Cancer of the Small Intestine in Patients with Crohn's Disease

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Abstract. *Due to an increase in the number of long-term cases of Crohn's disease, the risk of combined cancer in these patients has been assessed in numerous articles. Most of these reports have involved patients with cancer of the large intestine, while cases of cancer of the small intestine combined with Crohn's disease are very rare. We experienced two cases of cancer of the small intestine combined with Crohn's disease. In both cases, the patients had suffered from Crohn's disease for over 10 years and a second operation was performed after a long period without treatment following the first operation, which had achieved a favorable outcome. In both cases of combined cancer, the patients experienced ileus; however, it was difficult to discern this from ileus due to the presence of Crohn's disease. Therefore, making a definitive diagnosis of combined cancer was not possible before surgery, and the definitive diagnosis was obtained based on an intraoperative pathological diagnosis. It is thought that tumor markers transition in a manner parallel to the progression of cancer, providing a clue for cancer diagnosis. In patients with Crohn's disease, there is a pressing need to establish a method for diagnosing cancer of the small intestine at an early stage.*

Cancer of the small intestine occurring in combination with Crohn's disease is not as common as cancer of the large intestine; however, the relative risk is high. In addition, since cancer of the small intestine developing in patients with Crohn's disease occurs in infected regions, it is very difficult to detect the disease at an early stage. This is because X-ray images of small intestine cancer are similar to the images of strictures in patients with Crohn's disease. The development of small intestine cancer in patients with Crohn's disease is very rare; however, when it does occur, it leads to a poor prognosis. Therefore, the diagnosis and treatment of this condition are associated with problems that must be addressed.

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Case Reports

Case 1 involved a 36-year-old female. She was diagnosed with Crohn's disease at 23 years of age. She suffered from diabetes as a complication, and her family history included a younger sister who also suffered from Crohn's disease. At 25 years of age, she experienced ileus due to stricture, for which she underwent surgery. Because she was diabetic, intestinal resection was avoided, while strictureplasty and bypass were performed. The patient demonstrated good progress after the surgery and visited the hospital once a year. Eleven years after the first operation, she began to suffer from nausea and abdominal pain. A computed tomography (CT) scan was performed, which led to a diagnosis of hypertrophy of the small intestinal wall (Figure 1A). A small bowel series of X-rays was performed, which resulted in a diagnosis of expansion of the oral side and the strictures that frequently occur in the small intestine inside the pelvis (Figure 2A). Treatment administered *via* an ileus tube was performed for two weeks. The patient's subjective symptoms, such as nausea and abdominal pain, improved; however, no improvement was observed in the expansion of the small intestine on an X-ray examination. Therefore, a second operation was performed. The findings of laparotomy revealed advanced adhesion between the intestines, as well as the presence of nodules in Douglas' pouch of the peritoneum. Since these findings were quite different from those observed during regular laparotomy in patients with Crohn's disease, an intraoperative pathological diagnosis was made by evaluating pieces of the intestinal resection tissue and nodules. The results showed well-to-moderately differentiated adenocarcinoma. Measurement of

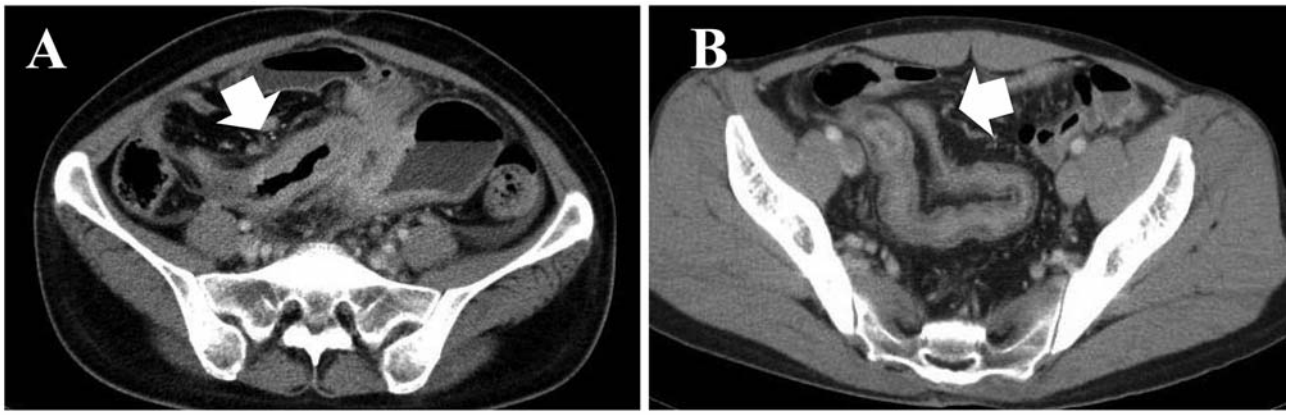

Figure 1. *A computed tomography (CT) image obtained before surgery in case 1 (A), and case 2 (B). Both images show hypertrophy of the small intestinal wall near the lesion (arrow).*

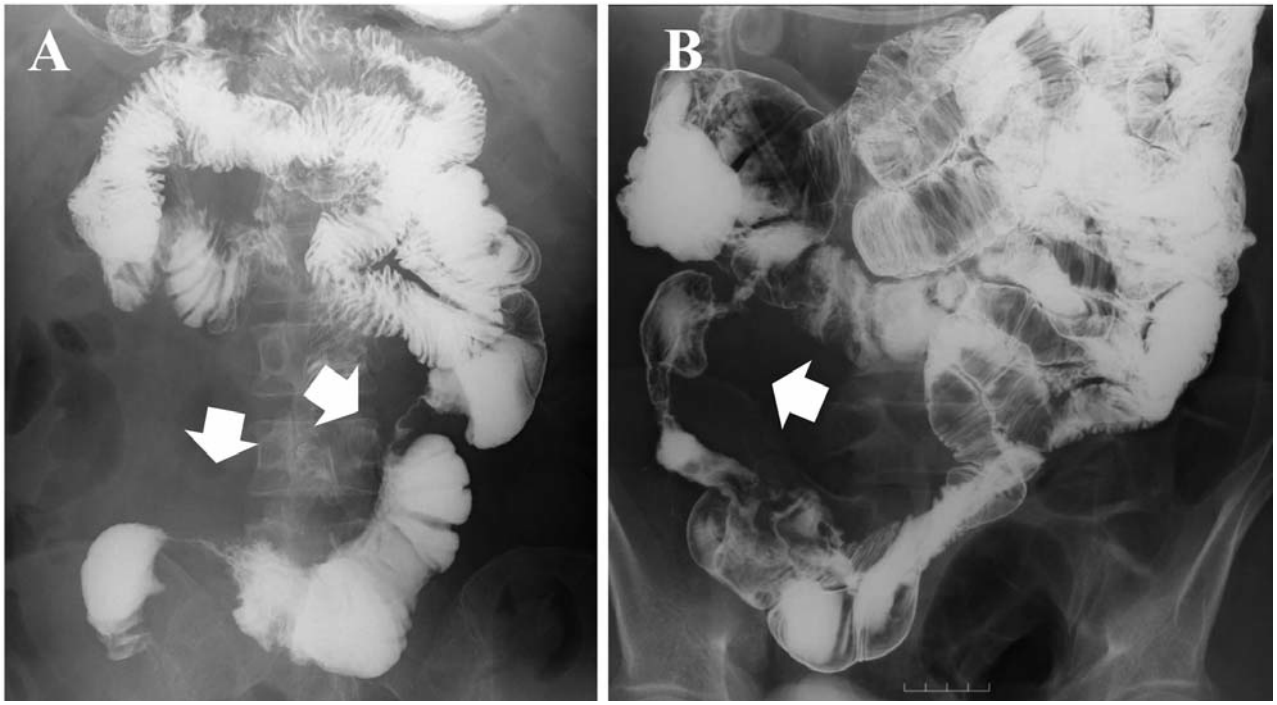

Figure 2. *Results of the small bowel X-ray series in case 1(A), and case 2(B). Both patients display multiple strictures (arrow). It is difficult to distinguish Crohn's disease from the cancer.*

the levels of tumor markers during surgery revealed a clearly high carbohydrate antigen 19-9 (CA19-9) level of 962 U/ml (Table I). The final pathological diagnosis indicated the presence of cancerous lesions in two locations: in a region that was excluded during the bypass procedure and in the stricture on the oral side of the bypass (Figure 3A and B). After the operation, treatment with FOLFOX (levofolinate, fluouracil, oxaliplatin) and bevacizumab was commenced. Following the initiation of chemotherapy, the CA19-9 level returned to normal for a short period. However, in the sixth month after the operation, a CT scan revealed a pelvic tumor, thought to be a site of recurrence, that coincided with an increased in the CA19-9 level (Table I). Chemotherapy was subsequently administered as treatment for recurring large intestine cancer; however, an increase in the number of pelvic tumors could not be suppressed, resulting in the patient's death one year and six months after the operation.

Table I. *Transition of tumor markers.*

	Before surgery	After surgery		
		3 Months	6 Months	9 Months
Case 1				
CEA	2.1	2.2	4.3	19.3
CA19-9	962	32	66	413
Case 2				
CEA	13.2	4.0	10.2	15.7
CA19-9	358	60	49	24

CEA: Carcinoembryonic antigen ; CA19-9: carbohydrate antigen 19-9.

The second patient was a 45-year-old male. The disease presented as abdominal pain and melena at 22 years of age; therefore, he had been suffering from the disease for 23 years. At 23 years of age, the patient underwent appendectomy due to appendicitis, and at that time was diagnosed with Crohn's disease. At 25 years of age, ileocecal resection was performed due to stenosis of the ileum. The patient's progress after the operation was favorable, and 13 years passed without any treatment. At 38 years of age, the patient developed an aching sensation in the right side of the abdomen. For the next seven years, he received medical therapy, primarily centered on prednisolone. Since ileus had also appeared at that time, the patient was admitted to this hospital. The CT findings were similar those of case 1, which lead to a diagnosis of hypertrophy of the small intestinal wall (Figure 1B). A small bowel series of X-rays revealed an anastomotic site in the region of the previous surgery with multiple areas of stenosis on the oral side (Figure 2B). A fistula was also found near the anastomotic region, and the intestinal tract on the oral side had expanded. During colonoscopy, we were unable to insert the scope because the stenosis on the oral side was too severe. For this reason, we determined that the areas of stenosis were due to recurrence of Crohn's disease in the anastomotic region, and we performed surgery. The area around the anastomotic region was very hard, and nodules were found in the peritoneum. It was determined that the patient's symptoms were caused by advanced cancer; therefore, an intraoperative pathological diagnosis was made. The results indicated the presence of well-differentiated adenocarcinoma. We performed right hemicolectomy including the area of stenosis. The final pathological diagnosis was a cancerous lesion at the stricture on the oral side of the anastomosis formed during the previous operation (Figure 3C). After surgery, we administered chemotherapy with FOLFOX and bevacizumab. To date, there has been no obvious recurrence on imaging examinations.

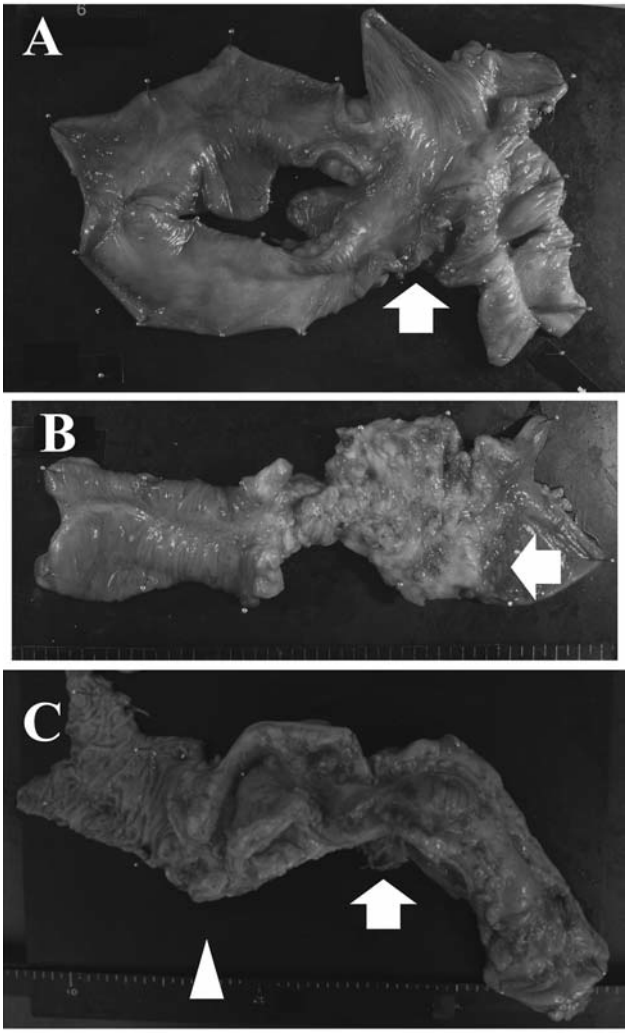

Figure 3. *Resected specimens in case 1. Cancer (arrows) was found in the region excluded during the previous bypass operation (A) and the stricture lesion (B) on the oral side of the bypass. Findings of the resected specimen in case 2 (C). Cancer (arrow) was found in the lesion in the stricture on the oral side of the anastomosis (triangle) created during the previous operation.*

Discussion

The incidence of Crohn's disease has steadily increased, with both the overall number of patients and the number of long-term cases increasing. It is known that cancer can develop in the digestive tract, including the small and large intestines, as a result of long-term chronic inflammation (1-4). The cumulative risk is 0.2% in the first 10 years and 2.2% in the first 25 years after the onset of Crohn's disease (5).

The first case of cancer of the small intestine combined with Crohn's disease was reported by Ginzburg *et al*., (6) in 1956. This condition is not as common as large intestine

cancer combined with Crohn's disease; however, the relative risk is very high (7, 8). Cancer of the small intestine combined with Crohn's disease does not involve the specific symptoms observed at the onset of small intestine cancer and does not display spindle-shaped benign strictures without protrusions. Therefore, making a diagnosis of this disease is very difficult, even when using X-ray examinations (9). Consequently, the rate of diagnosis before surgery is very low at 3.0% (9). In both cases discussed here, examinations performed before surgery did not lead to a definitive diagnosis, and cancer was diagnosed based on intraoperative pathological methods. It is difficult to detect small intestine cancer combined with Crohn's disease at an early stage. Positron- emission tomography (PET) and multidetector-row computed tomography (MDCT) scans have been used; however, their efficancy is uncertain.

The patients presented here exhibited increases in the levels of tumor markers before and during surgery. There is a possibility that regular assessment of tumor markers can provide clues to the detection of combined cancer.

Risk factors for carcinogenesis among patients with Crohn's disease include chronic inflammation accompanying the ileitis type, stricture and fistula development, and a long disease duration (10, 11). Both of the presented cases were long-term cases lasting over 10 years, accompanied by the development of stricture lesions. Small intestine cancer combined with Crohn's disease is often diagnosed in an advanced stage, and the present cases demonstrated highly advanced stages of cancer accompanied by peritoneal metastasis. There is no effective chemotherapy regimen for small intestine cancer (12). For this reason, the prognosis of patients with small intestine cancer combined with Crohn's disease is very poor (13). One of the two patients presented, died one year and six months after surgery.

Conclusion

We experienced two cases of cancer of the small intestine combined with Crohn's disease in which a definitive diagnosis was made using pathological methods during surgery. In each case, the patient's symptoms before surgery did not lead to a definitive diagnosis of cancer, and the disease was already in a fairly advanced stage when the operation was performed. The levels of tumor markers had clearly increased; therefore, it is believed that such findings may provide clues to cancer diagnosis.

When treating patients with long-term Crohn's disease, it is necessary to always keep the risk of combined cancer in mind. A major future task is to establish a method to diagnose cancer at an early stage.

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