Case Report

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Endovascular Treatment and Follow-up of Retroperitoneal Hemorrhage Caused by Bilateral Giant Renal Angiomyolipoma

Hüseyin Mert Durak[1], Berk Yasin Ekenci[1], Hilmi Sarı[1], Onur Ergun[2], Hayriye Şahinli[3], Ahmet Nihat Karakoyunlu[1]

[1]*University of Health Sciences Turkey, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Clinic of Urology, Ankara, Turkey*
[2]*University of Health Sciences Turkey, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Clinic of Radyology, Ankara, Turkey*
[3]*University of Health Sciences Turkey, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Clinic of Medical Oncology, Ankara, Turkey*

Abstract

Tuberous sclerosis is a multisystem neurocutaneous genetic disease that might be seen in one live birth in 6,000-10,000. Angiomyolipomas (AML) are the most common renal lesions that could be seen in 80% of tuberous sclerosis patients. Nephron-sparing surgery or selective arterial embolization are methods that could be used in the treatment of AML. Here in we present the case who has been admitted to our emergency department with retroperitoneal bleeding due to bilateral giant AML and treated with the endovascular method.

A 55-year-old woman, who has been followed regularly in our hospital since 2016 with the diagnosis of tuberous sclerosis. The patient was admitted to the emergency department of our hospital with complaints of right upper quadrant pain and dizziness. On computed tomography, 4 cm of free fluid was observed at the posterior part of the right kidney posterior, consistent with hemorrhage. On renal angiography, selective arterial angioembolization (SAE) was performed on the inferior segmental artery, which is feeding the AML. Surgical intervention was not considered in the foreground because the patient has bilateral giant AML and would not be anephric. It was decided to begin the patient on everolimus (mTOR inhibitor) treatment. In the patient's first year follow-up, imaging was performed with non-contrast computed tomograpy. Computed tomograpy showed no size change in giant AML in both kidneys. Although the patient's creatinine levels increased to 3.04 mg/dL and urea to 148 mg/dL during the follow-ups, she did not need hemodialysis.

AML, which is seen as a part of tuberous sclerosis, is one of the important causes of mortality in tuberous sclerosis, which causes life-threatening bleeding and requires surgical or endovascular treatments. Nephron-sparing surgery could be difficult in bilateral cases. Therefore, SAE should be considered an important treatment option in emergencies.

Keywords: Angiomyolipoma, MTOR ınhibitors, therapeutic embolization, tuberous sclerosis

Introduction

Tuberous sclerosis (TSC) is a multisystem neurocutaneous genetic disease that might be seen in one live birth in 6,000-10,000 (1,2). TSC is inherited in an autosomal dominant manner and 66% of patients have sporadic mutations (3). It is a multisystem disease which is typically involving the brain, skin, kidneys, heart, eyes, and lungs. The specific features of the disease include glial-neuronal-retinal hamartomas, subependymal giant cell tumors, cardiac rhabdomyoma, renal-extrarenal angiomyolipomas (AML), and pulmonary lymphangioleiomyomatoses (LAM) (4). AML are the most common renal lesions that could be seen in 80% of TSC patients (5). It should be treated in patients with large tumors, fertile women, patients who have difficulty in accessing follow-up or emergency care, and patients with have acute or recurrent bleeding episodes (6). Nephron-sparing surgery or selective arterial embolization are methods that could be used in the treatment of AML (6). Here in we present the case who has been admitted to our emergency department with retroperitoneal bleeding due to bilateral giant AML and treated with the endovascular method.

Case Report

A 55-year-old woman, who has been followed regularly in our hospital since 2016 with the diagnosis of TSC with LAM

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Address for Correspondence: Berk Yasin Ekenci, University of Health Sciences Turkey, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Clinic of Urology, Ankara, Turkey
Phone: +90 555 326 77 51 **E-mail:** ekenciberk@gmail.com **ORCID-ID:** orcid.org/0000-0002-5939-4548
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(Figure 1), intracranial tubercles (Figure 1), bilateral renal AML (Figure 2), and who did not come to her follow-up due to the coronavirus disease-2019 pandemic. The patient was admitted to the emergency department of our hospital with complaints of right upper quadrant pain and dizziness in December 2021. Pyschial examination was normal and the patient was conscious, oriented, and cooperative. Arterial blood pressure was 90/60 mmHg and heart rate was 106/min. In the laboratory tests; hemoglobin (Hgb) was 7.4 g/dL, creatinine was 1.78 mg/dL and urea was 95 mg/dL. Ultrasonography (USG) revealed intrabdominal minimal free fluid and a dense collection area in the retroperitoneal area, which was thought to originate from AML. The patient's vitals were stable and the second Hgb value was 7.1 mg/dL. Computed tomography (CT) was performed on the patient. On CT, 4 cm of free fluid was observed at the posterior part of the right kidney posterior, consistent with hemorrhage (Figure 2). The patient was consulted by the interventional radiology clinic and renal angiography (RA) was planned for the patient by interventional radiology clinicians. On RA, selective arterial angioembolization (SAE) was performed on the inferior segmental artery, which is feeding the AML, using 500-700 micron microparticles (Figure 3). After RA, the Hgb value was 6.9 g/dL and 2 units of erythrocyte suspension (ES) were transfused to the patient. The patient's vitals were stable after RA and Hgb was 8.7 g/dL, and creatinine was 3.16 mg/dL after transfusion. On the control CT which was performed four days after the SAE procedure, it was observed that the hematoma area began to resorb (Figure 2). The patient was followed up in nephrology and our clinic for 15 days and she was discharged without any necessary hemodialysis and additional ES replacement. In the controls, which was one month after discharge, Hgb was 10 g/dL and creatinine: 1.89 mg/dL. There were no hematomas or collection areas observed on USG. Surgical intervention was not considered in the foreground because the patient has bilateral giant AML and would not be anephric. The patient was evaluated for initiation of a mammalian target inhibitor of the rapamycin protein complex (mTOR). It was decided to begin the patient on everolimus (mTOR inhibitor) treatment. AFINITOR® preparation was administered at a dose of 10 mg 1*1 for one year. During the period of treatment, the patient did not experience any side effects and the patient was followed up with USG. Six months after the start of the treatment on the USG there was an appearance compatible with bilateral giant angiomyolipoma of 129*60 mm in the right kidney and 128*45 mm in the left kidney. These dimensions were the same as pre-treatment dimensions and did not increase in size. In the patient's first year follow-up, imaging was performed with non-contrast CT due to elevated creatinine and CT showed no size change in giant AML in both kidneys (Figure 4). During the treatment, severe flank pain and hematuria did not occur in the patient. Although the patient's creatinine levels increased to 3.04 mg/dL and urea to 148 mg/dL during the follow-ups, she did not need hemodialysis.

Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

Discussion

AML are benign mesenchymal tumors that could occur sporadically or as part of TSC (7). AML belongs to a family called PEComas (perivascular epithelioid cell tumors) which are characterized by the proliferation of perivascular epithelioid cells. Although classical AML are completely benign, the epithelioid type could make a malignant transformation, but this condition is rare. Malignant transformation might manifest as local recurrence or distant metastasis (8-10).

TSC is known to result from a mutation in the *TSC1 (chromosome 9q34)* or *TSC2 (chromosome 16p13)* gene (11). These genes encode the hamartin and tuberin proteins which are inhibiting a serine-threonine kinase known as mTOR (the mammalian target of rapamycin). As a result of removal of inhibition, it causes excessive growth and proliferation in tissues due to the irregular stimulation of cell growth and proliferation (12).

AML could be seen in 80% of all TSC patients. Although AML is benign, it has been proven to be the most common cause of death associated with TSC, because of it causes severe retroperitoneal bleeding that requires dialysis and transplantation as a result of chronic renal failure (11). On the other hand, LAM occurss with the destruction of alveolar tissue in the pulmonary parenchyma

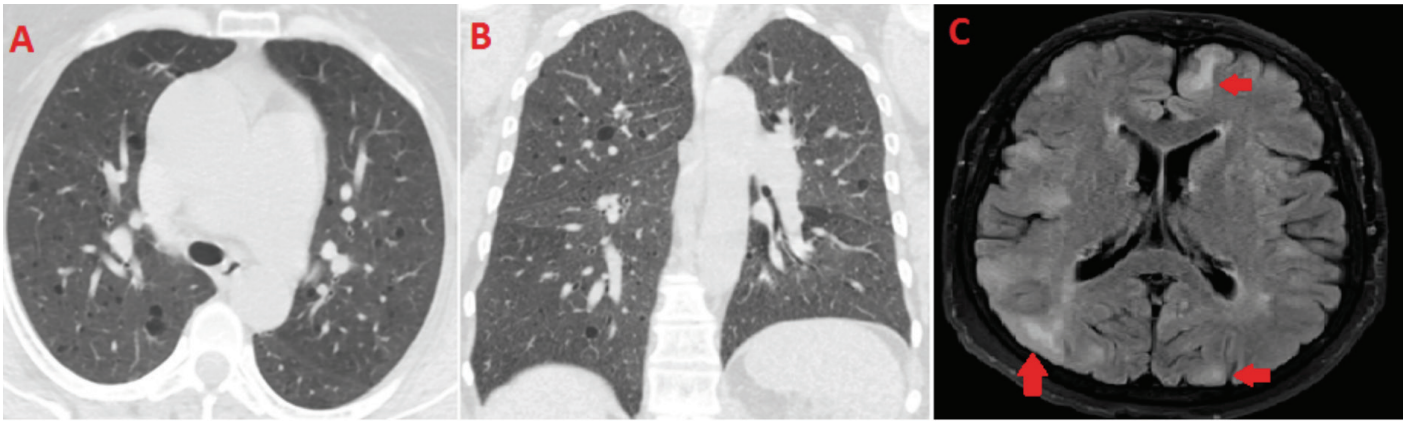

Figure 1. A) In high-resolution CT (HRCT), multiple thin-walled cysts are observed in both lung parenchyma (lymphangioleiomyomatosis). **B)** Lymphangioleiomyomatosis in HRCT (coronally section). **C)** In cranial MRI, cortical tubercles are seen as hyperintense in the T2 FLAIR sequence and shown with red arrows

CT: Computed tomography, MRI: Magnetic resonance imaging

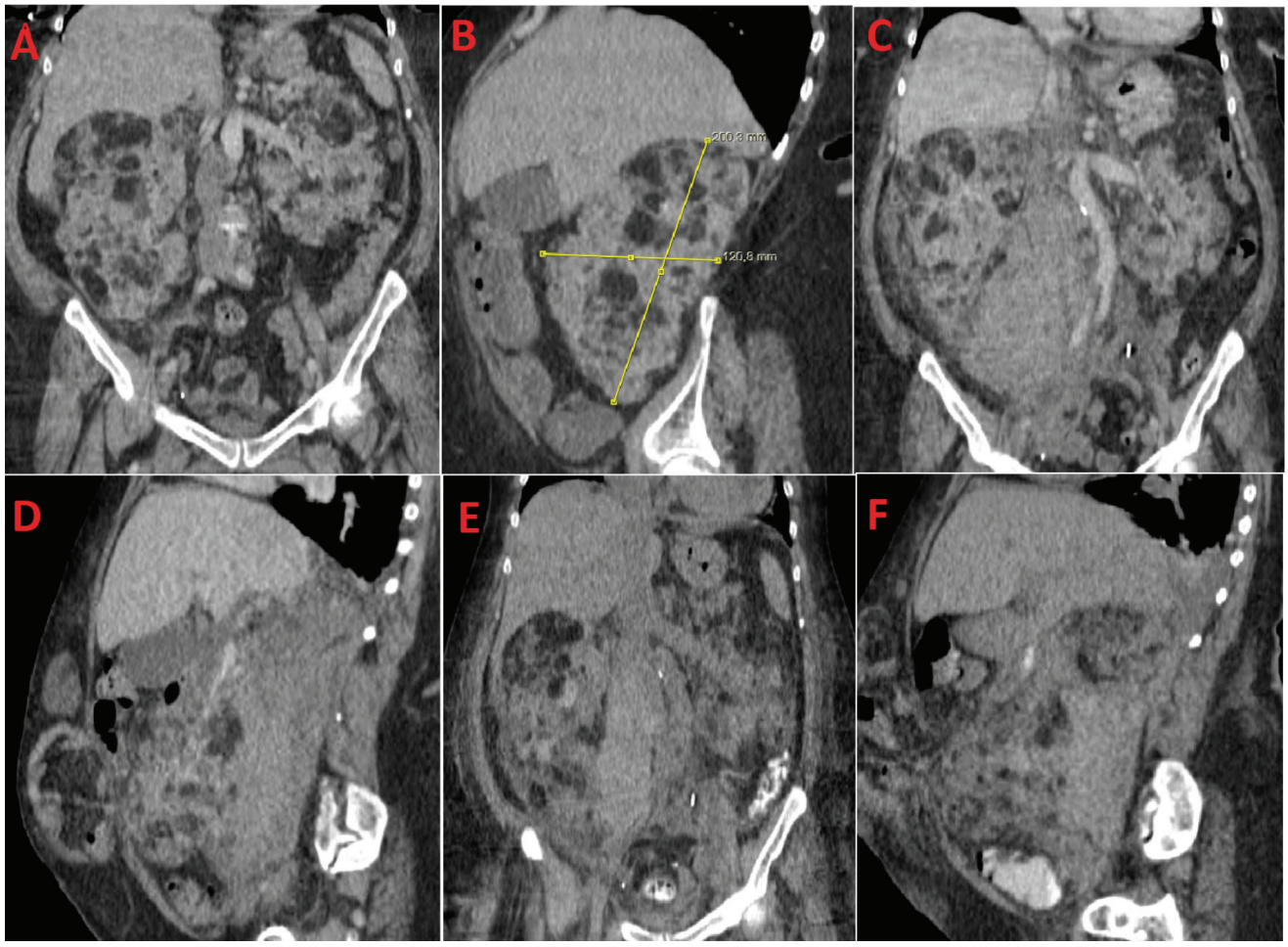

Figure 2. A) Image of bilateral giant angiomyolipomas on computed tomography (CT) of 2019. **B)** Image of right giant angiomyolipoma on CT of 2019. **C)** Retroperitoneal hematoma image due to bleeding thought to originate from right giant angiomyolipoma on the CT performed at the emergency admission of the patient. **D)** Hematoma image in the retroperitoneal area on CT performed at the emergency admission of the patient. **E)** On the CT wich performed on the 4th day after selective arterial angioembolization (SAE), it is observed that the retroperitoneal hematoma size is decreasing (coronal section). **F)** On the CT which performed on the 4th day after SAE, it is observed that the retroperitoneal hematoma size is decreasing (sagittal section)

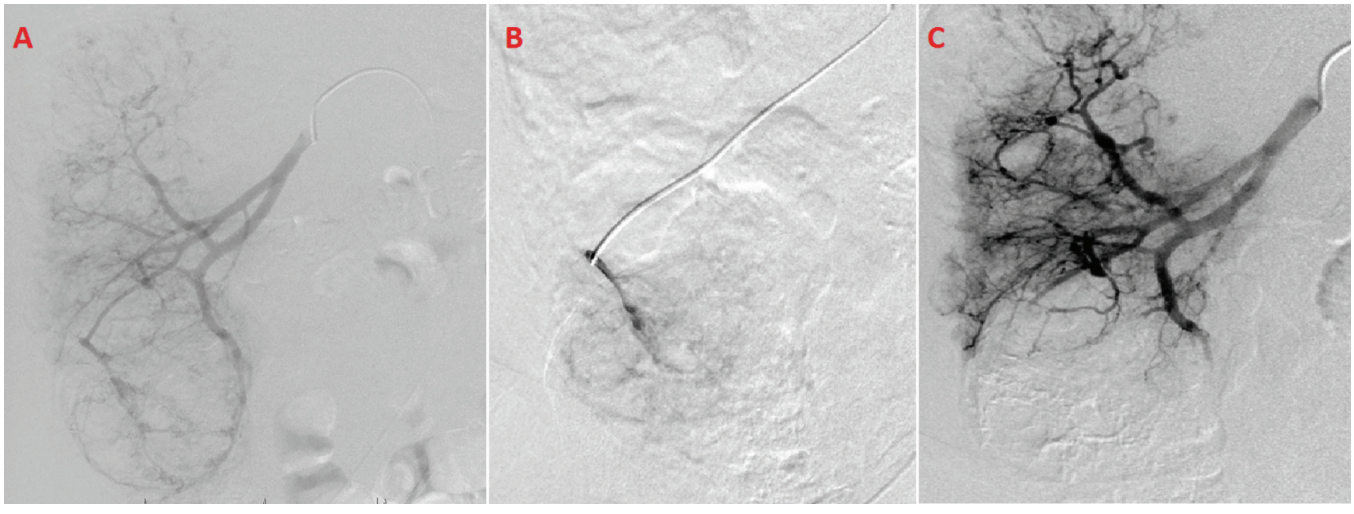

Figure 3. A) Demonstration of arterial branches in the right renal angiography (RA). **B)** Selective embolization with microparticles of the inferior segmental artery which is feeding the giant angiomyolipoma. **C)** RA image after selective embolization

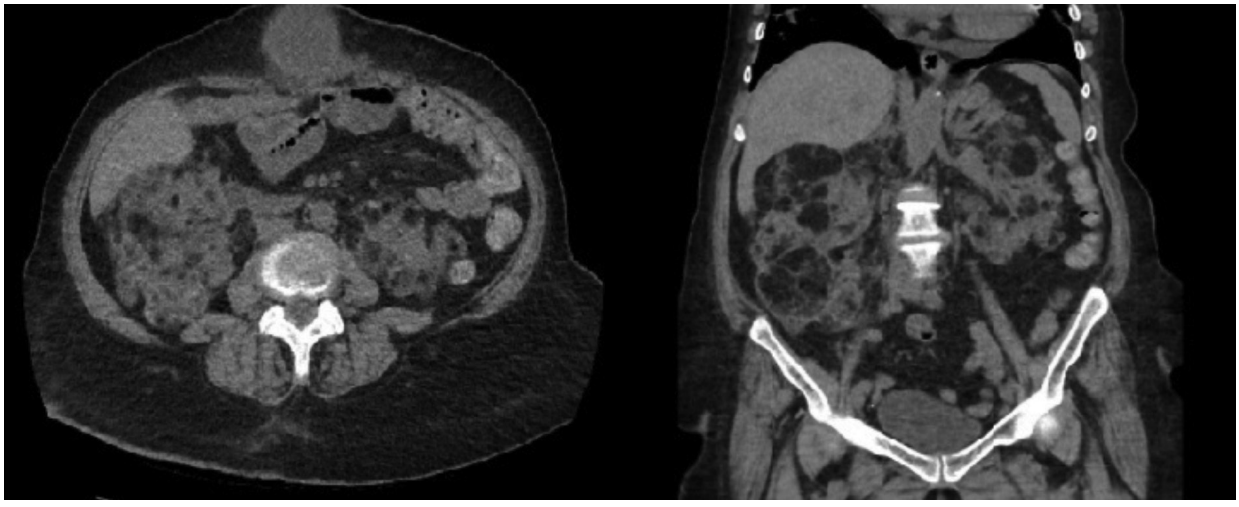

Figure 4. Control CT image at one year after the procedure
CT: Computed tomography

with cystic changes and proliferation of smooth muscle cells and it is third most common cause of TSC morbidity (13).

The main complication of AML is bleeding into the retroperitoneal or collecting system which could be mortal. Bleeding is usually caused by spontaneous rupture of the tumor. Major risk factors for bleeding in AML are; tumor size, grade of angiogenic component, and presence of TSC (14-16).

Usually, USG, CT, and magnetic resonance imaging could diagnose AML by detecting the presence of adipose tissue. However, AML with little adipose tissue content might not be seen clearly. If the lesions could not be identified as benign on initial evaluation, these should be treated as renal cell carcinomas (9-10).

Still, the relationship between the size of AML and the risk of bleeding has not been demonstrated. As conventionally known, a 4 cm tumor size is limited for therapy, and should not be an indication for treatment in patients with AML (14). According to the European Association of Urology guidelines, treating AML is indicated in patients with large tumors (no recommended intervention threshold), fertile women, poor follow-up or access to emergency care, and acute or recurrent bleeding episodes (6). Nephron sparing approach should be preferred as much as possible in the treatment of AML. SAE, which is a minimally invasive treatment, is an alternative to surgery but more recurrences and the need for secondary treatment are the main disadvantages of SAE (14).

An intracellular pathway called the "mammalian target of rapamycin", which plays a role in the regulation of cell proliferation and could be inhibited by rapamycin, is essentially a serine/threonine protein kinase. It consists of two different multi-protein 19 complexes (mTORC1 and mTORC2). The functional process of PI3K/AKT and mTOR protein, which is an important signaling pathway, is closely related to receptor tyrosine kinases (RTK). During malign transformation, various RTK such as vascular endothelial growth factor receptor, platelet-derived growth factor receptor-a, epidermal growth factor, c-Met could be secreted from cancer cells. The PI3K/AKT/mTOR signaling pathway is frequently used to shape the function of cancer cells for these RTKs (17).

Rapamycin acts through mTOR complex 1 and mTOR complex 2. Sirolimus (rapamycin) binds to the cytosolic immunophilin FK506 binding protein (FKBP-12), blocking the FRAP (rapamycin-associated protein - also called mTOR) signaling pathway (17).

Everolimus, produced as a derivative of mTOR inhibitor rapamycin, is used to prevent organ rejection in organ transplants and as an anticancer treatment in oncology (18). Everolimus was approved in 2010 by the US Food and Drug Administration (FDA) for the treatment of TSC-associated subependymal giant cell astrocytoma. Then, in 2012, everolimus was approved by the FDA to treat AML in TSC patients (19). The chemical structure of everolimus differs from sirolimus in that it has 2 hydroxyethyl groups at carbon number 40. Therefore, everolimus is pharmacokinetic and pharmacodynamically different from sirolimus. It has a shorter half-life, 28 hours, and is used twice time daily. The time to reach its constant concentration in the blood is four days and it reaches earlier (six days) compared to sirolimus. Also, unlike sirolimus, no induction dose is required (17).

In randomized controlled studies, it is stated that inhibition of the mTOR pathway using everolimus reduces the size of bilateral AML and surgery could be delayed with this treatment (18). Although it was observed that there was no decrease in AML dimensions during the treatment process in our case, retroperitoneal bleeding did not occur and the patient did not need nephrectomy or hemodialysis. Also, serious adverse effects of everolimus which are anemia and fatigue, as well as hypokalemia, lymphopenia, and vomiting did not observe in our case (20).

Conclusion

AML, which is seen as a part of TSC, is one of the important causes of mortality in TSC, which causes life-threatening

bleeding and requires surgical or endovascular treatments. Nephron-sparing surgery could be difficult in bilateral cases. Therefore, SAE should be considered an important treatment option in emergencies.

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Ethics

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Authorship Contributions

Surgical and Medical Practices: B.Y.E., H.S., O.E., H.Ş., Concept: H.M.D., H.S., A.N.K., Design: H.M.D., B.Y.E., O.E., A.N.K., Data Collection or Processing: H.M.D., H.S., H.Ş., Analysis or Interpretation: H.S., H.Ş., Literature Search: B.Y.E., H.S., H.Ş., A.N.K., Writing: H.M.D., H.S., O.E., A.N.K.

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