

## Immunohistochemistry Division

8267 Elmbrook, Suite 100, Dallas, Texas 75247-4009

Lab (214) 638-2000, ext 2037, Fax (214) 237-1730

Website: [www.propathlab.com](http://www.propathlab.com) E-mail: [rmiller@propathlab.com](mailto:rmiller@propathlab.com)

## Focus on Antibodies - December 2000

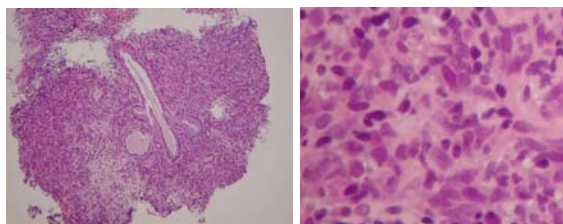
### Cytokeratin 5/6

**Cytokeratin 5/6** (CK 5/6) is a very useful antibody in diagnostic surgical pathology. One of the most important aspects of this marker is that it characteristically stains squamous carcinomas strongly and diffusely, but generally stains adenocarcinomas focally, weakly, or not at all. As such, it can be used as a marker of squamous differentiation when trying to assess the nature of poorly differentiated carcinomas. At ProPath, we use this marker commonly in the following situations:

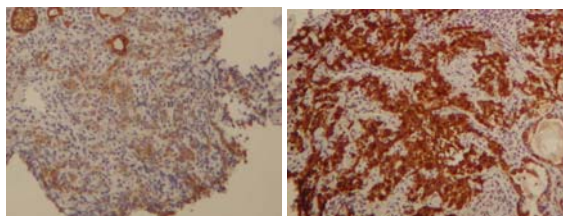
**Confirmation (or exclusion) of squamous differentiation.** Classically, pathologists are taught that squamous differentiation can be recognized by either the identification of intercellular bridges or cytoplasmic keratinization on standard H&E sections. However, anyone with substantial experience in diagnostic pathology knows that the identification of these features can be highly subjective, and often carcinomas are diagnosed as squamous in origin based on a "squamoid" appearance on the H&E section. Unfortunately, however, this "squamoid" appearance can be very misleading, as similar features can be observed in many poorly differentiated adenocarcinomas as well. In this situation, the identification of strong and diffuse reactivity with CK 5/6 provides strong supportive evidence for a squamous tumor. Conversely, the lack of expression of CK 5/6 renders a squamous tumor highly unlikely. CK 5/6 can be particularly useful in dealing with small biopsy specimens (lung, cervix, etc), where the differential diagnosis includes poorly differentiated squamous cell carcinoma (composed of small cells) vs poorly differentiated adenocarcinoma vs. small cell carcinoma.

### **Diagnosis of Variants of Squamous**

**Carcinoma.** Because **lymphoepithelioma** represents a poorly differentiated variant of squamous carcinoma, CK 5/6 can be used as a confirmatory immunostain to recognize this tumor, since lymphoepitheliomas express strong and diffuse CK 5/6. In biopsy specimens this tumor can be quite subtle and difficult to recognize, particularly when it presents as a metastatic lesion, illustrated nicely in the photomicrographs below.



H&E sections of bronchial bx on an elderly woman with a lung lesion. A reactive or inflammatory lesion was considered by several pathologists who reviewed the H&E.

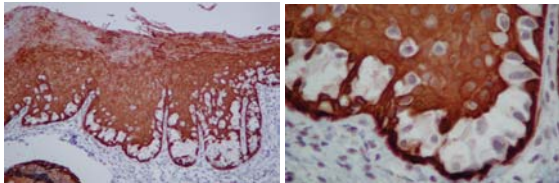


Immunostains (low power) for CK low molecular weight (8,18) (left) and CK 5/6 (right). There is only weak reactivity with CK-lmw, but intense reactivity with CK 5/6. In conjunction with the morphology, this finding was interpreted as supporting the diagnosis of "lymphoepithelioma-like" carcinoma of the lung. However, further history obtained from the referring pathologist indicated that the patient had a nasopharyngeal carcinoma diagnosed 1 year earlier. At that point, the tumor was felt to reflect metastatic nasopharyngeal carcinoma (lymphoepithelioma).

In addition to lymphoepithelioma, CK 5/6 also stains other variants of squamous carcinoma,

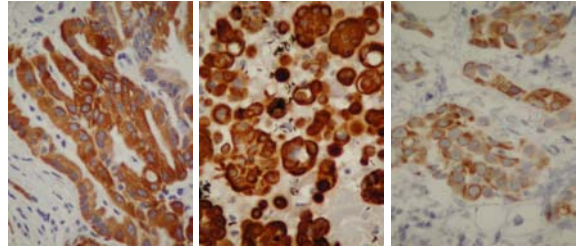
including **basaloid squamous carcinomas** and **papillary "squamotransitional" carcinomas** of the uterine cervix, so it can be very useful in identifying these unusual variants of squamous carcinoma. Other tumors that characteristically show strong staining with CK5/6 include **cutaneous basal cell carcinomas** and some other types of **cutaneous adnexal tumors** (such as microcystic adnexal carcinoma, eccrine poroma, spiradenoma, and some cases of sebaceous carcinoma).

**Diagnosis of Paget's Disease:** As previously discussed in the September 2000 issue of ProPath's Focus on Immunohistochemistry, since CK 5/6 does not stain neoplastic cells of Paget's disease strongly and diffusely, but does stain Bowen's disease in this fashion, it is an important marker of value in that differential diagnosis.



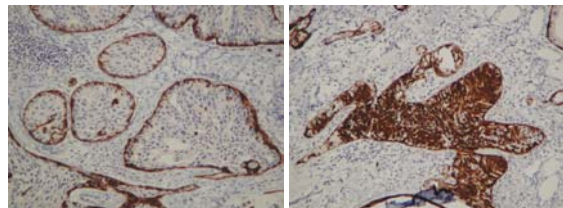
CK 5/6 immunostains on a case of vulvar Paget's disease, showing lack of staining of the intraepidermal Paget's cells, with strong staining of squamous cells.

**Diagnosis of Epithelial Mesothelioma:** With rare exceptions, the only tumor with glandular morphologic features that shows strong diffuse staining with CK5/6 is epithelial mesothelioma, so this fact can be exploited in its diagnosis. At ProPath we have seen several cases of epithelial mesothelioma presenting as metastatic disease (one in the subcutaneous tissue of the abdomen, and one as a cervical lymph node metastasis), and in such cases, strong reactivity of the tumor cells with CK5/6 may provide the first hint that the tumor is actually a mesothelioma, rather than a metastatic adenocarcinoma. (Parenthetically, strong expression of CK 5/6 is not universal in mesothelioma, and in our experience calretinin is a more useful single "positive" marker of mesothelioma). CK 5/6 staining of sarcomatoid or desmoplastic mesotheliomas is reportedly weak or negative, so that must also be kept in mind. Obviously, since squamous carcinomas express CK 5/6 strongly, this marker will not allow the distinction of squamous ca vs. mesothelioma.



CK 5/6 immunostains on 3 epithelial mesotheliomas, present in a pleural needle bx specimen (left), a pleural fluid cell block specimen (center), and a mesothelioma presenting as a soft tissue metastasis in the subcutaneous tissue of the abdomen (right). In the last case, the original H&E diagnosis rendered was metastatic adenocarcinoma, and an extensive 6 week workup for a primary site followed, which was negative. At this point immunophenotyping allowed the diagnosis of metastatic mesothelioma to be rendered, and mesothelioma was confirmed on a subsequent pleural fluid specimen.

**Differential diagnosis of breast DCIS vs epithelial hyperlasia:** There is a recently published paper (4) that reports CK 5/6 may be a useful adjunct in the interpretation of problematic breast biopsies, where the distinction of DCIS or atypical hyperplasia from florid hyperplasia may be difficult on morphology alone. These authors noted that >95% of cases of atypical ductal and lobular hyperplasia and DCIS were negative for CK 5/6, whereas areas of florid epithelial hyperplasia stained strongly. Since this report is so recent, we have not yet had the opportunity at ProPath to thoroughly evaluate these findings, although small numbers of cases studied in our lab have agreed with these reported results.



CK 5/6 immunostains are negative in the cells of DCIS (left), but are strongly positive in an area of epithelial hyperplasia (right). Note that CK 5/6 stains myoepithelial cells on the periphery of the ducts involved by DCIS (left).

#### REFERENCES:

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2. Am J Surg Pathol 22(10):1215-21, 1998
3. Adv Anat Path 5(1):53-60, 1998
4. Histopathol 37:232-240, 2000

Rodney T. Miller, M.D.  
Director of Immunohistochemistry  
(214) 237-1631 [rmiller@propathlab.com](mailto:rmiller@propathlab.com)