

# PROPATH

## THE FOCUS

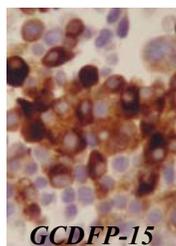
### Immunohistochemistry

## Breast Carcinoma vs. Pulmonary Adenocarcinoma

July 2002

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

Some authors have estimated that 4-9% of patients with breast carcinoma will eventually develop second pulmonary carcinomas. As a result, many pathologists have been faced with the problem of trying to determine whether a particular lung carcinoma represents metastatic breast carcinoma or a new primary pulmonary adenocarcinoma. This month, we will briefly review antibodies that may be useful in addressing this differential diagnostic problem.



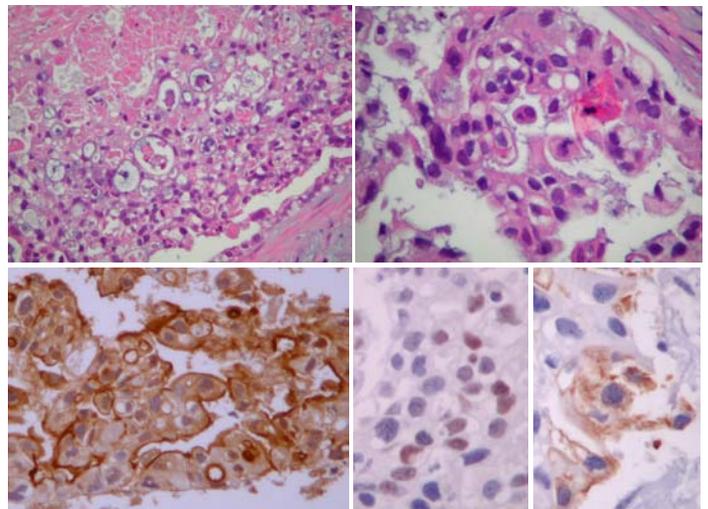
**GCDFP-15 (gross cystic disease fluid protein-15):** This marker has good specificity for breast carcinoma, although its sensitivity is not high, as only about 50% of breast carcinomas express this marker. Another potential problem with this marker (particularly when dealing with small biopsy specimens) is that it is often

expressed in a focal fashion, occasionally in only a very small percentage of tumor cells. Therefore, the possibility of sampling error must always be kept in mind when dealing with small biopsy specimens stained for this marker. Although I have seen it very rarely expressed in lung carcinoma (<1% of cases), reactivity with this marker supports breast origin over lung origin.

**TTF-1 (thyroid transcription factor-1) and PE-10 (surfactant protein A):** These two antibodies are well-known for their ability to serve as markers of pulmonary origin. Only nuclear reactivity with TTF-1 should be assessed, and TTF-1 stains roughly 75% of pulmonary adenocarcinomas. The sensitivity of PE-10 (a cytoplasmic antigen) is substantially less, and from my experience I would estimate that about 30-40% of pulmonary adenocarcinomas express PE-10. It is also important to keep in mind that thyroid carcinoma may express both of these markers (particularly TTF-1), so metastatic thyroid carcinoma to the lung is a potential diagnostic trap. In this situation, identification of reactivity with monoclonal CEA can provide additional support for a primary pulmonary origin, since substantial CEA reactivity is very uncommon in papillary and follicular carcinomas of the thy-

roid. (Parenthetically, medullary carcinoma of the thyroid characteristically expresses strong and diffuse CEA). I have never personally observed expression of TTF-1 in a breast carcinoma.

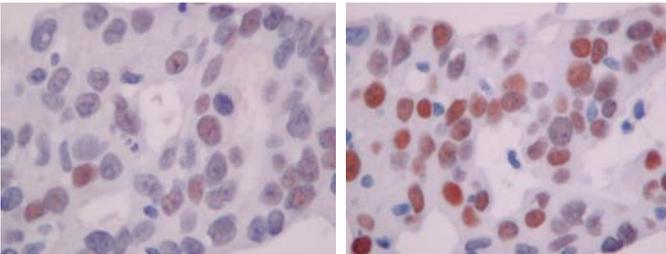
**Villin:** Villin is a marker that is expressed in a very high percentage of GI and related (pancreatic, bile duct, etc.) adenocarcinomas, but it is also expressed in a subpopulation of pulmonary adenocarcinomas. Since it is extremely uncommon for breast carcinoma to show substantial villin immunoreactivity, identification of this marker in a tumor provides evidence against a breast primary origin.



*H&E sections (top left and top right) of a lung tumor biopsy from a 65 year-old female with a prior history of ER negative, PR negative invasive ductal breast carcinoma. Original slides on the breast tumor were not available for comparison. The villin immunostain (bottom left) was strongly positive, rendering breast origin highly unlikely. Pulmonary origin was confirmed by positivity for TTF-1 (bottom middle) and PE-10 (bottom right).*

**Estrogen and Progesterone Receptors:** It is well-known that estrogen and progesterone receptors are expressed in the majority of breast carcinomas. Although past conventional wisdom dictated that lung adenocarcinoma was always negative for ER, it is important to realize that a small but significant percentage (probably

about 5-10%) of lung adenocarcinomas do indeed express estrogen receptors (at least when using the 1D5 antibody), and I have seen expression of ER in unequivocal lung adenocarcinomas on multiple occasions. In most instances it is expressed in a "low-level" fashion in lung adenocarcinoma, with a subpopulation of tumor cells showing weak to moderate reactivity. However, on a few occasions I have observed strong reactivity in lung tumors, including several from male patients. When employing the 6F11 clone, Dabbs et al have reported ER positivity in 67% of lung adenocarcinomas! I have not personally observed significant expression of progesterone receptors in lung adenocarcinoma. Obviously, it is always helpful if one is aware of the ER and PR status of the original breast tumor when dealing with potential second primary carcinomas in patients with a prior history of breast carcinoma.



*Immunostains on lung FNA cell block from a female smoker with prior breast carcinoma. The ER immunostain (left) showed moderate positivity, but the TTF-1 immunostain (right) was strongly positive. Further history indicated that this patient had a small tubular carcinoma with no regional node metastases, that was morphologically different from the lung tumor. This case represented a primary pulmonary adenocarcinoma that expressed ER. Obviously, relying on a single ER immunostain to work up this case may have led to an erroneous diagnosis, underscoring the importance of appropriate panels of immunostains in working up such cases.*

**BCL-2:** Alsabeh et al published a paper in 1996 calling attention to the potential application of BCL-2 immunostaining to this differential diagnostic problem. In a series of 208 breast carcinomas, 79.3% of the breast tumors expressed BCL-2, in contrast to only 5.6% of 54 lung adenocarcinomas. As such, immunoreactivity with BCL-2 supports breast over lung primary origin.

**HBME-1:** Miettinen and Kovatich found that HBME-1 showed significant expression in only 9% (3 of 34 cases) of invasive ductal carcinomas examined, whereas this marker showed significant expression in 45% (23 of 51 cases) of lung adenocarcinomas. As such, expression of HBME-1 favors lung primary over breast primary.

**S100 Protein and CEA:** Some authors report S100 reactivity in 15-30% of breast carcinomas, but only rarely in lung adenocarcinoma. In addition, others report that CEA may also be useful in this situation, in that strong diffuse expression of CEA is more common

in lung carcinoma than breast carcinoma. However, in my practice I have not been impressed with utility of CEA for distinguishing lung from breast carcinoma.

**SUMMARY:** In summary, I think the combination of TTF-1, GCDFP-15, villin, ER, and PR represents a useful initial panel to attempt to distinguish breast carcinoma from pulmonary carcinoma (keeping in mind that some lung carcinomas may show expression of ER). If the initial battery of immunostains is not diagnostic, other markers such as PE-10, BCL-2, HBME-1, and S100 protein would be reasonable markers to consider.

#### REFERENCES:

1. Miettinen M, Kovatich AJ: HBME-1. A Monoclonal Antibody Useful in the Differential Diagnosis of Mesothelioma, Adenocarcinoma, and Bone Tumors. *Applied Immunohistochemistry* 3(2): 115-122, 1995.
2. Alsabeh R, Wilson CS, Ahn CW, et al: Expression of BCL-2 by Breast Cancer: A Possible Diagnostic Application. *Modern Pathology* 9(4):439-444, 1996.
3. Raab SS, Berg LC, Swanson PE, Wick MR: Adenocarcinoma in the Lung in Patients with Breast Cancer. A Prospective Analysis of the Discriminatory Value of Immunostains. *American Journal of Clinical Pathology* 100:27-35, 1993.
4. Wick MR, Lillemo T, Copland GT et al: Gross Cystic Disease Fluid Protein-15 as a Marker for Breast Cancer: Immunohistochemical Analysis of 690 Human Neoplasms and Comparison with Alpha-Lactalbumin. *Human Pathology* 20(3):281-287, 1989.
5. Kaufman O, Dietel M: Thyroid Transcription Factor-1 is the superior immunohistochemical marker for pulmonary adenocarcinomas and large cell carcinomas compared to surfactant proteins A and B. *Histopathology* 36:8-16, 2000.
6. Dabbs DJ, Liu Y, Raab SS et al: Immunohistochemical Detection of Estrogen Receptor in Pulmonary Adenocarcinomas is Dependent Upon the Antibody Used. *Modern Pathology* 13(3):208A, abstract #1227, 2000.
7. Bejarano PA, Baugman RP, Biddinger PW et al: Surfactant Proteins and Thyroid Transcription Factor-1 in Pulmonary and Breast Carcinomas. *Modern Pathology* 9(4):445-452, 1996.
8. Nicholson AG, McCormick CJ, Shimamoto Y et al: The Value of PE-10 (SP-A, Lung), a Monoclonal Antibody against Pulmonary Surfactant, in Distinguishing Primary and Metastatic Lung Tumours. *Histopathology* 27(1):57-60, 1995.

#### Rodney T. Miller, M.D.

Director of Immunohistochemistry  
214 237-1631, Fax 214 237-1770  
rmiller@propathlab.com

Prior Editions are available on our website

# PROPATH

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