MITF Family Translocation RCC

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ABSTRACT

Renal cell carcinoma (RCC) is a heterogeneous group of cancers that is increasingly distinguished due to advances in diagnostic methods. Among these cancers, microphthalmia-associated transcriptional factor (MITF) translocation RCCs are an extremely rare subtype. Translocation-associated RCC (t-RCC) is a group of uncommon tumors, which are characterized by recurrent gene rearrangements of transcription factors E3 and EB loci. The treatment of choice for Xp11t-RCC is radical nephrectomy. However, nephron-sparing surgeries are also used for small tumors. In this case report, we present a 16-year-old female patient who underwent a radical nephrectomy for a right renal mass, and the histopathology was an MITF family translocation RCC.

INTRODUCTION

Renal cell carcinoma (RCC) is a heterogeneous group of cancers that is increasingly distinguished due to advances in diagnostic methods. Among these cancers, microphthalmia-associated transcriptional factor (MITF) translocation RCCs are an extremely rare subtype. Translocation-associated RCC (t-RCC) is a group of uncommon tumors that are characterized by recurrent gene rearrangements of transcription factor E3 (TFE3) and transcription factor EB (TFEB) loci[1]. The MITF family translocation RCC comprises of Xp11 translocation RCC harboring TFE3 and t (6; 11) RCC harboring TFEB gene fusions. Initially, these neoplasms were identified in children; however, it has been demonstrated that they can occur in adults as well[2].

Recently, several other genes have been identified, and a wide spectrum of morphologies has been described. For this reason, a diagnosis is usually challenging and is based on histology. A differential diagnosis includes the most common renal cell neoplasms and pure epithelioid PEComa/epithelioid angiomyolipoma of the kidney. Although the majority of RCCs can be diagnosed with only a morphological assessment, MITF family t-RCC also requires the confirmation of TFE3 or TFEB rearrangement. There are three approaches to diagnosing MITF family t-RCC: immunohistochemistry, fluorescent in situ hybridization (FISH), and RT-PCR)/5′-rapid amplification of cDNA ends (5′-RACE)/karyotyping. However, chromosomal rearrangement and FISH is considered the gold standard[2].

Xp11 translocation RCC was first officially recognized in the 2004 WHO renal tumor classification, and it harbors gene fusions involving TFE3. The t (6; 11) RCCs harbor a specific alpha-TFEB gene fusion and were first officially recognized in the 2013 International Society of Urologic Pathology Vancouver classification of renal neoplasia. Both TFE3 and TFEB loci belong to the MITF family; therefore, according to the recent 2016 classification of the WHO, these tumors are now categorized as MITF family translocation-associated RCCs (MITF-RCCs)[3].

The treatment of choice for Xp11t-RCC is radical nephrectomy; however, nephron-sparing surgeries are also used for small tumors.

In this case report, we present a 16-year-old female patient who underwent radical nephrectomy for a right renal mass, and the histopathology was an MITF family translocation RCC.

CASE PRESENTATION

A 16-year-old Bahraini female patient with no known case of medical illness presented to a urology clinic with a history of hematuria, which was episodic and painless.

There were no other symptoms, including constitutional ones, associated with the hematuria.

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A full urological investigation was done. A urine analysis confirmed the presence of red blood cells. All laboratory blood tests were within normal ranges.

IMAGING STUDIES

- Abdominal ultrasound: an oval soft tissue lesion measuring 37.2 x 32.6 x 32.2 mm involving the lower half of the right kidney and seen abutting the lower calyx and partially extending to the renal pelvis.
- **MRI**: An oval soft tissue lesion measuring 37.2 x 32.6 x 32.2 mm involving the lower half of the right kidney and seen abutting the lower calyx and partially extending to the renal pelvis.
- A computer tomography scan of the chest, abdomen, and pelvis: a right renal neoplastic lesion with infiltration of pelvicalyceal system was observed. No evidence of soft tissue, nodal, or bony metastatic lesion was found.
- The patient underwent laparascopic right radical nephrectomy. The post-operative course was uneventful.
- A microscopic examination found a unifocal tumor with a size of 4.5 cm.

Histology subtype: MITF family translocation RCC.
Histology: grade 3.
No sarcomatoid rhabdoid features were identified.

- Immunohistochemistry: Figure 2

AMACR: was positive (diffuse).
Melan-A: was positive (focal weak).
HMB45: was negative.
Pax-8: was negative.
TFE-3: positive.

- Final diagnosis: MITF family translocation RCC (pT3a N1 Mx). Renal mass (4022-21-8), Positive for rearrangement of TFE3 gene by fluorescence in situ hybridization.
- The patient has been referred to medical oncology for an opinion regarding adjuvant (tyrosine kinase inhibitor (TKI)) therapy.

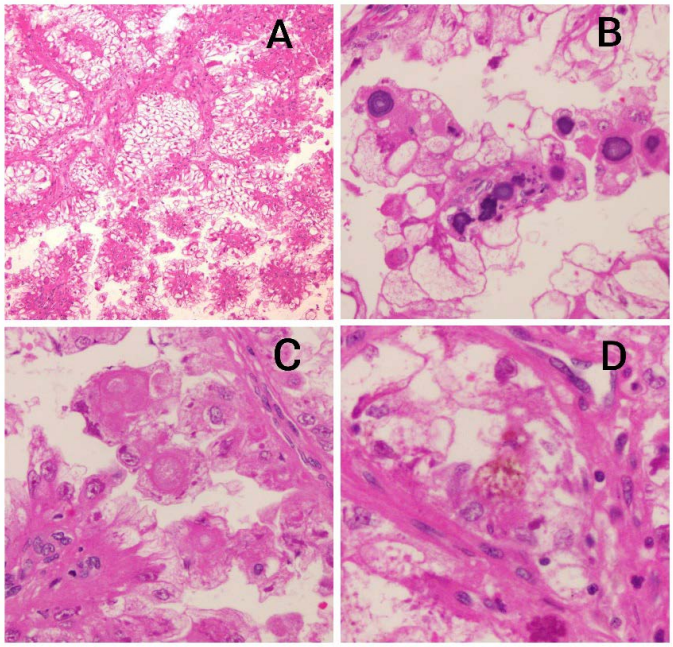


Figure 1: microscopic views of the tumor showing the following characteristic appearances; A: Tumor cells with abundant clear to eosinophilic cytoplasm with well-defined cell border arranged as alveolar and papillary patterns, B: Scattered psammoma bodies (calcified bluish round structures), C: Eosinophilic hyaline globules within tumor cytoplasm, D: Melanin pigment in the tumor cells

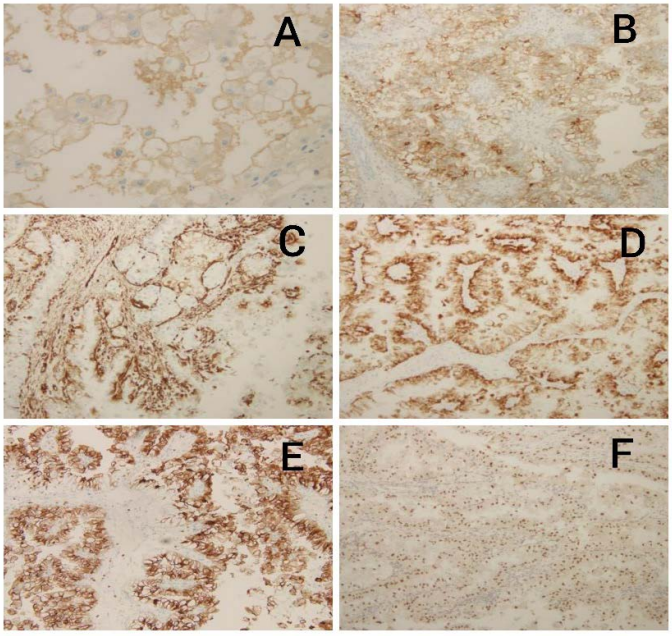
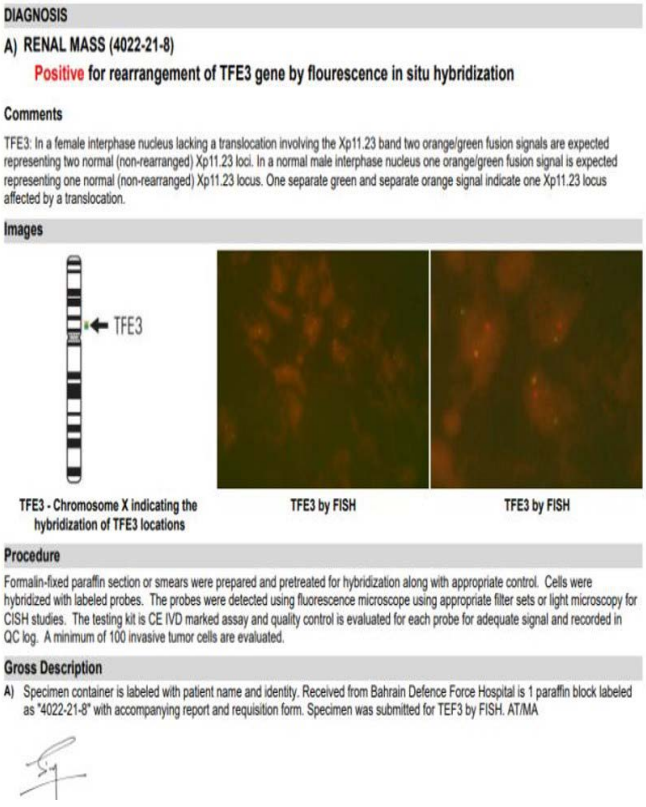


Figure 2: Immunohistochemistry study of the tumor showing positive reaction for the following markers A:CD117 (C-Kit), B:CD10, C: Vimentin, D: AMACR, E: RCC, F: TFE3


DIAGNOSIS

A) RENAL MASS (4022-21-8)

Positive for rearrangement of TFE3 gene by flourescence in situ hybridization

Comments

TFE3: In a female interphase nucleus lacking a translocation involving the Xp11.23 band two orange/green fusion signals are expected representing two normal (non-rearranged) Xp11.23 loci. In a normal male interphase nucleus one orange/green fusion signal is expected representing one normal (non-rearranged) Xp11.23 locus. One separate green and separate orange signal indicate one Xp11.23 locus affected by a translocation.

Images

TFE3 - Chromosome X indicating the hybridization of TFE3 locations

TFE3 by FISH

TFE3 by FISH

Procedure

Formalin-fixed paraffin section or smears were prepared and pretreated for hybridization along with appropriate control. Cells were hybridized with labeled probes. The probes were detected using fluorescence microscope using appropriate filter sets or light microscopy for CISH studies. The testing kit is CE IVD marked assay and quality control is evaluated for each probe for adequate signal and recorded in QC log. A minimum of 100 invasive tumor cells are evaluated.

Gross Description

A) Specimen container is labeled with patient name and identity. Received from Bahrain Defence Force Hospital is 1 paraffin block labeled as "4022-21-8" with accompanying report and requisition form. Specimen was submitted for TEF3 by FISH. AT/MA

DISCUSSION

Translocation-associated RCC (t-RCC) is a rare subtype of RCC containing recurrent gene rearrangements of the TFE3 or TFEB loci. TFE3 and TFEB are two of the four members of the MITF family that regulate gene expression and differentiation in a number of cell types (including melanocytes and osteoclasts). Indeed, the established function of MITF family proteins in melanocytic and osteoclastic differentiation has important implications for the immunohistochemical

evaluation of tumors with TFE3 and TFEB gene rearrangements[4]. It has strong female predominance, usually among ages 35 or below. Furthermore, it is usually at a high stage at diagnosis[5]. The outcome of MITF family translocation RCC is highly variable with an indolent to aggressive behavior form[6]. Although multiple studies claim that Xp11 translocation RCCs in children have a relatively indolent course, there is, however, a high percentage of aggressive cases in young adults. Of all Xp11 translocation RCCs, patients with ASPL-TFE3 fusion seem to have the worst prognosis and tend to have lymph node metastasis, but it is still unclear whether the fusion partner plays a prognostic role[6]. A study was done to evaluate the clinical and pathologic features and the prognostic relevance of unclassified RCC with TFE3 over-expression in an adult series. The study evaluated tumor specimens from 25 patients with unclassified RCC; 32% were positive for TFE3 and the remaining were negative for TFE3 staining. After a 36-month mean follow-up, 5-year cancer-specific survival was 15.6% for TFE3-positive patients and 87.5% for TFE3-negative patients[7].

The treatment of choice for Xp11t-RCC is radical nephrectomy; however, nephron-sparing surgeries have also been used for small tumors. For metastatic patients, therapies targeting the vascular endothelial growth factor receptor, immunotherapy, mTOR inhibitors, and target therapies for the MET signaling pathway are possible options[8-11].

Vascular endothelial growth factor receptor-tyrosine kinase inhibitor (VEGFR-TKI) appeared to demonstrate some efficacy, and if combined with the immune checkpoint inhibitor (ICI), it might be a useful tool for the treatment of metastatic Xp11.2 tRCC as it was able to estimate progression-free survival (PFS) and overall survival (OS) distributions in a study done on 45 patients with metastatic Xp11.2 tRCC in Peking University Cancer Hospital. The result was that median PFS and median OS were 7.4 months (4.5–8.8) and 17.9 months (12.4–24.4), respectively. First-line treatment mainly included sunitinib (n = 14), sorafenib (n = 15), axitinib (n = 6), and pazopanib (n = 5), and the median PFS of these regimens were 7.4 months, 5.4 months, 9.4 months, and 8.9 months, respectively. Two patients who received VEGFR-TKI plus ICI as first-line therapy had a PFS of more than 16.6 months and 25.6 months[12].

Some studies suggest that response rates of VEGFR-TKI and ICIs are limited. A study to check the efficacy of cabozantinib (a TKI that inhibits VEGFR, MET, and AXL) was done on 24 patients (21 with TFE3 and 3 with TFEB translocations). The proportion of patients with an objective response was 16.6%, including 1 complete response and 3 partial responses. For 11 (45.8%) patients, stable disease was the best response. The median follow-up was 14 months while the median PFS was 8.4 months (range: 1–34+) and the median OS was 17 months (range: 2–43).

CONCLUSION

MITF family translocation RCC is a rare subtype of RCC and the outcome is highly variable.

Authorship Contribution: All authors share equal effort contribution towards (1) substantial contributions to conception and design, acquisition, analysis and interpretation of data; (2) drafting the article and revising it critically for important intellectual content; and (3) final approval of the manuscript version to be published. Yes.

Potential Conflict of Interest: None

Competing Interest: None

Acceptance Date: 29 October 2022

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