Squamous Cell Carcinoma of the Rectum: Report of Two Cases

Na Rae Kim, M.D., Dong Hae Chung, M.D., Jeong Heum Baek, M.D.*, Yeon Ho Park, M.D.*, Hee Bun Kyung, M.D., Mi Sook Roh, M.D.*, Seung-Yeon Ha, M.D.

Departments of Pathology, and Surgery*, Gachon University Gil Hospital, Incheon, Department of Pathology, Dong-A University School of Medicine†, Busan, Korea

INTRODUCTION

Squamous cell carcinoma (SCC) of the rectum is rare; the incidence has been estimated to be 0.01-0.02% of all colorectal tumors.1 Since Schmidtmann’s first report of a pure colonic SCC, fewer than 80 cases of primary SCCs have been reported involving the colorectum.2,3 Two cases of rectal SCC have been reported in the Korean literature.4,5 Rectal SCC is associated with chronic diseases, such as ulcerative colitis, prior radiation, or schistosomiasis.6 The poor prognosis of this tumor may be caused by a delayed diagnosis. Herein we describe two additional cases of SCC arising from the rectum, and briefly discuss the pathogenic theories, associated condition, and treatment strategies.

CASE REPORT

Case 1 was a 44-year-old Korean woman who had a 3-month history of lower abdominal pain and...
Presented with acute onset of rectal bleeding. Her medical and family histories were unremarkable. Serum tumor markers, including CEA, CA19-9, and CA125 were within normal limits. Testing for human immunodeficient virus-1 was seronegative. A digital rectal examination revealed a palpable mass on the anterior wall of the mid-rectum. No abnormal findings were detected on routine serologic findings. A colonoscopy revealed an ulcerofungating mass, measuring 6.0×5.0×1.5 cm, located in the rectum 8 cm proximal to the anal verge; the mass was biopsied. Abdomino-pelvic computed tomography and magnetic resonance images showed an eccentric wall thickening and enhancement with exophytic mass formation in the upper-to-mid-rectum measuring 5.5×3.5×2.6 cm. Magnetic resonance images showed fat obliteration between the rectal mass and uterus which was suspicious for adhesions or invasion into uterus (Fig. 1). Hydronephroureterosis with decreased parenchymal enhancement by the rectal mass in the left kidney was also shown due to obstruction. A double J catheter was inserted. She underwent a Hartmann’s procedure and hysterectomy with bilateral salpingo-oophorectomy and pelvic lymph node dissection. Combined chemotherapy (5-FU and mitomycin C, 5 cycles) and radiotherapy (28 fractions for a total dose of 5,040 rad) were administered 4 weeks after surgery. The radiation field included the rectum, pararectal, parametrial, presacral, internal, external, and common iliac lymph nodes. Thirteen months after the Hartmann’s procedure, attacks of vomiting and abdominal distension developed. An abdomino-pelvic computed tomography showed aggravated diffuse fluid filling the small bowel and enhancement in the pelvic cavity with diffuse edematous bowel wall thickening, suggesting radiation-related changes. Diffuse mesenteric fat haziness with a small amount of ascites suggested secondary changes due to small bowel obstruction. On laparotomy, an intra-abdominal fluid collection was absent, but omentoperitoneal adhesions were prominent. The small bowel had two definite sites of obstruction, 150 cm and 200 cm below the ligament of Treitz. The small bowel showed chronic dilatation and edematous wall changes due to severe adhesions. Adhesiolysis, an ileocecectomy, and segmental small bowel resection with an omentectomy were performed. The resected segments included portions of the ileocecum 200 cm below the ligament of Treitz and 8 cm from the ileocecal valve. There were no recurrent masses or peritoneal seeding noted. She was alive and well at the 6 month follow-up after the second operation.

Case 2 was a 43-year-old woman who presented with severe constipation and indigestion for 1 month. A rectal examination revealed a palpable mass. There was no involvement of the anorectal junction. A barium enema and computed tomography of the pelvis showed a rectal mass adherent to the sacrum, but a bone scan showed no active lesions. A colonoscopy was performed, which revealed a large, circumferential, ulcerated, hard mass located 6 cm above the anal verge. A cervicovaginal smear was within normal limits. Because the patient declined palliative chemoradiotherapy, a diverting loop T-colostomy was performed with palliative pain control. She succumbed 6 months post-operatively.

1. Pathologic findings

Grossly, an ovoid-shaped ulcerative mass was identified in the rectum of case 1 (Fig. 2). The cut surface of the mass was white and friable, and extended into the perirectal fat. Microscopically, the infiltrated...
tumor formed nests, sheets, or strands of oval-shaped cells, which had abundant eosinophilic cytoplasm and a large, often vesicular nucleus (Fig. 3A). The tumor cells showed intercellular bridges and central keratinization, and the tumor was diagnosed as a well-differentiated SCC (Fig. 3B). A colonoscopic biopsy of case 2 showed a well-differentiated invasive SCC with areas of keratinization (Fig. 3C). Neither case 1 nor 2 showed koilocytic changes in the SCC and adjacent rectal mucosa.

Immunohistochemically, the tumor cells of case 1 were positive for CK7 (OV-TL 12/30, 1:100 dilution; DAKO, Glostrup, Denmark), CAM 5.2 (prediluted; DAKO), pancytokeratin (AE1/AE3, 1:100 dilution; DAKO), and p63 (prediluted; Dako), and negative for CK20 (ks20-8, 1:50 dilution; DAKO). Metastatic carcinomas were detected in four of six left iliac pelvic lymph nodes. No metastasis was demonstrated in 18 perirectal lymph nodes or in the uterine wall. The segmental small bowel resection and omentectomy specimen in case 1 revealed chronic inflammation and scattered atypical stromal cells with marked serosal fibrosis and intersegmental adhesions, which was consistent with radiation changes with no residual mass.

We also analyzed the prevalence of human papillomavirus (HPV) in rectal carcinoma by a PCR-based DNA microarray system provided by HPV-DNA chip test (MyHPVChip; Biomedlab Co., Ltd., Seoul, Korea) using paraffin blocks. The chip contained 24 typespecific probes consisting of 16 high-risk HPV groups (16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 54, 56, 58, 59, 66, 68) and 8 low-risk HPV groups (6, 11, 34, 40, 42, 43, 44, and 70). DNA was isolated from tumor samples with a DNA isolation kit (Qiagen, Hilden, Germany), and target HPV DNA was amplified by PCR with HPV 1st primer F (20mer, 5'-GCM CAG GGW CAT AAY AAT GG-3'), HPV 1st primer R (20mer, 5'-CGT CCM ARR GGA WAC TGA TC-3'), HPV 2nd primer F (23mer, 5'-TTT GTT ACT GTG GTA GAT ACT AC-3'), and HPV 2nd primer R (25mer, 5'Cy5-GAA
The sequences of $\beta$-globin primers were as follows: $\beta$-globin primer F (22mer, 5'-GGT TGG CCA ATC TAC TCC CAG G-3') and $\beta$-globin primer R (22mer, 5'-TGG TCT CCT TAA ACC TGT CTT G-3'). Hybridization signals were visualized under a fluorescence scan at a laser power of 80% and PMT 80 by a confocal laser scanner (GSI Lumonics, Ottawa, Canada). From the acquired image, the HPV genotype was identified and the signal intensity was analyzed with calculation of the signal-to-noise ratio (SNR). If the SNR value of the HPV signal was $>5.0$, HPV was confirmed to be positive. Cases 1 and 2 had no HPV signals.

**DISCUSSION**

Rectal SCC arising from the columnar epithelium of the rectum is rare. To establish a diagnosis of colorectal SCC, the following criteria should be met: 1) metastasis from other sites to the colon must be excluded; 2) a squamous-lined fistula tract must not involve the affected bowel because it may be a source of SCC; and 3) SCC of the anus with proximal extension must be excluded.

Rectal SCC is an uncommon neoplasm with a mysterious histogenesis. Several theories about the pathogenesis have been suggested. First, some suggest that this tumor originates from a pluripotent stem cell capable of multidirectional differentiation. Second, others suggest the theory of proliferation of uncommitted basal cells into squamous cells, which undergo malignant transformation due to chronic injury of the glandular epithelium. Third, rectal SCC could also be derived from a persistent embryonic nest of committed or uncommitted ectodermal cells, which may migrate to the rectum during the embryonic phase and aberrantly proliferate when stimuli exist, such as chronic irritation. Grinvalsky and Helwing reported that anal ducts extend cephalad beneath the rectal mucosa for a considerable distance, the exact distance being unknown. They postulated that rectal SCC could arise from these transitional-cell anal ducts. Another theory is squamous differentiation of adenomas and adenocarcinomas. Balfour proposed the theory that SCC of the colon does not exist and it probably represents metastatic disease of unknown primary or squamous degeneration of a pre-existing adenocarcinoma, but it has not gained wide acceptance. Recently, the role of HPV in malignant transformation has been confirmed in several organs, including cervical and anal carcinomas, malignant tumors of the head and neck region, as well as esophageal cancer and colorectal squamous cell carcinomas, although the present two cases were negative for HPV. The clear association and effect between HPV and SCC of various organs has not been firmly established for rectal SCCs. However, a report suggesting that immunosuppression status by HIV infection induces the replication of what may otherwise have been a low-level, undetectable HPV infection with the development of anal cancer precursors. Other risk factors for rectal SCC include parasites and inflammatory bowel disease, especially ulcerative colitis. SCC of the colon and rectum, originating proximal to the transitional zone, is a rare complication of idiopathic inflammatory bowel disease.

Based on a diagnostic endoscopic biopsy, there can be difficulty either in distinguishing SCC of the rectum from that of the anus or other poorly differentiated tumors. The immunonpositivities for CAM 5.2 and 34$\beta$E12 are useful markers in rectal SCCs, while immunonpositivities for p63 and AE1/AE3 share features of anal and rectal SCCs because the immunomarker for CAM5.2 stains rectal adenocarcinoma and rectal SCC, but not anal SCC. Immunostaining for CK20, which most commonly stains glandular epithelium of the lower gastrointestinal tract, is reactive in all of the rectal adenocarcinomas, whereas immunostaining for CK7, which most commonly stains glandular epithelium of the upper gastrointestinal tract, is largely negative in rectal adenocarcinomas.

The clinical symptoms of rectal SCC are similar to those of adenocarcinoma (a change in bowel habits, pain, tenesmus, rectal bleeding, anorexia, and weight loss). The natural course and management of this malignancy has not been clearly defined due to the rarity of the disease. There is evidence that the prognosis is similar to colorectal adenocarcinoma for stage I-II node-negative disease. Nodal involvement signifies a worse prognosis than for similar stage adenocarcinoma. Small cell or undifferentiated histolo-
gic characteristics are associated with a particularly poor prognosis. The recommended therapy for rectal SCC is surgical resection of the affected rectum, either by low anterior resection or by abdominoperineal resection, depending on the location of the tumor and the patient’s preference. Primary chemoradiotherapy, as currently utilized in anal cancer, can be extended to primary SCC of the rectum. Recent data has shown that most patients treated with upfront chemoradiation followed by surgery did well. Sphincter-preserving surgery is usually possible, regardless of the use of pre- or post-operative therapy (chemotherapy alone, radiation alone, or chemoradiation). However, large randomized prospective trials are needed to determine the efficacy and benefits on survival and prognosis of complementary therapies.

REFERENCES