Synchronous Small Cell Neuroendocrine Carcinoma and Adenocarcinoma of the Colon: A Link for Common Stem Cell Origin?

Seth Lipka, MD1, Jorge Hurtado-Cordovi, MD2, Boris Avezbakiyev, MD3, Lester Freedman, MD4, Toshimasa Clark, MD5, Kaleem Rizvon, MD6, and Paul Mustacchia, MD6

1Department of Medicine, University of South Florida Morsani College of Medicine, Tampa, FL
2Department of Hematology–Oncology, Miller School of Medicine, University of Miami, Miami, FL
3Department of Medicine, Division of Hematology and Oncology, Nassau University Medical Center Associated with North Shore-Long Island Jewish Health Care System, East Meadow, NY
4Department of Pathology, Nassau University Medical Center Associated with North Shore-Long Island Jewish Health Care System, East Meadow, NY
5Department of Radiology, Nassau University Medical Center Associated with North Shore-Long Island Jewish Health Care System, East Meadow, NY
6Department of Medicine, Division of Gastroenterology, Nassau University Medical Center Associated with North Shore-Long Island Jewish Health Care System, East Meadow, NY

Abstract
Synchronous carcinomas have been recognized for over a century, with synchronous primary adenocarcinoma of the colon reported to range from 2–11% of cases involving this type of malignancy. Small cell carcinomas occur frequently with colorectal adenomas; however, despite these reports and a known adenoma-to-carcinoma sequence, scarce literature exists on synchronous colorectal adenocarcinoma and small cell carcinomas. We present a rare cancer of synchronous small cell neuroendocrine carcinomas and discuss a possible link between these two cancers.

Introduction
Colorectal adenocarcinoma is the most common colorectal malignancy. Small cell neuroendocrine carcinomas (SCNC) are rare entities accounting from 0.1–3.9% of colorectal cancers. The estimated prevalence of synchronous primary adenocarcinoma of the colon is 2–11%. SCNC is frequently associated with adjacent colorectal adenomas, but it is rarely associated with colorectal adenocarcinoma. Histologically, SCNC is largely heterogenous, ranging from glandular to squamous in differentiation supporting derivation from a pluripotent stem. We describe a rare case of a synchronous SCNC and adenocarcinoma of the colon and review the current literature discussing a possible pathogenetic link between these two entities.

Case Report
A 63-year-old African American male with a history of HIV and chronic HCV presented to the emergency room with malaise, abdominal pain, hematochezia, constipation, and a 50-pound weight loss over the prior 5 months. The abdominal pain was diffuse, located primarily in the right lower quadrant, constant, burning, non-radiating,
Small Cell Neuroendocrine Carcinoma of the Colon

Lipka et al

Histologically, neuroendocrine tumors are classified based on tumor differentiation (well vs. poorly differentiated) and tumor grade (grade 1–3). Differentiation, tumor grade, Ki-67 proliferation index and mitotic counts are used to assess aggressiveness and prognosis. High-grade neuroendocrine carcinomas include both SCNC and large cell neuroendocrine carcinoma.

Discussion

Neuroendocrine tumors of the colon and rectum are divided into either carcinoid tumors with low-grade atypia and malignancy or neuroendocrine cell carcinomas with high-grade atypia and malignancy. Histologically, neuroendocrine tumors are classified based on tumor differentiation (well vs. poorly differentiated) and tumor grade (grade 1–3). Differentiation, tumor grade, Ki-67 proliferation index and mitotic counts are used to assess aggressiveness and prognosis. High-grade neuroendocrine carcinomas include both SCNC and large cell neuroendocrine carcinoma.

SCNC of the gastrointestinal tract were first described by Mckeown in 1952, when he published two cases of esophageal tumors morphologically indistinguishable from SCNC found in the lung. Colonic SCNCs were later introduced into the medical community by Gould in 1978. The most common site of metastasis is the liver, followed by the lymph nodes, bones, and bone marrow. In one study, the highest
Small Cell Neuroendocrine Carcinoma of the Colon

Incidence of colonic neuroendocrine tumors occurred in the cecum (48%), followed by the ascending (16%), sigmoid (13%), descending (11%), and then transverse colon (6%).

Synchronous carcinomas have been recognized for over a century, first described in the 1880s by Billroth, Czerny, and Fenger. The estimated prevalence of synchronous primary adenocarcinoma of the colon is 2–11%. Cunliffe et al theorized that the entire colorectal mucosa is unstable and at risk for malignant change in those found to have synchronous and metachronous colorectal carcinomas. One study showed colorectal adenomas in 35% of patients with synchronous colorectal adenocarcinomas compared with only a 15% occurrence rate in those with isolated colorectal adenocarcinoma. Colorectal neuroendocrine tumors are frequently associated with secondary primary tumors, with an annual incidence reported of 3–15%. 17,18

The typical clinical presentation is similar to other colonic masses and includes hematochezia, abdominal pain, altered bowel habits, and signs of bowel obstruction. SCNC may, rarely, secrete hormones such as vasoactive intestinal peptide, antidiurectic hormone, calcitonin, serotonin, parathyroid hormone related protein, or adrenocorticotropic hormone. Morphologically, SCNC is indistinguishable from small cell carcinoma of the lung; occasionally, immunohistochemical staining for thyroid transcription factor-1 (TTF-1) can help distinguish the two. These malignant cells typically contain minimal cytoplasm, fusiform cell shape, granular nuclear chromatin, and small or absent nucleoli. Positive neuroendocrine markers for this tumor include neuron-specific enolase, chromogranin, synaptophysin, and CD56 (neural cell adhesion molecule). Despite these markers, the diagnosis of SCNC remains morphological rather than immunohistochemical due to the rarity of the disease. One case series reports LMWK, CK 19 and pancytokeratin, TTF-1 negative stain may be helpful to differentiate SCNC from pulmonary small cell carcinomas, and additional stains CDX2, mCEA, CD56, synaptophysin, NSE, and chromogranin to differentiate high-grade neuroendocrine from non-endocrine poorly differentiated adenocarcinoma.

Treatment for gastrointestinal SCNC is derived from case reports and small retrospective series with no existing expert panel guidelines. The histopathological similarity between SCNC of the colon and lung has led many clinicians to treat SCNC of the colon identically to that of the lung. Treatment is usually surgical for localized disease, whereas metastatic and non-resectable disease is treated with radiation therapy and a backbone of cisplatin, etoposide, cyclophosphamide, and doxorubicin. Gastointestinal SCNC is highly aggressive and, without appropriate treatment, survival is usually measured in weeks.

The histogenesis of gastrointestinal SCNC is largely debated, with a number of theories linking neuroendocrine carcinoma and adenocarcinomas. Contrary to the initial hypothesis by Pearse et al that neuroendocrine carcinoma origin is derived from the amine precursor uptake and decarboxylation cell from neural crest cells, several reports link SCNC with adenomatous colorectal adenomas, suggesting a common stem cell origin similar to that seen in colorectal adenocarcinoma. The morphological differentiation of SCNC from squamous to glandular suggests a divergent differentiation from pluripotent stem cells derived from the endoderm. Recent studies indicate that colonic endocrine cells originate from an endodermal stem cell capable of multidirectional differentiation. Reports of admixed endocrine cells

Figure 4. (A) H&E stain (100x) of colonic mucosa infiltrated by small cells. (B) H&E stain (100x) of small round cells with abundant nucleus and scanty cytoplasm. (C) Immunohistochemical stain positive for neuron specific enolase (40x). (D) Immunohistochemical stain positive for synaptophysin (40x).

Figure 5. Large mass: 8 x 6 x 5 cm; 7 cm to S mass, 10 cm to ileal margin. Small mass: 4 x 3 x 1 cm; 7 cm to D margin.
residing in colonic adenocarcinomas, as well as reports of amphiocrine tumors with both exocrine and endocrine characteristics in the same cell support this theory.4

Vortmeyer et al theorized that a progenitor stem cell could differentiate into two or more diverse cell lines and could account for the development of synchronous, yet histologically different, tumors along the gastrointestinal tract.23 He demonstrated through genetic analysis that poorly differentiated neuroendocrine carcinoma and associated adenocarcinoma appears to be derived from the same cell origin. Although neuroendocrine tumors are easily distinguishable from adenocarcinomas histologically, it is not uncommon to find adenocarcinomas lesions with sections of neuroendocrine differentiation.17 Kato et al reported a CK20 positive (a common marker found in colorectal adenocarcinoma) large cell neuroendocrine tumor that occurred synchronously to a colorectal adenocarcinoma.24 Several cancer predisposing syndromes—such as Li-Fraumeni—promote the development of multiple, histologically different malignancies. These findings support the theory that different types of gastrointestinal neoplasm might originate from a common stem cell clone and/or may share a similar genetic mutation(s) during early oncogenesis.

In conclusion, we believe our case may support a common link between the pathogenesis of these two distinct entities and possible future research in this area.

Disclosures

Author contributions: All the authors contributed equally to the manuscript. S. Lipka is the article guarantor.

Financial disclosure: None of the authors cited above have any conflict of interest. This manuscript did not receive any funding from any organization.

Informed consent was obtained for this case report.

Received: May 12, 2013; Accepted: November 18, 2013

References

1. Saclarides TJ, Szeluga D, Staren ED. Neuroendocrine cancers of the colon and rectum. Results of a ten-year experience. Dis Colon Rectum. 1994;37(7):635–42.
2. Cheng-Cou L, Chih-Wei W, Chung-Rong C, et al. Neuroendocrine carcinomas of the colon and rectum: Results of a 15-year experience. J Soc Colon Rectal Surgeon (Taiwan). 2008;19:87–95.
3. Slater G,aufses AH, Szporn A. Synchronous carcinoma of the colon and rectum. Surg Gynecol Obstet. 1990;171(4):283–7.
4. Gaffey MJ, Mills SE, Lack EE. Neuroendocrine carcinoma of the colon and rectum: A clinicopathologic, ultrastructural and immunohistochemical study of 24 cases. Am J Surg Pathol. 1990;14(11):1010–1023.
5. Sarsfield P, Anthony PP. Small cell undifferentiated (“neuroendocrine”) carcinoma of the colon. Histopathology. 1990;16(4):357–363.
6. Mills SE, Allen MS Jr, Cohen AR. Small-cell undifferentiated carcinoma of the colon. Am J Surg Pathol. 1983;7(7):643–651.
7. Wick MR, Weatherby RP, Welland LH. Small-cell neuroendocrine carcinoma of the colon and rectum. Hum Pathol. 1987;18(1):9–21.
8. Higuchi T, Sugihara K. Diagnosis and treatment of colorectal neuroendocrine cell tumor, Nihon Geka Gakkai Zasshi. 2008;109(3):152–6.
9. Rindi G, Klöppel G, Alhm H, et al. TNN Staging of foregut (neuro)endocrine tumors: A consensus proposal including a grading system. Virchows Arch. 2006;449(4):395–401.
10. McKeown F. Oat-cell carcinoma of the esophagus. J Pathol Bacteriol. 1952; 64:889–91.
11. Gould VE, Chejfec G. Neuroendocrine carcinomas of the colon. Ultrastructural and biochemical evidence of their secretory function. Am J Surg Pathol. 1978;12(1):31–8.
12. Kim Y, Park H, Jang K, et al. Concurrent large cell neuroendocrine carcinoma and adenocarcinoma of the ascending colon: A case report. J Korean Soc Colonoprotol. 2011;27(3):157–161.
13. Brenner B, Tang L, Klimstra DS, Kelsen DP. Small-cell carcinomas of the gastrointestinal tract: A review. J Clin Oncol. 2004;22(13):2730–2739.
14. Czerny LL. Ausdr Heidelberger Chirurgischen Klinik. Nochtgart zur darrmresection. Berl Klin Wechs.1880;17:683.
15. Chen HS, Sheen-Chen SM. Synchronous and “early” metastrophic colorectal adencarcinoma. Analysis of prognosis and current trends. Dis Colon Rectum. 2000;43(8):1093–9.
16. Cunliffe WJ, Hasleton PS, Tweedle DE, Schofield PF. Incidence of synchronous and metachronous colorectal carcinoma. Br J Surg. 1984;71(12):941–3.
17. Ballantyne G, Savoca P, Flannery J, et al. Incidence and mortality of carcinoids of the colon: Data from the Connecticut Tumor Registry. Cancer. 1992;69(10):2400–5.
18. Berardi R. Carcinoid tumors of the colon (exclusive of the rectum): Review of the literature. Dis Colon Rectum. 1972;15(5):383–91.
19. El Demellawy D, Khalifa MA, Simii M, et al. Primary colorectal small cell carcinoma: A clinicopathological immunohistochesmical study of 10 cases. Diag Pathol. 2007;2:35.
20. Pearse A. The APUD cell concept and its implications in pathology. Pathol Annu. 1974;9(0):27–41.
21. Okuyama T, Korenaga D, Tamura S, et al. The effectiveness of chemotherapy with cisplatin and 5-fluorouracil for recurrent small cell neuroendocrine carcinoma of the rectum: Report of a case. Surg Today. 1999;29(2):165–169.
22. Palvio DH, Sorensen FB, Kloeve-Mogensen M. Stem cell carcinoma of the colon and rectum: Report of two cases and review of literature. Dis Colon Rectum. 1985;28(6):440–445.
23. Vortmeyer AO, Lubensky IA, Merino MJ, et al. Concordance of genetic alterations in poorly differentiated colorectal neuroendocrine carcinomas and associated adenocarcinomas. J Natl Cancer Inst. 1997;89(19):1448–53.
24. Kato T, Terashima T, Tomida S, et al. Cytokeratin 20-positive large cell neuroendocrine carcinoma of the colon. Pathol Int. 2005;55(8):524–9.