

Renal tumours with eosinophilic cytoplasm

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Renal cell carcinoma - comparative features

	Percentage cases	Macroscopic	Microscopic	Genetics
Conventional (clear cell)*	75	Yellow-white/variegated	Clear/granular	3p deletions; abnormal VHL gene in 70% cases
Papillary*	10-15	As above (+fine yellow streaks)	Papillae	trisomies 7 and 17 and Y deletions
Chromophobe*	3-5%	homogenous grey/brown	fine reticular cytoplasm; perinuclear haloes	Hypodiploid (monosomies)
Collecting duct	<1%	variable	high grade nuclei; often hobnail cells in collecting ducts	unknown



*may have areas in which cells have eosinophilic cytoplasm

Adult papillary tumor with oncocytic cells: clinicopathologic, immunohistochemical and cytogenetic features of 10 cases Lefevre M et al Am J Surg Pathol 2005;29:1576-1581

- All cases +ve for CD10, vimentin and AMACR
- 3/10 CK7+ve
- No trisomy 7 or 17 in 5 cases analysed
- No recurrences or metastases (median f/u 62 months)
- ?? May be related to papillary carcinoma group [the most recent classification groups these tumour with papillary RCC]



'Recent' additions to classification of renal cell carcinoma

- Papillary renal carcinoma subtyping:
 - type 1
 - type 2*
- Hereditary papillary renal cell carcinoma
- Solid variant papillary renal cell carcinoma*
- MITF/TFE family translocation-associated renal cell carcinoma (e.g. carcinoma associated with Xp11.2 translocations/*TFE3* gene fusion)
- Clear cell papillary renal cell carcinoma
 - Renal angiomyoadenomatous tumour (RAT)
- Acquired cystic disease-associated renal cell carcinoma*
- Hereditary leiomyomatosis associated renal cell carcinoma
- Renal cell carcinoma associated with succinate dehydrogenase mutations*
- Medullary carcinoma (patients with sickle cell trait)
- Tubulocystic carcinoma (previously known as 'low grade collecting duct carcinoma')*
- Mucinous tubular and spindle cell carcinoma
- Thyroid-like follicular carcinoma of kidney*
- Hybrid oncocytic tumour (HOCT)
- Renal cell carcinoma following therapies (post-neuroblastoma, post-transplant, post-chemotherapy)*



* Frequently composed, at least in part, of cells with variably eosinophilic cytoplasm

Renal oncocytoma

- Can be multifocal/bilateral
- Stellate scar may be absent
- Nested, tubulocystic or mixed patterns
- Abundant stroma in places (often myxoid/hyalinised)
- Abundant pink finely granular cytoplasm
- Perinuclear clearing absent



Renal oncocytoma (Amin et al., 1997 Perez-Ordonez 1997)

- 150 cases
- Mean size 4.4cm (range 0.6-15cm)
- Gross or microscopic scar absent in 46% cases
- 42% cases had prominent nucleoli (equivalent to the nucleoli seen in Fuhrman grade III or IV renal cell carcinoma)
- Nuclear pleomorphism present in 50% cases and conspicuous in 12.5% cases, including foci of bizarre cells (extensive atypia in 30% cases in series of Perez-Ordonez et al., 1997)
- Nuclear chromatin when atypical appeared hyperchromatic/smudged/degenerate
- 9.7% cases had oncoblasts (30% in series of Perez-Ordonez et al., 1997)



Small cell variant of renal oncocytoma – a rare and misleading type of benign renal tumour (Hes *et al.*, 2001)

- 3/134 cases of oncocytoma dominated by a small cell component
- Two were thought to be malignant by referring pathologists
- Areas of more typical oncocytoma found in all three cases
- All were negative for chromogranin and synaptophysin



Renal oncocytoma

(Perez-Ordenez *et al.*, 1997; Amin *et al.*, 1997; Trpkov *et al* 2010)

Acceptable

- Nuclear pleomorphism
- Large nucleoli
- Macroscopic invasion of perinephric fat
- Mitoses (exceptional cases [$<2/10$ HPF; 1 regular MF in 2/80 cases])
- ?Vascular invasion (v rare)
- Focal clearing in hyalinised areas
- Limited foci ($<5\%$ area) with chromophobe-like histology
- Oncoblasts

Not acceptable

- Necrosis (minimal microscopic foci may be allowed)
- Atypical mitoses
- Mitosis in an area with cytological atypia
- Extensive clear, or papillary areas
- Sarcomatoid areas
- Gross involvement of renal vein



Renal oncocytoma

- May be related to intercalated cells of collecting ducts
- Two genetic groups:
 - losses of chromosomes 1 and Y (Crotty *et al.*, 1992)
 - translocations involving breakpoint 11q13 [t(5:11)(q35;q13) Fuzesi *et al*, 1998]



Renal oncocytoma – differential diagnosis

- Chromophobe renal cell carcinoma, eosinophilic variant
- Conventional (clear cell) renal carcinoma [if oncocytic area sampled e.g. on core biopsy]
- Epithelioid (oncocytoma-like) angiomyolipoma
- Renal cell carcinoma, unclassified (low grade, oncocytoma-like)



Chromophobe renal cell carcinoma

- Prominent cell boundaries ('plant cell' appearance)
- Prominent perinuclear haloes
- 'Raisinoid' nuclei
- Positive colloidal iron stain
- Two cell types *may* be seen
 - cells with abundant pale reticular cytoplasm
 - cells with eosinophilic finely granular cytoplasm



Chromophobe renal cell carcinoma

- Lipid and glycogen usually absent
- Numerous perinuclear 150-450nm microvesicles (EM) [rare subplasmalemmal clusters or single scattered microvesicles found in oncocytomas]
- Vesicles do not survive wax embedding
- Adequate sampling essential
- Genetics – hypodiploidy (monosomies 1, 2, 6, 10, 13, 17, 21, sex chromosomes)
- Abnormalities of mitochondrial DNA



Discriminant nuclear features of renal oncocytoma and chromophobe renal cell carcinoma (Tickoo and Amin 1998)

- 16 chromophobe carcinomas, 21 oncocytomas studied
- All chromophobe carcinomas had wrinkled "raisinoid" nuclei ('koilocytoid atypia')
- All oncocytomas had predominantly round, relatively uniform nuclei (19% had foci of "degenerative" nuclear atypia)
- Binucleation/multinucleation was significantly more common in chromophobe carcinoma (none had "degenerate" nuclear atypia)
- Nucleoli more commonly seen in oncocytoma



Eosinophilic and classic chromophobe renal cell carcinoma have similar frequent losses of multiple chromosomes from among chromosomes 1,2,6,10 and 17, and this pattern of genetic abnormality is not present in renal oncocytoma Brunelli M *et al* 2005;18:161-169



Immunohistochemical profile of common epithelial neoplasms arising in the kidney

Carbonic anhydrase 9 (CAIX)	c-kit (CD117)	CK7 (cyto/memb)	CK20 (cyto/memb)	Vimentin	GATA-3
Clear cell +ve	-ve	-ve (rare focal/weak, *1.3%+ve)	-ve	+ve	-ve
Papillary -ve	-ve	+ve (typically 80% at least in type 1, may be -ve in type 2)	-ve	+ve (variable)	-ve
Chromophobe -ve	+ve	+/- (peripheral accentuation noted in various series and increased by 20% as reported elsewhere) Note: "80% typical staining pattern" without (occasionally focal staining only)	-ve	-ve	-ve
Oncocytoma -ve	+ve	-/+ ve (Typical staining pattern - focal staining tubular cells or small groups of cells)	-ve	-ve (except scanty sclerotic tubules)	-ve
Collecting duct -ve/focal +ve	-ve	+/-	-ve/occasional +ve	+ve	-ve (80% cases)
Urothelial carcinoma +ve (f)	-ve	+ve (diffuse/strong)	-/+ (<50% cases +ve)	+ve (variable)	+ve (80%, 30% if accompanied by The Christie NHS West Yorkshire Trust)



Claudin 7

- Typically -ve to focally +ve on oncocytoma
- +ve in most cases of chromophobe carcinoma



The following three slides illustrate a cautionary tale in immunohistochemistry

Cytokeratin 14 immunoreactivity distinguishes oncocytic tumour from its renal mimics: an immunohistochemical study of 63 cases (Chu and Weiss, Histopathology 2001;39:455-462)

- 30 oncocytic tumours from various organs (8 renal oncocytomas); 33 renal cell carcinomas studied
- ABC method used for immunohistochemistry
- All 30 cases of oncocytic tumour reported to show cytoplasmic granular CK14 immunoreactivity
- CK14 found in 4/33 cases renal cell carcinoma (weak staining)
- Conclusion: "homogenous granular cytoplasmic CK14 is sensitive and specific for oncocytic tumours"



Renal oncocytomas do not express cytokeratin 14 (Folpe AL *et al* 2004)

- 30 renal oncocytomas examined for CK14 expression
- ABC method used
 - (i) 20 cases had routine avidin-biotin blocking -pre 1^o Ab
18/20 showed 3+ coarse granular staining
 - (ii) 10 cases had prolonged biotin blocking -pre 1^o Ab
all were entirely negative
 - (iii) 4 (of the above 10) were run as negative controls (no 1^o antibody) but with routine biotin blocking
all showed 2+ or 3+ positivity with granular pattern
- Oncocytomas are biotin-rich tumours with a potentially significant diagnostic pitfall



Can renal oncocytoma be differentiated from its renal mimics?
The utility of anti-mitochondrial, caveolin 1, CD63 and
cytokeratin 14 in the differential diagnosis (Mete *et al.*, 2005)

CK14 was of no value in differential diagnosis



S100A1: a powerful marker to differentiate chromophobe renal cell carcinoma from oncocytoma Li G *et al*

Histopathology 2007;50:642-647

- 14/15 (93%) oncocytomas were positive (coarse cytoplasmic) for S100A1 by immunohistochemistry
- All 9 chromophobe carcinomas were negative
- 6/9 clear cell carcinoma and 4/6 papillary renal carcinoma were positive
- S100A1 gene expression by RT-PCR correlated with the immuno results



Overexpression of KIT (CD117) in chromophobe renal cell carcinoma and renal oncocytoma (Pan *et al.*, 2004; Liu 2007; Allory *et al* 2008)

- 55-83% of chromophobe carcinomas +ve membrane staining
- 58-100% of oncocytomas +ve
- All 380 conventional RCC, 113 papillary RCC, 6 collecting duct and 6 unclassified RCCs –ve. All 23 angiomyolipomas –ve
- No c-kit mutations found
- Petit *et al.*, 2004 and Lui *et al*, 2007 found virtually identical immunohistochemical results



Cluster analysis of immunohistochemical profiles delineates CK7, vimentin, S100A1 and c-kit (CD117) as an optimal panel in the differential diagnosis of renal oncocytoma from its mimics Carvalho JC *et al.*

Histopathology 2011;58:169-179

- Tissue microarray study (3 cores from each tumour)
- S100A1 was positive in oncocytoma but negative in all but 1 of 16 chromophobe carcinomas (this marker is also expressed in papillary and clear cell carcinoma)



Colloidal iron staining in differential diagnosis (Tickoo *et al.*, 1998; Skinnider and Jones 1999)

Histological subtype

Staining pattern

Chromophobe RCC	→	Diffuse, strong, reticular
Oncocytoma	→	Focal weak, fine, dustlike
Clear cell RCC	→	Focal coarse droplets
Papillary RCC	→	Strong, coarse droplets



Diagnostic significance of mitochondria in four types of renal epithelial neoplasms (Erlandson *et al.*, 1997; Tickoo *et al*, 2000)

- Oncocytomas, chromophobe carcinoma, papillary and conventional (clear cell carcinoma) studied
- Mitochondrial cristae were tubulovesicular or mixed lamellar and tubulovesicular in chromophobe carcinomas, including the eosinophilic variant
- Mitochondria had lamellar cristae in oncocytomas, clear cell and papillary renal cell carcinomas
- Close relationship suggested between microvesicles in chromophobe carcinoma and mitochondria
- ?defective mitochondriogenesis may be the source of the microvesicles



Birt-Hogg-Dubé syndrome

Pavolich *et al Am J Surg Pathol* 2002;26:1542-1552; Cannata-Ortiz *et al* 2011

- Rare autosomal dominant condition
- Mutations in FLCN or BHD gene (17p 11.2)
- Benign hamartomatous skin lesions (fibrofolliculomas), pulmonary cysts with increased risk of pneumothorax and renal tumours
- Patients develop tumours with hybrid features between chromophobe carcinoma and oncocytoma 'hybrid oncocytic tumours' (HOCT)
- Tumours are typically multiple and/or bilateral
- A recent study in 2011, [abstract] (458 renal tumours from 68 BHD patients) found 54% were hybrid tumours; 39.5% were chromophobe carcinoma; 3% were clear cell carcinoma. 47% patients had multiple bilateral tumours. No patient with hybrid tumour(s) only developed metastatic disease



Renal oncocytosis: a morphologic study of fourteen cases

Tickoo SK *et al Am J Surg Pathol* 1999;23:1094-101



Metastatic renal oncocytoma

Oxley JD *et al J Clin Pathol* 2007;60:720-722

12cm renal tumour in radical nephrectomy with features of renal oncocytoma in 8 blocks taken

Metastases in liver 9 years later with identical histology

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

van der Kwast Th, Perez-Ordóñez B *J Clin Pathol* 2007;60:585-586 [Commentary]



Thorough sampling always required before a diagnosis of oncocytoma can be made!

A confident diagnosis of renal oncocytoma is not possible or recommended for renal core biopsies

