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Everolimus Treatment and Selective Artery Embolization Application in a Case of Tuberous Sclerosis-Related Bilateral Renal Angiomyolipoma

Tüberoskleroz İlişkili Bilateral Renal Anjiyomiyolipom Olgusunda Everolimus Tedavisi ve Selektif Arter Embolizasyonu Uygulaması

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Abstract

Angiomyolipomas are the most common benign mesenchymal tumors of the kidney. Although they are often seen sporadically, they can also be observed as a part of the tuberous sclerosis complex (TSC). They occur at an earlier age in cases associated with tuberous sclerosis (TS), bilateral mass and epithelioid formation. There are various treatment approaches such as active surveillance, nephron-sparing surgery, nephrectomy, angioembolization, and use of mammalian target of rapamycin (mTor) inhibitors. Our case was a patient with bilateral multiple renal angiomyolipomas associated with TS. We applied mTOR inhibitor and angioembolization therapy to this patient. In our article, we tried to evaluate our success rate in our treatment and the treatment regimens to be applied in these patients.

Keywords: angiomyolipoma, tuberous sclerosis, everolimus

Öz

Anjiyomyolipomlar böbreğin en sık görülen iyi huylu mezenkimal tümörleridir. Sıklıkla sporadik olarak görülse de tüberoskleroz kompleksinin (TSC) bir parçası olarak da görülebilir. Tüberoskleroz (TS) ilişkili olgularda daha erken yaşta, bilateral kitle ve epiteloid formasyonda karşımıza çıkar. Aktif izlem, nefron koruyucu cerrahi, nefrektomi, anjiyoembolizasyon, rapamisinin memeli hedef (mTOR) inhibitörleri gibi çeşitli tedavi yaklaşımları vardır. Bizim olgumuz tüberoskleroz ile ilişkili bilateral multiple renal anjiyomiyolipomları olan bir hasta idi. Bu hastaya tedavi olarak mTOR inhibitörü ve anjiyoembolizasyon tedavisi uyguladık. Yazımızda tedavimizdeki başarı durumumuzu ve bu hastalarda uygulanacak tedavi rejimlerini yorumlamaya çalıştık.

Anahtar kelimeler: anjiyomiyolipom, tüberoskleroz, everolimus

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Introduction

Angiomyolipomas (AMLs) are the most common benign mesenchymal tumors of the kidney, mainly composed of smooth muscle, dysmorphic vessels and mature adipose tissue, causing regional complications. They are responsible for 1-3% of kidney tumors with an incidence of 0.3-3% in general population and a female-to-male ratio of 2:1 [1]. Fifty to seventy percent of the cases consist of sporadic renal AMLs, characterized by a smaller size (average 1-4 cm), slower growth rate (0.19 cm/year), unilateral presentation, and an average age at disease onset ranging between 43 and 53 years at the time of diagnosis [2,3]. The remaining 30-50% of the cases are associated with genetic syndromes such as sporadic lymphangioleiomyomatosis (LAM) and tuberous sclerosis complex (TSC) [3]. The latter is due to an autosomal dominant mutation of the TSC1 (9q34) or TSC2 (16q13.3) genes, with activation of the mammalian target of rapamycin (mTOR) intracellular signaling pathway, associated with a multisystemic disease, greater number of lesions, higher growth rate (1.25 cm/year), lower mean age at diagnosis (18 years), and development of considerable complications during follow-up [4].

Factors determining the necessity and type of treatment include the presence of symptoms, an aneurysm >5 mm in the mass, the size of the lesion, its association with a disease complex (TS and LAM), kidney reserve, pregnancy plan, patient compliance, occupation, and activity status. Most (82-94%) of the patients with a mass lesion larger than 4 cm are symptomatic and 50-60% of them may bleed at any time. Major risk factors for bleeding are tumor size, grade of angiogenic component, and synchronous presence of TS [5,6].

Although selective arterial embolization is effective in controlling bleeding in emergency situations, research on its effectiveness in long-term treatment continues [7]. In addition to surgical and embolization treatment options, studies are continuing on drug treatments using mTOR inhibitors, which are thought to play a role in the pathogenesis, especially in the treatment of multiple, unresectable or metastatic AMLs accompanying disease complexes such as TS or LAM. The aim of our study is to evaluate the treatment with everolimus and selective arterial embolization, and subsequent follow-up period of a patient who applied to our clinic, and received the diagnosis of renal AML.

Case

A 38-year-old female patient was admitted to the outpatient clinic due to bilateral flank pain. In the physical examination of the patient, a mass lesion was palpated on the right side of the flank. She was not tachycardic, and her respiratory function test results were within normal limits. The patient had hypopigmented macules widely spread on her face and body, fibromas on her face, without any history of epileptic seizures. Laboratory test results, and hemoglobin levels were within normal limits. She had no hematuria. Histopathological examination of biopsy specimen obtained from the fibromatoid skin lesion revealed the presence of an angiofibroma. No pathological finding was found in brain MRI. The patient received the diagnosis of TS, with bilateral AMLs detected on computed tomography **(Figure 1).**

Since as a result of an aggressive surgical approach of bilateral nephrectomy, the patient may remain anephric, we decided to use less invasive methods by communicating to the patient. In order to reduce the size of bilateral renal masses, mTOR inhibitor (everolimus) treatment was started. To ease the patient's tolerance, treatment was started at daily doses of 5 mg, and then continued with 10 mg everolimus. The treatment was continued for 1 year, and stopped after the decrease in the size of the mass slowed down in the follow-up **(Figure 2)**. Bilateral selective angioembolization was decided because the mass enlarged by 20% as detected in the imaging performed 3 months after the drug was discontinued. Everolimus treatment combined with embolization was started because of the rapid growth tendency of the mass after everolimus treatment was stopped. The patient's recurrent pain decreased after the procedure, and the character of the mass changed as detected on imaging **(Figure 3)**. The drug treatment was continued for 1 more year and then stopped. The mass lesions of the patient did not enlarge during the follow-up period of nearly 18 months, and she is still being monitored every 6 months.

Despite development of complications of everolimus treatment such as oral aphthous lesions and dyspeptic complaints, the patient did not discontinue the treatment. No secondary infections were observed after everolimus treatment. During the follow-up period of the patient, her hemoglobin levels did not decrease, and any signs of bleeding were not observed in the imaging tests performed.

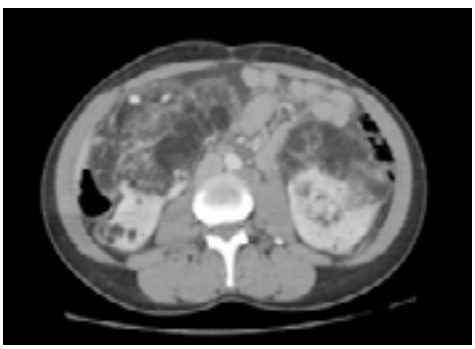

Figure 1. Ct scan image at the time of diagnosis

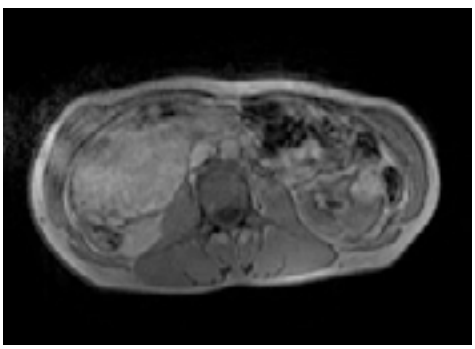

Figure 2. MR image 3 months after treatment with mTOR inhibitor

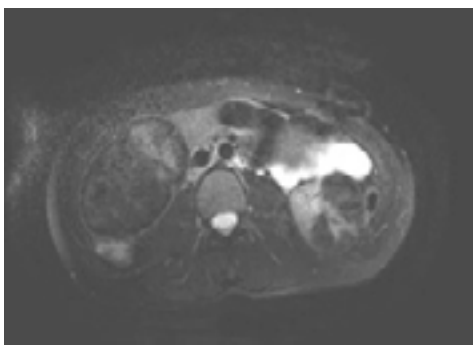

Figure 3. MR image 1 month after arterial embolization

Discussion

AMLs are usually asymptomatic, but they may also present with mass, flank pain, and hematuria, most commonly related to the size of the lesions, and sometimes accompanied with bleeding into the retroperitoneal region. Patients have symptoms such as palpable abdominal mass, hematuria, flank pain (Lenck's triad), and mass lesions may reach large sizes, disrupting the kidney structure and leading to hypertension, renal failure and even death. Tumors with a size of 4 cm and above carry the risk of spontaneous bleeding because of their abnormal vascularity and aneurysmal structures. Symptoms develop in 68-80% of the patients with masses larger than 4 cm, bleeding episodes are observed in approximately 50-60%, and hypovolemic shock develops in 1/3 of the patients presenting with potentially life-threatening hemorrhage. The most important risk factors for bleeding are the size of the tumor, the grade of the vascular component, and the presence of TS. The risk of spontaneous bleeding is observed in 13%, and 51% of the cases with mass lesions measuring <4 and >4 cm, respectively [8].

Although the majority of AMLs are benign, a small number of them may have an aggressive behavior pattern and may cause local invasion. The mass lesions are histologically classified in classical and epithelioid types. Most of the sporadic ones are of the classical type. Epithelioid AML is a rare variant of AML with a tendency to malignant transformation and is mostly associated with the TSC. It is considered a locally aggressive tumor. Epithelioid AMLs can be confused with renal cell carcinoma due to the absence of adipose tissue and the presence of pleomorphic epithelioid cells.

In cases with TS, pathognomonic skin lesions, neurological findings and clinical findings may be associated with the involvement of other organs. Although the natural history of renal AML is not clearly understood, it is known that the number and size of renal AMLs increase with age. Tumors in patients with TS and multiple AMLs grow larger compared to those with isolated lesions [9]. It has been stated that AML cases associated with TS should be closely monitored because of the possibility of their being bilateral, multifocal, and gradual enlargement over time [7]. The goal of treating symptomatic AML is to preserve nephrons and kidney function. Therefore, selective arterial embolization, laparoscopic or open partial nephrectomy, open or laparoscopic cryoablation or radiofrequency ablation should be the priorly preferred treatment modalities, only in case of absolute necessity total nephrectomy should be performed [6]. Although effective treatment is provided by total nephrectomy in large or hemorrhagic masses, nephron-sparing partial nephrectomy is usually an option [10]. In addition, preoperative selective arterial embolization is an option that facilitates surgery in cases of acute bleeding or in the presence of large masses. As a minimally invasive procedure our patient with bilateral renal masses received combined treatment with everolimus and arterial embolization to refrain from the adverse effects of bilateral surgical procedure such as relevant complications and renal dysfunction. Reduction in the size of the mass observed in the follow-up of the patient, also reduced the risk of bleeding.

The European Association of Urology (EAU) guidelines indicate that the most appropriate approach for AML would be active surveillance. Selective arterial embolization is recommended as first-line therapy if active monitoring will no longer be performed. If surgical treatment is to be preferred, the guidelines suggested that many patients can be managed with nephron-sparing surgery, and that some patients require radical nephrectomy. In addition, it is stated that tumor volume can be reduced with mTOR inhibitors (everolimus and sirolimus) and surgery can be delayed with this treatment [1].

The mTOR regulates cell proliferation, autophagy, and apoptosis by participating in multiple signaling pathways in the body. The mTOR signaling pathway, which is often activated in tumors, not only regulates gene transcription and protein synthesis so as to modulate cell proliferation and immune cell differentiation but also plays an important role in tumor metabolism. Therefore, the mTOR signaling pathway is a hot target in anti-tumor therapy research. In recent years, a variety of newly discovered mTOR inhibitors have entered clinical trials, and a variety of drugs have been proven to have higher efficacy in combination with mTOR inhibitors [11].

In a study examining 524 patients who underwent transarterial embolization with the diagnosis of AML, self-limiting postembolization syndrome developed in 35.9% of the patients without any case of mortality. A 38.3% reduction in tumor size (mean 3.4 cm) was detected in an average follow-up period of 39 months after embolization. During the follow-up period, 20.9% of patients required unplanned repeat embolization or surgery. Reasons for reinterventions included: AML revascularization (30%), unchanged or increasing tumor size (22.6%), persistent or recurrent symptoms (16.7%), and acute retroperitoneal hemorrhage (14.3%) [12]. In our patient, while the largest diameter of the mass was 11.5 cm after everolimus treatment, it decreased to 7.5 cm after angioembolization and reoperation was not required.

Although everolimus treatment continues to be used at the conventional dose (10mg), lower doses have been used in some studies. In the study of patients with TS-related AML, Hatano et al. compared treatment with daily doses of 5 mg and 10 mg, and any difference was not seen in the efficacy of the treatment, while less treatment-related side effects were observed in the 5 mg group [13].

There is no definite information about the duration of everolimus treatment, some studies have claimed that intermittent treatment may be more successful in reducing side effects. Hatano et al. had observed that the side effects were observed less frequently when the treatment was started again. In this study with ongoing follow-up, retreatment was not required in 31% of the patients, because lack of growth in the size of the mass, although 1.5 years had passed after the treatment was discontinued [14]. We have observed that our patient could more easily tolerate retreatment. The conditions for stopping and restarting treatment vary in studies, and large series of patient groups are needed to ensure standardization of the retreatment protocol.

Conclusion

Treatment is mostly required for symptomatic, large, multifocal, bilateral masses that are associated with TS and tend to enlarge with age. In the selection of the treatment method, care should be taken to protect the kidney functions to the maximum extent. Combined treatment with everolimus and selective arterial embolization can be used as minimally invasive treatment method, but close follow-up is important, keeping in mind that re-angioembolization may be required due to the growth tendency of the mass

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Conflict of Interest: The authors declare that they have noconflict of interest.

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