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Case Report

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Tuberous Sclerosis-Associated Giant Renal Angiomyolipoma and Giant Cell Tumor of Bone: A Case Report

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Abstract

Tuberous sclerosis complex (TSC) is a multisystem hereditary illness that affects nearly all body organs. Loss-of-function mutations in TSC1 or TSC2 genes, whose protein products function as a complex to constrict the activity of the mammalian target of rapamycin complex 1 (mTORC1), lead to the overactivation of the mammalian target of rapamycin (mTOR) signaling pathway. The current study reports a tuberous sclerosis patient with giant renal angiomyolipoma (RAML) and a giant cell tumor of bone(GCTB), exploring the possible mechanisms of TSC complicating GCTB and the more optimal treatment for massive RAML patients with solitary kidney.

Keywords: Tuberous sclerosis; Renal angiomyolipoma; Giant cell tumor of bone

Introduction

There are many different clinical presentations of tuberous sclerosis complex, characterized by hamartomas that damage several organ systems, especially the kidneys and the brain **[1]**. The prevalence of TSC was found to be 1 in 6,000 and 1 in 10,000 **[2,3].** Here, we present a case report of a female patient with unique clinical features of TSC who was diagnosed with TSC according to the most recent version of the International Tuberous Sclerosis Complex Diagnostic Criteria.

Case Presentation

The 19-year-old patient with a history of childhood-onset epilepsy and a diagnosis of left kidney angiomyolipoma was admitted to Chengdu Third People's Hospital in June 2010. The patient without low back pain, dysuria, or gross hematuria had a face that was covered with a number of small papules and nodules. The patient's responses and expressions were a little bit slower than normal while the physical examination was performed. The patient had a firm lump in the left upper abdomen that had a smooth surface and a moderate

degree of pain when palpated. The following findings emerged from the laboratory tests: the electrolytes, liver enzymes, cardiac markers, and coagulation were all within normal ranges. In contrast, the Hemoglobin (HGB) level was only 52 g/l and the hematocrit was only 19.5%. The following information was obtained from a Contrast-Enhanced Computed Tomography (CE-CT) scan after that. There were multiple circular mixed-density shadows in both kidneys, and fat density was seen in them. The above lesions were inhomogeneous enhancement on the enhanced scan. There was an 84×59 mm lesion in the left kidney, and the parenchyma of In the left lobe of the liver, there were two quasi-circular fat density shadows with diameters of 15 mm and 5 mm, respectively. Additionally, the results of the cerebral MRI were as follows: There were multiple aberrant signal spots in the left frontotemporal parietal, occipital, and right parietal lobes. In T2WI and FRAIR, a signal that was somewhat high was observed, while in T1WI, the signal that was observed was iso-low. The EEG was dominated by waves, particularly significant in the occipital region, which was moderately abnormal. There was no abnormality in the color of the ultrasound of uterine appendages. Renal isotope examination indicated that the left glomerular filtration rate was 16.8 mL/min/1.73 m^2, and the right was 41.1 mL/min/1.73 m^2. As conservative treatment was ineffective, the patient suffered a left nephrectomy. Renal angiomyolipoma was verified by immunohistochemistry **(Figure 1)** (HMB45 +, MelanA +, and SMA +) and pathology. After the operation, the patient recovered without any complications.

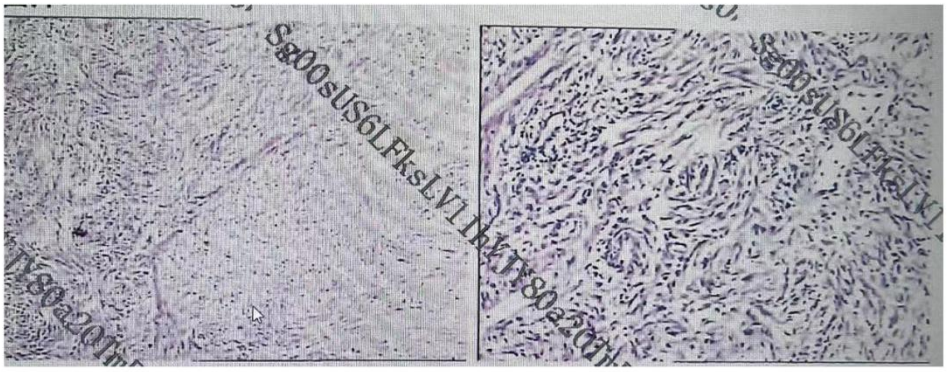

Figure 1: There was an abundance of vascular tissue, with some fatty and smooth muscle cells strewn around.

The patient was admitted to Chengdu Third People's Hospital again in January 2011 for left lateral malleolus swelling and pain with limited mobility. Normal were blood routine, coagulations, renal functions, the electrolytes, liver enzymes, cardiac and tumor markers. Abdominal ultrasonography showed the following results: Multiple slightly stronger echo masses can be seen in the right renal parenchyma, about 2.5 cm×2.3 cm at most, and several more marginally stronger echogenic groups of different sizes in the liver parenchyma, about 2.1 cm×1.8 cm at most. MRI of the tibiofibular showed the following results. The distal end of the left fibula was enlarged, and a large area of abnormal signal focus with expansive growth was seen in it, showing an iso-low signal in T1WI and a high signal in T2WI. There was a separation in focus, the bone texture was unclear, and the local bone cortex became thinner and fractured. Immunohistochemical findings corroborated the pathological findings during post-operative examination **(Figure 2):** S-100-, CD68+, SMA+.

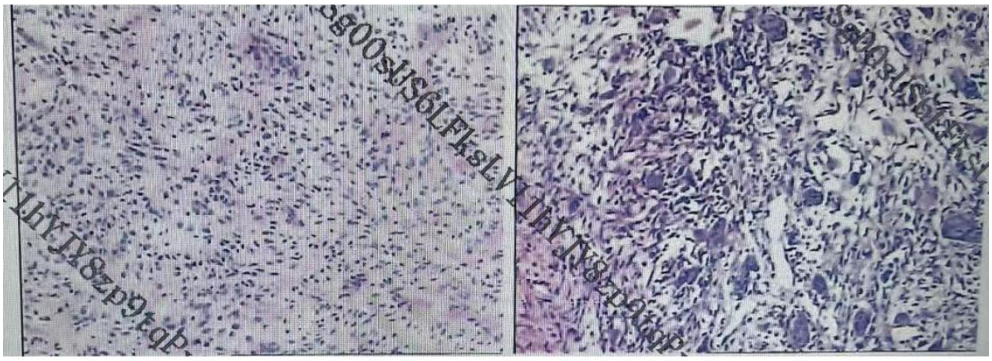

Figure 2: Frozen paraffin section showed spindle cells and scattered multinucleated giant cells in the left ankle mass, which was consistent with giant cell tumor of bone.

It is a pity that the patient was admitted to the emergency department of Chengdu Third People's Hospital in September 2022 for abdominal pain. Laboratory tests were carried out, and the following findings were obtained: The red blood cell count was 3.11×1012/l; the HGB was 78 g/l; the white blood cell count was 14.39×109/l; the serum albumin level was 34.9 g/l. Ultrasonography showed the following results: Multiple slightly strong echo masses were detected in the liver parenchyma, with a clear boundary, about 3.0×2.3 cm at most, and located in the left outer lobe. Multiple slightly strong echo masses were detected in the right renal parenchyma, some of which protruded outward from the kidney, about 3.0×2.6 cm at most. The right renal collecting system was separated, and the diameter of the dark area was about 1.4 cm. A slightly strong echo mass with diffuse distribution can be found in the abdominal cavity. The boundary was not clear. The largest one was located under the xiphoid process, with a size of about 12.5×7.6 cm. The second largest one was in the right lower abdomen, with a size of about 9.0×5.0 cm. A CT scan of the abdomen and pelvis showed the following results: A substantial mixed-density shadow was seen in the right abdominopelvic cavity, about 178×81×250 mm in size. Fat, liquid, and solid-density shadows were caught in it. The local boundary was unclear. The ileocecum and ascending colon were compressed, and the pancreas was displaced to the left and front under pressure. Two fatty-like low density shadows can be seen in the liver, and the larger one was about 24×22 mm in the left lobe of the liver. The right kidney structure is unclear **(Figure 3).** After scanning the CT, it was considered that the abdominal cavity tumor was coming from the right renal angiomyolipoma. Although the enormous abdominal cavity tumor produced compression symptoms, the patient had undergone a left nephrectomy 12 years ago. As only the right kidney was left, and the patient's renal function was relatively normal, no operation was performed.

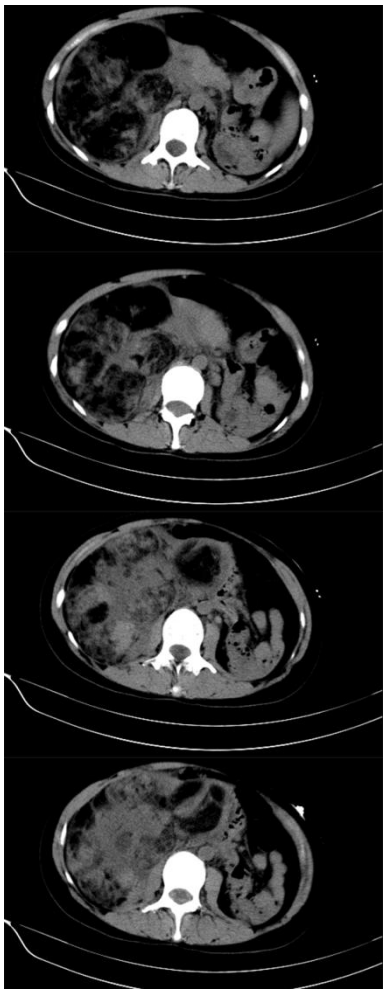

Figure 3: Computed tomography scans. Huge mixed density tumor in right abdominal and pelvic cavity. The surrounding tissue was squeezed.

Discussion

Nearly eighty percent of instances of typical angiomyolipomas arise by chance, while twenty percent of cases occur in people with TSC **[4]**. Loss-of-function mutations in either TSC1 or TSC2 can lead to constitutive activation of mTOR, which can contribute to uncontrolled growth and is the underlying cause of the TSC disease **[2].** TSC patients feature renal angiomyolipomas, lymphangioleiomyomatosis, facial angiofibromascardiac rhabdomyoma, epilepsy, retinal hamartoma, and gingival fibromas. In addition to this, there is a higher likelihood that TSC-associated RAMLs will be big and multifocal **[5].** Detection and identification of RAML at an early stage can lower the risk of significant complications **[6].** Most angiomyolipomas requiring medical attention were typically treated with transarterial embolization or surgical excision prior to the release of everolimus in 2012, a rapamycin derivative blocking the mTOR pathway via acting on mTORC1 **[7].** Whatever, surgical treatment for RAML is considered the optimal approach as for serious complications or tumor size greater than 4 cm **[8]**. The indication of tumor size, though, has recently come under scrutiny. Chronopoulos and colleagues found that tumors that are less than eight centimeters in diameter are typically symptomless **[9].** Everolimus has recently been suggested for use in the first-line preventive strategy for TS-associated RAMLs at a dose of 10 mg orally daily **[6].**

It is well-known that the upstream regulator of mTORC1, except for TSC1 or TSC2, also includes the PI3K/AKT signaling pathway **[10].** It has been established that the AKT/mTOR signaling pathway is an important one that contributes to the expansion of Cancer Stem Cells (CSCs). It has been established that CSCs have the capability of playing a part in the production of GCTB **[11]**. The above may explain why the tuberous sclerosis patient suffered from GCTB one year later. GCTB is extremely rare in patients with tuberous sclerosis, and to our knowledge, no report involving GCTB has been previously reported in the literature. According to the updated 2021 guideline, there is no description of tuberous sclerosis with GCTB. The report of a TS patient with RAML and GCTB would provide new insights into this disease. By concentrating on the mTOR signaling pathway, the anticancer drug rapamycin has been shown to be effective in inhibiting CSCs **[12].** Rapamycin is not only a specific allosteric inhibitor of mTORC1 but also targets the catalytic site and prevents the feedback-mediated PI3K/AKT activation and therefore can potentially offer broader, more potent, and more sustained mTOR inhibition **[13]**. It contributes to the enhancement of treatment methods that are now being utilized to treat several malignancies, such as nasopharyngeal carcinoma **[14],** and even GCTB in the future. It was revealed by Flavio Faziolipoint et al. that patients with sarcomas overexpressed mTOR, which proved the important function that the AKT/mTOR pathway plays in GCTB patients **[15]**. Unfortunately, due to various reasons, the patient did not use everolimus, undergo MRI or enhanced CT, or renal function and blood pressure every 1-3 years during the up to 12 year follow-up. As the patient had seizures about once a month and had a giant RAML, she had a relatively high quality of life, could survive for a long time, and had given birth to a healthy child over the past 12 years. This time we found a considerable angiomyolipoma deriving from her solitary kidney in the abdominal cavity, whose renal function was almost normal. In cases of large TS-associated RAML, total nephrectomy is recommended above conservative treatment as the treatment of choice to limit the danger of potentially life-threatening bleeding **[16].** Which is the best choice for this patient is still in doubt. The patient planned to receive everolimus treatment this time. Because of the complicated circumstances, the patient is still under close follow-up.

Conclusion

The technical difficulties of treating large RAML with nephron-sparing medication is something that we would want to highlight in our case report. Second, it is essential to do more research on the mechanism through which TS complicates GCTB. Third, additional investigation into the volume-reducing effect of mTOR inhibitors for large RAML is required in the form of future studies. Lastly, patients who have kidney illness absolutely need to have their renal function monitored on a consistent basis and receive close follow-up.

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