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Case report

Tuberous sclerosis complex and polycystic kidney disease contiguous gene syndrome with Moyamoya disease

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ABSTRACT

Tuberous sclerosis complex (TSC) and autosomal dominant polycystic kidney disease (ADPKD) are two diseases sharing close genetic loci on chromosome 16. Due to contiguous gene syndrome, also known as contiguous gene deletion syndrome, the proximity of TSC2 and PKD1 genes increases the risk of co-deletion resulting in a shared clinical presentation. Furthermore, Moyamoya disease (MMD) is a rare vaso-occlusive disease in the circle of Willis. We present the first case of TSC2/PKD1 contiguous gene syndrome in a patient with MMD along with detailed histopathologic, radiologic, and cytogenetic analyses. We also highlight the clinical presentation and surgical complications in this case.

1. Introduction

Tuberous sclerosis complex (TSC) is a pleiotropic neurocutenous disease affecting kidneys, brain, lungs, and skin [1]. TSC is diagnosed clinically depending on the number of symptoms present. This disease results from the genetic mutation of TSC1 or TSC2, which encodes for hamartin and tuberin respectively. Furthermore, the TSC2 gene lies adjacent to PKD1 gene coding for Polycistin-1 on chromosome 16p, therefore mutations in the region can also lead to Polycystic Kidney Disease type 1 (PKD1) in a process known as contiguous gene syndrome [2]. PKD1 and TSC2 each have been associated with Moyamoya disease (MMD) [3,4], an uncommon vaso-occlusive disease of major blood vessels in the circle of Willis. However, to date there have been no reports of all three diseases occurring together. In our report, we present the first case of a patient with TSC2/PKD1 contiguous gene syndrome and MMD, and we highlight the surgical complications associated with bilateral nephrectomy in such a patient.

1.1. Case report

Our patient is a 19-year-old Caucasian male with a history of tuberous sclerosis complex (TSC), autosomal dominant polycystic kidney disease (ADPKD), Moyamoya disease (MMD), seizure disorder, hypertension and hyperlipidemia, who was admitted for bilateral nephrectomy in preparation for renal transplant due to end stage renal disease (ESRD) and concern for increased risk of renal cell carcinoma. The patient's father was also diagnosed with TSC and ADPKD, and the patient's paternal grandfather passed away due to a kidney disorder. His renal ultrasound (Fig. 1) revealed enlarged bilateral kidneys, both with innumerable simple and complex cysts replacing the renal parenchyma. The intervening parenchyma was hyperechoic without normal corticomedullary differentiation. No masses or hydronephrosis were identified in either kidney by ultrasound.

Magnetic resonance angiogram of the brain showed vascular occlusion of both internal carotid arteries consistent with MMD. Vascular flow was not visualized in either anterior or middle cerebral arteries. The right posterior cerebral artery was occluded just distal to its origin. The left posterior cerebral artery showed a focal area of narrowing near its origin but was still patent. There was evidence of collateralization from extracranial vessels in the vascular territory of the left posterior cerebral artery. Almost complete occlusion of the arterial supply by MRI above the level of the circle of Willis with the exception of the left posterior cerebral artery (Fig. 2). Posterior communicating, vertebral, and basilar arteries were patent without abnormal areas of narrowing. Furthermore, MRI revealed multiple partially calcified subependymal masses bilaterally, and cortical and subcortical tubers with scattered calcifications consistent with TSC.

Following bilateral nephrectomy, complications included stroke with right sided severe impairment (left anterior communicating artery (ACA) and middle cerebral artery (MCA) ischemic stroke with midline shift), seizure activity in left temporal lobe, hyperkalemia and retroperitoneal hematoma. CT scan showed diffuse edema in

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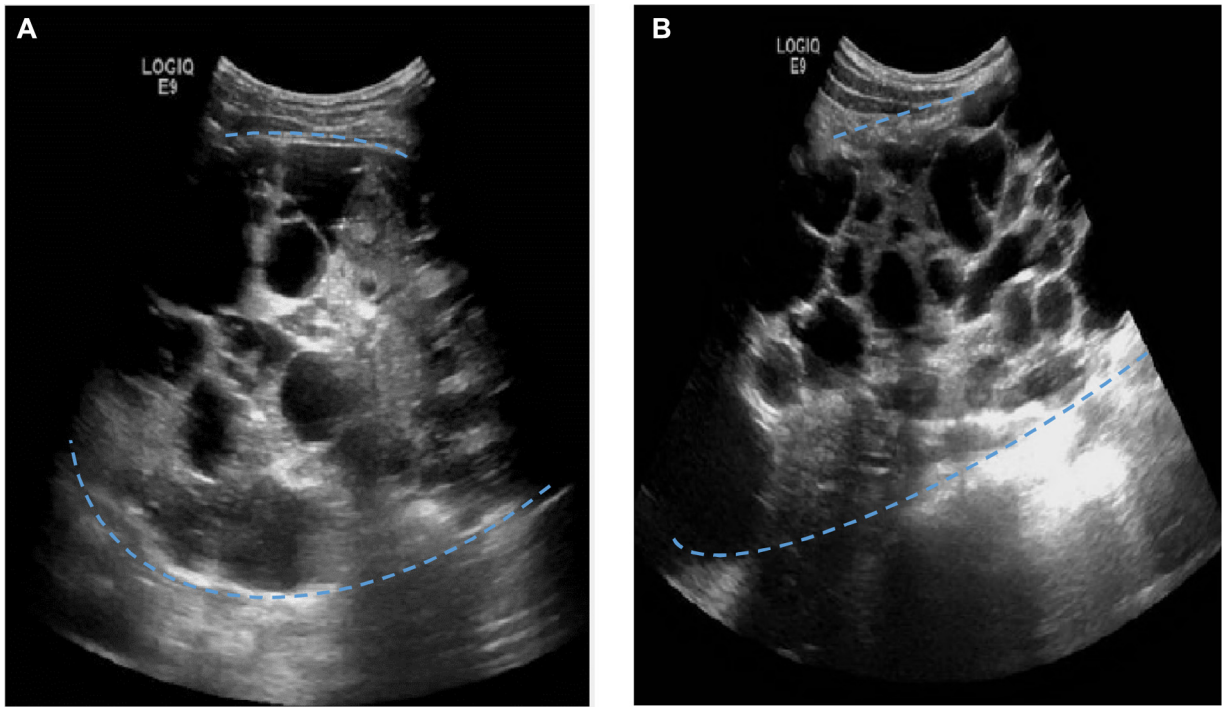

Fig. 1. Ultrasound of kidneys. A: Coronal view of left kidney. B: Sagittal view of right kidney.

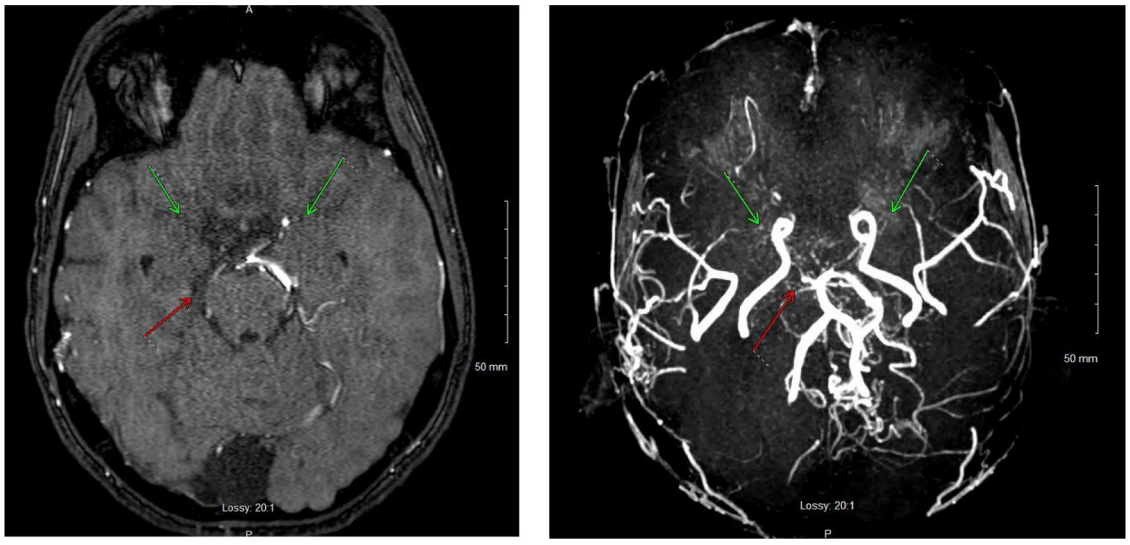

Fig. 2. MRA through the Circle of Willis (right) with 3D imaging (left) demonstrates loss of normal signal through the bilateral MCAs (green arrows), right PCA (red arrow), and bilateral ACAs. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the anterior left frontal lobe concerning for cerebral infarct in the ACA territory. MRI/MRA results were consistent with MMD causing acute ischemic stroke to the left frontal lobe. Given these results, stroke was likely due to thrombosis of one of the extracranial collateral vessels supplying the left frontal lobe. The patient was immediately transferred to the intensive care unit (ICU), and intubated for airway protection. After stabilization, he was discharged to an extended care facility.

Both kidneys were evaluated by pathology following nephrectomy. The right kidney was enlarged and measured $26 \times 14 \times 8.5$ cm and weighed 1687 g. Upon sectioning, the entire renal parenchyma was replaced by cysts ranging from 0.2–4.1 cm in diameter and filled with serous fluid. An $11 \times 6 \times 5$ cm mass with a lobulated, gray-tan, fleshy cut surface was identified at the lower pole, abutting the renal capsule. No necrosis or hemorrhage was identified within the mass (Fig. 3). The left kidney was also enlarged and measured $26 \times 14 \times 7.5$ cm, and weighed 1627 g. The parenchyma was also replaced with cysts ranging from 0.2 to 4 cm in diameter. However, no masses were present in the left kidney.

Histologic sections from both kidneys showed findings consistent with ADPKD. The cysts were lined with a single layer of cuboidal or squamous eosinophilic epithelial cells (Fig. 4). The sections from the tumor mass from the right kidney consisted of components of angiomyolipoma including mature adipose tissue, tortuous thick walled blood vessels with little or abnormal elastic tissue, and perivascular sheets of irregularly arranged smooth muscle cells (Fig. 5). The lesion was positive for immunoperoxidase stains for HMB-45 and Melan-A and negative for cytokeratin