Adenocarcinoma Associated with Perianal Fistulas in Crohn's Disease

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Abstract. *Aim: The purpose of the present study was to examine the possible relation between anorectal carcinoma and infliximab therapy for Crohn's disease. Patients and Methods: This study reviewed the medical records of patients with perianal Crohn's disease, who have required surgical intervention at the Tohoku University Hospital since May 2002, when infliximab was approved as a remedy for Crohn's disease in Japan. Results: Ninety-two patients underwent surgery due to perianal Crohn's disease between May 2002 and December 2011. Four out of 92 patients were diagnosed as having anorectal carcinoma associated with perianal fistula. All four patients had advanced carcinoma, and received infliximab before the diagnosis of cancer was made. Infliximab was administered due to an exacerbated anal lesion in three patients. Conclusion: Careful inspection and obtaining of a biopsy sample under anesthesia is recommended for patients with Crohn's disease who have long-standing anal fistulas, especially before infliximab administration due to a possible exacerbation of anal symptoms.*

Long-standing Crohn's disease carries a significant risk of cancer development in the gastrointestinal tract (1). Anorectal adenocarcinoma arising at long-standing anorectal fistulas is rare (2); however, it has recently been regarded as a challenging disease because of difficulty in diagnosis, advanced stage at surgery and poor prognosis (3-6).

The monoclonal antibody against tumor necrosis factor-α (TNFα), infliximab was approved in Japan as a therapeutic agent for Crohn's disease in May 2002, and is currently one of the standard remedies for Crohn's disease including refractory anal fistulas. Although several large-scale observational studies reported a negative association between infliximab administration and the incidence of malignancy in patients with Crohn's disease (7-10), the development or progression of malignancies, including anorectal cancer, associated with TNFα antibody administration is still a matter of concern (11-13).

The current study reviewed patients with Crohn's disease who required surgical intervention for an anal lesion at this institute since May 2002, and describes the details of four patients who developed anorectal carcinoma associated with a perianal fistula.

Patients and Methods

The computerized database of the Department of Surgery, Tohoku University Hospital was searched for all patients with Crohn's disease who required surgical intervention under hospitalization between May 2002 and December 2011. The database includes diagnosis, clinical history, surgical procedure, and therapeutic agents administered before surgery for each case. A detailed review of the medical records of patients with anorectal carcinoma associated with anal fistula in patients with Crohn's disease was undertaken.

Results

One hundred and fifty surgical procedures were performed with hospitalization for 92 patients with perianal Crohn's disease between May 2002 and December 2011. The details are summarized in Table I. Twenty-three out of 92 patients had received infliximab therapy prior to surgery, and four patients (one male) were diagnosed as having anorectal carcinoma associated with a perianal fistula.

Clinical course of the four patients before the diagnosis of anorectal cancer (Table II). The mean age at diagnosis of anorectal cancer was 40 years (25-68 years). All four patients had Crohn's disease involving both the small and large bowel. The time interval between the diagnosis of Crohn's disease or onset of anal lesions and diagnosis of anorectal carcinoma was 19.1±9.1 (mean±SD) years and

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Table I. *Summary of the 150 surgeries for perianal lesion for 92 patients with Crohn's disease between May 2002 and December 2011.*

Gender	Male, 60; female, 32
Age at surgery	35.1±9.8 years
Crohn's disease duration	14.2±7.6 years
Perianal fistula duration	11.3±7.7 years
Infliximab prior to surgery	Yes, 23 patients
	No, 69 patients
Concomitant rectal disease	Rectal lesion, 20 patients
	RVF, 5 patients
Surgery	Seton drainage, 65 surgeries
	Fecal diversion, 43
	Abdominoperineal resection, 19
	Others (dilatation, fistulectomy *etc.*), 23

RVF: Rectovaginal fistula.

14.4 ± 8.3 years, respectively. Three out of the four patients had undergone intestinal surgery for an intestinal lesion, and concomitantly had fecal diversion because of their severe perianal lesion. Three patients had undergone anal surgery (incision and drainage in one, seton drainage in two) for their perianal fistula and/or abscess. The most frequent symptom before diagnosis of anorectal carcinoma was anal pain and fluid discharge. Patient 4 complained of a palpable anal tumor (3 cm) without any other symptoms. Two patients were smokers, while the other two patients had no history of smoking.

Preoperative findings of anorectal cancer (Table III). All four patients had a trans-sphincteric fistula. Three patients had concomitant severe anal strictures. Computed tomography (CT) or magnetic resonance imaging (MRI) demonstrated a thickened rectal wall or anal abscess, and the maximum standardized uptake value (SUVmax) of F-18 fluorodeoxyglucose (FDG) positron-emission tomography (PET) ranged between 2.0 and 8.7. None of these findings were useful in distinguishing inflammation from cancer. The serum carcinoembryonic antigen (CEA) levels at the diagnosis of cancer were extremely high in two patients, but were not elevated in the other two patients. Adenocarcinoma was histologically detected in the biopsy specimens of two patients, but was not detected in spite of repeated biopsies in the other patients. Patients 2 and 3 received a histological diagnosis of carcinoma based on the tumor specimens obtained during surgery.

Pharmacological therapy for Crohn's disease prior to anorectal cancer diagnosis (Table IV). All four patients received infliximab (5 mg/kg) and 5-aminosalicylic acid (5-ASA) for Crohn's disease. The mean time between infliximab administration and cancer diagnosis was 5.5 months (4-9 months). Three patients (patient 1-3) were treated with infliximab due to the exacerbation of their anal lesion, *i.e.* exacerbated anal pain with or without increased fluid discharge. The anal symptoms improved with infliximab therapy in one of these patients (patient 3); the remaining two patients did not respond to infliximab therapy. Infliximab was administrated to patient 4 because of an entero-cutaneous fistula, which responded well to this therapy.

Two patients received infliximab as an episodic therapy and the other two patients received it as a scheduled therapy. The mean duration of infliximab therapy was 16 weeks (6-32 weeks).

Surgical and pathological findings, postoperative treatment and outcome (Table V). The anorectal carcinoma was surgically resected in three patients. Patient 1 underwent total proctocolectomy with end-ileostomy because of concomitant severe Crohn's colitis. The carcinoma directly invaded the vaginal wall in two out of three female patients, and the vaginal wall was partially resected (patient 3), or totally resected with hysterectomy (patient 4). The tumor was not resected because of diffuse peritoneal dissemination in patient 2.

Three patients had mucinous adenocarcinoma and one patient had both mucinous and signet ring-cell carcinoma. The resection margin was positive in all three patients who underwent resection.

Postoperative radiation therapy was performed for the three patients who underwent resection, with or without chemotherapy. Patient 4 was treated with panitumumab, after a distant recurrence was diagnosed in the lung. Patient 2 did not receive either radiation or chemotherapy because her general condition was debilitated. Three out of four patients died at 5-23 months after surgery. Only one patient is still alive at 63 months after surgery without recurrence (patient 3).

Discussion

Adenocarcinoma arising from an anal fistula in patients with Crohn's disease is rare. The incidence is estimated to be 0.3-0.7% of all patients with Crohn's disease (14, 15). Laukoetter reported that the incidence of cancer arising from Crohn's disease-associated fistulas is 0.2/1000 person years (1). Iesalnieks described 65 cases with anorectal carcinoma arising from a perianal fistula in patients with Crohn's disease reported from January 1946 until September 2009, including their own six cases (3). Four patients with Crohn's disease were diagnosed as having anorectal carcinoma associated with an anal fistula between May 2002 and December 2011 in this Institute, accounting for 4.3% of 92 patients that underwent surgery for perianal Crohn's disease during the same period.

Carcinoma associated with an anal fistula in patients with Crohn's disease has several characteristics: A long-standing perianal fistula prior to cancer development, typically of

Table II. *Crohn's disease patients with anorectal carcinoma arising from an anal fistula.*

	Patient 1	Patient 2	Patient 3	Patient 4
Age (year), gender	25, Male	68, Female	34, Female	33, Female
Crohn's disease duration	7.2 years	29.5 years	19.4 years	20.3 years
Crohn's disease type	Small and large bowel	Small and large bowel	Small and large bowel	Small and large bowel
Anal fistula duration	7.2 years	23.0 years	7.3 years	19.9 years
History of intestinal surgery	No	Yes	Yes	Yes
Fecal diversion before cancer	No	Yes	Yes	Yes
History of anal surgery	No	Incision and drainage	Seton drainage	Seton drainage
Symptoms prior to diagnosis	Anal pain	Anal pain, fluid discharge	Anal pain, fluid discharge	Anal tumor
Smoker	Yes	No	No	Yes

Table III. *Preoperative findings of anorectal carcinoma.*

	Patient 1	Patient 2	Patient 3	Patient 4
Clinical				
Type of anal fistula	Trans-sphincteric	Trans-sphincteric	Trans-sphincteric	Trans-sphincteric
Anal stricture	++	++	++	–
Other	–	Abscess	Anal ulcer	Anal tumor
Imaging				
CT	N/A	Thickened rectal wall	Thickened rectal wall	N/A
MRI	Thickened rectal wall perianal abscess	Thickened rectal wall, perianal abscess	Thickened rectal wall,	Perianal abscess
SUVmax (FDG-PET)	N/A	2.0	8.7	3.1
Serum CEA (ng/ml)	1.20	118.9	91.4	1.60
Histological diagnosis of biopsy before surgery	Adenocarcinoma	N/A	No malignancy (granulation)	Adenocarcinoma

Anal stricture, ++: unable to examine (digital examination, anoscope) without anesthesia due to pain and/or stricture; CT: computed tomography; MRI: magnetic resonance imaging; SUVmax: maximum standardized uptake value; FDG-PET: F-18 fluorodeoxyglucose positron-emission tomography; CEA: carcinoembryonic antigen; N/A: not available.

more than 10 years; rapidly growing and advanced cancer at the time of diagnosis; difficulty in diagnosis due to concomitant inflammation and/or strictures; imaging examinations including CT and MRI seem to have a low sensitivity in detecting cancer (2, 3). The present report described the details of four patients with Crohn's disease who developed anorectal carcinoma associated with an anal fistula. All patients had advanced anorectal cancer at the time of surgery, and three of them died due to their cancer.

Delayed diagnosis and poor prognosis can mainly be attributed to the difficulty in making an accurate diagnosis of anorectal cancer in these cases. Thomas *et al*. reviewed 61 cases of carcinomas arising in perineal fistulas in Crohn's disease and described that a malignancy was suspected and proven in only 20% of the patients (2). Symptoms are usually non-specific; clinical inspection or endoscopic examination is often insufficient due to anal pain and stricture, and imaging studies including CT, MRI or FDG-PET have a low sensitivity for detecting cancer that develops under inflammation, as described in the present study and others (3, 4). Therefore, scheduled examinations and biopsy performance under anesthesia would have been necessary to diagnose anorectal cancer arising from a long-standing perianal fistula at an earlier stage in those patients. Annual surveillance for malignancy has been previously recommended in patients with a 10-year history of perianal Crohn's disease (3); however, another report described the mean interval between the onset of perianal Crohn's disease and anal cancer diagnosis in 14 patients to be 6.9 years (4). Anorectal cancer developed as early as seven years after the onset of the anal lesion in the current series. Therefore, a seven-year interval from the onset of perianal lesions may be an appropriate period to consider surveillance for anorectal carcinoma.

A preventive perineal resection might be considered in patients with Crohn's disease who have a severe perianal lesion, considering the poor prognosis of patients with anorectal cancer. Cirincione *et al*. reported that three patients

Table IV. *Pharmacological therapy for Crohn's disease prior to cancer diagnosis.*

	Patient 1	Patient 2	Patient 3	Patient 4
IFX	Yes (5 mg/kg)	Yes (5 mg/kg)	Yes (5 mg/kg)	Yes (5 mg/kg)
Other	5-ASA, antibiotics	5-ASA	5-ASA, PSL	5-ASA, antibiotics
Time between IFX administration and cancer diagnosis	4 Months	9 Months	4 Months	5 Months
Target of IFX therapy	Anal lesion	Anal lesion	Anal lesion	Intestinal lesion
Scheduled or episodic	Episodic	Scheduled	Episodic	Scheduled
Frequency of IFX injection	3 Times/6 weeks	4 Times/21 weeks	3 Times/6 weeks	5 Times/32 weeks

5-ASA: 5-Aminosalicylic acid; IFX: infliximab; PSL: prednisolone.

Table V. *Surgical and pathological findings, postoperative treatment and clinical outcome after surgery.*

	Patient 1	Patient 2	Patient 3	Patient 4
Surgery	Total proctocolectomy, end-ileostomy	Laparotomy and biopsy	APR, partial resection of vagina	Posterior pelvic exenteration
Stage (TNM)	Stage IV (T3N1M1)	Stage IV (TxNxM1)	Stage III (T4N2M0)	Stage III (T4N0M0)
Histology	muc.	muc.	muc.	muc. +sig.
Resection margin	Positive	(Not resected)	Positive	Positive
Postoperative treatment				
Radiation	Pelvic, 60 Gy	–	Pelvic, 50 Gy	Pelvic, 45 Gy
Chemotherapy	–	–	S-1	mFOLFOX6, Pmab
Recurrence	Pelvic and distant	–	No	Distant
Outcome	Death at 23 months	Death at 5 months	Alive at 63 months	Death at 14 months

APR: Abdominoperineal resection; muc: mucinous adenocarcinoma; sig: signet-ring cell carcinoma; Pmab: Panitumumab; S-1: a tegafur-based oral 5- fluorouracil pro-drug combined with a dihydropyrimidine dehydrogenase inhibitor (5-chloro-2,4-dihydroxypyridine) and an orotate phosphoribosyltransferase inhibitor (potassium oxonate).

developed anorectal carcinoma among 25 patients that underwent Hartmann's procedure for severe anorectal Crohn's disease, and recommended perineal proctectomy for all patients undergoing low Hartmann's procedure for severe anorectal Crohn's disease that cannot undergo rectal preservation (16). Three of the present cases had undergone fecal diversion because of their severe perianal lesions prior to cancer development. In addition, no adequate biopsy specimens could be obtained because of the severe anal strictures in two of those patients. Therefore, perineal resection should be considered for severe perianal Crohn's disease that requires permanent fecal diversion, especially when complicated by anorectal strictures.

Four patients with anorectal cancer were found among the 23 patients with Crohn's disease who had undergone infliximab therapy, while no individual was found among the other 69 patients without infliximab treatment. A small number of cases developing anorectal cancer after infliximab therapy have recently been reported (12, 13). However, there is no evidence that infliximab administration induced cancer development. Large-scale studies to determine the effect of infliximab on the incidence of cancer demonstrate that the incidence of cancer development in patients with Crohn's disease does not differ between those treated and those not treated with infliximab (7-10). It, therefore, seems that the association between Crohn's disease and infliximab treatment in the present series is co-incidental rather than causative, because the mean time between infliximab administration and cancer diagnosis was quite short (5.5 months) and only episodic in two patients. In addition, three out of four patients received infliximab therapy because of an exacerbation of their anal lesions, which might have actually represented cancer development rather than inflammation. However, although the role of TNFα in cancer progression remains controversial (17, 18), infliximab administration is generally avoided for patients with malignancies because TNFα suppression may enhance tumor growth (19). Therefore, special attention regarding malignant transformation should be paid for patients with Crohn's disease who have long-standing anal fistulas, especially when they complain of exacerbated symptoms (*i.e.* increased pain, fluid discharge) from a perianal lesion. Although treatment with infliximab is generally recommended for most patients with complex perianal Crohn's disease, careful

inspection and histological examination under anesthesia is recommended for such patients before infliximab administration.

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