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Immunohistochemistry

Immunohistochemical Features of Squamous Differentiation

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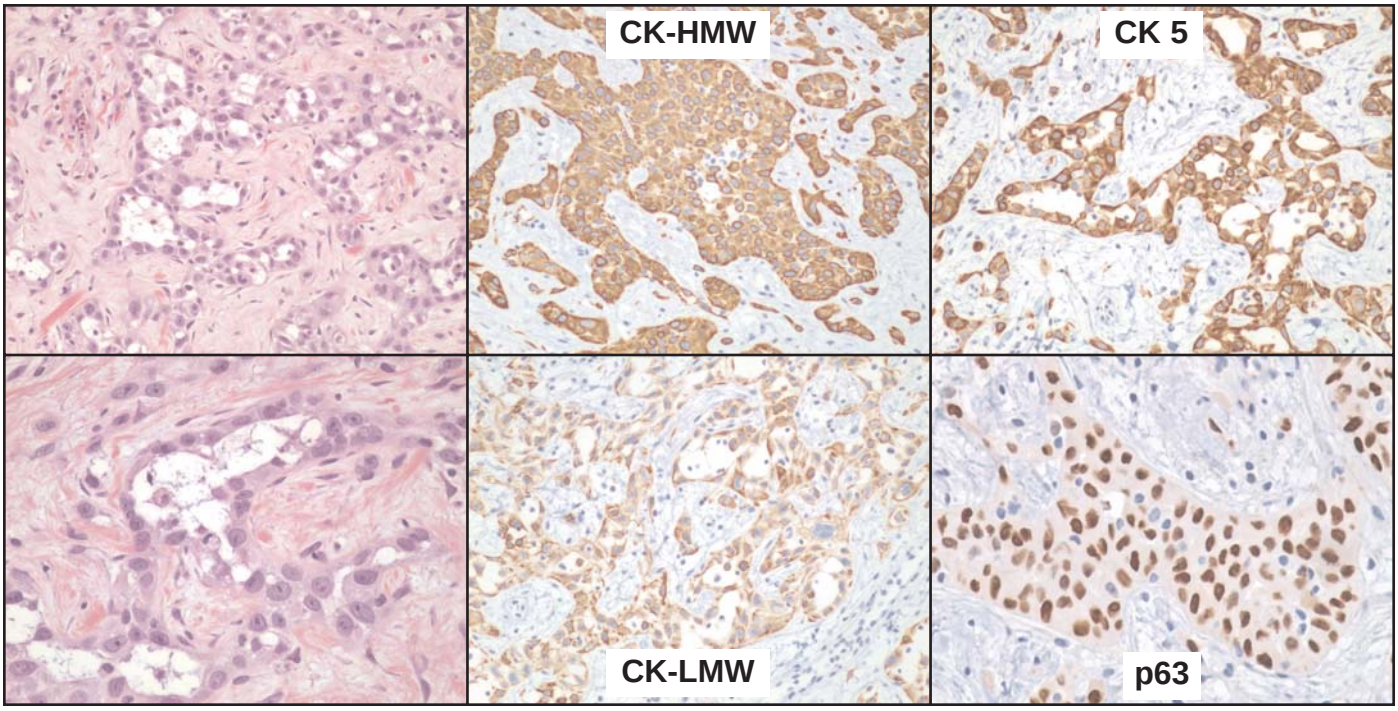
Squamous differentiation is a common finding in tumor pathology. As any experienced surgical pathologist knows, many different types of tumors can have "squamoid" morphologic features. However, appearances can be deceiving, and many "squamoid" tumors are not true squamous proliferations. When I was a pathology resident, I was taught that there are only two reliable morphologic features that reflect squamous differentiation: identification of intercellular bridges and tumor cell keratinization. Alas, these criteria are also imperfect. I have seen a number of urothelial carcinomas that show beautiful intercellular bridges (the first of which I misdiagnosed as a squamous carcinoma in my younger days), and when I look too hard at high magnification, I seem to be able to find them in many different tumors (just like “melanin pigment” in tumor cells). In some cases distinction of true keratinization from "pseudokeratinization" can be a challenging task, and I have seen tumor necrosis misinterpreted as tumor keratinization on multiple occasions (secondary to necrotic cell debris that I like to call "necrokeratin"). This month, we briefly review immunohistochemical features of squamous differentiation, in the hopes that this information will aid readers in recognizing true squamous tumors and distinguishing them from mimics.

One characteristic feature of squamous carcinomas is **strong and diffuse expression of high molecular weight cytokeratin (clone 34βE12)** (assuming of course, that your high molecular weight stain has good sensitivity). I have never seen a squamous carcinoma that has lacked this finding. It is not specific for squamous carcinoma, as other tumors may also demonstrate this as well. However, if a tumor does not express strong and diffuse high molecular weight cytokeratin, you are safe in concluding that it is not a squamous tumor.

Expression of low molecular weight cytokeratin (keratins 8 and 18, using clones 5D3, CAM5.2, Zym 5.2, or equivalent) is highly variable in squamous tumors. Many of the more poorly-differentiated squamous carcinomas express low molecular weight cytokeratin extensively. In contrast, the highly differentiated squamous carcinomas (that are morphologically so obvious that you would never think of having to resort to immunostains) may express little or no low molecular weight cytokeratin. The same can be said for expression of cytokeratin 7 in squamous tumors. As such, another clue to a squamous tumor may be a **marked predominance of expression of high molecular weight cytokeratin over low molecular weight cytokeratin**.

Expression of cytokeratin 5 (or cytokeratin 5/6) is analogous to the expression of high molecular weight cytokeratin in squamous tumors. With few exceptions, squamous tumors typically express **strong and diffuse cytokeratin 5**. An important point to keep in mind is that tumors besides squamous carcinomas may also express strong and diffuse cytokeratin 5, including mesothelioma, cutaneous basal cell carcinoma, cutaneous adnexal tumors, myoepithelial tumors, and some high grade breast carcinomas (see the July 2005 edition of this newletter for more information on these so-called



Photos from a scalp tumor of a 78 year-old male with a history of lung adenocarcinoma. The presence of gland-like formations led to an initial morphologic diagnosis of adenocarcinoma, thought to be metastatic. However, the immunostains show classic features of squamous carcinoma, including the predominance of high molecular weight over low molecular weight cytokeratin, and the strong and diffuse coexpression of cytokeratin 5 and nuclear p63. This case represents an example of the so-called "acantholytic" variant of squamous carcinoma, a known mimic of adenocarcinoma.

"basal-like" or "basaloid" breast cancers). As such, strong expression of cytokeratin 5 by itself is not sufficient to interpret the tumor as squamous in nature. Many different kinds of tumors express focal or patchy cytokeratin 5, and to my knowledge this finding does not have any particular significance (although in cases with squamous differentiation, cytokeratin 5 highlights these areas very nicely).

Nuclear expression of p63 is also a characteristic feature of the large majority (probably 80-90%) of squamous tumors. Again, it is not specific, as other tumors may also show this finding, including cutaneous basal cell carcinomas, cutaneous adnexal tumors, myoepithelial tumors, and urothelial carcinomas. In contrast to their frequent expression of cytokeratin 5, mesotheliomas are negative for p63.

When a squamous tumor is in the differential diagnosis, I always order both cytokeratin 5 and p63. In the appropriate diagnostic setting, **strong coexpression of cytokeratin 5 and nuclear p63 is virtually diagnostic of squamous differentiation**. There are a few other things that may coexpress these two markers in a strong and diffuse fashion, including basal cell carcinoma, cutaneous adnexal tumors, and myoepithelial tumors, so if those possibilities are in the differential diagnosis, additional markers may need to be employed.

In summary, squamous tumors virtually always show strong and diffuse expression of cytokeratin HMW, and they may show a predominance of high molecular weight over low molecular weight cytokeratin. Additionally, they typically show strong and diffuse expression of cytokeratin 5 and nuclear p63. Use of these markers should be of value in the identification of squamous tumors when they enter into the differential diagnosis of a problem case.

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