

Case report

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소아 결절성 경화증에서 나타나는 다양한 신증상들

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Various Renal Manifestations in Children with Tuberous Sclerosis Complex

Tuberous sclerosis complex (TSC) is a genetic disorder that affects multiple organ systems and causes tumors. It is important that physicians are aware of the manifestations of TSC, and that they follow the recommendations for screening and evaluation. Several types of renal abnormalities may develop in individuals with TSC. Individuals with TSC may require ongoing treatment that can be adapted for each arising manifestation of renal disease. Herein, we report 4 patients with TSC who presented with a range of different renal manifestations, including angiomyolipoma, renal cell carcinoma, renal infarction, renal cyst, and nephrolithiasis.

Key words: Tuberous sclerosis, Angiomyolipoma, Renal cell carcinoma, Renal infarction, Renal cyst, Nephrolithiasis

Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant inherited disorder characterized by the development of hamartomas in multiple organs, such as skin, brain, heart, eyes, lungs, teeth, oral cavity, and kidneys. Population-based studies suggest a TSC prevalence of 1 in 9,000 individuals in the general population, but its incidence has been estimated to be 1 in 6,000 among live births [1].

Bourneville first identified TSC in 1880 in a patient with CNS abnormalities in the brain tubers [2]. Since then, variable clinical manifestations have been revealed. Genetic studies of TSC demonstrated that this disorder is associated with either a mutation of the *TSC1* gene on chromosome 9q34 that encodes hamartin or the *TSC2* gene on chromosome 16p13.3 that encodes tuberin [3]. Tuberin proteins form hamartomas on multisystemic organs in TSC patients.

Renal pathology is a particularly important abnormality stemming from TSC due to its high frequency, occurrence, and mortality. A study by Leung and Robson [2] showed that 80% of tuberous sclerosis patients demonstrate renal hamartomas by 10.5 years of age, and the number and size of renal hamartomas increase with age. Because renal hamartomas are associated with a high risk for fatal conditions like aneurysms or hemorrhages, close follow-up starting at diagnosis is necessary [4].

Here, we report four cases of renal manifestations of TSC, including angiomyolipoma (AML), renal cell carcinoma (RCC), renal infarction, multiple renal cysts, and calcification. These cases support the need for confirming renal diseases in patients with TSC.

Case report

Case 1

A 25-year-old woman complained of abdominal pain and presented with a palpable mass to our emergency room. At nine years of age, brain magnetic resonance imaging and abdominal ultrasonography (US) identified subependymal multiple nodules and angiomyolipomas; thus, she was diagnosed with TSC. At the age of 18, a

bilateral renal AML measuring 7.7 cm was identified on her left kidney, and a 4.6 cm AML was found on her right kidney (Fig. 1). In 2011, abdominal computed tomography (CT) showed that the masses had grown to 15.5 cm and 8.2 cm, respectively (Fig. 1). Selective arterial embolization (SAE) was performed; after 10 months of embolization, the masses were reduced to 12.8 cm and 5.6 cm in size, respectively (Fig. 1). During two years of follow-up, there were no significant interval changes in either the size or shape of the AMLs.

Case 2

An 18-year-old boy was referred to our pediatric nephrology department after experiencing hematuria and hypertension. After having a seizure at the age of three, the patient's clinical workup revealed subependymal nodules, cortical tubers, and retinal nodular hamartomas, which led to a diagnosis of TSC. We performed abdominal US to evaluate hematuria and observed a 9-cm-sized mass on his right kidney (Fig. 2). Renal biopsy revealed renal cell carcinoma, for which radical nephrectomy was performed (Fig. 2). The tumor was limited to the single kidney and had an exact size of 9.3×7.6 cm.

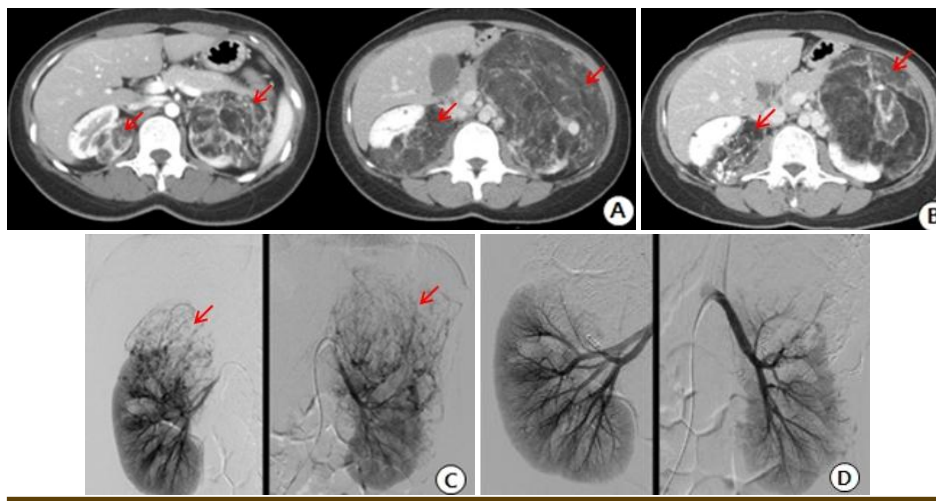


Fig. 1. Angiomyolipoma (AML) on both kidneys: Changes of AML (arrow) with age in abdominal computed tomography before (A) and after (B) selective arterial embolization. Bilateral hypervascular masses (arrow) before (C) and after (D) selective arterial embolization in renovascular angiogram.

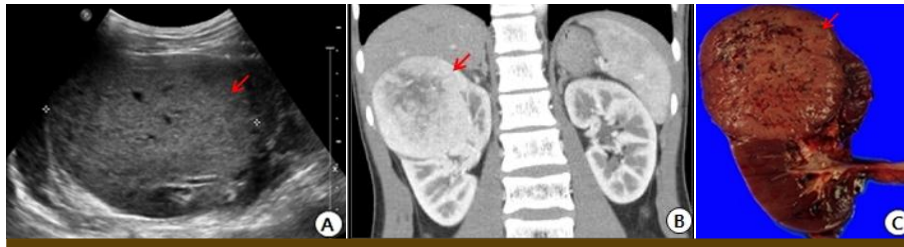


Fig. 2. Renal cell carcinoma (arrow) on the right kidney: Ultrasonography (A), abdominal computed tomography (B), and gross photograph (C).

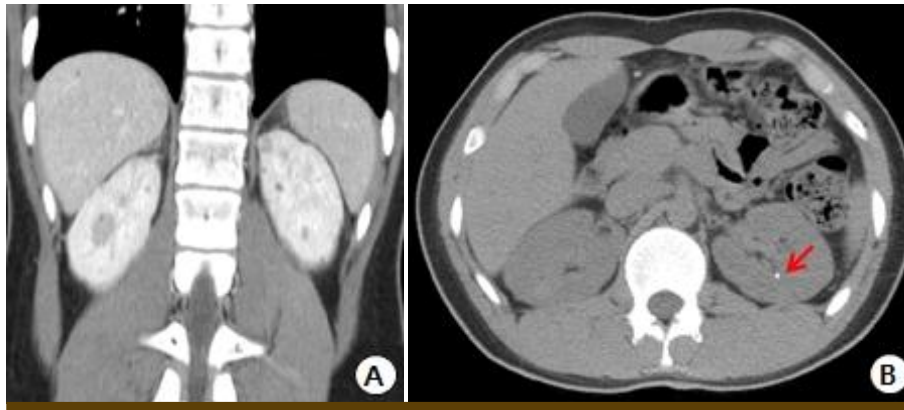


Fig. 4. Bilateral multiple renal cysts (A) and nephrolithiasis (arrow) on the left kidney (B).



Fig. 3. Wedge-shaped renal infarction (arrow) of the left lower pole in abdominal computed tomography.

Case 3

An 11-year-old boy was found to have a wedge-shaped kidney infarction and multiple renal cysts on his left kidney during scheduled CT follow-up in January 2012 (Fig. 3). The patient, who suffered from developmental cognitive impairment, was diagnosed with TSC when

he was two years old after identification of cortical tubers, subependymal nodules, cardiac rhabdomyoma, and renal AMLs. Because his symptoms do not directly affect his kidneys, he is under close observation.

Case 4

A 17-year-old boy presented with left flank pain to the department of pediatric nephrology. He had multiple red facial papules and hypomelanotic macules and had been diagnosed with TSC when he was 12 years old due to findings of cortical tubers, cardiac rhabdomyoma, and hepatic AML. Abdominal CT was performed to evaluate the flank pain, and multiple renal cysts and a small nephrolithiasis were observed (Fig. 4). The patient was released under conservative care.

Discussion

TSC patients experience renal complications with various manifestations and at various stages of disease.

Renal AML is an uncommon benign tumor that is made up of adipose tissue, blood vessels, and smooth muscle tissue; 50-70% of people with TSC develop renal AMLs [5]. One patient, who had giant bilateral AMLs (case 1), experienced abdominal discomfort at the age of 18 due to AMLs 7.7 cm and 4.6 cm in size. Koo et al [6] recommend angioembolization or surgical intervention for symptomatic tumors larger than 4 cm. We suggested several options at that initial presentation, but the patient refused treatment and was lost to follow-up for several years. Three main treatment options for AMLs are total nephrectomy, partial nephrectomy, and SAE. Although SAE is generally the treatment of choice, tumor size, number of tumors, re-growth rate, tumor position, and the patient's age and condition all must be considered when selecting a treatment option. SAE has the benefit of preserving renal function and avoiding surgical risk while effectively relieving pain [7]. After performing SAE in our case 1 patient, the bilateral masses were reduced and her pain was relieved.

Renal cell carcinoma (RCC) is a rare disease in adolescents and is also an uncommon complication of TSC. RCC develops in fewer than 2% of TSC patients. Some studies have suggested that the average age for RCC development among TSC patients is 28 years, but others have suggested 50 years [8, 9]. Accompanied with gross hematuria, a rapidly growing fat-poor mass should signal malignancy, even in pediatric TSC patients. However, it is difficult to make a differential diagnosis between fat-poor AML and RCC through imaging. We performed a biopsy on the case-2 patient and were able to clearly diagnose renal cell carcinoma of eosinophilic cell type; there was no evidence of invasion. During two years of follow-up after performing a radical nephrectomy on the right kidney, there were no signs of recurrence.

Renal cysts are a common renal manifestation of TSC, observed in about 32% of patients [10]. Symptoms, sizes, and numbers of cysts vary from an asymptomatic single cyst to a severe polycystic condition. Polycystic kidney disease can occur in TSC patients due to contiguous deletions in the *TSC2* and *PKD1* genes, which could easily lead to chronic renal failure [11]. The case-3 patient had multiple small cysts in both kidneys and a

wedge-shaped low-density lesion. The lesion seemed to be a sequela of infarction, and cortical defects were found in the same lesion on dimercaptosuccinic acid scan. To our knowledge, renal infarction with TSC is a very rare presentation, and this is the first case report to document it. We suspect that this presentation was caused by stenosis of the main vessels due to multiple nearby tumor and cystic lesions.

The patient documented in case 4 had multiple cystic lesions on his kidneys and pancreas. Renal cystic disease is a risk factor of nephrolithiasis. Cystic lesions disrupt distal tubular function and cause hypocitraturia [12]. Another nephrolithiasis risk factor is long-term use of topiramate, which is an anti-epileptic drug that is known to inhibit carbonic anhydrase and lead to decreased citrate excretion [13].

In conclusion, TSC patients can have various renal manifestations, including angiomyolipoma, renal cell carcinoma, renal infarction, multiple renal cysts, and nephrolithiasis. Therefore, scheduled follow-up examination is necessary for the early detection and proper treatment of the renal disease.

한글요약

결절성 경화증은 과오종의 발생을 특징으로 하는 유전 질환으로, 피부, 뇌, 심장, 눈, 폐, 구강, 신장 등의 다양한 장기들을 침범한다. 신장에서 관찰 가능한 다양한 병변들은 발생 빈도와 사망률이 높기 때문에 주의를 필요로 하며, 신장 증상의 이른 발생 시기를 고려하여 소아 연령에서부터 적절한 진단과 관리가 중요하다. 저자들은 소아 연령에서 발생한 거대 혈관근육지방종, 신세포암, 신경색, 신낭종, 그리고 신결석증 등이 동반된 결절성 경화증 4례를 경험하였기에 보고하는 바이다.

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