

Neoplastic imitators of small bowel Crohn's disease

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OBJECTIVE: To identify the problem of small bowel neoplasia masquerading as Crohn's disease. **DATA AND METHODS:** Sixteen articles reviewing the frequency of small bowel neoplasia were identified. Articles were selected if they assessed frequency of small bowel tumours in the general population. All articles were retrospective reviews of experience. Data on frequency were extracted and compiled. Three case reports as illustrative examples and a Medline search of small bowel neoplasms with manual searching of references from identified articles are presented. **RESULTS:** A total of 2507 cases of small bowel tumours was compiled. The frequency of tumours in decreasing order was adenocarcinoma, carcinoid, lymphoma, leiomyoma, leiomyosarcoma, adenoma and lipoma. **CONCLUSIONS:** Crohn's disease is the most prevalent disease affecting terminal ileum. Malignant disease may affect the terminal small bowel in ways which are clinically indistinguishable from Crohn's disease. Surgery is the last therapeutic option for Crohn's disease, whereas it is potentially curative and therefore the first option for small bowel neoplasia. Misdiagnosing malignant processes as being Crohn's disease causes delays in effective treatment and worsens prognosis.

Key Words: Crohn's disease, Small bowel neoplasia

Imitateurs néoplasiques de la maladie de Crohn du grêle

OBJECTIF: Identifier le problème de néoplasie du grêle se présentant comme une maladie de Crohn. **DONNÉES ET MÉTHODES:** Seize articles relatifs à la fréquence des néoplasmes du grêle ont été inventoriés. Ils ont été retenus quand ils évaluaient la fréquence des tumeurs du grêle dans la population générale. Tous étaient des analyses rétrospectives, dont les données ont été extraites et compilées. Trois observations ont servi d'exemples et les auteurs ont utilisé les références des articles publiés sur le sujet pour se constituer une bibliographie

SMALL BOWEL NEOPLASIA IS A RELATIVELY infrequent gastrointestinal tumour despite the large surface area of the small bowel. Numerous different histological types of small bowel neoplasms exist, and the incidence of the less common tumour types is significant.

The diagnosis of Crohn's disease usually is made on the basis of clinical and radiographical findings in addition to treatment response. Unfortunately, the most frequent area of involvement is the distal small bowel which often is inaccessible to biopsy without surgery. Surgery is not appropriate in the early evaluation of patients with suspected uncomplicated Crohn's disease. Since histological confirmation often is impossible, the diagnostic armamentarium is limited and the door to misdiagnosis is opened. This study concentrates on the neoplastic imitators of Crohn's disease of the small bowel.

CASE ONE

A 30-year-old woman presented to her family doctor with a several month history of fatigue, nausea and crampy periumbilical abdominal pain. She was diagnosed with Crohn's disease and began treatment with azathioprine and prednisone. The patient's symptoms promptly resolved, but within two

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médicale pertinente à l'aide de Medline. **RÉSULTATS:** On a relevé 2 507 cas de tumeurs du grêle – adénocarcinomes, carcinoïdes, lymphomes, léiomyomes, léiomyosarcomes, adénomes et lipomes, par ordre décroissant. **CONCLUSIONS:** La maladie de Crohn est l'affection la plus fréquente de l'iléon terminal. Les atteintes malignes du grêle peuvent donner un tableau clinique identique à celui de la maladie de Crohn. Mais si la chirurgie est la dernière option thérapeutique pour cette dernière, elle peut guérir la néoplasie du grêle, pour laquelle elle constitue le premier choix thérapeutique. Le diagnostic erroné d'une néoplasie maligne du grêle peut donc retarder le recours à une intervention efficace et assombrir le pronostic.

months her crampy pain recurred, intensified and shifted to the right lower quadrant. She also developed night sweats and a bowel habit of four or five loose, watery bowel movements daily.

On admission to hospital, a vague mass was palpable in her right lower quadrant, and she had normocytic anemia, mild leukocytosis, guaiac positive stools and a positive tuberculin skin test. Pelvic ultrasound demonstrated a poorly defined mass in the right iliac

fossa, consistent with a septic complication of Crohn's disease. Small bowel follow-through and peroral pneumocolon are shown in Figure 1.

At laparotomy, a 15 x 8 x 7 cm tumour was found to have eroded through the small bowel wall and to have involved regional lymph nodes. Pathology revealed mixed cellularity Hodgkin's disease, clinical stage IVB. Treatment consisted of five cycles of mechlorethamine, vincristine, procar-

bazine, prednisone (MOPP), and the patient is well 14 years later. *Prednisone may improve symptoms in a variety of diseases. When such improvement is short-lived, re-evaluation is warranted.*

CASE TWO

A 51-year-old woman presented to her family doctor with a two-year history of crampy right lower quadrant abdominal pain. She had associated loose bowel movements up to five times daily, alternating with constipation. A gastroenterologist diagnosed her as having Crohn's disease, and she began treatment with sulphasalazine. She continued to do well for three years, with two to three flare-ups per year (all of which settled promptly with short courses of prednisone). When one episode was slower to settle, she had a small bowel follow-through and subsequent laparotomy (Figure 2).

A mass in her terminal ileum with associated peritoneal seeding was

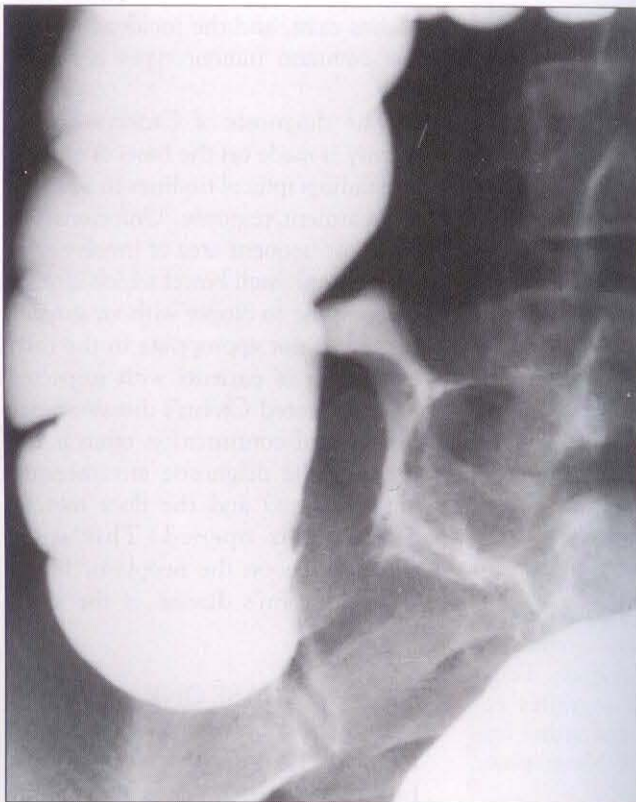


Figure 1) Above Spot film from barium enema showing narrow terminal ileum with nodular indentations. Right Spot film from small bowel follow-through with air in the colon (peroral pneumocolon) showing long segment of small bowel narrowing. The nodular indentations are less apparent

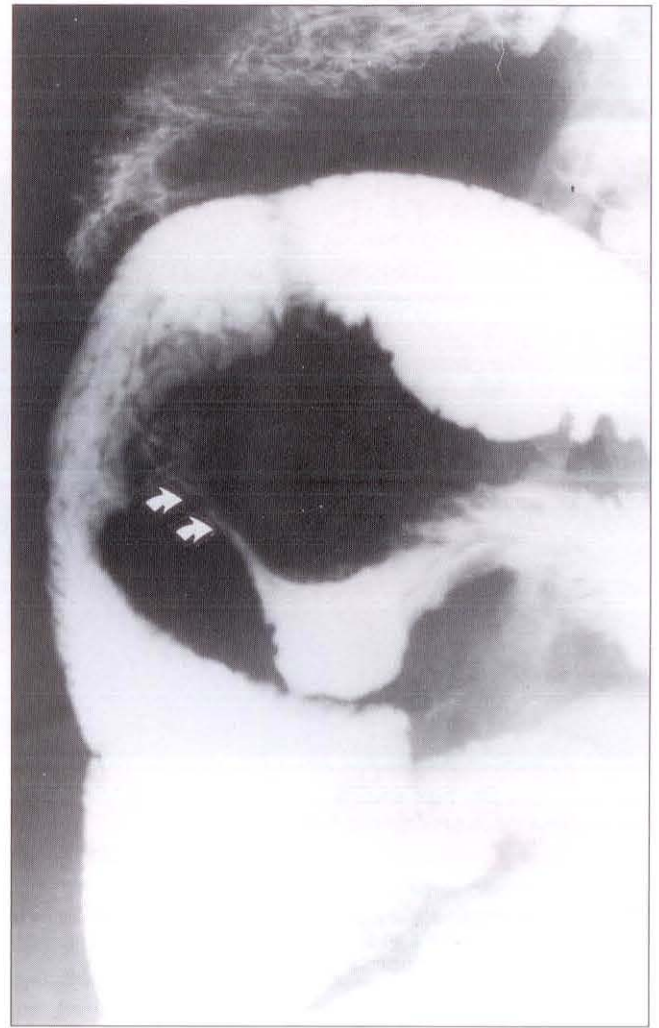
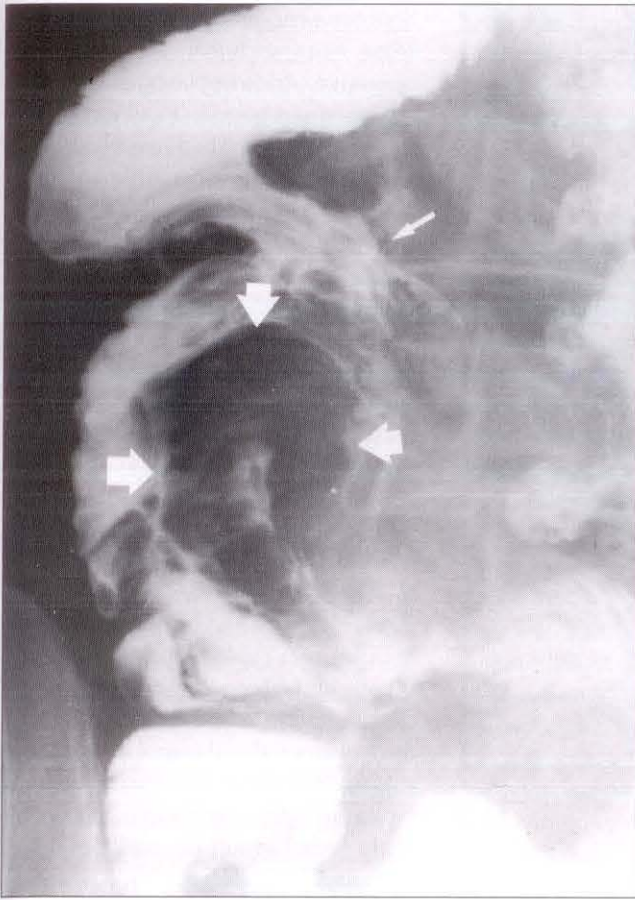


Figure 2) Above Spot film showing large ileocecal valve (large arrows) with deformity and angulation of the ascending colon (small arrow). Right Spot film from small bowel follow-through showing short segment of strictured terminal ileum (arrows). The mucosa proximally is normal

found, resected and subsequently proven to be a carcinoid tumour. The patient declined chemotherapy and is alive five years later. *An abrupt change in the usual pattern of disease for a particular patient warrants reinvestigation.*

CASE THREE

A 35-year-old female developed iron deficiency anemia during a pregnancy. When her anemia persisted after the termination of her pregnancy, she was seen by a gastroenterologist who diagnosed her as having ileocecal Crohn's disease (Figure 3).

Treatment consisted of 5-aminosalicylic acid and prednisone; however, within three months the patient was admitted for investigation of worsening right lower quadrant pain. Computed tomography scan, ultrasound and indium scan suggested abscess. At surgery, a 6 x 5 x 2 cm mass was resected from

her ileocecum. Pathology revealed a poorly differentiated adenocarcinoma of the cecum which had eroded through the terminal ileum. All five sampled regional lymph nodes were involved.

The patient began treatment with 5-fluorouracil and levamisole, yet developed a pelvic side wall recurrence. This was resected but her disease again recurred. Because of her failing condition and evidence of distant metastases, the treatment objective was changed to palliative, and she died shortly thereafter. *Unfortunately, neoplastic processes may mimic Crohn's disease.*

CROHN'S DISEASE

Crohn's disease is a regional chronic inflammatory enteritis that most commonly involves the terminal ileum, but may occur anywhere from the mouth to the anus (1). Its incidence in the West

appears to be increasing (2); whether this represents a true increase or increased clinician vigilance is uncertain. The prevalence in North America has been estimated at 10 to 70 per 100,000 (1) and the incidence has been estimated at five to seven per 100,000 per year (3).

The clinical presentation of Crohn's disease of the small bowel is varied and frequently nonspecific. Accordingly, radiology remains a major diagnostic tool. In contrast to patients with colonic Crohn's disease, plain film examination in patients with Crohn's disease of the small intestine is unrewarding (4) in the absence of obstruction or perforation. Small bowel follow-through with fluoroscopy is the most commonly used technique of small bowel examination at the authors' centre. In cases where small bowel follow-through does not adequately display the terminal ileum,

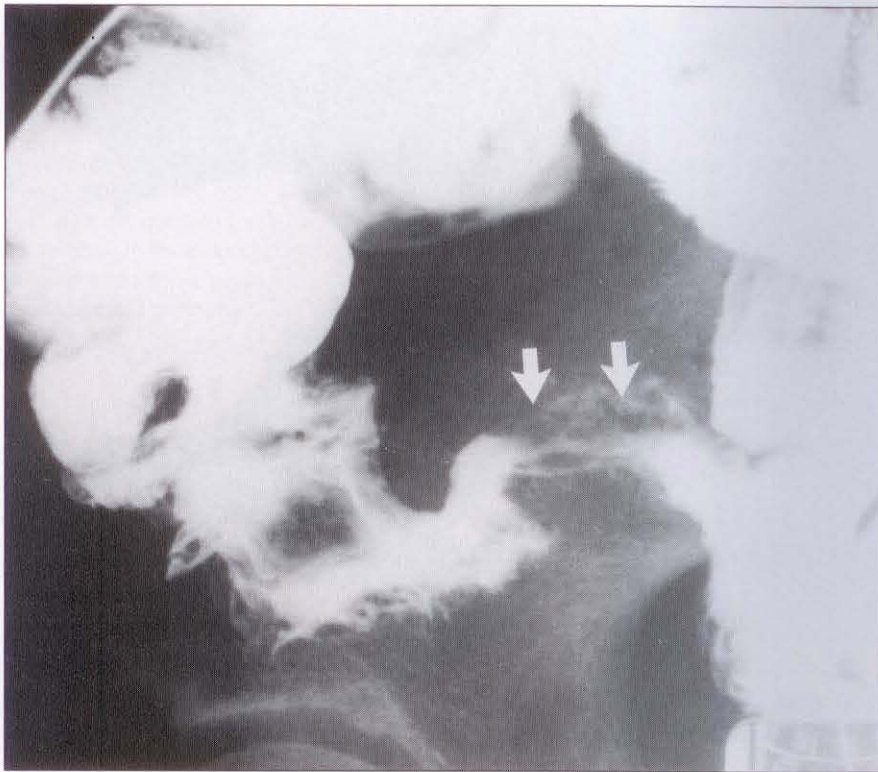


Figure 3) Spot film from small bowel follow-through showing narrowing of the terminal ileum (arrows) and the cecum deformed by tumour

TABLE 1
Differential diagnosis of Crohn's disease involving the small bowel

Infectious
Viral
Bacterial
Mycobacterial
Fungal
Parasitic
Vascular/ischemic
Radiation
Endometriosis
Adjacent inflammatory disease
Appendicitis
Pelvic inflammatory disease
Neoplastic

air contrast peroral pneumocolon (5) or enteroclysis (6) is used.

Early findings with small bowel follow-through include superficial erosions, aphthous ulcers and mucosal thickening or granulation. Later, cobblestoning, fissuring or ulceration may be seen. Luminal constriction is common, secondary to mucosal disease, mesenteric adenopathy or abscess formation. Atypical findings include dif-

fuse small bowel involvement, relative ileal sparing, sharp angulation and large or multiple mass effect (4).

Ancillary radiographic procedures are used when the appearance is atypical, the diagnosis is in question or complications are suspected. Such procedures include computed tomography scanning (7), ultrasound (8) and radionuclide imaging (9). Computed tomography scanning particularly is useful to demonstrate fistulous tracts (7) and thickened bowel walls. The most sensitive imaging technique is indium III granulocyte scanning. Measurements of fecal excretion of indium or of the scintigraphic fall in splenic activity are directly correlated with disease activity (10). Indium-labelled granulocytes localize diseased segments reproducibly and reliably (9). Ultrasound imaging can also be used reliably to assess disease extent. In one study, when rectal disease was excluded, ultrasound detected 91% of lesions that had been identified by indium scans (11).

Crohn's disease is incurable. Surgery is indicated only when medical management fails or complications occur.

Strictures can successfully be treated in some cases with balloon dilation, or operative stricturoplasty (12). When resection is required, the objective is to remove only overtly diseased segments with the smallest possible resection margins (no evidence exists that wider resection margins reduce recurrence) (13). Post resection recurrence virtually is inevitable and can be confirmed endoscopically at anastomotic sites in 85% of patients within three years of surgery. Clinical manifestations of recurrent disease occur at a cumulative rate of 10% per year (14). Surgery is delayed as long as possible.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of Crohn's disease is broad and must be considered at diagnosis (Table 1). Infectious causes represent the broadest group of Crohn's disease imitators and include viral, parasitic, bacterial and fungal causes. Neoplastic disease is less common, but represents the most serious and potentially lethal group of small intestinal diseases (Table 2).

SMALL BOWEL TUMOURS

Small bowel malignancies are strikingly rare. Despite its large surface area, the small bowel is responsible for less than 25% of all gastrointestinal neoplasms and less than 2% of malignant gastrointestinal tumours (15). Several theories have been presented to explain this low malignancy frequency. Proposed factors include rapid intestinal transit, high alkalinity, low bacterial populations (15) and the presence of intestinal hydroxylases (16). The putative effects of these factors are to decrease production, increase clearance and inactivate any potential carcinogens.

Numerous conditions are predisposing factors for small bowel cancer. Celiac sprue has been associated with lymphoma (17) and has been implicated in the pathogenesis of adenocarcinomas (18). *Dermatitis herpetiformis* has also been associated with a disproportionate number of small bowel adenocarcinomas (19). Crohn's disease patients have a well-characterized increased risk of small intestinal aden-

ocarcinoma compared with the general population (20,21); patients with familial multiple polyposis syndromes have an increased risk of malignancy. Those with an increased risk of small bowel tumours include Gardner's syndrome (22) and Peutz-Jeghers syndrome (23). More recently, the acquired immune deficiency syndrome has been associated with gastrointestinal Kaposi's sarcoma (24) and gastrointestinal B cell lymphoma (25).

Tumours of the small bowel initially present with nonspecific symptoms of dyspepsia, anorexia, malaise and vague abdominal pain (15). These complaints are sufficiently common not to alarm attending physicians.

Later symptoms which prompt investigation include intermittent or partial small bowel obstruction, intussusception and overt or chronic blood loss (26). Malignant disease may present in the above ways, but also is associated with visceral pain, weight loss, nausea, vomiting and complete small bowel obstruction (27). A mass may frequently be palpated with malignant disease, but is uncommon with benign growths (28).

The key to small bowel neoplasm diagnosis is a high index of suspicion. Contrast radiography is the principal initial investigation, yet its sensitivity and specificity are low. The estimated diagnostic accuracy of small bowel follow-through in the diagnosis of small bowel malignancy is 50% (29). Frequently techniques other than small bowel follow-through are required. One report identified 48 lesions missed by small bowel follow-through using enteroclysis (30). Adjunctive techniques include angiography, red blood cell scans and computed tomography scans (15). Angiography may help diagnosis and localize small bowel tumours. Tumour blush may be seen in vascular tumours, and displacement of the normal vascular pattern may be seen in hypovascular tumours. Actively bleeding lesions can be localized with angiography or red blood cell scans. Computed tomography scans are useful in defining the extent of disease and may predict resectability.

Laboratory investigations are not

helpful in diagnosing small bowel neoplasms. Tumour markers have no role in diagnosis with the exception of carcinoid tumours which may elevate urinary 5-hydroxyindoleacetic acid. Other abnormal findings are nonspecific and reflect the overall health of the patient. Definitive diagnosis, therefore, is made by pathological examination of surgical (or rarely endoscopic) specimens. In the hands of a skilled colonoscopist, the ileocecal region frequently can be visualized, and occasionally the terminal ileum may be cannulated. If so, endoscopic biopsies can speed diagnosis.

Findings of 2507 cases of small bowel tumours reported in the literature between 1959 and 1986 are summarized in Table 3 (26,27,31-44). Because many reviews classified carcinoid tumours separately and did not differentiate between benign and malignant carcinoids, the current authors have followed suit. It is important to remember that carcinoid behaviour ranges from benign to malignant.

This compilation deals with small bowel tumours as a uniform group. The relative frequency, however, varies by site within the small bowel. For malignancies, adenocarcinoma is seen most commonly in the proximal small gut, and ileal disease is rare. The vast majority of carcinoids occur in the ileum and approximately half of small intestinal sarcomas are ileal. Lymphomas are almost nonexistent proximally, with 48 and 47% occurring in the ileum and jejunum, respectively (45).

The relative frequency of metastatic disease almost certainly is underrepresented by this summary. Only one of the studies reviewed (34) included metastatic disease in its series. The frequency in that series was 6.5% (seven of 104 cases) comprising three known metastases of melanomatous origin, two metastases from gastrointestinal sources, one from lung and one of melanomatous origin without a known primary. Metastases to the small bowel have been well-characterized and may be due to hematogenous, lymphangitic or transperitoneal spread (46). Metastases are most commonly from cervix, lung, esophagus, ovary and melanoma (47).

TABLE 2
Neoplasms which may mimic Crohn's disease of the small bowel

Primary	
Malignant	Lymphoma
	Adenocarcinoma
	Sarcoma
Intermediate	Carcinoid
Benign	Adenoma
	Leiomyoma
	Lipoma
	Hemangioma
Secondary	
Metastases	Lung
	Gastrointestinal
	Genitourinary
	Melanoma
	Peritoneal carcinomatosis
	Adjacent cecal tumours

TABLE 3
Summary of 16 retrospective reviews of the relative frequency of small bowel tumours

Small bowel tumour type	Frequency (%)
Malignant	
Adenocarcinoma	691 (27.5%)
Lymphoma	238 (9.5%)
Leiomyosarcoma	166 (6.5%)
Sarcoma	72 (3%)
Miscellaneous	41 (1.5%)
Anaplastic	9 (less than 1%)
Metastases	7 (less than 1%)
Carcinoid	649 (26%)
Benign	
Leiomyoma	226 (9%)
Adenoma	126 (5%)
Lipoma	113 (45%)
Hemangioma	78 (3%)
Lymphangioma	21 (less than 1%)
Neurofibroma	18 (less than 1%)
Miscellaneous	18 (less than 1%)
Fibroma	17 (less than 1%)
Hamartoma	8 (less than 1%)
Islet cell adenoma	7 (less than 1%)
Endometrioma	2 (less than 1%)
Total	2507

Based on references 26,27,31-44

The four most frequently encountered malignancies were adenocarcinoma, carcinoid, lymphoma and leiomyosarcoma. Five-year survival rates for these tumours is grim, with the possible exception of lymphoma (its prognosis is dependent upon histology). Five-year survival from adenocarcinoma is 20% (47), and is 50% for both carcinoid (48) and leiomyosarcoma (43). Of course the major predictor of survival is disease extent (both microscopic and macroscopic) at diagnosis, thereby implying increased survival with earlier diagnosis and treatment.

DISCUSSION

Disease of the small bowel can present in a limited number of ways. Clinical signs and symptoms, and radiographic and laboratory findings are nonspecific and cannot reliably distinguish Crohn's disease from malignancy.

Differentiation between Crohn's disease and cancer is essential because treatment and prognosis are drastically different. The mainstay of Crohn's disease therapy is medical, with surgery being noncurative and used only in cases of medical management failure or in the presence of complications. This contrasts the primary role of surgery in the treatment of small bowel neoplasia in which surgery offers a potential cure.

If a misdiagnosis is made, the prognosis is worsened by the resultant delay in definitive treatment.

The incidence of Crohn's disease is five to seven per 100,000 (3), whereas the incidence of small bowel neoplasia, when considered as a single entity, is 0.7 to 1.6 per 100,000 (47). If only terminal ileal neoplasia is considered, the difference would be greater. Since Crohn's disease is chronic, and patients with small bowel neoplasms are either cured or die, the differences in prevalence is even greater. Therefore, the statistically probable diagnosis of a patient with undiagnosed terminal ileal disease is Crohn's disease. For this reason, it is tempting to diagnose any patient who has abdominal pain and terminal changes with Crohn's disease. The researchers contend that in the absence of histology, diagnosis of Crohn's disease should be one of exclusion – forcing the clinician to consider processes which may mimic Crohn's disease.

The authors have presented three cases of small intestinal disease which initially masqueraded as Crohn's disease, but subsequently were proved to be malignant. These cases demonstrate the need for diagnostic re-evaluation when response to treatment does not follow a predicted course.

It is not clear how final outcomes

may have been altered by earlier recognition of the final diagnosis; conceptually at least, earlier demonstration of malignant disease may have led to more effective treatment with potentially reduced suffering, morbidity and mortality.

The intention of this paper is not to suggest that all patients with atypical presentations or disease courses undergo surgery for diagnosis, but rather to point out the need for careful scrutiny in accepting the diagnosis of Crohn's disease when histology is absent.

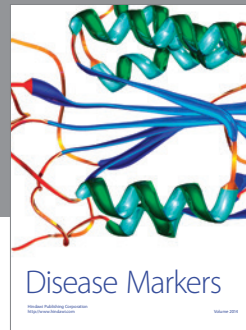
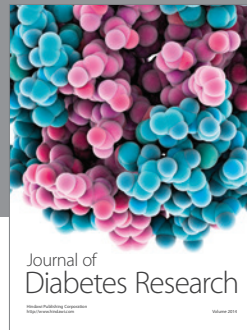
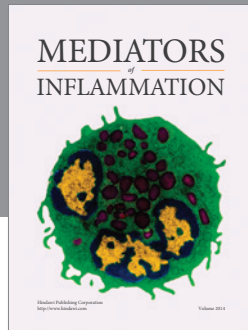
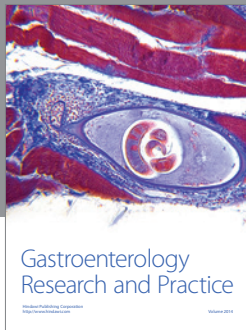
The authors have summarized reviews of the past 30 years to provide some insight into the relative frequency of neoplastic diseases of the small bowel, demonstrating a preponderance of carcinoid and adenocarcinoma when the small bowel was considered as a whole. The terminal ileum alone has a different spectrum of disease, with the majority of tumours being carcinoid, followed closely by sarcoma, lymphoma and adenocarcinoma.

Prognosis for all of these tumours is affected greatly by extent of disease at diagnosis. The consequences of a delay in diagnosis, therefore, are enormous, and the need for clinician awareness of neoplasia as a Crohn's disease imitator cannot be overemphasized.

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