



## Oncology

# Efficacy of Everolimus for Treating Renal Angiomyolipoma with Inferior Vena Cava Thrombus Associated with Tuberous Sclerosis: A Case Report



Daiki Ikarashi<sup>a,\*</sup>, Yoshiharu Mue<sup>b</sup>, Ei Shiomi<sup>a</sup>, Misato Takayama<sup>a</sup>, Renpei Kato<sup>a</sup>, Yoichiro Kato<sup>a</sup>, Kazuyuki Ishida<sup>b</sup>, Takaya Abe<sup>a</sup>, Tamotsu Sugai<sup>b</sup>, Wataru Obara<sup>a</sup>

<sup>a</sup> Department of Urology, Iwate Medical University School of Medicine, Iwate, Japan

<sup>b</sup> Department of Pathology, Iwate Medical University School of Medicine, Iwate, Japan

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## ABSTRACT

Here we report a case of 57-year-old woman with renal angiomyolipoma associated with tuberous sclerosis complex involving inferior vena cava thrombus. We could perform less invasive nephrectomy with thrombectomy because everolimus administration reduced the inferior vena cava thrombus. To the best of our knowledge, this is the first report the use of everolimus before performing surgery to treat renal angiomyolipoma with inferior vena cava thrombus.

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## Introduction

Renal angiomyolipoma (AML) is a common mesenchymal tumor of the kidney. AMLs occur sporadically or in association with tuberous sclerosis complex (TSC) where they can be classically multiple, bilateral and growing in 20–30% of AML patients.<sup>1</sup> AML, which is often incidentally diagnosed by routine imaging studies, is occasionally aggressive and invades the renal vein and inferior vena cava (IVC). Here we report a case of a patient with AML with IVC thrombus associated with TSC in whom preoperative treatment with everolimus reduced the IVC thrombus.

## Case presentation

A 57-year-old woman visited our hospital for the treatment of a right renal AML with IVC thrombus. Her medical history included a

facial angiofibroma and cardiac catheter ablation for paroxysmal supraventricular tachycardia. Her daughter had a cardiac rhabdomyoma and was diagnosed with mental retardation but not TSC. Our patient was diagnosed with bilateral renal AML 5 years earlier. She also suffered from a spontaneous rupture of the left renal AML that was treated using embolization and underwent an annual computed tomography (CT) examination.

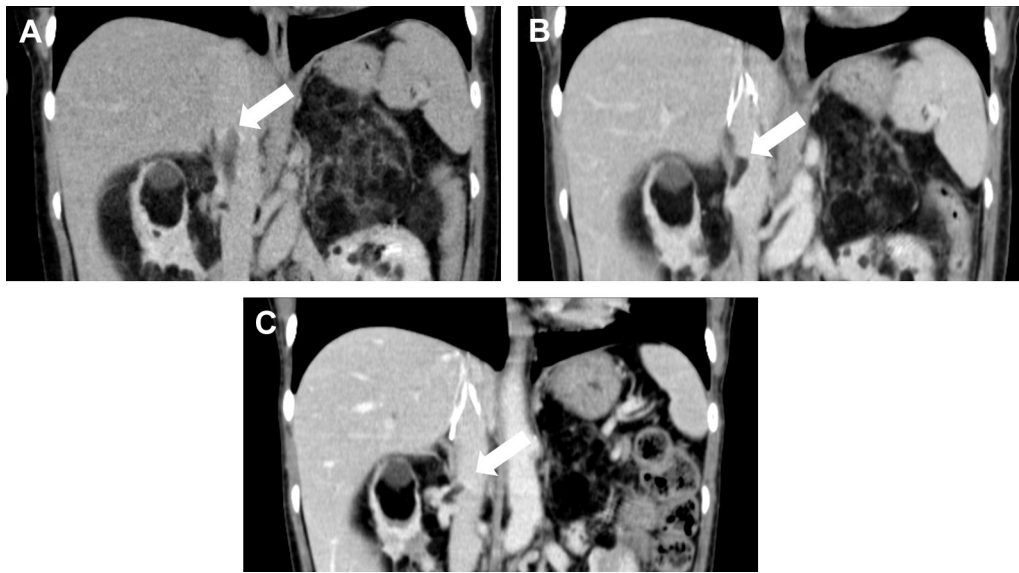
Physical examination revealed a facial angiofibroma and a cesarean section scar. Enhanced CT of the chest to pelvis revealed bilateral multiple renal AMLs with a tumor thrombus in the right renal vein and IVC (Fig. 1A). Lymphangiomyomatosis was present in the lung, and CT of her head revealed subependymal nodules. Based on these findings, she was diagnosed with TSC.

We first considered surgery; however, cecal cancer was detected during examinations for anemia. Therefore, we administered everolimus (10 mg/day) during the treatment of cecal cancer and placed a temporary IVC filter in the diaphragm. There was a prominent effect of the IVC thrombus from the level of the hepatic vein to the renal vein, which was associated with everolimus treatment for 3 and 6 months with no adverse event (Fig. 1B, C). We performed open right nephrectomy and thrombectomy without mobilizing the liver. The thrombus did not adhere to the wall of the vein, and a fibrin clot was not observed. Gross examination revealed

List of abbreviations: AML, angiomyolipoma; TSC, tuberous sclerosis complex; IVC, inferior vena cava; CT, computerized tomography; mTOR, mammalian target of rapamycin; CR, complete response; H&E, hematoxylin and eosin.

\* Corresponding author. Department of Urology, Iwate Medical University, 10-1 Uchimarui, Morioka, Iwate 020-8505, Japan. Fax: +81 019 623 1527.

E-mail address: [heart-of-albirex1@hotmail.co.jp](mailto:heart-of-albirex1@hotmail.co.jp) (D. Ikarashi).



**Figure 1.** (A) Coronal contrast-enhanced computed tomography (CT) showing the right renal angiomyolipoma (AML) with inferior vena cava (IVC) thrombus located at the level of hepatic veins. (B, C) Coronal contrast-enhanced CT showing the IVC thrombus located at the level of the renal vein after everolimus administration for 3 and 6 months.

multiple 1–3 cm yellowish masses in the right kidney and a 3-cm-long thrombus extended from the renal vein (Fig. 2A, B). Her postoperative course was uneventful, and she did not require further adjuvant treatment.

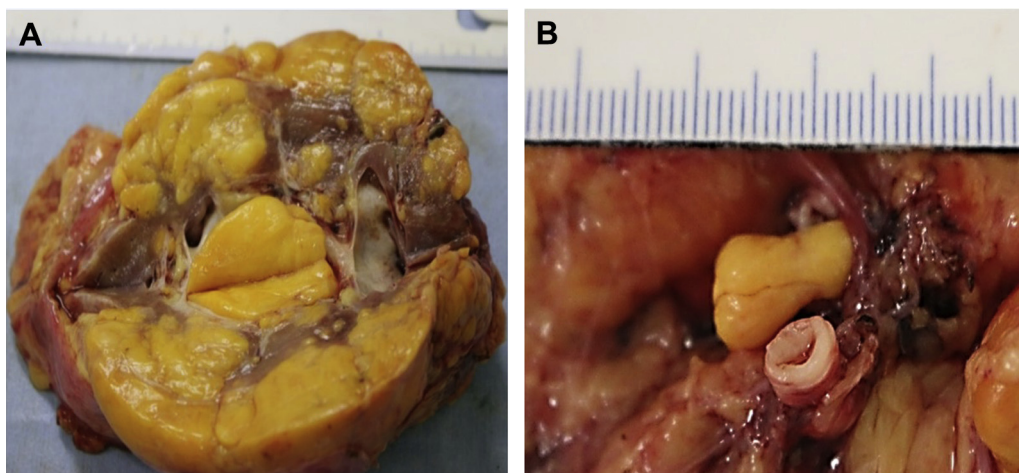
The histopathological examination of the primary tumor revealed classical AML characterized by mature adipose tissue, smooth muscle cells, and thick-walled blood vessels, whereas the IVC thrombus mainly comprised mature adipocytes without epithelioid component (Fig. 3A, B).

## Discussion

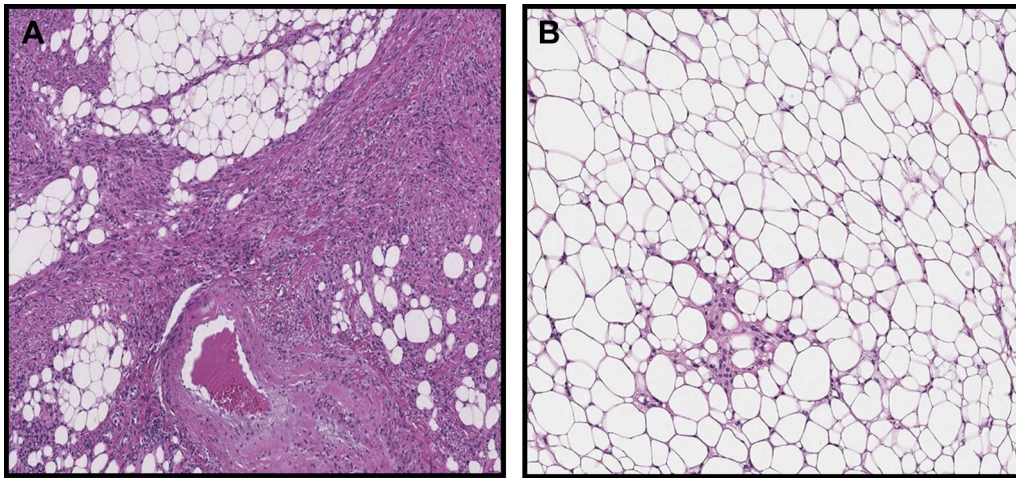
AML is a common renal mesenchymal tumor comprising blood vessels, smooth muscles, and adipose tissue. Renal AMLs occur sporadically (80%) and in association with TSC (20%). Further, renal AMLs associated with TSC are frequently bilateral and multifocal.<sup>1</sup> Our patient had bilateral and multifocal AML. We diagnosed renal AML associated with TSC because she had a facial angiofibroma, lung lymphangiomyomatosis, and subependymal nodules.

AML occurs most frequently as a benign tumor, and most patients with AML are asymptomatic; therefore, it is often discovered incidentally. The management of AML is usually conservative, unless the tumors are large or symptomatic. Most studies recommend surgery for patients with large tumors (>4 cm). Symptoms, such as fever, pain, hematuria, palpable mass, renal dysfunction, and anemia (Wunderlich syndrome), usually appear when AMLs exceed 4 cm.<sup>2</sup> AML presenting with intervascular thrombus is not as rare. In 1982, Kutcher et al reported the first patient with AML with intervascular thrombus, and approximately 45 similar cases were subsequently reported.<sup>3</sup> AML with intervascular thrombus should be surgically removed even if the patient is asymptomatic because it confers the potential risk of pulmonary thrombosis, which may cause sudden death.<sup>4</sup>

The efficacy of everolimus for treating renal AML with TSC is high. For example, a clinical trial found 80.3% of patients showed  $\geq 30\%$  shrinkage of the tumors after they were administered everolimus for 6 months.<sup>5</sup> However, everolimus treatment alone may not cure TSC–AML as the clinical study did not report patients who achieved a complete response.



**Figure 2.** (A, B) Gross examination showing the right kidney and tumor thrombus protruding from the right renal vein.



**Figure 3.** Histopathological findings (H&E,  $\times 20$  magnification). (A) Primary tumor was composed by mature adipose tissue, smooth muscle cells, and thick-walled blood vessels. (B) The tumor thrombus was mainly comprised lipoid cells.

Upon initial diagnosis, we assumed that treatment would involve nephrectomy with IVC thrombectomy; however, an ileocecal cancer was detected. Therefore, we inserted an IVC filter and administered everolimus with the expectation that the tumor thrombus would not progress over the diaphragm during the treatment of the ileocecal cancer. We performed less invasive surgery because of the decreased extent of the tumor thrombus. To the best of our knowledge, this is the first report on surgery used to treat a patient with AML with IVC thrombus after everolimus administration.

Histopathology revealed that the tumor thrombus comprised a fat component, which is generally not effectively treated using everolimus. In contrast, there were no changes, or most of the primary tumor was slightly reduced. We examined pathological and molecular studies to determine the difference in the effect of everolimus on the primary tumor and tumor thrombus. Histopathological analysis did not detect a difference in cell degeneration and necrosis. Subsequently, we studied the mechanism of action of the mammalian target of rapamycin (mTOR) inhibitor on TSC–AML. We used immunohistochemistry to determine the differences in the expressions of S6K1 and 4EBP1 which are downstream targets of mTOR signaling pathway. However, we did not detect a difference in the expressions of mTOR-related molecules in either tumor. In this case, the precise mechanism that IVC thrombus reduced is unclear.

### Conclusion

To our knowledge, this is the first report on a patient with TSC–AML with IVC thrombus who underwent nephrectomy and thrombectomy after everolimus administration. Our findings

indicate that everolimus may be effective for treating renal AML associated with a thrombus. A number of additional case studies will be necessary to confirm our findings and support the suggested treatment.

### Conflict of interest

None.

### Consent

Written consent was obtained from the patient for this case report.

### Acknowledgments

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