

Immunohistochemistry Division

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

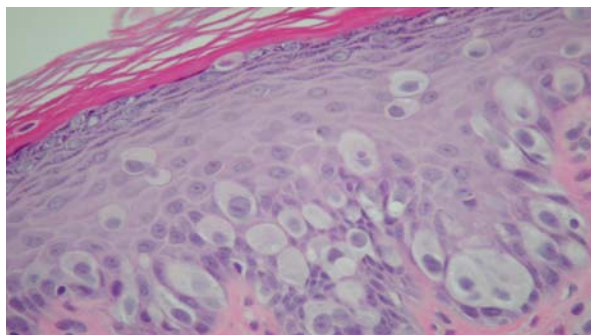
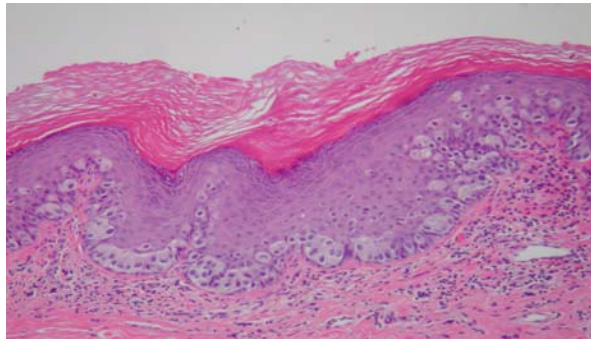
Lab (214) 638-2000, ext 2037, Fax (214) 237-1730

<http://www.propathlab.com/> E-mail: rmiller@propathlab.com

Focus on Antibodies - September 2000

Antibodies Useful in the Diagnosis of Cutaneous Paget's Disease

Paget's disease of the skin is a relatively common form of intraepidermal adenocarcinoma that is often easy to diagnose on H&E examination in florid cases. However, in certain situations, distinguishing Paget's disease from Bowen's disease (intraepidermal squamous carcinoma) and melanoma can be difficult, a fact well known to diagnostic surgical pathologists.

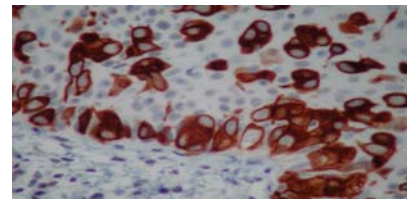
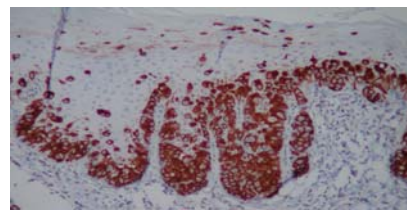


H&E sections of a vulvar biopsy on a 68 year old female. The differential diagnosis included Paget's disease vs. melanoma.

When the diagnosis of Paget's disease requires the use of ancillary methods, immunohistochemistry (IHC) can be an

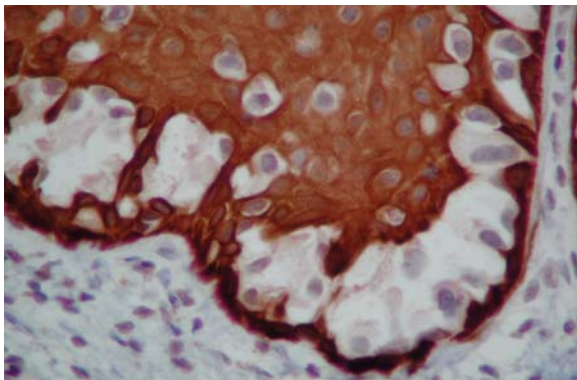
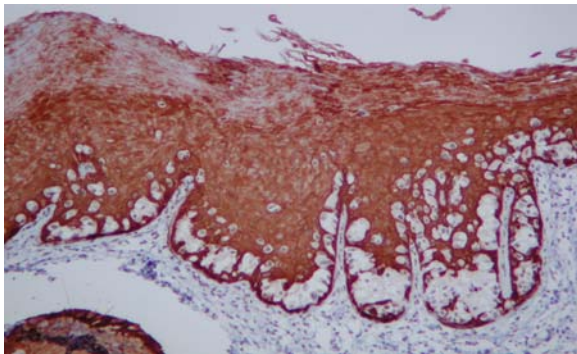
indispensable tool to aid in the accurate classification of these biopsies. A number of antibodies that may be useful in this situation are discussed below.

Cytokeratin 7: Neoplastic cells of Paget's disease express large amounts of cytokeratin 7, so immunostains for cytokeratin 7 characteristically highlight Paget's cells very nicely. One exception to this finding is in some cases of perianal Paget's disease associated with underlying rectal carcinoma. In these cases, the Paget's cells may express Cytokeratin 20 and lack expression of Cytokeratin 7. Unfortunately, some cases of Bowen's disease also express strong cytokeratin 7, so a marker of squamous differentiation is also recommended.



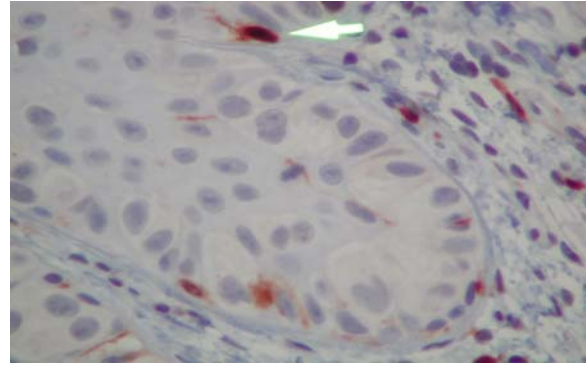
These photomicrographs depict the strongly positive cytokeratin 7 immunostain on the vulvar biopsy at low (left) and high (right) power, highlighting the Paget's cells. This type of strong staining with Cytokeratin 7 essentially excludes melanoma.

Cytokeratin 5/6: This is an excellent marker of squamous differentiation, so it can be very useful in identifying Bowen's disease. Characteristically, squamous carcinomas (and normal squamous epithelium) express cytokeratin 5/6 strongly and diffusely, so it highlights the benign squamous epithelium in the background, and will stain those cases of Bowen's disease that express cytokeratin 7, allowing distinction of Bowen's disease from Paget's disease. (Although a few scattered cells in Paget's disease may show expression of cytokeratin 5/6, Paget's disease lacks the strong and diffuse expression of cytokeratin 5/6 that is observed in cases of Bowen's disease).



These immunostains for cytokeratin 5/6 highlight the benign squamous cells in the epithelium, but the Paget's cells do not stain. In the case of Bowen's disease, the atypical cells in the epithelium would also show strong diffuse immunoreactivity with cytokeratin 5/6, similar to that observed in the background benign squamous epithelium.

S100 Protein: S100 protein stains the vast majority of melanoma cells strongly, including intraepidermal melanoma. Therefore, this is a useful marker to employ in cases where melanoma is in the differential diagnosis. Some cases of Paget's disease may also express S100 protein, so it is crucial to include markers of epithelial differentiation in the panel of immunostains, such as cytokeratin 7 and cytokeratin 5/6.



This S100 immunostain on the vulvar biopsy highlights a number of normal cellular elements (such as melanocytes or Langerhan's cells, see arrow), but the Paget's cells in this case are negative for this marker. In conjunction with the positive cytokeratin 7 stain and the negative cytokeratin 5/6 stain, the diagnosis of Paget's disease is firmly established.

POSSIBLE TRAPS:

Some authors have noted that "Toker cells" in the nipple epidermis also express cytokeratin 7, so attention must be paid to morphologic features to make certain that there is sufficient cytologic atypia in these cases to warrant a malignant interpretation. Normal intraepidermal Merkel cells may also be cytokeratin 7 positive. Some authors have also reported the finding of cytokeratin 7 positive cells in the nipple epidermis when there is an underlying benign proliferative nipple duct lesion, but in this situation, the cells in question are cytologically bland. In some cases of perianal Paget's disease, addition of cytokeratin 20 is also suggested to identify cases that may be associated with an underlying rectal carcinoma. Some authors suggest including PSA and prostatic acid phosphatase stains in male patients.

CONCLUSION:

In most cases, the differential diagnosis of Paget's disease of the skin vs. melanoma vs. Bowen's disease can be effectively addressed using immunostains to cytokeratin 7, cytokeratin 5/6, and S100 protein.

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