ISSN: 2754-4931

Journal of Gastroenterology & Hepatology Reports

SCIENTIFIC Research and Community

Review Article

Open Access

The Clinical Brilliance of Immunohistochemistry "IHC" in Gastrointestinal Oncology

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Received: March 20, 2025; **Accepted:** April 04, 2025; **Published:** April 12, 2025

Introduction

Immunohistochemistry, or "IHC," is a powerful tool in clinical diagnostics within the field of gastrointestinal oncology and anatomical pathology. It is utilized to assist in classification of neoplastic, infectious, and inflammatory diseases. The technique generally involves the specific binding between an antibody and antigen to detect and localize specific antigens within tissue samples, usually examined with light microscopy. Biopsies are collected in a number of ways, including snaring, fine needle aspiration, endoscopic mucosal resection, and more; these samples are then processed by a pathologist. This information can be vital in clinical decision making for patients with potential malignancy.

Discussion

Immunohistochemistry utilizes antibodies to stain proteins in tissue samples and can be applied in transmitted light or fluorescence microscopy. It can also be combined with techniques like polarized light to identify multiple proteins.

When malignancy is suspected, tissue can be collected in a number of ways: during an intraoperative consultation for assessment of malignant margins, as a minute biopsy during an outpatient procedure, or even as a routine submission where there is minimal clinical suspicion for malignancy. Once the tissue is collected, our pathology colleagues begin the process of gross examination. The tissue sample, no matter the size, is assessed macroscopically for size, shape, texture, surface lesions and their relation to any margins, and any other orientation designated by the surgeon. Traditionally, the specimen is marked with an India ink to preserve the orientation of the specimen, since staples and sutures placed by the surgeon cannot remain throughout the subsequent steps. The specimen is placed in a plastic cassette with a specific orientation relevant to the clinical question in mind, and sent to histology for processing.

Once the slides have been processed and the block is faced for cutting, a 4-micron unstained slice can be taken for immunohistochemistry (IHC). Appropriately controlled IHC can be used to identify various undifferentiated neoplasms, using different markers that might include: Epithelial Membrane Antigen (EMA); Leukocyte Common Antigen (LCA) or CD45; S-100 Protein (S-100), Placental Alkaline Phosphatase (PLAP); Alpha Fetoprotein (AFP); Octamer Binding Transcription Factor 4 (OCT4); Human Chorionic Gonadotropin (HCG) [1-20].

In general, carcinomas are cytokeratin positive and EMA positive, melanomas are both S-100 positive and can be desmin/vimentin positive, sarcomas are desmin/vimentin positive, lymphomas are LCA/CD45 positive, neuroendocrine tumors (NETs) are cytokeratin positive, EMA positive, and chromogranin/synaptophysin positive, while germ cell tumors are OCT4/HCG positive and AFP/PLAP positive.

There are a number of IHC patterns for identifying potential primary malignancies which the pathologist may use for medical decision making. IHC positive staining for SATB2 and the combination of CK-20 positivity and CK-7 negativity are highly suggestive of colorectal cancer. CK-7 positivity and CK-20 positivity are highly suggestive of pancreatic or biliary cancer, but could be mucinous ovarian cancer and urothelial tumors. CK-7 negativity and CK-20 negativity are suggestive of hepatocellular cancer but could also suggest renal cell carcinoma, head and neck cancer, or squamous cell lung cancer. Finally, CD-117 positivity along with DOG-1 positivity is consistent with GIST. For this reason, the IHC profile must be taken into its morphological context by a trained GI pathologist. Combining IHC analysis with clinical and imaging techniques enhances patient outcomes and improves prognosis [21-25].

Table 1: Common IHC Markers and their Correlating General Tissue Diagnoses

Tumor	Cytokeratin	EMA	S-100	Desmin Vimentin	LCA	Chromogranin Synaptophysin	OCT4/HCG	AFP/PLAP
Carcinoma	+	+						
Melanoma			+	+				
Sarcoma				+				
Lymphoma					+			
NETs	+	+				+		
Germ Cell								
Tumors							+	+

The Foregut Tumors - Esophagus and Stomach

Gastric and esophageal tumors commonly include squamous cell carcinomas and adenocarcinomas. Esophageal cancer is one of the most common malignancies worldwide with squamous cell cancer being less prevalent than adenocarcinoma in the United States. Gastric adenocarcinoma is the 5th leading cause of cancer and the 4th highest cancer mortality worldwide. Esophageal and gastric adenocarcinoma are frequently diagnosed at an advanced stage with poor prognosis. Histological classification is the gold standard in differentiating tumor origins and guides targeted therapy [26-30].

Esophageal squamous cell carcinoma (SCC) exhibits a distinct molecular profile. IHC staining with programmed death-ligand 1 (PDL-1) is the most widely used in detecting esophageal SCC. PD-L1 is found on certain cells and will interact with PD-1, an immune checkpoint protein on lymphocytes. The interaction results in lymphocyte apoptosis, regulating the body's immune response. Therefore, tumor cells expressing PD-L1 can inactivate attacking cells. The Combined Positive Score is the standard method of testing for PD-L1. In contrast to PD-L1, Epidermal Growth Factor Receptor (EGFR) is not as commonly used in practice, although it has perhaps the most promise. In a phase III trial, there were some improved outcomes in the expression of EGFR on IHC when using erlotinib, an EGFR inhibitor. However, there is not an established scoring method in EGFR IHC to adapt the immunomarker officially into practice. PD-L1 is also associated with adenocarcinoma of the gastroesophageal junction (GEJ) and stomach, though less significantly than with SCC of the esophagus. Several studies have associated PD-L1 overexpression with an effective response to immune checkpoint inhibitors. The P53 gene product is another marker utilized in the detection of esophageal SCC. P53 is a cell growth regulator and suppressor; when mutated, it actually stabilizes the p53 protein, dually allowing its detection while causing cell proliferation. In a study by Sarbia et al, of 204 tumors identified to be esophageal SCC following resection, 137 of them were shown to express p53 genes [31]. While P53 detection can assist with prognosis in some cancers, it has no impact on prognosis of an individual with esophageal SCC.

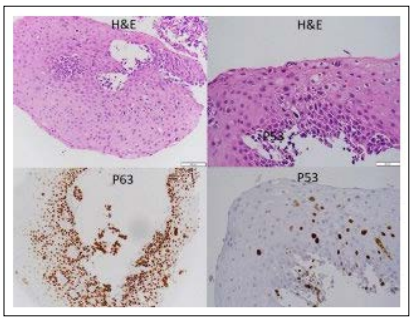

Figure 1: Positive p53 and p63 Staining of Esophageal Squamous Cell Carcinoma

Gastric adenocarcinomas and esophageal adenocarcinomas have similarities in their genetic profiles. HER2 is seen in up to about 20% of esophageal and gastric cancers; however, it is less associated with esophageal SCC. It is more commonly seen in intestinal-type carcinomas compared to diffuse-type carcinomas. Recognized as a biomarker in breast cancer, HER2 is now an established molecular marker for GEJ and gastric adenocarcinoma due to the phase III ToGA trial. IHC and in situ hybridization can both be used to assess HER2 overexpression; however, IHC is preferred to be used first. Microsatellite Instability can be seen in up to 5% of esophageal adenocarcinoma and about 6-9% of gastric adenocarcinomas, particularly in older women, intestinal-type tumors, and antral tumors. IHC is used to detect MMR proteins when evaluating for microsatellite instability. Additional testing includes PCR, which detects instability in microsatellite repeats. FGFR2 protein overexpression is rare in gastric cancer. It is not as well established and is less used in clinical practice. Studies show that Bemarituzumab, an anti-FGFR2b antibody, is known to be effective against GEJ and gastric adenocarcinomas with FGFR3 overexpression on IHC.

Although common foregut tumors are often grouped together, IHC reveals distinct molecular profiles, highlighting their different origins. Given that esophageal SCC has a genetic makeup distinct from esophageal and gastric adenocarcinoma, classifying these tumors as separate disease processes is crucial in clinical practice. Genetic composition plays a key role in guiding treatment, underscoring the importance of IHC in diagnosis.

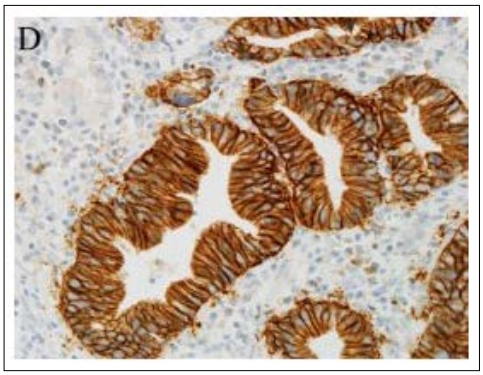

Figure 2: Positive HER2 Staining of Esophageal Adenocarcinoma

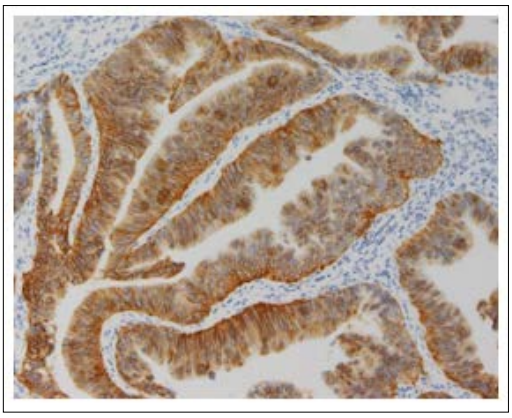

Figure 3: Positive HER2 Staining of Gastric Adenocarcinoma

Hepato-Pancreato-Biliary (HPB) Tumors

Pancreas

Pancreatic cancer is one of the leading cancer-related causes of mortality. It is often diagnosed at an advanced stage and has a poor prognosis. Therefore, there are many efforts in the scientific community to establish diagnostic techniques for early detection. Pancreatic ductal adenocarcinomas (PDACs) make up the majority of pancreatic tumors at about 85%. Clinical techniques such as endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) pose challenges in making diagnoses.

IHC is a useful tool in screening tests; however, biomarkers are not consistent in their diagnostic value. Most cases of PDAC express cytokeratins such as CK7, CK19, CK18, and sometimes CK20. Other markers that are generally positive include CEA, CA125, MUC1, MUC4, and MUC5AC. Carbohydrate Antigen 19-9 (CA 19-9) is a widely familiar gold standard molecular marker, but high levels can also be seen in pancreatitis. CEA and MUC1 staining serve as useful markers for distinguishing PDAC tumor glands from reactive ductular glands. While tumor glands generally exhibit both apical and cytoplasmic expression, reactive glands either lack expression or show only apical expression of these markers. One study aimed to review published articles to more clearly define IHC biomarkers for the diagnosis of pancreatic cancer [23]. Using measures of sensitivity and specificity, they found promise in the following markers: maspin, pVHL, KOC, S100P, galectin-1, THBS2, mesothelin, and IMP3. The most specific markers were galectin-1, maspin, KOC, and S100P with maspin displaying a sensitivity almost equal to specificity. Therefore, the investigation of pancreatic cancer IHC has established useful biomarkers besides CA 19-9 that improve diagnostic methods and prognosis.

Liver

According to the American Cancer Society, the incidence rate of liver cancer has more than tripled since 1980 while the death rates have more than doubled. Internationally, liver cancer is one of the most common fatal malignancies and often has a poor prognosis. Hepatocellular carcinoma (HCC) is the most common hepatic malignancy, making up roughly 90% of primary liver tumors. The most effective treatment options include chemotherapy and immunotherapy. Since most cases of liver cancer are diagnosed in the later stages, surgery is suitable for only a small percentage of patients, about 5-15%. Alpha-fetoprotein (AFP) is a commonly used tumor marker for HCC; however, the sensitivity and specificity can vary depending on patient history and AFP cut-off values used. It is best used along with other clinical diagnostic techniques as it can be elevated in both acute and chronic liver conditions. When combined with other molecular markers, AFP has the potential to be an early diagnostic indicator for HCC.

Challenges arise in diagnosing both well-differentiated and poorly differentiated hepatocellular neoplasia, making IHC important in directing clinicians. Well-differentiated HCC mimics benign liver tissue, such as focal nodular hyperplasia and hepatocellular adenoma. However, certain immunomarkers could be beneficial in making a distinction. CD34 highlights increased vascularity and glypican-3 (GPC3) is generally overexpressed in HCC. Heat shock protein 70 (HSP-70), a molecular chaperone expressed in response to stress, may also be helpful. In contrast, poorly differentiated HCC can be similar to malignancy from other sites, such as metastasis and cholangiocarcinoma. Studies have shown arginase-1 (ARG1) to be a highly useful cytoplasmic and nuclear marker with great sensitivity and specificity with indications that it may play a regulatory role in the development of HCC. Other beneficial markers include hepatocyte paraffin-1 (HepPar1), CD10, bile salt export pump, and polyclonal carcinoembryonic antigen [32-34].

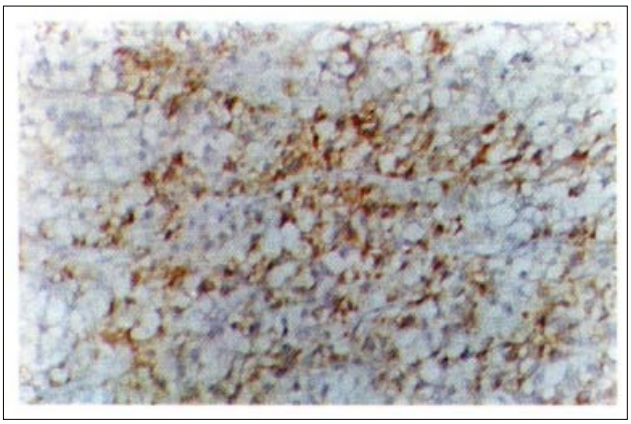

Figure 4: Positive Alpha-Fetoprotein Staining of Hepatocellular Carcinoma

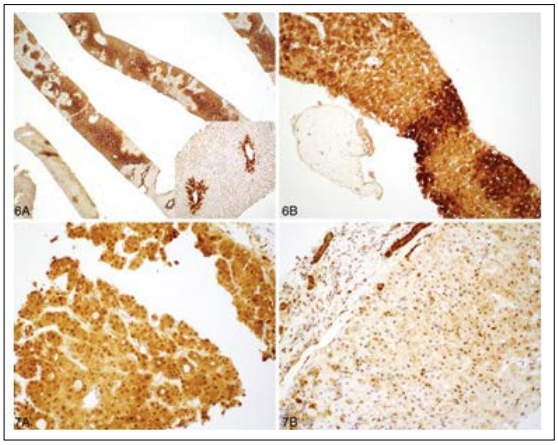

Figure 5: Positive Alpha-Fetoprotein Staining of Hepatocellular Carcinoma

Biliary Ductal Tumors

Cholangiocarcinoma is a rare and aggressive malignancy in which the epithelium of the biliary duct undergoes malignant transformation. Although rare, its incidence is increasing. There are different types of cholangiocarcinoma depending on their location, such as intrahepatic, perihilar and distal. Neoplasm of

the bile duct is most commonly adenocarcinoma, while other variants, such as adenosquamous or clear cell, are less frequently encountered. The initial diagnostic work-up usually includes CA19-9, which has been shown to have poor specificity but a 100% sensitivity in identifying intrahepatic cholangiocarcinoma (iCCA). The commonly reactive immunomarkers are CK7 and CK19, while less notable markers include CAM5.2, AE1/AE3, CEA, and MOC-31. In contrast to pancreaticobiliary carcinomas, biliary ductal neoplasms are more likely to express CK7 and less likely to express CK20, CK17, and p53. It is important to keep in mind that cholangiocarcinoma IHC overlaps with carcinomas of many sites, particularly gastrointestinal origins, making it difficult to distinguish from metastasis. In differentiating from hepatocellular carcinoma (HCC), CK7 is not expressed in hepatocytes. CK20 is generally negative in iCCA and HCC, but it has typically shown positivity in extrahepatic cholangiocarcinoma. Studies have shown that Glypican 3 is generally downregulated in cholangiocarcinoma (intrahepatic and extrahepatic) while it is strongly expressed in HCC. Overall, it is difficult to distinguish iCCA from other common hepatic malignancies by only relying on clinical data and imaging. Therefore, IHC staining can be a powerful tool in identifying cholangiocarcinoma and guiding treatment plans.

The Hindgut Tumors "Colorectal" (CRC)

According to the National Cancer Institute, colorectal cancer is responsible for roughly 7.6% of all new cancer cases, and 8.7% of cancer-related deaths in 2024. This makes CRC one of the most common and most deadly forms of cancer; this will unfortunately continue to worsen due to its link to economic development. It has been shown that as countries develop, oftentimes diet and habits worsen, such as tobacco and alcohol use, consumption of red meat, and participation in sedentary lifestyles, to name a few. Due to this fact, CRC incidence is expected to grow, and the need for early screening, accurate diagnosis, and prompt treatment will, as well.

There is a strong association between microsatellite instability and colorectal carcinoma (CRC). As described above, immunohistochemistry is performed for MMR proteins. The loss of staining for MLH1 and PMS2 is the most common abnormal pattern. Normal cells unaffected by tumor growth should stain positive for all markers.

Common immunomarkers in detecting colorectal cancer include CDX2, Villin, GPA33, SATB2, CK7, and CK20. CDX2 is a nuclear transcription factor expressed in intestinal epithelial cells. The rate of expression of CDX2 in colorectal cancer ranges from 26.7% to 100%. While known as a specific marker, it is not positive in every case and its expression can be affected by different methods of testing. The use of CDX2 as a prognostic marker remains unclear, however, many studies have concluded that loss of protein expression is associated with aggressive carcinomas and poor survival. Villin is specific to adenocarcinoma. Expression of the protein is associated with a better prognosis. GPA33 is expressed in most CRCs, particularly well-differentiated cancers. SATB2 is positive in almost all well differentiated colorectal adenocarcinomas (CA). Loss of its expression has been associated with an increase in invasive potential. SATB2 has a high specificity, so it may be useful for primary and metastatic CRCs. CK7 and CK20 are often used together to differentiate malignancies. Greater than 90% of colonic adenocarcinomas are CK7-/CK20+. In contrast to the majority of colorectal tumors, studies have shown that microsatellite unstable tumors tend to have reduced expression of CK20. CDH17 is a cadherin involved in cell adhesion and proliferation. It is a highly specific marker for the intestinal epithelium and is correlated with metastasis. CEA antigen expression is high in metastatic cancer; therefore, it is useful for IHC of late tumors. The level of CEA is directly related to tumor stage such that there are more elevated levels in well differentiated adenocarcinomas relative to early tumors. BRAF is a protein kinase gene. In addition to CRC, it is found in melanoma, papillary thyroid carcinoma, ovarian serous tumors, gliomas, hepatobiliary carcinomas, and hairy cell leukemias. BRAFV600E is the most common mutation in CRC. There is debate over its efficacy.

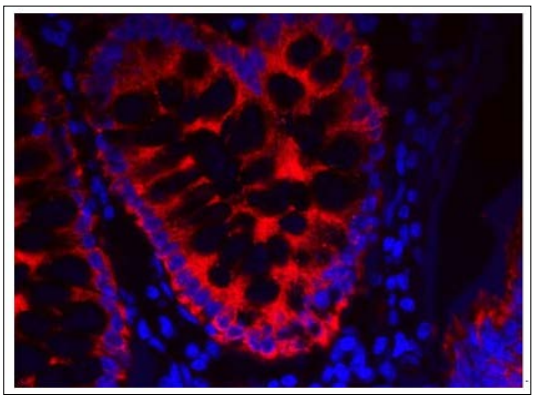

Figure 6: IHC Detection of Cytokeratin 18 in Human Colon Carcinoma Tissue by Immunofluorescence

Gastrointestinal Stromal Tumors

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal neoplasm of the gastrointestinal tract and the most common small intestine malignancy. At the same time, however, the tumor is very rare, accounting for 0.1-3.0% of gastrointestinal malignancies. GIST develops from interstitial cells of Cajal, which are the pacemaker cells of the gastrointestinal tract due to their role in regulating peristalsis. It is difficult to determine the true incidence of GIST because of the variable diagnostic criteria, but recent studies imply an increasing incidence over the last few decades. Most GISTs occur in the middle-aged population and are generally located in the stomach. They can either be indolent or aggressive, therefore early diagnosis and treatment can result in a great prognosis.

Immunohistochemistry and morphology are important diagnostic modalities and help to differentiate GISTs from other mesenchymal tumors, such as leiomyoma. They arise by over-expression of the tyrosine kinase receptor KIT and most commonly occur due to mutations in c-kit gene or platelet derived growth factor receptor alpha gene. Certain immunomarkers exist to identify these tumors. Overexpression of Kit (CD117) is a sensitive and specific marker found in 90% of GISTs. DOG-1 (a calcium-dependent chloride channel protein anoctamin) is a novel marker also found in more than 90% of GISTs. CD34 is an additional common marker expressed about 70% of cases. Other markers include desmin which is positive in 25% of GISTs and smooth muscle actin (SMA), a less common marker seen in less than 5% of GISTs. When identifying these mesenchymal tumors, there are no specific findings on endoscopy or endoscopic ultrasound. Therefore, immunohistochemical analysis must be incorporated for definitive diagnosis.

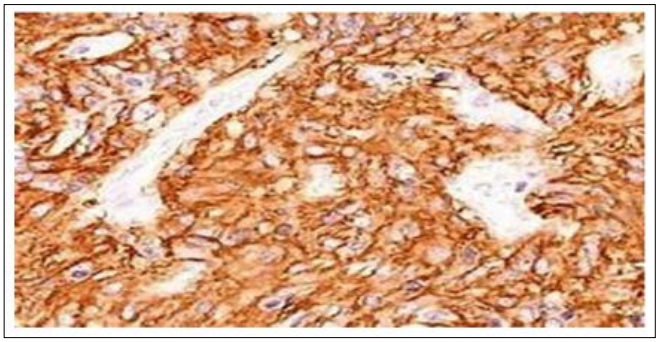

Figure 7: Positive CD-117 Staining in GIST

Mucosa-Associated Lymphoid Tissue Lymphoma

Mucosa-associated lymphoid tissue lymphoma (MALT lymphoma) is characterized by the infiltration of B cells in the marginal zone around the follicles in lymphoid tissue. The neoplastic proliferation of B cells gives rise to lymphoma. There is a strong association with Helicobacter pylori (H. pylori), hence the most common site is the stomach, accounting for 35% of MALT lymphomas. In comparison, intestinal MALT lymphoma is rare with the small intestine only accounting for about 3.4%. While most cases of MALT lymphoma have an indolent course, about 2% further progress to diffuse large B-cell lymphoma (DLBCL), a more aggressive disease with a worse prognosis. In immunohistochemistry, MALT lymphoma cells express CD20, CD79a, and BCL2 but lack BCL6, CD5, CD10, and CD23. It is necessary to differentiate MALT lymphoma from other types of lymphoma, such as follicular lymphoma (CD10+ and BCL6+) and mantle cell lymphoma (CD5+, cyclin D1+, and SOX11+). The Hans algorithm is used to classify the cell of origin (COO) in DLBCL by evaluating the expression of CD10, Bcl-6, and MUM-1 (multiple myeloma 1), with a 30% threshold for each marker. The presence of a double-expressor phenotype is determined by assessing Bcl-2 and c-myc expression, using cutoffs of 50% and 40%, respectively. Additionally, Epstein-Barr virus-positive DLBCL (EBV DLBCL) is identified through Epstein-Barr virus in situ hybridization (EBV ISH) staining. Patients with gastric MALT lymphoma generally have a favorable clinical course, however, optimal diagnostic modalities, such as biopsy and IHC, are crucial in tailoring treatment.

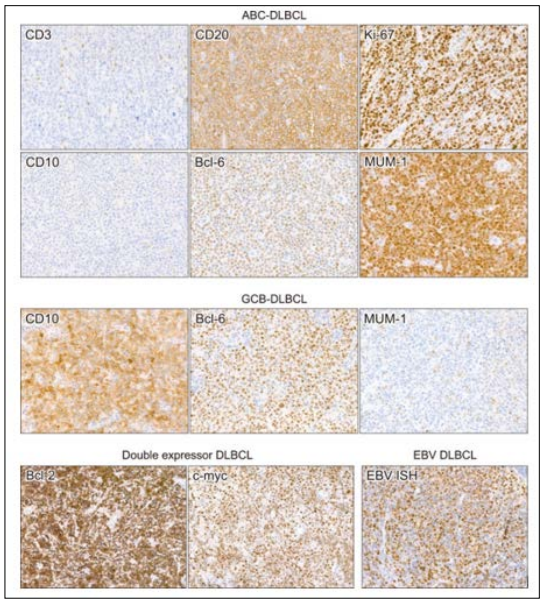

Figure 8: Representative Immunohistochemical Staining Images of Various Types of Diffuse Large B-Cell Lymphomas

Neuroendocrine Tumors

Neuroendocrine neoplasms can arise in many different organs with the gastrointestinal tract being a common site. The 5th edition of the 2019 World Health Organization classification of digestive tumors describes important updates and advancements, including a new system for the classification of neuroendocrine neoplasms. Previously, grade 3 neuroendocrine tumors (NETs) were regarded as neuroendocrine carcinomas (NECs). However, studies have demonstrated genetic variations between grade 3 NETs and NECs. The new update provides distinction between well-differentiated NETs and poorly differentiated NECs. Most gastrointestinal neuroendocrine neoplasms are well differentiated while NECs are relatively rare. NETs can vary in their morphological features, but generally tumor features consist of clusters or sheets of cells with round to ovoid nuclei.

Gastrointestinal NETs most commonly arise in the midgut, notably the ileum and appendix. The application of IHC in the diagnoses of such tumors has been well studied. Traditionally, markers include synaptophysin and chromogranin A, with the former considered more sensitive and the latter more specific. In recent years, there have been studies investigating the expression of somatostatin receptors (SSTRs). In a study done by Popa et al, results demonstrated that well differentiated NETs had increased expression of SSTR2 and SSTR5 compared to high-grade NETs [26]. They found an inverse correlation with neuroendocrine tumor grade, where immunohistochemical reactivity of SSTRs decreased with increasing malignancy. Additional NET markers include cytokeratins and CD56. Although NECs typically express CD56, its presence should be cautiously evaluated due to its low specificity. Insulinoma-associated protein 1 (INSM1) has emerged as a key neuroendocrine marker with a higher sensitivity than synaptophysin or chromogranin A. However, it can be positive in other types of tumors so it should not be used alone for neuroendocrine differentiation. Gastrointestinal neuroendocrine neoplasms are often diagnosed late in the disease process due to most patients being asymptomatic. In the differentiation of NETs, IHC evaluation is a necessary tool and research continues to discover novel immunomarkers to aid in the diagnostic process.

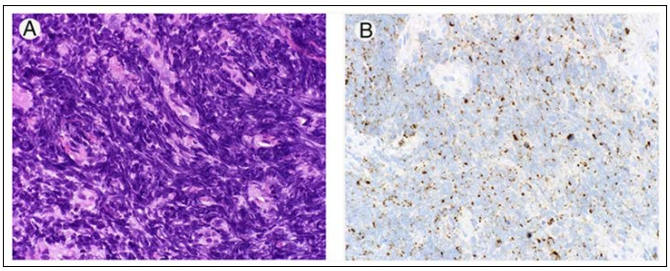

Figure 9: Chromogranin A (CgA) Expression by Small Cell Neuroendocrine Carcinoma.

Conclusion

In the workup of various GI tumors particularly when faced with metastatic neoplasms of unknown primary, the performance of high-quality endoscopy is of prime importance, tissue acquisition is critical because "tissue is the issue", and finally the skills of an expert GI pathologist are crucial to this multidisciplinary team approach for proper diagnosis and management.

When tumor mass has positive IHC staining for CDX-2, or the combination of CK-20 positivity and CK-7 negativity, it is highly suggestive of colo-rectal cancer. When the tissue sample has IHC staining that is CK-7 positive and CK-20 positive it is suggestive

of pancreatic or biliary cancer (Hepato-Biliary-Pancreatic HBP origin), but could be mucinous ovarian cancer or urothelial tumor. If the tissue sample has IHC staining that is CK-7 negative and CK-20 negative, it is suggestive of hepatocellular cancer, but could be renal cell cancer, head and neck cancer, or squamous cell lung cancer. If the tissue sample has IHC staining that is CD-117 positive and DOG-1 positive, it is virtually diagnostic of a stromal cell tumor (GIST).

Given the frequent overlap of IHC markers between organs and organ systems, it is of utmost importance to take into consideration a patient's clinical context to appropriately delineate where a malignant tissue could have originated. It is the hope of many pathologists, gastroenterologists, hematologists, and oncologists that as more markers are identified and clinical assays are developed, malignancy will be identified more promptly and with higher sensitivity.

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