

IHC News

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Geisinger seminar in anatomic pathology

Geisinger's Anatomic Pathology Department announces its upcoming seminar in diagnostic surgical pathology and immunohistochemistry (IHC). Intended for practicing pathologists, fellows, residents and other healthcare professionals, the seminar features didactic lectures and case-based presentations by Geisinger faculty and four international experts in the field of anatomic pathology and IHC.

When: Sept. 16 – 18, 2016

Where: Geisinger Medical Center,
Danville, PA 17822

Credit designation: A maximum of 17.5 AMA
PRA Category 1 Credits

Registration fee: \$300 (For registration
and additional information,
visit go.geisinger.org/AnatomicPath.)

Topics: Updates on GI, GU, soft tissue
tumors, pulmonary pathology and diagnostic
immunohistochemistry

Course director: Fan Lin, MD, PhD, director of
Anatomic Pathology, Geisinger Health System,
Danville, PA

**Featured guest faculty (a half-day lecture
from each guest speaker):**

Philip Cagle, MD; Houston Methodist Hospital,
Houston, TX

Jonathan Epstein, MD; The Johns Hopkins
Hospital, Baltimore, MD

Andrew Folpe, MD; Mayo Clinic, Rochester, MN

John Hart, MD; The University of Chicago
Medical Center, Chicago, IL

Geisinger faculty:

Authors of the *Handbook of Practical
Immunohistochemistry – Frequently Asked
Questions, 2nd edition*: Eric Chen, MD, PhD;
Tammie Ferringer, MD; Fan Lin, MD, PhD;
Haiyan Liu, MD; Jeff Prichard, DO; Myra
Wilkerson, MD

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New antibodies available at Geisinger IHC Lab

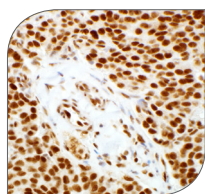


Figure 1A

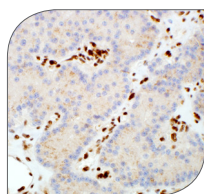


Figure 1B

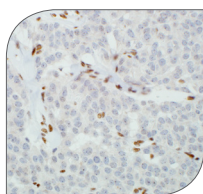


Figure 1C

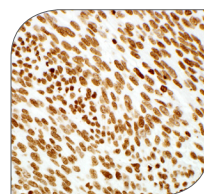


Figure 2: Trimethylated
lysine 27 of histone
(H3K27me3)

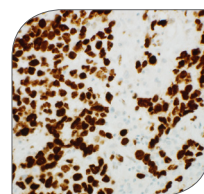


Figure 3: Promyelocytic
leukemia zinc
finger (PLZF)

ATRX/DAXX

Nuclear staining of a pancreatic neuroendocrine tumor (NET) as shown in **Figure 1A**.

It has been reported to be lost in approximately 50 percent of metastatic pancreatic NETs, as shown in **Figures 1B (ATRX)** and **1C (DAXX)**. Note that expression of ATRX/DAXX is seen in stromal cells, endothelial cells and inflammatory cells as an internal positive control.

Figure 2: Nuclear staining of a leiomyosarcoma. Loss of H3K27me3 expression has been reported in 50 percent of malignant peripheral nerve sheath tumors.

Figure 3: Nuclear staining of a yolk sac tumor. PLZF has been reported to be negative in other germ cell tumors.

Review of select 2016 USCAP abstracts

[1749] ATRX/DAXX Loss Is Highly Specific for Metastatic Pancreatic Neuroendocrine Tumors. Michelle Heayn, et al.

Immunolabeling for ATRX and DAXX was performed on 289 metastatic neuroendocrine tumors (NETs) from 114 patients. The sites of origin included 41 pancreas, 60 small intestine, 5 colorectum, 1 stomach and 7 lung. The results showed that metastatic pancreatic NETs in 20 of 41 (49%) patients had ATRX and/or DAXX loss. In contrast, all metastatic NETs originating from the small intestine, colorectum, stomach and lung showed preserved expression of both ATRX and DAXX.

Conclusions: Loss of ATRX and/or DAXX in metastatic NETs is a highly specific and moderately sensitive marker of pancreatic origin.

[89] Loss of H3K27 Trimethylation Distinguishes Malignant Peripheral Nerve Sheath Tumors (MPNST) from Histologic Mimics. Inga-Marie Schaefer, et al.

The differential diagnosis of malignant peripheral nerve sheath tumor (MPNST) is challenging. Immunohistochemistry using a rabbit monoclonal antibody directed against trimethylated lysine 27 of histone H3 (H3K27me3; 1:500 dilution; clone 07-449; Millipore) was performed on 100 MPNSTs (70 sporadic, 10 neurofibromatosis type 1 [NF1]-associated, 10 radiation-associated, 10 epithelioid; 31 low, 36 intermediate, 33 high grade) and 200 other benign and malignant spindle cell neoplasms that represent potential mimics. 51 (51%) of MPNSTs, including 34 (49%) sporadic, 7 (70%) NF1-associated, 10 (100%) radiation-associated, and no epithelioid MPNSTs were negative for H3K27me3. Among other tumor types, 4 (20%) unclassified post-radiation sarcomas were negative for H3K27me3, whereas all other neoplasms were positive.

Conclusions: Loss of H3K27me3 is highly specific for MPNST (although only modestly more sensitive than S-100 protein and SOX10) and may be a useful diagnostic immunohistochemical marker.

[1051] PLZF: A Sensitive and Specific Biomarker for Yolk Sac Tumor. Shana Straub, et al.

Immunohistochemical evaluation of the expression of promyelocytic leukemia zinc finger (PLZF) protein was performed on 67 adult germ cell tumors (GCTs), including 62 testicular primary GCTs, 2 ovarian yolk sac tumors (YSTs), 1 mediastinal YST, and 2 retroperitoneal metastatic testicular YSTs. YST was consistently reactive with PLZF. Among the 15 testicular YSTs in mixed GCTs, all (100%) presented with moderate to diffuse PLZF staining. PLZF reactivity was present in all the growth patterns of YST. PLZF also picked up small foci of YST intermixed/embedded in other GCT subtype elements of mixed GCT. Additionally, diffuse PLZF immunoreactivity was observed in 2/2 recurrent metastatic YSTs, 1/1 mediastinal YST, and 2/2 ovarian YSTs. PLZF was also diffusely expressed in spermatocytic seminoma (n=2) and carcinoid (n=1). All the other non-YST GCTs were completely nonreactive with PLZF.

Conclusions: This study demonstrated that PLZF moderately to diffusely immunoreacted with all YSTs and, except in spermatocytic seminoma and carcinoid, no immunoreactivity was observed in the other types of GCT. In conclusion, PLZF is a highly sensitive and specific marker for YST, superior to other currently available YST biomarkers such as alpha-fetoprotein and glypican-3.

[1783] The Diagnostic Utility of TCTE3 as a Novel Immunohistochemical Marker for Pancreatobiliary Tumors. Chaohui L. Zhao, et al.

Expression of T-complex-associated-testis-expressed 3 (TCTE3) was immunohistochemically evaluated on tissue microarray (TMA) sections from 224 adenocarcinomas from 10 different locations in the GI tract, including gastroesophageal junction (GEJ), (20), stomach (30), ampulla (16), pancreas (36), extrahepatic common bile duct (CBD) and gallbladder (15), cholangiocarcinoma (19), hepatocellular carcinoma (20), small intestine other than ampulla (12), colon (32) and rectum (24). TCTE3 expression was characterized by a strong, well-defined cell membrane/cytoplasmic pattern. Positive TCTE3 stain was found in 86% of pancreatic duct adenocarcinomas, 47% of cholangiocarcinomas, 56% of ampullary adenocarcinomas, 27% of CBD/gallbladder adenocarcinomas, 35% of GEJ adenocarcinomas and only

3% of gastric and 6% of colon cancers. No expression was found in any of the small intestinal (other than ampulla) cancers, rectal cancers, and hepatocellular carcinomas. TCTE3's sensitivity and specificity for the diagnosis of pancreatic cancer in this current series were 86% and 83%.

Conclusions: The results demonstrate that TCTE3 may have diagnostic utility for pancreatic ductal carcinoma and in the separation of gastric cancer and small intestinal cancer from tumors of the pancreatobiliary tree.

[1900] *ROS1* Immunohistochemistry as a Screen for *ROS1* Rearrangements in Lung Adenocarcinoma:

Application in Clinical Practice. Prodipto Pal, et al.

ROS1 gene rearrangements occur in 1–2% of lung adenocarcinomas and predict response to crizotinib therapy. The optimal approach to *ROS1* translocation detection has not yet been established; however, many labs depend on fluorescence in situ hybridization (FISH). *ROS1* IHC using clone D4D6 (Cell Signaling Technology) was performed on 943 lung tumors. Positive *ROS1* protein expression was detected in 19 cases (2%). Of these, FISH confirmed a rearrangement in 8, was negative in 7, and gave no result in 4.

Conclusions: *ROS1* protein was detected as moderate to strong and diffuse staining by IHC and is 100% sensitive and 93% specific for a rearrangement by FISH or next-generation sequencing (NGS). Tumors with negative or equivocal *ROS1* expression are consistently negative for *ROS1* rearrangement. *ROS1* IHC is a reliable screening tool in clinical practice; reflexive confirmation using FISH or molecular techniques should be restricted to tumors with moderate to strong and diffuse expression.

[796] Hepatoid Carcinomas of the Gastrointestinal Tract: A Reappraisal of Morphological and Immunohistochemical Features. Angela R. Shih, et al.

IHC for alpha-fetoprotein (AFP), hepatocyte paraffin 1 (HepPar1), glypican 3, and arginase 1, and in situ hybridization (ISH) for albumin was performed in 51 GI hepatoid carcinomas. Tissue microarray controls (n=461), including carcinomas of the pancreas, colon, stomach, gallbladder, ampulla, and esophagus, were also evaluated. The most sensitive marker across all subtypes was glypican 3 (91% sensitivity), followed by albumin (88% sensitivity) and AFP (82% sensitivity). Arginase 1, the least sensitive marker, was only positive in type I tumors (35% sensitivity in type I). All controls were negative for albumin. HepPar1 had poor specificity and was reactive in 15% of carcinomas.

Conclusions: Type I and II hepatoid carcinomas are morphologically distinct compared to type III tumors. Glypican 3, albumin, and AFP are sensitive and specific markers of hepatoid carcinoma in the GI tract, while HepPar1 lacks specificity. Type II hepatoid carcinomas are under-recognized in Western countries.

[1630] Distinctive Morphologic Pattern and In Situ Hybridization for Albumin Distinguishes Intrahepatic Cholangiocarcinoma from Metastatic Adenocarcinoma. Tanupriya Agrawal, et al.

The distinction of intrahepatic cholangiocarcinoma (IHCC) from metastatic adenocarcinoma is challenging. Histologic patterns in 101 cases of IHCC were evaluated, including anastomosing, tubular, pancreatic, undifferentiated, large duct and cribriform. Targeted sequencing for IDH1/2 mutations and in situ hybridization for albumin were done. All tumors tested for albumin (60 cases) were positive; and 6 of 18 (33%) cases revealed IDH1/2 mutations.

Conclusions: The presence of an anastomosing growth pattern is highly suggestive of IHCC. This pattern was noted in 64% of cases. Intratumoral albumin supports a diagnosis of IHCC and, when seen in isolation, could also differentiate IHCC from metastatic adenocarcinoma. The combination of an anastomosing histological pattern and albumin reactivity, with or without detection of IDH1/2 mutations, should allow for a definitive diagnosis of IHCC in the vast majority of cases.

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