SAS Journal of Surgery
Abbreviated Key Title: SAS J Surg
ISSN 2454-5104
Journal homepage: https://www.saspublishers.com

OPEN ACCESS

Urology

Adult-Onset Renal Cell Carcinoma Associated with Xp11.2 Translocation/TFE3 Gene Fusion: 2 Case Reports and Review of Literature

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DOI: 10.36347/sasjs.2023.v09i02.014 | **Received:** 07.12.2022 | **Accepted:** 14.01.2023 | **Published:** 23.02.2023

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Abstract | **Case Report**

Renal cell carcinoma (RCC) is the most common type of kidney cancer in adults, it represents 90-95% of neoplasms arising from the kidney. The Xp11.2 RCC translocation is a subtype of RCC that is defined by different translocations involving the Xp11.2 chromosome, all of which result in transcription factor E3 (TFE3) gene fusions. We presented 2 adult cases of Xp11-RCC, one patient had lymph node metastases and the second patient also had liver metastases. Both patients improved with surgical treatment by radical total nephrectomy with lymph node dissection, in addition to neoadjuvant medical treatment.

Keywords: Renal cell carcinoma, Translocation, Xp11.2, TFE3.

INTRODUCTION

Xp11.2 Translocation renal cell carcinoma is a new rare recognized type that represents only 1% of renal cell carcinoma, It was originally described as a pediatric subtype of RCC representing 30 % of all cases in the pediatric and adult population.

Translocation Xp11.2 RCC is a result of several gene fusions involving the transcriptional factor gene E3 located in the Xp11.2 chromosomes and multiple other partners.

According to the 2004 classification of the World Health Organization (WHO), Xp11.2 Translocation RCC is established as a distinct subset of RCC.

We describe down below two cases of adult Xp11.2 renal cell carcinoma and their evolution.

CASE PRESENTATION

CASE 1

This is the case of a 48 years old malepatient, without any notable comorbidities,nor any toxic history.

Two months prior to his hospitalization he suffered from left flank and lower back pain, fatigue, loss of appetite and an estimated weight loss of 15 kg. Neither fever nor hematuria was reported in the anamnesis. The physical found a normal blood pressure of 11/7 cmHG, slightly discolored conjunctiva and a palpable left flank mass.

An abdominal ultrasound was performed showing a left renal lesion , then completed by a Ct scan with contrast IV injection (Figure 1, 2) objectifying an irregular enormous mass, measuring 15x16x21cm centered on the upper pole of the left kidney containing compartments of fluid consistency.

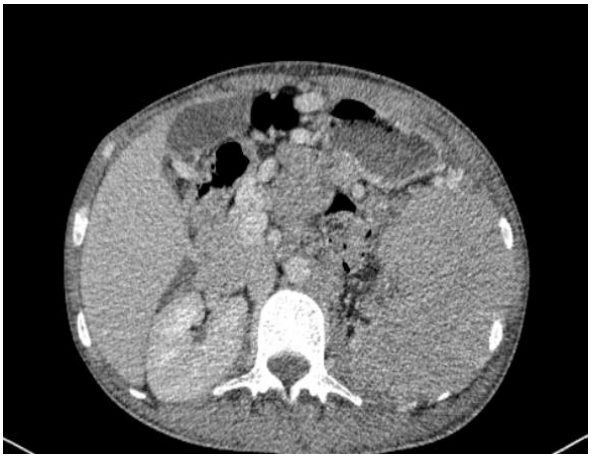

Figure 1: Axial view of the left kidney tumor

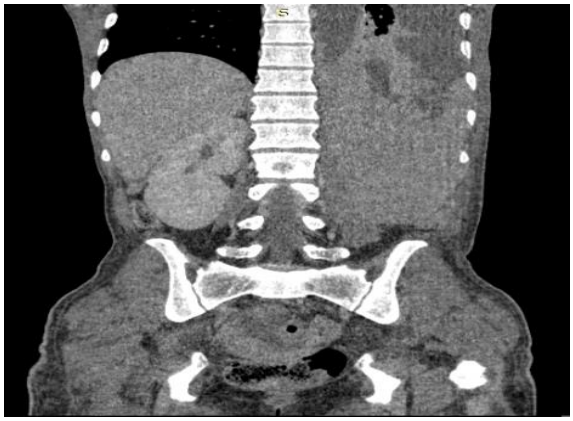

Figure 2: Sagittal view of the left kidney tumour

The lesion invades the upper segmental renal vein with a thrombus reaching the main renal vein, as well as the splenic artery. It's in close contact with the aorta on a 90 degrees circumference and 65mm of height; it infiltrates the adrenal compartment and the spleen.

The mass pushes back against the stomach, the pancreas, the portal vein and communicates with the liver with a border of separation.

The tumor protrudes from the renal fascia and presents an intimate contact with the posterior and lateral abdominal wall.

Multiple lymph nodes were identified: retroperitoneal latero aortic adenopathies surrounding the renal artery (23x21mm, 1"x18mm) and a right external iliac 18x10mm; as well as perirenal and hypogastric ones.

Thus the tumor was classified T4N1M0 (tnm2009).

The laboratory tests showed an anemia hb=9,9g/dl and a normal kidney function creat 5,8mg/l and urea 0,23g/l.

The patient was admitted to the operating room, then were found, in peroperative, an enormous retroperitoneal tumor adherent to the spleen, pancreas and diaphragm.

The patient benefited of a radical nephrectomy including the renal fascia, a splenectomy, and a resection of the pancreas tail as well as a part of the left diaphragmatic dome, taking the tumour all in a single piece followed by lymph node dissection.

The resection piece weighted 27kg consisting of a left kidney measuring 23x14x9cm, a pancreas tail measuring 5x1, 5x5 cm, a spleen of 14x11x4cm and a part of the diaphragm measuring 19x16 cm. Macroscopically the tumor was of a whitish color, friable consistency and containing necrotic and hemorrhagic sub-parts. Sixteen lymph nodes were identified, the largest of which measures 1,4 cm in a diameter.

Microscopically, it was an undifferentiated carcinomatous process of sarcomatoid and rhabdoid morphology, composed of large cells with rounded or elongated nuclei with dense and heterogenous chromatin; and an abundant and basophilic cytoplasm. The presence of papillary architecture contingent was noted, with fibro-inflammatory stroma and many mitosis elements.

The tumor infiltrates the spleen, the pancreas, and the diaphragm, with 2 metastatic lymph nodes.

The resection margins were negative in the pancreas and ureter, while it was positive in the diaphragm section.

The immunochemistry showed the presence of antibodies such as: anti CD10, anti EMA, anti vimentine, anti INI1, anti CK7, anti TFE3, anti racemase; while being negative for others (anti ck7, anti PAX5).

The anatomopathology and immunohistochemistry study concluded (figure 3) the aspect of a kidney carcinoma with TFE3 translocation (OMS 2016) with sarcomatoid and rhabdoid components (figure 4).

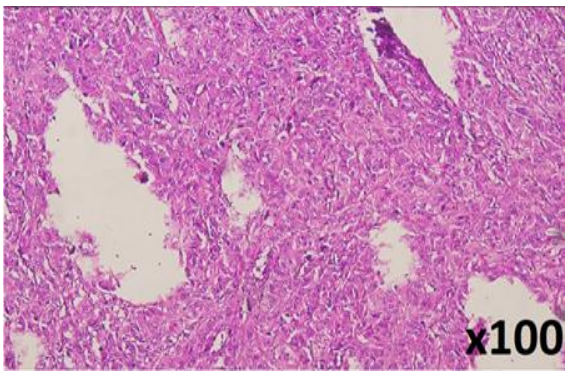

Figure 3: Histologic aspects of the renal cell carcinoma

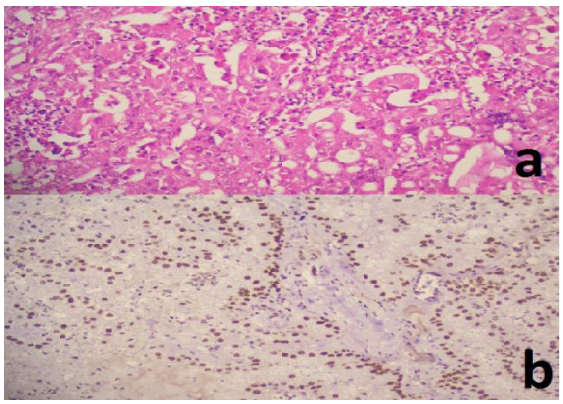

Figure 4: Immunohistochemical aspect of sarcomatoid and rhabdoid component (a) and the TFE3 translocation (b)

The patient then was referred to an oncological consultation for adjuvant therapy. A control Ct-scan found a peritoneal carcinomatosis, an endothoracic extension with pleural effusion with an OMS score of 3 and a normal pre- therapeutic assessment, the patient was put under Pazopanib 400mg\day, starting half dose at first.

CASE 2

A 24-year old single woman, with a medical history of Hodgkin Lymphoma treated with chemotherapy, presented to a local hospital with fatigue and low back pain in February 2016.

The anamnesis revelead that she was suffering from fluctuating pain on the left side of her abdomen for several months, she has a decreased appetite, was feelling nauseaus and had a weight lost of 20 kgs, in the last few weeks she experienced short episodes of hematuria.

Physical examination showed a palpable mass in the left flank and no palpable lymph nodes in the head or neck area, axilla or in the inguinal region were detected.

The laboratory tests revealeda negative Urine cytology for malignancy.

Ultrasonography and Computed tomography (CT-scan) showed a large tumor of the left kidney, 115 mm in diameter with adjacent retro peritoneal pathological lymph nodes (Figure 5). The process extended to the adjacent anatomical structures with a small caliber of the arterial and the renal vein and one liver's metastasis (Figure 6).

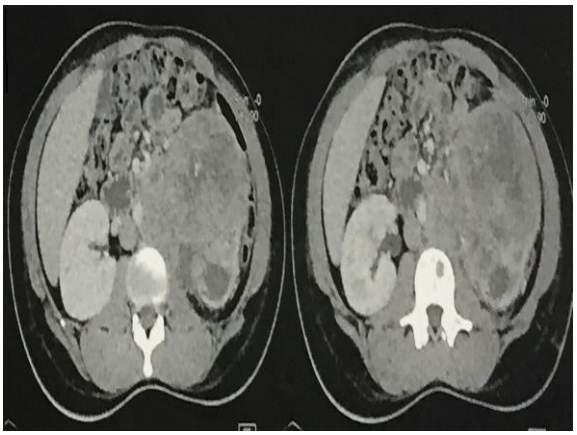

Figure 5: CT-scan axial image of the left kidney tumor

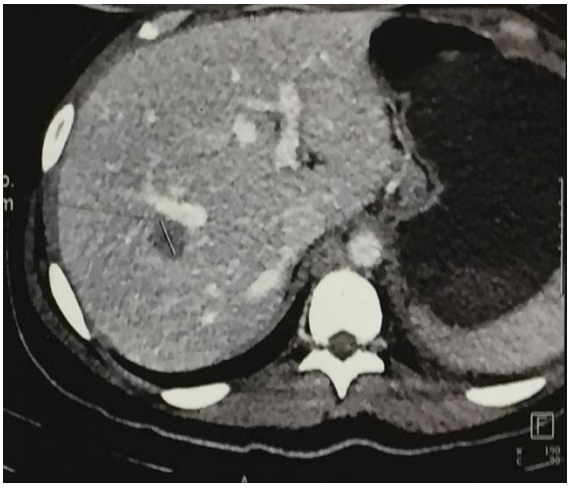

Figure 6: CT-scan axial image of the liver metastasis

The patient was diagnosed with Renal Cell Carcinoma of clinical stage T3aN1M1, with intermediate risk according to the Memorial Sloan Kettering Cancer Center risk classification.

The needle biopsy of the left kidney was performed and two large fragments were sent for permanent pathologic analysis. Histological examination disclosed a solid alveolar tumor consisting of epitheloid cells with granular eosinophilic cytoplasm, big round nucleous with prominent nucleolus. The differential diagnosis considerations were clear cell renal carcinoma (cRCC), epitheloidangiomylipoma (eAML) and a MiTF family translocation carcinoma (MiTF-RCC) the immunohistochemic profile argued against a CCR (HMB45+. TFE3+. CA IX -.VIMENATINE-) the strong expression of PAX8 argued against an eAML. Although there was no typical morphological aspects of an MiTF- RCC in this small biopsie specimen like the papillary growth pattern with clear cells and psammoma-calcificatie. The fluorescence in situ hybridization showed a defect in the TFE3-gene suggestive of Xp11 translocation carcinoma.

Although sunitinib treatment was administered for 3 months at the initial hospital, the status of the primary lesions remained unchanged but liver metastatic lesion has disappeard. Thus, the patient was referred to our hospital for further treatment in June 2016.

The patient underwent radical nephrectomy with homolateral adrenalectomy (Figure 7) followed by targeted therapy based on TKIs.

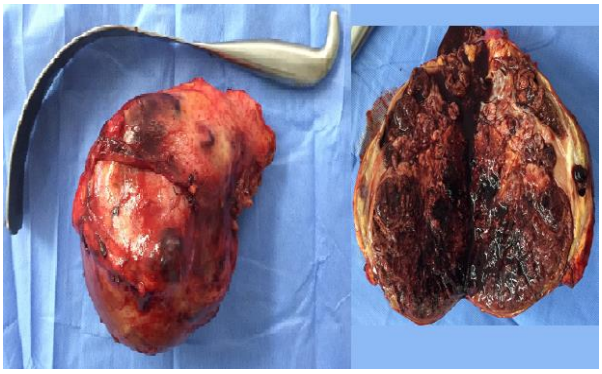

Figure 7: Macroscopic images of the kidney and tumor

In the macroscopic examination of the specimen (figure 7): The delivery piece weighed 1100g. It measured 18 x 12 x 10cm. It was well encapsulated. At the cut a greyish-white tumor measuring 11 x 10 x 9cm occupied the entire renal parenchyma. The tumor was the site of an extensive necrosis representing almost 80% of the surface of the tumor. We noticed the presence of macroscopic infiltration of the peri-renal fat and of the ureteral section. The adrenal gland was macroscopically invaded.

Under microscopic study, the tumor was of architecture that varied from one zone to another. The appearance of the cells was also variable from one zone to another. Thus, the tumor was essentially of papillary architecture. The papillae were sometimes slender and sometimes thick. The cells were provided with a round or elongated nucleus, distinctly anisocaryotic and sometimes strongly nucleolated. The papillae was sometimes bordered by a single cellular layer, sometimes they were laminated. The axis contained vessels and hyaline globules. Elsewhere, masses or tubes of varying sizes were present, the cytology of which was made either of the cells described above or of cells with clear cytoplasm and a clearly visible cytoplasmic membrane with the presence of lymphovascular invasion. The tumor infiltrated the peri-renal fat and the hilum. The adrenale was largelyi nfiltrated. In addition, TFE3 immunostaining was positive. Thus, the pathologicaldiagnosiswas Xp11.2 translocation RCC (figure 8).

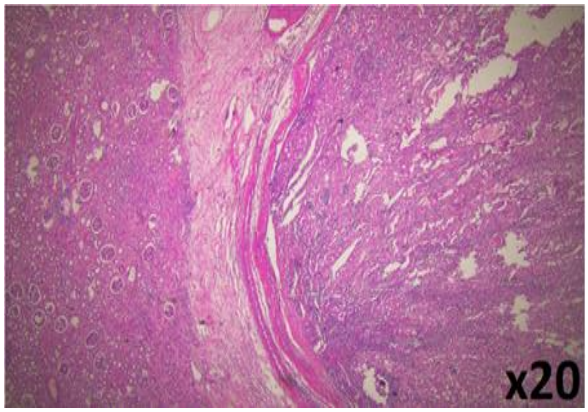

Figure 8: Histologic aspect of renal cell carcinoma

Sunitinib treatment was resumed 2 month after surgery. After 11 months of follow-up, computed tomography revealed no sign of local or distant recurrence.

DISCUSSION

Xp11.2 translocation renal cell carcinoma is considered a rare entity described as a new variant of renal cell carcinoma, (according to the 2004 WHO), representing 20% to 40% of pediatric renal cell carcinoma [1] and only 1% to 1,6 % in the adult population.

According to the Argani and cell studies, Xp11.2 translocation renal cell carcinoma is associated with several gene rearrangements involving the TFE3 gene on chromosome Xp11.2, it implies several fusions with at least one of the five gene partners, including ASPL on 17q25, PRCC on 1q21, PSF on 1q34, NonO on Xq12, and CLTC on 17q23 [2, 3].

Xp11.2 translocation renal cell carcinoma was initially described in 1995 by Dijkhuizen and all [4], however, there is a lack of reported cases concerning the translocation RCC in the adult population, while the literature was very limited concerning the population aged 60 yo and over. Yet, there are numerous reported cases, including the pediatric Xp11.2 translocation RCC [5, 6].

According to multiple studies, the translocation RCC occurs in a particular female population [5, 7], while there is a reported case of bilateral translocation RCC in Japan [8].

The clinical manifestation of Xp11.2 translocation RCC is non-specific; it includes macroscopic haematuria and lumbago that represent the main symptoms, while the diagnosis is frequently established at a later stage with lymph nodes damage and/or metastatic extension in 46% of cases according to the literature [5, 7].

This type of tumor appears to be different from a clear renal cell carcinoma in computed tomography (CT), it is generally a solid mass with cystic rearrangements well encapsulated, located in the cortex, and often associated with peritumoral calcifications.

On microscopic examination, the Xp11.2 translocation renal cell carcinoma presents a lot of similarities with the clear cell and papillary RCC [10], the typical morphology contains large polygonal cells arranged in a papillary structure with eosinophilic to clear cytoplasm.

The diagnosis of Xp11.2 translocation renal cell carcinoma is based on immunohistochemistry tests using an antibody for the proteins which contain the C-terminal portion of TFE3 [11], knowing that this type of

carcinoma presents an overexpression of the protein TFE3. Therefore, numerous studies have shown that there is a significant amount of false positive IHC tests for TFE3.

Reverse transcription polymerase chain reaction (RT-PCR) and Fluorescence in situ hybridization (FISH) are two helpful modalities to diagnose Xp11 TRCC.

The treatment of Xp11.2 TRCC is identical with the other types of renal cell carcinoma; surgical removal constitutes the first option of therapeutic strategies for the located Xp11.2 TRCC even for the patient's withcoregionallymphnode extension.

For patients with hematogenous metastasis, the therapeutic options include immunotherapy using cytokines, such as interleukin 2 (IL-2), alpha interferon (INF), and multi-kinase inhibitors.

According to Malouf and all, using targeted therapies such as VEGFR and/or mTOR inhibitors for patients with Xp11.2 TRCC in the metastatic form has a better response in terms of progression-free survival PFS [14].

Therefore, studies have shown that using Rampamycine inhibitors might be efficient concerning the translocation of Xp11.2 TRCC [15].

Other targeted therapies might be applied as Sunitinib, Sorafenib, and Everolimus [16].

According to the Armah and Parwani revues [17], there is a clinical and pathological heterogeneity between the adult and the pediatric form of Xp11.2 translocation renal cell carcinoma, with a poor prognosis concerning the adults and teenagers over 16 yo comparing to the childhood population.

Early discovery, accurate diagnosis, and close monitoring are mainly essential in terms of dealing with the Xp11.2 TRCC.

Until now, studies have failed to establish a clear algorithm in terms of surveillance after a radical nephrectomy.

CONCLUSION

Renal cell carcinoma associated with Xp11.2 translocations/TFE3 gene fusions is a rare subtype of renal cell carcinoma. This occurs mainly in juveniles, but rarely seen in adults with lymph nodes or organ metastases and a worse prognosis.

The main treatment for localized Xp11.2 RCC is radical surgery for renal cell carcinoma. In the case of advanced renal cell carcinoma with lymph node metastasis, lymph node dissection is also performed. Targeted therapy has shown its place in adult Xp11.2 RCC patients with metastasis.

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