ORIGINAL ARTICLE

# Tabulation of myeloid, lymphoid and intestinal malignancies in Crohn's disease

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A variety of malignant complications occur in Crohn's disease, and previous studies have recorded an increased intestinal cancer risk. The present investigation tabulated myeloid and lymphoid malignancies compared with intestinal cancers in 1000 consecutively evaluated patients with Crohn's disease who were followed over an extended period by a single clinician. Myeloid and lymphoid neoplasms were present in 0.5% of patients, while cancer in the intestinal tract was detected in 1%. Most of these patients with a malignancy had Crohn's disease for a prolonged period of more than 20 years and had negative outcomes, including death or presentations with advanced disease. In this cohort, lymphoma was not detected in a single patient after definition of Crohn's disease, possibly reflecting the limited use of immunosuppressives or infused biological agents in this clinical practice. Bypassed rectal 'stumps' were associated with subsequent colorectal cancer in half of all males with colon cancer in this series, suggesting an important risk factor following colectomy in Crohn's disease. Epithelial dysplasia was detected in only a single male patient before colorectal cancer, implying that this histopathological marker may be a poor predictor of subsequent colon cancer development in Crohn's disease, an inflammatory bowel disease process that is typically patchy or focal in distribution in the intestinal tract.

**Key Words:** *Colon cancer; Crohn's disease; Immunosuppressives; Infliximab; Leukemia; Multiple myeloma, Small intestinal cancer*

## Fréquence des tumeurs myéloïdes, lymphoïdes et intestinales dans le contexte de la maladie de Crohn

La maladie de Crohn (MC) est associée à différentes complications malignes, et des études ont déjà fait état d'un risque accru de cancer de l'intestin. La présente recherche porte sur la fréquence des tumeurs myéloïdes et lymphoïdes par rapport à celle des cancers de l'intestin chez 1000 patients consécutifs, atteints de la MC et suivis sur une longue pério de par un même clinicien. Les néoplasmes myéloïdes et lymphoïdes étaient présents chez 0,5 % des patients, tandis qu'un cancer de l'intestin a été décelé chez 1 % d'entre eux. La plupart des patients touchés souffraient de la MC depuis au moins 20 ans et avaient connu une évolution défavorable, y compris la mort ou une maladie rendue à un stade avancé. Aucun lymphome n'a été décelé dans la cohorte après la confirmation du diagnostic de la MC, ce qui pourrait s'expliquer par le recours limité aux immunosuppresseurs et aux agents biologiques en perfusion dans la pratique clinique. Les moignons pontés de rectum ont été associés à l'apparition ultérieure d'un cancer colorectal chez la moitié de tous les hommes souffrant d'un cancer du côlon dans la présente série, ce qui donne à penser à l'existence d'un important facteur de risque à la suite d'une colectomie dans le contexte de la MC. Un seul cas de dysplasie épithéliale a été décelé chez un patient masculin avant l'apparition d'un cancer colorectal; ce marqueur histopathologique se montrerait donc un faible prédicteur de l'apparition ultérieure d'un cancer du côlon dans le contexte de la MC, maladie inflammatoire de l'intestin qui se caractérise par une atteinte régionale ou focale du tube digestif.

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Investigations have recorded an increased intestinal cancer risk in Crohn's disease (1-3), including some cohort and population based studies from Canada, where reporting of malignant diseases is legally required (4,5). Ascertainment has been based on multiple sources, including physician notifications, pathology, hospitalizations, mortality and autopsy records (4,5). Other literature reports have also described both myeloid and lymphoid malignancies in Crohn's disease (3,5-16).

In 1979, Greenstein et al (6) described an excess of lymphomas in 1227 patients with Crohn's disease thought to be related to associated immunological deficiencies, use of immunosuppressive medications, or increased exposure to ionizing radation. In 1982, Hanauer et al (7) reported the presence of leukemia in Crohn's disease. Later, additional cases of Crohn's disease with either myeloid or lymphoid malignancies, including both Hodgkin's and nonHodgkin's lymphoma, were recorded (8-14). Finally, rare cases of multiple myeloma have been noted (15,16). More recent studies related to risk in Crohn's disease, particularly for lymphoma, appear to differ in their conclusions, but concerns have been expressed related to the use of immunosuppressives (13) as well as infused biological agents (9), both having been hypothesized to play a role in lymphoma pathogenesis. Some of the difficulty related to assessing the risk of lymphoma and other hematological malignancies in Crohn's disease may reflect the following: methods of data collection (eg, multiphysician teaching hospital cohort studies versus administrative coding based diagnoses in population studies) and data expression; precision of the initial diagnosis, especially of Crohn's disease; duration of clinical follow-up; and differing methods of treatment, including the frequency of intestinal resection.

For over two decades, a single clinician database of 1000 consecutive patients with Crohn's disease has been developed with extensive follow-up, averaging over 10 years. This population was defined previously as female-predominant (56.1%), diagnosed most often before age 40 (84.4%) and more than 95% born in Canada (17). Most had ileal and/or colonic involvement with stenosing or penetrating complications of Crohn's disease (17) and almost half required an earlier intestinal resection. In the present report, the results of a prospectively tabulated list of myeloid and lymphoid malignancies, along with intestinal cancers, are detailed. Of note, this cohort appeared to be 'pharmacologically-naive' because only about 10% were treated with a nonsteroid immunosuppressive medication or a newer infused 'biological' agent.

## MATERIALS AND METHODS

One thousand consecutive patients with Crohn's disease were evaluated. All patients were seen directly by the author, and a diagnosis of Crohn's disease was established based on defined criteria (18). Usually, endoscopic biopsy specimens or surgically-resected intestinal materials were available for review. For some referred patients with an already established diagnosis, endoscopic, operative and pathological reports were available. In some, but not all patients, tissue section materials were available. In this prospective database, treatments administered were recorded, including medications and intestinal resections. Reporting malignant disease is legally required in British Columbia and linkage on progress with treatment is provided to referring physicians.

**TABLE 1**
**Treatments for Crohn's disease***

| Treatment | Number |
|---|---|
| 5-ASA | 701 |
| 5-ASA alone | 181 |
| Steroids† | 531 |
| Metronidazole | 296 |
| Immunosuppressants (nonsteroid) | |
| Aza/6-MP | 99 |
| Cyclosporine | 7 |
| Methotrexate | 11 |
| Biological agents | |
| Infliximab† | 5 |
| ISIS 2302† | 1 |
| IL-10† | 1 |
| Surgical resection | 441 |

*n=1000. Most patients required more than one form of treatment. †Some received oral budesonide in a published clinical trial (19); others received infliximab (20), ISIS 2302 (21) or IL-10 (22) in clinical trials or compassionate release through another physician. 5-ASA 5-Aminosalicylic acid; Aza Azathioprine, 6-MP 6-mercaptopurine; ISIS 2302 antisense drug, Isis Pharmaceuticals, USA; IL-10 Interleukin 10*

A small number of patients (less than 0.3%) in this database had received medication in a multicentre clinical trial (19) or on a compassionate basis through an investigator at another university teaching centre (20-22). For the purposes of this evaluation, medications were classified as a 5-Aminosalicyclic acid (5-ASA) or steroids, without reference to the specific corporate tradename, route or dose of administration. Table 1 lists the differing treatments for this cohort. Almost half of the patients in this series required an intestinal resection (44.1%). Most received a 5-ASA medication or a corticosteroid. About 10% also received a nonsteroid immunosuppressive (ie, azathioprine, 6-mercaptopurine, cyclosporine, methotrexate) or a biological form of treatment, similar to the rates of use reported elsewhere for another Canadian province (5), but less than reported use rates of up to 30% in American and European referral-based centres (11,13,23).

## RESULTS

### Myeloid and lymphoid malignanices

Myeloid and lymphoid malignancies were detected in 0.5% (ie, five/1000) of the patients with Crohn's disease seen in this largely referral-based population and followed for a

mean period of more than 10 years. Although low, this figure markedly exceeds the combined cumulative age-standardized annual incidence rates for myeloid leukemia (males 35.6; females 28.0), lymphoid leukemia (males 47.7; females 29.0) and multiple myeloma (males 46.2; females 31.9) previously reported in the British Columbia population for the 10-year period of 1990 to 1999, inclusive (expressed per 100,000) (12). Of these, no patient had received an immunosuppressive medication (ie, azathioprine, 6-mercaptopurine, cyclosporine, methotrexate) or a biological agent. In one patient, Hodgkin's disease was diagnosed more than 10 years before the detection of Crohn's disease, and, therefore, was not considered an incident case complicating the course of the Crohn's disease. In one other patient, a diagnosis of myelogenous leukemia was made after the diagnosis of Crohn's disease but within one year, and might be considered a 'concurrent diagnosis'. Thus, if these two cases were excluded from the 'incidence' calculation of established disease, 0.3% or three/1000 may be a more precise incidence estimate. To date, in the present cohort of 1000 patients with Crohn's disease followed over an extended period (mean of more than 10 years) by a single clinician, there were no observations of a patient with a nonHodgkin's lymphoma.

Tables 2 and 3 detail the characteristics of the Crohn's disease in five patients with a myeloid or lymphoid malignancy, as well as their outcomes. Except for the woman diagnosed with Crohn's disease more than a decade after successful treatment of Hodgkin's disease, the other four patients were men and were diagnosed with Crohn's disease at a relatively older age compared with the previously published age of diagnosis (before age 40 years in more than 80%) in this Crohn's disease patient population (17). All of these male patients with Crohn's disease died, usually two

**TABLE 2**
**Characteristics of Crohn's disease in myeloid and lymphoid malignancies***

| Sex, age (years)† | Year diagnosed | Disease site | Behaviour | Treatment |
|---|---|---|---|---|
| Myelogenous leukemia | | | | |
| Male, 54 | 1973 | Ileum only | Stricturing | SP/5-ASA, steroids, ileocolic resection |
| Male, 55 | 1981 | Colon only | NS/NP | SP |
| Lymphocytic leukemia | | | | |
| Male, 59 | 1985 | Colon only | NS/NP | SP |
| Multiple myeloma | | | | |
| Male, 36 | 1959 | Ileum only | Stricturing | SP, ileocolic resection |
| Hodgkin's lymphoma‡ | | | | |
| Female, 20 | 1972 | Ileum and colon | Penetrating | SP/5-ASA, steroids, metronidazole, TPN, ileocolic resection |

**n=5, or 0.5% of 1000 patients with Crohn's disease. †Age at diagnosis of Crohn's disease.*
*‡In the only patient with a diagnosed lymphoma, Hodgkin's disease was defined at age 10, about a decade before diagnosis of Crohn's disease and not included in calculation of incidence rate. No patient with a nonHodgkin's lymphoma was detected. NP Nonpenetrating; NS Nonstricturing; SP Sulfasalazine; SP/5-ASA Sulfasalazine/5-Aminosalicylic acid; TPN Total parenteral nutrition*

**TABLE 3**
**Outcomes of myeloid and lymphoid malignancies in Crohn's disease**

| Sex, age (years)* | Year diagnosed | Duration† | Chemotherapy and/or radiation | Deceased |
|---|---|---|---|---|
| Myelogenous leukemia | | | | |
| Male, 75 | 1994 | 21 years | Yes | Yes |
| Male, 55 | 1981 | 8 months | No | Yes |
| Multiple myeloma | | | | |
| Male, 66 | 1989 | 30 years | Yes | Yes |
| Lymphocytic leukemia | | | | |
| Male, 68 | 1994 | 9 years | No | Yes |
| Hodgkin's lymphoma | | | | |
| Female, 10 | 1962 | ‡ | Yes | No |

**Age of diagnosis of hematologic or lymphoproliferative malignancy. †Duration of Crohn's disease before diagnosis of malignancy.*
*‡Female with Hodgkin's disease diagnosed at age 10 years while Crohn's disease diagnosed at age 20 years and not included in calculation of incidence rate*

or more decades after the diagnosis of Crohn's disease was established. In one case, a myelodysplastic syndrome (24) predated frank acute myeloid leukemia followed by a progressive rapid downhill clinical course and death only one year after the diagnosis of Crohn's disease.

**Intestinal malignancies**

Tables 4 and 5 detail the characteristics of Crohn's disease in 10 patients who developed an intestinal malignancy and their outcomes. Although most were men, an intriguing finding in this cohort was that women had intestinal adenocarcinomas detected in the small intestine or proximal transverse colon while men only had cancers detected distally in the rectum, most often in rectal stump mucosa. Of these 10 patients, only two men who developed rectal cancer had received azathioprine. Most developed an intestinal malignant complication after about two or more decades with Crohn's disease, although in one case, the diagnosis of a small bowel adenocarcinoma was established within a year of diagnosis of Crohn's disease. Despite recognition of increased predisposition to cancer in the small intestine and colon in Crohn's disease, a significant number (ie, 40%) in this series already had advanced disease (eg, nodes, liver) at the time of their initial diagnosis of colon cancer. Of those with colon cancer, most were young men with rectal cancer, and of these, half were located in a rectal stump. One patient's malignant disease presented initially with a dramatic rectal perforation and metastatic disease in the liver despite a previous colonoscopy with negative multiple site colonic biopsies for dysplasia within the year before death.

**TABLE 4**
**Characteristics of Crohn's disease in intestinal malignancies***

| Sex, age† | Year diagnosed | Disease site | Behaviour | Treatment |
|---|---|---|---|---|
| Colonic adenocarcinoma | | | | |
| Male, 29 | 1965 | Colon only | NS/NP | SP/5-ASA |
| Male, 24 | 1968 | Ileum and colon | Penetrating | SP/5-ASA, Aza, ileocolonic resections |
| Male, 29 | 1983 | Colon only | Penetrating | SP, steroids, TPN |
| Male, 30 | 1967 | Ileum and colon | Penetrating | Subtotal colectomy, ileocolonic resection |
| Male, 30 | 1965 | Colon only | NS/NP | SP |
| Male, 24 | 1958 | Colon only | Penetrating | Steroids, Aza, Partial colectomy |
| Female, 32 | 1981 | Ileum and colon | Stricturing | 5-ASA, steroids, ileocolonic resection |
| Small bowel adenocarcinoma | | | | |
| Female, 32 | 1983 | Ileum and colon | Stricturing | 5-ASA, ileocolonic resection |
| Female, 21 | 1977 | Ileum and colon | Penetrating | 5-ASA, steroids, ileocolonic resection |
| Female, 61 | 1977 | Ileum and colon | Penetrating | Ileocolonic resection |

**n=10 or 1% of 1000 patients with Crohn's disease †Age at diagnosis of Crohn's disease and year of diagnosis of Crohn's disease. 5-ASA 5-Aminosalicylic acid; Aza Azathioprine; NP Nonpenetrating; NS Nonstricturing; SP Sulfasalazine; SP/5-ASA Sulfasalazine/5-Aminosalicylic acid; TPN Total Parenteral Nutrition*

**TABLE 5**
**Outcomes of intestinal malignancies in Crohn's disease**

| Sex, age* | Year diagnosed† | Duration | Location/metastases/type | Treatment |
|---|---|---|---|---|
| Colonic adenocarcinoma | | | | |
| Male, 59 | 1995 | 30 | Rectum, nodes, adenoca | APR/rad-chem |
| Male, 46 | 1990 (died 1992) | 22 | Rectal stump, nodes and lungs, mucinous adenoca | APR/rad-chem |
| Male, 36 | 1990 (died 1990) | 7 | Rectum (perforation), liver, adenoca | None |
| Male, 48 | 1985 | 18 | Rectal stump, adenoca | APR/rad |
| Male, 50 | 1986 | 20 | Rectum, adenoca | Low ant resection |
| Male, 54 | 1998 | 40 | Rectal stump, adenoca and squamous cell cancer | APR/rad-chem |
| Female, 52 | 2001 | 20 | Trans colon, adenoca | Ileocolic resection |
| Small bowel adenocarcinoma | | | | |
| Female, 50 | 2001 | 18 | Ileum adenoca; liver metastases | Ileocolic resection |
| Female, 26 | 1982 | 5 | Ileum adenoca | Ileocolic resection |
| Female, 61 | 1977 | 1 | Ileum adenoca | Ileocolic resection |

**Age of carcinoma diagnosis. †Year of diagnosis of carcinoma; for female with diagnosis in 1977, Crohn's disease diagnosed 10 months earlier in the same year APR Abdominoperineal resection surgery; rad-chem radiation and chemotherapy*

**Dysplasia in colorectal biopsies**

Although no patient had systematic surveillance colonoscopies and biopsies, all 14 patients (excluding the Hodgkin's disease patient) had multiple site colonic biopsies before the diagnosis of malignancy, and most had undergone multiple endoscopic procedures (total 32) each with multiple biopsies, in some instances by other expert clinicians in other centres during the previous five years. This investigation was not designed to systematically evaluate the role of surveillance and multisite biopsy in the detection of cancer or 'precancer' in Crohn's disease. However, it is noteworthy that in the course of a routine, albeit focused, clinical practice, only a single patient had dysplastic changes in one colorectal biopsy detected before a diagnosis of invasive intestinal cancer. Subsequent pathological review of all endoscopic colorectal biopsies done before the detection of intestinal cancer (with the knowledge of intestinal cancer development) in 14 patients failed to reveal any additional biopsy specimens with dysplasia, in spite of the distal location of the cancers in most of these patients with Crohn's disease. In addition, all colonic biopsies done in most patients in this group after the diagnosis and treatment of malignancy were also negative for dysplasia or malignancy.

## DISCUSSION

This study enumerated myeloid and lymphoid malignancies in a single clinician database for Crohn's disease, defined prospectively during a period of over 20 years, and compared these with intestinal cancers. In this cohort with extensive follow-up averaging over 10 years, five patients had a myeloid or lymphoid malignancy (0.5%) and 10 developed an intestinal carcinoma (1%), all exceeding the rates for British Columbia (12). Of note, in the present study, Crohn's disease was never observed to be complicated by lymphoma, although Hodgkin's disease was detected a decade before Crohn's disease in a single patient. Given the author's personal experience with the detection of lymphoma (25-31), including those observed to complicate another intestinal disorder, celiac disease, the complete absence of a lymphoma complicating the clinical course in a large cohort of Crohn's disease seemed surprising. These results, however, concurred with an extensive evaluation of a large general practice population database from the United Kingdom where no increased risk of lymphoma was seen in Crohn's disease, but concern related to nonsteroidal immunosuppressive use as a risk factor for lymphoma was expressed (11). Similarly, lymphomas were recorded after the use of infused biological agents, such as infliximab (9), while immunosuppressive use was associated with a low but real risk of lymphoma in inflammatory bowel disease (13). In this series, the complete absence of lymphoma, therefore, might simply reflect the limited use of immunosuppressive medications (excluding steroids) and infused biological agents in this clinical practice.

The present report contrasts the findings in another larger population based Canadian study that showed an increased lymphoma risk in males with Crohn's disease, even though the patient characteristics appeared similar and the frequency of immunosuppressive use in both groups was historically limited (5). This may reflect the inherent limitations of administrative databases that use coded diagnoses rather than data based on direct physician contact and follow-up. Erroneous initial coding for Crohn's disease could lead to the conclusion that Crohn's disease was complicated (rather than mimicked) by lymphoma during a later hospitalization. Alternatively, a patient with Crohn's disease or a complication (eg, perianal abscess, fistula) might be coded with a less specific code and not included in a database, affecting incidence data. Coding based primarily on hospital data may reflect a more active or refractory disease phenotype, or result in Berkson's bias, a form of detection bias. In the present study, these forms of data collection bias were largely avoided, in part related to the extended period of follow-up by a single clinician and the legal provincial requirement for notification of malignant disease. Alternatively, if the experience in the treatment of rheumatoid arthritis or organ transplantation is considered (32-35), immunosuppressive dose or duration of use may be important, especially if prolonged. Future studies may help to further elucidate these issues in Crohn's disease patients, particularly if maintenance treatment is contemplated.

The present study also enumerated the intestinal cancers seen in 10 Crohn's disease patients in this study (1%). The clinical features of the intestinal cancers were similar to those noted in earlier studies, including: the long history of Crohn's disease, often over 20 years predating cancer; the relatively young age of intestinal cancer diagnosis in Crohn's disease; and the appearance of other histopathological types, including mucinous adenocarcinoma (4). In this series, cancers were also detected in bypassed or excluded segments of intestine (ie, rectal 'stump' cancer), a potentially important risk factor following colonic resection. Interestingly, in this study, there was a predilection for proximal intestinal cancer in females compared with more distal colorectal cancer in males. Although data on the effects of endogenous sex hormones and their potential effects on the subsite distribution of colon cancer are very limited (35), the findings here raise the possibility that sex hormones may play a role in the distribution of cancers along the length of the intestinal tract in younger patients with Crohn's disease complicated by malignant disease. Further studies on the effects of commonly used estrogen formulations and hormone replacement therapies in Crohn's disease are needed.

The outcome for patients with a malignancy in Crohn's disease, based on this limited experience, has been disconcerting. All patients diagnosed with a myeloid or lymphoid malignancy in this series, and most with an intestinal cancer complicating the course of Crohn's disease, either died or currently have advanced disease. In Crohn's disease, epithelial dysplasia occurs in the small and large intestine, which supports the concept of a dysplasia-carcinoma sequence in Crohn's disease (36), but also highlights that

most cases of carcinoma in Crohn's disease are detected, even in large tertiary referral centres, incidentally at surgery (37). Unfortunately, specific recommendations for screening and surveillance colonoscopy even in chronic extensive Crohn's colitis have been supported by only very limited data in older patients (38). The present report fails to provide support for systematic surveillance to detect epithelial dysplasia as a 'precancer' marker in Crohn's disease. Although a formal program of surveillance was not done in this population, all patients had endoscopic studies with biopsies. In this series, epithelial dysplasia was observed in one endoscopic biopsy in only a single patient before the diagnosis of colon cancer. Even subsequent review of these earlier endsocopic biopsies, despite knowledge of a cancer diagnosis, did not increase the yield of dysplasia detection and dysplasia was not detected in subsequent endoscopic biopsies after diagnosis of cancer in these patients with Crohn's disease. Conceivably, because of the focal nature of dysplastic change in most cases of inflammatory bowel disease in general, and even more so in Crohn's disease, a disorder with a normally patchy distribution, the likelihood of establishing a productive program of screening for epithelial dysplasia or focal neoplasia in Crohn's disease is low. Other, more reliable predictive tools, possibly molecular or genetic markers that might predict future intestinal cancer in Crohn's disease, are needed

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