RBM10-TFE3 renal cell carcinoma: the role of tissue morphology and molecular diagnostics

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Abstract

RBM10-TFE3 renal cell carcinomas are a rare and recently described tumour type with a range of morphology including a biphasic pattern. There are well-known specific difficulties in establishing a diagnosis with TFE3 immunohistochemistry being technically difficult and strongly dependent on good tissue fixation. The more robust conventional break-apart fluorescence in-situ hybridization has specific technical limitations when confronted with this tumour subtype, with false-negative results. We present a diagnostic case for which a next-generation RNA sequencing approach confirmed the presence of a RBM10-TFE3 fusion transcript.

Keywords next-generation sequencing; RBM10-TFE3; renal cell carcinoma; translocation tumour

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Case report

Histology slides from a male patient aged 63 years referred to our institution for consideration of clinical trials were reviewed. A diagnosis of clear cell renal cell carcinoma (RCC) was made 20 years ago in a right nephrectomy containing a 3.5 cm tumour confined to the kidney (pT1a). The tumour recurred 8 years later in para-aortic lymph nodes and subsequently progressed with lung metastasis.

Macroscopically, the recurrent tumour mass was nodular, measured up to 65 mm and had a cream to yellow and partly necrotic appearance.

Microscopically, the tumour formed large nodules having a mixed papillary and solid/alveolar architecture and pushing margin (Figure 1a). There was central tumour necrosis with poorly preserved tumour cells and architecture present. The tumour had a biphasic appearance with complex branching thin fibro-vascular papillary cores lined by low columnar to cuboidal, stratified epithelium. Some of these larger tumour cells had clear cytoplasmic vacuoles, displacing small round nuclei towards the periphery. Other tumour cells had pale cytoplasm and a round to oval vesicular nucleus bearing an easily seen nucleolus (Fuhrman Grade 3). Some cells had fine yellow-brown cytoplasmic pigment. There were no associated foamy macrophages. Scattered psammoma bodies were present (Figure 1b).

A second tumour cell morphology was seen within the solid/alveolar areas, forming islands of smaller polygonal tumour cells that had well defined pale cytoplasm. The nuclei were small, centrally placed, irregular and oval. Some had longitudinal nuclear grooves. Small, irregular eosinophilic extra-cellular and proteinaceous deposits were seen admixed in this component (Figure 1c).

Tumour cell immunohistochemistry showed strong expression of INI-1, PAX8, E-Cadherin and CD10 (luminal). In the solid/alveolar areas, the smaller tumour cells expressed Vimentin (strong and membranous) and the larger tumour cells expressed RCCAg (strong) and AMACR (moderate and patchy). Melan-A was expressed in the smaller tumour cell islands (strong) and surrounding larger tumour cells (moderate) of the solid/alveolar areas (Figure 1d), as well as focally within tumour cells of the papillary areas. Cam5.2, AE1/AE3, CK903, EMA, CD117, HMB45 and CAIX were not expressed. TFE3 immunohistochemistry that had been performed at original hospital was previously interpreted as equivocal.

The morphology and immunohistochemical features were suggestive of an Xp11 translocation RCC. Molecular characterization was performed using the Illumina TruSight RNA Pan-Cancer Panel to detect novel transcripts due to gene rearrangements and a TFE3-RBM10 fusion was detected.

Discussion

RBM10-TFE3 rearrangement is an uncommon and recently described subtype of the Xp11 class of microphthalmia-associated transcription factor (MiT) family translocation RCCs.[1] The median age at diagnosis is reported as 46 years (range 31–71 years)[2–5]; our patient initially presented at 43 years and had a long interval to retroperitoneal lymph node and lung metastasis (overall survival 20 years). This is certainly the longest follow-up period for this tumour type in the literature so far.[4]

The mixed papillary and solid/alveolar architecture comprising large clear cell tumour cells, scattered psammoma bodies and an immunoprofile showing relative absence of cytokeratin and EMA expression but some expression of melanocytic markers, is suggestive of an Xp11 translocation RCC.[1,5] A

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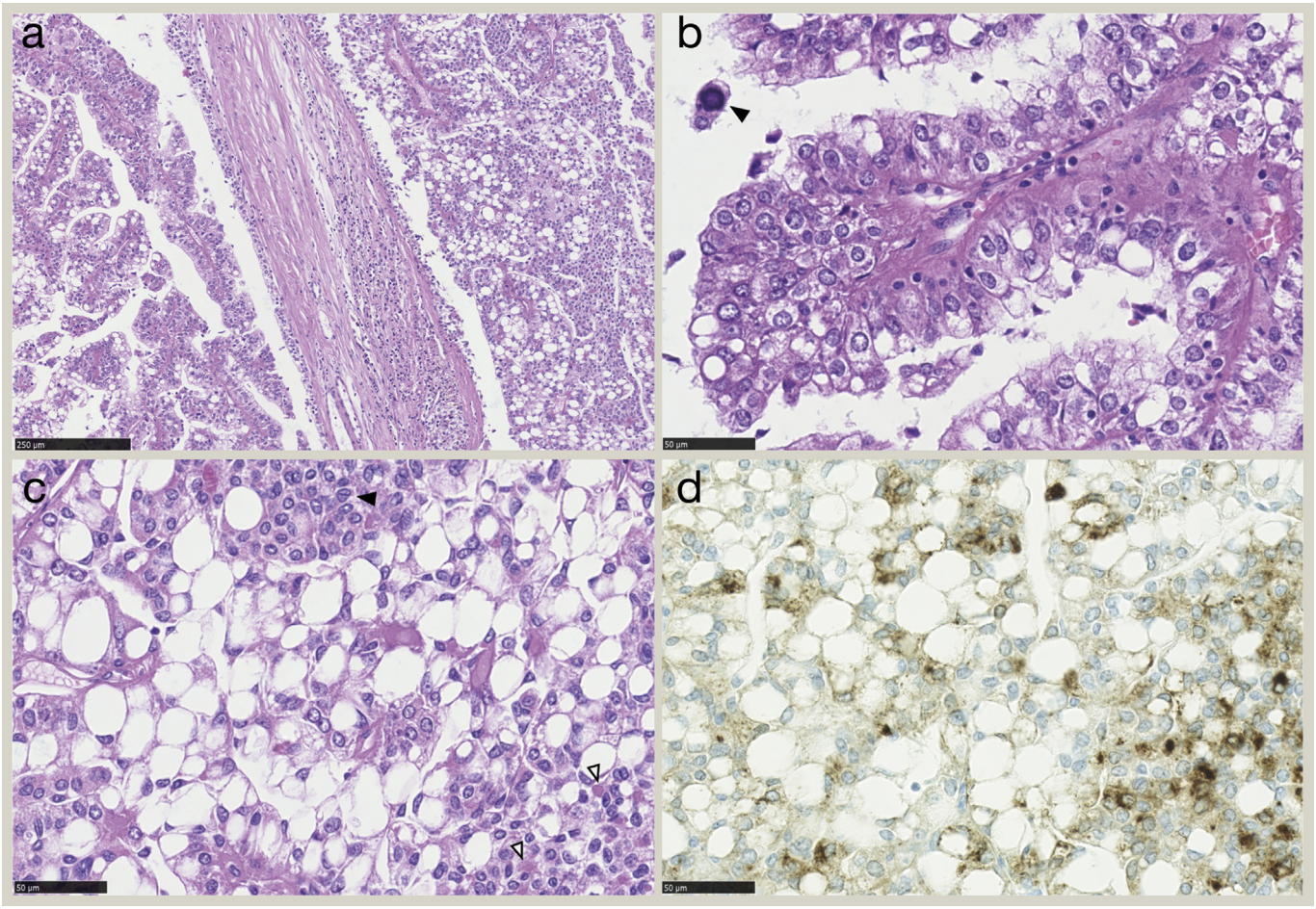

Figure 1 RBM10-TFE3 translocation renal cell carcinoma. **(a)** Nodules of tumour showing a papillary architecture (left) and solid/alveolar architecture with biphasic tumour cell populations (right) separated by a dense fibrous capsule, ×10 objective magnification. **(b)** Papillary area tumour cell morphology and psammoma body (black arrow head), ×40 objective magnification. **(c)** Solid/alveolar area with biphasic tumour cell morphology, some of the smaller cells demonstrate a longitudinal nuclear groove (black arrow head) and the smaller cell nests are associated with eosinophilic and irregular extracellular proteinaceous deposits (white arrow heads), ×40 objective magnification. **(d)** Melan-A immunohistochemistry demonstrating strong expression within small tumour cells and moderate expression within surrounding larger tumour cells of the solid/alveolar tumour area, ×40 objective magnification.

biphasic pattern of tumour morphology in which clusters of small polygonal cells are found within the typical sheets and nests of larger epithelioid cells has been described in subsets of Xp11, including some RBM10-TFE3 cases,[2,5] but is more typical of the better known t(6;11) class of MiT family translocation RCCs.[1]

TFE3 immunohistochemistry is described as consistently and diffusely nuclear positive in RBM10-TFE3 RCCs,[2,4,5] reflecting an increase in fusion-protein expression relative to the native protein.[3] However, this finding is not unique to this tumour type.[2,6] An evaluation of TFE3 immunohistochemistry across a cohort that included fluorescence in-situ hybridization (FISH) detected TFE3 gene rearrangement tumours, performed at two pathology sites showed marked inter-site variability of TFE3 immunohistochemistry sensitivity and specificity.[6] This reflects the well-known technical difficulties of establishing TFE3 immunohistochemistry.[1] In particular, as in this case, TFE3 immunohistochemistry is highly sensitive to fixation artefact making interpretation equivocal.[6]

RBM10 and TFE3 genes lay in relatively close proximity on the short-arm of the X chromosome. A paracentric inversion, which causes a reversal in the orientation of a chromosomal segment involving both loci, may result in subtle break apart FISH patterns with potential for false-negative results.[3] Next-generation RNA sequencing should be considered for the detection of fusion-transcripts to confirm TFE3 rearrangement.[1,3,5,6]

Conclusion

RBM10-TFE3 RCCs are diagnostically challenging and uncommon but may be underreported. Outcome data for cases within the literature are incomplete, however long-term survival may be achievable despite recurrence and metastasis. Morphology and standard immunohistochemistry are pivotal to identifying translocation RCCs. TFE3 immunohistochemistry has general technical challenges and FISH may be equivocal in RBM10-TFE3 RCCs. Next-generation RNA sequencing should be considered as an alternative diagnostic approach. ◆

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Practice points

- RBM10-TFE3 RCCs are rare but have only recently been described in the literature.
- This tumour type can occur in patients of relatively young age. Outcome data are limited and incomplete, however long-term survival may be achieved irrespective of recurrence and metastasis.
- Morphology and standard immunohistochemistry can be suggestive of a translocation RCC.
- Confirmatory TFE3 immunohistochemistry has general technical challenges and is sensitive to fixation artefact, while break apart FISH appearances may be equivocal due to the nature of the RBM10-TFE3 gene rearrangement.
- Next-generation RNA sequencing can provide an alternative approach for diagnostic confirmation.

Self assessment multiple choice questions

1. Which melanocytic immunohistochemical marker is most consistently reported to be expressed in RBM10-TFE3 RCCs?

A. HMB45
B. Melan-A
C. S100
D. SOX10
E. MITF

Correct answer (B)

2. In which cellular compartment should TFE3 immunohistochemistry be interpreted?

A. nuclear
B. nuclear and cytoplasmic
C. cytoplasmic
D. cytoplasmic and membranous
E. membranous

Correct answer (A)

3. What form of chromosomal rearrangement typically occurs between RBM10 and TFE3 genes, resulting in the expression of aberrant RBM10-TFE3 fusion protein?

A. chromosomal duplication
B. pericentric inversion
C. chromosomal translocation
D. paracentric inversion
E. chromosomal deletion

Correct answer (D)