Small Cell Carcinoma of the Colon Arising in a Carcinoid Tumor

M. WASIF SAIF

Section of GI Cancers and Experimental Therapeutics, Tufts University School of Medicine, Boston, MA, U.S.A.

Abstract. *Small cell carcinomas of the gastrointestinal tract are rare and clinically aggressive tumors. A case is presented of a 70 year-old woman who presented with small bowel obstruction and was found to have a cecal mass. She underwent right hemicolectomy, and histopathology showed a small cell carcinoma arising in the background of a carcinoid tumor. Although small cell carcinomas of the colon have frequently been found in association with colonic adenomas, this appears to be the first report of a low-grade carcinoid tumor in combination with a small cell carcinoma.*

Small cell carcinoma (SmCC) of the gastrointestinal (GI) tract is a rare cancer, estimated to comprise of 0.1-1% of all gastrointestinal malignancies. In a systematic review of the 544 cases of GI SmCC reported in the literature between 1970 and 2003, the mean age of presentation was 64 years, with a male predominance (1). The most common sites of origin for these tumors were the esophagus and stomach, then the colon and rectum. A case of a 70 year-old woman who was diagnosed with small cell carcinoma, arising in the background of a carcinoid tumor in the cecum is presented in the current report. Although small cell carcinomas of the colon have frequently been found in association with colonic adenomas, this appears to be the first report of a low-grade carcinoid tumor in combination with a small cell carcinoma.

Case Report

A 70-year-old woman with a history of osteoarthritis, ascending thoracic aneurysm stable for 10 years, chronic myelogenous leukemia (CML) in remission on dasatinib, and hypothyroidism presented with abdominal pain, nausea and vomiting. She had no signs or symptoms of carcinoid syndrome. On Cat-Scan she had a small bowel obstruction and mucosal thickening of the cecum was seen. The patient underwent a colonoscopy, which revealed a cecal mass, and then underwent a right colectomy.

Macroscopic examination of the hemicolectomy specimen revealed a firm mass measuring 10×9.5 cm and involving the entire entire cecum, ileocecal valve, and appendix. There was gross involvement of the entire colonic wall and the tumor extended into the pericolic fat. Histologically the appearance was of a small cell carcinoma arising in the background of a carcinoid tumor. The mitotic rate was high with >40 mitoses/10 high-power fields. The tumor stained strongly- positively for synaptophysin, negatively for chromogranin, and negative for the lung markers (thyroid transcription factor 1) TTF-1 and napsyn. Staged with the TNM staging system of malignant tumors, the tumor was pT4 with invasion into the serosa and extension to the radial surface of the colon, pN1 with 73/82 lymph nodes involved with tumor. There were no pulmonary nodules on chest CT. Octreotide scan performed after the surgery showed no abnormal accumulation of radiotracer. Serum carcinoembryonic antigen was within normal limits. Although no chromogranin-A levels were available prior to surgery, one month postoperatively the chromogranin-A levels were 60 ng/ml.

At three months postoperatively the patient had right flank pain and on labs her creatinine and had increased from 0.8 to 1.5 mg/dl. A CT of the chest, abdomen and pelvis revealed new perinephric soft tissue nodules, a ureteral deposit and a 7.3×4.8 cm right adnexal mass causing right hydronephrosis. Chromogranin A level at that time had increased to 1,050 ng/ml. A right ureteral stent was placed and she began chemotherapy with carboplatin and etoposide, cycled every three weeks. After three cycles of chemotherapy the adnexal mass had decreased in size to 3×2.7 cm and the chromogranin A level decreased to 528 ng/ml. She continues on treatment.

Discussion

SmCC of the GI tract is a rare cancer, with the most common sites of origin in the decreasing order: esophagus → stomach → colon → rectum. Despite the varied locations of these

Correspondence to: M. Wasif Saif, MD, MBS, Director, Section of GI Cancers and Experimental Therapeutics, Tufts University School of Medicine, Boston, MA 02111, 800 Washington Street, Boston, MA 02111, U.S.A. Tel: +1 6176365627, Fax: +1 6176368538, e-mail: wsaif@tuftsmedicalcenter.org

Key Words: Colon carncer, carcinoid tumor, small cell carcinoma.

tumors, some clinical features are consistent across the sites of origin: most tumors are diagnosed at advanced stage with regional lymph node involvement, and most patients have distant metastases at the time of diagnosis. The most common sites of metastatic disease are liver, distant lymph nodes, and bone. In most series, 70-80% of patients have liver metastases at the time of diagnosis (2, 3).

TNM staging has in some cases been used to stage these tumors. A more practical approach is to stage these tumors in the manner of the Veterans' Administration Lung Study Group, which categorizes small cell lung cancer into two stages: limited disease or extensive disease, with the former defined as tumor that can be safely encompassed in a tolerable radiation field. This results in some difficulties staging GI SmCC, because fixed organs of the GI tract such as the esophagus and rectum are much more amenable to radiation than regions such as the colon. In practice, both staging systems have been used, and both have been shown to correlate well with outcome (4).

The histological features of GI SmCC are similar to those of pulmonary SmCC. Cells are characterized by large nuclei with granular, or salt-and-pepper chromatin and scant cytoplasm. Immunohistochemical markers for neuroendocrine cells such as synaptophysin, chromogranin and CD56 are often positive. Since SmCC of the lung is so much more common than SmCC of the GI tract, chest imaging and specific markers for cells of lung origin such as TTF-1 or napsyn have been used as evidence to support an extrapulmonary origin (5).

Mixed histologies are often observed in GI SmCC; colorectal SmCCs were associated with overlying adenomas in 45% and squamous differentiation in 21% in one pathological study of 38 cases (2). No studies have had sufficient case numbers to clearly establish risk factors for GI SmCCs, but risk factors for esophageal cancer such as achalasia and Barrett's esophagus have been present in some patients with esophageal SmCC, and most cases of gastric SmCCs have been reported from Japan, where the incidence of gastric cancer is higher than in the West (1). Several case reports have noted SmCCs in the setting of inflammatory bowel disease, which also increases the risk of colorectal adenocarcinoma (6-8). It is therefore believed that the risk factors for GI SmCC parallel those for adenocarcinoma of the same type. In a series of poorly-differentiated colorectal neuroendocrine tumors, loss-of-heterozygosity analysis was undertaken on colorectal SmCC and associated adenocarcinoma or adenoma (9). In cancers with deletion of p53 or DCC (deleted in colorectal cancer gene), microdissected specimens of both components contained identical alleles of p53 and DCC, showing that both components have the same clonal origin (9). Other studies have identified identical mutations in oncogenes such as K-ras and p53 in SmCC and adjacent adenoma (6). This supports the hypothesis that GI SmCC arises from a multipotent stem cell that retains the ability to differentiate into both adenocarcinomatous and neuroendocrine components of the tumor (9). However SmCC arising in the presence of carcinoid has not, to our knowledge been reported previously, and carcinoid has not been demonstrated to be a risk factor for SmCC.

The treatment and prognosis of SmCC of the GI tract is highly dependent on stage. Systemic chemotherapy is a mainstay of treatment for both pulmonary and GI SmCC, mainly with etoposide and either carboplatin or cisplatin. Combinations using cyclophosphamide, doxorubicin, and a platinum agent have also been used. As in SmCC, patients have an objective but short-lived response to chemotherapy; in one series of SmCC of the colon, two out of the three patients had a partial response to a chemotherapy regimen consisting of cyclophosphamide, etoposide and cisplatin but these responses lasted just three and nine months (10). In another single-institution series that included 3 patients with colorectal SmCCs, chemotherapy with cisplatin and etoposide yielded similar results; responses were seen in two out of the three patients but both had progression of disease at 7 and 8.7 months, and no response to second-line chemotherapy with topotecan (11). Although study of one series of GI neuroendocrine tumors treated with cisplatin and etoposide reported a 67% response rate and overall survival of 19 months (13), this series included patients with carcinoid and neuroendocrine non-small cell tumors. Case series limited to tumors with small cell histology report a mean overall survival of 10-12 months (7, 14). No cases appear to have reported use of targeted-agents, although one case series of colorectal SmCCs reported that 7/10 tumors overexpressed epidermal growth factor receptor (EGFR) by immunohistochemistry, and this could represent a treatment option in future (15).

Other adverse prognostic factors include the size of the primary tumor (>5 cm), performance status, and weight loss (1, 16, 17).

One difference between GI and pulmonary SmCC is the potential role of locoregional therapy. In a study based on cases from the SEER registry, extrapulmonary and pulmonary SmCC were examined to determine the effect of treatment modality on survival (12). In this study pulmonary and GI SmCC had a similarly dismal 5-year survival of 5% and 7%, respectively. Both surgery and radiation were found to improve 5-year overall survival in GI SmCC, although due to the limitations of the SEER registry, the timing of surgery and radiation (adjuvant or neoadjuvant), and the concomitant use of chemotherapy could not be studied. However in one retrospective study of 199 patients with esophageal SmCC, local therapy-alone was found to be insufficient, with improvement in median overall survival from 5 to 20 months with the addition of multimodal therapy (16). In one case of a patient with colorectal SmCC and multiple liver lesions,

complete metabolic response was observed on positron emission tomography (PET) and long-term survival was achieved only after chemotherapy and chemoembolization of liver metastases (18). Since the disease metastasizes early in its clinical course, most recommendations have been for early chemotherapy or chemoradiation, followed by surgery for limited disease. Surgery however should be performed early in cases with complications from local disease, such as the small bowel obstruction our patient presented with.

The rarity of GI SmCC makes it unlikely that any prospective clinical studies will ever become available to guide recommendations for treatment. In the absence of these recommendations single-institution case series and case reports form the basis of evidence with which to treat patients. In this case the patient has had a partial response to systemic chemotherapy for extensive disease. However multidisciplinary evaluation and locoregional treatment can achieve long-term survival in a small minority of patients when combined with systemic chemotherapy.

Acknowledgements

Author thanks Idella Middleton for editing the manuscript.

References

1 Brenner B, Tang LH, Klimstra DS and Kelsen DP: Small cell carcinomas of the gastrointestinal tract: A review. J Clin Oncol *22*: 2730-2739, 2004.
2 Burke AB, Shekitka KM and Sobin LH: Small cell carcinomas of the large intestine. Am J Clin Pathol *95*: 315-321, 1991.
3 Hung SS: Small cell carcinoma of the colon. A case report and literature review. J Clin Gastroenterol *11*: 335-339, 1989.
4 Brenner B: Shah MA, Gonen M, Klimstra DS, Shia J and Kelsen DP: Small-cell carcinoma of the gastrointestinal tract: a retrospective study of 64 cases. Br JC *90*: 1720-1726, 2004.
5 Ordonez NG: Value of thyroid transcription factor-1, E-cadherin, BG8, WT1, and CD44S immunostaining in distinguishing epithelial pleural mesothelioma from pulmonary and nonpulmonary adenocarcinoma. Am J Surg Pathol *24(4)*: 598-606, 2000.
6 Hayashi H, Miyagi Y, Sekiyama A, Yoshida S, Nakao S, Okamoto N, Koganei K and Sugita A: Colorectal small cell carcinoma in ulcerative colitis with identical rare p53 gene mutation to associated adenocarcinoma and dysplasia. J Crohns Colitis *6(1)*: 112-115, 2012.
7 Yaziji H and Broghamer WL Jr.: Primary small cell undifferentiated carcinoma of the rectum associated with ulcerative colitis. South Med J *89*: 921, 1996.
8 Kosomidis C, Efthimiadis C, Anthimidis G, Vasiliadou K, Tzeveleki I, Fotiadis P and Basdanis G: Small cell carcinoma in ulcerative colitis – new treatment option: A case report. World J Surg Oncol *8*: 100-104, 2010.
9 Vortmeyer AO, Lubensky IA, Merino MJ, Wang CY, Pham T, Furth EE and Zhuang Z: Concordance of genetic alterations in poorly differentiated colorectal neuroendocrine carcinomas and associated adenocarcinomas. J Nat Cancer Inst *89(19)*: 1448-1453, 1997.
10 Acea Nebril B, Bouso Montero M, Arnal Monreal F, Gómez Freijoso C, Sánchez González F and Freire Rodríguez D: Undifferentiated small cell carcinoma (oat-cell type) of the colon. Prognostic and therapeutic implications. Rev Esp Enferm Dig *88(8)*: 533-538, 1996.
11 Kim JH, Lee SH, Park J, Kim HY, Lee SI, Nam EM, Park JO, Kim K, Jung CW, Im YH, Kang WK, Lee MH and Park K: Extrapulmonary small-cell carcinoma: a single-institution experience. Jap J Clin Oncol *34(5)*: 250-254, 2004.
12 Grossman RA, Pedroso FE, Byrne MM, Koniaris LG, and Misra S. Does surgery or radiation therapy impact survival for patients with extrapulmonary small cell cancers? J Surg Oncol *104*: 604-612, 2011.
13 Moertel CG, Kvols LK, O'Connell MJ and Rubin J: Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin. Evidence of major therapeutic activity in the anaplastic variants of these neoplasms. Cancer *68*: 227-232, 1991.
14 Bernick PE, Klimstra DS, Shia J, Minsky B, Saltz L, Shi W, Thaler H, Guillem J, Paty P, Cohen AM and Wong WD: Neuroendocrine carcinomas of the colon and rectum. Dis Colon and Rectum *47(2)*: 163-169, 2000.
15 El Demellawy D, Samkari A, Sur M, Denardi F and Alowami S: Primary small cell carcinoma of the cecum. Ann Diagnostic Pathol *10*: 162-165, 2006.
16 Casas F, Ferrer F, Farrús B, Casals J and Biete A: Primary small cell carcinoma of the esophagus: A review of the literature with emphasis on therapy and prognosis. Cancer *80(8)*: 1366-1372, 1997.
17 Brennan SM, Gregory DL, Stillie A, Herschtal A, Mac Manus M and Ball DL: Should extrapulmonary small cell cancer be managed like small cell lung cancer? Cancer *116(4)*: 888-895, 2010.
18 Power DG, Asmis TR, Tang LH, Brown K and Kemeny NE: High-grade neuroendocrine carcinoma of the colon, long-term survival in advanced disease. Med Oncol *28*: S169-S174, 2011.

Received February 9, 2013
Revised March 18, 2013
Accepted March 19, 2013