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Case Report

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MIT FAMILY TRANSLOCATION RENAL CELL CARCINOMA, REPORT CASE

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ABSTRACT

Renal cell carcinomas (RCCs) are a heterogeneous group of cancers. Translocation-associated renal cell carcinoma (t-RCC) is a relatively uncommon subtype of renal cell carcinoma characterized by recurrent gene rearrangements involving the TFE3 or TFEB loci. TFE3 and TFEB are members of the microphthalmia transcription factor (MiT) family, which regulates differentiation in melanocytes and osteoclasts, and MiT family gene fusions activate unique molecular programs that can be detected immunohistochemically. Here we report a case of 17-year old girl presenting right lumbar mass. Abdominal ultrasound and computed tomography revealed heterogeneous renal mass invading the liver with hepatic, ganglionic and bone metastases. Histopathology revealed MiT Family Translocation-Associated Renal Cell Carcinoma. The patient was treated with targeted therapy because surgery is impossible.

KEYWORDS: MiT Family translocation renal, cell carcinoma, targeted therapy.

INTRODUCTION

MiT family translocation renal cell carcinomas (RCCs) are particular neoplasms with their clinically aggressive behavior and histopathologically distinctive appearance.[1] These tumors tend to occur in young age group and consist of nearly 40% of pediatric and 1.6-4% of adult RCCs, and were first included as a separate classification of neoplasia by the WHO in 2004, regarded as "Xp11.2 translocation carcinomas".[1,3] The author reported the case of a 17-year-old girl diagnosed with MiT Family translocation renal cell carcinoma at an advanced stage.

CASE REPORT

17-year old girl, from a consanguineous marriage, without particular pathological antecedents, who presented to the emergency department for right-sided lumbar pain that had progressed for 8 months without hematuria or other signs associated. Abdominal examination revealed a non-tender, palpable and poorly limited mass in the right upper quadrant of the abdomen. Physical examination revealed a microphthalmia (figure 1) without cervical, axillary or inguinal lymphadenopathy. The patient underwent an ultrasound examination and a hyperechoic mass sized 75x50mm was identified in the right retroperitoneal area, possibly originating from the right kidney with right paraaortic lymph nodes the largest of which measured 37x20mm.

Figure 1: Image Showing a Microphalmia.

An computed tomography (CT) scan contrast injection revealed a tumor lesion (approximately 130x85x75 mm.) with heterogeneous enhancement and calcified contents in the right kidney. This lesion invades the upper half of the kidney, extends upwards to the liver which is infiltrated without separation. Hepatic, bone and metastatic lesions with multiple lymphadenopathies were also noted. (Fig. 2).

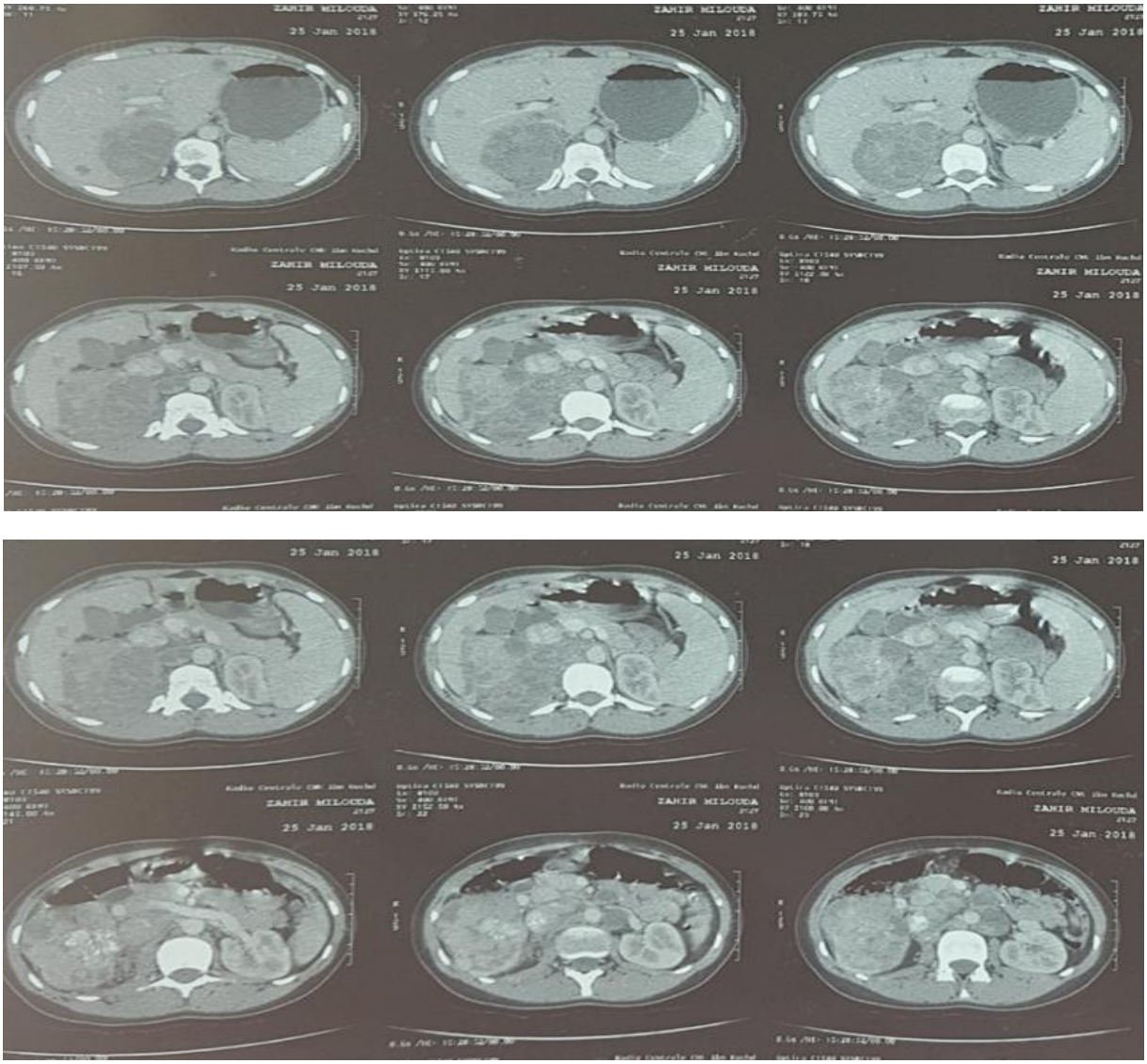

Fig. 2: Computed Tomography (CT) contrast injection showed a heterogeneous mass (approximately 130 x 85 x 75 mm) with enhancement and calcified content in the right kidney. invades the upper half of the kidney, extends upwards to the liver that is infiltrated with no separation limit.

The radical nephrectomy was not achieved because the stage is locally advanced especially absence of separation with the liver.The radical nephrectomy was not realized because the stage is locally advance especially absence of separation with the liver and inferior vena cava then we realized a percutaneous ultrasound-guided renal mass biopsy. Both results from histopathological analysis and immunohistochemistry confirmed that such lesion was a rare case of MiT family translocation renal cell carcinoma. The patient was treated with targeted therapy with favorable evolution.

DISCUSSION

MiT family translocation RCCs were recently grouped and added to the WHO classification of renal tumors. This category includes rearrangements of TFE3 and TFEB loci. The former is located in the chromosome 11 (Xp11.2 locus), while the latter is found in the chromosome 6. The most commonly observed translocations involving TFE3 are t(X; 17)(p11.2; q25) and t(X; 1)(p11.2; q21), which lead to fusions of TFE3 to ASPL and PRCC genes, respectively, resulting in augmented expression of their genetic products.[1,2]

Differently from RCCs not related to translocation of MiT family genes, that usually affect individuals in the

6th and 7th decades of life, corresponding to 2–3% of all malignancies in adult patients,[1] RCCs related to Xp11.2 translocation represent up to 40% of RCC among pediatric patients, although RCCs are generally infrequent among children and adolescents.[4,5] Thus, a high index of suspicion for this disease is necessary, especially in the young age group as the case of our patient.[5,6]

Prior exposure to cytotoxic chemotherapy is currently the only known risk factor for development of MiT family translocation RCCs as opposed to conventional risk factorsCCRs - such as smoking, obesity and hypertension - which are well described in the literatur.[1,3,8] However, our patient had no history of previous exposure to chemotherapy or other risk factors.

The symptoms are usually non-specific and include hematuria, flank pain, palpable abdominal mass and/or systemic symptoms of anemia, fatigue and fever. The diagnosis of renal tumors is frequently incidental, usually suspected at first by US then further investigated by CT or magnetic resonance.[6] On imaging, Mit family translocation RCCs figure as heterogeneous formations arising from the renal medulla often confined to the kidney, despite few descriptions of exophytic growth and involvement of the renal sinus.[1,8] Nodal spreading, on the other hand, in spite of its presence in around 47% of the patients by the time of the diagnosis, is identified by CT only in about 25% of the cases.[2,7] Thus, the features of the renal mass identified by both US and CT correspond to the heterogeneous and exophytic appearance of RCC associated to MiT family translocation, and the nodal involvement of the disease was detected by CT in the case of this patient, despite the limitations of the method. The radiological features have failed to identify any specific radiological features of this tumour.[7]

Macroscopically, the gross features of MFt-RCC are similar to those of clear cell RCC; they are typically solid, tan-gray tumors with frequently necrosis, hemorrhage, and occasional papillary formations,aspects that are demonstrated as heterogeneity at imaging.[2,3,5] The description of the tissues found in the renal tumor and the excised lymph nodes of our patient match to the presentation of RCCs often reported in the literature.

Microscopically, these tumors are often composed of large, epithelioid cells with abundant clear to eosinophilic/granular cytoplasm arranged in branching, papillary structures with delicate fibrovascular cores and/or a nested architecture; the nuclei are generally high grade and enlarged with variable nuclear membrane irregularity and nucleolar prominence Psammomatous calcifications may not be present. These features are most characteristic of ASPL-TFE3 t-RCC. PRCC-TFE3 t-RCC, on the other hand, might demonstrate a more nested, papillary, or compact architecture with cells that have less abundant cytoplasm and lower nuclear grade than ASPL-TFE3 t-RCC. However, although certain microscopic features might correlate with the molecular subtype of Xp11 t-RCC, the degree of morphologic overlap between these subtypes prevents definitive classification on a purely histologic basis. Furthermore, although these features should generally raise suspicion for Xp11 t-RCC, the overall morphologic spectrum of Xp11 t-RCC is quite variable and can overlap other RCC subtypes; this underscores the need to consider this entity in the differential diagnosis of renal tumors with clear cell and/or papillary features.

The most commonly used immunostaining parameter for detection of Xp11.2 translocation is nuclear positivity for TFE3, with high sensitivity (97,5%) and specificity (99,6%). Nevertheless, issues related to the staining technique may lead to either false-positive or false-negative results. Therefore, fluorescent in situ hybridization (FISH) method may be useful in order to overcome the problems related to non-reliable immunostaining assays. Other features of the translocation tumors at immunostaining are positivity for renal epithelial transcription factor PAX8 and negativity for carbonic anhydrase IX (CAIX), besides positivity for cathepsin-K in about 60% of these tumors.[4,5] So, positivity for both TFE3 and PAX8 in the samples taken from our patient confirms the presence of translocation of Xp11.2 in this case of RCC.[1,3]

The current management of this tumor is similar to that forconventional RCC. For localized tumor, including patients with positive regional lymph nodes, surgery is the treatment of choice. For patients with hematogenous metastases, the current options are immunotherapy using cytokines, such as interleukin-2 and interferon-alfa, and multikinase inhibitors. A studyanalyzed the outcome of targeted therapy (vascular endothelialgrowth factor receptor-targeted agents and/or mTOR inhibitors) inpatients with Xp11 translocation/TFE3 fusion gene metastatic RCC and found longer median progression-free survival compared with 2months when receiving a cytokine-based regimen.[1,3,4] Our patient treated by targeted therapy based on tyrosine ikinase inhibitors with favorable clinical evolution.

The prognosis depends mainly on the tumoral staging and the age of the patient by the time of diagnosis. Children and adolescents up to 16 years of age tend to have more indolent tumors and more favorable prognosis, even in the presence of nodal metastasis, but still in the absence of hematogenic spread. Comparatively, adult patients tend to present tumors with more aggressive behavior, most of them already present systemic metastasis at the time of diagnosis, and the average survival after diagnosis is of around 18 months.[5,8]

CONCLUSION

MiT family translocation carcinoma is a rare histological type of cancer more prevalent among children and young

adults and with worse prognosis among older subjects. Although uncommon, t-RCC is an important consideration in the differential diagnosis of high-grade epithelioid neoplasms involving the kidney, particularly in children and young adults. The morphologic spectrum of t-RCC is diverse and has potential overlap with common RCC subtypes (CCRCC and PRCC), which represent the main differential diagnostic considerations. Rarely, entities such as syndromic RCC subtypes (ie, HLRCC-associated RCC and TS-associated RCC), the recently characterized renal tumors with clear ells and prominent fibromuscular stroma (TCEB1-mutated RCC), and a distinctive set of non epithelial renal tumors (EAML, ASPS, PEComa, and melanotic epithelioid neoplasms) may also merit consideration. The diagnostic workup for t-RCC may benefit from screening immunohistochemistry. Dual-color, break-apart FISH for TFE3 gene rearrangement may be helpful in diagnostically challenging cases or if molecular confirmation is needed (for example, for clinical trial enrollment).

Conflict of interest

The following authors have no financial disclosures.

Patient consent

This report does not contain any personal information that could lead to the identification of the patient.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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