5-2019

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Background

- Several variant histologic patterns of clear cell renal cell carcinoma (RCC) are well known, particularly sarcomatoid and rhabdoid features.
- However, we have encountered rare cases in which a high-grade adenocarcinoma not otherwise specified (NOS) pattern or urothelial carcinoma-like component would be difficult to appreciate as clear cell RCC.

Design

- We retrieved 26 tumors with histologically typical clear cell RCC juxtaposed to a high-grade non-clear cell component.
- A high-grade non-clear cell component was defined as non-sarcomatoid, non-rhabdoid areas that would be difficult to assign as renal cell in origin if viewed in isolation.
- Tumors were studied with immunohistochemistry and fluorescence in situ hybridization (FISH) or sequencing.

Results

- Median percentage of poorly differentiated component was 50% (IQR20-70).
- All tumors showed abrupt transition from clear cell carcinoma to poorly-differentiated areas, with micropapillary (7/26; 27%), urothelial-like (10/26; 39%), and adenocarcinoma NOS features (9/26; 35%).
- Carbonic anhydrase IX (CA-IX) was uniformly positive in the well-differentiated component (20/20), but the poorly differentiated component showed a median positivity of 82.5% (IQR 65-100).
- The poorly differentiated component was positive for CK7 (5/19; 26%), CK20 (3/12; 25%), AMACR (7/12; 58%), PAX8 (12/15; 80%), and showed intact FH (6/6; 100%). CDX2 was uniformly negative.
- Chromosome 3p loss or *VHL* mutation was present in 8/13 (62%), tested with either FISH (n = 9) or sequencing (n = 4).
- All tested cases were negative for *TFE3* (0/11) and *TFEB* (0/9) rearrangements using FISH.
- With follow-up, 5/21 (24%) patients were alive with metastatic disease and 5/21 (24%) had died of disease on follow up. One metastasis with biopsy material was composed only of the poorly-differentiated component and was near-negative for CA-IX.

Results

Table 1: Clinicopathological features

	Age	Sex	Size	Site	Grade	Stage	Nodes	Metastasis	% clear cell / poorly-diff	*TFE3* FISH	*TFEB* FISH	*VHL* FISH or molecular
1	52	M	6.8	L	4	pT3a	pN0	NA	40%/60%	Negative	Negative	Deletion
2	70	F	15	R	4	pT4	pN0	AWD	80%/20%	Negative	Negative	Deletion
3	76	M	6	R	4	pT3a	pNX	NA	70%/30%	NA	NA	NA
4	59	M	5.8	R	4	pT1b	pN0	AWD	70%/30%	Negative	Negative	No deletion
5	64	M	5.5	L	4	pT1b	pN0	NED	40%/60%	Negative	Negative	No deletion
6	69	M	3.9	R	3	pT1a	pNX	AWD	30%/70%	Negative	Negative	Deletion
7	65	F	15	R	4	ypT3a	pNX	NED	30%/70%	Negative	Negative	No deletion
8	52	M	13	L	4	pT3a	pNX	NED	60%/40%	Negative	NA	Deletion
9	51	M	4.7	R	3	pT3a	pNX	NA	90%/10%	Negative	Negative	No deletion
10	61	M	6	L	3	pT3a	pNX	NA	20%/60%	Negative	Negative	NA
11	61	F	6.6	L	4	pT3a	pNX	NA	NA	NA	NA	*VHL* mutation
12	61	M	13.1	R	4	pT3a	pNX	DOD	70%/30%	Negative	Negative	No deletion
13	43	M	9.9	R	4	pT4	pN1	DOD	95%/5%	NA	NA	NA
14	60	F	6.5	L	4	pT3b	pN1	NED	20%/80%	NA	NA	NA
15	65	M	6	R	4	pT3a	pNX	NED	30%/70%	NA	NA	NA
16	56	M	14	L	4	pT3b	pN0	NED	20%/80%	NA	NA	NA
17	38	M	7.6	R	4	pT3a	pNX	DOD	30%/70%	Negative	NA	NA
18	48	M	4.5	L	3	pT1b	pN0	NED	80%/20%	NA	NA	NA
19	37	M	10.8	R	4	pT2b	pNX	NED	80%/20%	NA	NA	NA
20	41	M	16.2	L	3	pT3a	pN1	DOD	60%/40%	NA	NA	*VHL* mutation
21	73	F	9	L	3	pT3a	pN1	DOD	40%/60%	NA	NA	*VHL* mutation
22	62	F	14.6	L	4	pT3	pN1	DOOC	20%/80%	NA	NA	NA
23	68	F	5.5	R	4	pT1b	pN1	NA	20%/80%	NA	NA	NA
24	54	M	22	L	4	pT3	pN1	AWD	95%/5%	NA	NA	NA
25	47	M	11.3	L	4	pT3	pN1	NA	10%/90%	NA	NA	NA
26	58	M	8.7	L	4	pT3	pN1	AWD	90%/10%	NA	NA	*VHL* mutation

Table 2: Immunohistochemistry

	CAIX - clear cell / poorly differentiated RCC	PAX8	CK7	AMACR	CK20	Other
1	100%/40%	0%	0%	0%	0%	intact FH
2	80%/50%	0%	0%	NA	0%	intact FH
3	NA	NA	NA	NA	NA	
4	80%/80%	90%/70%	0%/0%	0/0%	0%/0%	
5	100%/100%	10%/10%	0%/0%	100%/80%	0%/0%	
6	100%/100%	40%/70%	0%/10%	100%/100%	0%	
7	100%/80%	0%/20%	0%	0%	0%/60%	
8	100%/100%	20%/95%	0%/0%	80%/50%	0%/0%	CD10+, Vimentin+
9	100%/100%	100%/100%	5%/0%	0/70% weak	<5%/0%	Vimentin+, CD10+, Melan negative
10	100%/70%	NA	15%	100%	0%	
11	100%/100%	100%/100%	0%/0%	NA	0/90%	RCC 90%, INI retained, CD10+
12	85%/85%	0%	0%	0	0	EMA+, AE1/3+, CD10+, vimentin+
13	75%/70%	NA	0	NA	15%	Vimentin+, Cam5.2, CD10+
14	100%/50%	NA	NA	NA	NA	Vimentin+
15	NA	NA	NA	NA	NA	
16	100%/100%	NA	0	NA	NA	
17	100%/20%	100%	0	NA	NA	
18	100%/100%	100%	NA	NA	NA	
19	NA	100%	NA	NA	NA	
20	90%/70% weaker	100%	0%/15%	80%/100%	NA	
21	100%/100%	100%	0%/70%	NA	NA	
22	NA	NA	NA	NA	NA	
23	NA	NA	NA	NA	NA	
24	NA	NA	NA	NA	NA	
25	100%/0%	NA	0%/0%	NA	NA	Vimentin+
26	100%/0%	NA	0%/0%	100%/100%	NA	

Figures

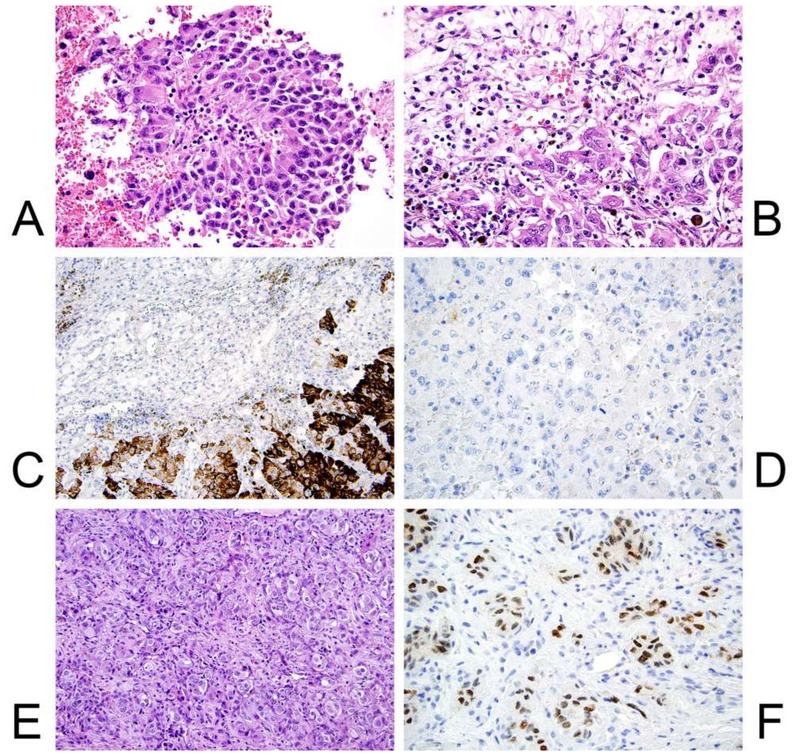

Figure 1: The tumor from patient 7 demonstrated poorly-differentiated, urothelial carcinoma-like morphology (A) with abrupt transition to conventional clear cell features (B, top). Cytokeratin 20 was substantially positive in the poorly-differentiated component (bottom, C) and CA-IX was markedly decreased to negative in these areas (D). A metastatic lesion involving the jaw was composed only of the poorly-differentiated component (E) and was negative for CA-IX but positive for PAX8 (F).

Conclusion

- Clear cell RCC with a poorly differentiated component resembling adenocarcinoma or urothelial carcinoma is a novel source of morphologic heterogeneity that has not been previously well characterized.
- Potential pitfalls include decreased or absent CA-IX staining the high-grade component and aberrant positivity for cytokeratin 7 or 20.
- With the increasing use of renal mass biopsy and biopsies of metastatic sites for targeted therapy, pathologists should be aware of this entity and consider the possibility of clear cell RCC even for morphologically unusual tumors.