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Case Report

Goblet Cell Carcinoid of the Rectum with Lymph Node Metastasis: Report of a Case

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Abstract
We report an unusual case of goblet cell carcinoid (GCC) of the rectum. A 75-year-old man was admitted to our hospital with anal bleeding, and a hard tumor was felt on the anterior wall of the lower rectum during rectal examination. We performed colonoscopy, and found a 30-mm type 2 tumor in the lower rectum and anal canal. Histological examination of biopsies revealed rectal adenocarcinoma. Based on these findings, we diagnosed rectal adenocarcinoma and performed Miles' operation with lymph node dissection. Histological examination revealed an invasive lesion composed of signet-ring-like cells. Seven regional lymph node metastases were seen microscopically. The tumor produced copious mucin, which was stained with Alcian blue. Immunohistochemistry was positive for synaptophysin, chromogranin A, CD56, carcinoembryonic antigen, p53, Ki-67, E-cadherin, and cytokeratin 20. The final diagnosis was GCC of the rectum.

Key words Goblet cell carcinoid · Rectum · Lymph node metastasis

Introduction

Goblet cell carcinoid (GCC) is a rare tumor with the histological and histochemical features of goblet cell-type mucin-containing tumor cells arranged in round or oval clusters, demonstrating immunoreactivity for the neuroendocrine markers, chromogranin or synaptophysin. It is found mainly in the appendix and rarely in the rectum. Although their malignant potential remains unclear, GCCs are more aggressive than typical carcinoid tumors. In this report, we describe the treatment and histopathological aspects of an unusual case of GCC of the rectum and review the relevant literature.

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Case Report

A 75-year-old man with a history of benign prostatic hyperplasia consulted his local physician about occasional anal bleeding, which he had first noticed about 1 month earlier. He was referred and admitted to our hospital for investigations and treatment. On digital rectal examination, a hard tumor was palpable on the anterior wall of the lower rectum, but no abdominal tumor mass or superficial lymph nodes were felt. Routine laboratory findings were unremarkable, with the exception of a slightly elevated carcinoembryonic antigen (CEA) level (6.3 ng/ml).

Colonoscopy revealed a 30-mm type 2 tumor, mainly in the lower rectum but invading the anal canal (Fig. 1). Histological examination of colonoscopic biopsies suggested rectal adenocarcinoma, in the form of poorly differentiated adenocarcinoma and/or signet-ring cell carcinoma. Barium enema confirmed a type 2 tumor in the lower rectum and anal canal. Contrast-enhanced computed tomography (CT) showed a mass in the lower rectum, but no obvious lymph node metastasis or remote metastasis.

Thus, with a provisional diagnosis of rectal adenocarcinoma, we performed Miles' operation with lymph node dissection. Macroscopically the type 2 tumor, which measured 38 × 28 mm, invaded horizontally over the dentate line (Fig. 2a) and vertically to the muscularis propria. Seven regional lymph node metastases were seen microscopically. Histological examination revealed an invasive lesion composed of signet-ring-like cells (Fig. 2b). In most areas, the tumor had produced copious mucin, suggesting a mucinous carcinoma. The mucin produced by the tumor cells was stained with Alcian blue (Fig. 2c, upper part), as were the goblet cells in the

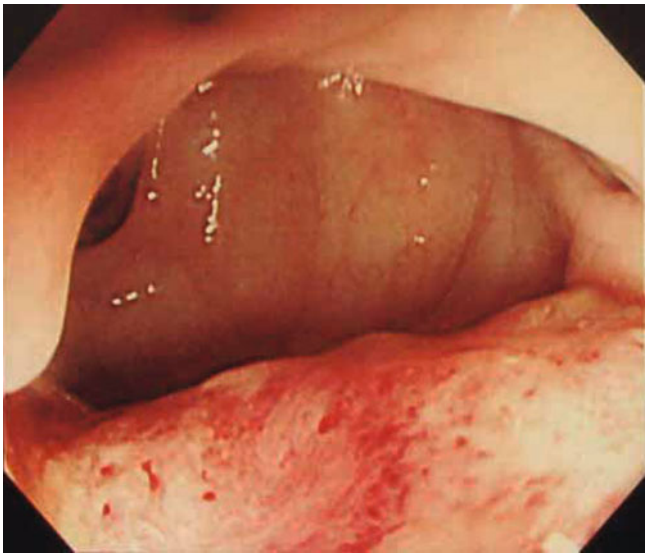
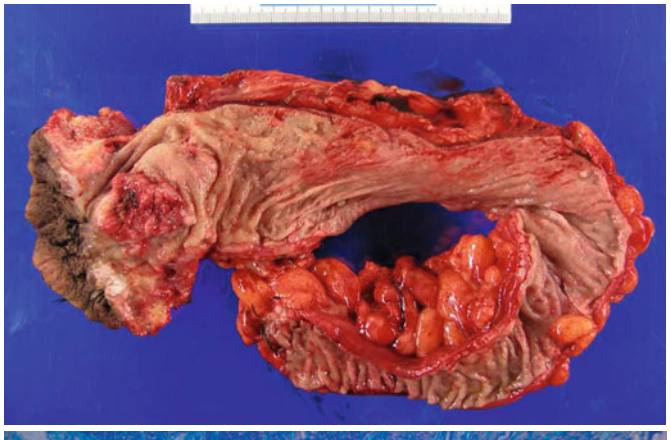
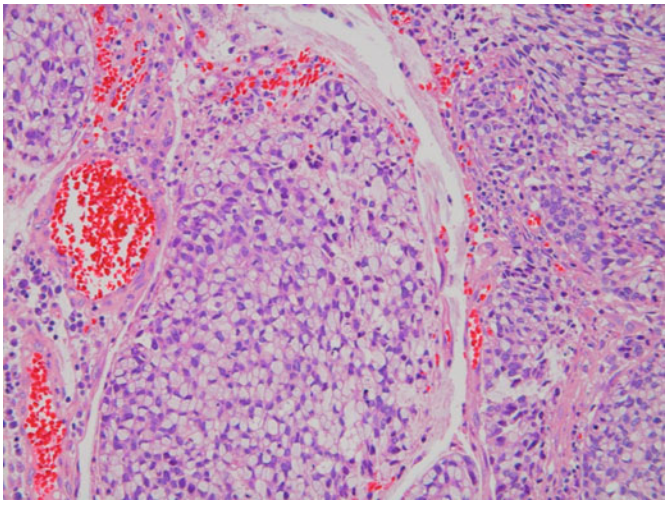


Fig. 1. Colonoscopy revealed a type 2 tumor, mainly in the lower rectum

colonic mucosa (Fig. 2c, lower left). However, insufficient nuclear atypia of the tumor cells with a lack of tumor cell necrosis and glandular differentiation prompted us to assess the neuroendocrine nature of the tumor. Immunohistochemically the tumor cells were positive for synaptophysin (Fig. 3a), chromogranin A (Fig. 3b), and CD56 (N-CAM) (Fig. 3c). Almost all the tumor cells were positive for CD56 in the cell membrane, whereas nearly half of the tumor cells contained synaptophysin-positive fine cytoplasmic granules. A few chromogranin A-positive cells were found in the tumor cell clusters. The tumor was also immunohistochemically positive for CEA, p53, Ki-67, E-cadherin, and cytokeratin (CK) 20 (Fig. 3d,e,f,g, and h, respectively). These findings confirmed a final diagnosis of GCC of the rectum. The lymph node metastases showed similar histological and immunohistochemical results to those of the primary site.

The patient underwent intestinal resection for adhesional ileus about 4 weeks postoperatively, and a





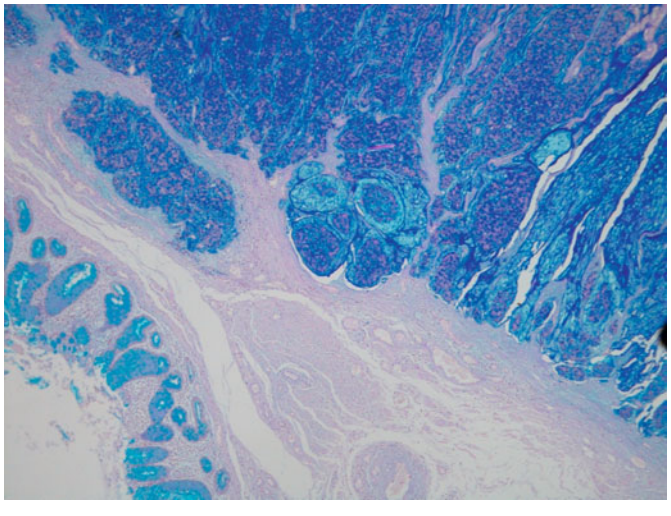


Fig. 2. **a** Gross appearance of the surgical specimen. The type 2 tumor had invaded horizontally over the dentate line. **b** Hematoxylin–eosin staining revealed an invasive lesion composed of signet-ring-like cells (×140). **c** The mucin produced by the tumor cells was Alcian blue positive (×28)

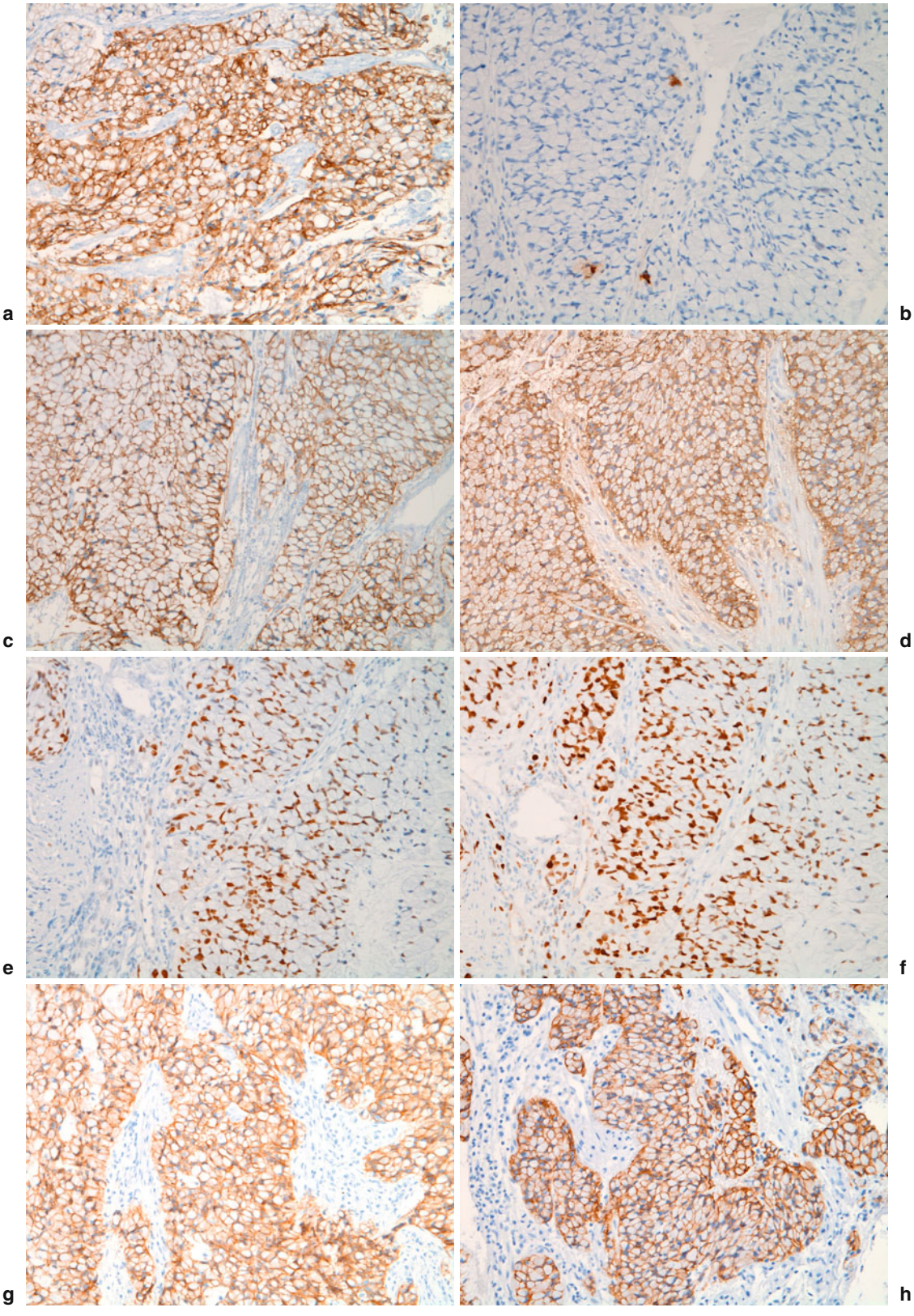


Fig. 3. **a** Most of the signet-ring-like cells were stained positively for synaptophysin (×160). **b** Some of the tumor cells were positive for chromogranin A (×160). **c** CD56 (N-CAM) was strongly expressed in the cell membrane of the tumor cells (×160). **d** Carcinoembryonic antigen was strongly expressed in the cell membrane of the tumor cells (×160). **e** Almost all of the nuclei of the tumor cells were positive for p53 (×160). **f** Almost all of the nuclei of the tumor cells were positive for Ki-67 (×160). **g** E-cadherin was strongly expressed in the cell membrane of the tumor cells (×160). **h** Cytokeratin 20 was strongly expressed in the peripheral cytoplasm of the tumor cells (×160)

follow-up CT scan 15 months after the initial surgery showed bilateral multiple pulmonary metastasis. At the time of writing, the patient was scheduled to receive chemotherapy with a modified FOLFOX-6 regimen.

Discussion

Goblet cell carcinoid, also variably known as adenocarcinoid, mucinous carcinoid, or crypt cell carcinoma, is a rare neoplasm with distinct histologic and clinical features.[1] According to the World Health Organization (WHO) histological classification of tumors of the appendix, carcinoid-related tumors are classified as carcinoid (well differentiated neuroendocrine neoplasm) and mixed endocrine–exocrine carcinoma. The latter is classified further as tubular carcinoid, GCC (mucinous carcinoid), and mixed carcinoid adenocarcinoma. According to the WHO classification, the histological characteristics of GCC are described as "small, round nests of signet-ring-like tumor cells resembling normal goblet cells." It is also described that "lumens are infrequently observed in GCC."[2]

The first large series describing these tumors was reported by Subbuswamy et al. in 1974.[3] Goblet cell carcinoid is not uncommon in the appendix, but it is rarely found in colorectal lesions. Based on a MEDLINE search, fewer than 600 cases of this type of tumor in the appendix have been diagnosed worldwide.[4] However, only seven cases of GCC in the colon or rectum have been reported: one in the sigmoid colon, one in the splenic flexure, and five in the rectum.[5–10] Two of these patients had recurrence after surgery (Table 1).

It is controversial whether GCC tumors should be considered as variants of adenocarcinoma or as part of the carcinoid tumor spectrum.[11,12] Höfler et al. reported that GCCs are derived from undifferentiated stem cells and are different to typical carcinoids that originate from endocrine cells in the mucosal stroma.[13] The fundamental morphologic features common to all GCCs include the presence, at least focally, of mucin-containing, goblet-shaped epithelial cells arranged in round or oval clusters at the primary site; and neoplastic cells that usually demonstrate focal positive immunoreactivity for the neuroendocrine markers, chromogranin or synaptophysin.[14] The diagnosis of GCC of the appendix is seldom made preoperatively or macroscopically because the tumor cells proliferate sparsely and do not form nodules. Most cases manifest as an acute abdomen, and the remaining tumors are found in appendices removed incidentally at laparotomy for an unrelated condition.[15,16] Similarly, to our knowledge no case of GCC of the colon or rectum has been diagnosed preoperatively, although a carcinoid tumor of the sigmoid colon was suspected after colonoscopic biopsy in one case.[5–10] The

Table 1. Reported cases of goblet cell carcinoid tumors in the colon or rectum

No.	First author (year)[Ref]	Age (years)	Sex	Location	Tumor size (mm)	Tumor depth	Metastasis	Peritoneal seeding	Treatment	Adjuvant chemotherapy	Recurrence site	Prognosis
1	Lyss (1981)[5]	32	M	Splenic flexure	70 × 55	T3	Lymph nodes	Yes	Total colectomy (accompanied by UC)	5-FU, streptozotocin	None	Alive
2	Hattori (2007)[6]	76	M	Sigmoid colon	40 × 10	T3	Lymph nodes	Yes	Sigmoidectomy	Leucovorin/ UFT	None	Alive
3	Ishii (2001)[7]	71	M	Rectum	42 × 35	T4	Lymph nodes	No	Miles' operation	None	Scrotum, abdominal wall	Died
4	Yagihashi (1999)[8]	55	M	Rectum	11 × 9	T1	Lymph nodes	No	Low anterior resection	None	None	Alive
5	Kato (2002)[9]	44	M	Rectum	n.d.	T3	None	No	Total colectomy (accompanied by UC)	None	Liver, brain, peritonitis carcinomatosa	Died
6	Hernandez (1974)[10]	71	F	Rectum	22 × 20	T2	None	n.d.	Transanal resection	None	None	Alive
7	Hernandez (1974)[10]	60	F	Rectum	n.d.	n.d.	None	n.d.	Only biopsy	None	None	Alive

UC, ulcerative colitis; 5-FU, 5-fluorouracil; UFT, tegafur uracil; n.d., not described

present case was diagnosed as rectal adenocarcinoma based on the preoperative colonoscopic biopsy findings, because signet-ring-like cells with copious mucin had invaded the lamina propria of the biopsy specimen. Histopathologically, GCC closely resembles signet-ring cell carcinoma; however, retrospective examination of the specimen from our patient suggests that GCC might be histologically differentiated from signet-ring cell carcinoma by the fact that the cancer cells tend to cluster rather than infiltrate diffusely. Although further studies are necessary to confirm this, the present case suggests that the cluster formation of signet-ring-like tumor cells invading the stroma may help establish a histopathological diagnosis of GCC. The biopsy specimen was retrospectively positive for chromogranin A, p53, Ki-67, E-cadherin, and CK20. If the biopsy specimens had been examined immunohistochemically, GCC of the rectum would have been diagnosed preoperatively. According to the immunohistochemical finding of p53, it seems likely that the tumor had high potential for malignancy. Horiuchi et al. performed immunohistochemistry with the anti-p53 antibody on a GCC tumor of the appendix. Most tumor cells were strongly positive, whereas cells from benign carcinoid tumors investigated simultaneously were negative. Horiuchi et al. suggested that GCC has a more aggressive phenotype than benign carcinoid tumors, but no correlation has been made with its metastatic potential.[17] In the present case, almost all of the tumor cell nuclei were positive for Ki-67, and E-cadherin was strongly expressed in the cell membrane of the tumor cells. Li et al. reported a case of GCC with high Ki-67 levels resulting in metastasis and death. Hence, high levels of Ki-67 might be an indicator of poor survival. Li et al. also reported the preservation of E-cadherin in GCC and its loss in pure signet-ring adenocarcinoma.[18] Alsaad et al. compared the expression of CK20 in 17 cases of appendiceal GCC and 25 cases of classic carcinoid. Immunohistochemistry showed that all 17 (100%) GCC tumors exhibited strong and diffuse immunopositivity for CK20, whereas only 4 (16%) of the classic carcinoid tumors showed immunolabeling for CK20 in 25%–50% of cells.[19] The positivity for CK20 in the present case, indicating a pattern specific for colon cancer, is interesting in terms of investigating the developmental processes of GCC and adenocarcinoma.

A review of 57 published papers on GCC of the appendix revealed that concomitant distant metastasis was diagnosed in 11.2% of the patients; the ovaries being the most common site (3.6%), followed by abdominal carcinomatosis (1%). Furthermore, local lymph node involvement was seen in 8.7% of patients at the time of diagnosis.[4] Although rare, several other patterns of metastasis were identified, including to the liver, bowel wall, rectum, and pancreas.[20] In the present case, a CT scan done 15 months after the initial surgery showed bilateral multiple pulmonary recurrences. Goblet cell carcinoid with pulmonary recurrence has been described rarely. The reported 5-year survival of patients with GCC ranges from 45% to 84%.[1,21–26] Although its prognosis is thought to be somewhere between that for adenocarcinoma and pure carcinoid, a recent article reported that carcinoids in the colorectum are associated with survival similar to that of poor and well/moderately differentiated adenocarcinomas.[1,27,28] Mizushima et al. reported that the overall 5-year survival rate of patients with primary signet-ring cell carcinoma was significantly lower than that of those with well or moderately differentiated adenocarcinoma and those with poorly differentiated adenocarcinoma or mucinous carcinoma (24.1% vs 77.5% and 57.7%, respectively).[29] Further studies comparing the survival associated with GCCs with that associated with common adenocarcinomas in stage-matched cases are required based on the clear evidence.

According to a review by Pahlavan et al., of reported GCCs, simple appendectomy was performed in nearly 25% of cases, and was particularly common in the early reports. The most common surgical treatment (almost 35%) was appendectomy with right hemicolectomy, especially in recent reports. Oophorectomy was also performed in about 11% of female patients. Pahlavan et al. recommended right hemicolectomy for all patients because of the moderately aggressive behavior of the tumor.[4] On the other hand, Varisco et al. support appendectomy alone to treat localized disease when the following features are absent: cecal involvement, two or more mitotic figures per high-power field, and moderate or severe atypia.[20] As lymph node metastasis was identified in four of seven reported cases of colorectal GCC, high anterior resection, low anterior resection, or Miles' operation with lymph node dissection is recommended for patients with GCC of the rectum.

Peritoneal carcinomatosis is the most common disease-specific cause of death of GCC patients.[1] The survival benefit of chemotherapy is not established, despite several studies on adjuvant chemotherapy for GCC. One study showed that adjuvant chemotherapy with 5-fluorouracil (5-FU) and leucovorin was minimally effective against GCC, with a trend toward improved mean survival, but without significance.[1] There is also a case report of appendiceal GCC and bilateral Krukenberg's of the ovaries treated with 5-FU and streptozotocin, and the patient was still alive after 7 months of follow-up.[26] Another study described that a FOLFOX chemotherapy regimen comprising oxaliplatin combined with 5-fluorouracil and leucovorin was helpful in inducing complete and persistent remission of GCC with metastasis to the ovaries, peritoneal cavity, and lymph nodes.[27] Even though it was not prescribed rou-

tinely, most protocols included 5-FU in the review of reported GCCs by Pahlavan et al. They also recommended 5-FU for all GCC patients, because peritoneal seeding can occur before lymph node metastasis and has a proven advantage against metastatic disease.[4] Two patients with GCC in the colon or rectum with peritoneal seeding were given adjuvant chemotherapy.[4,5] In the present case, multiple pulmonary recurrence was observed 15 months after the patient's initial surgery, despite curative resection. The patient was about to start chemotherapy with a modified FOLFOX-6 regimen, which is widely adopted as a treatment for recurrent colorectal adenocarcinoma. We believe that adjuvant chemotherapy is necessary for rectal GCC even after curative resection.

In summary, we reported a case of GCC of the rectum with lymph node metastasis. Further investigations are needed to establish the optimal management of this unusual tumor.

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