CASE REPORT

Bilateral renal cell carcinoma in a paediatric patient with tuberous sclerosis complex

Ana Teresa Gil, Ana Brett, Carolina Cordinhã, Clara Gomes

Pediatric Nephrology Unit,
Pediatric Hospital Carmona
da Mota, Hospital Center and
University of Coimbra,
Coimbra, Portugal

Correspondence to
Dr Ana Teresa Gil,
ateresagil@gmail.com

SUMMARY

Tuberous sclerosis complex (TSC) is a genetic neurocutaneous disorder characterised by seizures, mental retardation and hamartoma formation in multiple organs, mainly in the brain, skin, kidney, liver, lung and heart. Renal manifestations occur in about 60–80% of all patients with TSC and their rate increases with age. We report the case of a 17-year-old boy with tuberous sclerosis who presented with abdominal pain associated with kidney failure. Investigation revealed bilateral renal lesions, suggesting angiomyolipomas. On further work-up, malignancy was suspected and the patient underwent bilateral partial nephrectomy with histological diagnosis of bilateral renal cell carcinoma. This is a rare complication of TSC, particularly in a paediatric setting. Adequate surveillance of kidney disorders in patients with TSC is warranted, to guarantee an early diagnosis and treatment.

BACKGROUND

Tuberous sclerosis complex (TSC), an autosomal dominant disease, is a relatively frequent disorder, seen in approximately 1:6000 people worldwide.¹ Affected patients are at risk of development of tumoral lesions in a number of organs, namely brain, skin, kidney, liver, lung and heart.²

TSC is caused by mutations in either one of the two tumour suppressor genes: the TSC1 gene (on chromosome 9q34) or the TSC2 gene (on chromosome 16p13).^{3–4} Both mutations impact the same organ systems, but it is believed that TSC2 mutations lead to a more severe outcome, including more acute renal involvement.^{5–6}

A set of diagnostic criteria, established at the Tuberous Sclerosis Complex Consensus Conference in 1998, are used to diagnose TSC.⁷ The phenotype in TSC is highly variable, even in patients with identical mutations. The classic triad (Vogt's triad) is characterised by seizures, mental retardation and facial angiofibromas. However, less than 40% of patients have all three features and some patients may have none.⁸ Likewise, the diagnosis may not become evident until adulthood since clinical symptoms may appear gradually.⁹

Although TSC most often presents with neurological symptoms, renal involvement is common, occurring in 50–80% of patients and increases with age.^{5–10} The most frequent renal lesions are angiomyolipomas (AMLs) and renal cysts, both of which may lead to chronic kidney disease (CKD).^{8–10} Renal cell carcinoma (RCC) is a rare complication of TSC in children,¹¹ more commonly reported in adults.

The case of an adolescent with TSC and malignant renal disease is presented, with the aim of increasing awareness to this association in a paediatric setting.

CASE PRESENTATION

A 17-year-old boy, diagnosed at the age of seven with TSC, was admitted to his local hospital in March 2012 with right lumbar pain.

The pain had started 24 h prior to admission, after a coughing bout and was described as a continuous pain that radiated to his right thigh. He had a 5 day history of upper respiratory tract infection, but with no fever, gastrointestinal or genitourinary symptoms.

Regarding his medical history, the patient was diagnosed with TSC at 7 years of age after he presented with new onset of seizures and was recognised to have hypopigmented macules. He is chronically medicated with sodium valproate.

On physical examination, he was found pale, had trouble walking and had symptoms of pain when pressure was applied to his right abdominal quadrant, which was tender on palpation but without rebound tenderness or rigidity. Murphy's punch sign was negative bilaterally.

Laboratory investigation showed: haemoglobin 10.4 g/dL, leucocytes 4900/μL, C reactive protein (CRP) 9.3 mg/dL, serum creatine 219 μmol/L, urea 12.9 mmol/L, with normal electrolytes, suggesting kidney failure. The abdominal ultrasound showed a heterogeneous mass with 8.1×7.2 cm on the right kidney. The patient was transferred to a referral centre for follow-up.

In the tertiary centre he repeated blood tests, which confirmed anaemia (9.6 g/dL) and kidney failure and showed an elevated erythrocyte sedimentation rate (112 mm/h) and rising CRP (15.3 mg/dL). The autoimmune panel (antinuclear antibody, extractable nuclear antigen, antineutrophil cytoplasmic antibody and complement) was normal. Urinalysis showed nephrotic proteinuria (urine protein/creatinine ratio: 209 mg/mmol). He was initially prescribed with intravenous antibiotics (ceftriaxone and flucloxacillin), as a renal abscess was suspected. High blood pressure was noted and he was started on oral nifedipine and atenolol.

A new renal ultrasound showed bilateral diffuse hyper-reflectivity and bilateral mass lesions (10 cm of diameter on the right kidney and 2.1 cm on the left kidney), which were predominantly solid, with significant inner abnormal vasculature. The mass on the left kidney had two foci of calcification. These aspects suggested AML

To cite: Gil AT, Brett A, Cordinhã C, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-010015

although malignancy could not be excluded as both lesions were highly vascularised.

With treatment, he maintained a low glomerular filtration rate (33 mL/min/1.73 m²), which, when associated with anaemia and his kidney pattern on ultrasound, confirmed the diagnosis of chronic kidney failure. He was started on calcitriol, calcium carbonate and darbepoietin.

An abdominal CT scan without contrast showed possible bilateral AML with internal haemorrhage, although the possibility of RCC could not be excluded. An MRI confirmed these findings, suggesting a possible malignant aetiology for the lesion in the left kidney. Therefore, a biopsy of the lesion in the left kidney was performed, which showed a histological appearance of RCC, clear cell type, Fuhrman grade 1.

TREATMENT

Accordingly, he was transferred to the adult Urology Department and had a bilateral partial nephrectomy. A nodule was excised from the left kidney with 1.8×1.5×1.5 cm, with well-defined limits and a free surgical margin. The histological appearance of this nodule confirmed RCC, clear cell type, Fuhrman grade 3. From the right kidney a mass with 6.5×5×5 cm was removed, which on macroscopic appearance showed cystic and haemorrhagic areas, close to the surgical margin (1 mm) without invasion of the renal capsule. Microscopically the lesion showed eosinophilic cytoplasm cells in the core and clear cells in the peripheral areas, and was histologically classified as a chromophobe RCC (immunohistochemical phenotype: positive epithelial membrane antigen (EMA), with rare cells reactive to HMB-45 and cytokeratin 7). The remaining renal parenchyma had typical abnormalities of TSC.

According to the TNM staging classification system the patient had a T1B N0 M0 RCC.

OUTCOME AND FOLLOW-UP

After surgery, the patient remained clinically stable, without any newly identified lesions, and with a glomerular filtration rate of 26 mL/min/1.73 m², corresponding to CKD stage 4.

DISCUSSION

Renal manifestations are a common finding in TSC and play a significant role in disease burden, as they frequently progress to CKD and are the most common cause of death in these patients.¹² An adequate surveillance is essential for early detection of renal lesions and effective management, as these are rarely symptomatic in initial stages of TSC.⁵

Patients with TSC should remain under medical surveillance and should be periodically examined, to assess for development and progression of renal lesions. The TSC Consensus Conference recommends ultrasound screening of the kidneys every 1–3 years in older children with TSC.⁷ This case report illustrates the need for early and frequent renal imaging in paediatric patients with TSC.

AMLs, the most frequent renal tumours in TSC, are mesenchymal hamartomas composed (in varying proportions) of smooth muscle cells, adipocytes and abnormal blood vessels.⁵ In patients with TSC they are usually cortical, multifocal and bilateral.⁹ These lesions have a high risk of intralesion haemorrhage, which can cause discomfort or pain and can invade adjacent normal renal parenchyma, consequently compromising renal function.⁵ AMLs usually appear during childhood and adolescence and then stabilise throughout adulthood.⁸ In this case report, AML was initially considered the most likely aetiology

for the kidney lesions, as these showed significant inner abnormal vasculature.

The actual incidence of renal malignancies in patients with TSC is unknown. The estimated incidence of RCC varies between 2.2% and 5%,^{5 8 13} similar to that of the general population,² with a higher frequency in women.^{14 15} However, the median age of diagnosis of RCC in TSC is reported as 28 years,¹⁵ 25 years earlier than the average age at diagnosis in the general population,¹¹ with sporadic case reports among paediatric patients.^{14–21} Usually thought to be a complication diagnosed in adulthood, it is important to remember that although scarce, RCC may appear in a paediatric setting.

The diagnosis of RCC using only imaging techniques is difficult, as it is hard to differentiate RCC from AMLs that lack a prominent lipomatous component.¹¹ Thus, frequently, biopsy and histological diagnosis are necessary.

An unusual characteristic of RCC in TSC is its histological heterogeneity. Clear-cell, papillary and chromophobe carcinoma subtypes, as well as oncocytomas, have all been reported in patients with TSC.^{14 17} In this case report, bilateral renal masses were found, one corresponding to RCC clear-cell type, the most frequent histological type of RCC in TSC^{14 15} and the other to a chromophobe RCC, with EMA-positive antibodies. The latter presented some atypical features, as only a few reactive cells to cytokeratin 7 antibodies and occasional cells reactive to HMB-45 were found. AMLs are known to exhibit immunoreactivity for melanocytic markers, namely HMB-45 and melanin A antibodies.⁸ Although HMB-45 positivity, albeit scarce, in this patient's lesion suggests that his tumour might be related to an AML,¹⁴ it also presented with other immunohistochemical features more suggestive of chromophobe RCC (EMA and CK7 antibodies).²² Malignant transformation of AMLs has, nevertheless, been reported and seems to have a poor prognosis.^{18 23}

Regarding treatment, nephrectomy must be undertaken with caution in patients with TSC, as the remaining kidney is prone to develop additional masses.⁵ Outcomes of these patients vary, as these tumours frequently metastasise.¹⁴

This case report illustrates the importance of a close surveillance of patients with TSC, in particular of renal manifestations of disease, since these occur in a large number of patients and can become malignant over time. Accurate and timely diagnosis, as well as appropriate therapy, is crucial for a good outcome.

Learning points

- ▶ Renal involvement in tuberous sclerosis complex is common and increases with age.
- ▶ Renal angiomyolipomas can grow substantially and can cause pain or kidney failure.
- ▶ Renal malignancy is rare before adulthood but can occur.
- ▶ Close control of disease progression, with ultrasound screening of the kidneys every 1–3 years, will lead to an early diagnosis and may help to prevent further renal damage.

Contributors ATG developed the idea for the article, collected clinical data, performed the literature search and wrote the article. AB carried out the literature research, helped to collect clinical data and in writing the article. CC was involved in critical revision of the manuscript. CG managed the patient, was involved in critical revision of manuscript. All the authors approved the final version.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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