRAF FLT3 MET CDH1 GNA11 MLH1 SMO CDKN2A GNAS MPL SRC CSF1R GNAQ NOTCH1 STK11 CTNNB1 HNF1A NPM1 TP53 EGFR HRAS NRAS VHL ERBB2 IDH1 PDGFRA ERBB4 JAK2 PIK3CA).

Oncogenes and tumor suppressor genes with SNPs are as follows: ERBB4, FGFR3, PDGFRA, KDR, CSF1R, RET, HRAS, FLT3, STK11, and *SMARCB*1. Detailed information about SNPs found in this patient is summarized in **Table S1**.

3.3. Immunophenotypic Analysis of *SMARCB*1/*INI*1 Protein

To investigate the inactivation of *SMARCB*1/*INI*1 at protein level, immunohistochemistry was done. Immunohistochemistry showed weak and partial losses of *SMARCB*1/*INI*1 protein in the nuclei of tumor cells (**Figure 2(a)**) compared to positive control (**Figure 2(b)**).

4. Discussion

Here, we present a case with EAML who showed dramatic response to temsirolimus but suffered from rapid disease progression after cessation of treatment. Furthermore, we report a novel mutation of *SMARCB*1/*INI*1 tumor suppressor gene and reduced *SMARCB*1/*INI*1 protein expression in EAML.
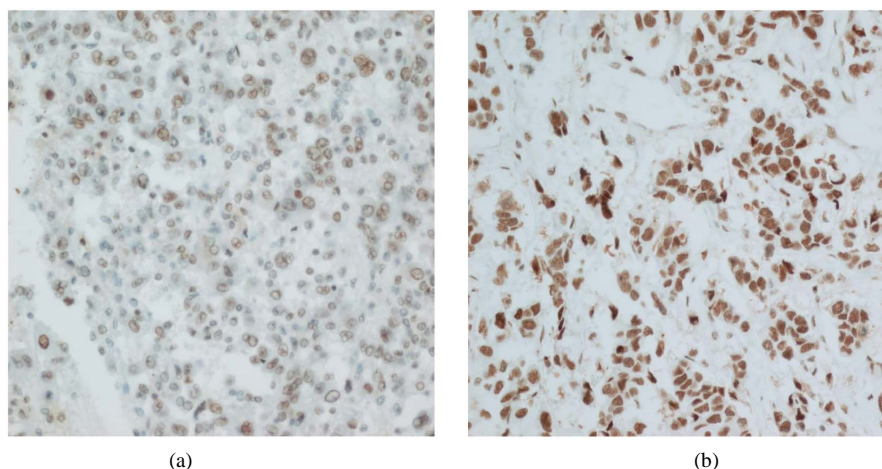
Figure 2. Pathological examination of tumor and results of immunohistochemistry. (a) Weak and partial losses of *SMARCB*1/*INI*1 protein in nuclei of tumor cells; (b) *SMARCB*1/*INI*1 protein in nuclei of positive control.

Recent clinical trials have proven the effectiveness of mTOR pathway inhibition with sirolimus or everolimus in patients with AML associated with TSC [8] [9]. However, little is known about the effectiveness of mTOR inhibitors in EAML, which is potentially malignant subtypes of AML. Some reports suggested that mTOR inhibitors were effective in EAML [13]-[15]. On the contrary, others reported that mTOR inhibitors were not effective in EAML [16] [17]. The present case of EAML showed initially significant response to temsirolimus but rapidly progressed after cessation of temsirolimus therapy. Initial dramatic response to temsirolimus in this patient implies that mTOR pathway activation caused by inactivating TSC1/TSC2 mutations can also be one of pathogenesis of EAML, just like AML. However, non-sustained response to temsirolimus and rapid disease progression implies additional novel pathogenesis of EAML. Thus, we need to consider whether there is novel tumorigenic properties of EAML beyond mTOR pathway activation and whether mTOR inhibition also can be the best treatment option for unresectable EAML patients, as shown in AML patients.

*SMARCB*1/*IN*1 gene is a member of the SWI/SNF chromatin remodeling complex and is involved in the chromosomal instability and the regulation of cell cycles [18]. Additionally, *SMARCB*1/*IN*1 gene is defined as a candidate of tumor suppressor gene in diverse soft-tissue malignancies, including malignant rhabdoid tumors, chondrosarcoma, synovial sarcoma, and epithelioid sarcomas [19]-[24]. Those tumors showed inactivation of *SMARCB*1/*INI*1 gene or reduced expression of *SMARCB*1/*INI*1 protein. In the mechanistic aspects, previous study have shown that *SMARCB*1/*INI*1 stimulate the p16/Rb tumor suppressor pathway by activation of CDKN2A and inhibition of CDK/cyclinD [25]. Of note, malignant rhabdoid tumor cell lines with *SMARCB*1/*INI*1 inactivation showed responsiveness to Cdk/cyclin inhibitors (4-HPR, flavopiridol) [26] [27].

5. Conclusion

In this study, we suggest that mTOR inhibitors also can be effective against EAML. However, considering previous contradictory reports and non-sustained response to temsirolimus in this case, the efficacy of mTOR inhibitors in EAML needs to be supported in further studies. Furthermore, we speculate that the results of novel missense mutation of *SMARCB*1/*INI*1 gene and reduced expression of *SMARCB*1/*INI*1 protein in this EAML patient can be one of the explanations of novel tumorigenic properties of EAML and this results also highlight the possibility of novel targeted therapy in EAML beyond mTOR inhibitors.

Funding

The authors have no support or funding to report.

Competing Interests

The authors have declared that no competing interests exist.

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Supporting Information

Table S1. Single-nucleotide polymorphism in Cancer Hotspot Panel (Ion AmpliSeq™).

Chromosome	Position	Gene symbol	Genotype	Ref	Variant	Var freq	dssnp137
chr2	212812097	ERBB4	T/C	T	C	72.4	rs839541
chr4	1807894	FGFR3	A/A	G	A	100	rs7688609
chr4	55141055	PDGFRA	G/G	A	G	100	rs1873778
chr4	55152040	PDGFRA	C/T	C	T	47.601626	rs2228230
chr4	55972974	KDR	T/A	T	A	48.567531	rs1870377
chr4	55980239	KDR	T/T	C	T	100	rs7692791
chr5	149433596	CSF1R	G/G	T	G	100	rs2066934
chr5	149433597	CSF1R	A/A	G	A	100	rs2066933
chr10	43613843	RET	G/T	G	T	48.661417	rs1800861
chr11	534242	HRAS	A/G	A	G	48.418491	rs12628
chr13	28610183	FLT3	G/G	A	G	100	rs2491231
chr19	1220321	STK11	C/C	T	C	100	rs2075606
chr22	24176287	*SMARCB*1	G/A	G	A	63.929147	rs5030613

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