PROPATH
THE FOCUS
Immunohistochemistry

Immunohistochemistry in the differential diagnosis of clear cell carcinomas from the kidney, liver, and lung

April 2005

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

Clear cell carcinoma is a common specimen seen by many surgical pathologists. Given an appropriate clinical context (for example, a patient with a large kidney mass), determining the nature and origin of a clear cell carcinoma can be very easy. However, in other situations this can be a challenging task, primarily because of the tremendous degree of overlap in the morphologic appearance of clear cell carcinomas from different primary sites. This month, we discuss the utility of a number of immunostains in the differential diagnosis of the more common types of clear cell carcinoma.

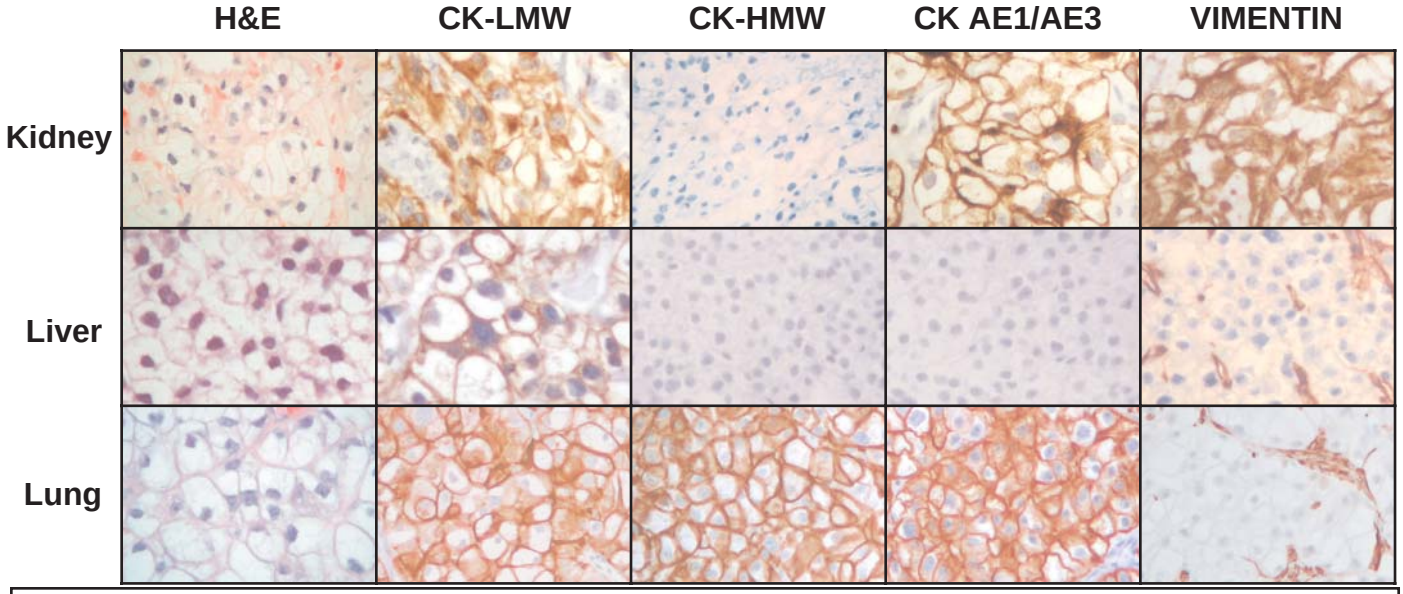
Clear cell carcinoma can arise as a primary site in virtually any organ in the body. It is also well known that there are many other types of clear cell neoplasms, including mesenchymal, melanocytic, neuroendocrine, and even lymphoid clear-cell tumors. However, if we limit our discussion to clear cell carcinomas, in our consultation service at ProPath the most common primary sites that we see are kidney, lung, and liver (clear cell hepatoma).

Low molecular weight cytokeratin should be performed in essentially all of these cases, primarily to document the fact that you are indeed dealing with a carcinoma, rather than another type of clear cell neoplasm. Virtually all clear cell carcinomas of the kidney and clear cell hepatomas express low molecular weight cytokeratin, although on some occasions the expression may be focal or weak. Most clear cell carcinomas of the lung also express low molecular weight cytokeratin, although there is a subpopulation of clear cell squamous carcinomas that may lack staining with this reagent (these tumors stain with high molecular weight cytokeratin).

High molecular weight cytokeratin (clone 34βE12) is a very useful reagent to approach this differential diagnosis. In the vast majority of cases, clear cell carcinoma of the kidney and clear cell hepatoma are completely negative for reactivity with this antibody. As such, if substantial high molecular weight cytokeratin reactivity is observed, you are usually safe crossing kidney and liver off of your list of potential primary sites. Parenthetically, to my knowledge substantial expression of high molecular weight cytokeratin also renders adrenal cortical carcinoma highly unlikely.

Cytokeratin AE1/AE3 is worthwhile to employ in this situation, primarily because most hepatomas are negative or only focally weakly reactive for this antibody. We have seen a small number of hepatomas that express strong cytokeratin AE1/AE3, but they represent <5% of the cases of hepatoma that we see on our consultation service. As such, strong reactivity with AE1/AE3 usually allows one to place clear-cell hepatoma much lower on the list of potential primary sites. The large majority of lung carcinomas express AE1/AE3, and most clear cell carcinomas of the kidney also express AE1/AE3, although it may be patchy and weak, a point to keep in mind when dealing with a small sample of tumor.

Vimentin is an important antibody for approaching this differential diagnosis. The vast majority of hepatomas are negative for vimentin, whereas



Typical immunostaining result in clear cell carcinoma of the kidney, clear cell carcinoma of the lung, and clear cell hepatoma

Clear cell ca	CK-LMW	CK-HMW	AE1/AE3	Vimentin	TTF-1	CEAm
Liver	+	-	- (few foc+)	- (rare foc+)	-	-
Kidney	+	-	+ (rare-)	+	-	-
Lung	+(rare-)	+(few-)	+	+ or -	+ or -	+ or -

Expected immunophenotype observed in most clear cell carcinomas of the liver, kidney, and lung

essentially all clear cell carcinomas from the kidney express vimentin. As such, substantial expression of vimentin argues against clear-cell hepatoma. Clear cell lung carcinoma expresses vimentin in a variable fashion, some cases positive, some cases negative.

Because of its specificity for lung tumors, **TTF-1** is worth adding to the antibody panel, since reactivity with TTF-1 argues in favor of pulmonary primary origin (although clear-cell squamous carcinoma of lung is TTF-1 negative). We have never seen TTF-1 reactivity in renal cell carcinoma or in hepatoma.

Monoclonal CEA (we prefer clone COL1) can also be of use in this situation, since clear cell carcinoma of the kidney and clear-cell hepatoma are negative for monoclonal CEA (although we have seen a small number of hepatomas that show a focal canalicular pattern of staining with monoclonal CEA, similar to but substantially weaker than the canalicular pattern that can be seen with polyclonal CEA). A significant proportion of pulmonary clear cell carcinomas express CEA, which if present argues against kidney and liver origin.

By employing this relatively small panel of antibodies, one can often determine the most likely possibility for primary origin of a clear cell carcinoma. In some situations, additional immunostains may be required to firm up the diagnosis, but that discussion is beyond the scope of this newsletter.

Rodney T. Miller, M.D.
Director of Immunohistochemistry
214-237-1631 • Fax 214-237-1770
rmiller@propathlab.com

Prior Editions are available for download on our website.

PROPATH
The Leader in Pathology Services

8267 Elmbrook Dr, Ste 100 • Dallas, Texas 75247-4009
(214) 638-2000 • Fax: (214) 905-3457
www.propathlab.com