

## Case Report

# A Tuberos Sclerosis Girl with Huge Nephromegaly

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### Abstract

Tuberos sclerosis is a common life long disease requiring long-term follow-up. It is well known for its multiple organ involvement. We describe one patient who has developed huge bilateral renal angiomyolipomas. The revised diagnostic criteria, recommended surveillance protocol and major complications of the tuberous sclerosis complex are discussed and the management of these huge renal masses in our patient is discussed.

**Key words** Angiomyolipoma; Tuberos sclerosis

### Case History

A 20 years old adolescent girl was admitted for investigation of abdominal distension in April 2002. She was a known case of tuberous sclerosis and had been followed up in our Department for many years.

She presented with recurrent convulsion since six months of age and a diagnosis of tuberous sclerosis was made. She was treated with anti-convulsants and the condition was under control and there was no more fit since 2 years of age. Electroencephalography (EEG) and ultrasonography (USG) of the abdomen were normal. Computerised tomography (CT) of the brain revealed multiple periventricular calcifications with no hydrocephalus. Echocardiogram was normal. Her mentality was normal and was studying in normal school.

At 10 years of her age we detected mild hepatomegaly. USG of the abdomen revealed a 6.5 cm hypoechoic harmatoma in the right lobe of liver. Both her kidneys were

mildly enlarged with no hydronephrosis, and multiple small angiomyolipoma in both kidneys were found with the largest diameter measuring about 1.8 cm.

She was followed up with another abdominal USG in 1994 when she was 12 years old, which showed no interval change. Repeat ultrasonography of the abdomen in 1999 revealed also multiple small echogenic nodules in both kidneys, with increased in number and size when compared with previous scans. In early 2002, the patient noticed rapid increase in abdominal girth. She ignored the abdominal distension until it got bigger and bigger. She was then admitted to our hospital for work-up of massive abdominal distension in April 2002.

She was noticed to be pale without jaundice. Neurocutaneous signs including facial adenoma sebaceum, Shagreen patches, hypopigmented lesions and subungual fibromas were present. There was neither café-au-lait spot nor any stigmata of chronic liver disease. Her abdomen was grossly distended with an everted umbilicus (Figure 1). There was hepatomegaly with a liver edge palpable at 4 cm below the right costal margin. There were also bilateral huge ballotable kidneys. Ultrasonography showed bilateral huge masses, which almost occupied the whole abdominal cavity. CT abdomen detected huge heterogeneously enhanced fat-containing mass (Figure 2).

Laboratory investigations detected iron deficiency anemia with hemoglobin level around 9 g/dL. Her renal function, liver function and clotting profile were normal. Markers for malignancy such as alpha-fetal protein, CEA, hCG and

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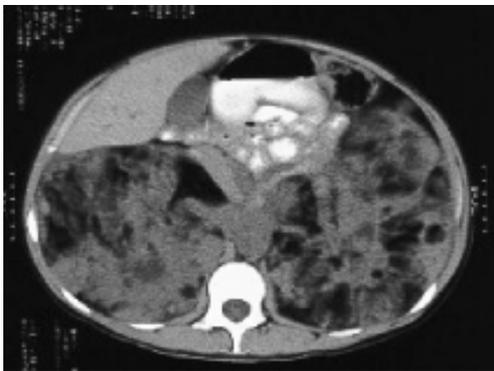
ceruloplasmin were all negative. Urinalysis was normal as well. Her serum creatinine and creatinine clearance were 50  $\mu\text{mol/L}$  and 123  $\text{ml}/1.73 \text{ m}^2/\text{min}$ , respectively. Radionuclear scan was performed which showed that both kidneys were distorted with multiple areas of decreased uptake.

She had selective arterial embolisation done trying to shrink the size of one angiomyolipomas (AML). However, she failed the procedure as the lesion was too large with numerous feeding arteries. It is not possible to avoid damaging the remaining normal renal tissue. Unilateral nephrectomy of the left side larger lesion was performed on June 2002 to relieve the abdominal distension and to reduce the risk of spontaneous haemorrhage. The pathological specimen was sent for gross (Figure 3) and microscopic examination (Figure 4).

She defaulted our follow-up appointment afterward and come back on July 2003, with recurrence of abdominal

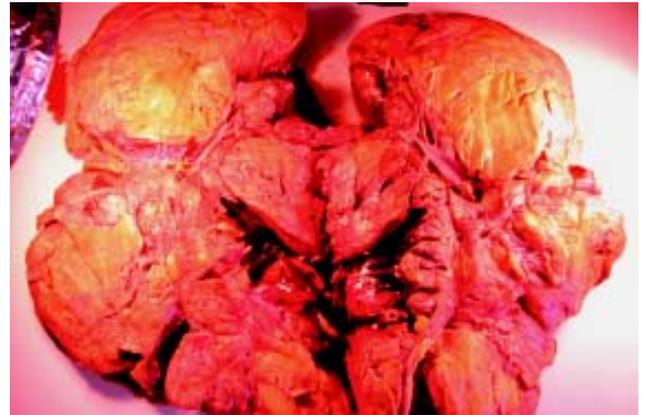


**Figure 1** The grossly distended abdomen of our patient.

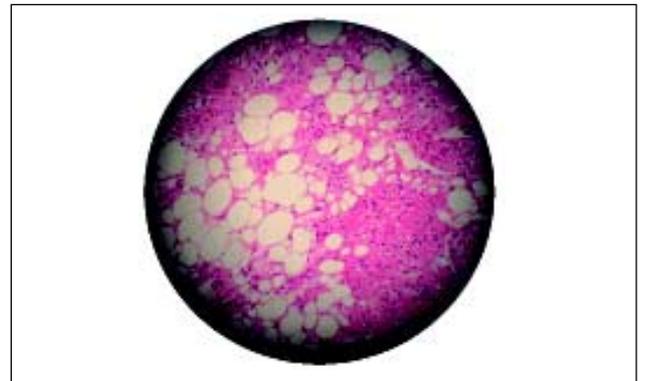


**Figure 2** CT abdomen detected a huge heterogeneously enhanced and fat-containing mass,  $>10 \text{ cm}$  at both renal bed and extended to the pelvic cavity. They almost replaced all normal parenchymal tissue and displaced all bowel loops. They were angiomyolipomas (AML) that originated from the kidneys. There was no active bleeding seen.

distension. She noted to have derangement in renal function with urea raised to 15.8  $\text{mmol/L}$  and creatinine raised to 167  $\mu\text{mol/L}$ . The serum creatinine clearance was 38  $\text{ml}/\text{min}/1.73 \text{ m}^2$  only. Repeat abdominal ultrasonography shows that the right AML have enlarged as compared with previous



**Figure 3** Gross examination of the bisected mass showed the atrophic kidney encased by the mass. The gross specimen revealed a lobulated yellowish tumour mass weighted 5.6 kg and measured 29  $\text{cm} \times 23 \text{ cm} \times 18 \text{ cm}$ . Cut section showed lobulated adipose tumour encasing the left kidney. The kidney was distorted by the tumour mass and measured 8  $\text{cm} \times 5 \text{ cm} \times 5 \text{ cm}$ . Cut section showed predominantly adipose tissue with foci of haemorrhage. The hilar region showed no tumour involvement and the vessels were patent.



**Figure 4** Histological examination of the specimen showed the adipose, vascular and muscle tissues, the three elements of an angiomyolipoma. There were areas of mature adipose tissue that blended with hyalinized vessels and proliferation of myoid-spindled cells. A few discrete area of necrosis were noted. There were occasional giant cells and bizarre nuclei. Mitosis was inconspicuous. No epitheloid cells were seen. The tumour cells were positive for HMB-45.

scan. We managed her chronic renal failure conservatively and plan to remove the remaining kidney when she was symptomatic and then commence renal replacement therapy.

## Discussion

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder that causes significant complications in multiple organ systems as the disease progress. Roach<sup>1,2</sup> had put forward a recommended evaluation protocol in the Tuberous Sclerosis Consensus Conference for Diagnostic Evaluation in 1999 for the rational use of diagnostic studies in patients with TSC. Regular screening by means of neurodevelopmental testings, eye examination, electroencephalography, electrocardiography, echocardiography, renal ultrasonography, computed tomography and magnetic resonance imaging were suggested (Table 1).

It was found that the nervous system and the renal system are the two most commonly involved organ systems in patients with TSC.<sup>3</sup> Common renal lesions include angiomyolipomas, renal cysts, and renal cell carcinoma. In a cross sectional study of renal involvement in tuberous sclerosis done by Cook<sup>4</sup> in 1996, the prevalence of renal involvement was 61%. AML were detected in 49%, renal cysts in 32%, and renal carcinoma in 2.2%. By age of 10 years, nearly 75% TSC patients have evidence of one or more renal AML.

AML are hamartomatous or benign tumour-like lesions that occur primarily in the kidney, but is also present in the liver and other organs. It is a mixture of fat cells, smooth muscle, and dysmorphic vessels. Most of them showed

positive immuno-reactivity for HMB-45 (melanoma-associated antigen), which served as a marker of AML.

Renal AML vary greatly in size. During the first decade of life, the number and size tend to increase, but symptomatic renal AML seem to occur less often in children than in adults. Large AML cause diffuse abdominal discomfort, haematuria, hypertension, and impaired renal function. Fifty percent were asymptomatic. The most serious complication is bleeding with symptoms of pain at the back, flank, or abdomen and can lead to shock and death. Bilateral, multiple AMLs can cause renal insufficiency, usually in patients who also have renal cystic disease. Among TSC patients, AML is an important cause of morbidity, including end-stage renal failure, which is a leading cause of death in these patients.

### *How Fast Could the Renal AML Grow?*

The condition was alarming in our patient in view of the rapid growth of the tumour. In fact for one report<sup>5</sup> of 'giant' bilateral AML, the total tumour load is 5.5 kg. Hamaguchi<sup>6</sup> observed the natural history of AML in one of his patients and calculated the doubling time for the AML, which is 1,370 days for the first period of four years and about 2,075 days for the second period of 11 years. It is observed that AML are commonly larger in women than in men and they occasionally grow rapidly during pregnancy, which suggests that hormones may play a role in stimulating the growth of AML. Colombat<sup>7</sup> reported a case of AML which showed 10% of the nuclei expressed oestrogen receptors and 5% showed progesterone receptors. The oestrogen and progesterone immunoreactivity suggested that AML could be hormonally dependent, which may be an explanation for the rapid growth of the renal AML in our patient.

**Table 1** Diagnostic evaluation

Assessment	Initial testing	Repeat testing
Neurodevelopmental testing	At diagnosis and at school entry	As indicated
Ophthalmic examination	At diagnosis	As indicated
EEG	If seizures occur	As indicated for seizures
ECG	At diagnosis	As indicated
Renal USG	At diagnosis	Every 1-3 years
Cranial CT	At diagnosis	Children/Adol; every 1-3 years
Cranial MRI	At diagnosis	Children/Adol; every 1-3 years
Echocardiography	If cardiac symptoms occur	If cardiac dysfunction occur
Chest CT	At adulthood (women only)	If pulmonary dysfunction occur

### **Are All Renal AMLs Benign?**

Actually is the hamatoma really so 'benign'? The answer is 'No'.<sup>8</sup> There were a number of reports of malignant transformation. Among the reports concerning malignant transformation, Kawaguchi<sup>9</sup> mentioned diffuse atypical epitheloid cells in his case report, which were immunoreactive for p53 in addition to HMB-45. It was suggested that p53 mutation may play an important role in malignant transformation of renal AML and can be a useful marker to detect the malignant component inside the AML. However, the exact actual incidence of malignancy in TSC is unknown. It is clear that in TSC malignant tumors occur with a much lower frequency than do benign tumors. Malignant change is an important part of the differential diagnosis of atypical AMLs in individuals with TSC, particularly those that lack fat density on radiographic imaging studies.

### **How Should We Approach the Large AML in Our Patients?**

For the management of the AML, it depends very much on the size and symptoms<sup>10</sup> of the patient. Lesions were classified as small (<4 cm), medium (4-8 cm) or large (>8 cm) based on the single largest lesion in each kidney.

For those lesions less than 4 cm in diameter, most centres advocate a 'Wait and See' approach. Small asymptomatic lesions tends to remain stable but should be periodically evaluated. Medium-sized lesions have the most variable behaviour, about 54% requiring intervention to treat haemorrhagic complications.<sup>10</sup> These lesions should be followed closely with serial imaging studies, and if significant changes in size or symptoms are noted, or the patient is at great risk for frank trauma, elective intervention should be initiated promptly to increase the chances of renal salvage. Large asymptomatic AML will most likely be symptomatic and should be treated electively prior to the development of symptoms and potential complications.<sup>6</sup> It is fortunate that there was no bleeding in our patient despite the very huge size of the masses.

Selective arterial embolisation is the current advocated first-line treatment for AML.<sup>10,11</sup> The hamatomatous lesions distort and damage renal parenchyma and can lead to haemorrhage especially when there is invasion of the capsule. To reduce the risk of haemorrhage, transarterial embolisation is used to necrose the AML, while normal tissue is spared and hence renal function is preserved.

If the patient has extensive and bilateral AMLs, as in our patient, the decision to operate should be made between

the balance of the risk of spontaneous rupture with retroperitoneal haemorrhage to immediate commencement of renal replacement therapy, since loss of renal parenchyma inevitably leads to renal failure.<sup>10</sup>

### **Conclusion**

In conclusion, our patient illustrated that regular clinical and radiological surveillance is necessary in the long-term management of patients with tuberous sclerosis. One of the most important organ involvements is the development of renal angiomyolipoma. This condition is potentially lethal and may result in significant morbidity. Early recognition and prompt intervention is necessary in selected cases to prevent the progression to renal insufficiency.

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