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REVIEW: 50TH ANNIVERSARY ISSUE

Emerging entities in renal cell neoplasia: thyroid-like follicular renal cell carcinoma and multifocal oncocytoma-like tumours associated with oncocytosis

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Summary

The list of accepted entities of renal cell neoplasia has burgeoned since the turn of the century through recognition of rare tumour types and the discovery of genetic mutations driving renal neoplasia syndromes. This growth has not finished and in this report we present examples of each of these types which were not included in the 2016 World Health Organization classification of renal neoplasia, but are candidates for inclusion in the next edition of the classification. Thyroid-like follicular renal cell carcinoma is a rare tumour type with a distinctive microscopic appearance resembling follicles of the thyroid gland. Thirty-nine cases have been described and the findings have been reasonably consistent. Oncocytoma-like tumours associated with oncocytosis arise as a result of somatic mutations in the mitochondrial genome. The differential diagnosis is mainly with the renal lesions of the Birt–Hogg–Dubé syndrome, which is the result of germline mutations in the *folliculin* gene. Patients with oncocytoma-like tumours associated with oncocytosis are at great risk of developing renal failure as the proliferating lesions replace the renal parenchyma. Oncocytoma-like tumours have never been found to metastasise.

Key words: Kidney; carcinoma.

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INTRODUCTION

Both the 2016 and the preceding edition of the World Health Organization (WHO) classification of renal neoplasia have added new entities to the list of recognised tumours.[1,2] However, the possibilities are not yet exhausted. In this report we are providing a preview of two emerging entities which we believe will have strong cases for being added to the WHO classification in the next edition 5–10 years from now. These are thyroid-like follicular renal cell carcinoma and an entity with a less settled name which, for the purposes of this review, we will call oncocytoma-like tumours associated with oncocytosis.

THYROID-LIKE FOLLICULAR RENAL CELL CARCINOMA

Background

In 2004, at the annual meeting of the United States and Canadian Academy of Pathology (USCAP), cases of a renal tumour composed of structures closely resembling thyroid follicles of variable size were reported and the study was published in 2009.[3] In the intervening years, two case reports of similar tumours were published.[4,5] Since then, 30 more cases have been described (Table 1).[6–25] It should be noted that Case 10 was also reported by Vicens *et al.*,[26] Case 17 was also reported by Wu *et al.*,[27] Case 20 was also reported by Tang *et al.*[28] and by Li *et al.*,[29] while Case 30 was also reported by Li *et al.*[30] Six tumours[19,20] had distinctive appearances which reminded some of the authors more of atrophic changes in renal cortex than thyroid neoplasia. For the present analysis those cases will be integrated with the others and we will discuss the differences and similarities in a section after our analytical review.

Clinical features

The patients' ages ranged from 19 to 83 years (median 35 years, mean 41 years). The ratio of women to men was nearly 2:1 (24 women and 14 men). About one-third of the patients were symptomatic at presentation with haematuria, flank pain or abdominal pain. In the remainder of the patients, the tumours were incidental findings. One patient (Case 27) presented with bilateral tumours.[20] Approximately 10% of the patients had concurrent or historical haematopoietic neoplasia: Hodgkin lymphoma (Cases 12 and 25), lymphoblastic leukaemia (Case 22) and myeloid leukaemia (Case 19). Cases 11 and 19 also had prostatic adenocarcinoma; Case 29 had a history of urothelial carcinoma and Case 30 had had an ovarian teratoma. Case 33 had a history of thyroid cancer.

Follow-up information was presented for all but three patients, in one of whom the renal tumour was found at autopsy. The follow up periods ranged from 1 to 168 months (median 20 months). In no patient did the carcinoma cause death. About 10% of the patients developed metastases. In Case 2 a lung metastasis was resected after 2 months.[5] In Case 29, metastases to the skull and meninges developed.[22] For both of these cases the metastases were proven histologically to be

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Table 1 Cases of thyroid-like follicular renal cell carcinoma

Case	Author	Age	Gender	Presentation	Size, mm	Stage
1	Jung[4]	32	F	Incidental	118	T2bNX
2	Sterlacci[5]	9	F	Incidental	50	T1bNXM1
3	Amin[3]	53	F	Incidental	21	T1aNX
4	Amin[3]	29	F	Incidental	19	T1aNX
5	Amin[3]	45	M	Incidental	35	T1aNX
6	Amin[3]	83	M	Incidental	21	T1aNX
7	Amin[3]	35	M	Incidental	30	T1aNX
8	Amin[3]	50	F	Incidental	40	T1aN0
9	Xu[6]	36	F	Hematuria	100	T2aNX
10	Dhillon[7]	34	F	Hematuria, flank pain	62	T1bN1M1
11	Alessandrini[8]	76	M	Hematuria	45	T3aN0
12	Alessandrini[8]	41	F	Incidental	50	T1bNX
13	Dhillon[9]	34	M	Flank pain	28	T1aNX
14	Khoja[10]	31	F	Hematuria, flank pain	40	T1aN0
15	Malde[11]	29	F	Abdominal pain	65	T1bN0
16	Volavšek[12]	34	M	Incidental	55	T1bNX
17	Wu[13]	25	F	Incidental	30	T1aNX
18	Wu[14]	26	F	Incidental	40	T1aNX
19	Berens[15]	58	M	Incidental	30	T1aN0M0
20	Lin[16]	65	M	Hematuria, flank pain	130	T3aNX
21	Lin[16]	59	M	Incidental	60	T3aNX
22	Wu[17]	19	F	Abdominal pain	20	T1aNX
23	Ghaouti[18]	68	F	Incidental	11	T1aNX
24	Hes[19]	30	F	Incidental	30	T1aNX
25	Hes[19]	35	M	Incidental	30	T1aNX
26	Hes[19]	29	F	Incidental	35	T1aNX
27	Oshiro[20]	19	M	Incidental	44, 42	T1bNX
28	Dawane[21]	49	F	Abdominal pain	24	T3aNX
29	Dong[22]	68	F	Incidental	50	T1bNXM1
30	Chen[23]	35	F	Incidental	30	T1aNX31
31	Chen[23]	41	M	Hematuria, flank pain	60	T3aNX
32	Chen[23]	25	F	Incidental	25	T1bNX
33	Chen[24]	55	F	Hematuria, flank pain	40	1aN1
34	Chen[24]	29	F	Incidental	20	T1aNX
35	Chen[24]	20	M	Incidental	40	T1aNX
36	Chen[24]	40	F	Incidental	25	T1aNX
37	Chen[24]	49	F	Incidental	30	T1aNX
38	Muscara[25]	27	M	Incidental	50	T1bNX
39	Ito[130]	51	F		30	

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thyroid-like follicular carcinoma of the kidney. In Case 10, metastases to lung and lymph node were present at presentation.[7] In Case 33 lymph node metastases developed.[24] All four of these patients were women and older than the median age.

Gross pathology

In addition to the authors' descriptions, gross photographs were published for 14 of the cases. The diameter of the tumours ranged from 11 mm to 130 mm (median 35 mm, mean 43 mm). Three were 100 mm in diameter or larger. The tumours were almost always well-circumscribed and a pseudocapsule was seen to surround many of them. The parenchyma was usually brown or tan, although some were described as yellow or grey (Fig. 1). The gross photos showed brown, tan and grey parenchyma. Areas of haemorrhage or necrosis, or both were mentioned for about half the tumours. Cysts, often small, were also seen in about half the tumours. Some were described as spongy. In a few cases the authors remarked that the parenchyma resembled thyroid tissue. Whether this struck the observers before they saw the microscopic appearances of the tumours is not mentioned. Central areas of fibrosis were observed in two tumours. Gross or microscopic invasion of perinephric tissues was found in 13% of the cases (Cases 11, 20, 21, 28, and 33). No mention was found of vascular invasion nor extension into the renal pelvis.

Microscopic pathology

Microscopically, the pseudocapsules were composed of fibrous tissue and in some there was a component of smooth muscle. The most striking microscopic feature was the strong resemblance to thyroid tissue or thyroid neoplasia with follicular architecture. At low magnification the tumours

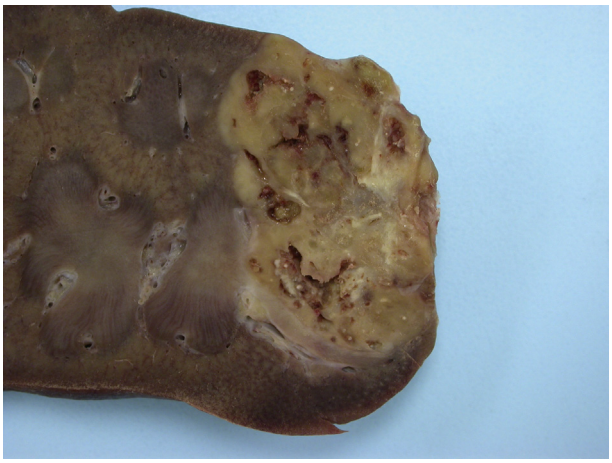

Fig. 1 Thyroid-like follicular renal cell carcinoma with a well-circumscribed border and solid and cystic light brown cut surface.

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