GEISINGER IHC

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NEWS

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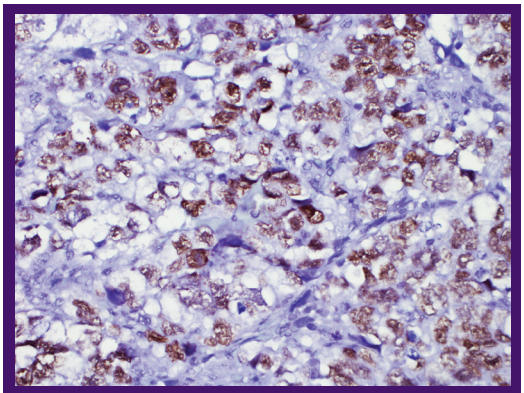
Geisinger IHC Antibody Updates

SOX proteins are a group of DNA-binding transcription factors regulating normal cellular development and differentiation. Their roles in tumorigenesis have also been actively investigated. Recent studies have demonstrated clinical utilities for IHC detection of specific SOX proteins in the diagnosis and prognostication of various tumors. In Geisinger's IHC laboratory, we recently introduced three antibodies to specific SOX proteins (SOX2, SOX10, and SOX11) with established clinical applications.

SOX2 is a transcription factor regulating embryonic stem cell pluripotency. Recent studies have shown that immunostaining with SOX2 protein has clinical utility in the diagnosis of mixed germ cell tumors.[1,2] A strong nuclear immunoreactivity for SOX2 is predominantly observed in the embryonal carcinoma component and primitive neuroectoderm of immature teratomas, but not in other components, including seminoma (similarly in ovarian dysgerminoma), intra-tubular germ cell neoplasia, and choriocarcinoma. Thus, SOX2 is useful in the distinction of seminoma from embryonal carcinoma and potentially in diagnosing early carcinomatous differentiation in seminoma.



SOX2 in embryonal carcinoma

Another potential clinical utility of SOX2 immunostaining is to differentiate between squamous cell carcinomas and adenocarcinomas of the lung, esophagus and anal canal.[3,4] Some recent studies have shown that SOX2 expression is seen in 80-90% of squamous cell carcinomas compared to 10-20% of adenocarcinomas arising from the lung and GI tract.

In our laboratory, using TMAs of 1020 tumors from various organs, not only did we validate these observations, but also extended the knowledge of SOX2 immunoreactivity to many other tumor types. A summary of the immunostaining data is shown in this table.

Tumor	Positive % (N)
SCC, lung	93% (39/42)
ADC, lung	17% (12/71)
ADC, endocervix	36% (5/14)
ADC, endometrium	13% (5/39)
Melanoma, skin	23% (17/74)
Embryonal CA	100%(16/16)
Yolk sac tumor	44%(4/9)
Urothelial CA, bladder	6% (2/31)
ADC, colon	2% (1/43)

References:

1. Gopalan A, Dhall D, Olgac S, et al. *Mod Pathol.* 2009; 22(8):1066-1074.
2. Chang MC, Vargas SO, Hornick JL, Hirsch MS, Crum CP, Nucci MR. I*nt J Gynecol Pathol.* 2009. 28(4): 347-355.
3. Long KB, Hornick JL. *Hum Pathol.* 2009;40(12):1768-1773.
4. Brcic L, Sherer CK, Shuai Y, Hornick JL, Chirieac LR, Dacic S. *Am J Clin Pathol.* 2012:138(5):712-718.

(continued on page 2)

Geisinger IHC Antibody Updates *(continued from page 1)*

SOX10 is a neural crest transcription factor required for differentiation and maturation of melanocytes and Schwann cells. Clinically, it has been primarily used as a marker for melanocytic differentiation.[1] It is particularly useful in making a diagnosis of desmoplastic melanoma because most of these tumors show strong diffuse positive nuclear reactivity.[2] Regarding this particular application, several studies have shown that SOX10 performs with a similar sensitivity but a higher specificity when compared to S100 immunostaining.[2,3] It may also be useful in assessing metastatic melanoma cells in sentinel lymph nodes.[4] In this regard, SOX10 immunostaining demonstrates superior performance to S100 because it does not stain Langerhans cells and dendritic cells. Although SOX10 has been a great marker for melanocytes, it is important to realize during clinical application that other cell types may also show strong and diffuse nuclear immunoreactivity. These include Schwann cells from schwannomas and neurofibromas; myoeptithelial cells from salivary glands, bronchial and mammary ducts and lobules; sustanticular cells in paragangliomas; cells from various brain tumors, including astrocytomas, oligodendrogliomas and medulloblastomas. It has also been reported in some clear cell sarcomas[3] with minimal melanocytic differentiation.

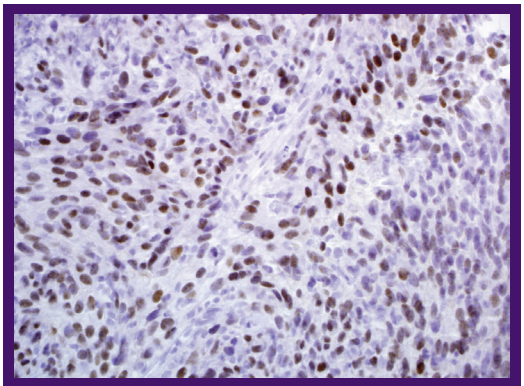
SOX11 is a transcription factor involved in embryonic neurogenesis and tissue remodeling. A recent study identified it as a useful immunohistochemical marker for diagnosis of mantle cell lymphoma (MCL) because of its relatively specific nuclear expression in MCL compared with other lymphomas and benign lymphoid tissue.[1] Several subsequent studies have further demonstrated that a strong nuclear immunoreactivity of SOX11 is seen in both cyclin D1 positive and negative MCL.[2,3] It has also been shown to be helpful in distinguishing CD5 positive diffuse large B cell lymphoma (DLBL) from MCL.[4] However, it is worth noting that positive nuclear immunoreactivity for SOX11 has also been reported in a subset of hairy cell leukemias with cyclin D1 overexpression,[4] some lymphoblastic lymphomas, and rarely Burkitt lymphomas.[5]

Immunohistochemical Panel Update

Useful Immunomarkers for Diagnosis of Germ Cell Tumors

Marker	Seminoma	Embryonal CA	Yolk sac tumor	ChorioCA
SALL4	+	+	+	+ or -
LIN28	+	+	+	+ or -
OCT4	+	+	-	+ or -
SOX2	-	+	-/+	-
NANOG	+	+	-	-
CD30	-	+	-	-
CD117	+	-	-	-
D2-40	+	-	-	-
Glypican-3	-	-	+	-
AFP	-	-	+	-
Beta-HCG	-	-	-	+
CD10	-	-	-	+

Note: CA – carcinoma; chorioCA – choriocarcinoma
Legend: + greater than 75% of cases positive; – less than 5% of cases positive
+/- 50-75% of cases are positive; -/+ <50% of cases are positive



SOX10 in spindle cell melanoma

References:

1. Nonaka D, Chiriboga L, Rubin BP. *Am J Surg Pathol*. 2008;32(9):1291-1298.
2. Palla B, Su A, Binder S, Dry S. *Am J Dermatopathol*. 2013;35(5):576-581.
3. Karamchandani JR, Nielsen TO, van de Rijn M, West RB. *Appl Immunohistochem Mol Morphol*. 2012;20(5):445-450.
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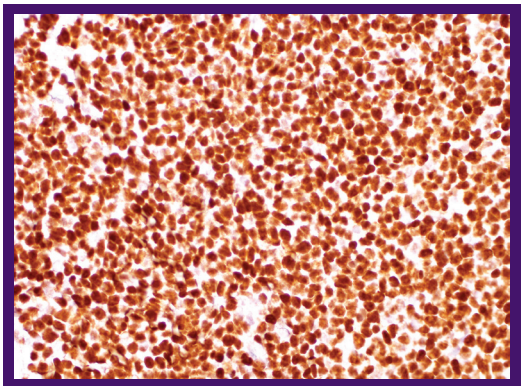

SOX11 in cyclin D1 negative mantle cell lymphoma

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1. Ek S, Dictor M, Jerkeman M, Jirström K, Borrebaeck CA. *Blood*. 2008; 111(2):800-805.
2. Nordström L, Andréasson U, Jerkeman M, Dictor M, Borrebaeck C, Ek S. *BMC Cancer*. 2012;12:269.
3. Soldini D, Valera A, Solé C, et al. *Am J. Surg Pathol*. 2013. (Epub ahead of print)
4. Chen YH, Gao J, Fan G, Peterson LC. *Mod Pathol*. 2010;23(1):105-112.
5. Zeng W, Fu K, Quintanilla-Fend L, Lim M, Ondrejka S, Hsi ED. *Am J Surg Pathol*. 2012;36(2):214-219.

Selected abstracts from the 2013 Annual CAP Meeting in Orlando, FL

1. **Role of Surfactant Protein A (SPA) in Identifying Metastatic Tumors of Lung Origin in Cytopathology Samples. Humberto E, et al. UPMC, Pittsburgh, PA.**

   The authors studied 122 consecutive cytology specimens procured from nonpulmonary sites. Cytoplasmic SPA immunoreactivity was identified primarily in metastatic lung adenocarcinomas, except for two breast carcinomas. In the study, SPA alone demonstrated a sensitivity of 66.1%, specificity of 95.8%, PPV of 94.9% and NPV of 56.8% for pulmonary adenocarcinomas. Together with TTF1, the sensitivity increased to 82.1% and NPV increased to 82.1%, with the same specificity and similar PPV.

2. **Comparison of High-Molecular-Weight Cytokerins 5/14 and 5/6; p40 and Desmoglein 3+ Cytokeratin 5 in Squamous Cell Carcinomas. Sirohi D, et al. University of Texas Health Science Center, San Antonio, TX.**

   The authors compared the sensitivity and specificity of cytokeratin 5/6 and 5/14 (Cell Marque clones D5 and EP1601Y), p40 and desmoglein3+CK5 (DG3+CK5; Biocare) in establishing a diagnosis of squamous cell carcinoma (SCC) using tissue microarray. The data showed that for pulmonary SCC, CK5/14 and DG3+CK5 demonstrated superior sensitivity and specificity to the other two antibodies. However, p40 appeared to show more staining in poorly differentiated SCCs. p40 also showed consistent immunoreactivity in urothelial carcinoma (88%), more than CK5/14 (13.6%) and DG3+CK5 (27.1%), respectively. CK5/6 showed the most immunoreactivity with non-squamous cell carcinomas and proved to be the least specific antibody for this application.

3. **Immunohistochemical Profile of Malignant Mesotheliomas of the Pleura and Peritoneum: A report of 504 Cases from a Single Institution. Kraynie AM, et al. Duke University, Durham, NC.**

   The authors summarized IHC staining patterns (broad-spectrum cytokeratin, calretinin, CK5/6,WT-1, D2-40, TTF-1, CEA, BerEP4, and B72.3) of 504 mesotheliomas, including 440 cases from pleura and 64 cases from peritoneum. 320 were categorized as epithelial, 76 sarcomatoid, and 108 biphasic types, respectively. The results showed that calretinin was the most sensitive marker for epithelial tumors (98%), with CK5/6, WT-1, and D2-40 having similar levels of sensitivity (89-92%). Biphasic tumors showed less sensitivity for these markers. Sarcomatoid tumors were positive for broad-spectrum cytokeratin (92%), calretinin (47%), D2-40 (55%) and vimentin (95%).

4. **Immunohistochemical Distinction Between Intrahepatic Cholangiocarcinoma and Pancreatic Ductal Adenocarcinoma. Lok T, et al. UCLA, Los Angeles, CA.**

   The authors evaluated the utility of a 6-marker panel (S100P, pVHL, MUC5AC, IMP3, maspin and CK17) in differentiating intrahepatic cholangiocarcinoma (ICC) from metastatic pancreatic ductal adenocarcinoma (PDA). They studied IHC staining patterns in 41 ICCs and 60 PDAs and identified a specific pattern (S100P-, pVHL+, MUC5AC- and CK17-) essentially indicative of ICC. Some of their results are shown in the following table:

Patterns	ICC (%) n=41	PDA (%) n=60	P Value
S100P-/pVHL+/MUC5AC-/CK17-	24 (58.5)	0	<0.001
S100P+/pVHL-/MUC5AC+/CK17+	1 (2.4)	22 (36.7)	<0.001
S100P+/pVHL-/MUC5AC+/CK17-	4 (9.8)	16 (26.7)	0.66
S100P-/pVHL-/MUC5AC-/CK17+	1 (2.4)	11 (18)	<0.02

For additional information about these and other abstracts from the 2013 CAP meeting, please see *Arch Pathol Lab Med*. 2013; 137(10):1344-1526.

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