

## Cytokeratin AE1/AE3

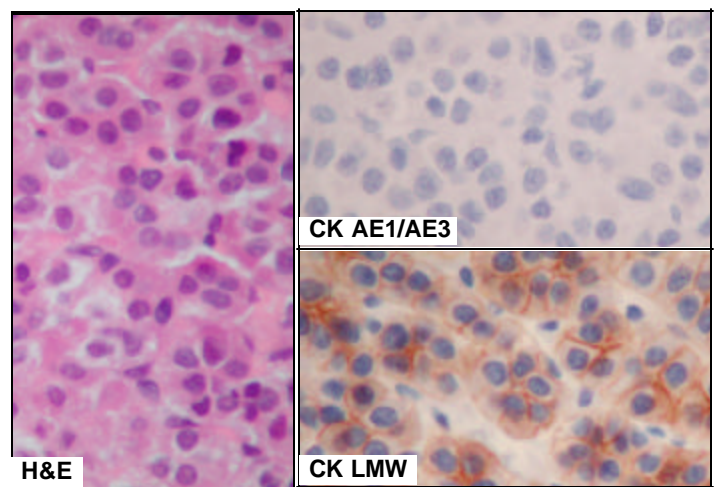
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This month, we review the spectrum of reactivity and the utility of cytokeratin AE1/AE3, a very commonly used reagent in diagnostic immunohistochemistry.

As its name implies, cytokeratin AE1/AE3 is a mixture of two different clones of anti-cytokeratin monoclonal antibodies, AE1 and AE3. Both of these individual clones detect certain high and low molecular weight keratins. AE1 detects the high molecular weight cytokeratins 10, 14, 15, and 16, and also the low molecular weight cytokeratin 19. Clone AE3 detects the high molecular weight cytokeratins 1, 2, 3, 4, 5, and 6, and the low molecular weight cytokeratins 7 and 8. By combining these two reagents, a single reagent with a broad spectrum of reactivity against both high and low molecular weight cytokeratins is obtained. Notably absent from this cocktail is reactivity to cytokeratin 18, one of the simple epithelial cytokeratins (along with cytokeratin 8), that is expressed in hepatoma and many other carcinomas.

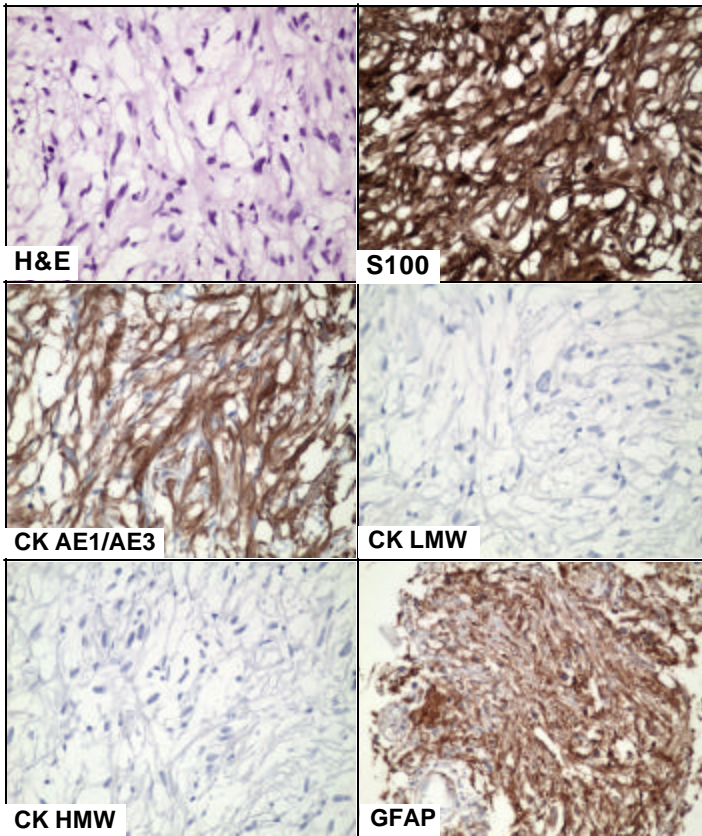
Because of its broad reactivity, cytokeratin AE1/AE3 has been referred to as a "pancytokeratin" by some pathologists. However, since it does not detect all cytokeratins (such as 17 and 18), it is not really a pancytokeratin reagent. Personally, I think the use of the term "pancytokeratin" in diagnostic reports is counterproductive, since if not further qualified, this term does not provide information on the particular clones present within the reagent used, information that can be of critical importance in a number of differential diagnostic situations. In addition, I fear that some pathologists may be lulled into a false sense of security by assuming that a negative "pancytokeratin" stain rules



*Photomicrographs of scalp nodule from a 65 year old man. The cytokeratin AE1/AE3 was completely negative, but the cytokeratin LMW stain was positive. This provided the first clue to the correct diagnosis of metastatic hepatocellular carcinoma.*

out an epithelial neoplasm, which is clearly not the case with a so-called "pancytokeratin" reagent like cytokeratin AE1/AE3.

There are several important points that must be kept in mind when studying tumors with cytokeratin AE1/AE3. Although it can be used as a reasonably effective "epithelial screen" to search for epithelial differentiation in poorly differentiated malignant tumors, as implied above, it is important to recognize that a negative cytokeratin AE1/AE3 stain by itself is not sufficient evidence to rule out carcinoma. The most common carcinoma that is negative for cytokeratin AE1/AE3 is hepatocellular carcinoma. In fact, hepatomas are characteristically negative or only



*Photomicrographs from a fine needle biopsy of a pleural mass in 64 year old female. The strongly positive S100 supported the H&E impression of schwannoma, but the strongly positive cytokeratin AE1/AE3 was at first perplexing. However, Cytokeratin LMW and HMW were negative, making an epithelial tumor highly unlikely. As expected in this situation, the tumor cells expressed strong GFAP. As such, this case represents a schwannoma with expression of GFAP, accompanied by strong AE1/AE3 expression, a common feature of GFAP-containing tumors.*

focally weakly positive with cytokeratin AE1/AE3. Undoubtedly, this is a reflection of the fact that cytokeratin AE1/AE3 does not react with cytokeratin 18, one of the principal cytokeratins that is expressed in hepatoma. Also, I have seen a significant number of renal cell carcinomas that have been negative with cytokeratin AE1/AE3, and also a number of adrenal, prostate, and neuroendocrine carcinomas that have been negative with this reagent. In these situations, the tumor is nearly always reactive with antibodies to low molecular weight cytokeratin (8 and 18), recognized by clones CAM5.2, 5D3, Zym5.2, or similar reagents. Because of the inability of cytokeratin AE1/AE3 to detect all carcinomas, in my own practice, I generally try to make certain that the tumor is negative for cytokeratin AE1/AE3, low molecular weight cytokeratin, and high molecular weight cytokeratin (34 $\beta$ E12)

before I feel comfortable excluding the possibility of epithelial differentiation.

The other interesting feature of cytokeratin AE1/AE3 is that it typically stains glial tumors strongly, and sometimes other non-epithelial tumors that express glial fibrillary acidic protein (GFAP), such as schwannoma. Obviously, it is critical to keep this point in mind when faced with the differential diagnosis of high-grade glioma versus metastatic carcinoma in brain biopsies. In fact, one could argue that it is appropriate to avoid using cytokeratin AE1/AE3 in this context, since glial tumors that are strongly positive for cytokeratin AE1/AE3 are negative for low molecular weight cytokeratin (8, 18) and high molecular weight cytokeratin (34 $\beta$ E12). Therefore, employing low molecular weight cytokeratin and high molecular weight cytokeratin in this situation would lessen the risk of misinterpretation of cytokeratin AE1/AE3 reactivity as an accurate reflection of epithelial differentiation.

In summary, cytokeratin AE1/AE3 is a very useful antibody cocktail, but it has several limitations that must be kept in mind when using this reagent. If employing cytokeratin AE1/AE3 as a sole marker of epithelial differentiation as part of a diagnostic panel of immunostains, hepatocellular carcinoma will typically be missed, and a certain percentage of renal cell, adrenal, prostate, and neuroendocrine carcinomas will also go unrecognized as epithelial tumors. Secondly, it is important to realize that cytokeratin AE1/AE3 stains glial tumors strongly, and on occasion will also strongly stain mesenchymal neoplasms that express GFAP (such as schwannoma).

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