

PROPATH

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Immunohistochemistry

High Molecular Weight Cytokeratin (34 β E12)

May 2002

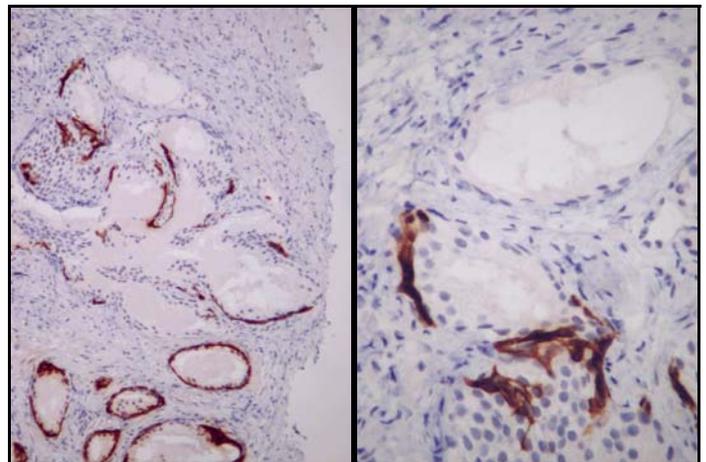
by Rodney T. Miller, M.D., Director of Immunohistochemistry

Antibodies to high molecular weight cytokeratin (CK-HMW) (clone 34E1 β 2) are commonly used by diagnostic surgical pathologists. This month, we briefly review the main diagnostic uses of high molecular weight cytokeratin.

CK-HMW in Prostate Pathology: The utility of CK-HMW in the interpretation of difficult prostate biopsies is firmly established. As is well known, the identification of an associated CK-HMW-positive basal layer in an atypical small gland proliferation excludes the possibility of invasive prostate adenocarcinoma. Conversely, invasive prostate adenocarcinomas do not contain an associated CK-HMW-positive basal layer around the proliferating neoplastic small glands of interest. One important point to know about CK-HMW in prostate biopsies is that occasionally small individual acinar structures on the very periphery of a benign prostate lobule may lack an associated CK-HMW-positive basal layer. Therefore, by itself, the complete absence of CK-HMW around 1 or 2 small acinar structures does not necessarily mean that they represent carcinoma. As such, there is a certain quantitative aspect that comes into play when deciding how many glands must lack stainable CK-HMW before a confident diagnosis of adenocarcinoma can be rendered. I do not know of any precise number of glands lacking CK-HMW that is required to diagnose adenocarcinoma, although undoubtedly this number varies among pathologists and will also vary depending on the degree of associated cytologic atypia and other features of a particular biopsy. An additional point to know is that occasional prostate adenocarcinoma cells may express CK-HMW, so the presence of this marker in a cell does not necessarily mean that it represents a prostatic basal cell. However, it is highly unusual for CK-HMW to be strongly and diffusely expressed in prostatic adenocarcinoma (and indeed, I have never personally observed it). Parenthetically, cytokeratin 5/6 and p63 have also been used by

some authors as markers of prostatic basal cells.

When dealing with transurethral resection specimens it is important to realize that thermal artifact may damage CK-HMW and make it more difficult to detect, so caution is advised in interpreting “negative” immunostains in areas of prostate tissue showing thermal artifact.



CK-HMW immunostain on prostate, showing partial loss or discontinuity of CK-HMW positive basal cells on the peripheral aspects of a benign lobule (left). This may result in occasional individual benign acini that completely lack an associated CK-HMW positive basal layer (right, top)

CK-HMW in Carcinomas of Unknown Primary Origin:

Knowledge of the typical spectrum of CK-HMW in different types of epithelial tumors can assist greatly in selected cases of tumor of unknown primary origin. There are certain tumors that characteristically lack significant expression of CK-HMW, and therefore the identification of CK-HMW in a tumor of unknown origin can serve to place these possibilities low on the list and direct the search for a primary site elsewhere.

Renal cell carcinoma of clear cell type is one of the tumors that characteristically lacks CK-HMW. Since this is a common neoplasm that may morphologically mimic a variety of other tumors, identification of significant CK-HMW in a tumor of unknown origin renders a renal cell carcinoma of clear cell type extremely unlikely. Many pathologists have seen cases of patients with a prior history of renal cell carcinoma who subsequently develop lung tumors, and if the lung tumor has clear cell features, morphology alone is frequently not able to distinguish metastatic renal cell carcinoma from a primary pulmonary carcinoma with clear cell features. In this situation, identification of CK-HMW (even if focal) in the pulmonary tumor renders metastatic renal cell carcinoma of clear cell type highly unlikely (including cases of the granular cell variant of clear cell renal carcinoma). Other tumors that may enter into the differential diagnosis in selected patients (such as breast carcinoma, transitional cell carcinoma, etc.) frequently also express CK-HMW, assisting in their distinction from renal cell carcinoma. Focal CK-HMW has been reported in a few chromophobe cell carcinomas, and I have also seen focal CK-HMW in high-grade papillary renal cell carcinoma, so that point is worth remembering if the morphology suggests those as possibilities.

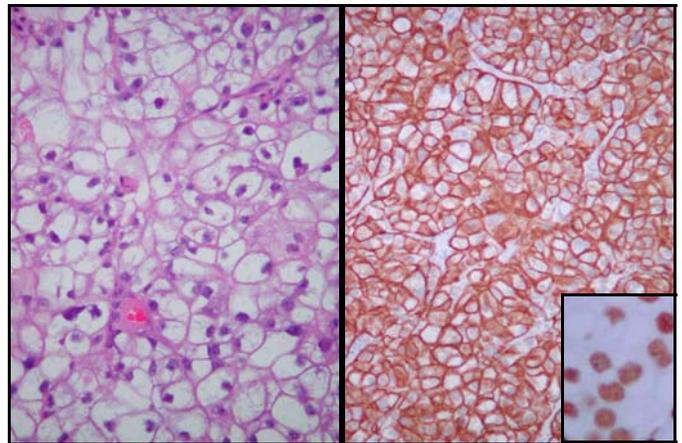
Hepatoma also characteristically lacks expression of CK-HMW, and therefore the expression of significant CK-HMW in a liver tumor provides strong evidence against the interpretation of primary hepatocellular carcinoma. Hepatoma also characteristically lacks expression of cytokeratin AE1/AE3 or expresses it in only a focal weak fashion, so that antibody (actually a cocktail of two antibodies) also frequently has great utility in attempting to differentiate hepatoma from other tumors with similar morphology.

Squamous Cell Carcinoma characteristically expresses CK-HMW in a strong and diffuse fashion. Therefore, the lack of this finding in a poorly differentiated tumor renders squamous cell carcinoma highly unlikely. Although squamous cell carcinomas may also express strong and diffuse low molecular weight cytokeratin (CK-LMW) (particularly when they become very poorly differentiated), a tumor that shows a marked predominance of CK-HMW over CK-LMW is likely to be squamous in nature (and can often be confirmed by strong and diffuse staining with cytokeratin 5/6 and strong diffuse nuclear expression of p63).

Prostate Adenocarcinoma, as mentioned above, also typically lacks expression of CK-HMW, although on occasion these tumors may show occasional scattered

positive cells. However, the identification of strong and diffuse reactivity with CK-HMW renders prostatic adenocarcinoma extremely unlikely. If such a tumor is arising in the prostate, it is likely to be a squamous carcinoma (which may occur rarely in the prostate), or even more likely, it may actually represent a high-grade transitional cell carcinoma of the bladder that is secondarily invading the prostate.

In summary, identification of significant reactivity with CK-HMW in a carcinoma of unknown primary origin renders renal cell carcinoma of clear cell type, hepatoma, and prostate carcinoma extremely unlikely.



85 year-old female presented with metastatic disease, including tumor in the lung, liver, and kidney. H&E examination of a lung needle biopsy showed a clear cell carcinoma (left). Subsequent CK-HMW immunostaining was strongly positive (right), excluding the possibilities of metastatic clear cell carcinoma of kidney and metastatic clear cell hepatoma. The tumor was strongly positive for TTF-1 (inset) and CEA, conclusively establishing the diagnosis of clear cell carcinoma of primary pulmonary origin.

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