

## Appendiceal carcinoids in Crohn's disease

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Earlier investigations demonstrate an increased risk for colon cancer in Crohn's disease. For other intestinal neoplasms, such as carcinoids, studies are limited. In Crohn's disease, repeated endoscopic and imaging studies along with intestinal resections may facilitate clinical recognition of neoplastic diseases, including appendiceal neoplasms. To date, however, only sporadic cases of appendiceal carcinoids have been described in Crohn's disease. In the present study, in a single clinician database of 1000 Crohn's disease patients, three of the 441 patients who had undergone intestinal resection had appendiceal carcinoids, all of which were pathologically confirmed. All were observed in female patients and were not suspected before surgical treatment. In one case, even though management was not altered, the tumour had already invaded serosal fat indicating a potential for more advanced disease. In this series, a carcinoid tumour was found in a resection specimen during a later clinical case review and another was a microcarcinoid, implying that these tumours may be overlooked in Crohn's disease. The percentage detected in the entire database (0.3%) exceeds the reported rates of detection of appendiceal carcinoids after removal of the appendix for appendicitis, as well as the rate of detection of appendiceal carcinoids in autopsy studies. This percentage would be higher if only those having an intestinal resection were considered (0.68%). Additional studies are needed to further define this risk of appendiceal carcinoids in Crohn's disease.

**Key Words:** *Appendiceal carcinoid; Carcinoid syndrome; Crohn's disease; Inflammatory bowel disease*

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Earlier studies have suggested that patients with Crohn's disease may have an increased colon cancer risk (1-3). In Canada, cohort and population-based studies from British Columbia (4) and Manitoba (5), respectively, have also confirmed this enhanced colon cancer risk in Crohn's disease. In addition, the coexistence of other intestinal neoplasms, including carcinoids, has been described (6-12), including a report from Alberta that provided the initial Canadian description of ileal carcinoids in Crohn's disease (13). Because most appendiceal carcinoids are discovered coincidentally during the pathological examination of the appendix for other causes, their clinical relevance, if detected during the course of Crohn's disease, is unknown.

Some have speculated that the association of Crohn's disease and carcinoid tumours, although uncommon, is more fre-

### Carcinoïdes appendiculaires et maladie de Crohn

**RÉSUMÉ :** Des études ont démontré que la maladie de Crohn augmente le risque de cancer du côlon. Pour les autres néoplasmes de l'intestin comme les carcinoïdes, les études sont limitées. Dans les cas de maladie de Crohn, des examens répétés par endoscopie et par imagerie ainsi que des résections intestinales peuvent faciliter le dépistage clinique de maladies néoplasiques, notamment les néoplasmes appendiculaires. À ce jour, toutefois, seuls des cas sporadiques de carcinoïdes appendiculaires ont été décrits en rapport avec la maladie de Crohn. La présente étude porte sur la base de données d'un clinicien englobant 1000 cas de maladie de Crohn. Sur 441 patients ayant subi une résection intestinale, trois présentaient des carcinoïdes appendiculaires, confirmés par des analyses de pathologie. Il s'agissait de femmes dans les trois cas. Rien ne laissait présager la présence de ces tumeurs avant la chirurgie. Dans un cas, la tumeur avait déjà envahi la couche adipeuse de la séreuse, évoquant la possibilité d'une maladie parvenue à un stade plus avancé; la prise en charge de la patiente n'a pas été modifiée. Un examen ultérieur a permis de déceler une tumeur carcinoïde dans un spécimen réséqué; une autre était de type microcarcinoïde. Ces observations donnent à penser que ces tumeurs passeraient inaperçues en présence de la maladie de Crohn. La proportion de ce type de tumeurs observée dans l'ensemble de la base de données (0,3 %) dépasse le taux connu de détection de carcinoïdes appendiculaires signalé après appendicectomie (pour appendicite), ainsi que le taux de détection de carcinoïdes appendiculaires observé à l'autopsie. Cette proportion serait plus élevée (0,68 %) si seules les résections intestinales étaient prises en compte. Il faut effectuer des études supplémentaires pour mieux établir le risque de carcinoïdes appendiculaires dans les cas de maladie de Crohn.

quent than currently appreciated (9) and may be more than fortuitous (13). In part, this could be related to similarities in clinical presentation with diarrhea or partial bowel obstruction, as well as pathological changes of fibrosis and thickening of the intestinal wall. Indeed, carcinoid tumours, especially if located in the ileum, may completely mimic Crohn's disease (14,15). In contrast, others have argued against an increased risk for carcinoids in Crohn's disease based on clinical experience (16).

Over the past 20 years, a single clinician database for Crohn's disease, now with 1000 consecutive patients, was developed, with a mean follow-up period of over 10 years. In this series, 441 patients to date have undergone an intestinal resection during their clinical course. Although appendiceal

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carcinoids in Crohn's disease have been noted, a review of reported pathological studies from this single clinical practice revealed three additional new cases, including an advanced lesion that had extended into serosal fat. In Crohn's disease, endoscopic studies, other imaging evaluations and resections including the ileocecal region are relatively common, and as a result, the detection and pathological definition of coexistent carcinoids may be facilitated. The detection of carcinoids in Crohn's disease could also affect critical management decision, so this limited experience in Crohn's disease was evaluated.

## CASE PRESENTATIONS

### Case one

A 25-year-old woman was evaluated in 1971 for abdominal pain, diarrhea and weight loss. Endoscopic and barium contrast studies showed small and large intestinal involvement with Crohn's disease, including ulceration with stricture formation in both the midjejunum and the distal 60 cm of the terminal ileum. Biopsies of the proximal jejunum and the colorectum revealed granulomatous inflammation. In 1977, a side-to-side ileocolonic bypass was done, and, in 1979, a 30 cm strictured jejunal segment was resected, showing granuloma formation. In 1982, a right hemicolectomy with resection of the distal 24 cm of ileum and the bypassed segment was done; transmural acute and chronic inflammatory changes with granulomas and fibrosis were recorded. In 1984, anemia with bleeding developed; ulceration in the neoterminal ileum was visualized and another ileocolonic resection was done, including the anastomosis and 20 cm of distal ileum. In 1989, a review of her resected specimens showed a small carcinoid tumour in the distal appendix. In 1999, two jejunal strictures (total length, 42 cm) and the anastomosis were resected. From then to September 2002, treatment included oral 5-aminosalicylate, oral budesonide and parenteral nutrition.

### Case two

A 19-year-old woman first developed abdominal pain, fever and diarrhea in 1984. Her examination revealed abdominal tenderness, anal tags and a tender anal fissure. Erythema nodosum was present in both lower extremities. Barium studies of the upper and lower gastrointestinal tract showed changes consistent with Crohn's disease of the colon, and colonoscopy revealed focal areas of ulceration and granulomatous inflammation. In 1985 and 1986, episodes of abdominal pain and diarrhea were treated with steroids. In 1988, perianal fistulae were treated with multiple perianal fistulotomies. In 1989, severe anorectal pain with fever and weight loss developed. Anorectal stenosis with ulceration and multiple draining fistulous tracts were present. Oral metronidazole was given, resulting in a reduction in fistula drainage, but after several weeks a painful lower extremity peripheral neuropathy developed so the medication was terminated. In 1990, a loop ileostomy was done. Drainage persisted, and after eight months a large perineal ulcer developed. In 1991, a total proctocolectomy and a distal ileal resection were done. Active granulomatous inflammation was present throughout the entire resected specimen. In addition, a small carcinoid tumour of the distal appendix was detected with extension beyond the

appendix, including focal penetration into serosal fat. There was no metastatic disease or evidence for retroperitoneal fibrosis. Except for a short hospitalization in 1997 for an ileostomy obstruction that spontaneously resolved, she has remained well to September 2002 with no recurrent disease.

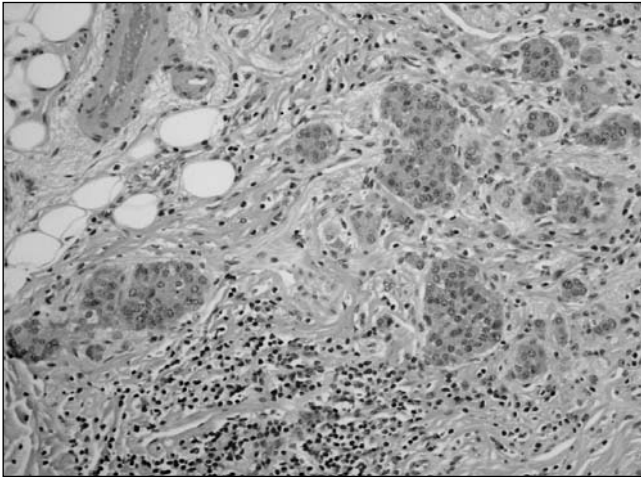
### Case three

A 16-year-old female patient first developed abdominal pain and diarrhea in 1984. Barium radiographic studies of the upper and lower gastrointestinal tracts revealed a 7 cm distal ileal stricture, consistent with Crohn's disease. In 1985, a perianal abscess was drained. In 1986, a small bowel obstruction resolved with corticosteroids. Flexible sigmoidoscopy showed focal linear colonic ulcers. Multiple anal fistulae and perineal sinus tracts were also excised, and granulomatous inflammation was present. In 1997, abdominal pain with diarrhea led to further evaluation. Endoscopic studies showed scattered aphthoid mucosal ulcers, inflammatory changes and granulomas. The patient's symptoms resolved completely with budesonide. In March 2002, the patient developed abdominal pain, diarrhea and weight loss despite 5-aminosalicylate and budesonide. A barium study showed two distal ileal strictures, which were then resected. The pathological evaluation showed granulomatous inflammation, and sections through the midportion of the appendix revealed a cluster of carcinoid cells typical of a microscopic carcinoid (Figures 1 and 2). In September 2002, she was well on oral 5-aminosalicylate alone.

## DISCUSSION

Previous investigations have suggested an increased risk of intestinal cancer in Crohn's disease (1-3), including cohort- and population-based studies from both British Columbia and Manitoba (4,5). Carcinoids in Crohn's disease also occur (6-16), but it is not clear whether the risk for this tumour type is increased, especially because these are only a very small fraction of all intestinal tumours (17). While the coexistence of carcinoid tumours and Crohn's disease may be rare, their detection may be very important, because these neoplasms have been shown to clinically simulate Crohn's disease, particularly if there is ileal involvement (8,14,15). Moreover, similar complications (eg, retroperitoneal fibrosis) may occur in both disorders (18,19). In addition, most carcinoids in patients with Crohn's disease have been rarely suspected clinically, and so their unanticipated detection during surgery might potentially alter management. Finally, neuroendocrine modulation of immunologically mediated molecular events in inflammatory bowel disease might conceivably result, particularly if a coexistent carcinoid secretes a kinin or another potent peptide that affects the action of an inflammatory mediator (20-22).

In Crohn's disease, patients are frequently (and sometimes repeatedly) evaluated with endoscopic and other imaging modalities. In addition, a high percentage of patients with Crohn's disease undergo ileocolonic resection, providing additional tissues that may facilitate other diagnoses, including unsuspected carcinoid tumours. In this study, a systematic evaluation of a Crohn's disease clinical database for pathologically confirmed carcinoid tumours was done. In 1000 consecutive

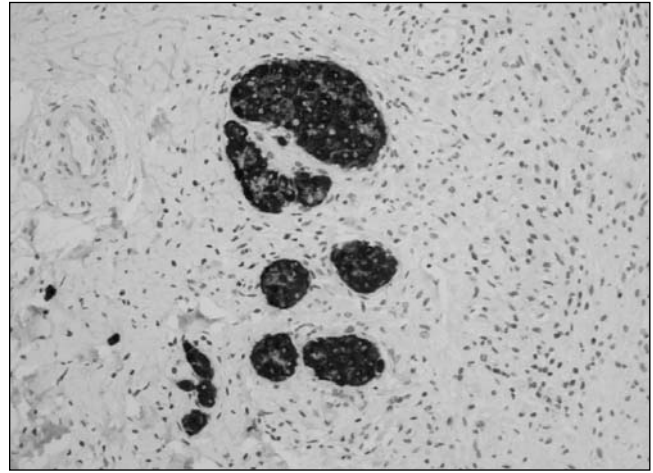


**Figure 1)** Microscopic carcinoid in the appendix in Crohn's disease (Hematoxylin and eosin stain, original magnification  $\times 200$ )

patients followed for an extended mean period of approximately 10 years, 441 had intestinal resective surgery, and three carcinoid tumours were defined. These were all located in the appendix of resected specimens for Crohn's disease.

Appendiceal carcinoids occurring concomitantly in Crohn's disease appear to be rarely recorded in the world literature. The first report of these coexistent conditions was in a child in 1981 (6). Since then, another six reports of appendiceal carcinoids have been described in Crohn's disease, all in adults (7-12). Of these, only one described the involvement of the adjacent ileum and cecum, so it could not be determined whether the carcinoid in this specific report originated in the appendix and was an advanced lesion at the time of detection (8). In the present series, three new cases of appendiceal carcinoid tumours were detected. None was suspected before surgical intervention. Of these, two were macroscopically detectable lesions and, pathologically, one had already invaded through the serosal fat. To date, this patient has remained well over 10 years after removal with no evidence of metastatic disease, implying that the resection done for Crohn's disease, as in other cases localized to the appendix alone, was sufficient. The third case was a microscopically detected lesion only appreciated after 'routine' sectioning of the appendix from the ileocolic resection specimen. These findings also further emphasize that the pathological evaluations in this study were on resected tissues from patients obtained in the course of a 'routine', but focused, clinical practice. It is not known whether additional early carcinoids would have been detected with systematic and more extensive tissue sampling. Because over 50% of the patients in this study have not required an intestinal resection to date, it is conceivable that more carcinoids will eventually be detected.

In this series, an appendiceal carcinoid was detected in 0.3% of patients with Crohn's disease. Although the precise definition of carcinoid risk is difficult to establish, these results are at least comparable with the only other similarly large, but multiphysician, series that described a 0.2% risk for carcinoids in 3326 patients with both ulcerative colitis and Crohn's disease. As in the present study, these occurred primarily in the appendix without systemic features of the typical carcinoid syndrome (16). Although the authors of that report thought



**Figure 2)** Grimelius stain of the appendix in Figure 1, showing microcarcinoid in Crohn's disease (Original magnification  $\times 200$ )

that their results did not support an increased risk for carcinoid tumours in inflammatory bowel disease, recent pathological studies have clarified the magnitude of carcinoid risk in resected appendicitis (0.24%) and autopsy studies of noninflamed appendixes (0.03%) (12). Similar data have been reported in an older referral-based population from the Mayo Clinic by Moertel et al (23), who examined the rates of detection of appendiceal carcinoids for a variety of surgical indications (0.32%) as well as their autopsy experience (0.026%). Although controlled data on the risk of carcinoids are not available, these results imply that there may be as much as a 10-fold increased risk of carcinoid tumour development, at least in the appendix, in patients with Crohn's disease, compared to autopsy data from referral-based populations (23). Additional studies, defining the site of carcinoid tumour formation, are needed to further elucidate this observation in patients with inflammatory bowel diseases. In this series, it is conceivable that carcinoid tumour incidence is even higher because fewer than 50% have had an intestinal resection.

No case here displayed clinical features of the carcinoid syndrome; however, pathological evidence for an invasive carcinoid tumour was reported in the second case, suggesting a potential for this development. Others have suggested that a right hemicolectomy is justified in young patients with tumours over 2.0 cm in size with a low risk of operative morbidity or mortality; however, vascular involvement and invasion of the mesoappendix are also features that may favour a more radical approach (24). Although the patient from case two has remained well and additional treatment has not been required, the unanticipated detection of a carcinoid during surgical resection could potentially alter medical or surgical management. Future studies are needed to determine whether the peptide hormones synthesized and secreted by carcinoids can affect the inflammatory process (20-22) and either intensify or ameliorate disease activity.

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