Primary adenocarcinoma in an enterocutaneous fistula associated with Crohn’s disease

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Increasing numbers of intestinal adenocarcinomas in patients with Crohn’s disease have been reported, but the strength of this association still needs to be elucidated. Adenocarcinoma has also been documented in different types of fistulous tracts associated with Crohn’s disease. The first case of well-differentiated mucinous adenocarcinoma involving only enterocutaneous fistulae is reported in a patient with long-standing Crohn’s disease complicated by persistent abdominal wall fistulous tracts. The malignant lesion arose from neoplastic transformation of columnar epithelium lining portions of the fistulae occurring as a result of either re-epithelialization of these inflammatory tracts or mural implantation of mucosal tissue secondary to prior ulceration. The patient has remained disease-free eight years after surgical resection of the tumour. Even though intestinal carcinoma is not as strongly associated with Crohn’s disease as with ulcerative colitis, intestinal carcinoma should be considered in the setting of long-standing disease, previous intestinal exclusion surgeries and complications such as enterocutaneous or other types of fistulous tracts. The prognosis of such patients may be excellent with early diagnosis and treatment.

Key Words: Adenocarcinoma, Crohn’s disease, Enterocutaneous fistulae, Fistulous tracts

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Crohn’s disease was first described as a distinct clinical and pathological entity in 1932 (1). The first reports of Crohn’s disease patients who subsequently developed cancer of the large or small intestine were published in 1948 and 1956, respectively (2,3). Since then, the number of reported cases has increased significantly, but it is still unclear whether patients with Crohn’s disease are at higher risk of developing intestinal malignancies. There have also been reported cases of adenocarcinoma in enterocolonic, enterovesicular, enterovesiculocutaneous, rectovaginal and perineal fistulae associated with Crohn’s disease (4-8). To date only five cases of adenocarcinoma in enterocutaneous fistulae have been reported, but in all these cases the carcinoma involved both the fistulous tract as well as segments of either contiguous small or large bowel (5,8,9). In this paper we describe the first case of mucinous adenocarcinoma that originated from and remained confined to an enterocutaneous fistula in a patient with Crohn’s disease.

CASE PRESENTATION

A 55-year-old male was initially diagnosed with Crohn’s ileitis in 1965, at age 23. He underwent segmental ileal resection in 1970 and 1972 to treat active disease refractory to medical therapy. A total of 62 cm of terminal ileum was removed. In 1972, he developed two anterior abdominal wall fistulae with persistent mild drainage of a serous material. One was located in the midline, just caudal to the umbilicus, and the other in the right peri-umbilical area. The drainage from these fistulae fluctuated in concert with his Crohn’s disease activity. Maintenance therapy with sulfasalazine provided acceptable control of the disease. By 1974, one of the fistulae had healed, but in that year he developed a third fistula located in the left upper abdominal quadrant, from which there was draining of fecal and purulent material along with passage of gas. A fistulogram revealed a connection to the small bowel. The drainage settled spontaneously and the patient declined any further investigative or therapeutic efforts. He remained on sulfasalazine thereafter. A therapeutic trial with metronidazole to close the fistulae in 1981 was discontinued soon after initiation due to adverse effects. For most of the 1980s, the patient’s clinical course was relatively unremarkable with only infrequent mild symptoms that occurred whenever he was noncompliant with his medication.

In 1989 the patient experienced a severe exacerbation of his disease, with worsening diarrhea, intense abdominal cramps, fever, chills and an approximately 8 kg weight loss. Over a period of three months he also developed an inflammatory lesion on his anterior abdominal wall at the site of one of his fistulae, from which profuse drainage of fecal and purulent material occurred through six fistulous tracts (Figure 1). Barium enema and fistulogram showed a small enterocolonic fistula between the terminal ileum and sigmoid colon, as well as multiple interconnecting sinus tracts within the inflammatory abdominal wall mass that communicated with the enterocolonic fistula (Figure 2). Small bowel follow-through did not reveal obstruction. Treatments with metronidazole and azathioprine were attempted for one month, but these were discontinued due to gastrointestinal adverse effects and sepsis, respectively. The patient’s systemic and gastrointestinal symptoms gradually improved with sulfasalazine, but the draining abdominal wall lesion did not change. Surgery to excise the inflammatory mass and tracts, as well as the involved segment of small bowel and the enterocutaneous fistula, was performed.

Pathological examination of the surgical specimen revealed well-differentiated mucinous adenocarcinoma within and around the fistulous tracts, primarily within the abdominal wall mass (Figure 3). No small bowel mucosal origin for adenocarcinoma was identified. Multiple fistulous tracts were lined by columnar epithelium with areas of neoplastic transition to infiltrating adenocarcinoma within subserosal and abdominal wall tissues. All four mesenteric lymph nodes were negative for adenocarcinoma. Ancillary resection of a smaller nondraining inflammatory mass in the left upper abdominal quadrant did not show any malignant lesion.

At eight years after surgery, the patient is tumour-free and has no evidence of fistula recurrence. His Crohn’s disease has been quiescent.
DISCUSSION

Since Crohn’s disease was initially described in 1932, increasing numbers of cases of adenocarcinoma of the large and small bowel in patients with this disease have been reported. The extent of the association between Crohn’s disease and intestinal adenocarcinoma is still not entirely clear. The relative risk of colorectal cancer in patients with Crohn’s disease has been calculated to range from 4.3 to 26.6 (10-12), and estimates of the relative risk of small bowel adenocarcinoma have ranged from six to 320 times that in a normal population (12-15). Five large population-based epidemiological studies involving 3747 patients with Crohn’s disease documented 21 cases of colorectal and seven cases of small bowel cancer, with relative risks ranging from 0.89 to 2.5 for colorectal malignancies and up to 50 for small bowel malignancies (16-21). Two of these population-based studies involving 468 patients did not document any case of small bowel cancer in the cohort of Crohn’s disease patients (17,18). The inconsistency in the relative risk of colorectal adenocarcinoma in Crohn’s disease may be due, in part, to referral bias in studies originating from tertiary care referral centres, which can generate an overestimation of this association. The relative risk of small bowel malignancy seems to be significantly higher in Crohn’s disease patients than in the general population, but caution must be applied to the interpretation of these data. Small bowel cancer is not a common condition; therefore, the publication of a relatively small number of cases in patients with Crohn’s disease may result in high relative risk estimates.

In this paper we report the first case of adenocarcinoma...
involving enterocutaneous fistulae only, in a patient with long-standing Crohn’s disease complicated by persistent abdominal wall fistulous tracts. Our review of the literature revealed only two cases of carcinoma of enterovesiculo-cutaneous fistulae (5,8) and three similar cases involving enterocutaneous fistulae in patients with Crohn’s disease (8,9) (Table 1). When he was diagnosed with adenocarcinoma, our patient had a 24-year history of Crohn’s disease and a 17-year history of persistent abdominal wall enterocutaneous fistulae. This time lag for the development of a malignant lesion is consistent with that in previously reported cases. Except for one case – which did not include details regarding the duration of Crohn’s disease before the diagnosis of the carcinomatous fistula – all lesions occurred more than 10 years after the initial diagnosis. In one case, the patient had Crohn’s disease for 38 years. For small bowel adenocarcinoma, Hawker et al (22) documented a mean delay of 19.2 years, with a range of up to 47 years.

There is no uniformity in the anatomical location of disease among the reported cases. Including this case, two patients had ileitis, one had ileocolitis and one had colitis primarily. In the previously reported five cases, the malignant lesion was not confined to the enterocutaneous fistula; it also involved the surrounding inflamed segments of bowel. These observations support the notion that intestinal cancers in Crohn’s disease occur at sites of intestinal involvement (23). In one case, the tumour originated from an excluded segment of small intestine (8). It has been postulated that bypass or defunction with bacterial stasis in such segments has a carcinogenic effect (24). There have been many published reports of intestinal carcinoma arising in surgically bypassed bowel (22,24), but the most important contributing factor to carcinoma development in patients with excluded intestine may be the long duration of Crohn’s disease, rather than the excluded bowel (8,24). As intestinal exclusion surgeries have become increasingly infrequent as a therapeutic modality in the treatment of Crohn’s disease in recent decades, the proportion of carcinoma in excluded small intestine in Crohn’s disease has fallen dramatically (8,24).

In contrast to the patients in the five reports of adenocarcinoma of enterocutaneous fistulae associated with Crohn’s disease, our patient had a malignant lesion confined to the fistulous tracts, with no direct involvement of the communicating segment of small bowel. Adenocarcinoma most likely arose from neoplastic transformation of columnar epithelial lining portions of the fistulae occurring as a result of either re-epithelialization of inflammatory tracts from the small bowel mucosa or mural implantation of viable mucosal tissue secondary to prior ulceration. Chronic fistulous tracts in Crohn’s disease can re-epithelialize, which would preclude permanent healing (25). The absence of small bowel mucosal and mural involvement supports the negative mesenteric node status observed.

**CONCLUSIONS**

Even though intestinal carcinoma is not as strongly associated with Crohn’s disease as with ulcerative colitis, intestinal carcinoma must be considered in the setting of long-standing disease, previous intestinal exclusion surgeries and complications such as enterocutaneous or other types of fistulous tracts. If accurate diagnosis is made without delay, the prognosis of these patients after appropriate treatment may be excellent.

**REFERENCES**

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