

Case Report

Metastatic Bilateral Clear Cell Renal Carcinoma in Tuberous Sclerosis Complex: A Case Report

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Abstract

Malignant tumors of the kidney, particularly clear cell renal carcinoma (CCRC), are fearful entities due to their aggressiveness and metastatic potential. They occasionally arise in predisposing hereditary syndromes such as Tuberous Sclerosis Complex (TSC). Herein, we present a case of A 33-year-old nulligravida woman presented with intermittent right-sided low back pain evolving for approximately 15 years. Imaging, including contrast-enhanced abdominal CT scan, revealed the presence of bilateral poorly defined heterogeneous solid-cystic masses with enhancement after contrast injection suggestive of bilateral renal tumors. Bilateral renal biopsy was performed, and histological examination revealed bilateral clear cell renal carcinoma (CCRC) with International Society of Urological Pathology (ISUP) nuclear grades of 2. Further staging with thoracic CT scan revealed bilateral pulmonary lymphangioleiomyomatosis (Figure 5) associated with multiple bone metastases. The tumor was classified as intermediate risk according to Heng prognostic criteria, and the case was discussed in a multidisciplinary tumor board meeting. The specific treatment of metastatic CCRC in the setting of TSC has not been reported in the literature to our knowledge. Subsequently, the patient was referred to medical oncology for initiation of tyrosine kinase inhibitor therapy. We reviewed the patient at 6 months, 12 months and 18 months and the evolution was satisfactory, she expressed no complaints and weighed 58kg.

Keywords

Phakomatosis, Renal Cell Carcinoma, Tuberous Sclerosis Complex, Kidney Biopsy.

1. Introduction

Renal tumors represent the third most common urological cancer in Burkina Faso after prostate and bladder cancer. [1] Among them, clear cell renal carcinoma (CCRC) is a fearful entity characterized by its aggressiveness and metastatic

potential.

Genetic syndromes play a crucial role in predisposition to CCRC, particularly Tuberous Sclerosis Complex (TSC). TSC is an autosomal dominant hereditary phakomatosis linked to

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mutations in tumor suppressor genes TSC1 and TSC2. [2, 3] The TSC1 gene, discovered in 1997, is located on chromosome 9q34 and encodes the protein hamartin [4]. TSC2, discovered in 1993, is located on chromosome 16p13 and encodes the protein tuberin [5]. In the general population, the incidence of TSC at birth is estimated at 1/6000 and its prevalence is estimated at 1/10,000 [6, 7].

TSC predisposes to tumor development in various tissues and organs. [3] Renal involvement is found in 60% of cases, predominantly manifesting as angiomyolipomas and renal cysts. However, renal carcinomas, focal segmental glomerulosclerosis, and interstitial fibrosis are rare. [8]

We report a case of metastatic bilateral clear cell renal carcinoma on TSC in a 33-year-old woman.

2. Case Report

A 33-year-old nulligravida woman presented with intermittent right-sided low back pain evolving for approximately 15 years. There was no history of fever, hematuria, or other associated signs. She had an Eastern Cooperative Oncology Group (ECOG) performance status of 1, a weight of 51 kg and stage 3 hypertension was discovered during our consultation.

On urological examination, a large, tender right kidney with firm consistency was noted on palpation.

Examination of the skin and appendages revealed multiple angiomas on the face, more pronounced on the wings of the nose and the right upper eyelid (Figure 1). Similar lesions were reported in her mother and older brother, who reside in a neighboring country.

Gynecological examination and examination of other organ systems were unremarkable.

Laboratory investigations revealed hemoglobin level of 11g/dl, leukocyte count of 4,100/mm³, platelet count of 220,000/mm³, serum creatinine level of 74 μ mol/l, and corrected serum calcium level of 2.2 mmol/l.

Imaging, including contrast-enhanced abdominal computed tomography (CT scan), revealed the presence of bilateral poorly defined heterogeneous solid-cystic masses with enhancement after contrast injection suggestive of bilateral renal tumors. These bilateral tumors completely disrupted the renal parenchyma with no fatty component present (Figure 2).

Bilateral renal biopsy was performed, and histological examination revealed bilateral clear cell renal carcinoma (CCRC) with International Society of Urological Pathology (ISUP) nuclear grades of 2 (Figure 3 and figure 4).

Further staging with thoracic CT scan revealed bilateral pulmonary lymphangioleiomyomatosis (Figure 5) associated with multiple bone metastases (Figure 6).

The patient had a Karnofsky performance status of 90% and was classified as intermediate risk according to Heng prognostic criteria.

Overall, the diagnosis was metastatic bilateral clear cell renal carcinoma with intermediate prognosis in highly probable TSC.

In a multidisciplinary tumor board meeting, it was decided to initiate tyrosine kinase inhibitor (TKI) therapy for the patient, considering the unavailability of immunotherapy in our setting, in accordance with the 2024-2026 guidelines of the French Urology Association (AFU) for metastatic renal tumors. The patient was subsequently referred to medical oncology for treatment initiation. We reviewed the patient at 6 months, 12 months and 18 months and the evolution was satisfactory, she expressed no complaints and weighed 58 kg.



Figure 1. Multiple facial angiofibromas.

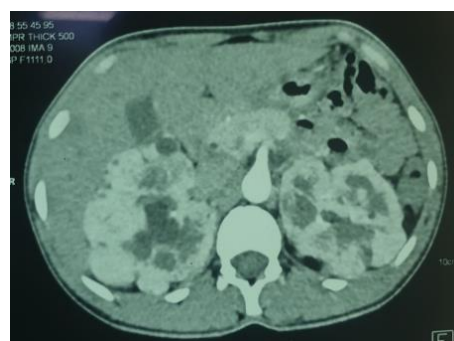


Figure 2. Axial contrast-enhanced CT scan showing bilateral solid-cystic renal mass.

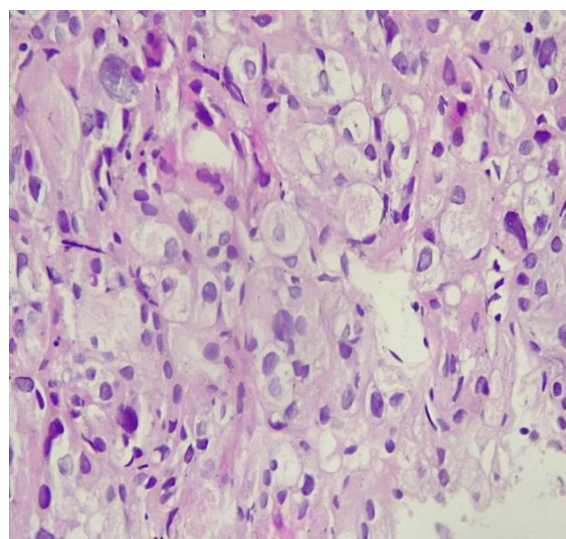


Figure 3. Right kidney histology: Proliferation of cells with clear cytoplasm and highly pleomorphic nuclei with significant cytonuclear atypia.

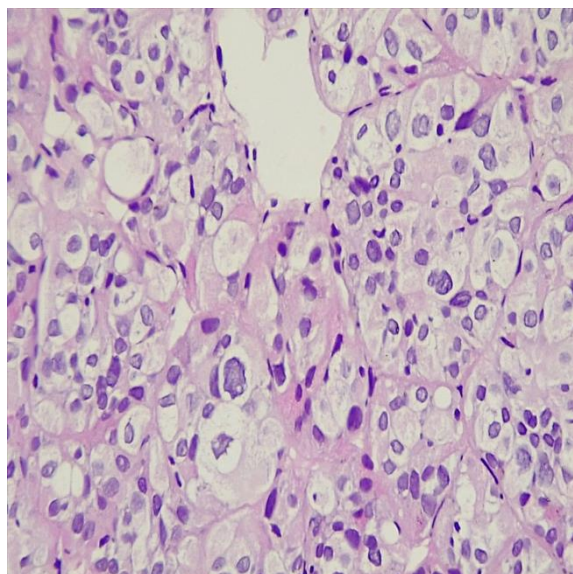


Figure 4. Left kidney histology: Proliferation of cells with clear cytoplasm and highly pleomorphic nuclei with significant cytonuclear atypia.

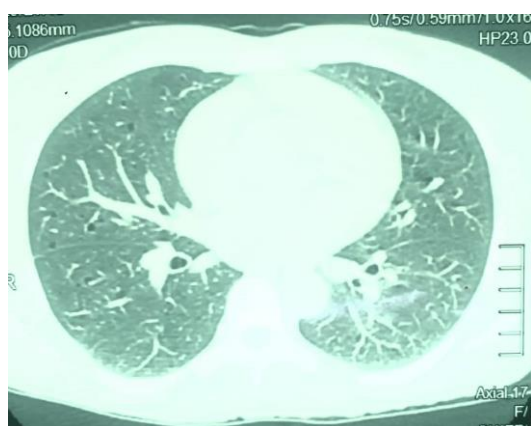


Figure 5. Thoracic CT angiography demonstrating bilateral pulmonary lymphangioliomyomatosis.

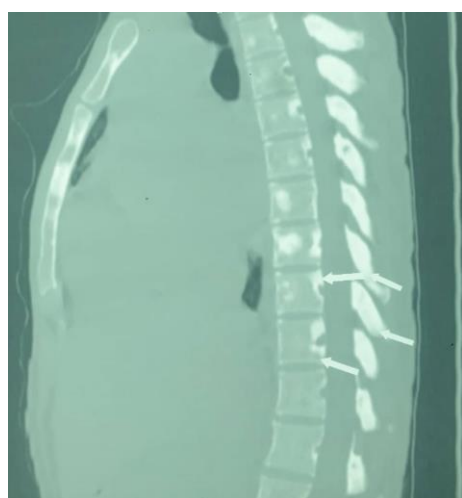


Figure 6. Multiple vertebral metastases.

3. Discussion

Clear cell renal carcinoma (CCRC) is a malignant tumor of the kidney known for its ability to progress asymptotically to advanced stages of the disease, thus compromising the patients' prognosis. When it occurs before the age of 45 or when it is multiple and/or bilateral, as in the case of our patient, it is recommended to undergo oncogenetic consultation to investigate a predisposing hereditary condition such as Tuberous Sclerosis Complex (TSC). [9]

TSC is a hereditary syndrome associated with significant morbidity and mortality, where renal involvement represents the second leading cause of death after neurological involvement. This is related to hemorrhagic accidents, end-stage renal disease, or, more rarely, malignant transformation. [8]

The diagnosis of TSC in our patient was based on clinical and radiological criteria in accordance with the 2012 consensus conference updated in 2021 on TSC. [10] Our patient met two major criteria, including more than three facial angiofibromas and pulmonary lymphangioliomyomatosis, which alone are sufficient to establish the definitive diagnosis of TSC. Additionally, she had two minor criteria, including multiple renal cysts and osseous lesions consistent with osteosclerosis. P. Maulaz et al. state that the search for mutations in the TSC1 and TSC2 genes is a long and expensive process with a very high positive predictive value but a low negative predictive value. [3] Indeed, in 15% of cases, the patient presents with TSC even though a genetic test is negative, due to a mosaic TSC genotype [11]. It is therefore accepted that the diagnosis of TSC is established when the clinical and radiological criteria are very suggestive. [3]

The absence of fatty components on CT scan and complete disruption of bilateral renal parenchyma justified the need for renal biopsies. This indication aligns with the updated 2021 consensus conference recommendations, which suggest that in TSC, when a renal tumor cannot be definitively identified as a fat-poor angiomyolipoma, a biopsy should be considered. [10] It also aligns with the indications from the French Urology Association (AFU) 2024-2026 regarding renal tumor biopsies [9], particularly in cases of diagnostic uncertainty on imaging.

The management of these specific cases of renal tumors in the context of genetic syndromes requires discussion within multidisciplinary teams (urologists, oncologists, oncogeneticists, etc.).

In the literature, few studies have addressed the association between CCRC and TSC, and documented treatments in these cases have included bilateral nephrectomy with renal transplantation, bilateral partial nephrectomy, nephrectomy plus contralateral partial nephrectomy, and nephrectomy combined with radiotherapy. [12, 13]

The specific treatment of metastatic CCRC in the setting of TSC has not been reported in the literature to our knowledge. Only cases of death due to metastases were mentioned. [13] In

our case, the therapeutic regimen was developed according to the AFU 2024-2026 guidelines for metastatic renal tumors. However, this recommendation does not consider the pathophysiological peculiarity of TSC involving the mammalian target of rapamycin (mTOR) pathway, with documented use and benefit of mTOR inhibitors in the treatment of multiple tumor manifestations of this hereditary phakomatosis. [2, 10]

In the literature there are recommendations for urological monitoring of patients with TSC. The reported protocols are variable but regular renal CT or Magnetic resonance imaging (MRI) monitoring every two years is the standard. [14, 15]

4. Conclusion

Metastatic Bilateral CCRC in TSC is rare, and its diagnosis is often delayed in our context. Its management should involve a multidisciplinary approach. Further studies are needed to evaluate the role of mTOR inhibitors in the specific case of metastatic CCRC in TSC compared to current molecules in the AFU 2024-2026 guidelines, including immunotherapy and TKIs.

Abbreviations

AFU	French Urology Association
CCRC	Clear Cell Renal Carcinoma
TSC	Tuberous Sclerosis Complex
TKI	Tyrosine Kinase Inhibitor
mTOR	Mammalian Target of Rapamycin
ISUP	International Society of Urological Pathology
MRI	Magnetic Resonance Imaging
CT	Computed Tomography

Author Contributions

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Conflicts of Interest

The authors declare no conflicts of interest.

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