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CASE REPORT

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A case of appendix adenocarcinoma associated with ulcerative colitis

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Abstract

Ulcerative colitis (UC) is a chronic relapsing inflammatory disorder of the colon. Patients with UC have an increased risk of developing colorectal cancer. However, appendix adenocarcinoma associated with UC is extremely rare.

KEYWORDS

adenoma-carcinoma sequence, appendix adenocarcinoma, dysplasia

1 | INTRODUCTION

Appendix adenocarcinoma associated with ulcerative colitis (UC) is extremely rare. Pathological examination of a man with 6-year history of UC revealed a primary appendix adenocarcinoma mixed with adenoma component. Dysplasia was not identified. The adenoma-carcinoma sequence, but not the dysplasia-carcinoma sequence, might be involved in this UC-associated appendix adenocarcinoma.

Ulcerative colitis (UC) is a chronic relapsing inflammatory disorder of the colon.[1] Patients with UC have an increased risk for developing colorectal cancer (CRC), known as UC-associated CRC.[2–4] The cumulative incidence of UC-associated CRC has been reported to be from 7.5% to 18.4% at 30 years after onset.[5] However, appendix adenocarcinoma associated with UC is extremely rare.

2 | CASE REPORT

A 52-year-old man with a 6-year history of UC (left-sided colitis) was admitted to our hospital because of umbilical pain and low-grade fever. Oral administration of 5-aminosalicylic acid had been discontinued one year earlier due to clinical remission. A colonoscopy performed one year earlier showed an endoscopic remission. At this time, a mild inflammation was observed around the appendix orifice. He had no family history of malignancies.

Physical examination on admission showed tenderness in the right lower quadrant of the abdomen, but there was no peritoneal irritation sign. Laboratory examination revealed an elevation of C-reactive protein (2.01 mg/dl), but tumor markers such as carcinoembryonic antigen and carbohydrate antigen 19–9 were within normal range. A contrast material-enhanced computed tomography scan showed a stenotic change of the proximal ascending colon

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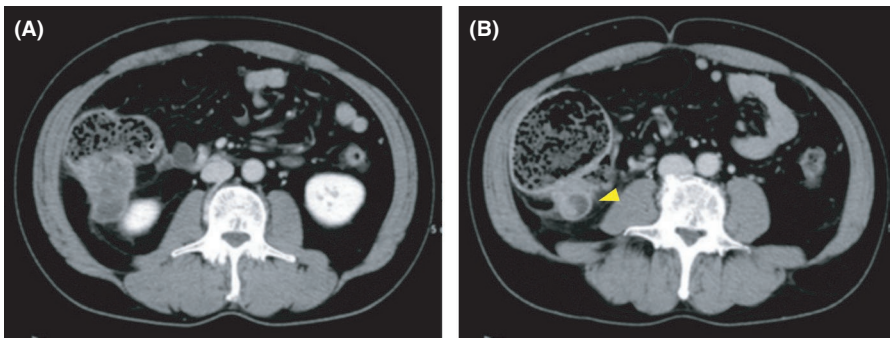

FIGURE 1 Computed tomography scan on admission. The appendix was dilated with the tumor exhibiting intraluminal growth (arrow head). This tumor extended to the serosal side of the proximal ascending colon

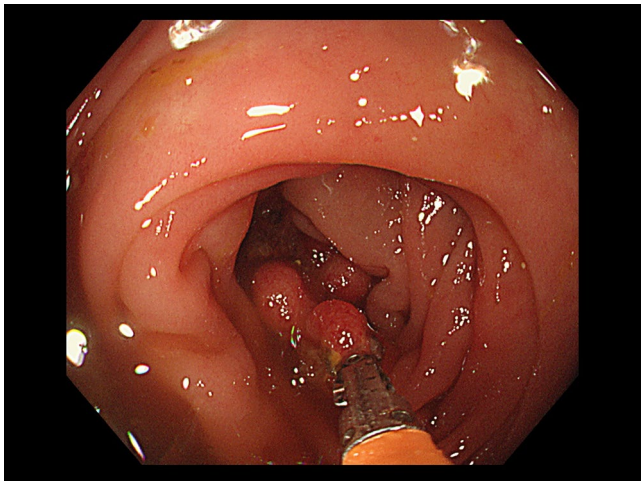

FIGURE 2 Endoscopic finding of the stenotic portion. Colonoscopy on admission showed a circumferential stenosis of the ascending colon. The lumen was spread by air supply, and intraluminal tumor growth was not observed. The mucosa was reddish but pathological examination of biopsy specimens showed no malignancy

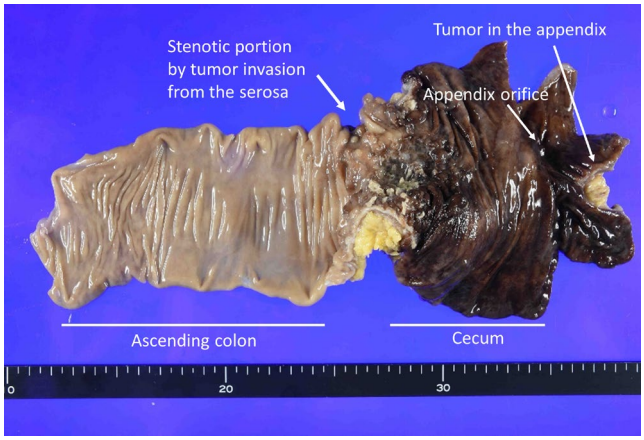

FIGURE 3 Macroscopic picture of resected sample (mucosal view). The appendix was strongly adhered to the serosal site of the ascending colon and formed a stenotic portion. A color change was observed in the cecum due to congestion

by a mass showing extramural growth (Figure 1A). The extramural part of the mass extended to the dilated appendix with intraluminal tumor growth (arrow head, Figure 1B). A colonoscopy on admission showed a circumferential stenosis of the proximal ascending colon, and the lumen was spread by air supply, suggesting extramural compression. (Figure 2). The mucosa surface was reddish, but intraluminal growth of the tumor was not observed. Pathological examination of biopsy specimens showed no malignancy.

A laparoscope-assisted right hemicolectomy was performed on the 9th day after admission. Macroscopically, the appendix was dilated and strongly adhered to the proximal portion of the ascending colon (Stage IIIB [T4b, N1a, M0] according to the TNM classification) (Figure 3). Pathological examination revealed a primary adenocarcinoma mixed with an adenoma component of the appendix (Figure 4). The tumor invaded the serosal side of the proximal ascending colon. Dysplasia was not identified in any pathologically examined specimens. Genomic analysis of carcinoma cells revealed the *KRAS* G13D mutation. His postoperative course was uneventful, and adjuvant chemotherapy (modified FOLFOX6[6]) was started from 6 weeks after surgery.

3 | DISCUSSION

Appendix carcinoma is rare and accounts for 0.4% of all gastrointestinal malignancies.[7] Furthermore, UC-associated appendix carcinoma is extremely rare, and only a limited number of cases have been reported.[8–11] The homology of pathogenesis between UC-associated appendix carcinoma and UC-associated CRC remains poorly understood.

Chronic mucosal inflammation is considered to be a main driver of UC-associated CRC,[12,13] and established risk factors include prolonged disease duration, extensive colonic involvement, family history of CRC, and coexistence of primary sclerosing cholangitis.[12–15] The severity of histologic inflammation is an independent risk factor.[13] However, the relationship between long-term mucosal inflammation and appendix carcinoma remains unclear, because previously published cases have shown that appendix carcinoma developed not only in patients with pancolitis but also in those with left-sided colitis.

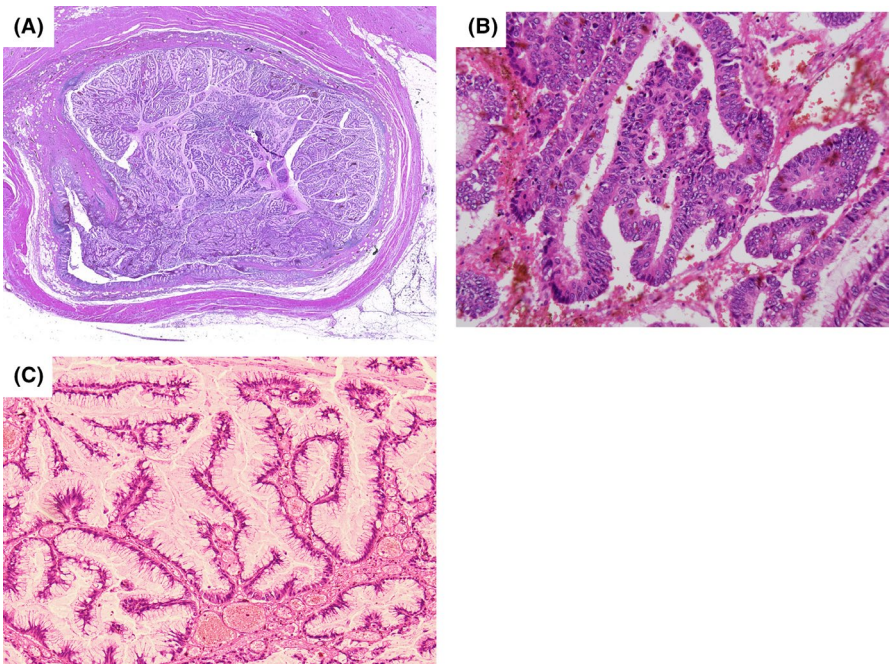

FIGURE 4 Pathological finding of the appendix. The tumor was arisen from the appendix wall and exhibited intraluminal growth. The tumor consisted mainly of carcinoma, but an adenoma component was also found. (A) Loupe image, (B) adenocarcinoma (×200), and (C) adenoma component (×200)

Sporadic CRC develops through the adenoma-carcinoma sequence,[15] but UC-associated CRC is characterized by the inflammation-dysplasia-carcinoma sequence.[16] A typical feature of UC is a continuous mucosal inflammatory lesion extending proximally from the rectum without any skip lesion. However, previous studies have reported that isolated peri-appendiceal inflammation is frequently observed as a "skip lesion" in more than half of patients with left-sided colitis or distal type colitis.[17,18] In this case, a colonoscopy performed 1 year earlier had revealed an isolated inflammation (mucosal redness and granularity) surrounding the appendix orifice. These findings indicate the presence of sustained inflammation in the appendix of patients with left-sided colitis as well as those with pancolitis, raising the possibility that like UC-associated CRC, continuous inflammation may be associated with the development of appendix carcinoma.

On the contrary, there are contrasting reports on the contribution of the inflammation-dysplasia sequence to UC-associated appendix adenocarcinoma. The presence of dysplasia is an important finding for the diagnosis of UC-associated CRC. However, dysplasia of the colonic mucosa was not identified in some previously published cases of UC-associated appendix carcinoma nor in the current case.[8,10,11] Furthermore, pathological examination in this case showed the presence of an adenoma component. These suggest that some UC-associated appendix carcinomas might develop via the noninflammatory carcinogenesis pathway.

Advances in the genetic approaches to cancer have led to the characterization of the genomic landscape of various types of tumors. Robles et al. revealed that the *KRAS* mutation was detected at a significantly lower rate in UC-associated CRC than in sporadic CRC.[19] Matsumoto et al. recently reported that UC-associated CRC developed through the inflammatory carcinogenesis pathway is characterized by the *TP53* mutation but those through the noninflammatory pathway are characterized by the *KRAS* mutation.[20] We detected the *KRAS* G13D mutation. This finding also lends support to the theory of a contribution by the noninflammatory carcinogenesis pathway in this case.

Although the standard surgical procedure to treat UC is total colectomy, this case was received right hemicolectomy due to the patient's strong refusal to total colectomy. This was based on the confirmation that there was no dysplasia in the left colon by preoperative endoscopy, and we are closely monitoring the appearance of dysplasia or cancer by follow-up endoscopy.

A preoperative diagnosis of appendix carcinoma has been reported to be extremely difficult, since there are no pathognomonic signs or symptoms.[21] In this case, a colonoscopy performed 1 year earlier revealed no evidence of appendix carcinoma. Since more than 70% of patients with appendix carcinoma present with clinical symptoms of acute appendicitis,[21] we should pay attention to such symptoms in the follow-up of UC patients presenting a skip lesion at the appendix orifice.

Finally, this case suggests an association between UC-associated appendix carcinoma and the noninflammatory carcinogenesis pathway. Genetic approaches will be helpful in defining the pathological mechanisms underlying this malignant disorder.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

All authors: contributed to the design of this manuscript. YK, AA, and HB: wrote the first draft. ST: made a pathological diagnosis. KM: made CT diagnosis. FN and OI: scientifically reviewed the manuscript. AA and BH: wrote the final version.

ETHICAL APPROVAL

Written informed consent was obtained from the patient.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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