

# Gastrointestinal and Liver Pathology at Rush

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## Case of the Month Answer – April 2008

*Contributed by Drs. Deborah Giusto and Shriram Jakate*

### **Diagnosis: Metastatic well-differentiated neuroendocrine carcinoma.**

Neuroendocrine tumors in the liver are usually metastasis from the gastrointestinal tract, pancreas or lung; while primary hepatic neuroendocrine tumors are extremely rare. Only about 30 cases of primary neuroendocrine tumors of the liver have been described in the literature.

Neuroendocrine tumors are classified as those originating from the foregut (including respiratory tract, thymus, stomach and pancreas), midgut (including small intestine, appendix, and right colon) and hindgut (including transverse and descending colon, sigmoid and rectum). Within the gastrointestinal tract, the ileum, appendix and rectum are the most common sites, followed by the colon, stomach and duodenum.

The carcinoid syndrome, which is a presenting feature in less than 10% of cases, is caused by high circulating levels of neuroendocrine system hormones. The features of the syndrome include flushing, diarrhea, asthma and tricuspid regurgitation. High serotonin levels are usually found as well, but other vasoactive substances such as histamine can be found. A large tumor mass is generally needed for a sufficient amount of circulating hormone for the patient to have symptoms. Also, because of the presence of a high first-pass metabolism of hormones in the liver, carcinoid syndrome is most often seen in patients with liver metastasis.

Neuroendocrine tumor cells are typically round to polygonal with finely clumped chromatin. The hallmarks of neuroendocrine tumors are their significant degree of monomorphism, uniformity of cell size and bland cytologic features (Figure 1 and 2).

Neuroendocrine tumors are typically strongly positive for the neuroendocrine markers, synaptophysin and chromogranin (Figure 3). Also, most neuroendocrine tumors stain for cytokeratin (CAM 5.2-figure 4), but up to 20% may be keratin negative. Immunohistochemical antibody panels have also been used to predict the origin of such neuroendocrine tumors. For instance, neuroendocrine tumors have been reported to differentially express CK7 and CK20. One study reported a high specificity for CK7 for lung neuroendocrine tumors and CK 20 for gastrointestinal neuroendocrine tumors; however, these findings have not been consistent in larger based studies. More recently, studies using antibodies against organ-specific transcription factors, including CDX2 and thyroid transcription factor (TTF-1) have shown to be specific in diagnosing metastatic neuroendocrine tumors for unknown primary sites. CDX2 (Figure 5) and TTF-1 have high specificities for gastrointestinal and pulmonary neuroendocrine tumors, respectively. Additionally, this study showed that strong CDX2 positivity was more consistently seen in ileal malignant neuroendocrine tumors than in pancreatic islet cell tumors. Our case showed positive staining for synaptophysin, chromogranin, CAM 5.2 and CDX2. Since our case showed strong staining with CDX2 and negative staining for gastrin, insulin, somatostatin and ACTH, a primary gastrointestinal site, such as ileum, was favored over a pancreatic primary.

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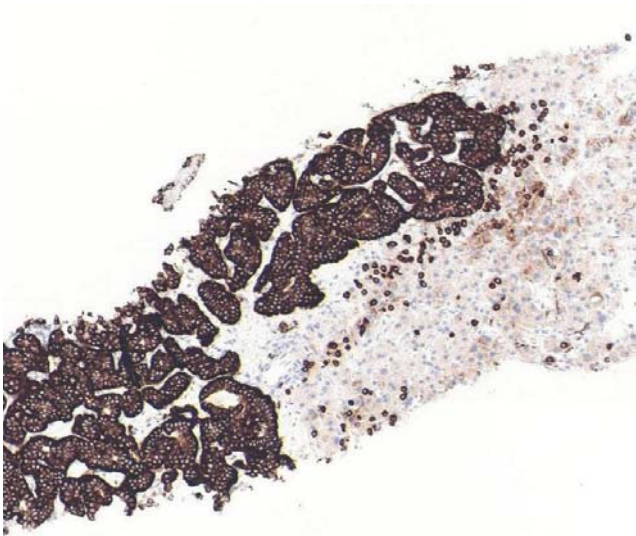


Figure 3. Synaptophysin immunohistochemical stain (40 x magnification).

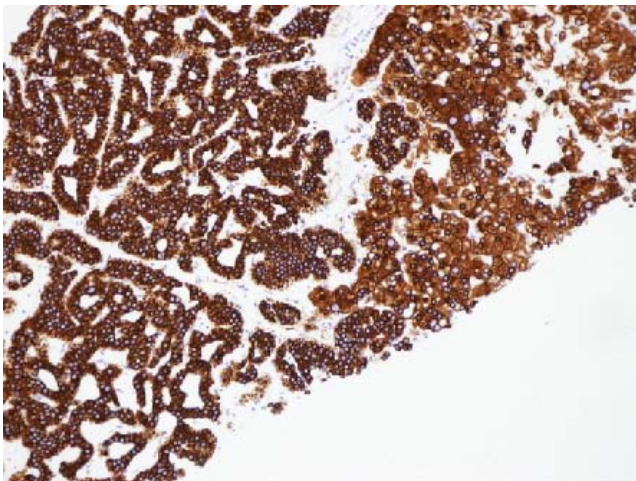


Figure 4. CAM 5.2 immunohistochemical stain (40 x magnification)

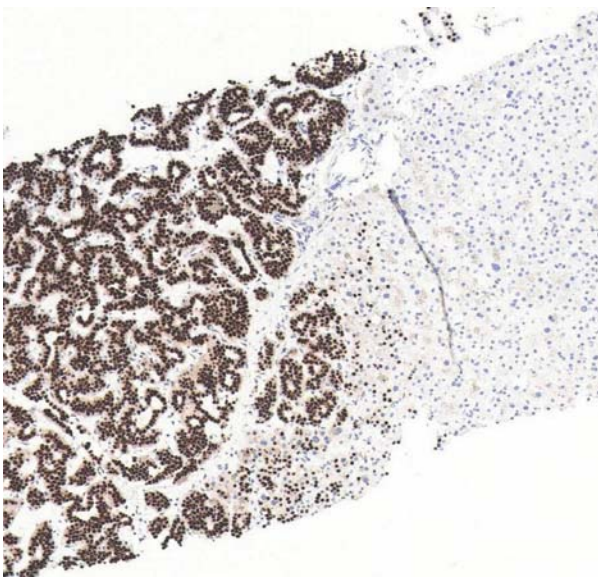


Figure 5. CDX2 immunohistochemical stain (40x magnification)

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## References:

1. Saqi A, Alexis D, Remotti F, and Bhagat G. Usefulness of CDX2 and TTF-1 in differentiating gastrointestinal from primary carcinoids. *Anatomic Pathology* 2004;123: 394-404.
2. Odze R, Goldblum J and Crawford J. *Surgical Pathology of the GI tract, Biliary tract and Pancreas*. 2004.