



## Immunohistochemistry Division

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## Focus on Immunohistochemistry – February 2001

### Immunophenotype of Renal Cell Carcinoma, “Clear Cell” Type

#### INTRODUCTION

Renal cell carcinoma of "typical" clear cell type is usually a straightforward diagnosis when one is examining the primary tumor, or a sizable biopsy of a metastatic deposit in a patient with a known renal mass. However, with the increasing use of less invasive biopsy techniques (such as fine needle aspiration cytology and thin needle biopsy), diagnostic pathologists are being required to do more and more with less and less (and with faster turnaround). As a result, it can be very difficult to definitively recognize renal cell carcinoma with a high degree of certainty in many of these types of specimens. Patients with known renal cell carcinoma may also develop lesions in other organs, and when fine needle aspiration biopsies or other small biopsies of such other lesions are obtained, it can be difficult to know whether these lesions represent metastatic disease or an unrelated process. In these situations, knowledge of the immunophenotype of clear cell carcinoma of the kidney can be extremely useful in providing specific and clinically useful diagnoses, frequently saving the patient the discomfort and expense of having to endure additional biopsy or other diagnostic procedures. In this situation, money spent on immunohistochemistry is certainly a wise investment in the overall scheme of patient care.

#### CLASSIC PHENOTYPE OF CLEAR CELL CARCINOMA OF KIDNEY

Below is the typical phenotype of clear cell carcinoma of the kidney, and this applies to tumors in this category of all histologic grade. It also applies to cases of the "granular cell variant" of renal cell carcinoma. It is important to note that the phenotype listed below **does not apply** to other types of renal cell tumor (such as chromophobe cell carcinoma,

collecting duct carcinoma, papillary carcinoma, oncocytoma, etc.), and space does not allow a discussion of those entities at this time. **LEGAL DISCLAIMER:** *There are exceptions to everything, so neither ProPath nor I bears any responsibility for use (or misuse) of the information below. In other words, if you blow the diagnosis on a case, you cannot sue us. (I only accept lawsuits if the stains have been done in my lab and my name is on the bottom line).*

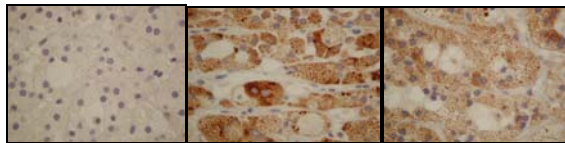
EMA	POS (may be focal)
CK-AE1/AE3	POS (a few cases neg)
CK-LMW (8,18)	POS (“100%”)
CK-HMW (34bE12)	Neg
CK-7	Neg (minority pos)
CK-20	Neg
Vimentin	POS (“100%”)
CEA (monoclonal)	Neg
CD10 (CALLA)	POS (90% of cases)
GCDFP-15	Neg
ER and PR	Neg
S100 protein	POS or Neg
TTF-1	Neg
Inhibin	Neg
MART-1 (A103)	Neg
CD117 (c-kit)	Neg
Villin	POS or Neg
Calretinin	Neg

This rather extensive list certainly does not mean to imply that every case requires use of all of the above antibodies to arrive at a definitive diagnosis. This is definitely not the case, and depending on the clinical situation, it may only take a small number of antibodies to address the clinical or pathological question posed by a particular clinical situation. When combined with knowledge of the

immunophenotype of common mimics of clear cell carcinoma of the kidney, the above list can serve as a guideline for selection of potentially useful markers.

### DISCUSSION OF SELECTED DIFFERENTIAL DIAGNOSTIC PROBLEMS:

**Renal cell carcinoma vs. Adrenal tumors:** Markers of potential utility in this situation include EMA, cytokeratin LMW, inhibin, A103, CD10 (CALLA), and perhaps calretinin. Adrenal tumors are characteristically negative for EMA and are generally negative for CD10 (CALLA), whereas renal cell tumors are positive for both of these markers in the large majority of cases. Adrenal tumors also frequently express inhibin and A103, markers that are absent in renal cell carcinoma. If given adequate tissue, the vast majority of renal cell carcinomas express cytokeratin LMW, a marker that may be absent in adrenal tumors. A number of adrenal tumors also express calretinin, which is not a feature of renal cell carcinoma.



Immunostains of a needle bx of an "intrarenal mass". The tumor cells were negative for EMA (left), and positive for A103 (middle) and inhibin (right), excluding renal cell carcinoma and confirming an adrenal cortical origin.

### Renal cell carcinoma vs. Breast carcinoma:

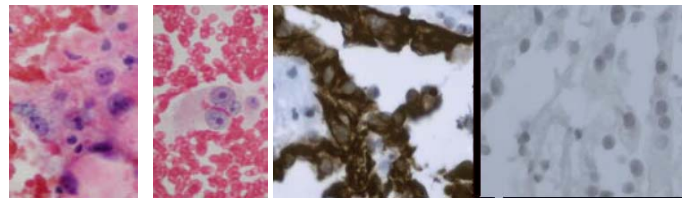
Expression of cytokeratin HMW is common in breast carcinoma, and expression of this marker alone is sufficient to exclude renal cell carcinoma. Many breast carcinomas do not express vimentin, and its absence in a tumor renders renal cell carcinoma highly unlikely. Obviously, expression of GCDFP-15 or estrogen receptors favors breast carcinoma over renal cell carcinoma. Strong and uniform expression of cytokeratin 7 or expression of monoclonal CEA also favors breast carcinoma.

### Renal cell carcinoma vs. Lung carcinoma:

Expression of cytokeratin HMW and monoclonal CEA is common in many lung carcinomas, and the identification of either of these markers excludes renal cell carcinoma. Also, the lack of expression of vimentin renders renal cell carcinoma highly unlikely. Other markers of potential utility include TTF-1 (expressed in roughly 75% of pulmonary adenocarcinomas but absent in renal cell carcinoma) and cytokeratin 7 (which is commonly strongly expressed in lung carcinomas).

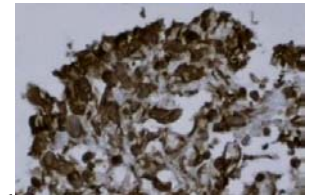
**Renal cell carcinoma vs. Hepatoma:** Like renal cell carcinoma, hepatoma lacks expression of cytokeratin HMW and monoclonal CEA, but both tumors express cytokeratin LMW. If strong expression of cytokeratin AE1/AE3 is identified, this favors renal cell carcinoma, since hepatomas are frequently

negative for AE1/AE3, or show only focal or weak reactivity with this reagent. In addition, hepatomas are characteristically negative for vimentin (in contrast to renal cell carcinoma), so vimentin is an important marker in this situation. EMA is absent in most hepatomas, although occasionally EMA may show a canalicular pattern in some hepatomas. (Other markers that may highlight a canalicular pattern in hepatomas include polyclonal CEA, villin, and CD10). Expression of HepPar1 also favors hepatoma. Although AFP commonly comes to mind when thinking of hepatomas, it actually is not one of the more useful markers, since its sensitivity for hepatoma is low, probably the range of 20%, although obviously the expression of this marker would favor hepatoma over renal cell carcinoma.



H&E stains (left 2 photos above) from an FNA of a lung mass on a patient also known to have a kidney mass. On morphology alone, the original pathologist could not distinguish lung carcinoma from metastatic kidney

carcinoma. The tumor cells were positive for CK-LMW (2<sup>nd</sup> from right above) but negative for CK-hmw, CEA, TTF-1, CK7, and CK20 (above right). The tumor cells were positive for vimentin and EMA (right). This phenotype strongly supported renal cell carcinoma, which was subsequently confirmed.



### Renal cell carcinoma vs. Seminoma:

EMA is an important marker in this differential diagnosis, since EMA is absent in seminoma (but present in renal cell carcinoma). Although many seminomas lack cytokeratin LMW, a certain percentage express this marker, often in a perinuclear glob pattern. Most of the seminomas that I have studied have also been negative for vimentin (with a few exceptions), and the absence of vimentin argues against renal cell carcinoma. Expression of CD117 (c-kit) is very common in seminoma, but not a feature of renal cell carcinoma. PLAP is not useful in this differential diagnosis, since it may be expressed by both renal cell carcinoma and seminoma.

### CONCLUSION:

Knowledge of the spectrum of reactivity and expected immunophenotypic patterns in renal cell carcinoma and its mimics can greatly assist in the cost-effective care and management of patients who suffer from these neoplasms.

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