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Malignancy of renal angiomyolipoma from tuberous sclerosis complex with *TSC2* mutation

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To the Editor: Tuberous sclerosis complex (TSC), with the birth incidence of 1:6000,[1] is an autosomal dominant inherited, multi-system disorder characterized by cellular hyperplasia and tissue dysplasia, among which, renal angiomyolipoma (AML) is one common comorbidity. However, malignancy of renal AML is rare. Herein, we shared a case of malignancy of renal AML from TSC in a young man.

A 24-year-old man with recurrent facial macules for 19 years characterized by a 3-month history of abdominal bloating, left abdominal mass and pain, without fever, vomit, diarrhea, dizzy, hypopsia, urinary urgency and frequency, dysuria, or hematuria. On admission, the temperature was 38.4°C, and there were multiple fibromas with 2 to 5 mm in diameter around cheek, tongue, occiput, back, and unguis; a fissure with 2 mm in length and 1 mm in depth among lingual surface; a mass with 130 mm in length and 100 mm in breadth upon left upper quadrant with poor mobility and palpation tenderness. The results of initial laboratory were as follows: white blood cell count of 15.7×10^9/L (78.6% neutrophils), red blood cell count of 3.4×10^9/L, hemoglobin level of 76.1 g/L, serum creatinine level of 53.8 μmol/L, and anemia screening of α thalassaemia. Urinalysis revealed specific blood ++ and leukocyte +/–. No remarkable findings were found in urine culture, blood culture, electrocardiograph, and chest radiography. Abdominal contrast-enhanced computed tomography (CT) showed: multiple AMLs in liver and bilateral kidneys, with a huge mass (20 cm × 14 cm × 12 cm in size and CT value, 28–89 HU) in the left kidney accompanied by tumor embolus and thrombosis in the left renal vein and postcava [Figure 1]. Cerebral CT scan indicated that multiple nodules and calcification consisted in the left frontal lobe, bilateral basal ganglia, and periventricular area. Further gene detection demonstrated that one heterozygous pathogenic variant exited c.1000delG, p.(Va1334fs) in exon 11 of *TSC2* (16p13|NM_000548.3 as cDNA reference sequences). A quantitative analysis of all 23 *TSC1* exons and all 42 *TSC2* exons was carried out using Multiplex Ligation Probe Amplification, which indicated that there were not any deletion mutations or duplications.

Tumor interventional therapy was advised before a repeated assessment surgical operation for radical cure. Due to the economic burdens, this patient returned to the local hospital to do a complete left nephrectomy with malignant epithelioid angiomyolipoma (EAML) as histopathological results. An excised mass with 27 cm × 18 cm × 11 cm in size and the histopathological examination indicated vessels, smooth muscle, adipose tissue, and epithelioid cells, combined with granular eosinophilic cytoplasms, pathologic mitosis, necrosis, and vascular invasion. The immunohistochemical profile revealed positive expression of human melanoma black-45 (HMB-45), cluster of differentiation 68 (CD68), and tumor protein 53 (P53) and negative expression for estrogen receptor, progesterone receptor, smooth muscle actin, nervous system S-100 (S-100), cytokeratin (CK)-pan, and myogenic differentiation antigen-1. Eight months after his discharge, he had been persistent cachexia.

According to diagnostic criteria and guidelines ratified in the second International TSC Consensus Conference,[2] the patient of this case had involved at least 4 definitely major features, which contained hypomelanotic macules (≥3, at least 5 mm diameter), ungual fibromas (≥2), subependymal nodules (≥2) and angiofibromas in kidney (≥2), and more than 2 minor features, such as intraoral fibromas (≥2) and liver hamartomas. Meanwhile, genetic tests in this case had confirmed that the patient got the presence of a TSC2 mutation in 16p13, which might relate to his α-thalassaemia since previous study had demonstrated that the α-globin gene cluster had been mapped to

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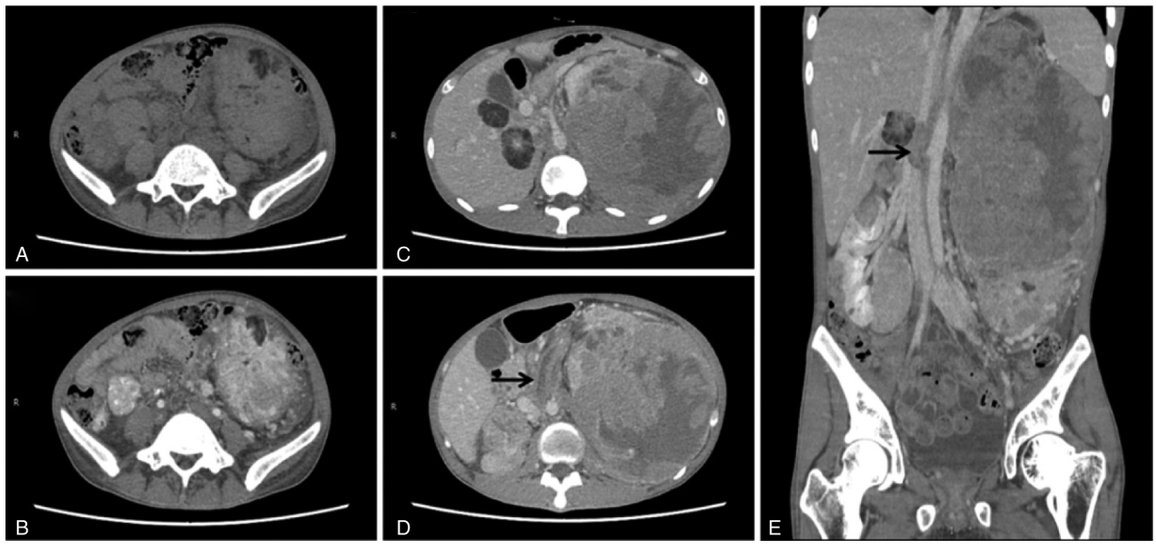

Figure 1: Abdominal contrast-enhanced CT images of EAML in a 24-year-old man. (A) Unenhanced CT scan showed a mass containing some fat content in the left kidney. (B) Contrast-enhanced CT image showed a progressive and heterogeneous enhancement of the tumor. (C) Unenhanced CT scan showed multiple angiomyolipomas in liver. (D) Contrast-enhanced CT image showed tumor thrombosis in left renal vein (black arrow). (E) Contrast-enhanced CT image showed tumor embolus in the post-cava (black arrow). CT: Computed tomography; EAML, epithelioid angiomyolipomas.

chromosome band 16p13.3 distal to the *TSC2* locus.[3] Unfortunately, as an autosomal dominant inherited disorder, his family members (parents and one older sister) denied any manifestations of TSC and rejected any genetic tests.

Renal involvements, characterized by renal AML, cyst and renal cell carcinoma, are remarkable manifestations in TSC, with a prevalence rate of 60% to 80%. As AMLs, most common in TSC, are confirmed to be influenced by estrogen and progesterone, they are rarely diagnosed before adolescence and large AMLs are usually found in women and would grow rapidly during pregnancy.[1] However, AMLs have been thought to be a benign course, and the severe complication is hemorrhage.

EAML has been thought to be a rare subtype of AML, with about 160 cases reported worldwide in English literature up to now. The previous research had summarized that EAML usually occurred at 30 to 80 years old, with the ratio of male/female 9:11.[4] Histological and immunohistochemical markers are crucial for the diagnosis of EAML. Histologically, EAML is presented with the proliferation of epithelioid cells with granular eosinophilic cytoplasms. Immunologically, EAML is characterized by uniformly positive expression for melanocytic markers HMB-45 and/or Melan-A. In contrast, the markers of epithelial cells (CK) and neural cells (S-100) are negative.[5] Moreover, an early series of 41 pure EAML cases of the kidney had demonstrated that clinicopathologic risk factors associated with disease progression (recurrence, metastasis, or death due to disease) included TSC, concurrent AML, necrosis, tumor size >7 cm, extrarenal extension and/or renal vein involvement, and carcinoma-like growth pattern according to univariate analysis; among the risk factors, carcinoma-like growth pattern and extrarenal extension and/or renal vein involvement were significant predictors of outcome.[6] Notably, the patient had also been confirmed to involve a heterozygous *TSC2* c.1000delG, p.(Va1334fs) (exon 11) variant, which was a frame-shift mutation influencing protein translation, but had never been reported before. To the best of our knowledge, more than 300 germline mutations had been described in the *TSC2* gene so far, which included missense, non-sense, frame-shift, and splice-site mutations among the 41 coding exons of *TSC2* gene. The genetic heterogeneity might correlate to the clinical variability.[7] It is probably that the genetic alteration of c.1000delG, p.(Va1334fs) in exon 11, as another novel mutation, most probably leads to the EAML of our patient.

Ultrasound scanning of the kidneys was encouraged every 1 to 3 years in older children and adults with TSC-associated renal AMLs. AMLs with larger than 4 cm in diameter and/or with an aneurysm larger than 5 mm in diameter, which would develop acutely life-threatening bleeding, should be eliminated by embolization first, or followed by nephron-sparing resection, or ablation.[2] Complete nephrectomy should be avoided because of potential secondary complications, increased risk of chronic kidney disease, and end-stage renal failure. In 2012, International TSC Consensus Conference for asymptomatic AMLs measuring more than 3 cm in diameter, mTORC1 inhibitors, such as rapamycin or everolimus, were the recommended first-line therapy.[2] Furthermore, only a few EAML cases with benefit from mTORC1 inhibitors had been reported; some research studies had revealed TSC2 deficiency in a patient with sporadic EAML as the mutation causative of an exceptional response to mTORC1 inhibitors.[8]

In summary, this rare case presented a young man with malignant EAML from TSC with a heterozygous *TSC2* c.1000delG, p.(Va1334fs; exon 11) variant. We hope that

it will offer us more information about TSC-related renal angiomyolipoma, especially the uncommon malignancy.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent form. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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Conflicts of interest

None.

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