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Case Report

Renal Carcinoma Associated with Xp11.2 Translocations and TFE3 Fusions, Confirmed by Flourescence in Situ Hybridization

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Abstract

Renal carcinoma associated with Xp11.2 translocations and TFE3 fusions (Xp 11.2 RCC) form a new and little known entity of the WHO classification. It accounts for at least one-third of pediatric RCCs and 15% of RCCs in patients <45 years of age. Renal carcinoma associated with Xp11.2 translocations and TFE3 fusions (Xp 11.2 RCC) is a rare pediatric renal carcinoma diagnosed by fluorescence in situ hybridization (FISH). We report a case of Xp 11.2 RCC in a 13 year old girl, presented with hematuria. Mass was detected on CECT. She underwent nephrectomy and histopathological examination confirmed renal cell carcinoma. Type was confirmed by FISH. Renal cell carcinoma in pediatric age with characteristic morphology need to be subcategorized using ancillary methods. The most sensitive and specific immunohistochemical markers for these neoplasms are TFE3 protein and cathepsin-K3. Complete surgical removal of the tumour mass including the kidney is the preferred therapy in patients with lower stage tumors

Keywords: Xp11.2 Renal Carcinoma, Pediatric Renal Carcinoma, Renal Carcinoma with Papillary Features, Rare Renal Carcinoma, Renal Carcinoma with Translocation, Molecular Pathology.

INTRODUCTION

Renal carcinoma associated with Xp11.2 translocations and *TFE3* fusions (Xp 11.2 RCC) form a new and little known entity of the WHO 2004 classification. It accounts for at least one-third of pediatric RCCs and 15% of RCCs in patients <45 years of age [1]. Xp 11.2 RCCs are defined by translocations involving Xp11.2 chromosome, all of which result in a gene fusion involving the TFE3 (transcription factor E3) gene [2, 3]. Complete surgical removal of the tumour mass including the kidney is the preferred therapy in patients with lower stage tumors. Prognosis depends also on the age: in children tumour is rather indolent, but in patients aged 16 or older Xp11.2 translocation carcinoma has a more aggressive clinical course [3].

CASE REPORT

Seventeen year old girl presented with hematuria. No h/o pain. No known co morbidity. O/E-vitals were stable. BP-150/88 mm Hg. Systemic examination was unremarkable. P/A-no mass was felt. CECT abdomen–right kidney was normal (fig.1).

She underwent radical nephrectomy. Following surgery, we received nephrectomy specimen with bosselated upper pole. On cut section, a well circumscribed grey-white, granular, friable neoplasm measuring 6.5x6x6 cm was noted. There were no areas of hemorrhage or necrosis. Renal capsule, ureter and renal vessels were free of tumour. Microscopic examination showed a tumour arranged as papillae (fig.2.A), lined by cells with moderate-abundant amount of clear-pale eosinophilic cytoplasm (fig.2.B), prominent cell borders, central oval-elongated nucleus with fine chromatin and inconspicuous nucleoli. Psammomma bodies (fig2.C) were seen in plenty. Hyaline nodules were seen occasional. Tumour emboli were seen in the vessels within the tumour. Foamy macrophages were not seen. Adjacent renal parenchyma was unremarkable. Immunohistochemistry (IHC) was done.

Tumour cells were positive for CK7 (fig2.D), CD10 (fig 3.A) and PAX8 (fig 3.B) and negative for HMB45 (fig 3.C). With this morphology in a young girl, renal carcinomas associated with Xp11.2 translocations / TFE3 gene fusion was suspected and so we proceeded with fluorescence in situ hybridization (FISH) to

demonstrate translocations involving chromosome Xp11.2. A TFE3 break- apart probe was used (that screens for the t(X; 17) (p11.2; q25) and t(X; 1) (p11.2;q21) chromosomal rearrangements). Result is as follows- Total number of cells scored – 140. Percentage Cells with no TFE3 translocation – 36. Percentage Cells with TFE3 translocation – 64. Result: Positive for the translocation involving the Xp11.2; TFE3 locus (fig. 3.D).

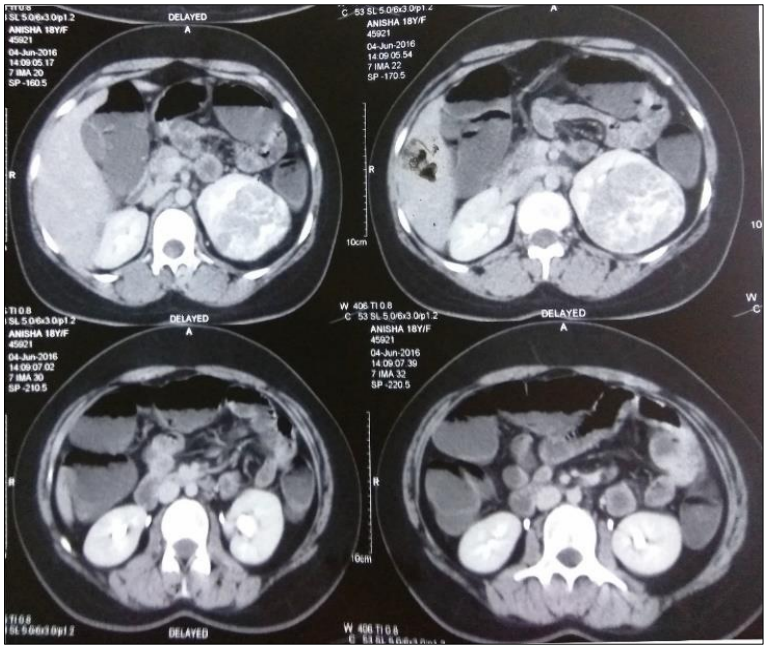

Fig. 1: CECT abdomen–Left kidney showed a well defined heterogenous soft tissue mass involving upper and mid pole 66x67x 65 mm with compression of upper calyces.

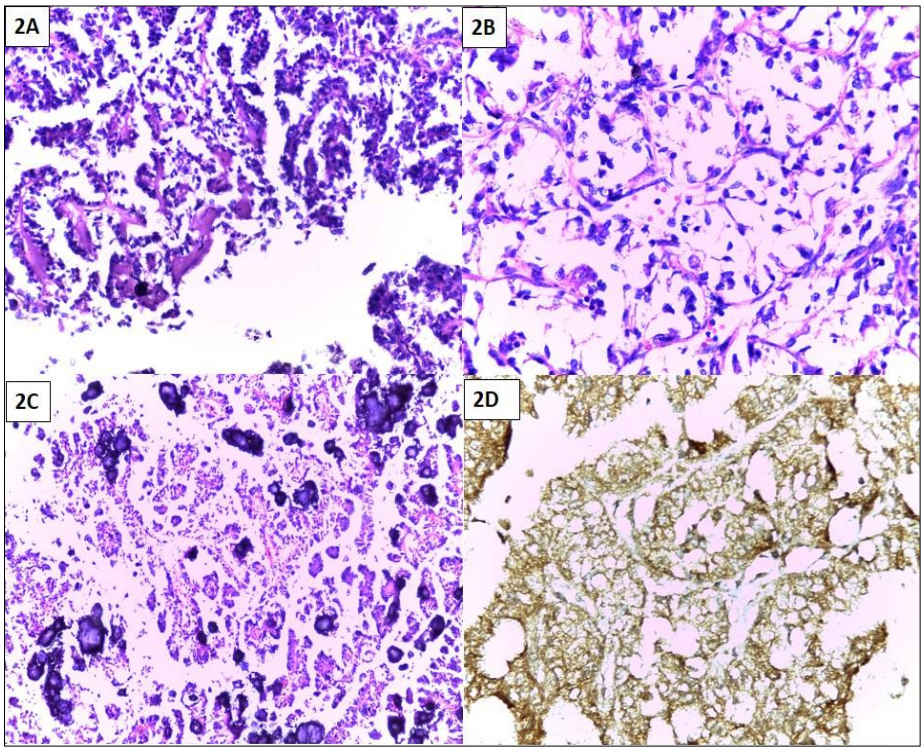

Fig. 2A: Neoplasm arranged as papillae (H&E 10x)
2B- Tumour cells with moderate amount of clear eosinophilic cytoplasm (H&E 40x)
2C- Numerous psammomma bodies (H&E 20x)
2D- Tumour cells are CK 7 positive (H&E 20x)

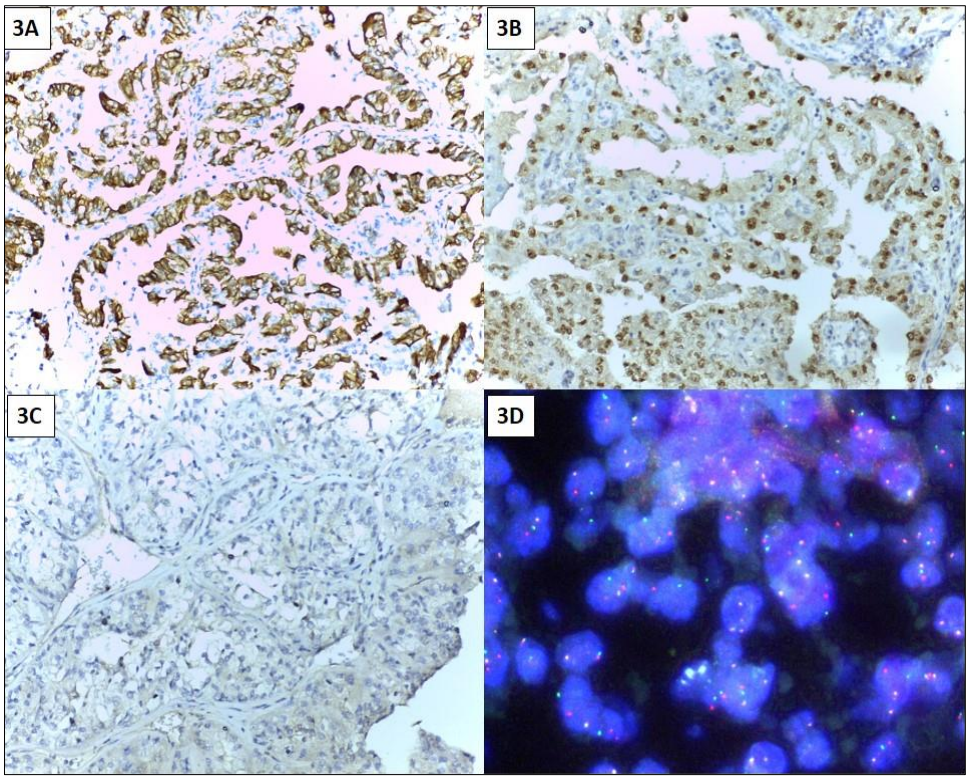

Fig. 3A: Tumour cells are CD 10 positive (H&E 20x)
3B- Tumour cells are PAX8 positive (H&E 20x)
3C-Tumour cells are HMB-45 negative (H&E 20x)
3D- FISH showing positive for the translocation involving the Xp11.2; TFE3 locus

DISCUSSION

Xp11.2 translocation renal cell carcinomas (Xp 11.2 RCCs) are rare tumors that occur primarily in children and young adults with a strong female predominance [1]. Approximately one-third of pediatric RCCs are Xp 11.2 RCCs; conventional clear cell RCCs make up about 15% of RCCs in children [2]. The most common symptom is hematuria. The radiological findings of Xp11.2 RCC are not specific [3].

Grossly, Xp11.2 RCC is indistinguishable from conventional RCC. Tumor size varies from 2.1 to 21 cm with mean size of 6.8 cm [2-4].

Histologically, Xp11.2 RCC has nested/ tubular/ papillary growth patterns**.** Tumor cells have clear to eosinophilic, granular cytoplasm and prominent cell borders. The nuclei are vesicular [2-4]. Psammomatous calcifications and foci of stromal eosinophilic hyaline globules may be numerous and widespread. The morphology of Xp11.2 RCC with different gene fusion partners may vary slightly. The papillary renal cell carcinoma (PRCC)-TFE3 variant is composed of intermediate-sized, clear cells, arranged in nested pattern, and shows few psammoma bodies; whereas the ASPL-TFE3 variant shows pseudopapillary pattern of voluminous clear or eosinophilic cells, and presence of extensive psammoma bodies [3]. The usual absence of foamy macrophages, nuclear grooves, stromal inflammatory cells, and necrotic background in Xp11.2 translocation RCC may be useful in distinguishing them from papillary and conventional clear cell RCC [3, 4]**.**

The most sensitive and specific immunohistochemical markers for these neoplasms are TFE3 protein and cathepsin-K [3, 4]. Strong expression of CD10 is common. Expression of melanocytic markers (Melan-A, HMB-45), and EMA is rare and weak [3].

To date, eight *TFE3* fusion partners have been reported, including papillary renal cell carcinoma (*PRCC*), alveolar soft part sarcoma locus (*ASPL*) [5], which are the most common ones. The gene rearrangements result in the over expression of TFE3, a member of the microphthalmia-associated transcriptional factor family (MiTF). Hence, these neoplasms are classified under the category of MiTF/TFE translocation carcinoma family [4]**.** In conclusion, the diagnosis of an Xp11.2 TRCC is based on microscopic appearance, TFE3 immunostaining, and genetic analyses.

Xp 11.2 RCC**s** are believed to be rather indolent. The tumor tends to be more aggressive in adults with widespread systemic metastases [3, 4]. TFE3 expression is associated with regional lymph node metastasis, and is accepted as a poor prognostic marker

[3]. Because of the small number of TFE3 gene fusion-related renal tumors described in the literature, the impact of current treatment modalities remains to be uncertain [5]. Sunitinib appears to be effective [5].

Statement of Conflict of Interest: Nil

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