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Clear cell renal cell carcinoma with focal psammomatous calcifications: a rare occurrence mimicking translocation carcinoma

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Clear cell renal cell carcinoma with focal psammomatous calcifications: a rare occurrence mimicking translocation carcinoma

Aims: Renal cell carcinoma (RCC) with clear cells and psammoma-like calcifications would often raise suspicion for MITF family translocation RCC. However, we have rarely encountered tumours consistent with clear cell RCC that contain focal psammomatous calcifications.

Methods and results: We identified clear cell RCCs with psammomatous calcifications from multiple institutions and performed immunohistochemistry and fluorescence and RNA *in-situ* hybridisation (FISH and RNA ISH). Twenty-one tumours were identified: 12 men, nine women, aged 45–83 years. Tumour size was 2.3–14.0 cm (median = 6.75 cm). Nucleolar grade was 3 (n = 14), 2 (n = 4) or 4 (n = 3). In addition to clear cell pattern, morphology included eosinophilic (n = 12), syncytial giant cell (n = 4), rhabdoid (n = 2), branched glandular (n = 1), early spindle cell (n = 1) and poorly differentiated components (n = 1). Labelling for CA9 was usually 80–100% of the tumour cells (n = 17 of 21), but was sometimes decreased in areas of eosinophilic cells (n = 4). All (19 of 19) were positive for CD10. Most (19 of 20) were positive for AMACR (variable staining = 20–100%). Staining was negative for keratin 7, although four showed rare positive cells (four of 20). Results were negative for cathepsin K (none of 19), melan A (none of 17), HMB45 (none of 17), TFE3 (none of 5), TRIM63 RNA ISH (none of 13), and *TFE3* (none of 19) and *TFEB* rearrangements (none of 12). Seven of 19 (37%) showed chromosome 3p deletion. One (one of 19) showed trisomy 7 and 17 without papillary features.

Conclusions: Psammomatous calcifications in RCC with a clear cell pattern suggests a diagnosis of MITF family translocation RCC; however, psammomatous calcifications can rarely be found in true clear cell RCC.

Keywords: clear cell renal cell carcinoma, psammoma bodies, TFE3, TFEB, TRIM63

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Introduction

Speaking at a local pathology meeting in San Francisco, CA in 2018 on the topic of tumours in the morphological differential diagnosis of clear renal cell carcinoma (RCC), the late Dr David Grignon (to whom this manuscript is dedicated) proclaimed that: 'finding psammoma bodies is a clue that that you are probably dealing with a translocation RCC; if you have a picture of a psammoma body in a clear cell RCC please email it to me as these are excruciatingly rare!'. After finding such an index case, ironically a few months after this meeting by A.R.S. and following discussion with S.R.W., a former trainee of Dr Grignon who had collected a few such tumours, a multi-institutional search was conducted to gather specimens for a clinicopathological review of psammomatous calcifications (a well-described morphological feature of *TFE3* rearranged RCC and *TFEB* altered RCC[1–9]) identified in clear cell RCC.

Materials and methods

The pathology archives of multiple institutions were searched for tumours in which a diagnosis of clear cell RCC was rendered, containing any admixed psammoma-like or punctate calcifications (excluding dystrophic calcification in fibrous stroma, Gamna–Gandy-like structures or metaplastic bone formation). All diagnoses were confirmed by at least two genitourinary pathologists. Clinicopathological features, including notable tumoral histology and pattern/extent of calcification, were recorded on all cases. Immunohistochemistry performed for CA9, CD10, AMACR, keratin 7, cathepsin K, melan A, HMB45 and TFE3 at the various institutions were noted with staining pattern semi-quantitatively scored. Fluorescence *in-situ* hybridisation (FISH) testing for *TFE3* rearrangement, *TFEB* rearrangement/amplification, chromosome 3p deletion, trisomy chromosome 7 and trisomy chromosome 17 was performed on a subset of cases, as described elsewhere.[8,10–12] Additionally, RNA *in-situ* hybridisation against target probe *TRIM63* (TRIM63 RNA ISH) was performed on a subset of cases, as described elsewhere.[7]

Results

A total of 21 tumours were retrieved from 12 institutions. All specimens were radical nephrectomies (11 left-sided, 10 right-sided). Patients were 12 men and nine women, with ages ranging from 49 to 83 years (mean = 63.1 years). Tumour sizes ranged from 2.3 to 14.0 cm (mean = 6.5 cm) and showed WHO/ISUP nucleolar grades of 3 (n = 14), 2 (n = 4) and 4 (n = 3). Most tumours were stage category pT3a (n = 11), followed by pT1b (n = 5), pT2a (n = 3) and pT1a (n = 2). The pattern of calcification was psammomatous in all tumours (100%), with six also showing another pattern of calcification (five with punctate calcification and one with ring-shaped calcification). These calcifications were not associated with necrosis. In all tumours, the extent of calcification was focal (located only in one to two slides/blocks). Regarding histomorphology, all tumours showed areas of typical clear cell RCC (Figures 1 and 2), with some other notable features as listed in Table 1. Of the immunohistochemistry recorded for this study (Table 1), CA9 showed positive membranous labelling in all tumours (21 of 21, complete membranous pattern), typically within 80–100% of the tumour cells (n = 17 of 21). Tumours with < 100% CA9 reactivity all contained eosinophilic cells and had a minimum of 50% staining, with the higher-grade component showing decreased staining compared to the well-differentiated component. All tumours studied (19 of 19) were also positive for CD10 and most (18 of 19) were also positive for AMACR (notably variable staining with AMACR, 20–100%). Tested tumours were typically negative for keratin 7 (16 of 20); however, four had rare cells positive, estimated as only 1% of cells. There was no staining for cathepsin K (none of 19), melan A (none of 17), HMB45 (none of 17) and TFE3 protein (none of five). TRIM63 RNA ISH was negative in 11 tested specimens, with one showing focal positivity with H-score of 85, interpreted as negative/non-specific. *TFE3* rearrangement was negative in all tested specimens (none of 19). Seven of 19 tumours (37%) showed chromosome 3p deletion. One tumour (one of 19) showed trisomy chromosomes 7 and 17; however, this lacked papillary morphology and showed a typical clear RCC immunoprofile (diffusely CA9 positive, CD10 positive, keratin 7 negative). *TFEB* showed no rearrangement or amplification all tested tumours (none of 12). This was a retrospective study, not interfering with diagnosis and patient management; the data are available on request from the authors.

Discussion

In the evaluation of RCC nephrectomies, psammomatous calcifications are not uncommon, prototypically seen in papillary RCC.[13] These calcifications can also

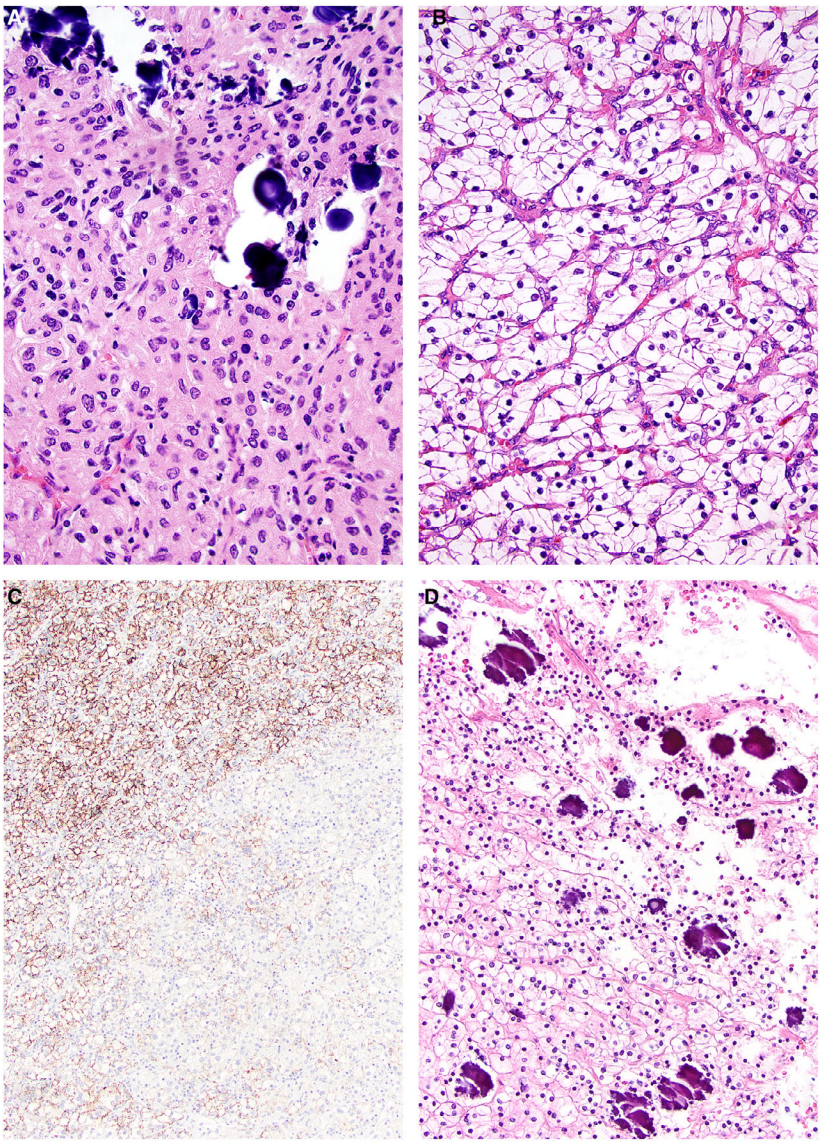

Figure 1. (**A**) This clear cell renal cell carcinoma shows more eosinophilic cells around the psammomatous calcifications; however, other areas of the same tumour (**B**) have typical clear cell morphology. Labelling for CA9 was typically diffuse, but sometimes decreased in the areas corresponding to eosinophilic cells or high-grade cells (**C**, lower right). Another tumour (**D**) shows larger, granular calcifications in addition to psammomatous calcifications.

be seen in some classical RCC subtypes (chromophobe RCC[14]), as well as in some more recently characterised entities (eosinophilic solid and cystic RCC,[15] biphasic hyalinising psammomatous RCC,[16] NF-mutated RCC[17] and RCC with sex-cord/gonadoblastoma-like features[18]). However, when encountering a renal cell carcinoma showing clear cell morphology and admixed psammomatous calcifications, the archetypal tumour type that comes to mind is the MiTF family translocation RCC (which includes *TFE3* rearranged RCC and *TFEB* altered RCC[1–9]). In fact, this is often considered a morphological clue to suspect a diagnosis of translocation RCC. To date, psammomatous calcifications encountered in clear cell RCC have not (to our knowledge) been well described or reported, thus being the focus of the current study.

Herein, we report our findings from 21 clear cell RCC tumours containing admixed psammoma-like or punctate calcifications. While the true incidence of this finding is unclear, based on our own experiences in high-volume nephrectomy practices of several of the co-authors, finding psammomatous calcifications in clear cell RCC is uncommon. Specifically, of the co-authors who had tabulated total clear cell RCC cases reviewed to identify clear cell RCC with admixed psammomatous calcifications, the incidence ranged from one study case per 75 clear cell RCC to one study case per 823 clear cell RCC (a cumulative incidence of approximately 1%). Interestingly, one co-

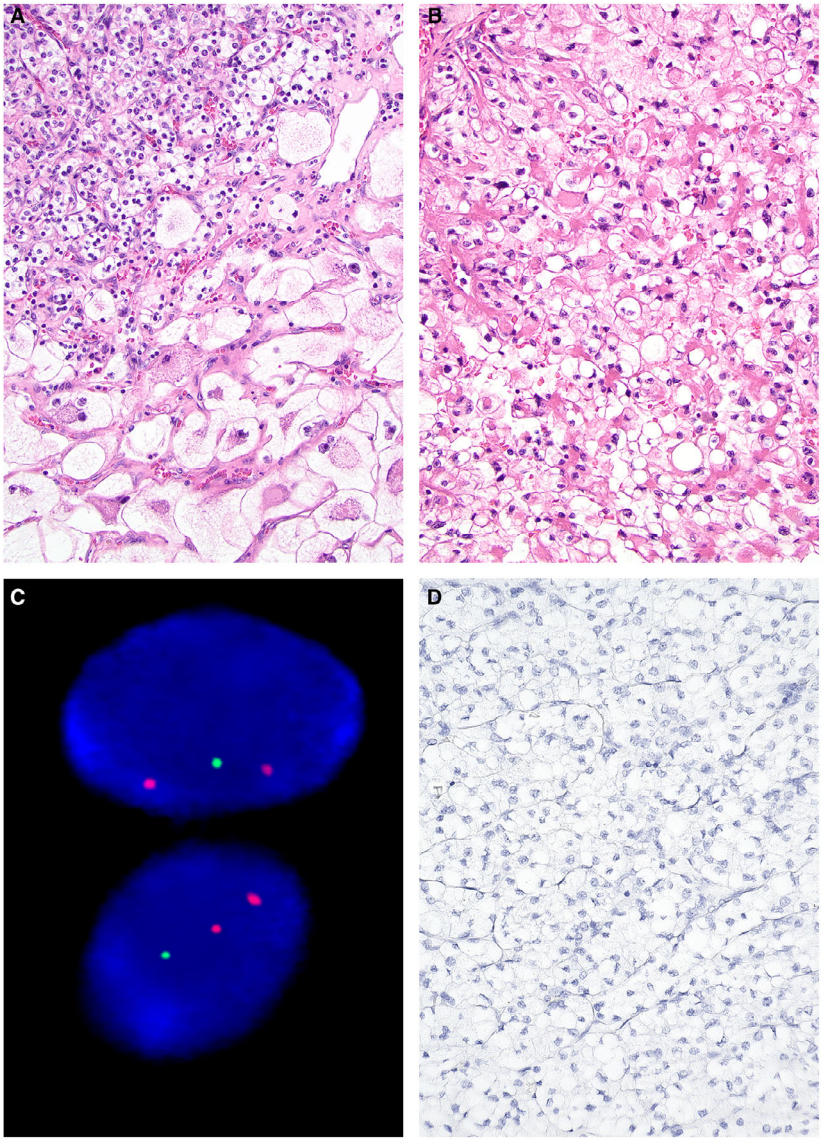

Figure 2. Other morphologies encountered in the clear cell renal cell carcinomas with psammomatous calcifications (not shown here) included syncytial-type giant tumour cells (**A**, lower right) or (**B**) rhabdoid cells. Fluorescence *in-situ* hybridisation shows two copies of the chromosome 3 centromere (red) per cell, but only one copy of 3p (green, **C**). RNA *in-situ* hybridisation demonstrates negative TRIM63 expression (**D**), arguing against translocation-associated renal cell carcinoma.

author, who had also recorded the number of MiTF family RCC discovered during retrospective case review (mainly by observing unusual tumour morphology coupled with concomitant psammomatous calcifications), noted 40 MiTF RCC identified among 843 RCC reviewed (an incidence of approximately 5%). This more than fivefold estimated incidence reiterates the notion that although psammomatous calcifications can occur in clear cell RCC, more often than not it raises the possibility of MiTF RCC. Nonetheless, based on the somewhat more extensive immunohistochemical panel employed by most co-authors than might be used for a typical clear cell RCC (see Table 1), it appears that MiTF family translocation RCC was a serious diagnostic considered based on the admixed psammomatous calcifications. Moreover, the expression of AMACR (often positive in MiTF family translocation RCC[19]) in our cohort exemplifies this as a potential immunohistochemical pitfall,[21] as variable AMACR positivity has been described clear cell RCC.[20,22] Given the well-known issues with TFE3 immunohistochemistry as a diagnostic marker for MiTF family translocation RCC,[12,23–26] only a minority of laboratories offer this marker in a clinical (non-research) setting.[27] Therefore, it may not be surprising that TFE3 immunohistochemistry was infrequently utilised among the co-authors of this study (24%, only five of 21 specimens; which showed a negative TFE3 stain).

While we acknowledge that testing for *TFE3* rearranged RCC and *TFEB* altered RCC by FISH methodology, as we performed in this study, has its own diagnostic issues,[4,9,23,28] particularly compared

Table 1. Clinicopathologic features of study cases

Case #	Age	Sex	Size (cm)	Stage	Grade	Notable histology	Pattern of calcifications	CA9	CD10	AMACR	KRT7	Cathepsin K	Melan A	HMB45	TRIM63	TFE3 IHC	TFE3 FISH	3p deletion	Chr 7	Chr 17	TFEB FISH
1	49	M	14.0	pT3aN1	3	Eosinophilic cells	Psammoma	100%	100%	70%	Negative	Negative	Negative	Negative	NA	NA	Negative	Negative	Disomy	Disomy	Negative
2	54	M	9.0	pT3aNx	3	NA	Psammoma	100%	100%	100%	Negative	Negative	NA	NA	NA	NA	Negative	Negative	Disomy	Disomy	Negative
3	83	M	5.0	pT3aNx	3	NA	Psammoma	100%	30%	95%	Negative	Negative	Negative	Negative	NA	NA	Negative	Negative	Disomy	Disomy	Negative
4	63	M	5.0	pT1bNx	3	Eosinophilic cells	Psammoma	100%	100%	30%	Negative*	Negative	Negative	Negative	Negative	NA	Negative	Positive	Disomy	Disomy	Negative
5	45	F	2.8	pT1aNx	2	NA	Psammoma	100%	100%	60%	Negative	Negative	Negative	Negative	Negative	NA	Negative	Positive	Disomy	Disomy	Negative
6	55	M	6.1	pT3aNx	3	NA	Psammoma	100%	5%	negative	Negative*	Negative	Negative	Negative	Negative	NA	Negative	Positive	Disomy	Disomy	Negative
7	85	F	3.0	pT3aNx	3	Eosinophilic cells, syncytial giant cells	Psammoma	100%	85%	35%	Negative	Negative	Negative	Negative	NA	NA	Negative	Negative	Disomy	Disomy	Negative
8	57	M	2.3	pT1aNx	2	NA	Psammoma	100%	80%	70%	Negative	Negative	Negative	Negative	NA	NA	Negative	Positive	Disomy	Disomy	Negative
9	54	F	7.0	pT3aN1	3	Poorly differentiated component	Psammoma	90%	40%	75%	Negative	Negative	Negative	Negative	Negative	NA	Negative	Negative	Disomy	Disomy	NA
10	79	M	6.5	pT1bNx	4	Rhabdoid	Psammoma	90%	100%	80%	Negative*	Negative	Negative	Negative	Negative	NA	Negative	Negative	Disomy	Disomy	NA
11	54	M	5.0	pT1bNx	2	Eosinophilic cells	Psammoma	90%	NA	NA	na	NA	NA	NA	NA	Negative	NA	NA	NA	NA	NA
12	59	M	8.5	pT2aN0	3	Eosinophilic cells, syncytial giant cells	Psammoma	80%	100%	80%	Negative*	Negative	Negative	Negative	Negative	NA	Negative	Negative	Trisomy	Trisomy	NA
13	59	F	8.2	pT2aNx	4	Eosinophilic cells, syncytial giant cells	Psammoma	60%	100%	80%	Negative	Negative	Negative	Negative	Negative	NA	Negative	Negative	Disomy	Disomy	NA
14	73	M	4.3	pT1bNx	3	Eosinophilic cells, hyaline globules	Psammoma	60%	NA	20%	Negative	Negative	Negative	Negative	NA	Negative	Negative	Positive	Disomy	Disomy	Negative
15	79	F	7.0	pT3aN0	3	Eosinophilic cells, syncytial giant cells	Psammoma	50%	100%	80%	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Disomy	Disomy	NA
16	57	M	8.5	pT3aNx	3	Branched glandular	Psammoma and punctate	100%	100%	40%	Negative	Negative	Negative	Negative	Negative	NA	Negative	Negative	Disomy	Disomy	NA
17	57	F	7.4	pT2aN0	2	NA	Psammoma and punctate	100%	75%	60%	Negative	Negative	NA	NA	Negative	NA	Negative	Positive	Disomy	Disomy	Negative

Table 1. (*Continued*)

Case #	Age	Sex	Size (cm)	Stage	Grade	Notable histology	Pattern of calcifications	CA9	CD10	AMACR	KRT7	Cathepsin K	Melan A	HMB45	TRIM63	TFE3 IHC	TFE3 FISH	3p deletion	Chr 7	Chr 17	TFEB FISH
18	71	F	NA	pT1bN0	3	Eosinophilic cells, early spindle cell change	Psammoma and punctate	100%	80%	60%	Negative	Negative	Negative	Negative	Negative	NA	Negative	Negative	Disomy	Disomy	Negative
19	60	F	4.8	pT3aNx	3	Eosinophilic cells	Psammoma and punctate	90%	100%	NA	Negative	NA	Negative	Negative	NA	Negative	NA	NA	NA	NA	NA
20	65	M	9.5	pT3aN1	4	Eosinophilic cells, rhabdoid	Psammoma and punctate	90%	NA	30%	Negative	Negative	Negative	Negative	Negative	NA	Negative	Positive	Disomy	Disomy	Negative
21	68	F	8.0	pT3aNx	3	Eosinophilic cells	Psammoma and ring-shaped	60%	100%	90%	Negative	Negative	NA	NA	Negative	Negative	Negative	Negative	Disomy	Disomy	NA

*1% reactivity for KRT7 is noted, but considered negative overall.

to next-generation sequence (NGS) testing, for this reason we tested all cases with available tissue blocks/unstained slides for TRIM63 RNA ISH staining. This novel biomarker has been shown to be both highly sensitive (90%) and specific (100%) for MiTF family translocation RCC,[7] and in the context of our study serves as a reliable 'screening tool' to exclude *TFE3* rearranged RCC and *TFEB* altered RCC, the key morphological differential diagnostic entities of clear cell RCC containing psammomatous calcifications.

Although we acknowledge that the rate of identifying chromosome 3p deletions in our study cohort (seven of 19, 37%) is less than what might be expected for clear cell RCC, in some instances variability in diagnostic cut-off values can contribute to wide rates of detection (38–100%).[29] Moreover, while we did not test for *VHL* gene abnormalities (mutations, deletions or methylations), which could represent the molecular oncogenesis in our cohort, we felt confident in our diagnoses based the fact that all our tumours showed at least some areas with typical clear RCC morphology coupled with strong positivity for CA9 immunohistochemical staining.

In summary, when encountering psammomatous calcifications in a RCC showing areas of clear cell morphology that is not overt papillary RCC, it may still be prudent to consider MiTF family translocation RCC and perform a diagnostic work-up. However, in this study we have shown that although finding psammoma bodies in a clear cell RCC may be uncommon, in rare instances it is not incompatible with the diagnosis.

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Conflicts of interest

All authors report no potential conflicts of interest.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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