Annals of Diagnostic Pathology 18 (2014) 351–357

Contents lists available at ScienceDirect

Annals of Diagnostic Pathology

Aggressive and nonaggressive translocation t(6;11) renal cell carcinoma: comparative study of 6 cases and review of the literature

Kvetoslava Peckova, MD [a], Tomas Vanecek, PhD [a], Petr Martinek, MSc [a], Dominic Spagnolo, MD [b], Naoto Kuroda, MD [c], Matteo Brunelli, MD, PhD [d], Semir Vranic, MD, PhD [e], Slavisa Djuricic, MD, PhD [f], Pavla Rotterova, MD, PhD [a], Ondrej Daum, MD, PhD [a], Bohuslava Kokoskova, MD [a], Pavla Vesela, MD [a], Kristyna Pivovarcikova, MD [a], Kevin Bauleth, MD [a], Magdalena Dubova, MD [a], Kristyna Kalusova, MD [g], Milan Hora, MD, PhD [g], Michal Michal, MD [a], Ondrej Hes, MD, PhD [a,h,*]

[a] Department of Pathology, Faculty of Medicine, University Hospital Plzeň, Charles University, Pilsen, Czech Republic
[b] Department of Pathology, PathWest Laboratory Medicine WA, Nedlands, Australia
[c] Department of Diagnostic Pathology, Kochi Red Cross Hospital, Kochi, Japan
[d] Department of Pathology and Diagnostic, University of Verona, Verona, Italy
[e] Department of Pathology, Clinical Center of the University of Sarajevo, Sarajevo, Bosnia and Herzegovina
[f] Department of Pathology, Mother and Child Health Institute of Serbia, Belgrade, Serbia
[g] Department of Urology, Faculty of Medicine in Plzeň, Charles University in Prague, Pilsen, Czech Republic
[h] Biomedical Centre, Faculty of Medicine in Plzen, Charles University in Prague, Pilsen, Czech Republic

ARTICLE INFO

Keywords:
Kidney
Translocation renal cell carcinoma
t(6;11)
Aggressive
Nonaggressive
Immunohistochemistry
Molecular biology

ABSTRACT

t(6;11) renal cell carcinoma (RCC) has been recognized as a rare and mostly nonaggressive tumor (NAT). The criteria for distinguishing aggressive tumors (AT) from NATs are not well established. A total of 6 cases were selected for the study. Five cases of t(6;11) RCCs behaved nonaggressively, and 1 was carcinoma with aggressive behavior. The tumors were analyzed morphologically using immunohistochemistry and by molecular-genetic methods. The specimen of aggressive t(6;11) RCC was from a 77-year-old woman who died of the disease 2.5 months after diagnosis. The specimens of nonaggressive t(6;11) RCCs were from 3 women and 2 men whose ages range between 15 and 54 years. Follow-up was available in all cases (2.5 months-8 years). The tumor size ranged from 3 to 14 cm in nonaggressive t(6;11) RCC. In the aggressive carcinoma, the tumor size was 12 cm. All tumors (6/6) were well circumscribed. Aggressive t(6;11) RCC was widely necrotic. Six (100%) of 6 all tumors displayed a solid/alveolar architecture with occasional tubules and pseudorosettes. Pseudopapillary formations lined by bizarre polymorphic cells were found focally in the aggressive t(6;11) RCC case. Mitoses, though rare, were found as well. All cases (AT and NAT) were positive for HMB-45, Melan-A, Cathepsin K, and cytokeratins. CD117 positivity was seen in 4 of 5 NATs, as well as in the primary and metastatic lesions of the AT. mTOR was positive in 2 of 5 NATs and vimentin in 4 of 5 NATs. Vimentin was negative in the primary lesion of the AT, as well as in the metastasis found in the adrenal gland. Translocation t(6;11)(*Alpha-TFEB*) or *TFEB* break was detected in 4 of 5 NATs and in the AT case. Aggressive tumor showed amplification of *TFEB* locus. Losses of part of chromosome 1 and chromosome 22 were found in 1 of 5 NATs and in the AT. Conclusions: (1) Aggressive t(6;11) RCCs generally occur in the older population in comparison with their indolent counterparts. (2) In regard to the histologic findings in ATs, 3 of 5 so far published cases were morphologically not typical for t(6;11) RCC. Of the 3 cases, 2 cases lacked a small cell component and 1 closely mimicked clear cell–type RCC. (3) Necroses were only present in aggressive t(6;11) RCC. (4) Amplification of *TFEB* locus was also found only in the aggressive t(6;11) RCC.

1. Introduction

t(6;11) translocation renal cell carcinoma (t(6;11) (TRCC) has been recognized as a new entity by the International Society of Urological Pathology 2012 conference and has subsequently been considered as a part of MiT family translocation carcinomas [1]. Regrouping TFEB and TFE3 translocation carcinomas together under the category of "MiTF/TFE family translocation carcinomas" was first suggested by Argani and Ladanyi [2–4], because the reason for regrouping of t(6;11) RCC and Xp11 TRCCs was similar morphologic, immunohistochemical, and molecular-genetic features. Translocation involving *TFEB* and *TFE3* induces the overexpression of these proteins and can be specifically identified by immunohistochemistry, where nuclear

* Corresponding author. Department of Pathology, Faculty of Medicine, Charles University Hospital Plzeň, Charles University, Alej Svobody 80, 304 60 Pilsen, Czech Republic. Tel.: +420 377104643; fax: +420 377104650.
E-mail address: hes@medima.cz (O. Hes).

http://dx.doi.org/10.1016/j.anndiagpath.2014.10.002
1092-9134/

labeling for TFEB is specific to t(6;11) RCC and nuclear positivity of TFE3 is specific to Xp11.2 translocations. However, recent articles have shown the limited reliability of immunohistochemical evaluation of TFE3 protein [5].

Together with the TFEB and TFE3, MiT family also involves MITF and TFEC, all of which have overlapping transcriptional activities [6]. The variations of the clinicopathologic spectrum of these tumors have yet to be determined. Contrary to the Xp11.2 TRCCs, where aggressive clinical behavior has frequently been documented, the t(6;11) TRCC presented mostly with a nonaggressive clinical course, thus having come to be considered as indolent, usually low-stage and low-grade tumors [7–9].

Up to date, 49 cases of t(6;11) TRCC have been reported, most without signs of aggressive behavior. [5,10,11]. Only 4 cases with aggressive behavior have been reported thus far (8%) [11–14].

In our study, we have compared 5 nonaggressive tumors (NAT) with 1 previously unreported aggressive metastazing tumor (AT), using the morphology, immunohistochemistry, and molecular-genetic examinations. Extensive research of the literature written in English has been undertaken to elucidate all known facts about aggressive t(6;11) TRCC that have been described so far.

2. Materials and methods

Out of 17 700 renal tumors and tumor-like lesions in the institutional and consultation files of Sikl's Department of Pathology, Charles University, Plzen, Czech Republic, 6 cases of t(6;11) RCC were identified. Four cases have been reported [15,16], and 2 new unpublished cases (including 1 aggressive metastazing case) have been added. The tissues were fixed in neutral formalin and embedded in paraffin and were cut into 4 to 5 μm thin sections and stained with hematoxylin and eosin.

2.1. Immunohistochemistry

The immunohistochemical study was performed using a Ventana Benchmark XT automated stainer (Ventana Medical System, Inc, Tucson, Arizona) on formalin-fixed, paraffin-embedded tissue. The following primary antibodies were used: cytokeratins (CAM 5,2, monoclonal, 1:200; Becton-Dickinson, San Jose, California), AE1-AE3 (monoclonal, 1:1000; BioGenex, San Ramon, California), CD10 (56C6, 1:20; Novocastra, Burlingame, California), c-kit (CD 117, polyclonal, RTU; DakoCytomation, Glostrup, Denmark), racemase/AMACR (P504S, monoclonal, 1:50; Zeta, Sierra Madre, California), vimentin (D9, monoclonal, 1:1000; NeoMarkers, Westinghouse, California), anti-melanosome (HMB45, monoclonal, 1:200; DakoCytomation), PAX8 (polyclonal, 1:25; Cell Marque, Rocklin, California), cathepsin K (3F9, monoclonal, 1:100; Abcam, Cambridge, UK), S100 (polyclonal, 1:400; DakoCytomation), Melan-A (A103,monoclonal, RTU; DakoCytomation), TFE3 (monoclonal, MRQ-37, RTU; Cell Marque), tyrosinase (polyclonal, 1:100; NeoMarkers, Westinghouse, Fremont California), mTor (monoclonal, Ser 2448, 49F9, 1:50; Cell Signaling, Danvers, Massachusetts). The primary antibodies were visualized using the supersensitive streptavidin-biotin-peroxidase complex (BioGenex). Appropriate positive controls were used.

2.2. Molecular-genetic study

Detection of *Alpha-TFEB* genomic junction, *Alpha-TFEB* fusion transcript, and chromosomal numerical changes was performed by polymerase chain reaction (PCR; case 2), reverse transcriptase PCR (cases 2 and 6), and array comparative genomic hybridization (aCGH) (case 2), respectively. All these methods were described in Petersson et al [15]. Fluorescence in situ hybridization (FISH) analysis was performed in cases 1, 3, 4, 5, and 6 using break apart probe *TFEB* ba (6p21) consisting of BAC probes RP11-328M4 a RP11-533O20 (BlueGnome, Cambridge, UK). In cases 5 and 6, FISH analysis of chromosomal loci 1p36 and 22q was performed using probes 1p36/1q25 and LSI 22BCR (VYSIS/Abbott Molecular, Des Plaines, Illinois). The tumor areas of the specimens were examined with an Olympus BX51 fluorescence microscope using a ×100 objective and filter sets Triple Band Pass (DAPI/Spectrum Green/Spectrum Orange) and Single Band Pass (Spectrum Green, Orange, and Aqua). Scoring was performed by counting the number of fluorescent signals in 100 randomly selected, nonoverlapping tumor cell nuclei. The slide was independently enumerated by 2 observers (P.M. and T.V.). Cutoff values for monosomy were set at 35% and 37% for 1p36 and 22q probes, respectively, and for polysomy at 10% for both probes. Cutoff for *TFEB* ba probe was set at 10%.

3. Results

3.1. Clinical features

The basic clinicopathologic data are summarized in Table 1. Cases 1 to 4 have been already reported [15,16]. In brief, the patients were 4 women and 2 men (all Caucasian) with age ranging from 15 to 77 years (mean, 35.3 years; median, 23 years). Follow-up was available for all patients (ranging from 2.5 months to 8 years; mean, 3.37; median, 3 years). Clinical data from the 2 new patients were as follows:

Case 5: a 15-year-old boy was referred to the hospital because of a palpable painless swelling of the abdomen. No hematuria was detected. Radical nephrectomy was performed; no adjuvant oncologic treatment was administered.

Case 6: tumor was found in a 77-year-old women. The patient complained of increasing back pain and renal colic. Computed tomographic (CT) scan revealed a tumor of the left kidney measuring 16.5 × 12.3 × 16.7 cm. The patient died of disease 2.5 months after diagnosis with metastases to ipsilateral adrenal gland (histologically confirmed) and lung (determined using CT and positron emission tomography/CT scanning).

3.2. Pathological findings

3.2.1. Gross pathology

Nonaggressive tumors were well circumscribed, largely encapsulated, and displayed gray to tan cut surface with focal hemorrhage. Focal cystic change was present in 1 case. There were no grossly visible foci of necrosis. Tumor size ranged from 3 to 14 cm (median, 5 cm). In all cases, the tumors were confined to the kidney. Hence, there was no infiltration of the perirenal or sinusoidal fat, neither was there renal vein invasion.

Aggressive tumor was partially encapsulated, well circumscribed with voluminous, mostly centrally located hemorrhagic necrosis. Cut surface was brown. Tumor measured 12 × 11.5 × 9 cm (Fig. 1).

3.2.2. Morphology

3.2.2.1. Cases 1 to 5 (NATs). On low power, all tumors displayed a solid or solid/alveolar architecture. The tumors were mostly surrounded by a fibrous pseudocapsule. Although only focally, groups of entrapped

Table 1
Main clinicopathologic data

Case	Age (y)	Sex	Size (cm)	Clinical manifestation	Follow-up
1	22	M	3	Incidental finding	8 y AW, then LE
2	24	F	14	Palpable mass	3 y AW, then LE
3	20	F	9.5	Incidental finding	5 y AW, than LE
4	54	F	7	Increasing pain right hip (nephrectomy)	AW 3 y after dg, then LE
5	15	M	10	Palpable mass	AW 1 y
6	77	F	12	Increased back pain, renal colic	DOD 2.5 mo after dg

Abbreviations: M, male; F, female; AW, alive and well; LE, lost of evidence; DOD, dead of disease; dg, diagnosis.

Table 2
Results of immunohistochemical examinations: nonaggressive cases

Case	HMB45	Melan-A	TFE3	CD10	CD117	Tyros	mTor	CAM 5.2	AE1/AE3	Cath	Vim	PAX8	MIB1
1	+++	++	−	+	++	+	−	Foc ++	−	+++	+	−	1-2/hpf
2	+++	++	−	Foc +	++	Foc +	Foc+	++	++	+++	+	Foc weak+	1-2/hpf
3	+++	−	−	Foc +	−	+ −	Foc+	Foc+	−	+++	+	++	0-1/hpf
4	++ focal	++	−	0	Foc ++	Not done	−	−	−	+++	Not done	Foc +	0-1/hpf
5	+++	+++	−	Foc ++	Foc ++	Foc+	−	Foc ++	Foc ++	+++	+	Foc ++	5-8/hpf

Abbreviations: Cath, Cathepsin-K; MIB1, antibody against Ki-67 antigen; Tyros, tyrosinase; vim, vimentin; hpf, high-power field; foc, focal.
"+" = weak positivity; "++" = moderate positivity; "+++" = strong positivity; "−" = negative.

tubules at the edge of the tumor were found. Degenerative changes were noted in 2 of the 4 cases. Microscopic foci of necrosis and fibrosis were seen in cases 1 and 2. All tumors contained areas with discohesive neoplastic cells. Some of these areas displayed tubulary architecture, whereas other areas showed a more solid architecture. The pseudorosettes were present in all tumors (Fig. 2). These pseudorosettes were formed by smaller lymphocyte-like cells, grouped around collagenous spheres, formed by basement membrane material. The small lymphocyte-like cells had scanty cytoplasm and round nuclei (Fuhrman grade 1). The pseudorosettes frequently contained areas with signet ring–like change or conspicuous clear cell change. In some tumors (cases 1, 3, and 4), the pseudorosettes were already apparent at low magnification. In case 2, the pseudorosettes were less apparent and discernible only at higher magnification and after serial sectioning. In the same case, there were long branching narrow tubules that were already very conspicuous at low-power magnification. These tubules were rimmed by one row of neoplastic cells with granular cytoplasm, having the nuclei aligned on the basement membrane, thus giving these structures a resemblance to glandular epithelium. Infrequently, areas with solid growth and moderate atypia (corresponding to Fuhrman nucleolar grade 2 or rarely 3) were observed (Fig. 3). Most of the neoplastic cells had abundant eosinophilic, slightly granular, and sometimes "feathery" cytoplasm. Populations of larger cells with voluminous clear to slightly eosinophilic cytoplasm were present in all tumors. In 2 cases (cases 1 and 2), we found areas with hyalinization formed by basal membrane material. Mitotic figures were exceptionally rare in 1 case (case 2), and atypical mitoses were absent. In addition to the above-described morphologic characteristics, small foci with morphologic features strongly resembling another translocation associated renal tumor, the ASPL-TFE3 renal carcinoma (Xp11.2 group), were detected in 1 case (case 2). In this area, alveolar and tubulopapillary structures were lined by large cells having voluminous clear to slightly eosinophilic cytoplasm. The nuclei in these areas were Fuhrman nucleolar grade 3.

3.2.2.2. Case 6 (AT). Tumor was mostly solid to solid-alveolar, composed of larger eosinophilic cells with the occasional presence of lymphocytes in the interstitium (Fig. 4). There were voluminous necrotic and hemorrhagic areas. Occasionally, large tubules and pseudotubules were scattered through tumorous mass. Cells were mostly voluminous, weakly eosinophilic with "cloudy" appearance. Nuclei were of grade 2 and 3 according to Fuhrman nucleolar grade. Pseudorosettes were located mostly within large pseudotubules. Only few mitotic figures were noted, no atypical mitoses were encountered. Foci of pseudopapillary to papillary formations were rarely noted. Papillae were lined by large, bizarre polymorphic cells with Fuhrman nucleolar grade 3 and 4 (Fig. 5).

3.2.3. Immunohistochemistry

3.2.3.1. NATs (cases 1-5). The immunohistochemical findings of NATs are summarized in Table 2. All of them were diffusely positive for Cathepsin K, HMB-45 (Fig. 6A), and Melan-A. Vimentin was positive in all cases, although positivity was weak. Expression of cytokeratins CAM 5.2 and AE1-AE3 was variable (Fig. 6B). CD10 and tyrosinase were weakly and focally positive in 4 of 5. Two of 5 cases were weakly and focally immunoreactive for mTOR. Four of 5 NATs were positive strongly but focally for CD117. PAX8 immunoreactive pattern was variable with negative (1/5) to moderate positive staining (1/5). Mostly tumors were focally positive (3/5). There was no diffuse expression of TFE3 in any of the tumors.

3.2.3.2. AT (case 6). The complete results of immunohistochemical examinations of primary aggressive t(6;11) RCC and metastatic lesion are summarized in Table 3. Both showed a strong, diffuse immunoreactivity for HMB-45, Melan-A, and Cathepsin-K. CAM 5.2 and CD10 were moderately positive. CD117 was positive in both primary and metastatic lesions. PAX8 was focally positive in primary and metastatic tumor. The neoplastic cells did not express TFE3, tyrosinase, mTOR, AE1/AE3, and vimentin in both primary and metastatic tumor.

3.3. Molecular-genetic findings

Results of molecular-genetic findings are summarized in Table 4. *TFEB* gene rearrangement or *Alpha-TFEB* translocation was found in 5 of 6 cases. One was unanalyzable. In AT, *TFEB* gene break was accompanied by its amplification. In 2 of 3 analyzed cases, including AT, loss of 1p36 and 22q was also detected.

4. Discussion

t(6;11) TRCC is recognized mostly as a low-grade NAT. This is in contrast to Xp11.2 TRCC. Most of Xp11.2 TRCCs are considered to be highly aggressive, high-stage, and high-grade tumors [1,16].

There are no well-established prognostic criteria predicting biological behavior that are applicable for t(6;11) TRCC.

t(6;11) TRCC is usually described as neoplasm with a distinctive biphasic pattern, comprising larger and smaller epithelioid cells, with the latter often clustered around basement membrane material; however, the full spectrum of the morphologic appearances of the t(6;11) TRCC is probably more variable [17–19]. The t(6;11) TRCCs express Cathepsin K, HMB-45, Melan-A, and usually PAX8. Nuclear labeling for TFEB protein by IHC is supposed to be a sensitive and specific assay for

Table 3
Results of immunohistochemical examinations—aggressive case

	HMB45	Melan-A	TFE3	CD 10	CD 117	Tyros	mTor	CAM 5.2	AE1/AE3	Cath	Vim	PAX8	MIB1
Prim	+++	+++	0	++	Foc ++	0	0	++	0	+++	−	Foc +	0-5/hpf
Meta	+++	+++	0	Foc ++	Foc ++	0	0	++	0	+++	−	Foc +	8-12/hpf

Abbreviations: Cath, Cathepsin-K; MIB1, antibody against Ki-67 antigen; Tyros, tyrosinase; Vim, vimentin; hpf, high-power field; Prim, primary tumor; Meta, metastasis to suprarenal gland; foc, focal.
"+" = weak positivity; "++" = moderate positivity; "+++" = strong positivity; "−" = negative.

Table 4
Molecular-genetic analysis

Case	Numerical changes	Translocation		
	aCGH or FISH (1p36 and 22q probes)	FISH *TFEB* ba probe	RT-PCR *Alpha-TFEB*	PCR *Alpha-TFEB*
1	NP	NA	NP	NP
2[a]	Loss 1p35.1 to p36.21 (aCGH) Loss 22q (aCGH)	NP	Positive	Positive
3	NP	Positive	NP	NP
4	NP	Positive	NP	NP
5	Negative (FISH)	Positive	NP	NP
6	Loss 1p36 (FISH) Loss 22q (FISH)	Positive (amplification)	Positive	NP

Abbreviations: RT, reverse transcriptase; NP, not performed; NA, not analyzable.
[a] Translocation t(X;17) (ASPL-TFE3) was analyzed in case 2 with negative result.

these neoplasms; however, there are many false-positive/negative staining as a result of fixation, autolysis, and other steps related to the tissue processing [5,20]. Furthermore, CD117 was found to be another potential distinguishing marker between the t(6;11) TRCC and Xp11.2 TRCC. CD117 is usually positive in t(6;11) TRCC, but not positive in most of Xp11.2 TRCCs [11]. In our series, one of the NATs was negative for CD117. Generally, positivity for CD117 was moderate, but mostly focal. In the AT, focal membranous positivity for CD117 was noted both in the primary tumor and in metastasis. Immunoreactivity with PAX8 was highly variable (negative to moderately positive) in our cases.

Fluorescence in situ hybridization assay for *TFEB* gene break or PCR-based analysis for the presence of *Alpha-TFEB* fusion is currently available even for paraffin-embedded material, which seems a more robust technique than immunohistochemical examination [1,21].

t(6;11) TRCC has long been considered as NAT. Even so, the possible late recurrence, similar to the behavior reported of Xp11.2 TRCC, and metastatic potential have been observed. Up to date, 4 aggressive cases of t(6;11) TRCC have been reported. The overview of 4 aggressive t(6;11) TRCC described in the literature and summary of our new case is outlined in Table 5[11,14].

The first case was described by Martignoni et al [12] in 2005. The tumor was found in 42-year-old woman who presented with paratracheal and pleural metastases 3 years after the surgery. However, later the question was raised, whether this tumor was indeed t(6;11) TRCC, Xp11.2 TRCC, or an unusual variant of TRCC with overlapping features between Xp11.2 and t(6;11) TRCC (Dr. Guido Martignoni and Dr. Matteo Brunelli's personal communication).

The second aggressive case of t(6;11) TRCC was reported by Camparo et al [13] in 2008. The size of the tumor was 20 cm, and it

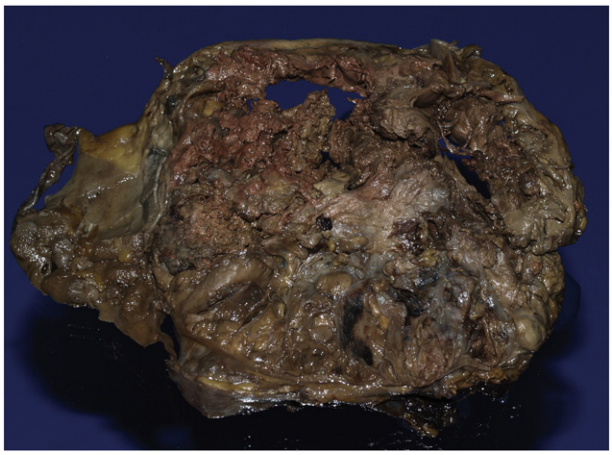

Fig. 1. Huge area of mostly centrally located necrosis was present on gross section of aggressive case.

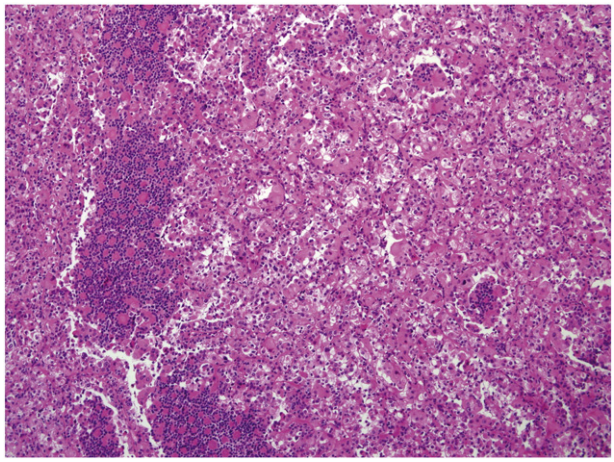

Fig. 2. In typical cases of nonaggressive cases, the pseudorosettes were formed by smaller lymphocyte-like cells grouped around collagenous spherules.

presented as an abdominal mass in a 36-year-old man who died after 3 months after the diagnosis with widespread metastatic disease.

Third malignant t(6;11) TRCC was described by Inamura et al [14] in 2012. A 37-year-old man had undergone a total nephrectomy in 1989. Eight years later, he presented with lung and mediastinal lymph node metastases. The renal tumor was originally diagnosed as clear cell–type RCC. Subsequently, he underwent a lymph node dissection and

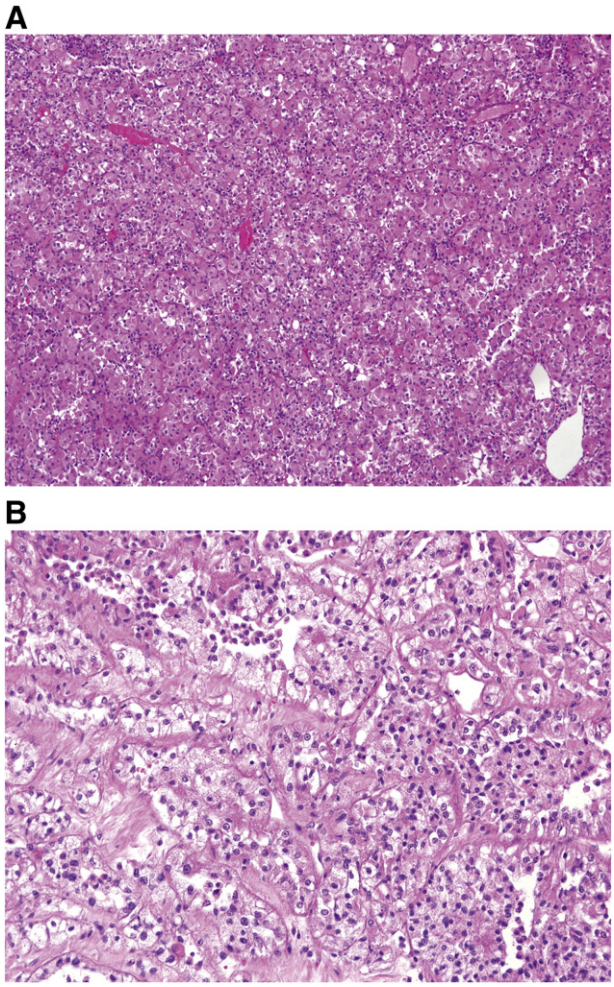

Fig. 3. Areas with solid growth and moderate atypia were observed both in nonaggressive cases (A) and in aggressive cases (B).

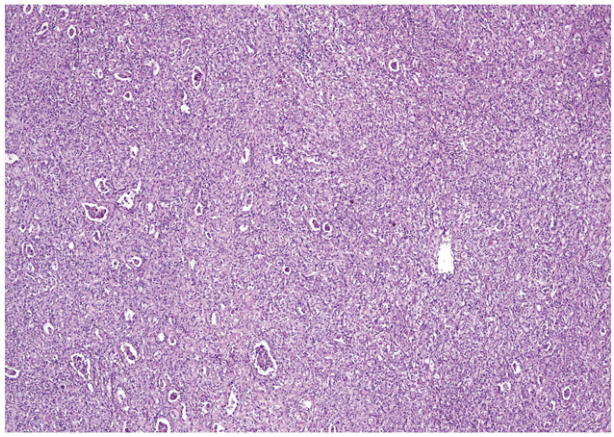

Fig. 4. Pseudorosettes in aggressive case were less conspicuous comparing with typical nonaggressive cases.

partial resection of the lung for the metastatic tumor measuring 4.5 cm. Karyotyping of the tumor revealed a t(6;11) (p21.1;q12 ~ 13) chromosomal rearrangement, a characteristic of the t(6;11) TRCC. Thirty months after second surgery, the patient died of multiple metastases to the lung and bone.

The fourth case was described by Smith et al [11] in January 2014. The tumor was found in a 34-year-old man. The patient developed rib metastasis 8 years after resection of the primary tumor.

The fifth case (currently described case) differs clinically from previously reported ATs mainly by age of the patient. The size of the tumor was relatively large; however, substantially larger NATs have been reported. Our patient died of disease 2.5 months after surgery.

Summarizing all available clinical data dealing with aggressive t(6;11) RCC cases, a few mutual characteristics have been observed. As regards clinicopathologic features, the aggressive t(6;11) TRCC appears to affect older population (mean, 45.2 years; median, 37 years) than nonaggressive cases (mean, 31.5 years; median, 30.5 years). Previously described ATs metastasized into the pleura (case 1), lung (cases 3 and 5), mediastinal lymph nodes (cases 1 and 3), bones (cases 3 and 4), and adrenal gland (case 5) (Fig. 7). The same 8-year interval between resection of the primary tumor and metastasis was observed in cases 3 and 4 (Table 5).

Size of the ATs was bigger (mean, 11.67 cm; median, 20 cm) than that of the NATs (mean, 7.43 cm; median, 4.75 cm).

Microscopic foci of necrosis were described in 1 nonaggressive case only [13]; however, it is not possible to get more information about presence/absence of necrotic foci from the previous literature. Grossly visible necrotic areas were present in 2 of 5 malignant tumors only.

Probably, the presence of grossly visible necrosis could be a possible adverse prognostic factor in t(6;11) TRCC. Mitotic figures were observed in 2 of 49 NATs and in 1 AT. However, presence/absence of mitotic activity has been seldom mentioned in the literature.

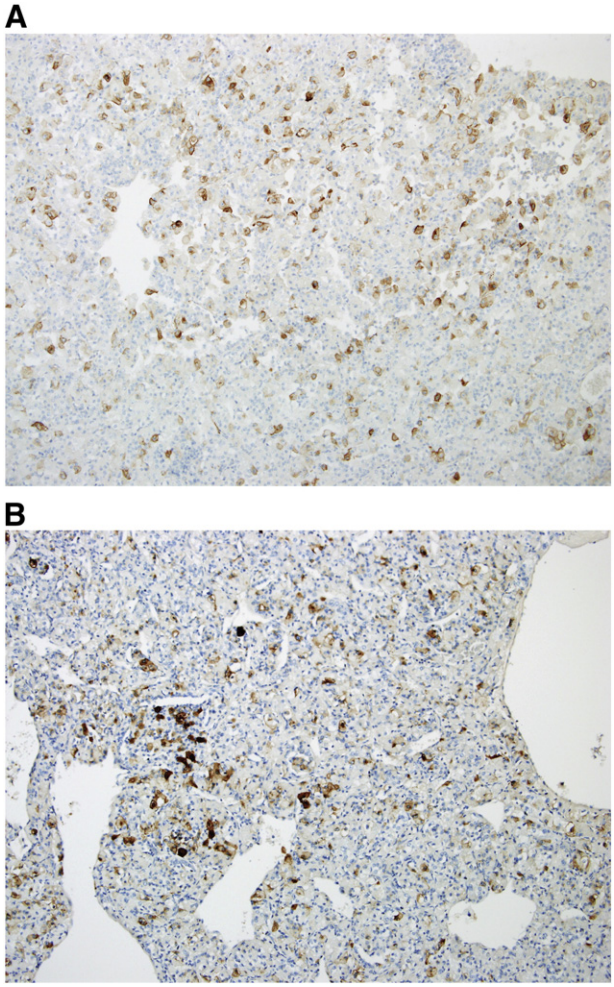

Fig. 6. All cases were positive for HMB45 (A) and cytokeratins (CAM 5.2 shown in case 2) (B).

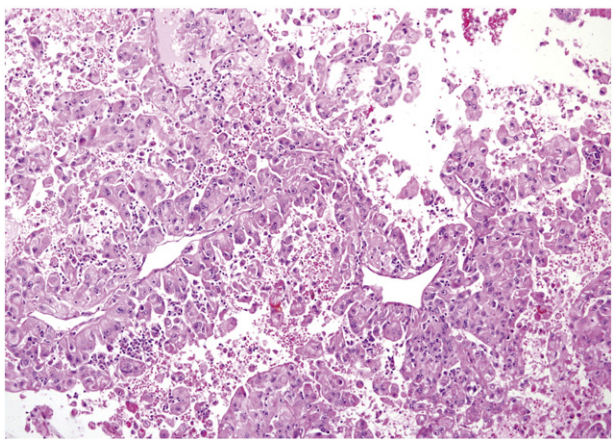

Fig. 5. In aggressive case, it was possible to find foci with papillary/pseudopapillary structures composed of bizarre atypical cells.

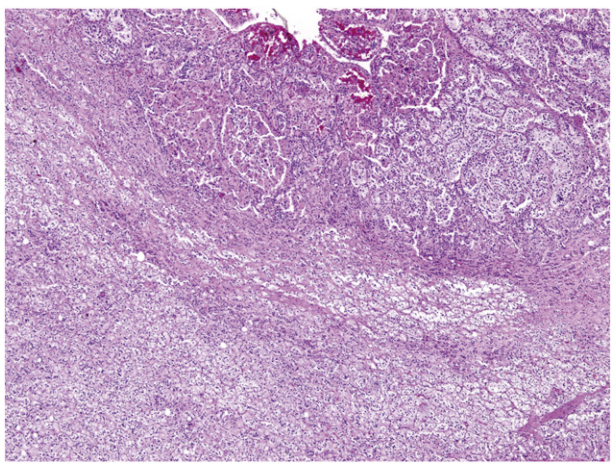

Fig. 7. Metastasis of t(6;11) RCC to the ipsilateral adrenal gland.

Table 5
Overview of the aggressive cases in the literature and current case

Case	Age (y)	Size (cm)	Necrosis	Vimentin	Mitoses	Atypical mitoses	TFEB rearrangement	Meta
Case 1: Martignoni et al Martignoni et al [12]	42	NA	None	+	None	None	NP	Paratracheal lymph nodes, pleura
Case 2: Camparo et al [13]	36	20	+ (5%)	+	Not known	Not known	NA	Not known (deceased)
Case 3: Inamura et al [14]	37	NA	Not known	+	Not known	Not known	+	Lung, mediastinal lymph node, bone
Case 4: Smith et al [11]	34	3	Not known	Not known	Not known	Not known	+	Rib
Case 5: currently described new case	77	12	+ (40%)	−	+	None	+	Adrenal gland and lung

Abbreviations: NP, not performed; NA, nonavailable; Meta, metastasis; y, years.
"+" = positive; "−" = negative.

Histologically, 2 ATs (cases 2 and 4; Table 5) lacked a small cell component. One AT (case 3; Table 5) showed features of unusual morphology for t(6;11) TRCC and was initially diagnosed as clear cell–type RCC. Morphology in the current aggressive case (case 5; Table 5) was compatible with the usual features of t(6;11) TRCC; however, some minor variations were noted (for further details, see the Results section). Papillary and pseudopapillary formations lined by high-grade cells were not described in any of NATs according to the literature. However, similar focal architecture has been described in 1 NAT but with low-grade neoplastic cells.

Aggressive tumor (case 5; Table 5) showed amplification of *TFEB* locus. No information about copy number changes of TFEB loci is mentioned in previous articles dealing AT; however, as this phenomenon was found in our set only in AT, it could be a genetic hallmark of aggressive t(6;11) RCC. Analysis of other ATs is, however, necessary to confirm this hypothesis.

Translocation t(6;11) (Alpha-TFEB) or *TFEB* break was detected in 4 NATs and 1 AT.

Losses of part of chromosomes 1 and 22 were found in our AT. However, identical findings were shown in nonaggressive case (case 2 in the original series) published previously [15]. Thus, chromosomal aberration pattern does not seem to predict/rule out potential aggressive behavior.

Regarding the histopathologic differential diagnosis, the morphology and immunohistochemical pattern of t(6;11) TRCC could mimic Xp11.2 TRCC. The most distinctive histologic pattern of the Xp11 TRCC is presence of both clear/eosinophilic cells, mostly papillary architecture and, in some cases, abundant psammoma bodies. However, Xp11.2 TRCCs can also produce pattern or unusual morphology mimicking other types of RCCs [22]. The biphasic morphologic variant with population of larger polygonal cells mixed with smaller cells clustering around hyaline material has been already described in Xp11.2 TRRCC. Such cases can simulate t(6;11) TRCC. On the other hand, the t(6;11) TRCC can mimic Xp11.2 TRCC as well [22]. The Xp11 TRCC is distinguished by chromosomal translocations with breakpoints involving the *TFE3*, which maps to the Xp11.2 locus. Differential diagnosis between both basic types of translocation carcinomas is complicated in difficult cases. Analysis of the morphology, together with immunohistochemical examination (TFE3, TFEB—if available, CD117, HMB-45, and Melan-A), should be supported by the molecular-genetic analysis.

Another tumor, which should be ruled out during the differential diagnostic process, is angiomyolipoma (AML), especially its epithelioid/oncocytic variety. Both t(6;11) TRCC and AML are positive for HMB-45 and Melan-A. It is important to note that some AMLs, as well as t(6;11) TRCC, may show only scattered HMB-45–positive cells. Angiomyolipoma is frequently composed, at least in part, of voluminous cells with slightly eosinophilic cloudy cytoplasm resembling in some aspects the neoplastic cells in t(6;11) TRCC. Angiomyolipoma frequently contains lipocytes, which are usually absent in t(6;11)-associated RCCs. Voluminous prominent vascular structures characteristic for AML could be present/absent in t(6;11) TRCC. Thus, it is not possible to use this morphologic feature for differential diagnosis. Moreover, the epithelioid variant of AML lacks usually lipocytic component (or it is inconspicuous), and vascular component could be less prominent [23]. The so-called oncocytic variant of AML is composed of large cells with voluminous eosinophilic cytoplasm arranged in solid arrangements [1,24]. Again, in unusual challenging cases, a good sampling is necessary and, in more difficult cases, analysis of translocation and/or TFEB protein performed by molecular-genetic techniques would be helpful.

5. Conclusions

We have compared all, to date reported, malignant cases of t(6;11) translocation carcinomas with one another and have tried to find some mutual features.

1. Aggressive t(6;11) RCCs generally occur in older population in comparison with their indolent counterparts.
2. In regard to the histologic findings in ATs, 3 of 5 cases were morphologically slightly different from nonaggressive t(6;11) RCC. Of the 3 cases, 2 cases lacked a small cell component and 1 closely mimicked clear cell–type RCC.
3. Grossly visible necroses were present in aggressive t(6;11) RCC only and could be potentially taken as a adverse prognostic factor.
4. Amplification of *TFEB* locus was also found only in aggressive t(6;11) RCC.

Further genetic and clinicopathologic investigations with additional new cases can further highlight this rare and peculiar variant of RCC.

Disclosure of conflict of interest

All authors declare no conflict of interest.

The study was supported by the Charles University Research Fund (project number P36) and by the project by the project CZ.1.05/2.1.00/03.0076 from European Regional Development Fund.

References

[1] Srigley JR, Delahunt B, Eble JN, Egevad L, Epstein JI, Grignon D, et al. The International Society of Urological Pathology (ISUP) Vancouver Classification of Renal Neoplasia. Am J Surg Pathol 2013;37(10):1469–89 [PubMed PMID: 24025519].
[2] Argani P, Ladanyi M. Recent advances in pediatric renal neoplasia. Adv Anat Pathol 2003;10(5):243–60 [PubMed PMID: 12973047].
[3] Argani P, Ladanyi M. Distinctive neoplasms characterised by specific chromosomal translocations comprise a significant proportion of paediatric renal cell carcinomas. Pathology 2003;35(6):492–8 [PubMed PMID: 14660099].
[4] Argani P, Ladanyi M. The evolving story of renal translocation carcinomas. Am J Clin Pathol 2006;126(3):332–4 [PubMed PMID: 16880145].
[5] Argani P, Yonescu R, Morsberger L, Morris K, Netto GJ, Smith N, et al. Molecular confirmation of t(6;11)(p21;q12) renal cell carcinoma in archival paraffin-embedded material using a break-apart TFEB FISH assay expands its clinicopathologic spectrum. Am J Surg Pathol 2012;36(10):1516–26 [PubMed PMID: 22892601].
[6] Medendorp K, van Groningen JJ, Schepens M, Vreede L, Thijssen J, Schoenmakers EF, et al. Molecular mechanisms underlying the MiT translocation subgroup of renal cell carcinomas. Cytogenet Genome Res 2007;118(2-4):157–65 [PubMed PMID: 18000366].
[7] Kuiper RP, Schepens M, Thijssen J, van Asseldonk M, van den Berg E, Bridge J, et al. Upregulation of the transcription factor TFEB in t(6;11)(p21;q13)-positive renal

cell carcinomas due to promoter substitution. Hum Mol Genet 2003;12(14):1661–9 [PubMed PMID: 12837690].
[8] Davis IJ, Hsi BL, Arroyo JD, Vargas SO, Yeh YA, Motyckova G, et al. Cloning of an Alpha-TFEB fusion in renal tumors harboring the t(6;11)(p21;q13) chromosome translocation. Proc Natl Acad Sci U S A 2003;100(10):6051–6 [PubMed PMID: 12719541. Pubmed Central PMCID: 156324].
[9] Geller JI, Argani P, Adeniran A, Hampton E, De Marzo A, Hicks J, et al. Translocation renal cell carcinoma: lack of negative impact due to lymph node spread. Cancer 2008;112(7):1607–16 [PubMed PMID: 18278810].
[10] Rao Q, Liu B, Cheng L, Zhu Y, Shi QL, Wu B, et al. Renal cell carcinomas with t(6;11)(p21;q12): a clinicopathologic study emphasizing unusual morphology, novel alpha-TFEB gene fusion point, immunobiomarkers, and ultrastructural features, as well as detection of the gene fusion by fluorescence in situ hybridization. Am J Surg Pathol 2012;36(9):1327–38 [PubMed PMID: 22895266].
[11] Smith NE, Illei PB, Allaf M, Gonzalez N, Morris K, Hicks J, et al. t(6;11) renal cell carcinoma (RCC): expanded immunohistochemical profile emphasizing novel RCC markers and report of 10 new genetically confirmed cases. Am J Surg Pathol 2014;38(5):604–14 [PubMed PMID: 24618616].
[12] Martignoni G, Tardarico R, Pea M, Pecciarini L, Gobbo S. t6;11 renal cell tumor. A clinicopathological study of two cases in adults. Mod Pathol 2005;18(Suppl 1):155A.
[13] Camparo P, Vasiliu V, Molinie V, Couturier J, Dykema KJ, Petillo D, et al. Renal translocation carcinomas: clinicopathologic, immunohistochemical, and gene expression profiling analysis of 31 cases with a review of the literature. Am J Surg Pathol 2008;32(5):656–70 [PubMed PMID: 18344867].
[14] Inamura K, Fujiwara M, Togashi Y, Nomura K, Mukai H, Fujii Y, et al. Diverse fusion patterns and heterogeneous clinicopathologic features of renal cell carcinoma with t(6;11) translocation. Am J Surg Pathol 2012;36(1):35–42 [PubMed PMID: 21959307].
[15] Petersson F, Vanecek T, Michal M, Martignoni G, Brunelli M, Halbhuber Z, et al. A distinctive translocation carcinoma of the kidney; "rosette forming," t(6;11), HMB45-positive renal tumor: a histomorphologic, immunohistochemical, ultrastructural, and molecular genetic study of 4 cases. Hum Pathol 2012;43(5):726–36 [PubMed PMID: 22051379].
[16] Hora M, Urge T, Travnicek I, Ferda J, Chudacek Z, Vanecek T, et al. MiT translocation renal cell carcinomas: two subgroups of tumours with translocations involving 6p21 [t (6; 11)] and Xp11.2 [t (X;1 or X or 17)]. SpringerPlus 2014;3:245 [PubMed PMID: 24877033. Pubmed Central PMCID: 4032393].
[17] Argani P, Lae M, Hutchinson B, Reuter VE, Collins MH, Perentesis J, et al. Renal carcinomas with the t(6;11)(p21;q12): clinicopathologic features and demonstration of the specific alpha-TFEB gene fusion by immunohistochemistry, RT-PCR, and DNA PCR. Am J Surg Pathol 2005;29(2):230–40 [PubMed PMID: 15644781].
[18] Argani P, Lae M, Ballard ET, Amin M, Manivel C, Hutchinson B, et al. Translocation carcinomas of the kidney after chemotherapy in childhood. J Clin Oncol 2006;24(10):1529–34 [PubMed PMID: 16575003].
[19] Suarez-Vilela D, Izquierdo-Garcia F, Mendez-Alvarez JR, Miguelez-Garcia E, Dominguez-Iglesias F. Renal translocation carcinoma with expression of TFEB: presentation of a case with distinctive histological and immunohistochemical features. Int J Surg Pathol 2011;19(4):506–9 [PubMed PMID: 19687027].
[20] Martignoni G, Bonetti F, Chilosi M, Brunelli M, Segala D, Amin MB, et al. Cathepsin K expression in the spectrum of perivascular epithelioid cell (PEC) lesions of the kidney. Mod Pathol 2012;25(1):100–11 [PubMed PMID: 21874011].
[21] Zhong M, De Angelo P, Osborne L, Keane-Tarchichi M, Goldfischer M, Edelmann L, et al. Dual-color, break-apart FISH assay on paraffin-embedded tissues as an adjunct to diagnosis of Xp11 translocation renal cell carcinoma and alveolar soft part sarcoma. Am J Surg Pathol 2010;34(6):757–66 [PubMed PMID: 20421778].
[22] Argani P, Olgac S, Tickoo SK, Goldfischer M, Moch H, Chan DY, et al. Xp11 translocation renal cell carcinoma in adults: expanded clinical, pathologic, and genetic spectrum. Am J Surg Pathol 2007;31(8):1149–60 [PubMed PMID: 17667536].
[23] Nese N, Martignoni G, Fletcher CD, Gupta R, Pan CC, Kim H, et al. Pure epithelioid PEComas (so-called epithelioid angiomyolipoma) of the kidney: a clinicopathologic study of 41 cases: detailed assessment of morphology and risk stratification. Am J Surg Pathol 2011;35(2):161–76 [PubMed PMID: 21263237].
[24] Martignoni G, Pea M, Bonetti F, Brunelli M, Eble JN. Oncocytoma-like angiomyolipoma. A clinicopathologic and immunohistochemical study of 2 cases. Arch Pathol Lab Med 2002;126(5):610–2 [PubMed PMID: 11958671].