## CASE REPORT

# A case of synchronous colorectal cancers including ascending and sigmoid colon cancer showing different genomic profiles in the examination of microsatellite instability, associated with acute appendicitis due to appendiceal goblet cell adenocarcinoma

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**Abstract : Background : Appendiceal goblet cell adenocarcinomas (GCA) are rare. Most patients who undergo appendectomy have acute appendicitis. The detection of synchronous colorectal cancer (SCRC) has increased with advances in diagnostic imaging and endoscopic examinations. However, only two cases of SCRC, including appendiceal GCA, have been reported to date. We recently encountered an extremely rare case of SCRC, involving appendiceal GCA, ascending colon cancer (ACC), and sigmoid colon cancer (SCC). Herein, we present this case and provide a discussion on the relevant literature. Case presentation : A 69-year-old man presented to our hospital with right lower abdominal pain. Based on contrast-enhanced computed tomography (CE-CT), the patient was diagnosed with SCRC and acute appendicitis caused by appendiceal neoplasm and ACC. The patient underwent emergency laparotomy, and right colectomy with lymph node dissection (LD). Intraoperatively, we palpated the remaining segment of the colorectum whenever possible and incidentally detected SCC. Therefore, sigmoid resection with LD was suggested. Conclusion : When treating acute appendicitis, it is important to consider the possibility of an extremely rare appendiceal tumor as the cause. If possible, CE-CT should be performed to ensure appropriate image interpretation during an unlikely SCRC event. J. Med. Invest. 72 : 194-201, February, 2025**

***Keywords*** **:** *appendiceal goblet cell adenocarcinoma, acute appendicitis, synchronous colorectal cancer*

## INTRODUCTION

Appendiceal goblet cell adenocarcinoma (GCA) was previously categorized as appendiceal goblet cell carcinoid (GCC). Appendiceal GCC usually exhibits features of both neuroendocrine tumors (NETs) and adenocarcinomas, comprising, mucin-secreting cells (goblet cells) with only a minor neuroendocrine component (1). They were renamed and reclassified as GCA in the current 5$^{-th}$ edition of the World Health Organization (WHO) classification (2019) of the digestive system (2). Appendiceal tumors are typically rare entities, accounting for 0.2 - 0.5 % of gastrointestinal tumors (GITs). Most cases of appendiceal GCA have been incidentally found after an emergency appendectomy for acute appendicitis, which make up for 2 % appendectomy cases (3). Appendiceal GCAs are extremely rare among GITs. The incidence of appendiceal GCA accounts for 14-19 % in the USA and In the USA (4), and only 3.5 % of appendiceal tumors were reported in a recent Japanese multicenter retrospective study (5).

Advances in colonoscopy and radiological imaging techniques, such as multidirectional computed tomography (CT) have resulted in a rise in incidence of synchronous colorectal cancer (SCRC) (6). The major pathways of colorectal cancer (CRC) progression are through chromosomal instability (CIN) and microsatellite instability (MSI). The CIN pathway in CRC typically includes the combination of mutations and loss of heterogeneity in tumor protein (p53) and adenomatous polyposis coli (APC) (7). There are three situations in which a patient may be predisposed to tumors arising from the MSI pathway and all pathways are associated with high MSI (MSI-H). The presence of SCRC is reported to have a relatively high correlation with the MSI pathway compared to solitary CRC. The rate of MSI-H in SCRC is reported to be higher than that of solitary CRC (8). However, some reports suggested that microsatellite status was discordant between lesions in patients with SCRC (9).

Anti-EGFR therapy and checkpoint blockade immunotherapy are effective only for lesions with wild-type KRAS and BRAF and lesions with loss of MMR protein expression in CRC. If the status of KRAS and BRAF status differs between lesions in a patient with SCRC, the status of KRAS and BRAF associated with recurrent metastases might not be clear. Therefore, KRAS and BRAF status at the site of recurrence should be investigated when considering anti-EGFR therapy (8). It is important to examine the MSI when selecting checkpoint blockade immunotherapy. In the future, liquid biopsy might be useful to examine KRAS and BRAF if the tissue from where recurrent metastases cannot be obtained (8).

The rate of SCRC cases including appendiceal cancer have been reported rear (6). In our search for published literature regarding SCRCs, including appendiceal GCAs, we found only two case reports (10, 11).

Most commonly, patients with appendiceal GCA/GCC, present with abdominal pain and acute appendicitis ; (›50%). Most

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appendiceal GCA/GCC are dissected by appendectomy or ileocecal resection for associated acute appendicitis and are pathologically. When acute complicated appendicitis occurs, such as peri- appendiceal abscess formation and/or perforation, the risk of peritoneal metastasis increases, resulting in a poor prognosis (12). The presence of phlegmon in acute appendicitis is significantly associated with the presence of underlying malignancies, and complicated appendicitis is often to perforation (13). Preoperatively, CT is often performed to examine the intra-abdominal cavity and the whole body. However, there are no specific guidelines pertaining to SCRCs in the workup for colorectal cancer (CRC), and further investigation is required (14). Particularly, in cases of acute complicated appendicitis, preoperative endoscopic examination of the colorectum (ESOCR) is extremely difficult and dangerous because of the risks including the accidental perforation.

We recently treated a 69-year-old man with acute complicated appendicitis caused by an appendiceal GCA. Preoperative contrast-enhanced CT and intraoperative findings revealed multiple simultaneous CRCs, including advanced ascending colon (AC) cancer (ACC) and sigmoid colon (SC) cancer (SCC). We performed right colectomy and sigmoid resection with lymph node dissection (LD). This report describes this case as well as two previously reported cases of appendiceal GCA with SCRC. We also discuss the problems associated with preoperative diagnosis and appropriate treatment when appendiceal malignant tumors with SCRCs are present in both colorectal segments (right and left, or right or rectum), Furthermore, we investigated microsatellite instability (MSI), KRAS mutation, and BRAF mutation of the advanced ACC and SCC, which recently became clinically important for molecular targeting therapy (8, 9, 15). On the other hand, only a few studies have conducted genomic examination for appendiceal malignancies, including appendiceal GCA (16). We deeply regret that we did not conduct genomic examination of appendiceal GCA in this study. Furthermore, germ line genetic tests to assess the genetic background of the lesions of SCRCs and accumulate the results for preventing metachronous CRCs.

In conclusion, it is important to confirm the genetic mutation of every lesion to perform the appropriate postoperative chemotherapy for SCRCs, with the addition of molecularly targeted agents and immune check inhibitors.

## CASE PRESENTATION

A 69-year-old male presented to our hospital complaining of dull pain in the right lower abdomen that had started 2 days earlier in the epigastrium and with fever (37.5℃). The patient had no significant family history of malignant neoplasms and was treated for hypertension at a nearby clinic. Physical examination revealed abdominal tenderness and positive Blumberg's sign in the right lower quadrant ; however, there was no evidence of muscular defense. The white blood cell count was 16,800/μL, with 92.9- % neutrophils, 4.8- % lymphocytes, and 2.0- % monocytes. Serum C-reactive protein was 27.12 mg/dL, serum CEA level of 1.9 ng/mL (normal range : 4.5 ≦ ng/mL), and serum CA19-9 level was 48.4 U/mL (normal range : ≦ 37.0 U/mL). Other blood chemistry findings were within normal limits. We suspected peritonitis due to acute appendicitis and immediately performed contrast-enhanced CT (CE-CT). Type 2 contrast tumor was observed in AC (Figs. 1.A, B). The appendix was significantly enlarged, and a 10 mm CE lesion was observed at the root of the appendix (Figs. 1.C, D). A peri-appendiceal abscess was strongly suspected based on the presence of a fluid collection and a wall-like structure surrounding the appendix and cecum (Fig. 1.C). However, no direct invasion of surrounding organs was observed (Fig. 1.D). Based on these findings, we diagnosed the patient with localized peritonitis due to acute appendicitis, caused by appendiceal neoplasm concurrent with an advanced ACC.

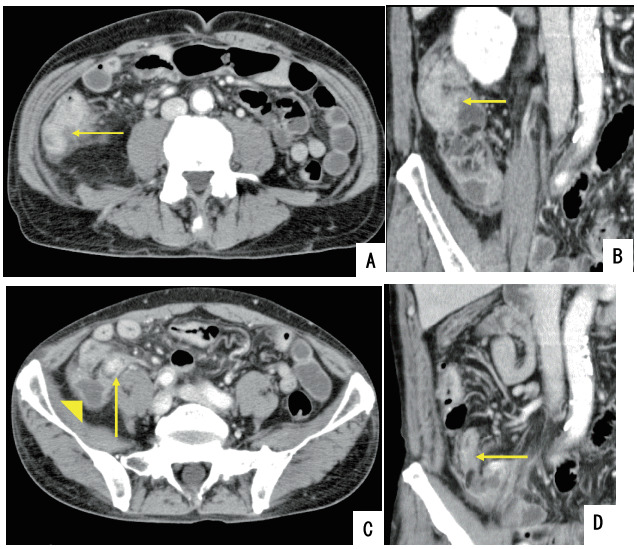


Fig. 1. Preoperative contrast-CT findings.
Fig. 1-A (transverse plane) and Fig. 1-B (coronal plane) : Type 2 contrast-enhanced tumor is observed in the ascending colon (arrow). Fig. 1-C (transverse plane) and Fig. 1-D (coronal plane) : The appendix is significantly enlarged, and a 10-mm CE lesion is seen at the root of the appendix. (Fig. 1-C arrow line). A peri-appendiceal abscess is strongly suspected based on the presence of a fluid collection and a wall-like structure surrounding the appendix and cecum (Fig. 1-C. arrowhead). However, no direct invasion of the surrounding organs is observed (arrow line in Fig. 1D).

Considering the risk of peritoneal spread due to perforation of the severely inflamed and destroyed appendix, we decided to perform an emergency surgery. Under general anesthesia, a laparotomy was performed through a right pararectal abdominal incision. Approximately 30 mL of purulent ascites was found in the right cecal fossa, but the formation of a peri- appendiceal abscess structure was not observed. The ileal intestine and peritoneum around the ileocecal region were markedly erythematous and edematous, respectively. The appendix was not yet perforated, but was markedly enlarged and dark red, suggesting gangrenous appendicitis. The appendiceal mesentery was prominently edematous and thickened. However, the appendiceal tumor was not adherent to the surrounding intestinal tract or peritoneum and showed no sign of disseminated metastases in the abdominal cavity. First, the AC and ileocecal regions were mobilized, the ileocolic and right colic arteries were dissected, and blood supply from the root of the middle colic artery (MCA) was maintained. The LD was added along with the superior mesenteric artery to the distal MCA site. Second, a right hemicolectomy with LD, including a 10 cm terminal ileum resection, was performed (Fig. 2.A). The ileum and transverse colon were anastomosed using functional end-to-end anastomosis (FEEA) (12) with a linear stapler. During the procedure, the intra-abdominal colorectum was examined by palpation, whenever possible, to identify other synchronous neoplasms. However, we could not palpate the descending and transverse colons sufficiently because the laparotomy was performed through a right pararectal incision. On palpating a tumor in the middle part of the SC, we immediately observed preoperative CE-CT and SC images (Fig. 3.B). Accordingly, the patient was diagnosed with advanced SCC. After SC mobilization, the rectal artery was excised, the

left colic artery was preserved, and LD was performed along the inferior mesenteric artery. After resecting the SC (Fig. 3A), reconstruction of the left colon was performed using FEEA (17). After rinsing the intra-abdominal cavity and placing the drainage in the Douglas`s cavity, the abdominal wall was closed in layers with sutures. The surgery time was 3 h 34 min, with blood loss during surgery of 175 mL.

Histopathological examinations were performed in our hospital, and results were described according to the 2018 Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma (JCCRC : 3rd English Edition 2019 ; Japanese 9th Edition 2018) (18) and the 2017 UICC for International Cancer Control TNM Classification of malignancy (19). Additionally, we described the results of KRAS and BRAF mutation analyses and the MSI of the AC and SC tumors, for appropriate the postoperative chemotherapy. In this study, germline genetic testing was not conducted. The histology and stage of each tumor were as follows.

*Lesion 1 (Fig. 2.B). Ascending colon tumor*

JCCRC : A, Type 2, 40×30 mm, tubular adenocarcinoma, well differentiated type (tub1), pT3 (SS), INFb, Ly0, v0, Pn0, PM0 (160 mm), DM0 (50 mm), pN0 (0/10), H0, P0, H0, pStageⅡa, R0, Curability A. Microsatellite instability-high (MSI-H) status was observed. KRAS mutation was not observed. BRAF mutation was observed.

UICC-TNM classification : T3, N0, M0, StageⅡA.

*Lesion 2 (Fig. 2.C). Appendix tumor*

JCCRC : V, T3 (SS), INFc, Ly0, V0, Pn0, PM0, pN0 (0/10), H0, M0, GCA with acute gangrenous appendicitis. pStageⅡa.

UICC-TNM classification : T3, N0, M0, Stage ⅡA.

The genetic examination of this tumor was not conducted.

*Lesion 3 (Fig. 3.A). Sigmoid colon tumor*

JCCRC : S, Type 2, 25×25 mm, tubular adenocarcinoma, moderately differentiated type (tub2), T3 (SS), INFb, Ly1b, V1a (VB), Pn0, PM0 (55 mm), DM0 (25 mm), N2a (6/11), H0, P0, M0, Stage Ⅲb, R0, CurA. MSI-H status was not observed. KRAS mutation was not observed. BRAF mutation was observed.

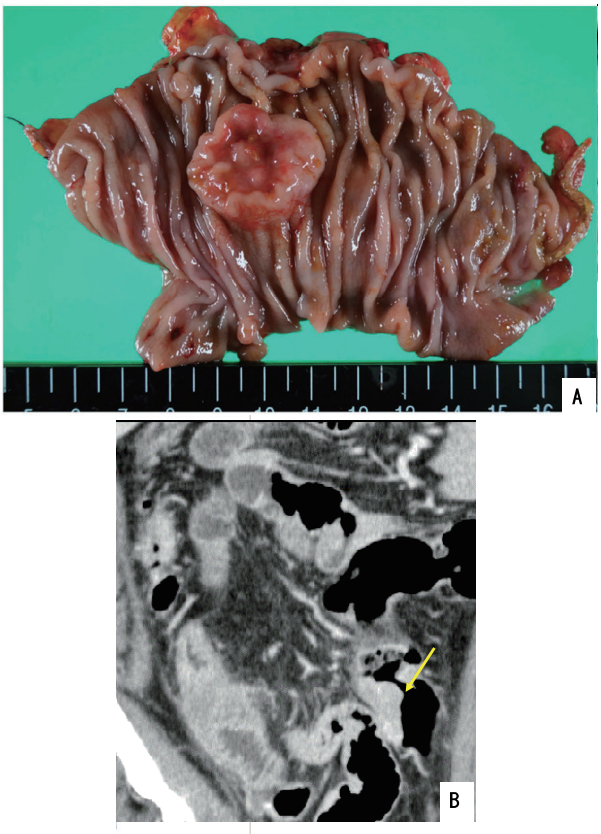


Fig. 3. A : Type 2 sigmoid colon tumor, tubular adenocarcinoma, moderately differentiated type (tub2). Several polyps are observed in the sigmoid colon ; B : Preoperative contrast- enhanced CT showing the enhanced elevated tumor in the sigmoid colon (arrow line).

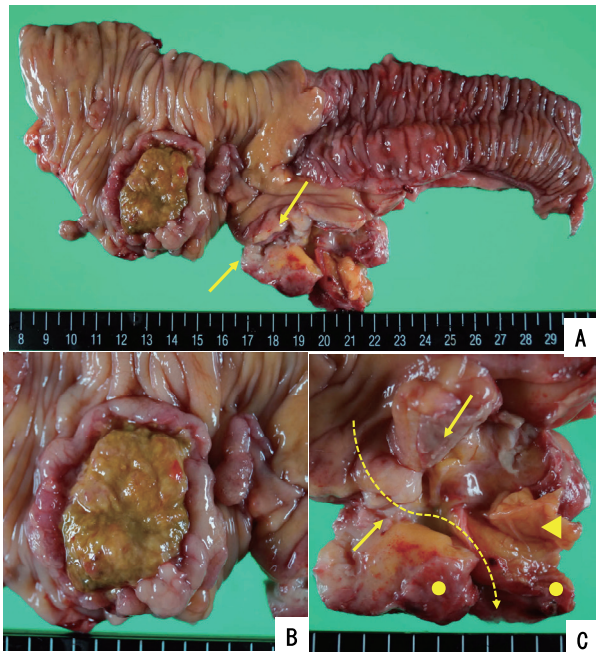


Fig. 2. Gross visualization of the resected right colon, appendix (arrow line), and ileum. Type-2 tumor and several polyps are observed in the ascending colon. The wall thickening is observed at the root of the appendix ; B : Type 2 tumor in the ascending colon. moderately differentiated adenocarcinoma (tub2). C : Appendiceal GCA is observed circumferentially at the base of the appendix (arrow line). The wavy dotted line indicates the longitudinal incision line of the appendiceal lumen. The maximum width of the appendiceal GCA is 22 mm, but there is no evidence of direct invasion to the surrounding organs or appendiceal mesentery. Appendiceal wall has the appearance of necrotic changes despite the absence of perforation (disc mark), and the mesentery of the appendix is markedly swollen and edematous (arrowhead).

*UICC-TNM classification : T3, N2a, M0, Stage IIIC*

The patient's postoperative course was good ; he resumed food intake on postoperative day (POD) 4 and was discharged on POD 14. We explained the need for postoperative chemotherapy ; however, the patient refused to provide informed consent. Three months after surgery, a colonoscopy was performed, which revealed six polyps ranging in size from 3 to 10 mm. The histopathological diagnosis of the biopsy sample from the 10- mm poly was a serrated adenoma. We strongly persuaded him to take endoscopic submucosal or mucosal resection of the remaining polyps. Unfortunately, the patient did not provide consent. Since then, we have been calling him every 6 months for follow-up. Four and a half years after surgery, the patient remains in good health and continues to run his family business.

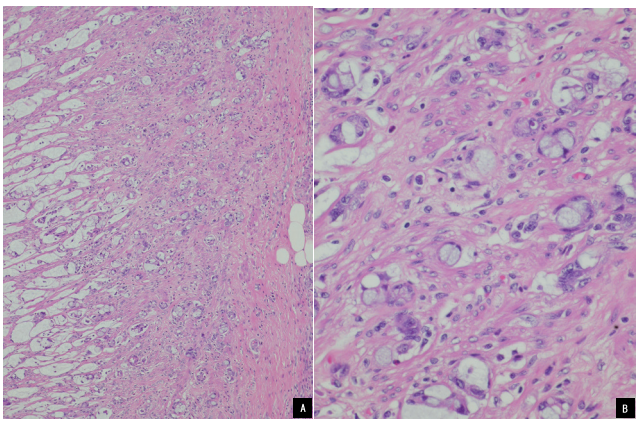

Fig. 4. Microscopic findings of the appendiceal tumor, goblet cell adenocarcinoma ; A : Luminal growth with round to oval tumor clusters and mucin pools is seen prominently in all layers of the appendiceal wall (hematoxylin and eosin staining, ×10) ; B : Clusters or aggregates of cells with abundant mucin-filled cytoplasm that compress the nucleus and resembles a goblet cell (hematoxylin and eosin staining, ×100).

## DISCUSSION

CRC is the most common malignant tumor of the gastrointestinal tract (GIT) (20). The appendix can develop a variety of tumors ; however, it occupies only a small portion of the gastrointestinal tract, and some of these tumors are unique to the appendix (21). Acute appendicitis is a common presentation in the emergency department. Appendiceal lumen obstruction is a common condition. Occasionally, tumors at the base of the appendix can lead to appendicitis via the same process as an appendicolith (22). Appendiceal GCA is categorized as a malignant epithelial neoplasm with highly malignant features, such as a high incidence of metastases and poor prognosis (12). According to the 2019 WHO classification (23), appendiceal tumors are classified into the following categories : hyperplastic polyps, sessile serrated lesions without dysplasia, mucinous neoplasms, GCA, NETs, neuroendocrine carcinomas, and mixed endocrine-nonendocrine neoplasms. This classification is based on an improved understanding of the different types of appendiceal neoplasms and accumulated knowledge gained from molecular studies (18). In the USA, the incidence of appendiceal GCA/GCC is approximately 14- 19% of appendiceal malignancies (4). In Japan, a multicenter cohort study of appendiceal neoplasms was conducted between January 2000 and December 2017, and among the 922 neoplasms, the incidence of appendiceal GCA was reported to be only 3.5% (5).

The most common features of appendiceal GCA are acute appendicitis and other appendiceal neoplasms, followed by non-specific abdominal pain or mass. Appendiceal GCAs show a submucosal growth pattern and tend to spread throughout the intestine. The most common metastasis sites are the right colon and ileum, followed by lymph nodes, peritoneum, and mesentery. Ovaries are a common site of metastasis in women. Fifty percent of the patients with appendiceal GCA develop disseminated metastasis with peritoneal carcinomatosis, and female patients often develop ovarian metastasis (12). The rate of perforation is 20- 23% (19, 20). There are no characteristic observations on radiological images regarding preoperative diagnostic methods for appendiceal GCAs. In the present case, CE-CT revealed a contrast-enhanced lesion, despite severe inflammation in the ileocecal area (24, 25). However, Loftus *et al*. reported that most appendiceal tumors are not identified on preoperative CT because many appendiceal tumors are small and lack calcification (26). Naar *et al*. reported that patients aged 〉 40 years with an appendiceal diameter greater than 10 mm are likely to have an underlying appendiceal neoplasm and described why a large diameter is associated with chronic and gradual obstruction of the appendiceal lumen by the tumor mass (13). Regarding the prognosis of appendiceal GCAs, Fields *et al*. evaluated 2552 patients with appendiceal GCA/GCC in the USA and reported that the 5-year survival rates for stages Ⅰ- Ⅳ was 91.5%, 90.9%, 57.0%, 18.9%, respectively (27).

Operative procedures and consensus guidelines recommended completion of right hemicolectomy for all appendiceal GCAs. On the contrary, Kowalsky *et al*. suggested that right hemicolectomy may not be necessary for all appendiceal GCAs because the T stage of the tumor correlates with the risk of lymph node metastasis, and a survival benefit from hemicolectomy was only observed in patients with T3/T4 tumors, in whom the risk of lymph node metastasis was greater than 10%. Omission of complete hemicolectomy is safe for patients with T1/T2 tumors and negative margins on appendectomy (28). In the present case, we performed a right hemicolectomy with LN (D3) following the JCCCR 2018 guidelines. The root of the MDA and a large segment of the transverse colon were preserved despite the curability A surgery of JCCCR.

SCRCs refer to tumors that are diagnosed at the same time or within 6 months of the initial diagnosis of another primary tumor (29). Most SCRCs consist of two lesions ; however, few patients have three or four lesions. In most cases, the number of pathological types of SCRC is limited to 1- 2, and it is unusual for the pathological findings of a patient with SCRC to show more than two subtypes without a family history of cancer (30). Recently, the detection of SCRCs has increased with the advancement of both colonoscopy and radiological imaging techniques, such as multidirectional- CT. SCRC is uncommon and occurs in 1.1– 10.7% of all patients with colorectal cancer (31). Considering the above results, and the incidence of appendiceal GCA (3.5-19%) (4, 5), we concluded that the cases of SCRCs, including appendiceal GCA, are extremely rare. We searched PubMed for appendiceal GCA associated with SCRCs using the following index terms : appendiceal GCA, carcinoid, synchronous/multiple colorectal cancer, and neoplasm. However, we retrieved only two studies (10, 11). Table 1 presents the findings of previously reported two cases of GCA associated with SCRCs as well as those of the present case.

Preoperative and intraoperative diagnosis of multiple SCRCs is extremely important but remains challenging. In our case, we could not preoperatively detect these on the CT scan but found it only by manual palpation and later upon re-evaluation of the same CT images. Li *et al*. reported that comprehensive intestinal exploration during surgery is important for detecting secondary cancers (30). As a preoperative examination for SCRCs, ESOCR is necessary to exclude the presence of synchronous colorectal tumors and lesions. If a complete preoperative colonic endoscopic evaluation is not performed, early ESOCR should be done within 3-6 months after surgery (32). Some authors have recommended the intraoperative ESORC to confirm the absence of other tumors after surgical resection of intestinal lesions (33). In our opinion, intraoperative ESOCR is extremely dangerous, especially in emergency surgery for appendiceal neoplasms in the context of acute complicated appendicitis because it can cause perforation of the appendiceal neoplasm and increase the risk of peritoneal contamination. Therefore, we believe that this procedure should not be performed routinely. In the present case, CT findings should be observed more carefully before emergency surgery. If we had detected SCC preoperatively, a laparotomy would have been performed through a median abdominal incision, and we

Table 1. Published reports of synchronous appendiceal goblet cell adenocarcinoma and colorectal cancer

| Author (published Year) | Gender / Age | Number of primary GCA and metastatic lesion of GCA | Number of SCRCs | Site | Discovery opportunity of primary GCA | Operation for GCA | Discovery opportunity of SCRC | Operation for SCRC and metastasis of GCA |
|---|---|---|---|---|---|---|---|---|
| Vincenti(7) (2022) | WOMAN /72 | 1(appendiceal GCA) No metastasis lesion of GCA | 1 | Cecum | Histopathological (postoperative) | Right colectomy | Colonoscopy (preoperative) | Right colectomy |
| Kinoshita(8) (2023) | WOMAN /78 | 1(appendiceal GCA) Metastasis of GCA to right ovary | 1 | Sigmoid colon | Laparoscopy (Intraoperative) | Appendectomy | Colonoscopy (preoperative) CT (preoperative) | Laparoscopic sigmoidectomy /bilateral adnexectomy |
| Present case | MAN /69 | 1(appendiceal GCA) No metastasis lesion of GCA | 2 | Ascending colon Sigmoid colon | Acute appendicitis CT (preoperative CT) | Right colon resection with Lymph nodes dissection | Palpation (intraoperative) CT (preoperative) | Sigmoidectomy with Lymph nodes dissection |

could have observed a more extensive and adequate colorectum.

Surgical resection is the most common treatment for SCRCs (34). However, bilateral colon and synchronous colorectal tumors often require resection of multiple segments. According to the sites of synchronous bilateral colon tumors and synchronous colorectal tumors, Wraps *et al*. recently reported an occurrence of 37.6%in the right-left colon, 58.8% in the right colon – rectum, and 19.8% in the left colon – rectum. When the right colon was involved, extended resection was most often performed in cases of bilateral location with the most common procedures being a right (extended) hemicolectomy, with sigmoid resection, and with low anterior resection (38.8%), consisting of a subtotal colectomy in 25.4%, and total colectomy in 4.5% cases (31). When SCRCs occur primary in two or more colorectal segments, especially in both the right and left segments, extensive colorectal resection and lymph node dissection pose a major issue in terms surgical invasion and the risk of anastomotic leakage due to insufficient blood supply (32). The initial surgical procedures for several SCRCs remain controversial ; surgical procedures for SCRCs should be individualized depending on tumor location, tumor stage, and the general health of the patient (35). Nguyen *et al*. divided the operative procedures for SCRCs into two subgroups : extended colectomy subtotal colectomy [STC], total colectomy [TC], or ileal pouch anal anastomosis, or segmental colectomy (double resection). To date, there is no clear data in the relevant literature to help surgeons select the right procedure for these complex cases. TC and STC have been reported to have the advantage of complete resection of any existing tumor or polyp. However, double resection has been evaluated to preserve the normal colon because it avoids severe postoperative diarrhea due to the preservation of the long segment of the colorectum (35). Extensive mesenteric resection causes loss of blood supply to the residual intestine and increases the risk of anastomotic leakage. Postoperative complications such as prolonged hospital stay, frequent diarrhea, and obstruction of the anastomotic site seriously affect quality of life. Li *et al*. reported that surgery for multiple SCRCs of the large intestine needs to be customized according to the tumor location, extent of invasion, distant metastasis, and patient health status (30).

Recently, laparoscopic operations have been widely performed for colorectal cancer. The laparoscopic appendectomy is now generalized for the operative procedure for acute appendicitis. In the present case, the patient was preoperatively suspected of having acute complicated appendicitis with an appendiceal neoplasm and was diagnosed with synchronous ACC. We considered the perforation of the appendix and metastasis due to dissemination. Interval appendectomy was not considered because of the same reason. Unfortunately, we kackled the necessary experience and technical expertise regarding laparoscopic surgery for colorectal cancer. Furthermore, all operations related to complicated appendicitis were performed under laparotomy in this patient. In our opinion, laparoscopic colectomy is the best method if operating surgeons have sufficient technical expertise and experience.

In Japan, adjuvant chemotherapy for the colon and rectum is confirmed, based on the JSCCR guidelines (36). In the present case, appendiceal GCA was Stage Ⅱa, ACC was Stage Ⅱa, and sigmoid colon cancer was Stage Ⅲc according to the JCCRC 2018 guidelines. Adjuvant chemotherapy should be administered in such cases because each adenocarcinoma is an advanced form of cancer. Unfortunately, chemotherapy could not be administered due to patient`s refusal. Standard chemotherapy regimens for appendiceal GCA metastases, such as 5-fuloorouracil (5-FU), leucovorin-based FOLFOX (5-FU, leucovorin, and oxaliplatin), and FOLFIRI (5-FU, folic acid, irinotecan) (12), have been recommended for other CRCs. RO surgery can be performed for all three SCRCs ; therefore, the recommended oxaliplatin combination therapy, such as capecitabine and oxaliplatin (CapeOX) or FOLFOX, is preferred.

The major pathways of genetic development of CRC are through chromosomal instability (CIN) and MSI. The CIN pathway in CRC typically includes the combination of mutations and loss of heterozygosity in tumor protein 53 and adenomatous polyposis coli (APC) (7). There are three situations in which a patient may be predisposed to tumors arising from the MSI pathway, i.e., Lynch syndrome, Lynch-like syndrome, and MLH-1 methylation, all of which are associated with MSI-H (8). In Western countries, the presence of SCRC is reported to have a relatively high correlation with the MSI pathway that solitary CRC – (solitary CRC : 12-17% vs SCRC : 30-37%) (8).

There is a hypothesis that SCRC occurs due to the field effect, which effect is a biological process in which large areas of cells at a tissue surface or within an organ are affected by carcinogenic alterations. This process inflated after exposure to an injurious environment, often over a lengthy period (37). One of the predispositions for developing SCRC is LS. Moreover, patients with LS tend to have MSI-H. On the other hand, some reports have suggested that microsatellite status was discordant between lesions in patients with SCRC (33). In the same patient, the concordance rates for MSI-H, KRAS-mutant, and BRAF-mutant between lesions are reported to be 9-30%,11-40% and 0-14%, respectively (8).

It has been reported that the subtypes of KRAS and BRAF are

directly linked to selecting patients for anti-epidermal growth factor receptor (EGFR) therapy. However, SCRC lesions have often been reported to show discordance in KRAS and BRAF subtypes (8). Giannini *et al*. reported that 42% of cases with SCRC had discordant subtypes of KRAS and BRAF (15). It is important to examine the MSI status when selecting checkpoint blockade immunotherapy. In Japan, Arakawa K *et al*. recently reported that the rate of MSI-H concordant cases accounted for only two out of 59 SCRC cases (3.4%), which is lower than that was reported in western countries. They suggested that the low rate of LS in Japanese patients might be the reason for low the MSI-H concordance among patients with SCRCs in their study and most of the tumors in patients with MSI-H CRC patients were observed on the right side (8). Carlin *et al*. also reported the location of 28 lesions in 14 patients of the mismatch repair discordant CRCs ; of these 20 proficient MMR tumors occured in the right colon and 8 tumors occurred in the left colon. They also showed BRAF-V600E status through immunohistochemistry and molecular analysis, which revealed that 10 cases were mutated, 3 cases were wild type, and 2 cases were not assessed (9). Arakawa *et al*. reported that the concordance rates of KRAS and BRAF subtypes among cases of SCRC were less than 50% and suggested that, in SCRCs, each lesion may develop from a different pathway : these results become clinically important (8). Anti EGFR therapy and checkpoint blockade immunotherapy are effective only for lesions with wild-type KRAS and BRAF lesions with loss of MMR protein in CRC. If the status of KRAS and BRAF differs between lesions in a patient with SCRC, the status of KRAS and BRAF associated with recurrent metastases might not be clear. We should observe MSI, KRAS, and BRAF for all three cancers because KRAS and BRAF status at the site of recurrence should be investigated when considering anti-EGFR therapy.

According to genomic profile of appendiceal GCA, several studies showed that the mutations in CRC-related genes (eg, KRAS, APC) are rare to absent in GCA. GCA obtains pathogenic somatic mutations that are not observed in NETs (23). Recently, Arai *et al*. reported that p53 (12/50, 24%), ARID1A (2/13, 15.4%), SMAD4 (5/53, 9.4%), and KRAS (4/53, 7.5%) are the most prevalent mutations in appendiceal GCA, whereas 21 minor mutant genes, including BRAF, account for a small subset of patients with appendiceal GCA. In addition, MSI-high/deficient mismatch repair, tumor mutational burden-high (≧17 mutations/Mb), and programmed death-ligand expression GCA were seen in 0 of 52 (0%), 0 of 53 (0%), and 1 of 51 (2.0%) cases, respectively. Only a few studies have conducted genomic examinations for appendiceal GCA (37). We should perform genomic examinations for appendiceal malignancies, including for this relatively rare appendiceal GCA.

Our report of the present study has several limitations. First, we performed this emergency operation at our hospital, which is not a high-volume institute. We could not determine the best operative procedure intraoperatively because of lacking enough experience of operations for the case with bilateral CRCs. Second, germline genetic testing was not available in our regional institute and was not conducted. Therefore, we could not deny completely the possibility of inherited diseases, especially Lynch syndrome. Third, this case is an extremely rare case comprising of triple advanced SCRCs, including appendiceal GCA. Therefore, we could not collect enough information on the same cases (7, 8). In future, we must conduct germ line genetic tests to assess the genetic background of the lesions of SCRCs and accumulate the results for preventing metachronous CRCs.

In conclusion, we performed right hemicolectomy and sigmoid resection with LD in a case of concurrent multiple colorectal cancers consisting of appendiceal GCA, which caused acute necrotizing appendicitis, ACC, and SCC. In the routine care of patients with acute appendicitis, it is important to consider the possibility of an appendiceal neoplasm and to be aware of the complications of SCRCs, as in the present case. Performing contrast-enhanced CT whenever possible and providing appropriate treatment based on appropriate measurements are essential. Furthermore, it is important to confirm the genetic mutation of every lesion to perform the appropriate postoperative chemotherapy for SCRCs, with the addition of molecularly targeted agents and immune check inhibitors.

## CONFLICT OF INTEREST

All authors declare no conflicts of interest associated with this work

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