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BRIEF REPORT

Histological and molecular characterization of TFEB-rearranged renal cell carcinomas

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Abstract

The 2016 WHO Classification of Tumors of the Urinary System recognizes microphthalmia transcription factor (MiT) family translocation carcinomas as a separate entity among renal cell carcinomas. TFE3 and transcription factor EB (TFEB) are members of the MiT family for which chromosomal rearrangements have been associated with renal cell carcinoma formation. TFEB translocation renal cell carcinoma is a rare tumor harboring a t(6;11)(p21;q12) translocation. Recently, renal cell carcinomas with TFEB amplification have been identified. TFEB amplified renal cell carcinomas have to be distinguished from TFEB-translocated renal cancer, because they may demonstrate a more aggressive behavior. Herein, we present a TFEB-translocated and a TFEB-amplified carcinoma cases and describe their distinct histological, immunohistochemical, and molecular characteristics. In addition, we review conventional morphology, immunophenotype, genetic background, and clinical outcome of TFEB-rearranged RCCs in the literature, with a special emphasis on important differential diagnoses and the diagnostic approach.

Keywords MITF · TFEB · Translocation · Amplification · Renal cell carcinoma · RCC

Introduction

Renal cell carcinomas (RCCs) have been classified mainly according to their microscopic morphology (e.g., clear cell, papillary, chromophobe), anatomical location of the tumor (collecting duct RCC) or a background renal disease (acquired cystic disease–associated RCC). In recent years, recurring genetic aberrations have been identified and increasingly serve as defining traits for renal cell carcinoma classification. The current 2016 WHO Classification of Tumors of the Urinary System recognizes microphthalmia transcription factor family (MITF) translocation carcinomas as a separate entity among renal cell carcinomas [1]. The MIT family comprises four transcription factors, MITF, TFEC, TFEB, and TFE3, of which the latter two have been implicated in sporadic renal cell carcinoma development. Whereas TFE3-translocated RCCs, often referred to as translocation carcinomas, make up about 30% of pediatric and 3% of adult renal cell carcinomas [2]; TFEB-rearranged carcinomas are exceedingly rare.

TFEB-rearranged RCCs are driven by TFEB overexpression [3, 4]. This can be facilitated by translocation of the *TFEB* gene to the transcriptionally active *MALAT-1*/*Alpha* locus on chromosome 11, or by amplification of the *TFEB* locus in t(6;11) or TFEB-amplified renal cell carcinomas, respectively. The prognosis of t(6;11) carcinomas seems to be favorable compared to RCCs without MITF aberrations whereas TFEB-amplified carcinomas often show an aggressive behavior. Therefore, it is crucial to recognize and accurately diagnose these tumors.

Herein, we present one TFEB translocation carcinoma and one TFEB-amplified carcinoma and highlight clinicopathological, immunohistochemical, and molecular characteristics as well as the most important differential diagnoses.

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Methods

Ethics commission/patient samples

This study was approved by the ethics commission of the Canton Zurich. Formalin-fixed paraffin-embedded (FFPE) samples of both tumors were sent to the University Hospital Zurich as consult cases.

Immunohistochemistry and fluorescence in situ hybridization

Immunohistochemical stains of the human melanosoma black 45 (HMB45, Dako, ref. no. M0634), melanosoma antigen (MelanA, Dako, ref. no. M7196), cytokeratins (cytokeratin AE1/AE3, Dako, ref. no. M3515), and paired box 8 (PAX8, Protein Tech Group, ref. no.10336-1AP) antigens were performed on representative whole-tissue sections on a Ventana Benchmark Ultra (Roche) instrument.

TFEB FISH analysis, with two probes flanking the *TFEB* gene on 6p21, was performed using the TFEB BA Probe Set Kit (Empire Genomics) according to the manufacturer's instructions. For each tissue slide, 100 nuclei where examined for TFEB split or amplification signals.

RNA sequencing

RNA was extracted from FFPE tumor tissue slides using the Maxwell 16 LEV RNA FFPE Purification Kit (Promega). The Qubit RNA HS Assay Kit (Thermo Fisher Scientific) and the Bioanalyzer RNA 6000 Pico Kit (Agilent) were used to measure RNA quantity and RNA quality, respectively. Library preparation was performed using the TruSight RNA Pan Cancer Panel Kit (Illumina). Library DNA quantity was measured using the Bioanalyzer DNA 1000 Kit (Agilent), followed by sequencing on a MiSeq instrument (Illumina). The *TFEB-MALAT1* translocation was detected using the FusionMap software [5], followed by verification of the translocation detection results by the "grep" command [6].

Array comparative genomic hybridization assay

Tumor DNA was extracted from FFPE tumor tissue sections using the QIAamp DNA FFPE Tissue kit (Qiagen). The OncoScanFFPE Assay Kit (Thermo Fisher Scientific) was used according to the manufacturer's instructions, and data was read out on a GeneChip Scanner 3000 7G (Thermo Fisher Scientific). Data files were analyzed using the Chromosome Analysis Suite (ChAS, version 3.2.0.1252, Thermo Fisher Scientific) und Nexus Copy Number (version 9.0, BioDiscovery).

t(6;11) renal cell carcinoma

The female patient was diagnosed at the age of 16 years without any comorbidities or previous chemotherapy. Fifteen months after partial nephrectomy, the patient shows no evidence of disease. Macroscopically, the tumor was well circumscribed and measured 6.4 cm across its largest dimension. It exhibited a solid, tan-gray cut surface with softened areas. No invasion of the renal capsule or of the renal pelvis or vessels was noted. Microscopically, the tumor showed the classic morphology with a prominent biphasic "rosette-like" pattern, low-grade nuclei (equivalent to an ISUP grade 2), and evidence of entrapment of benign renal tubules at the tumor periphery (Fig. 1a–c). Moreover, tumor cells expressed PAX8 and showed only patchy positivity for cytokeratins AE1/AE3. Characteristically, the tumor stained diffusely positive for MelanA and patchy positive for HMB45 (Fig. 1d, e). A FISH TFEB break apart probe was used to identify rearrangement of the *TFEB* locus (Fig. 1f). Split signals were detected in 51% of examined cells. Consistent with previous reports [8], RNA sequencing revealed two concurrent break points in the *MALAT-1* gene that fused to the start of exon 3 of the *TFEB* gene (Fig. 1g).

TFEB-amplified renal cell carcinoma

The male patient was diagnosed with a renal cell carcinoma at the age of 77 years. Interestingly, he had received a radical nephrectomy of the contralateral kidney approximately 23 years prior for another renal tumor (no histology available). The carcinoma was removed by partial nephrectomy and no relapse has occurred 11 months post-surgery. Macroscopically, the tumor was well circumscribed and measured 4.5 cm across its largest dimension. No evidence of invasion of the renal capsule, pelvis, or vessels was noted. Microscopically, the tumor showed a mostly solid growth pattern with sheets of large clear or eosinophilic cells, with a secondary papillary growth pattern and hemorrhage, and without tumor necrosis. Significant pleomorphism and prominent nucleoli were evident (equivalent to ISUP grade 4, Fig. 2a–c). Immunohistochemistry for PAX8 and MelanA showed diffuse and patchy positivity, respectively (Fig. 2d), and negativity for HMB45. FISH analysis revealed high-level amplification of the *TFEB* locus (> 10 copies per cell, Fig. 2e), and array comparative genomic hybridization assay showed complex gains and losses throughout the genome with a > 9.5-fold amplification of an approximately 10.5 Mbp segment at the TFEB locus, including other known cancer genes such as VEGFA and RUNX2 (Fig. 2f).

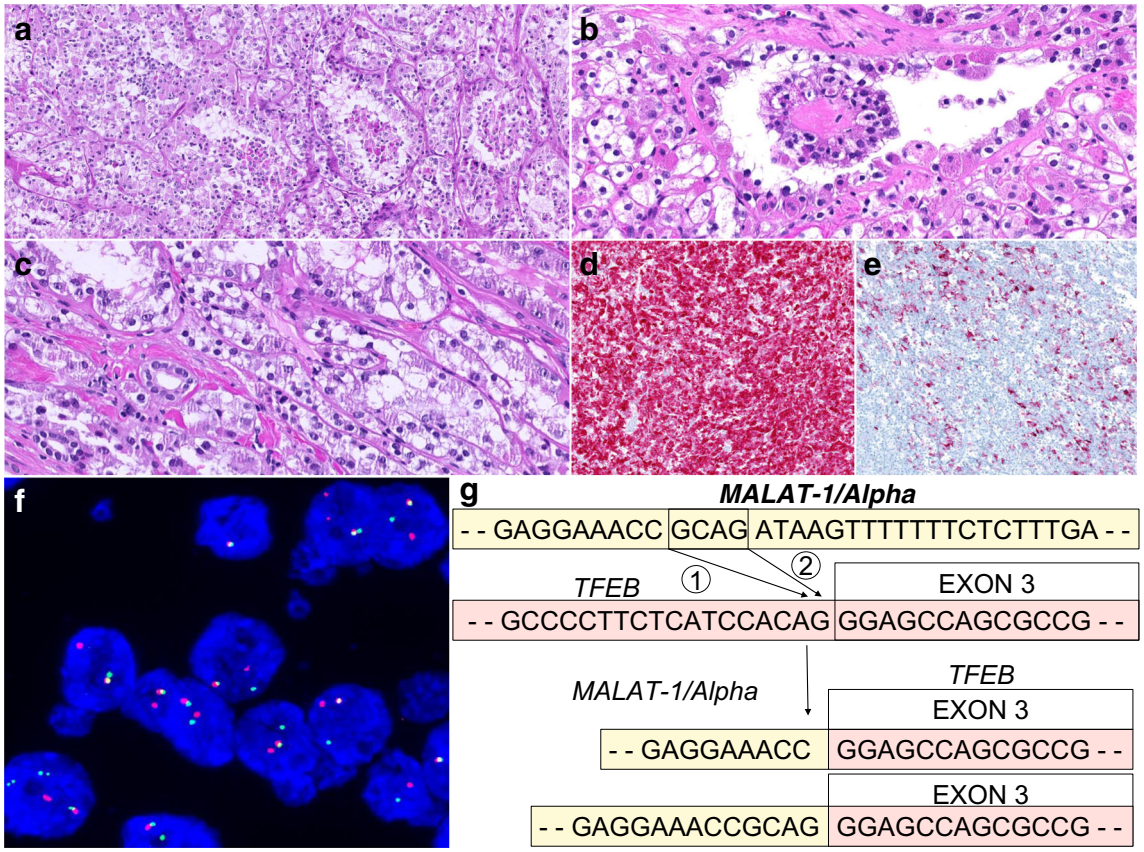

Fig. 1 Histological and molecular features of the t(6;11) renal cell carcinoma. Low-power view of the typical nested tumor architecture with thin fibrovascular septa and clear or eosinophilic cells (**a**), low-grade nuclei and a peculiar "rosette-like" biphasic growth pattern of hyaline basement membrane material being surrounded by two layers of tumor cells: one inner layer of small basophilic cells with high nuclear-cytoplasmic ratio and an outer layer with larger eosinophilic or clear tumor cells (**b**). In addition, t(6;11) RCCs often contain entrapped renal tubules at the tumor periphery (**c**). Immunostains show characteristic diffuse MelanA positivity (**d**) and patchy HMB45 positivity (**e**). TFEB break apart FISH showing *TFEB* genomic rearrangement (separated red and green signals) (**f**). Schematic representation of RNA sequencing results: two different break points in the previously described approx. 1.2 kbp break cluster region (BCR) within the *MALAT-1* gene fuse to the start of exon 3 of the *TFEB* gene (**g**) [7]

Discussion and review of the literature

TFEB translocation renal cell carcinoma

TFEB translocation renal cell carcinoma is a rare entity with only 78 tumors being published since the first description of the genetic aberration by Dijkhuizen et al. in 1996 [9] and the introduction as a new tumor entity by Argani et al. in 2001 [10]. t(6;11) carcinomas usually occur in young adults with an average age of 34 years. t(6;11) RCCs generally seem to be associated with a favorable prognosis, although some cases with aggressive clinical behavior have been described recently [11]. Besides the classic morphological features of t(6;11) RCCs illustrated in Fig. 1, a variety of atypical morphologies have been observed, including significant overlap with papillary or chromophobe RCCs [8] or even sclerosis and ossification [12, 13]. t(6;11) RCCs have a distinct immunohistochemical profile: They are frequently negative for cytokeratins, but usually express PAX8 and melanosome-associated antigens like MelanA, HMB45, and Cathepsin K [14] (Table 1, Supplementary Table 1).

On a genetic level, the TFEB translocation RCC is defined by the t(6;11)(p21;q12) translocation, placing the *TFEB* gene under the control of the long non-coding RNA (lncRNA) metastasis-associated lung adenocarcinoma transcript 1 promoter (*MALAT-1*, also known as *Alpha*). Since the *TFEB* gene ATG translation start, codon lies downstream of the fusion point in exon 3 of the *TFEB* gene; the entire protein is overexpressed by this translocation event [7].

TFEB-amplified renal cell carcinomas

The first published TFEB-amplified carcinoma case was described by Peckova et al. in 2014 as an aggressive variant with both TFEB translocation and TFEB amplification in a series of a t(6;11) RCC cases [15]. In 2016, Argani et al. described the first TFEB-amplified carcinomas without TFEB translocation as a separate entity from t(6;11) RCC [16]. To date, 54

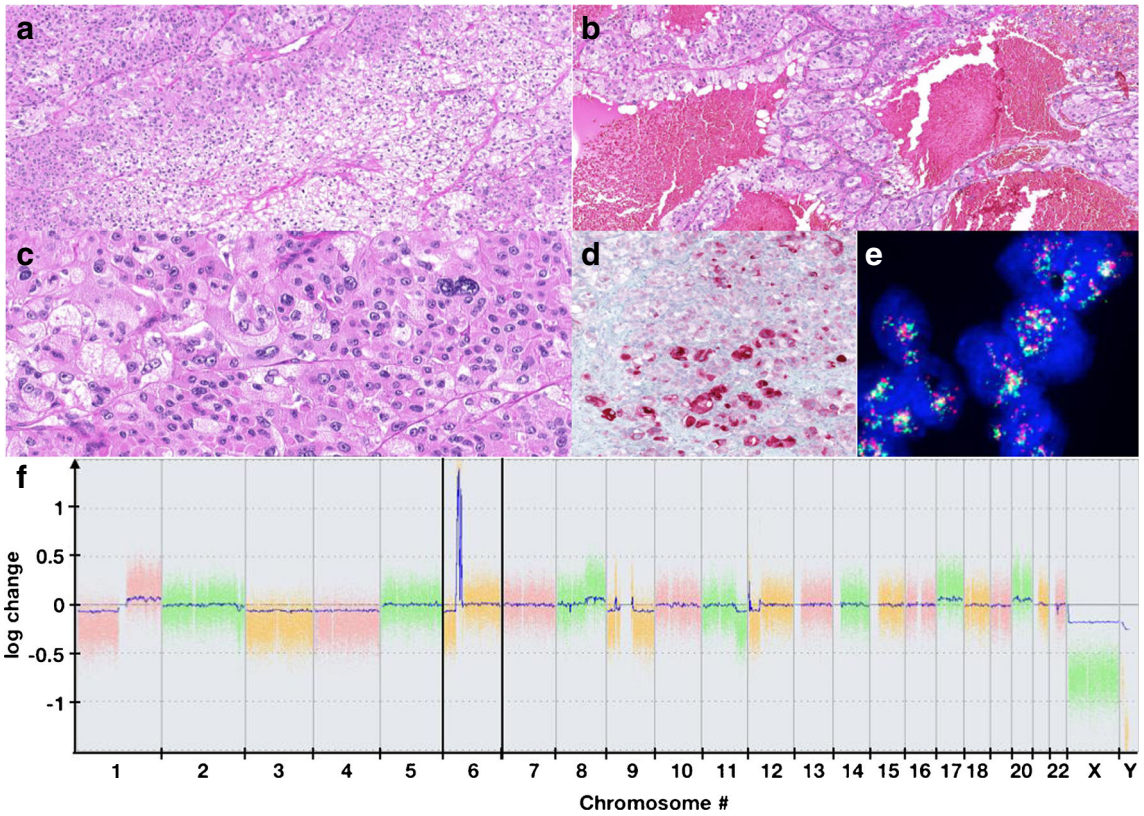

Fig. 2 Histological and molecular features of the TFEB-amplified renal cell carcinoma. Low-power view of a solid tumor area with large cells with clear or eosinophilic cytoplasm (**a**). Low-power view showing a tumor area with predominant papillary growth and extensive hemorrhage (**b**). High-power view showing prominent nucleoli and significant nuclear pleomorphism (reminiscent of ISUP grade 4) (**c**). MelanA immunohistochemical stain showing patchy positivity (**d**). TFEB FISH analysis indicating amplification of the *TFEB* locus (**e**). Weighted $\log_2$ ratio of genomic DNA copy numbers as assessed by array comparative genomic hybridization (aCGH) (**f**)

cases of TFEB-amplified carcinomas have been published (Supplementary Table 2), a minority of which bearing both TFEB translocation and amplification. On average, TFEB-amplified carcinomas are diagnosed at the age of 64 years and—unlike t(6;11) carcinomas—they show an aggressive clinical behavior with many patients presenting with advanced stage or metastatic disease at the time of diagnosis [16]. One recent study reported a 5-year survival rate of 48% [17].

ISUP grading is not validated for TFEB-rearranged renal cell carcinomas [18], but the nuclear features present in most TFEB-amplified RCCs are reminiscent of ISUP grades 3 and 4 in virtually all published cases. Many of the published cases exhibit a nested, tubulopapillary, or pseudopapillary architecture with large eosinophilic cells, often with hemorrhage and tumor necrosis. TFEB-amplified carcinomas express cytokeratins AE1/AE3; PAX8; and, to a lesser extent than t(6;11) carcinomas, the melanosome-associated antigens HMB45, MelanA, and Cathepsin K. Interestingly, TFEB-amplified RCCs are negative for TFEB expression by immunohistochemistry in 50% of published cases (Table 1, Supplementary Table 2).

In our case, the region around the *TFEB* gene was affected by the highest level of amplification, indicating a prominent role of the *TFEB* gene in tumorigenesis. However, the more

Table 1 Immunohistochemical characteristics of TFEB-rearranged RCCs and its main differential diagnoses

	Cytokeratins AE1/AE3	PAX8	HMB45	MelanA	Cathepsin K	TFEB
RCC without MITF rearrangements	+	+	–	–	–	–
Epithelioid angiomyolipoma	–	– (CD68+)	+	+	+	–
TFE3 translocation RCC	+/–	+	–	–	+/–	–
t(6;11) RCC	+/– (38%)	+ (93%)	+ (74%)	+ (90%)	+ (90%)	+ (90%)
TFEB-amplified RCC	+ (93%)	+ (100%)	– (15%)	+/– (60%)	+/– (61%)	+/– (50%)

+ indicates diffuse of focal staining; – indicates no staining; percentages in brackets represent proportions of positive staining reported in the literature (see also Supplementary Tables 1 and 2)

aggressive behavior of TFEB-amplified RCCs, as compared to t(6;11) RCCs, indicates that the extensive additional genomic aberrations found in all published TFEB-amplified RCCs also contribute to their tumor biology [17, 19, 20]. This is corroborated by the observation that TFEB expression is lower in some TFEB amplification carcinomas than in t(6;11) carcinomas [16].

Main differential diagnoses

The top differential diagnoses of TFEB-rearranged renal cell carcinomas include RCCs without MITF rearrangements (mainly clear cell, papillary, and chromophobe RCCs), TFE3/Xp11 translocation carcinoma, and epithelioid angiomyolipoma. RCCs without MITF rearrangements show a large morphological overlap with TFEB-rearranged RCCs. In fact, a recent study of the histological features of MITF-rearranged renal cell carcinomas failed to find any statistically significant characteristic of TFEB-amplified RCCs compared to RCCs without MITF rearrangements [21]. In the same study, the characteristic biphasic pattern of basement membrane material surrounded by two layers of tumor cells, psammoma bodies, nuclear pseudoinclusions, and entrapped benign renal tubules were significantly associated with TFEB translocation carcinomas when compared to RCCs without MITF rearrangements. Unlike RCCs lacking MITF aberrations, TFEB-rearranged renal cell carcinomas often stain positive for Cathepsin K, MelanA, and HMB45 while they often do not express cytokeratins (the latter being particularly true for t(6;11) RCCs, Table 1).

Similar to TFEB-rearranged carcinomas, the TFE3/Xp11 translocation carcinoma is driven by overexpression of a MITF family transcription factor. TFE3 translocation carcinoma is a high-grade tumor with a prognosis that is significantly poorer than papillary RCC and comparable to clear cell RCC [22]. The morphology of Xp11 carcinomas depends on the particular translocation present, but they generally exhibit overlapping features with TFEB-rearranged RCCs. Importantly, the biphasic growth pattern previously thought to be specific for t(6;11) RCCs also occurs in TFE3 translocation carcinomas [21]. Moreover, depending on the translocation variant, psammomatous calcification can be extensive. In contrast to TFEB-rearranged RCCs, TFE3 translocation carcinomas typically do not express melanocytic markers (Table 1).

An uncommon albeit important differential diagnosis of TFEB-rearranged renal cell carcinomas is the pure epithelioid angiomyolipoma, which can mimic a carcinoma morphologically and typically expresses Cathepsin K, MelanA, HMB45 while usually lacking cytokeratin expression. However, pure epithelioid angiomyolipoma stain positive for CD68 and negative for PAX8 while the opposite is the case for TFEB rearranged RCCs [11] (Table 1).

Diagnostic approach

Fluorescence in situ hybridization (FISH) is the gold standard for detecting *TFEB* gene rearrangements [12]. The challenge in diagnosing TFEB-rearranged renal tumors is their low incidence, making it simply impractical to screen all RCCs by FISH [23]. The clinical and morphological features described above are useful in raising the suspicion of a TFEB-rearranged RCC; however, their sensitivity for TFEB rearrangements is likely too low to trigger a FISH analysis. This is especially true for the TFEB-amplified renal cell carcinoma. In this regard, MelanA immunohistochemistry is particularly useful, because—more so than HMB45—it stains patchy or diffusely positive in 90% and 60% of t(6;11) and TFEB amplification carcinomas, respectively, while other RCCs are MelanA negative. Immunostains for Cathepsin K and the TFEB protein itself have been proposed as useful markers for detecting TFEB translocation carcinomas [12, 14]. However, since their sensitivities for detecting TFEB-rearranged RCCs is not superior to MelanA (Table 1) and since they are not established in many pathology laboratories, their significance for diagnosing TFEB-rearranged RCCs is uncertain. In addition, technical difficulties, including fixation artifacts, with the available antibodies limit their usability in routine practice.

In summary, TFEB translocation and TFEB amplification renal cell carcinomas represent two novel members in the family of RCCs with MITF aberrations. Their prognoses differ significantly from each other and from the main differential diagnoses. Therefore, it is crucial to recognize their distinct clinicopathological features for an accurate diagnosis. A reasonable algorithm for detecting TFEB-rearranged RCCs could start with a careful evaluation of the available clinical data and histomorphological features, followed by a small panel of immunohistochemical stains, including PAX8 and MelanA, and confirmation by FISH.

Authors' contributions N. W. and H. M. conceived and designed the study; provided histological descriptions of tumors; reviewed the literature; and wrote, edited, and reviewed the manuscript. C. W., F. K., and L.-C. H. provided FFPE tumor samples, clinical information, and macroscopic descriptions of tumors. M. R. and C. F. performed RNA sequencing. U. W. analyzed RNA sequencing data. J. T. performed the aCGH experiment and analyzed aCGH data. All authors critically read the manuscript, gave final approval for publication, and took full responsibility for the work as a whole.

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Compliance with ethical standards

This study was approved by the ethics commission of the Canton Zurich. Formalin-fixed paraffin-embedded (FFPE) samples of both tumors were sent to the University Hospital Zurich as consult cases.

Conflict of interest The authors declare that they have no conflict of interest.

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