Fine needle aspiration of a translocation/TFE3 fusion renal cell carcinoma metastatic to the liver: a case report

Sharda Lallu, Sarla Naran, Peter Bethwaite and Diane Kenwright

Abstract
A 20 year old male patient presented with a six weeks history of abdominal pain. On CT scan, a large liver mass involving segment 8 and part of segment 4 with concurrent large left renal mass was noted. Two lesions in both right and left lungs, and a small right pleural effusion were also present on imaging. An ultrasound guided fine-needle aspiration (FNA) of the liver revealed a cellular sample composed of dissociated and papillary groups of malignant cells with abundant cytoplasm admixed with clear and granular eosinophilic pattern, ovoid nuclei with finely granular chromatin, prominent nucleoli and intranuclear inclusions present in some cells. Cells were arranged in a nested pattern in a necrotic and bloody background. Immunohistochemical studies showed tumour cells to express CD10, AMACR, E-Cadherin, AE1/AE3; and negative staining for Hep-Par-1, EMA, CK7, CK20, CD30, TTF-1, CEA, Melan-A, HMB-45, vimentin and S100. A concurrent core biopsy sample from the large mass at the lower pole of left kidney reflected the FNA findings and demonstrated a similar immunohistochemical phenotype. FISH studies detected a heterogeneous and atypical TFE3 (Xp11.2) gene rearrangement in all 87 cells examined, which was performed on the kidney biopsy sections only.

Key words: FNA, liver, kidney, TFE3, Xp11.2 translocation carcinoma.


Introduction
Renal cell carcinoma (RCC) associated with Xp11.2 translocations/TFE3 gene fusion, is a recently recognized tumour entity, characterized by chromosome translocations involving the Xp11.2 breakpoint and resulting in gene fusion involving the TFE3 gene, as first described by de Jong et al (1). Xp11.2 translocation carcinoma is recognized in the 2004 WHO renal tumour classification (2). Renal translocation carcinomas are uncommon tumours, generally arising in children and young adults. In the paediatric literature they have sometimes been referred to as ‘juvenile carcinomas’ (3). RCC accounts for 2-3% of all adult malignancies. It rarely occurs in children where it represents 0.1 to 0.3% of all neoplasm and from 1.8 to 6.3% of all malignant renal tumours (4).

We describe a fine-needle aspiration (FNA) of the liver mass in a 20 year male initially diagnosed with a metastatic RCC. The cytological, histological, immunophenotypic, and interphase nuclear in situ hybridization presentation of the tumour is described.

Case report
A 20 year old male patient previously fit and well, presented with a two month history of abdominal discomfort, vomiting, fever, 10 kg weight loss, and extreme fatigue. On abdomen CT, there was a large liver mass (25cm) and a large heterogeneous mass (10cm) arising from the left kidney. A chest CT showed several enlarged mediastinal lymph nodes, the largest of these was right hilar lymph node which measured approximately 2.3 cm x 1.6 cm in its axial dimension. There were two lesions in both right and left lung fields and a small right sided pleural effusion. No gross abnormalities were detected in the spleen, pancreas, right kidney and right adrenal gland on CT scan. The left adrenal gland was difficult to identify confidently. An ultrasound guided FNA of the liver lesion was performed to determine the origin and aetiology.

Methods and materials
FNA of the hepatic mass was performed with a 22G spinal needle and smears were prepared on site and fixed in 95% ethanol and stained with Papanicolaou stain. The remaining material from the needle was washed in 30% ethyl alcohol in physiologic saline. From half of this material a filter preparation was made on size 5 μm Sartorius AG-Cellulose Acetate filter (Germany) using the cytosieve method and stained by Papanicolaou method. The remainder of the aspirate sample was spun down and from the sediment a cell block was made and fixed in 10% formalin, routinely processed and stained with Hematoxylin-eosin (H & E). Fluorescence in situ hybridization (FISH) assays were performed using formalin fixed sections from kidney biopsy.

Immunohistochemistry was undertaken using Bond™ Polymer Refine Detection (Leica). Sections from the cell block of FNA liver stained with CK7 (1:750 Dako), CK20 (1:200 Leica), cytokeratin AE1/AE3 (1:1000 Dako) EMA (1:750 Dako), HMB 45 (1:500 Dako), Melan A (1:200 Dako), S100 (1:4000 Dako), CD30 (1:25 ALS), TTF-1 (1:250, Leica), vimentin (1:4000 Dako), CEA (1:300 Dako), CD10 (1:50 Leica), Hep-par-1 (1:1000 Dako), AMACR (1:300 Dako), E-Cadherin (RTU Leica).

Results
Cytologic findings
Cytological preparations were highly cellular. The tumour cells were isolated and arranged in papillary clusters with large clusters demonstrating fibrovascular cores. The tumour cells had irregular nuclear outlines, finely granular chromatin and a single large nucleolus. The cytoplasm was abundant and admixed with clear and granular eosinophilic patterns (Figure 1). Additionally, scattered cells with intranuclear inclusions were seen in cell block section (Figure 2).

Figure 1. Smear preparation from FNA of liver showing papillary cluster of cells with irregular nuclear membrane, finely granular chromatin, prominent nucleolus and abundant granular cytoplasm (Papanicolaou Stain X 400).
Figure 2. Cell block preparation from FNA of liver showing dissociate and groups of cells-a few with intranuclear inclusions (Hematoxylin-eosin Stain X 400).

Histologic findings on kidney biopsy
Sections showed a papillary necrotic tumour composed of cells with eosinophilic cytoplasm and central ovoid nuclei with prominent nucleoli. The cells were arranged in a papillary and nested pattern. Fibrous bands and haemorrhage were noted. No psammoma bodies were seen (Figure 3).

Figure 3. Histology section of left renal biopsy showing cells with abundant eosinophilic cytoplasm and round to oval nuclei with prominent nucleoli arranged in nested pattern (Hematoxylin-eosin Stain X 400).

Immunohistochemical findings
Immunohistochemical staining on FNA cell block preparations showed positive staining for E-Cadherin, CD10 (Figure 4), AMACR (Figure 5), and cytokeratin AE1/AE3. Tumour cells showed negative staining for HMB45, Melan-A, S100, CD30, vimentin, CK7, CK20, EMA, CEA, TTF-1 and Hep-Par-1. Immunohistochemical staining on sections from kidney biopsy also showed strong positivity for E-Cadherin, AMACR, CD10. Tumour cells showed negative staining for CK7, EMA, Melan A and HMB 45.

Figur e 4. Immunohistochemical stains on cell block section showing positive staining for CD10 (CD10 x 400).

Figure 5. Immunohistochemical stains on cell block section showing positive staining for AMACR (AMACR X 400).

Cytogenetic analysis
Fluorescent in situ hybridization studies performed on kidney sections detected a heterogeneous and atypical TFE3 (Xp11.2) gene rearrangement in all 87 cells examined (Figure 6).

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IMAGES:

Kreatech TFE3
breakapart

COMMENT:
Interphase nuclear in situ hybridization studies detected a heterogeneous and atypical TFE3 (Xp11) gene rearrangement in all 87 cells examined.

SUMMARY/INTERPRETATION:
TFE3 (Xp11) gene rearrangement is a recognised finding in renal translocation carcinoma. The clinical significance of the atypical rearrangement is unclear.

Figure 6. FISH studies on kidney sections showing TFE3 (Xp11) gene rearrangement.
Discussion
Renal translocation carcinomas of the kidney are uncommon renal tumours usually arising in children and young adults. The average age, in a recent large series, was 24.7 years, with a median of 20 years and with a female to male ratio of 2.5:1. These tumours account for at least one-third of carcinomas seen in childhood and adolescence (5). In 2004, the Xp11.2 translocation RCC was introduced as a genetically distinct entity into the WHO classification of renal neoplasms. These tumours were formerly recognized as “juvenile carcinomas” in the paediatric literature, where they were considered as aggressive tumours displaying papillary and/or alveolar patterns with “voluminous” eosinophilic and/or clear cells (6).

Patients with translocation carcinoma usually present symptomatically with hematuria, abdominal pain, abdominal mass, or fever. The biologic behaviour of the tumour in this case is typical for patients with Xp11.2 RCC who typically have a poor prognosis due to advanced stage at presentation and aggressive biologic features compared with the TFE-negative unclassified RCC cases (7).

The majority of translocation carcinomas (90%) involve the transcription factor E3 (TFE3) located on Xp11.2. Another rare group of renal carcinomas showing a translocation t(6;11) (p21;q12) involving transcription factor EB (TFEB) has been recognised (6). Both TFE3 and TFEB belong to the microphthalmia transcription factor (MITF) subfamily. Definitive diagnosis of translocation carcinoma requires immunohistochemical identification of the nuclear transcription factor (TFE3, TFEB) and/or cytogenetic or molecular genetic (FISH, PCR) identification of the translocation (6). Importantly, the translocations associated with TFE3 and TFEB are associated with overexpressed proteins that can be identified by immunohistochemistry. TFE3 nuclear staining is specific for Xp11.2 translocation and nuclear TFEB staining is specific for t(6;11) (p21;q12) (3,5,6).

In a younger patient the main differential diagnoses include Wilms tumour, neuroblastoma, other variants of renal cell carcinoma, hepatocellular carcinoma, melanoma, germ cell tumour, lung carcinoma, and thyroid tumour; all of which may occur in children and young adults (8). There should be a high index of suspicion for translocation carcinoma in tumours showing papillary and nested patterns, where there is a mixture of clear and eosinophilic granular cells. The presence of voluminous cells may also be a clue to the diagnosis. The presence of collagen type IV hyaline nodule-like structures surrounded by tumour cells is also a clue to establishing a possible cytologic diagnosis of TFE3-RCC which was not identified in this case. The diagnosis of Wilms tumour, even in its monophasic epithelial form, was excluded as tumour cells were too large with an abundant cytoplasm. In the typical Wilms tumour the triphasic pattern of clusters, tubule like structures, and single blastematous cells may be identified. Neuroblastomas are small round cells tumours comprised of small round neuroblasts and the tumour usually exhibits neurofilibrillary components which was absent in our case and tumour cells were negative for S100. The usual phenotype of translocation carcinoma (CK7 - , AMACR + , CD10 + , EMA -) helps separate these from conventional clear cell renal carcinoma (CK7 -, AMACR-, CD10 + , EMA +) and papillary renal cell carcinoma (CK7 + , AMACR + , CD10 + , EMA+)(9,10).

Hepatocellular carcinoma may show overlapping cytologic features with translocation carcinomas but are easily identified by their typical immunophenotype including positivity for HepPar1. Melanoma was excluded as the tumour cells were negative for Melan-A and HMB 45. Negative staining for CD30, TTF-1 and CEA excluded the possibility of embryonal carcinoma and negative TTF-1 staining made a lung or thyroid primary site less likely.

Conclusions
The distinctive morphologic features of TFE3-RCC may allow recognition of this important subtype in cytologic material by recognition of the presence of tumour cells with abundant clear or granular, eosinophilic cytoplasm with nested and papillary architecture surrounded by dense hyalinised central cores in the right clinical context. Immunohistochemical and/or cytogenetic/molecular studies are essential for diagnostic confirmation.

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References


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