Renal oncocytoma, yet another tumour that does not fit in the dualistic benign/malignant paradigm?

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A debate on whether renal oncocytomas are benign neoplasms or malignant tumours

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Since its original description in 1942 and its establishment as a distinct entity in 1976, the metastatic potential of renal oncocytoma has been the subject of considerable controversy. Throughout the years, several reports have claimed a low metastatic potential for these tumours, yet the debate remains. The 2004 World Health Organization¹ classification of renal tumours categorises renal oncocytomas as benign neoplasms. One of the reasons for this debate is that renal oncocytomas may be confused with clear cell renal carcinomas with a dominant eosinophilic component and—a more difficult differential diagnosis—with the eosinophilic variant of chromophobe renal cell carcinoma, a tumour with recognised low metastatic potential. The latter entity was first described by Thoenes *et al*² in 1985, although general recognition of this lesion had to wait for another 5 years. This may have delayed the awareness of potential confusion between chromophobe renal cell carcinoma and renal oncocytoma. In a large study of 166 oncocytomas published in 1991, the differential diagnosis of chromophobe carcinoma was not mentioned, although the authors recognised granular cell carcinoma as a potential source of misdiagnosis.³ The resemblance of renal oncocytoma and chromophobe renal cell carcinoma was explicitly addressed in a small series of chromophobe renal cell carcinomas by Bonsib and Lager,⁴ following the earlier recognition that both oncocytomas and chromophobe renal cell carcinomas share a common origin from intercalating cells of the distal renal tubules.⁵

In the paper by Davis *et al*³ published in 1991, all previous cases of metastatic oncocytomas were dismissed on the basis of published morphological features. All but one of a subsequent large series of renal oncocytomas failed to identify a single case of metastatic oncocytoma

(table 1). A review of 954 primary non-urothelial renal tumours from the Sloan Kettering Cancer Center revealed a total of 70 oncocytomas, including 2 associated with metastatic disease.⁶ One of these patients had an asymptomatic liver metastasis confirmed by needle biopsy (fig 1), whereas another had multiple liver and bone metastases. In the latter case, no histological confirmation was performed to verify the oncocytic nature of the metastases. Although there was no evidence of a second primary tumour, it could be argued that a second occult primary tumour may have been responsible for the metastatic disease while the renal oncocytoma constituted an incidental finding. The study by Perez-Ordóñez *et al*⁶ had no ancillary histochemical, immunohistochemical or ultrastructural analysis, but the authors stated that cases of metastatic oncocytomas were microscopically indistinguishable from conventional non-metastatic tumours. Amin and Anthony⁷ described an additional oncocytoma with extensive skeletal metastases in 1999, but the published microscopy of the renal tumour resembles a chromophobe renal cell carcinoma and no histological confirmation of the bone metastases was performed.

Figure 1 Liver core biopsy showing a tumour with the appearance of an oncocytoma (left) within the liver parenchyma (right). The tumour is eosinophilic, does not show nuclear atypia and is arranged in small nests.

In the current issue of this journal, another metastatic renal oncocytoma is described.⁸ This tumour fulfils all accepted criteria for the diagnosis of renal oncocytoma—that is, architectural and cytological features, ultrastructural demonstration of large numbers of mitochondria, absence of Hale's colloidal blue staining, weak patchy staining for CD10, negativity for cytokeratin 7 and CD117, and positive epithelial membrane antigen expression. The histology of the liver metastasis, detected 9 years after the nephrectomy, showed the same features as the renal tumour, strongly supporting the notion that the liver metastasis was derived from the renal tumour.

Should we consider the latter case as the ultimate evidence of the existence of—however rare—renal oncocytomas with metastatic potential? This would have a significant impact on how these tumours are classified, questioning our dualistic approach to separate these tumours rigorously in benign and malignant subsets. Oncocytic tumours in other organs—for example, those of the adrenal or salivary gland—may occasionally show malignant behaviour, but this is associated with cytonuclear and histological features indicative of malignant behaviour. Although atypical features, such as focal necrosis, multinucleation, mitotic activity and degenerate atypia, have been described in renal oncocytomas, none of the two renal oncocytomas associated with metastatic disease had such features.^{6, 8} Similarly, perinephric invasion by oncocytoma (table 1) was also not related to atypia.^{3, 10, 6} Thus, renal oncocytomas share the lack of prognostic hallmarks with Leydig and Sertoli cell tumours of the testis, carotid body paragangliomas and pheochromocytomas, be it that the risk of metastatic disease is very low.

From a genetic point of view, oncocytomas are heterogeneous, and a subset of 10% of them shows loss of heterozygosity for chromosome 1 and/or chromosome X and/or 14, whereas another subset is characterised by translocations involving chromosome 11.^{11, 12} The abnormalities on chromosome 1 are shared with chromophobe renal cell carcinomas, which also carry additional chromosomal changes. This observation has led to the hypothesis that oncocytomas may progress to chromophobe renal cell carcinomas. In a case of oncocytosis (multiple oncocytomas and extensive oncocytic change in renal tubuli), a hybrid oncocytoma/chromophobe renal cell carcinoma was identified, with genetic changes supporting this view.¹³ It would be of interest to determine whether features of locally malignant behaviour, such as perinephric invasion, are related to a particular genotype of renal oncocytomas.

Table 1 Presence of malignant features in a large series of oncocytomas

Reference	Number of cases	Perinephric invasion, n(%)	Metastases*
Davis <i>et al</i> ³	166	17 (10)	0
Hartwick <i>et al</i> ⁹	23	0 (0)	0
Amin <i>et al</i> ¹⁰	80	11 (14)	0
Perez-Ordóñez <i>et al</i> ⁶	70	14 (20)	1
Dechet <i>et al</i> ¹⁴	138	0 (0)	0
Romis <i>et al</i> ¹⁵	32	0 (0)	0
Gudbjartsson <i>et al</i> ¹⁶	45	1 (2%)	0

*Histologically confirmed metastasis with morphology of oncocytoma.

From a practical point of view, any renal tumour fulfilling the currently established criteria of oncocytoma should be referred to as such, although a subset of oncocytomas sharing genetic or molecular features of chromophobe carcinoma may exist, explaining these rare instances of metastases. Interestingly, the presence of metastatic disease does not necessarily imply clinically aggressive malignant behaviour as the metastases may behave indolently, as was noted in both confirmed cases of liver metastasis of renal oncocytoma.

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