

CASE REPORT

Renal cell carcinoma or angiomyolipoma – diagnostic and therapeutic dilemmas in a 17-year-old female patient with tuberous sclerosis complex

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ABSTRACT

We present a case of a 17-year-old girl with tuberous sclerosis complex (TSC) with suspicion of renal cell carcinoma in the left kidney. Pathomorphological examination revealed domination of fusiform cells, and foci of adipocytes with a tendency towards perivascular proliferation. Immunohistochemistry revealed a positive reaction for markers of angiomyolipoma (AML): SMA (smooth muscle actin), HMB-45 (Human Melanoma Black-45), and MelanA (melanocyte antigen), and negative reaction for markers of renal cell carcinoma. In addition, positive reaction for TFE3 (transcription factor binding to immunoglobulin heavy-chain enhancer 3) was found in nuclei. The tumour was classified as a lipid-poor AML, and treatment with rapamycin was started in the patient. To the best of our knowledge, this is the first renal AML in a TSC patient in whom nuclear expression of TFE3 was found. Differential diagnosis of lipid-poor renal lesions in TSC patients is a demanding challenge requiring a dedicated, experienced multidisciplinary team.

KEY WORDS:

immunohistochemistry, renal cell carcinoma, tuberous sclerosis complex, lipid-poor angiomyolipoma.

INTRODUCTION

Tuberous sclerosis complex (TSC, Bourneville-Pringle disease) is an autosomal dominant phacomatosis caused by a mutation in tumour suppressor genes: *TSC1* (chromosome 9q34) or *TSC2* (chromosome 16p13), diagnosed on the basis of revised 2021 International Tuberous Sclerosis Complex Consensus Group (ITSCCG) criteria [1]. *TSC1* and *TSC2* genes encode inhibitors of the mTOR (mammalian target of rapamycin) signalling pathway, i.e. hamartin and tuberin. Uncontrolled activation of the mTOR pathway leads to the formation of hamarto-

mas, benign neoplasms, and, rarely, malignant neoplasms in virtually all parts of the body [2].

The spectrum of renal abnormalities in TSC involves angiomyolipomas (AML), renal cysts, glomerulocystic disease, oncocytoma, renal cell carcinoma (RCC), and renal artery abnormalities [1–3]. Most of the AMLs contain mature adipose tissue. The much less common lipid-poor variant of AML shows many pathomorphological and radiological similarities with RCC with different outcomes and standards of care [2, 4, 5]. The aim of the study is to present diagnostic and therapeutic dilemmas in an adolescent patient with TSC and suspicion of RCC. The final

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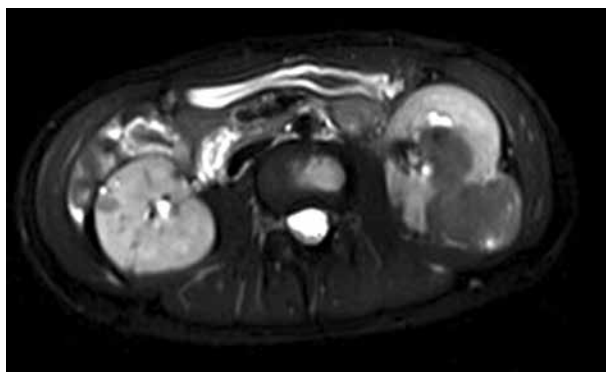


FIGURE 1. Lipid-poor masses in the left kidney of the presented patient (magnetic resonance imaging)



FIGURE 2. Macroscopic image of a tumour protruding from lower pole of the left kidney

diagnosis was made by operational biopsy, which revealed a rare pattern of immunohistochemical markers, including TFE3 (transcription factor binding to immunoglobulin heavy-chain enhancer 3) nuclear expression.

CASE REPORT

A 17-year-old girl with TSC was admitted to our tertiary centre of paediatric nephrology for final diagnostics and treatment of renal lesions. Her major and minor criteria, according to ITSCCG, together with other disease-related symptoms, were as follows: major criteria – numerous hypomelanotic macules, facial angiofibromas, fibrous cephalic plaques, shagreen patches, cardiac rhabdomyomas, lung lymphangiomyomatosis, and numerous bilateral renal angiomyolipomas; minor criteria – numerous renal cysts; other symptoms – developmental delay, epilepsy, and astrocytoma in the right retina. Five months before the present admission, she underwent routine ultrasonography, which revealed progression of renal lesions. She was referred to a local oncology centre where renal magnetic resonance imaging (MRI) showed large lipid-poor lesions in both kidneys. A PET-CT (positron emission tomography and computed tomography) scan revealed unclear renal lesions with an SUV max (maxi-

imum standardized uptake value) index of the largest left renal lesion of 8.26. The patient was qualified for tumorectomy with possible conversion to total left-sided nephrectomy. The patient was referred to our centre based on her parents' decision due to our experience with TSC paediatric patients.

On admission (age 17 9/12), she presented in good clinical condition, with numerous disease-related skin lesions and lower pole of the left kidney easily palpable; she was also found to have normal blood pressure of 117/82 mm Hg and regular heart rhythm of 80 beats per minute. She had normal complete blood count parameters (white blood cells $8.7 \times 10^3/\mu\text{l}$, haemoglobin 13.5 g/dl, platelets $256 \times 10^3/\mu\text{l}$), her inflammatory indicators were not elevated (C-reactive protein < 0.5 mg/dl, erythrocyte sedimentation rate 2 mm/h), and renal function tests (creatinine 0.6 mg/dl, urea 20 mg/dl) were normal. Neoplasm markers (serum alpha-fetoprotein, carcinoembryonic antigen, beta-HCG [human chorionic gonadotropin], neuro-specific enolase, chromogranin A) were negative. Her urinalysis was normal, and elevated albuminuria was found on daily urinary collection (186.3 mg/24 h). Renal MRI revealed the right kidney 111 mm in length and the left kidney 124 mm in length. Numerous focal lesions were revealed in the right kidney, i.e. cysts (up to 6 mm in length), lipid-rich AMLs (up to 9 mm in length), and lipid-poor lesions. Two lipid-poor lesions (10 and 15 mm in length, respectively) in the upper lateral part of the right kidney were found suspicious of being RCCs. In the left kidney, she was found to have large lipid-poor lesions: an exophytic lesion in the upper pole ($31 \times 30 \times 49$ mm) and a large, polycystic, partly exophytic lesion involving the central part and lower pole ($71 \times 55 \times 42$ mm), between them also some minor lipid-poor lesions (16×12 mm). According to the radiologist team, all lipid-poor lesions showed diffusion restriction in diffusion-weighted imaging, underwent heterogeneous contrast enhancement, and were indistinguishable between atypical AML and RCC (Figure 1).

After a multidisciplinary team meeting (nephrologists, oncologists, urologists, neurologists, radiologists), the patient was qualified for an open left renal biopsy. The lumbar section revealed a large tumour protruding from the lower pole of the left kidney (Figure 2), covered by an intact renal capsule without signs of infiltration of surrounding tissues. Three samples were obtained from the tumour. The pathomorphological examination showed a tumour with the domination of fusiform cells, with single foci of adipocytes with a tendency towards perivascular proliferation (Figure 3). The immunohistochemistry pattern was as follows: vimentin and SMA (smooth muscle actin) (Figure 4) in the majority of tumour cells, HMB-45 (Human Melanoma Black-45) (Figure 5), MelanA (melanocyte antigen), and desmin in some of the tumour cells, with negative reaction for cytokeratin, EMA (epithelial membrane antigen), WT-1 (Wilms tu-

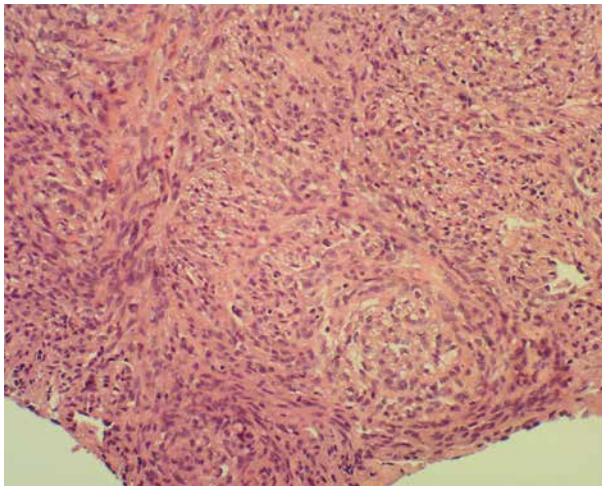


FIGURE 3. Microscopic examination of tumour in lower pole of the left kidney – domination of fusiform cells, with single foci of adipocytes with a tendency towards perivascular proliferation (light microscopy, haematoxylin-eosin staining)

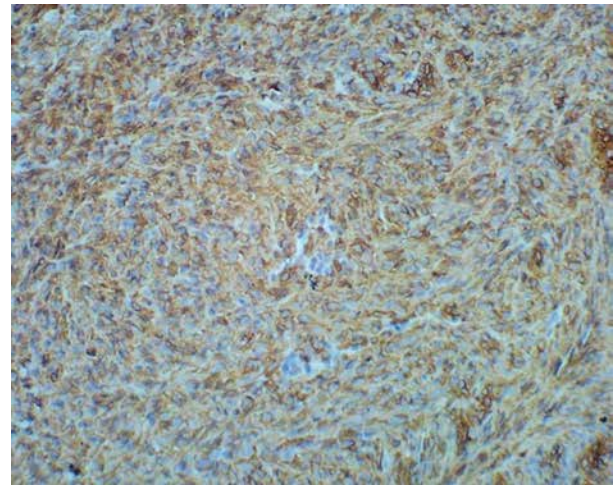


FIGURE 4. Microscopic examination of tumour in lower pole of the left kidney – positive reaction for smooth muscle actin (SMA) (immunohistochemistry)

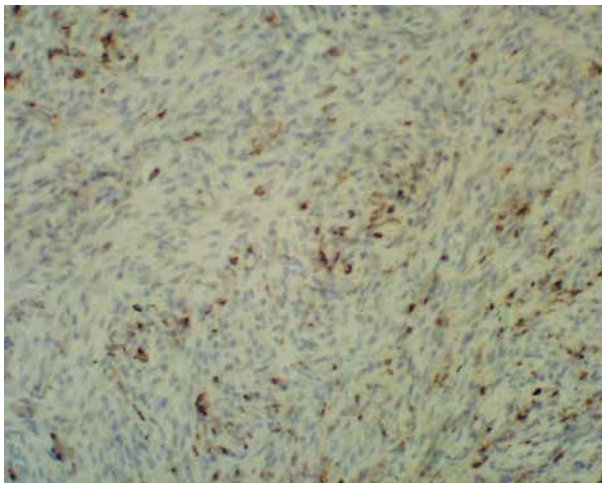


FIGURE 5. Microscopic examination of tumour in lower pole of the left kidney – positive reaction for Human Melanoma Black-45 (HMB-45) (immunohistochemistry)

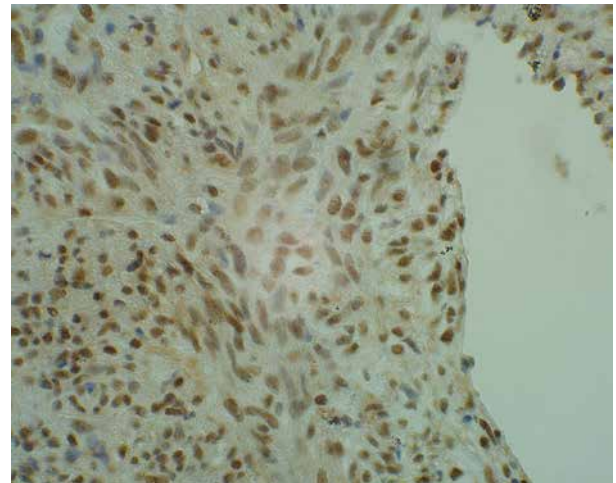


FIGURE 6. Microscopic examination of tumour in lower pole of the left kidney – positive nuclear reaction for transcription factor binding to immunoglobulin heavy-chain enhancer 3 (TFE3) (immunohistochemistry)

mour 1), C-kit (CD117), CALLA/CD10 (common acute lymphoblastic leukaemia antigen), CD34, and S-100. Nuclei showed a positive reaction for TFE3 (Figure 6). The tumour was classified as a mixed clear cell epithelioid and spindle cell variant/biphasic variant of lipid-poor angiomyolipoma. No signs of RCC were found in the obtained material.

The postoperative period was uncomplicated; repeated ultrasonographic examinations showed no biopsy complications. After a month, once the operation wound was completely healed, the patient was started on rapamycin dosed according to Polish recommendations (0.5 mg/m²/24 h o.d., i.e. 0.7 mg/24 h) [2]. Abdominal ultrasonography performed after a month revealed 2 lipid-poor hypochoic lesions in the left kidney (upper pole – 27 × 25 × 23 mm, and lower pole – 37 × 33 × 25 mm) – renal lesions seemed to be smaller than in previous studies. The patient was safely transferred to the nephrology adult centre.

DISCUSSION

Angiomyolipomas are the most abundant renal lesions in TSC individuals (55–80% of patients). AML belongs to a family of neoplasms called perivascular epithelioid cell tumours (PEComas). The World Health Organization (WHO) defines PEComas as “mesenchymal tumours composed of histologically, ultrastructurally, and immunohistochemically distinctive perivascular epithelioid cells” [6]. PEComas are a family of related mesenchymal neoplasms that include renal and extrarenal AMLs, lymphangiomyomatosis (LMs), clear cell myomelanocytic tumour (CCMMT) of the falciform ligament/ligamentum teres, and clear cell tumours of various sites [7]. The origin and pathogenesis of PEComa are still controversial and only partially understood; one hypothesis is that PEC has a pericytic origin. Inactivation of *TSC1* or *TSC2* genes, with subsequent activation of mammalian target

of mTOR pathway, has been associated with the pathogenesis of both syndromic and sporadic PEComas [8]. AMLs are found also in healthy individuals, although numerous tumours are always highly suggestive of TSC diagnosis. Renal AML can be classified histologically as typical (triphasic or lipid-rich) or atypical (lipid-poor, monophasic, or epithelioid). Typical, lipid-rich AMLs are benign tumours histologically characterized by (in varying proportions) proliferation of spindle cells, epithelioid cells, and adipocytic cells in concert with many abnormal, thick-walled blood vessels [6]. AMLs pose a risk of life-threatening spontaneous bleeding (Wunderlich syndrome) once the tumour diameter exceeds 30 mm [2, 6].

Lipid-poor AMLs, defined as AML containing less than < 25% lipid component, are rare findings in TSC patients (4.2% of renal lesions). Some tumours consist almost exclusively of one component. Epithelioid variant of AML (EAML) contains numerous epithelioid muscle cells with abundant eosinophilic and granular cytoplasm and few or no lipid cells. They always require differentiation with RCCs because they can histologically and radiologically resemble and be misdiagnosed as RCC. In addition, EAMLs by themselves carry a risk for malignant transformation [2, 6]. Although some studies have suggested an increased incidence of RCC, a meta-analysis has reported that TSC patients have no increased risk for the development of RCC [9]. However, the median age of diagnosis of RCC in TSC is reported as 28 years, 25 years earlier than the average age at diagnosis in the general population. RCC prevalence in TSC patients increases with age, and they have also been found in children [4, 5, 10–12]. The course of RCCs in TSC patients seems to be relatively indolent as distant metastases are rare findings in these subjects [4, 13]. Interestingly, TSC-RCC has a 2 : 1 female predominance. This contrasts with the general population, in which RCC has a male predominance. RCC in TSC has a heterogeneous histologic appearance, with at least 3 distinct morphologies [5].

Differential diagnosis based on radiological findings is demanding and not always ultimately conclusive. According to 2021 ITSCCG guidelines, abdominal MRI is a modality of choice to evaluate renal lesions in TSC patients and is recommended once in 1 to 3 years. Fat-poor AMLs usually have a slower growth velocity (< 5 mm/year) than RCC. Also, AMLs characteristically grow out of the kidney rather than compressing surrounding structures, which is more characteristic of carcinoma [1]. Renal tumour biopsy in TSC patients can be considered (according to the French Reference Centre on TSC [14] and Polish Society of Nephrology [2]) in cases of lipid-poor AML with calcifications, central necrosis, and rapid growth of mass without a lipid contingent or in cases of presence of a single lesion without a lipid component. Due to the rapid increase in size, ambiguous results of imaging studies, and high ¹⁸fluorine-fluorodeoxyglucose (¹⁸F-FDG) uptake in

PET-CT, the patient was qualified for surgical biopsy. The frequency of the RCC and AML markers, as well as markers found in the presented patient, are depicted in Table 1. HMB-45 and Melan-A are present in approximately 80% of AML tumours, but either one of these markers is seen in 100% of the cases. The Polish Society of Nephrology recommends staining for the presence of these markers in kidney samples obtained from TSC patients [2]. In the case of AMLs, the frequency of markers found varies depending on the proportions of lipid, smooth muscle, and vascular components. Thus, in cases of lipid-poor AMLs, additional markers should be sought, especially when the vascular component dominates [4]. Samples obtained from the patient revealed the presence of markers typical for PEComas and no RCC markers, which, together with cell morphology, enabled a final, definitive diagnosis of lipid-poor AML.

A subset of RCCs is characterized by rearrangement of genes encoding MiT family transcription factors – including TFE3 (Xp11 translocation – Xp11 tRCC) and TFE3 (t(6;11) translocation), which results in the over-activation of these genes [15]. These tumours are found mainly in children and young adults. Microscopically, Xp11 tRCC typically comprises epithelioid cells with clear to eosinophilic cytoplasm that show papillary and nested growth [15, 16]. Noteworthy, Mit family tRCCs may show immunohistochemical patterns typical for AMLs – positive reactions for HMB 45 and Melan-A and negative reactions for EMA and cytokeratin [17–19]. TFE3 nuclear expression did not exclude the diagnosis of AML in our patient, as TFE3 positive staining is also found in PEComa tumours [18, 19]. Recent work has identified a potential link between the TFE3/TFEB and RCC in TSC. mTORC1 phosphorylates TFEB and TFE3, leading to their cytoplasmic sequestration. However, surprisingly, TSC-RCC have nuclear localization of TFEB, despite high mTORC1 activity. Moreover, in cellular models of TSC, TFEB and TFE3 are found in nuclei, despite high levels of mTORC1 activity [5]. The strongly positive reaction for SMA was the confirmation of the diagnosis of AML, as RCCs (also those with t(6;11)) show a negative reaction with this antigen. Also, approx. 70% of Mit family tRCCs show a positive reaction for c-KIT (CD117), which was found negative in our patient [20]. To the best of our knowledge, this is the first renal AML in a TSC patient in whom nuclear expression of TFE3 was revealed.

Rare case reports and personal experience (SJ) of paediatric TSC patients with RCC showed that these children might present with flank pain [10, 12], anaemia [10, 12], accelerated erythrocyte sedimentation rate [10], and renal function impairment in case of bilateral tumours [10]. Our patient showed no clinical symptoms and had normal blood and urine tests and renal function tests, except for microalbuminuria. Finally, taking into account rapid growth, high ¹⁸F-FDG uptake, and ambiguous results of remaining imaging studies, we can-

TABLE 1. Frequency of angiomyolipoma and renal cell carcinoma markers and markers found in the presented patient

Marker	The percentage value of positive reactions in AML	The percentage value of positive reactions in RCC	Reaction in a renal biopsy specimen of the patient
CK-18	0%	100%	Negative
Vimentin	89%	87–100%	Positive for most cells
SMA	73–100%	0%	Positive for most cells
Carbonic Anhydrase IX	Scarce data (only single negative data reported)	57–100%	Not examined
PAX2, PAX8	0%	87–98%	Not examined
CD10/CALLA	0%	94–100%	Negative
S100A1	0%	57–94%	Negative
HMB-45	77–100%	0% ¹	Positive for some cells
Melan-A	82–87%	0% ¹	Positive for some cells
Tyrosinase	19–50%	0%	Not examined
CD117 (c-KIT)	0–40%	0% ²	Negative
CD 99	0%	0%	Positive for some cells
CD 56	0%	0%	Positive for some cells
Desmin	40–47%	0%	Positive for some cells
EMA	0%	64–80%	Negative
WT-1	0%	0%	Negative
CD 34	0%	0%	Negative
Nuclear TFE3	33%	0% ¹	Positive

AML – angiomyolipoma, RCC – renal cell carcinoma, CK-18 – cytokeratin 18, SMA – smooth muscle actin, PAX – paired box, CD – cluster of differentiation, CALLA – common acute lymphoblastic leukaemia antigen, S100A1 – S100 calcium-binding protein A1, HMB – Human Melanoma Black, MelanA – melanocyte antigen, cKIT – tyrosine-protein kinase KIT, EMA – epithelial membrane antigen, WT – Wilms tumour, TFE3 – transcription factor binding to immunoglobulin heavy-chain enhancer 3.

¹Negative in most cases of RCC, but may be positive in RCCs with t(6;11) translocation. ²In oncocyoma, chromophobe RCC and t(6; 11) RCC present in 70–80% of cases.

not exclude the presence of RCC in the deeper portions of the lesion or within other masses. Almost 20 cases have been reported so far, in which both RCC and AML have been found in the same tumour mass [21]. Moreover, some data suggest that TFE3 rearrangement-associated PEComas tend to pursue an aggressive course and have a poor prognosis [18]. These examples highlight the necessity of close radiological and clinical surveillance in our patient and all TSC patients with suspicious renal masses.

Considering the molecular background of the disease and based on ITSCCG, as well as Polish Society of Nephrology recommendations, mTOR inhibitors (sirolimus or everolimus) are medications of the first choice in the treatment of AMLs in TSC patients. The treatment is recommended in individuals with growing lesions > 30 mm in diameter [1, 2]. Bissler *et al.* showed a decrease in AML size in 80% of patients (16 out of 20) treated with rapamycin for 12 months. Of note, in 5 of these patients, the reduction was sustained for the following 12 months [22]. Polish guidelines recommend a relatively low dose and low C₀ levels compared to doses used in the transplanted patient. Numerous side effects of mTOR inhibition in TSC patients were described. For both sirolimus and everolimus, stomatitis and hypertriglyceridaemia

are the most common [23]. In the multicentre EXIST trials, most adverse events were mild, did not preclude further therapy, and gradually subsided with time [24].

CONCLUSIONS

Differential diagnosis of lipid-poor renal lesions in TSC patients is a demanding challenge requiring a dedicated, experienced multidisciplinary team.

DISCLOSURE

The authors declare no conflict of interest.

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