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Tuberous Sclerosis and Polycystic Kidney Disease
- A Case Report -

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Polycystic kidney disease is a relatively uncommon finding of tuberous sclerosis. Furthermore, the renal insufficiency by the severe polycystic kidney disease is extremely rare in tuberous sclerosis. The patient was a 27-year-old man, complaining of generalized seizure and progressive abdominal distension. His clinical features were chracterized by epilepsy, mental retardation, skin abnormalities including adenoma sebaceum, shagreen patch and ash-leaf spots. Abdominal computed tomography demonstrated numerous variable sized cysts throughout both kidneys. Clinical and laboratory findings revealed chronic renal failure due to severe polycystic kidneys. On reviewing the literature, the present case is the first report of polycystic kidneys associated with tuberous sclerosis in Korea.

Key Words : *Tuberous sclerosis, Polycystic kidney disease, Chronic renal failure*

INTRODUCTION

Tuberous sclerosis is an autosomal dominant disorder of unknown etiology that affects multiple body organs including skin, brain and kidneys (Kandt et al., 1992). Seizure, mental retardation and a variety of cutaneous lesions associated with visceral hamartomas characterize the inherited neurocutaneous disorder of tuberous sclerosis (Tallarigo et al., 1992). The characteristic renal lesion is the angiomyolipoma, present in 50 to 80% of patients with this disorder (Chonko et al., 1974). Renal cysts develop in approximately 20% of patients with tuberous sclerosis, serious "polycystic disease" in less than 5% (Stillwell et al., 1987). The incidence of renal failure has been considered to be rather low, presumably due to early death from neurological complications associated with repeated convulsive seizures (Critcheley and Earl, 1932). However, the development of more effective anticonvulsant drugs and of neurosurgical techniques and consequent longer survival may lead to more frequent presentation with renal involvement (Perot et al., 1966).

Recently, we experienced a young adult with chronic renal failure due to polycystic kidney disease associated with tuberous sclerosis. On reviewing the literature, we found polycystic kidney disease associated with tuberous sclerosis very rare in the world. To our best knowledge, the present case is the first report of polycystic kidneys with tuberous sclerosis in Korea.

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CASE REPORT

A 27-year-old man was admitted to the Chonnam University Hospital, with a 5 month history of both flank pain and progressive abdominal distension. He was the product of a normal pregnancy and delivery and had 6 healthy sisters. There was no familial history of cystic kidneys, renal disease, neurologic disease, or cutaneous lesions. His parents and 6 sisters had normal appearances on renal imaging and genetic counselling was provided to suggest he was a sporadic case.

Fig. 1. Facial lesions of the patient (adenoma sebaceum) are composed of multiple warty nodules, yellowish pink or brownish red in color, varying in size. These lesions are symmetrically distributed on the side of the nose, the nasolabial fold and the cheeks in the shape of a butterfly.

Generalized seizure has first developed when he was 3 years old and has occurred intermittently since then. Seizure attack was manifested by sudden loss of muscle tone and consciousness associated with "rolling back" of the eyes. Adenoma sebaceum on the face has appeared when he was 5 years old.

The patient appeared chronically ill and had a height of 168cm and a weight of 59kg. The pulse rate was 90/min, the blood pressure 190/100mmHg and the respiration rate 20/min. Physical examination revealed the presence of bilateral, irregular flank masses which were thought to be enlarged kidneys. The characteristic facial lesion was composed of multiple warty nodules, yellowish pink or brownish red in color, varying in size. These lesions were symmetrically distributed on both sides of the nose, the nasolabial fold and the cheeks in the shape of a butterfly (Fig. 1). The skin over the lumbosacral region of the back was marked by a rough thickening which was yellowish, brown plaques (shagreen patch). Hypopigmented spots were presented on the back (ash-leaf macules). He appeared to be of mild mental retardation on K-WAIS test. His intelligence quotient was scored at 52. His growth and developmental milestones appeared to be normal.

The hemoglobin was 5.2g/dl, hematocrit 31.7%, white cell count 7,100/mm^3 (neutrophil 53%, lymphocyte 21%), and platelet count 157,000/mm^3. Urinalysis showed pH 8.0, 100mg/dl protein, while microscopy of urine revealed 10-19 WBC/HPF, >100 RBC/HPF, and no casts. The blood urea nitrogen was 109mg/dl, serum creatinine

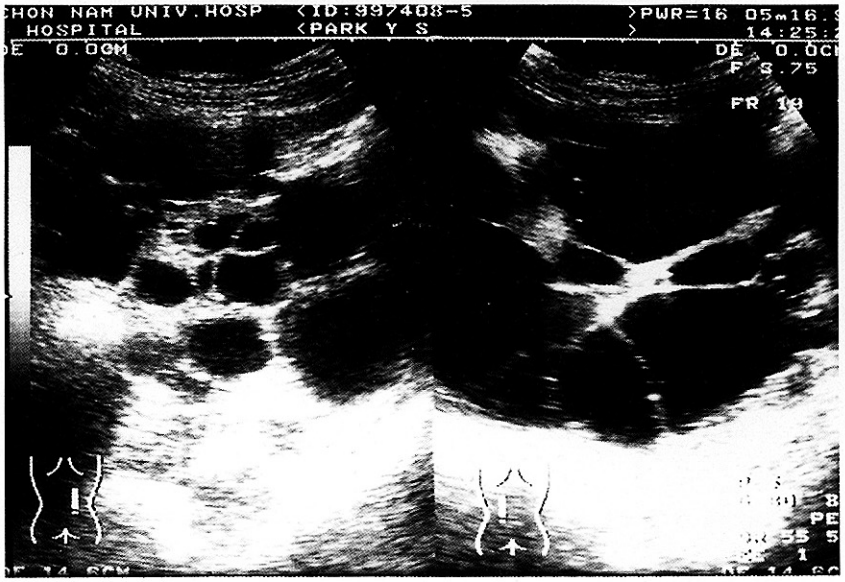

Fig. 2. Abdominal ultrasonogram shows multiple variable sized thin walled hypoechoic cystic masses throughout both kidneys; no cysts were identified in the liver, spleen and pancreas.

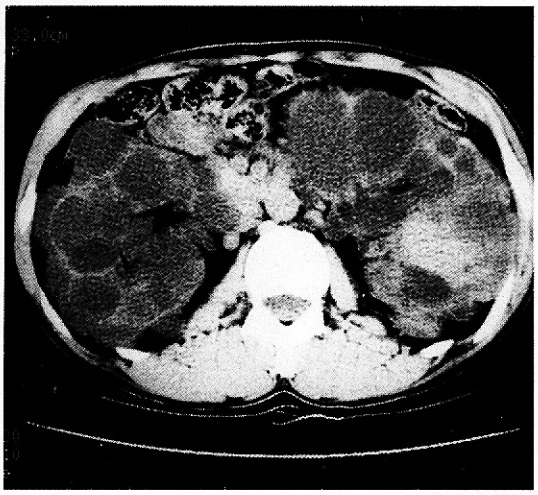

Fig. 3. Abdominal computed tomography shows multiple variable sized thin walled hypodense cystic masses throughout both kidneys. However, there was no evidence of angiomyolipoma in the kidneys and no cysts were identified in the liver, spleen and pancreas.

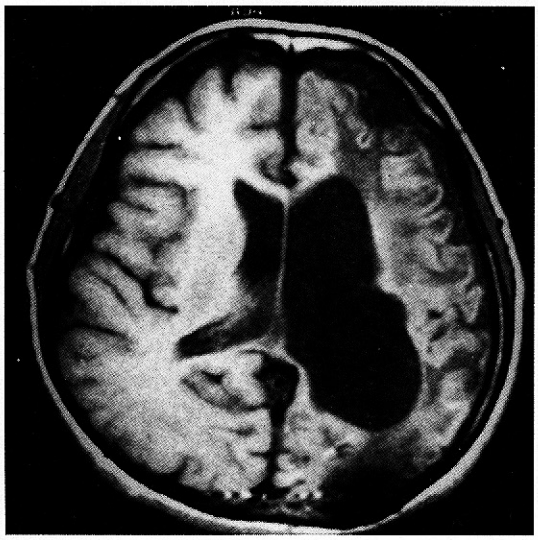

Fig. 4. Magnetic resonance imaging of the brain revealed marked dilatation of left lateral and 3rd ventricle. but, not showed obstructive lesions at aqueduct of sylvius. There was no evidence of characteristic cortical tuber, and subependymal nodule.

15.2mg/dl and endogenous creatinine clearance 3.4 ml/min. Serum sodium was 135mEq/L, potassium 5.2 mEq/L, chloride 105mEq/L, total calcium 3.2mEq/L, ionized calcium 1.7mEq/L, inorganic phosphorous 8.1 mg/dl, magnesium 2.3mEq/L and uric acid 7.9mg/dl.

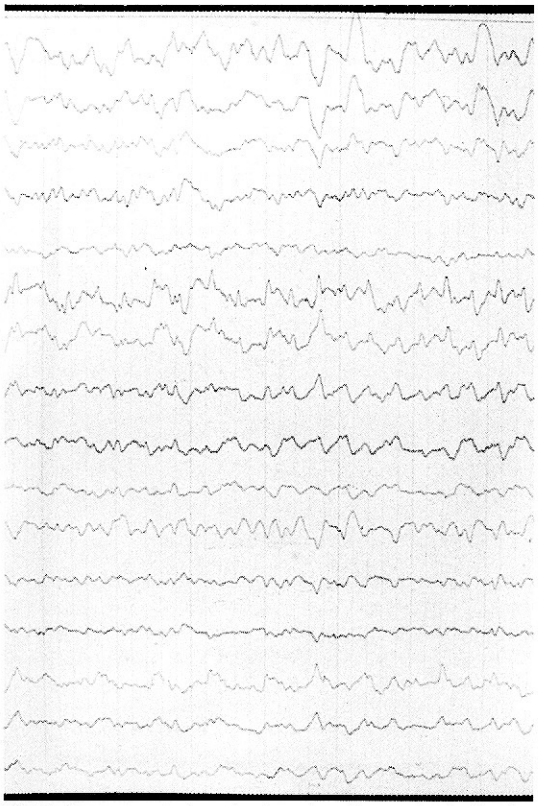

Fig. 5. Electroencephalogram showed a frequently discharging spike focus on the right frontal area and there was generalized paroxysmal epileptiform activity of poly-spikes and slow waves.

The liver function tests were within normal limits. The plasma renin activity was elevated to 5.1ng/ml/hr.

Chest X-ray findings showed mild cardiomegaly and slightly increased bronchovascular markings. Ophthalmoscopic evaluation did not reveal phacomas. Echocardiographic examination did not reveal cardiac rhabdomyoma. Roentgenograms of the skull series revealed punctate small calcific foci in left parietal area. Abdominal ultrasonography (Fig. 2) and computed tomography (Fig. 3) demonstrated multiple cystic masses throughout both kidneys; no cysts were identified in the liver, spleen and pancreas. Magnetic resonance imaging of the brain revealed left obstructive hydrocephalus, but, did not show characteristic tubers or nodules (Fig. 4). Electroencephalogram showed a frequently discharging spike focus on the right frontal area and there was generalized paroxysmal epileptiform activity of poly-spikes and slow waves (Fig. 5). Skin biopsies of the face and lumbosacral lesions were obtained and interpreted as adenoma sebaceum (Fig. 6A) and shagreen

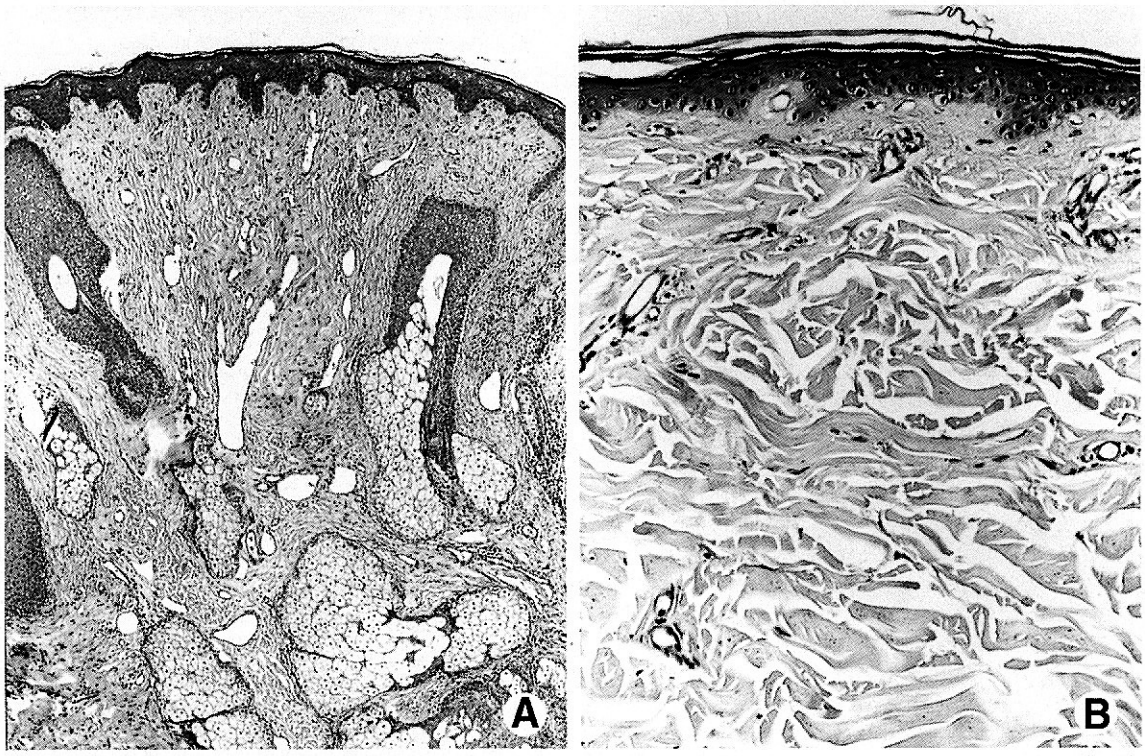

Fig. 6. Skin biopsy. **A**: Dermal fibrosis and dilatation of some of the capillaries suggesting angiofibroma, or so called adenoma sebaceum of the face. **B**: A dense, sclerotic mass of very broad collagenous bundles are seen in the lower dermis suggesting collagenoma, or so called shagreen patch.

patch (Fig. 6B), respectively. These findings in abdominal CT, brain MRI, electroencephalogram, skin biopsies as well as clinical characteristics led us to the diagnosis of chronic renal failure due to polycystic kidney diseases associated with tuberous sclerosis.

As for the management, the patient took diphenylhydantoin and carbamazepine for the control of seizures. The original episodes of loss of consciousness gradually ceased. The blood pressure was treated successfully with amlodipine and enalapril. He was supportively cared with analgesics and blood transfusion therapy. Arteriovenous fistula operation was done for long-term hemodialysis. The patient moderately improved on these supportive cares and was discharged, and since then he has been managed with maintenance hemodialysis and under surveilance at outpatient clinic.

DISCUSSION

Tuberous sclerosis is a hereditary developmental anomaly occuring in approximately 1 of every 100,000 births (Critchley and Earl, 1932). It is a systemic disorder characterized by epilepsy, mental retardation, skin abnormalities including adenoma sebaceum and ash-leaf spots, and hamartomas of many organs including angiomyolipoma of the kidneys and renal cysts (Avisror, 1983; Layzer, 1996). Although tuberous sclerosis is inhereted as an autosomal dominant gene, only 20-50% of patients have a family history (Lagos and Gomez, 1967; Layzer, 1996). A genetic mutation is believed to be responsible for the remainder. Our patient had no familial history of a certain inherited disease, but seizure attack had occurred intermittently since he was 3 years old. He appeared to be suffering from mild mental retardation on K-WAIS test. Nearly all patients have distinctive skin lesions, hypopigmented spots (Ash-leaf macule) which are more numerous on the trunk and are easier to see with a wood lamp. The next common feature is adenoma sebaceum, a papular, salmon colored eruption on the center of the face. Our patient had typical adenoma sebaceum on his face, which was

confirmed by skin biopsy, shagreen patch on lumbosacral lesion and ash-leaf macule on back. Renal angiomyolipomas are found in as many as 50% of cases (Chonko et al., 1974). Most frequently, they are multiple and bilateral. Solitary renal angiomyolipoma also have been noted but they usually have been noted in subjects without other evidence of tuberous sclerosis (Anderson and Tannen, 1969). However, renal angiomyolipoma was not noted in the present case.

Renal cysts occur less commonly. The tubular cysts in this disease are lined by a distinct, perhaps unique epithelium of markedly hypertrophic and hyperplastic cells with prominent eosinophilic cytoplasm (Stapleton et al., 1980). However, renal failure has not often been verified, presumably because of the early death of patients, 40% of whom are dead by the age of 5 years and up to 75% by the age of 20 years, all usually of neurologic complications (Scheig and Bernstein, 1961). The renal insufficiency likely results from parenchymal compression by the cysts, but the frequency of severe cystic disease is also low, occurring in fewer than 5% of patients (Stillwell et al., 1987). Parenchymal compression may also account for hypertension, which has been linked to hyper-reninemia (Yu and Sheth, 1985). Autosomal dominant polycystic kidney disease may present in young age and is indistinguishable radiographically from the polycystic kidney disease found in tuberous sclerosis. The definitive diagnosis of polycystic kidney disease in tuberous sclerosis can be made at biopsy. The finding of cysts lined with a hyperplastic epithelium containing cells which are strongly eosinophilic with large and hyperchromatic nuclei is thought to be unique for tuberous sclerosis (Bernstein and Robbins, 1991). In the present case cysts can't be differented from those in autosomal dominant polycystic kidney disease by renal imaging studies including renal computed tomography and ultrasonography. However, cysts were noted only in both kidneys. Clearly, our case demonstrates that cysts are unrelated to angiomyolipoma and also had end stage renal failure and hypertension due to severe polycystic kidney disease associated with tuberous sclerosis. A small but well documented minority of tuberous sclerosis patients present with a striking clinical picture of enlarged and polycystic kidneys recognized at birth or shortly thereafter (O'Callaghan et al., 1975 ; Stapleton et al., 1980 ; Webb et al., 1993). Webb et al. (1993) had reviewed 36 cases of polycystic kidney disease associated with tuberous sclerosis reported since 1970. There was a male predominance of 1.5 :1, and most patients (18/33) presented under 3 years with abdominal distension and enlarged kidneys. Eighteen of the 20 patients in whom blood pressure was recorded were hypertensive at presentation. The degree of involvement may vary from the presence of a few cysts to total cystic replacement.

Two different genetic loci have been identified : one on chromosome 9 (TSC1) and the other on chromosome 16p (TSC2) that is immediately adjacent to the gene for the most common form of autosomal dominant polycystic kidney disease (PKD1) (Nellist et al., 1993). Five large deletions were identified by pulse field gel electrophoresis (PFGE) and one was shown to disrupt both TSC2 and PKD1 (The European Chromosome 16 Tuberous Sclerosis Consortium, 1993 ; The European Polycystic Kidney Disease Consortium, 1994). These observations suggested that constitutional deletion of PKD1 might be important in the development of very severe, early onset polycystic kidney disease in some tuberous sclerosis patients. Brook-Carter et al. (1994) studied five tuberous sclerosis patients with the phenotype of grossly enlarged polycystic kidneys in infancy. They found deletions involving TSC2 and PKD1 in each case. The severity and early presentation of the cystic disease in these cases distinguishes it from changes seen in the kidneys of tuberous sclerosis patients without such deletions. These findings point to the existence of at least two molecular mechanisms of cystogenesis in tuberous sclerosis. Our patient had severe polycystic kidney disease and tuberous sclerosis, and its onset might be in child or before then. These findings raise the possibility of "contiguous gene" syndrome. For the confirmatory diagnosis DNA analysis for the presence of deletions in the TSC2 region using pulsed field gel electrophoresis (PFGE) or fluorescence in situ hybridization (FISH) and distinctive histopathological diagnosis are required. Such investigation will provide adequate information for the provision of accurate genetic counselling and prognosis.

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