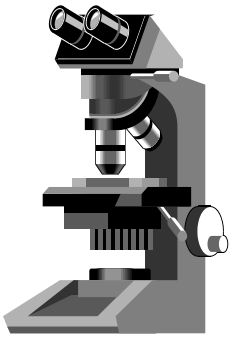
CALIFORNIA
TUMOR TISSUE REGISTRY

DIGESTIVE SYSTEM PATHOLOGY

Minutes – Subscription B

February 2016



California Tumor Tissue Registry
c/o: Department of Pathology and Human Anatomy
Loma Linda University School of Medicine
11021 Campus Avenue, AH 335
Loma Linda, California 92350
(909) 558-4788
FAX: (909) 558-0188
E-mail: cttr@llu.edu
Web site & Case of the Month: www.cttr.org

FILE DIAGNOSES

CTTR Subscription B February 2016

Case 1: **PANCREATIC NEUROENDOCRINE TUMOR, WHO GRADE I,** Pancreas

Case 2: **CAVERNOUS HEMANGIOMA**, Liver

Case 3: **METASTATIC HEPATOCELLULAR CARCINOMA,** Right Adrenal

Case 4: **VILLOUS ADENOMA,** Stomach

Case 5: **CLOACOGENIC CARCINOMA,** Anorectal junction

Case 6: **SIGNET RING CARCINOMA,** Stomach

Case 7: **EPITHELIOID GASTROINTESTINAL STROMAL TUMOR,** Stomach

Case 8: **DIFFUSE LARGE B-CELL LYMPHOMA,** Left Colon Mass

Case 9: **POLYPOID GANGLIONEUROMA,** Colon

Case 10: **METASTATIC MELANOMA,** Stomach

CASE #1: **Accession No. 31947**

DIAGNOSIS: PANCREATIC NEUROENDOCRINE TUMOR (PNET), WHO GRADE I, Pancreas

Diagnoses submitted in decreasing order of frequency:

Well-differentiated pancreatic neuroendocrine tumor
Neuroendocrine tumor, atypical
Neuroendocrine carcinoma
Solid pseudopapillary tumor

Discussion

Tumor consists of nests of cuboidal to polygonal cells with amphophilic cytoplasm and nuclei with salt and pepper chromatin. The morphologic features and immunoprofile are consistent with a well differentiated, Grade I pancreatic neuroendocrine tumor (PNET). The mitotic rate was 1 per 10 high power fields, with a 1.9% Ki-67 labeling index. There was extensive perineural invasion. All 28 regional lymph nodes were negative for metastatic disease.

Pancreatic neuroendocrine tumors (PNETs) are rare neoplasms representing <5% of all pancreatic malignancies. PNETs may be either functional or nonfunctional. Functional PNETs include insulinomas, gastrinomas, VIPomas, glucagonomas, and somatostatinomas. The clinical manifestations associated with these tumors are the result of excessive hormonal secretion and action. Non-functioning PNETs may first present with metastatic disease. The majority of PNETs occur sporadically, others may be associated with hereditary tumor syndromes (MEN, VHL, NF 1).

PNETs are divided into well-differentiated and poorly differentiated categories. Well-differentiated examples have characteristic *organoid* arrangements of the tumor cells, and strong and diffuse immunoexpression of neuroendocrine markers. Poorly differentiated PNETs have a more sheet like or diffuse architecture.

Grade refers to the inherent biologic aggressiveness of the tumor, and is measured by the proliferative rate (mitotic index per 10 high power fields or Ki-67 labeling index, <2, 2-20, >20)). Low-grade PNETs are relatively indolent, high-grade tumors are extremely aggressive, and intermediate grade examples have a less predictable, moderately aggressive course. In general, well-differentiated NETs are either low or intermediate grade, and poorly differentiated NETs are considered high grade in all cases. Low and intermediate grade PNETs are associated with prolonged survival when compared to pancreatic ductal carcinomas.

Markers of primary origin are available for metastatic NETs of unknown origin. For well-differentiated NETs, thyroid transcription factor-1 (TTF1) labeling favors pulmonary origin, CDX2 expression is typical of intestinal or pancreatic primaries, and PDX1 or Isl1 are most commonly expressed in pancreatic NETs.

Differential diagnosis:
Chronic pancreatitis (islet cell hyperplasia may resemble pancreatic endocrine neoplasms, there is no perineural invasion)
IPMN (small, incidentally identified pancreatic endocrine tumors compress the main pancreatic duct and present clinically, radiologically, and grossly as intraductal papillary mucinous neoplasm
Solid pseudopaillary neoplasm (alpha1-antitrypsin+, vimentin+, CD10+, PR+, nuclear staining for beta-catenin)

CASE #2: **Accession No. 31982**

DIAGNOSIS: CAVERNOUS HEMANGIOMA, Liver

Diagnoses submitted in decreasing order of frequency:
Cavernous hemangioma
Lymphangioma

Discussion
Liver tissue shows variably sized vascular spaces lined by endothelial cells with intervening fibrous stroma. Focalintravascular thrombi are present.

Hemangiomas are the most common primary hepatic tumor, more commonly found in women, and are usually asymptomatic. They may increase in size in pregnancy or with OCP use. They may be associated with multiple focal nodular hyperplasia syndrome. Hemangiomas may be capillary or cavernous type, and are usually solitary, 2-4 cm. Giant cavernous hemangiomas may require surgical resection as they may rupture. Elastin and trichrome stains help highlight the vasculature in old (fibrous) lesions.

Differential diagnosis: Peliosis hepatis (blood lakes, no fibrous septae), Hemangioendothelioma (focal atypia)

CASE #3: **Accession No. 31835**

DIAGNOSIS: METASTATIC HEPATOCELLULAR CARCINOMA (HCC), Right Adrenal

Diagnoses submitted in decreasing order of frequency:
Metastatic hepatocellular carcinoma
Adrenal cortical carcinoma
Neuroendocrine carcinoma, metastatic
Pheochromocytoma

Discussion

The adrenal mass shows medium sized tumor cells growing in cords and trabeculae with focal acinar growth pattern. Tumor cells contain granular eosinophilic cytoplasm, large nuclei with prominent nucleoli. Surrounding spindled endothelial cell rimming is present. Focal intracellular bile production is present. This is a case of metastatic well differentiated hepatocellular carcinoma (HCC) from a cirrhotic patient to the adrenal glands. HCC is Hep Par 1+; CD 10, pCEA and villin show canalicular staining.

The adrenal gland is the second most common site of hematogenous spread from HCC after the lung, present in up to 8.4% of cases at autopsy. Arterial spread via the aorta is postulated to be responsible for the metastatic spread. It is however rare to have adrenal metastasis as the first clinical manifestation.

CASE #4: **Accession No. 28470**

DIAGNOSIS: VILLOUS ADENOMA, Stomach

Diagnoses submitted in decreasing order of frequency:

Villous adenoma, polyp
Tubulovillous adenoma
Adenoma, foveolar type with low grade dysplasia
Hyperplastic gastric polyps, focal intestinal metaplasia
Adenocarcinoma arising from gastric adenoma, foveolar type
Signet ring cell carcinoma

Discussion

Gastric polyp shows tall villous projections lined by columnar cells with enlarged basally oriented nuclei. There was focal intramucosal carcinoma, other villous adenoma, polypoid low grade neuroendocrine tumor, chronic gastritis and intestinal metaplasia elsewhere.

Gastric adenomas account for 6-10% of gastric polyps. They are typically flat or polypoid isolated antral lesions, but may also occur in the corpus and cardia. All gastric adenomas should be removed as they are the precursors to gastric adenocarcinomas, the risk is higher in tumors >2cm and villous architecture. The remaining stomach needs to be examined to assess synchronous cancers arising in a dysplastic mucosa. Adenomatous polyps may be sporadic or associated with atrophic gastritis, intestinal metaplasia, and familial adenomatous polyposis and other polyposis syndromes. APC mutations, MSI may occur. Patients should be tested and treated for any active *H. pylori* infection.

Gastric adenomas may be villous, tubular, tubulovillous, sessile or stalked. They may be intestinal, gastric or mixed phenotype. Majority are intestinal type with goblet cells and Paneth cells, associated with H. pylori infection, intestinal metaplasia and more likely to develop high grade dysplasia and adenocarcinoma. Gastric type adenomas are usually solitary, lined by dysplastic mucinous foveolar cells, with normal mucosa in the background and less likely to have coexisting carcinoma.

CASE NO #5: **Accession No. 12753**

DIAGNOSIS: CLOACOGENIC CARCINOMA, Anorectal junction

Diagnoses submitted in decreasing order of frequency:

Infiltrating keratinizing squamous cell carcinoma with basaloid features
Cloacogenic carcinoma
Neuroendocrine carcinoma

Discussion

This basaloid variant of squamous cell carcinoma is also termed cloacogenic or transitional. Small undifferentiated tumor cells are seen growing in plexiform and nodular patterns with central necrosis. Tumor shows focal central keratinization.

Squamous cell carcinoma is the most common malignancy of the anal canal. It is rare, but the incidence is increasing. Tumors above the dentate line are usually non-keratinizing, more common in women, and occur

in the sixth decade. Tumors below the dentate line are more often keratinizing, more common in men, usually in third decade and are associated with HPV and radiation.

Differential diagnosis:

Basal cell carcinoma (smaller cells, less mitoses, peripheral palisading and retraction artifact)
Small cell carcinoma (neuroendocrine markers)
Verrucous carcinoma (exophytic growth pattern)

CASE #6: **Accession No. 31958**

DIAGNOSIS: SIGNET RING CARCINOMA, Stomach

Diagnoses submitted in decreasing order of frequency:
Signet ring carcinoma, poorly differentiated adenocarcinoma diffuse type

Discussion
This is a case of diffuse, poorly cohesive, signet ring type adenocarcinoma. Tumor cells are AE1/AE3 and CAM 5.2 +. There was extensive spread to the regional lymph nodes.

Gastric cancer is the fourth most commonly diagnosed cancer and the second most common cause of cancer-related death worldwide. The incidence of gastric cancer of the proximal stomach is on the rise. The 2010 WHO classification recognizes four major histologic patterns of gastric cancers: tubular, papillary, mucinous and poorly cohesive (including signet ring cell carcinoma). Intestinal type of gastric cancer is often related to Helicobacter pylori infection and intestinal metaplasia, the diffuse type is more often associated with genetic abnormalities and is more common in females and the young.

Poorly cohesive carcinomas are often composed of a mixture of signet ring cells and non-signet ring cells. There is often marked desmoplasia in the gastric wall giving rise to linitis plastica. There are no known risk factors except rare hereditary diffuse gastric cancer (autosomal dominant, with E-cadherin gene mutation - CDH1). Tumor cells show positive staining for: mucicarmine, Alcian blue-PAS, CEA, EMA, keratin, and villin

Differential diagnosis:
Lymphoma
Metastastatic disease (breast, lung)
Therapy changes
Xanthoma

CASE #7: **Accession No. 31955**

DIAGNOSIS: EPITHELIOID GASTROINTESTINAL STROMAL TUMOR, Stomach

Diagnoses submitted in decreasing order of frequency:
Gastrointestinal stromal tumor
Epithelioid GIST

Discussion

This patient had an epithelioid type of gastrointestinal stromal tumor of the stomach. The mitotic index was 1 per 50 HPF. Tumor size was 5 cm. Tumor cells are CD117 +. This GIST is intermediate risk for aggressive behavior.

Gastrointestinal stromal tumors occur predominantly in both male and female adults older than 50 years. Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract. They harbor specific mutations in the *KIT* or platelet-derived growth factor receptor α (*PDGFRA*) receptor tyrosine kinases, making them responsive to certain specific pharmacologic inhibitors.

Microscopically, most GISTs demonstrate 3 main histologic subtypes: spindle cell type (most common), epithelioid type, and mixed spindle and epithelioid type. Epithelioid GISTs are characterized by rounded cells arranged in nests or sheets, with variably eosinophilic to clear cytoplasm and vesicular nuclei. Activating mutations of platelet derived growth factor alpha (PDGFA) are often present in epithelioid GISTs. CD117/c-kit, CD34; DOG1 and Vimentin are positive.

Carney triad: young women with a combination of gastric GIST, paraganglioma, and pulmonary chondroma.. The associated GISTs exhibit an epithelioid morphology and appear to be at a higher risk for metastasis, particularly to lymph nodes.

Epithelioid GISTs must be distinguished from melanoma (also KIT +), carcinoma, seminoma (also KIT +), glomus tumor, and clear cell sarcoma.

CASE #8: **Accession No. 32118**

DIAGNOSIS: DIFFUSE LARGE B-CELL LYMPHOMA, Left Colon Mass

Diagnoses submitted in decreasing order of frequency:

Diffuse large B-cell lymphoma, non-germinal center type
Lymphoma, Follicular lymphoma

Discussion

Microscopic examination shows a diffusely infiltrative neoplasm with large sheets of cells without glandular formation or keratin production. The cells are monotonous with irregular nuclear membranes and prominent nucleoli with easily identifiable mitotic activity. Immunohistochemical staining revealed the tumor to be $CD20^{+}$, $BCL6^{+,}$ $MUM1^{+}$ and $PAX5^{+.}$ With a high Ki-67 index.. This is an example of a primary colonic diffuse large B cell lymphoma (DLBCL), non-germinal center B cell immunophenotype..

Primary colorectal lymphoma is a rare malignancy accounting for 3% of all gastrointestinal lymphomas and 0.1-0.5% of all colorectal malignancies. Cecum is the most common site of involvement for colorectal lymphomas, because of abundance of lymphatic tissue. Among primary colorectal lymphomas, the most common histological subtype of colorectal lymphoma is DLBCL. Other primary types include follicular, Burkitt and Mantle cell lymphomas. Lack of specific symptoms can lead to delayed diagnosis, often the primary lymphoma presents as a bulky mass on a physical examination. The gastrointestinal (GI) system is far more commonly a common site for secondary spread of non-Hodgkin lymphomas (NHL).

The etiology of DLBCL is unknown, but risk factors and predisposing conditions include immunodeficiency states and inflammatory bowel diseases. . Grossly there may be plaque-like expansion of mucosa / submucosa, bowel wall thickening, polyps ("multiple lymphomatoid polyposis" if multiple polyps throughout colon) or ulceration. Microscopically DLBCL consists of large size atypical lymphoid cells with prominent nucleoli and basophilic cytoplasm that have a diffuse growth pattern obliterating colonic gland architecture. DLBCL often is associated with genetic abnormalities in the BCL-6 gene, which leads to an uncontrolled cell cycle

CASE # 9: **Accession No. 29769**

DIAGNOSIS: POLYPOID GANGLIONEUROMA, Colon

Diagnoses submitted in decreasing order of frequency:
Ganglioneuroma, Ganglioneuromatosis
Schwannoma

Discussion
Polyp sections show a mixture of ganglion cells and spindles Schwann cells with diffuse growth within the submucosa and muscularis layers. Focal superficial ulceration of this large polyp was present. These foci are $S100^{+}$, NSE^{+}, and $Actin^{-}$. (**Please note** there was an error in the original paperwork with the glass slides that stated the tumor to be NSE negative).

Ganglioneuromas are rare benign tumors of the autonomic nervous system composed of mature ganglion cells and satellite cells. Colonic ganglioneuromas are uncommon. They may present as polypoid ganglioneuromas, ganglioneuromatous polyposis or diffuse ganglioneuromatosis. They may be associated with neurofibromatosis type 1 (NF-1 mutation), MEN 2B/3 (RET mutation,) or Cowden's disease (PTEN mutation).

The intramural proliferation of neural elements in this case resemble diffuse intestinal ganglioneuromatosis, which is associated with multiple endocrine neoplasia type 2B/3, however this patient presented with a solitary large colonic polyp at the hepatic flexure. Genetic sequencing studies would be helpful.

CASE #10: **Accession No. 17805**

DIAGNOSIS: METASTATIC MELANOMA, Stomach

Diagnoses submitted in decreasing order of frequency:
Malignant melanoma, metastatic
Angiosarcoma

Discussion
This gastric neoplasm shows polygonal, epithelioid and spindle cells diffusely infiltrating the mucosa and deeper tissue layers. Mitoses are readily apparent. No in-situ component or melanin pigment is identified. This is a rare example of metastatic melanoma to the stomach. Clinical history, morphologic features and pertinent special stains are useful for accurate diagnosis.

The stomach is regarded as a rare site for metastasis. Gastric masses are usually presumed to be primary carcinomas. Metastases to the GI tract can present at the time of primary diagnosis or decades later as the first sign of recurrence. In patients with a history of melanoma, a high index of suspicion for metastasis must always be maintained. Metastatic melanoma may mimic primary tumors microscopically especially if tumor cells are epithelioid, spindled and amelanotic. Primary gastric mucosal melanomas are extremely rare, patients often present with dysphagia. Junctional or *in-situ* melanoma component with intact epithelium overlaying invasive melanoma is the main criteria for diagnosis of primary melanoma. This can be very challenging as most lesions tend to be ulcerated at the time of biopsy. Tumor cells are S100, Melan A, HMB45, MART, Fontana-Masson positive.

Differential diagnosis:
GIST (CD 117, CD 34+)
Poorly differentiated adenocarcinoma (CK+)
Anaplastic large cell lymphoma
Sarcoma

References/Suggested Reading:

Hill, J. S., McPhee, J. T., McDade, T. P., Zhou, Z., Sullivan, M. E., Whalen, G. F. and Tseng, J. F. (2009), Pancreatic neuroendocrine tumors. Cancer, 115: 741–751. doi: 10.1002/cncr.24065

Pancreatic neuroendocrine tumors**,** E Batcher, P Madaj, AG Gianoukakis - Endocrine research, 2011, 35 – 43

Pancreas: August 2010 - Volume 39 - Issue 6 - pp 707-712, doi: 10.1097/MPA.0b013e3181ec124e
NANETS Guidelines
The Pathologic Classification of Neuroendocrine Tumors: A Review of Nomenclature, Grading, and Staging Systems, Klimstra, David S. MD*; Modlin, Irvin R. MD, PhD†; Coppola, Domenico MD‡; Lloyd, Ricardo V. MD, PhD§; Suster, Saul MD‖

Schmitt AM, Riniker F, Anlauf M, et al. Islet 1 (Isl1) expression is a reliable marker for pancreatic endocrine tumors and their metastases. *Am J Surg Pathol*. 2008;32:420-425

Saqi A, Alexis D, Remotti F, et al. Usefulness of CDX2 and TTF-1 in differentiating gastrointestinal from pulmonary carcinoids. *Am J Clin Pathol*. 2005;123:394-404.

Hepatogastroenterology. 1999 Jul-Aug;46(28):2523-8. Adrenal metastasis from hepatocellular carcinoma (HCC): report of 3 cases. Taniai N[1], Egami K, Wada M, Tajiri T, Onda M.

World J Surg Oncol. 2005; 3: 50. , Published online 2005 Jul 25. doi: 10.1186/1477-7819-3-50
PMCID: PMC1187929, Adrenal metastasis as first presentation of hepatocellular carcinoma
Kostas Tsalis,[1] Emmanouil Zacharakis,[1] Nikolaos Sapidis,[1] Ioannis Lambrou,[1] Evangelos Zacharakis,[1] and Dimitrios Betsis[1]

Carmack SW, Genta RM, Graham DY, Lauwers GY. Management of gastric polyps: a pathology-based guide for gastroenterologists. Nat Rev Gastroenterol Hepatol 2009; 6:331.

Am J Surg Pathol. 1996;20 Suppl 1:S8-22., Intestinal and diffuse gastric cancers arise in a different background of Helicobacter pylori gastritis through different gene involvement.
Solcia E[1], Fiocca R, Luinetti O, Villani L, Padovan L, Calistri D, Ranzani GN, Chiaravalli A, Capella C.

J Gastrointest Oncol. 2012 Sep; 3(3): 251–261. , doi: 10.3978/j.issn.2078-6891.2012.021

PMCID: PMC3418539, Gastric cancer: Classification, histology and application of molecular pathology
Bing Hu,[1] Nassim El Hajj,[2] Scott Sittler,[1] Nancy Lammert,[1] Robert Barnes,[1] and Aurelia Meloni-Ehrig[3]

Deepa T. Patil, Brian P. Rubin, (*2011*) Gastrointestinal Stromal Tumor: Advances in Diagnosis and Management. Archives of Pathology & Laboratory Medicine: October 2011, Vol. 135, No. 10, pp. 1298-1310. , doi**:** http://dx.doi.org/10.5858/arpa.2011-0022-RA

Risk of Aggressive Behavior in GISTs, Fletcher et al, 2002, *Human Pathology* 33(5):459-65

Rare Tumors. 2013 Apr 15; 5(2): 85–88. , Published online 2013 Jun 7. doi: 10.4081/rt.2013.e23
PMCID: PMC3719118, Primary Diffuse Large B-Cell Lymphoma of the Ascending Colon
Aram Barbaryan,[1] Alaa M. Ali,[1] Shawn G. Kwatra,[1] Raya Saba,[1] Suartcha Prueksaritanond,[1] Nasir Hussain,[1] Aibek E. Mirrakhimov,[1] Natalya Vladimirskiy,[1] Teresita Zdunek,[2] and Alan D. Gilman[1]

Doolabh N, Anthony T, Simmang C, et al. Primary colonic lymphoma. J Surg Oncol 2000;74:257-62

J Pediatr Surg. 2009 Jan;44(1):e17-20. doi: 10.1016/j.jpedsurg.2008.10.037. A ganglioneuroma of the sigmoid colon presenting as leading point of intussusception in a child: a case report. Soccorso G[1], Puls F, Richards C, Pringle H, Nour S.

J Clin Endocrinol Metab. 1998 Dec;83(12):4191-4., Germline RET codon 918 mutation in apparently isolated intestinal ganglioneuromatosis., Eng C[1], Marsh DJ, Robinson BG, Chow CW, Patton MA, Southey MC, Venter DJ, Ponder BA, Milla PJ, Smith VV.

Tumori. 2010 May-Jun;96(3):496-7., Metastatic gastric melanoma: a challenging diagnosis.
Bahat G[1], Saka B, Colak Y, Tascioglu C, Gulluoglu M.

Mayo Clin Proc. 2006 Apr;81(4):511-6., Metastatic malignant melanoma of the gastrointestinal tract.
Liang KV[1], Sanderson SO, Nowakowski GS, Arora AS

Malignant Melanoma of the Stomach Presenting in a Woman: A Case Report, Vedat Goral; Feyzullah Ucmak; Serdar Yildirim; Sezgin Barutcu; Serdar İleri; İlknur Aslan; Huseyin Buyukbayram, J Med Case Reports. 2011;5