Case Report

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Bilateral renal angiomyolipoma with left renal artery aneurysm in tuberous sclerosis: case report and literature review

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Introduction and importance: Tuberous sclerosis disorder (TSD) is a rare genetic disease that causes abnormal growths or tumors in various organs of the body. They are usually benign and asymptomatic. However, severe, rapidly growing tuberous sclerosis can be fatal. Renal angiomyolipomas are commonly associated with TSD, which can be further worsened by the presence of aneurysms and put the patient at risk for life-threatening hemorrhage.

Case presentation: A 29-year-old female presented to the emergency room complaining of right flank pain with an unknown past medical history of tuberous sclerosis. The patient was suspected to have TSD as she fulfilled one of the major features of TSD required to establish a possible diagnosis. On computed tomography scan imaging, bilateral fat-density nodules were revealed in both kidneys. The largest is 7 cm in the left kidney, located at the upper pole, and was associated with a bleeding aneurysm measuring 4 cm in diameter. While the other fatty nodule was recorded at 6 cm in the right kidney at the lower pole.

Clinical discussion: After evaluation, the patient was planned for diagnostic catheterization of the left kidney, through which selective angiography of the left kidney was done, and eventually, selective embolization of the branch supplying the left angiomyolipoma was performed.

Conclusion: The authors finally conclude that thorough investigations, including systemic manifestations, must be taken into consideration when suspecting tuberous sclerosis, and a conservative approach must always be prioritized before taking any decision toward invasive approaches.

Keywords: angiomyolipoma, bilateral renal angiomyolipoma, case report, renal angiomyolipoma, tuberous sclerosis

Background

Tuberous sclerosis disorder (TSD) is an autosomal dominant, uncommon illness with the potential for misdiagnosis. TSD is a condition of inability to regulate cell growth, proliferation, size, and cell cycle that causes benign tumors or cancerous hamartomas. Throughout a lifetime, several processes can affect the heart, kidneys, lungs, brain, skin, and retina[1]. As many as 80% of patients with TSD have angiomyolipomas (AML)[2].

More significant concern should be given to potentially fatal retroperitoneal hemorrhages caused by the rupture of dysplastic, aneurysmal blood arteries feeding the AMLs[3]. Additionally, these hemorrhages have the potential to harm nearby normal renal parenchyma, cause abdominal distention and blockage from mass effects, and end in hypovolemic shock and renal failure[4].

The clinical diagnostic criteria of TSD, as stated by the 2021 International Tuberous Sclerosis Complex, include 11 major features and 7 minor features[5]. The major features include hypomelanotic macules (≥3) with each measuring 5 mm in diameter at least, angiofibroma (≥3), ungual fibromas (≥2), shagreen patch, multiple retinal hamartomas, multiple cortical tubers or radial migration lines, subependymal nodule (≥2), subependymal giant cell astrocytoma, cardiac rhabdomyoma, lymphangiomyomatosis, and AML (≥2). Whereas minor features include: 'Confetti' skin lesions, dental enamel pits (≥3), intraoral fibromas (≥2), retinal achromic patch, multiple renal cysts, nonrenal hamartomas, and sclerotic bone lesions.

HIGHLIGHTS

- Tuberous sclerosis may present with only one major feature.
- Renal angiomyolipoma may be present in both kidneys with size variations.
- Renal angiomyolipoma may be associated with fatal aneurysms.

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Herein, we report a case with bilateral AML of the kidneys, the largest of which is 7 cm with a left renal artery aneurysm.

This case has been reported in line with the Surgical CAse REport (SCARE) Criteria[6].

Case presentation

A 29-year-old married female first came to the hospital on 16th March 2022 with a 3 days history of right flank pain. The pain was colicky in nature, radiating to the paraumbilical region, and was associated with nausea. There was no history of vomiting, fever, bowel habit changes, or other related symptoms. Her past medical history was significant for hydatid liver cysts and convulsions since childhood, for which she took antiepileptic medications until 13 years of age. She is now no longer suffering from convulsions. There was no history of genetic disease in her family.

On general physical examination, the patient looks uncomfortable due to pain, with no pallor, jaundice, or cyanosis. Her vital signs on admission were within acceptable limits. There were no neck swellings and no congested throat. Upon chest exam, the resting heart rate was within normal limits with normal heart and lung sounds. The abdomen was soft and depressible with no distention, and all inguinal orifices were intact, but right flank tenderness was noticed. An abdomen and pelvis ultrasound showed a 0.9 × 1.2 cm lesion in the region of the appendix, which is likely to be an inflamed, nonperforated appendix. The ultrasound also revealed that the right kidney was normal with no changes, but the left kidney showed pronounced hydronephrosis with semi-stones seen in the upper calyces.

A body computed tomography (CT) scan showed a well-defined isodense lesion measuring 4 cm at the upper pole of the left kidney with a central area of avid homogenous enhancement of 3 cm in the arterial and portal phase connected to the superior branch of the left renal artery, and significant washout at the delayed phase. Furthermore, bilateral fat-density nodules of the kidneys were seen, the largest was about 7 cm in the left kidney at the upper pole, and the other was 6 cm seen in the right kidney at the lower pole specifically (Fig. 1). These findings along with her past medical history were suggestive of renal angiomyolipoma predominantly on the left kidney with a left renal artery aneurysm.

However, based on CT findings, and the fact that fat could be associated with other diseases, a number of differential diagnoses were suggested. The first is renal cell carcinoma (RCC) in which macroscopic fat often occurs in the setting of calcification, large irregular tumors invading the renal sinus, and/or large necrotic tumors. Focal or diffuse signal loss in the opposed phase suggests microscopic fat, which is very common in clear cell RCC and less common in poorly fat AML. The presence of a large vessel extending into the renal cortex is suggestive of AML; unlike retroperitoneal liposarcoma invading the kidney, which is hypovascular and could show calcifications.

Other differentials would include Wilms tumor, oncocytoma as both may contain fat, and finally adrenal myelolipoma.

Urine culture showed pathogenic growth of *Escherichia coli* and yeast with positive antibiotic sensitivity. No further management was done after that, as the patient asked to be discharged in order to bring financial coverage for her treatment from the government.

After 10 days, the patient returned to the hospital complaining of bilateral flank pain for 1 week, which is more pronounced on the left side. It was colicky, radiating to the paraumbilical region, and was associated with nausea. There was no history of chronic constipation, vomiting, fever, dysuria, hematuria, or other related symptoms. On examination, the patient looked well, not dyspneic or pale, with a soft, lax abdomen, and no tenderness.

After evaluation, the patient was planned for diagnostic catheterization, through which the right common femoral artery was accessed using a 6Fr, 10 cm sheath, then exchanged to a 6Fr long sheath of 65 cm length, and selective angiography of the left kidney was done. The left renal artery was patent, and a large left kidney angiomyolipoma measuring 6 × 6 cm at the upper lateral pole was revealed. This angiomyolipoma was demonstrating several characteristic angiographic features on both arterial and venous phases. On the arterial phase, it appeared as a sharply marginated hypervascular mass with a dense early arterial network, and tortuous vessels giving the 'Sunburst' appearance with pseudoaneurysm. While on the venous phase, it shown a whorled onion peel appearance of peripheral vessels. Micro-aneurysms were also noticed and there were no arteriovenous shunts. Consequently, selective embolization of the upper lateral branch supplying angiomyolipoma was performed using Gel foam (Equison) and two tornado embolization coils measuring 2 mm × 2 cm. The embolization was successful without postoperative complications.

Regarding preintervention procedures, renal function tests and imaging studies (US, CT, and digital subtraction angiography) were performed prior to embolization. Renal function tests were within normal limits, and clusters of microaneurysms were identified and localized on DSA.

The patient has been followed up for about a year and a half since her last discharge and is being followed up with an MRI every 6 months to evaluate a left renal pseudoaneurysm after endovascular embolization. Renal function tests remained normal during clinical and MRI follow-ups. MRI showed distinct atrophy of the embolized areas without impairment of normal renal parenchymal perfusion and no associated bleeding.

Discussion

Tuberous sclerosis (TSC) disorder is a rare genetic autosomal dominant disorder with multisystem involvement and an estimated prevalence of 1 in 50 000 people worldwide[7], often diagnosed in childhood before the age of 10 years. However, diagnosis can occur at any age[8] and may affect both males and females equally[9].

Defects in hamartin and tuberin as a result of heterozygous mutations involving either TSC1 (chromosome locus 9q34.3) or TSC2 (16p13), respectively, would cause the disease. These contribute to a heteromeric protein complex that controls the mammalian target of rapamycin (mTOR) pathway's ability to regulate cell growth, proliferation, size, and cell cycle[7]. Both spontaneous and hereditary gene mutations are possible. About 1 in 3 individuals inherit a defective TSC1 or TSC2 gene; however, the majority of cases appear randomly and without any known family history. Children have a 50% chance of inheriting tuberous sclerosis from a diseased parent[10].

The clinical manifestations of TSC depend on the degree and range of tissues that are affected as benign tumor growths or hamartomas in the brain, kidney, heart, lung, or retina[11], epilepsy, neuropsychiatric, or skin manifestations. Renal and

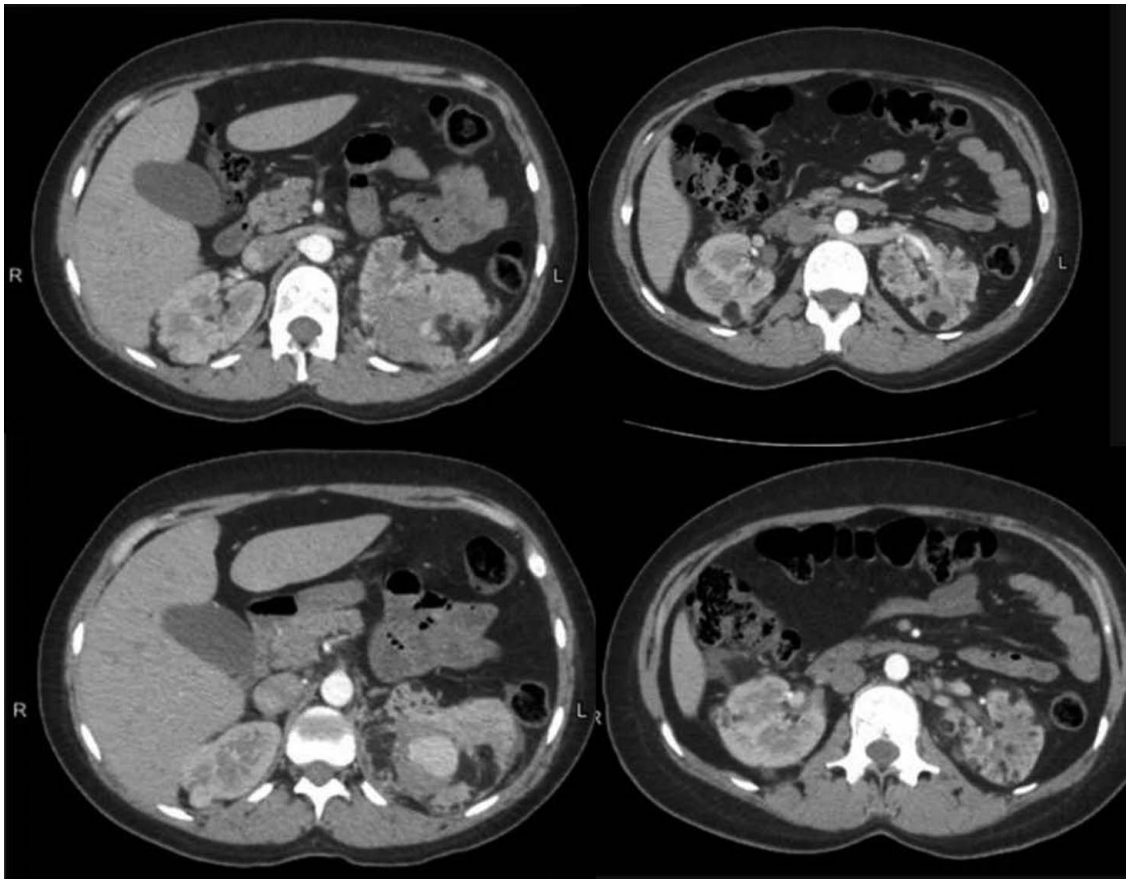

Figure 1. Abdominal computed tomography scan of the patient showed that both kidneys were enlarged and contained innumerable predominantly fat-density nodules consistent with multiple angiomyolipomas. In addition, there is mild bilateral perinephric stranding at the mid to lower pole.

neurological problems are the major causes of morbidity and death associated with the disease. Although less common, pulmonary complications can result in a high personal burden of sickness[2].

In TSC patients, some primary renal lesions might appear as benign angiomyolipoma (AML), epithelial cysts, oncocytoma, malignant angiomyolipoma, and RCC[12]. Renal angiomyolipoma is histologically made up of smooth muscle, blood vessels, fatty tissue, and connective tissue[13]. It is thought to be the most common benign kidney tumor, with a frequency ranging between 0.2 and 0.6%, more predominantly affecting females. In 80% of cases, they appear as sporadic, solitary entities. The remaining 20% of AMLs are associated with pulmonary lymphangioleiomyomatosis or tuberous sclerosis complex (TSC)[14]. The scale of symptom occurrence is considerably variable which is mostly asymptomatic. However, lesions over 3 cm are highly prone to be accompanied by symptoms including flank pain, tender abdominal mass, hematuria, renal function loss, and a higher risk of bleeding, necessitating treatment[2,15].

The 2021 International Tuberous Sclerosis Complex Consensus Group surveillance and management recommendation states that 'genetic diagnostic criteria' or 'clinical diagnostic criteria' can be used to diagnose tuberous sclerosis (TSC)[5]. The presence of a pathogenicity involving TSC1 or TSC2 in DNA from viable cells, regardless of clinical manifestations is sufficient for the genetic diagnosis. On the other hand, there are 11 major and 7 minor features in the clinical diagnostic criteria. In order for a potential diagnosis to be made, greater than or less than 2 minor features or one major feature are required. The patient in our case had bilateral renal angiomyolipoma, which suggested the diagnosis of TSC.

To identify the fat, MRI, CT, and ultrasound are used in the imaging workup of AML[15]. The majority of probable AMLs are evaluated with CT because of the potential similarity between the ultrasonic features of AML and RCC. More advanced imaging methods, such as MRI, may contribute to establishing a strong diagnosis of AML when lesions are fat-poor[16]. Our patient's CT revealed signs of bilateral fat-density nodules of the kidneys suggestive of bilateral renal angiomyolipoma.

A conservative approach is used for tumors less than 4 cm; however, excision or embolization is used to treat tumors greater than 4 cm and aneurysms greater than 5 mm[15].

Recently, several hopeful studies have suggested that TSC patients may be treated by preventing the development of TSC tumors using mTORC1 inhibitors resulting in a satisfactory safety profile and a volume reduction of angiomyolipoma by up to 50%. When rapamycin binds specifically to mTOR, mTOR activity is inhibited, which ultimately encourages the reduction of cellular growth[2]. As a consequence of randomized, double-blind, placebo-controlled clinical trials, EXIST-1 (efficacy and safety of everolimus for subependymal giant cell astrocytomas - SEGAs - associated with tuberous sclerosis complex) and EXIST-2 (everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic

lymphangioleiomyomatosis)[17,18], the European Medicines Agency and the Food and Drug Administration (FDA) authorized the use of everolimus for the treatment of adult patients who were at risk for complications and had renal angiomyolipoma related to TSC but did not need to have surgery right away[2].

An enhanced CT or abdominal MRI scan should be done to monitor AML's progression every 1–3 years. Blood pressure and kidney function tests should be checked annually. After selective arterial embolization or surgical intervention, patients who do not use everolimus must have MRI or enhanced CT scans every 3–6 months, and their blood pressure and renal function must be monitored[19].

The strength of our approach in this case is represented by the way we have established a diagnosis of AML as a first suspicion given her past medical history which was significant for convulsions since childhood.

As for the weaknesses and limitations, we could not afford direct management on her first presentation due to financial issues with the hospital and the need for formal governmental approval to cover her treatment plan.

Conclusion

We conclude that the presentation of bilateral angiomyolipoma should be taken seriously, and when necessary, thorough investigations should be considered to rule out tuberous sclerosis before making any interventions. The goal must be achieving the best results with the least invasive approach.

Ethical approval

The study is exempt from ethical approval in our institution.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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The study did not receive any funding.

Author contribution

O.D., F.D., and M.E.: data collection and study concept or design; A.B. and A.T.: writing the manuscript; O.D., M.E., and A. R.: review and editing the manuscript.

Conflicts of interest disclosure

The authors declare that they have no conflicts of interest.

Research registration unique identifying number (UIN)

1. Name of the registry: not applicable.
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