Squamous Cell Carcinoma of the Sigmoid Colon Presenting With Severe Hypercalcemia

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Clinical Practice Points

- Primary squamous cell carcinoma of the colorectum is an unusual gastrointestinal cancer. These cancers have an uncertain pathogenesis, and the clinical literature provides limited information on the natural history and response to treatment.
- This report discusses a patient who presented with severe symptomatic hypercalcemia (21.08 mg/dL). Colonoscopy found a partially obstructing mass in the sigmoid colon, and computed tomography of the abdomen found hepatic metastasis and para-aortic lymphadenopathy. A liver biopsy established the diagnosis of metastatic squamous cell carcinoma. This patient’s hypercalcemia responded to the usual management strategies for hypercalcemia, including hydration, calcitonin, and pamidronate.
- The patient was treated with carboplatin, paclitaxel, and cetuximab. His posttreatment course was complicated by acute gastroenteritis, health care–associated pneumonia, and possible peritonitis. In addition, follow-up radiographic studies found progression of hepatic disease with development of ascites and peritoneal disease. He died 5 months after diagnosis.
- This case shows that patients with squamous cell carcinoma of the colon can develop severe symptomatic hypercalcemia. This possibility needs to be considered in patients who present with hypercalcemia and do not have obvious parathyroid disease or a malignancy usually associated with hypercalcemia, especially bronchogenic carcinoma.
- The best treatment regimens for these patients who are not surgical candidates are unclear. These patients need more systematic study, possibly through the development of a national registry.

Introduction

Every year more than 145,000 new cases of colon cancer are diagnosed in the United States, with over 90% being adenocarcinomas.1 Primary squamous cell carcinoma (SCC) of the colorectum is a rare malignancy, with an incidence of fewer than 1 in 1000 diagnosed colorectal cancers.2-4 This report presents a 53-year-old man who presented with severe hypercalcemia secondary to metastatic SCC of the sigmoid colon.

Case Report

A 53-year-old man with a history of psoriasis presented to the emergency department in May 2013 with diffuse epigastric pain of approximately 2 months’ duration. His family reported him as being “confused” for 2 to 3 weeks. The patient’s physician had treated his epigastric pain with ranitidine without relief. The patient reported a marked decrease in appetite associated with a weight loss of over 50 pounds during the previous 3 months, nausea, vomiting, alternating episodes of constipation and diarrhea, and occasional dark stools. The patient had smoked cigarettes for more than 20 years. He also reported occasional use of alcohol but no illicit drug use. He had no personal history of malignancy. He did have a family history of lung and breast cancer.

Upon his admission, the physical examination found a middle-aged man, somewhat lethargic and disoriented to place and time. His vital signs were within the reference ranges; his oral mucosa was slightly dehydrated. His cardiopulmonary examination was unremarkable; no lymphadenopathy was evident. Abdominal examination found normal bowel sounds and diffuse epigastric tenderness. The liver was palpable 8 to 9 centimeters below the right costal margin, and the patient exhibited voluntary guarding. No splenomegaly, ascites, vascular redistribution, or abdominal masses were found. He had erythematous plaques in the upper and lower
extremities compatible with psoriasis. The rectal examination was deferred owing to the patient’s uncomfortable state.

Relevant laboratory test results included the following: white blood cell count, 18,000 cells/µL; hemoglobin level, 14.0 g/dL; sodium, 124 mEq/L; potassium, 3.6 mEq/L; calcium, 21.08 mg/dL (corrected); blood urea nitrogen, 25 mg/dL; creatinine, 1.4 mg/dL; albumin, 3.4 g/dL; and alkaline phosphatase, 319 IU/L. The parathyroid hormone (PTH) level was 8 pg/L (reference range, 15-65 pg/L). The PTH-related protein level was 48 pg/mL (reference range, 14-27 pg/mL), and the carcinoembryonic antigen level was 127.3 ng/mL (reference range, 0.2-3.4 ng/mL). All other laboratory results were within the reference ranges.

Computed tomography (CT) scans of the abdomen and pelvis (Figure 1) found a mass in the sigmoid colon, hepatic lesions, and para-aortic lymphadenopathy, compatible with metastatic disease. CT scans of the head and of the chest were negative. These radiographic studies did not find any lytic bone lesions. Intravenous fluids, calcitonin, and pamidronate were started. Colonoscopy found an ulcerated, partially obstructing mass in the sigmoid colon. The mass was circumferential (involving two-thirds of the lumen circumference) and measured 8 centimeters in length. No bleeding was present. He had external and internal hemorrhoids but no anal mass. Biopsy of the sigmoid colon mass found mucosal ulceration with evidence of a “healing injury.”

An ultrasonography-guided liver biopsy (Figure 2) found metastatic poorly differentiated carcinoma with squamous differentiation. Tumor cells were positive for cytokeratin (CK) AE1/AE3 and p63 immunostains and negative for CK20, CK7, and TTF1 (thyroid transcription factor 1 [NKX2-1]). There was not enough tissue for KRAS (Kirsten rat sarcoma viral oncogene homolog) and EGFR (epidermal growth factor receptor) analysis. A squamous cell antigen level had decreased from 127 to 85 ng/dL, and his calcium level remained within the reference range, suggesting some response to systemic therapy. The patient was discharged and readmitted in late August with progressive abdominal distention, nausea, and vomiting. Paracentesis suggested bacterial peritonitis, and he was treated with antibiotics. He was discharged home with hospice care and died in September 2013.

**Discussion**

SCC of the colorectum is a rare malignancy, with a frequency of 0.25 to 1 case per 1000 colon cancers diagnosed. In 2010, Sameer et al identified 114 cases in the worldwide literature. The most common location of SCC is the rectum, followed by the right colon. Miyamoto et al reported that up to 65% of these tumors occur in the rectosigmoid colon. Most patients with SCC of the colorectum are aged between 39 and 60 years, with a peak incidence around the sixth decade of life. Dyson and Draganov reported that 66% of these tumors occur in women and 34% in men, whereas Copur et al found a slight predominance in men. The diagnosis of colorectal SCC depends on histologic criteria and requires consideration of malignancies from other organs, including the anal region. An important first step is to rule out the presence of a fistulous tract lined by squamous cells from the anus. The most common
presenting symptoms of these patients are rectal bleeding, abdominal pain, changes in bowel habits, and weight loss. Hypercalcemia is an uncommon occurrence in patients with gastrointestinal malignancies and is rarely part of the initial clinical presentation.9,10 To the authors’ knowledge, this is the first case report of a patient with metastatic SCC of the colon presenting with severe, symptomatic hypercalcemia. He responded well to the usual treatment of hypercalcemia.

Several hypotheses have been proposed to explain the development of SCC in colorectal tissues. Multiple case reports suggest a strong association between SCC of the colorectum and inflammatory processes (such as ulcerative colitis), infections with Schistosoma spp or Entamoeba histolytica (or both), and radiation-induced tissue damage.4,8,11 An association between SCC of the colorectum and human papillomavirus (HPV) infection has been suggested but remains controversial. Audeau et al.12 evaluated the role of HPV in 20 patients with adenosquamous colorectal cancers and found no association. Nahas et al13 did not find evidence for HPV infection in 5 patients with rectal SCC. Inflammatory diseases may cause squamous metaplasia, from which carcinoma then develops. Other theories suggest that colorectal SCC may originate from pluripotent stem cells capable of squamous differentiation.2,7,13 This theory is supported by the observation that SCC is often found in the midst of poorly differentiated cells. Michelassi et al14 have suggested that epithelial damage causes proliferation of uncommitted basal cells and differentiation into squamous cells with subsequent malignant transformation. Histologic studies of colorectal adenocarcinomas have identified areas of squamous differentiation, suggesting the possibility that these carcinomas may arise from preexisting adenomas or adenocarcinomas.4,5,8 Other coexisting conditions associated with SCC of the colorectum include colonic duplication15 and the presence of malignancies, such as ovarian, prostate, endometrial, and breast cancer.17 Patients with second malignancies may have a genetic predisposition for tumor formation, but information on this possibility is not available in patients with colorectal SCC. The present patient did not have any inflammatory bowel disease or a second malignancy.

The rare occurrence of colorectal SCC limits the available information on how best to manage these patients. Surgical resection is the preferred approach in patients with localized disease or metastasis to regional lymph nodes. Unfortunately, the exact role and benefits of systemic adjuvant therapy or of neoadjuvant or adjuvant chemoradiotherapy remain unknown, as does the optimal follow-up in these patients. The prognosis of SCC of the colorectum has not been studied systematically, but some investigators have reported a worse prognosis (median 5-year survival of 32%) in patients with SCC than in patients with adenocarcinoma of the colorectum.2,4 This poor prognosis may be explained by the tendency for colorectal SCC to have more frequent locoregional or distant metastatic spread at the time of diagnosis.9 These findings suggest that patients with SCC of the colorectum may benefit from more aggressive interventions at the time of diagnosis. More problematic is the uncertainty about the best systemic therapy for patients with advanced stages of colorectal SCC. Recommendations based on case reports suggest the use of 5-fluorouracil with either mitomycin or cisplatin as a chemotherapeutic option.4 Copur et al6 and Miyamoto et al5 have suggested that the combinations of 5-fluorouracil/leucovorin and cisplatin or 5-fluorouracil plus cisplatin and etoposide are effective systemic therapies in this disease. Sanal et al16 reported a complete response to the combination of cisplatin and 5-fluorouracil in a patient with SCC of the colon with hepatic metastasis. Nahas et al13 have reported that patients treated with chemoradiotherapy and then surgery did well.17 In the authors’ opinion, the combination of carboplatin/paclitaxel/cetuximab helped control hypercalcemia in this patient. Cetuximab is an anti-EGFR antibody used in head and neck cancer, lung cancer, and colorectal carcinoma. More research is needed to establish the efficacy of these treatment options.

**Conclusion**

SCC of the colorectum is a rare condition associated with poor prognosis and no well-defined therapeutic options when surgery is not an option. The present case shows that SCC of the colorectum should be considered in the differential diagnosis of unexplained hypercalcemia. In addition, a national database should be created to track treatment and outcomes.
Disclosure

The authors have stated that they have no conflicts of interest.

References