

Solid Tumour Section

Mini Review

Kidney: t(6;11)(p21;q12) in renal cell carcinoma

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Identity

Alias

Alpha-TFEB renal cell carcinoma

Note

A distinctive renal neoplasm with epithelioid morphology, basement membrane production focal HMB45 immunoreactivity.

Classification

This is a recently described, novel type of renal cell carcinoma, which is most likely related to the recently-described and recognized Xp11 renal translocation carcinomas.

Clinics and pathology

Etiology

Not clear, but two of 12 confirmed cases have occurred in children who were exposed to prior cytotoxic chemotherapy, raising the possibility that this tumor may be induced by chemotherapy.

Epidemiology

There are 12 reported cases, 3 in males and 9 in females. The median age is 18 years (range: 6-53 years).

Pathology

On microscopic examination, these neoplasms feature nests and tubules of polygonal epithelioid cells, separated by thin capillaries. Papillary architecture may be seen. The majority of the tumor cells have abundant clear to granular eosinophilic cytoplasm, well-defined cell borders and round nuclei with small nucleoli. However, a second population of smaller epithelioid cells is also characteristic, typically (but not always) clustered around nodules of hyaline basement membrane material within larger acini. Mitoses are rare and necrosis is usually absent. The cases examined have generally been negative for cytokeratins by immunohistochemistry, but all have labeled at least focally for HMB45 and Melan A. We have recently found that the t(6;11) renal carcinomas demonstrate specific nuclear labeling for TFEB protein by IHC while other neoplasms and normal tissues do not. Hence, nuclear labeling for TFEB is a sensitive and specific diagnostic marker for this renal neoplasm with a TFEB gene fusion.

Treatment

Nephrectomy.

Prognosis

Unclear at the current time. One case has metastasized and killed the patient, proving that these are malignant neoplasms.

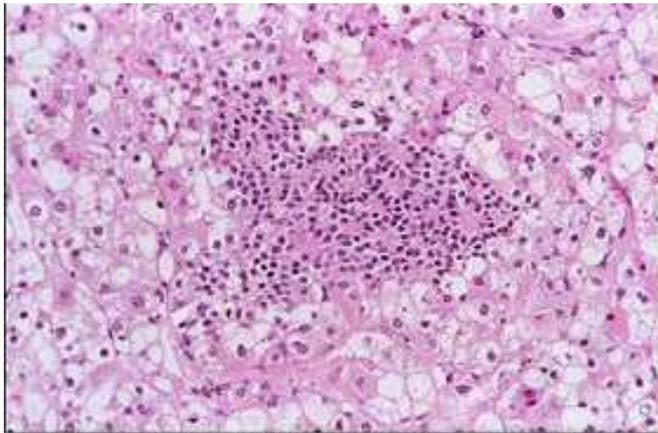


Figure 1: Low power view showing solid growth pattern and biphasic appearance

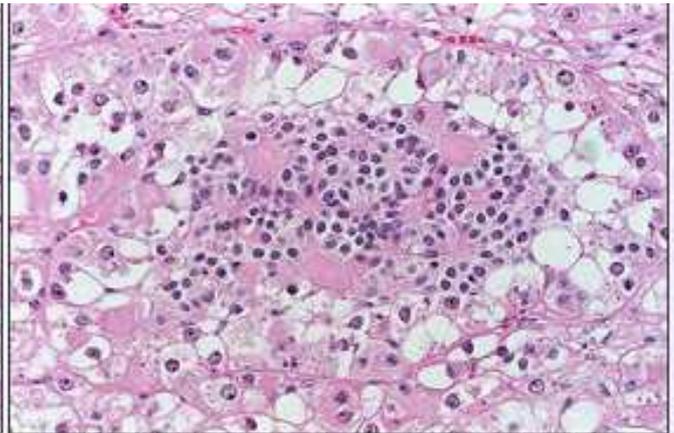


Figure 2: High power view highlighting biphasic appearance: larger epithelioid cells with clear cytoplasm, and smaller cells clustered around hyaline nodules.

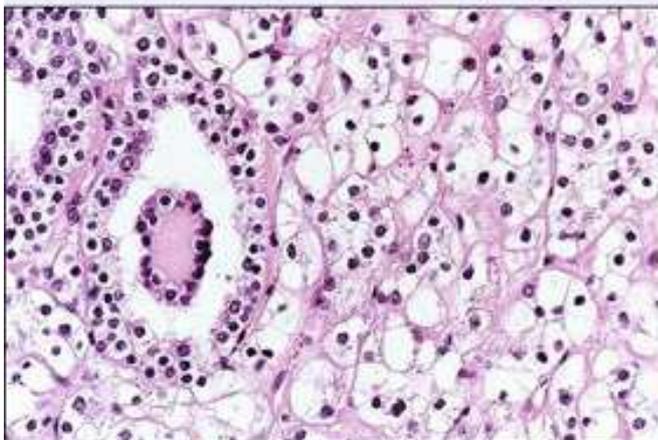


Figure 3: Intermediate power view showing solid and tubular architecture.

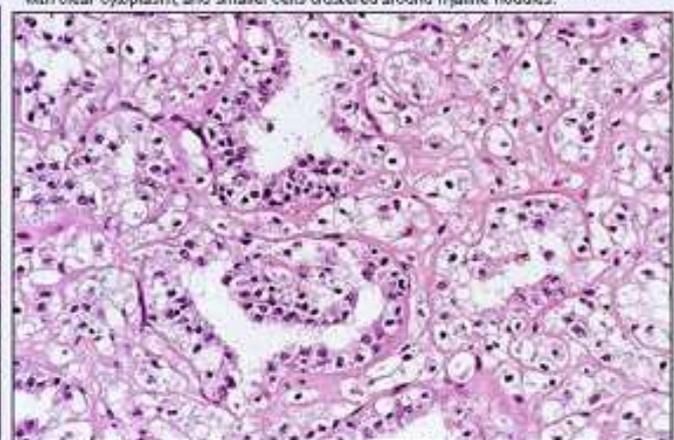


Figure 4: Intermediate power view showing abortive papillary formations.

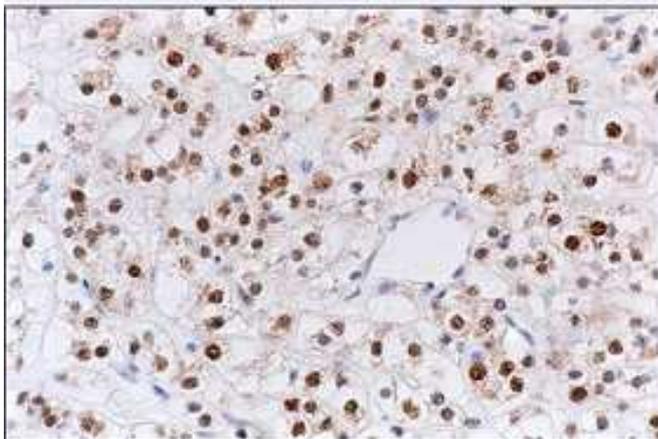


Figure 5: Immunohistochemical stain for TFEB strongly and diffusely labels tumor cell nuclei, not endothelial cells.

Genes involved and proteins

TFEB

Location

6p21

DNA / RNA

TFEB has 10 exons, with the ATG protein initiation codon located within exon 3.

Protein

TFEB is a transcription factor with a basic helix-loop-helix DNA binding domain, a leucine zipper dimerization domain¹⁸, and a nuclear localization signal, thought to be located C-terminal to the helix-loop-helix domain. TFEB is ubiquitously expressed.

TFEB, TFE3, TFEC and Mitf comprise the members of the microphthalmia transcription factor subfamily, which have homologous DNA binding domains and can bind to a common DNA sequence.

These four transcription factors may homo- or heterodimerize to bind DNA, and they may have functional overlap.

Alpha

Location

11q12

DNA / RNA

Alpha is an intronless, untranslated gene of unknown function.

Result of the chromosomal anomaly

Hybrid Gene

Description

The breakpoint on TFEB is within its second intron, just upstream of the TFEB initiation ATG codon, which results in retention of the entire TFEB coding region in the fusion gene. Although the Alpha promoter drives expression of the fusion gene, the Alpha gene does not contribute to the open reading frame. Therefore, the consequence of the Alpha-TFEB fusion is dysregulated expression of the normal full-length TFEB protein. The TFEB-Alpha fusion gene is also expressed.

Detection

RT-PCR is the standard molecular approach for detection of most translocation-associated gene fusions. This is because, in most leukemia and sarcoma translocations, genomic breakpoints are variably positioned within large introns, but the splicing of the transcripts encoded by fusion genes typically results in very consistent fusion points that can be tightly bracketed by appropriate primers to generate relatively small RT-PCR products (e.g. 100-300 bp).

In the t(6;11)(p21;q12), the lack of splicing between Alpha and TFEB results in a different and unique fusion transcript in each case that can vary considerably in size (over 1 kb) from case to case. Since RNAs extracted from clinical samples are usually partially degraded, amplification of targets in this size range is much more inefficient and the risk of false-negatives correspondingly increases. The Alpha fusion points in 7 fully characterized tumors were scattered over 1.2 kb. Because there are likely no functional consequences to different fusion points in Alpha (since it does not encode a native protein or a fusion protein with TFEB), additional Alpha fusion points outside of this breakpoint cluster region may well be found in the future. The fusion points in TFEB appear more tightly clustered; so far, all have been located in a 167 bp region near the 3' end of intron 2. Based on the sizes of these two breakpoint cluster regions, RT-PCR product sizes using a primer at the 5' end of Alpha in combination with a reverse primer in exon 3 of TFEB

could range in size to over 1.5 kb. This is a technical drawback for molecular diagnosis that could be addressed by using several assays with different Alpha primers scattered from the 5' to the 3' end of the gene. However the unique features of the Alpha gene as a translocation partner should result in a lack of splicing across the intron rearranged by the translocation. Indeed, this seems to be the case, since in all three cases with data on both the genomic junction sequence and the fusion transcript, the sequences have been identical. This indicates that the DNA PCR and RT-PCR products will be identical if a reverse primer that binds to TFE3 exon 3 is used. Because it is easier to isolate and amplify 1 to 1.5 kb target DNAs from clinical tumor samples than target RNAs of the same size (given the greater lability of RNA), detecting this fusion by long range DNA PCR may be a useful alternative for molecular diagnosis.

Fusion Protein

Note

The Alpha-TFEB gene fusion results in dysregulated expression of native TFEB protein.

Expression / Localisation

TFEB protein that is overexpressed as a result of the Alpha-TFEB gene fusion localizes to the nucleus as determined by immunohistochemistry. While it is ubiquitously expressed, native TFEB in cells without this translocation is not detectable by this assay.

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