

Crohn's disease of the esophagus: Three cases and a literature review

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I Rudolph, F Goldstein, AJ DiMarino Jr. Crohn's disease of the esophagus: Three cases and a literature review. *Can J Gastroenterol* 2001;15(2):117-122. Three cases of esophageal Crohn's disease (CD) are described, each with dysphagia and/or odynophagia caused by esophageal ulceration. All three patients had associated ileocolitis. One patient followed for a prolonged period responded to treatment with sulfasalazine and prednisone. A computer search back to 1967 produced 72 additional cases of esophageal CD. Among these 75 patients (total), who were, on average, 34 years old, esophageal disease was the presenting disease symptom in 41 patients (55%). The diagnosis was difficult in 13 patients, in whom no distal bowel disease was detected at the time of initial esophageal presentation. The most common presentation was dysphagia associated with aphthous or deeper ulcerations (52 patients). In 11 of these patients, oral aphthous ulcerations were also present. Esophageal stenosis or fistulas to surrounding structures were present in 27 patients and led to surgery in 17 patients. Most of the unfavourable outcomes were in this group of 27 patients with esophageal complications, including five deaths. Fourteen additional patients required surgery for CD of other areas. Responses of uncomplicated ulcerative disease of the esophagus tended to be favourable if the medical regimen included prednisone. Clinical patterns of esophageal CD were divided into three categories: ulcerative, stenosing and asymptomatic (acute disease in children).

Key Words: *Crohn's disease; Esophageal disease*

Trois cas de maladie de Crohn de l'œsophage et examen de la documentation

RÉSUMÉ : Voici trois cas de maladie de Crohn (MC) de l'œsophage caractérisée par une dysphagie et/ou une odynophagie causée par une ulcération œsophagienne. Les trois patients présentaient également une iléo-colite. Le suivi prolongé d'un patient a montré que ce dernier avait bien réagi au traitement à la sulfasalazine et à la prednisone. Une recherche informatisée des dossiers depuis 1967 a permis de relever 72 cas de MC de l'œsophage. Un trouble de l'œsophage a été le premier signe de la maladie chez 41 des 75 patients (55 %), âgés en moyenne de 34 ans. Le diagnostic a été difficile à poser chez 13 d'entre eux étant donné qu'aucune maladie intestinale distale n'avait été décelée au moment de l'apparition du premier signe de trouble œsophagien. La manifestation la plus courante a été une dysphagie associée à une ulcération aphtheuse ou profonde (52 patients); onze souffraient également d'aphtes buccaux. Vingt-sept patients présentaient une sténose œsophagienne ou des fistules et 17 d'entre eux ont dû être opérés. La plupart des résultats négatifs, dont cinq morts, ont été observés dans le groupe de patients présentant des complications œsophagiennes. Quatorze autres patients ont été opérés pour une MC touchant d'autres régions. Le traitement de la forme non compliquée de l'ulcération œsophagienne semblait donner de bons résultats si celui-ci comprenait de la prednisone. Les signes cliniques de la MC de l'œsophage ont été divisés en trois catégories : ulcères, sténose et absence de symptômes (maladie aiguë chez les enfants).

The prevalence of esophageal involvement in Crohn's disease (CD) has been estimated in the literature to be between 1% and 2% (1). However, the pediatric literature has reported a prevalence of 20% to 40% when all patients

were prospectively surveyed by means of esophagogastroduodenoscopy (EGD) during the acute phase of CD (2). Case reports are typically brief, and not all questions can be answered by reviewing them. Three cases of esophageal CD

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Figure 1) Discrete small ulcerations in the distal esophagus of the patient described in case 1. Markers indicate two ulcers

recently encountered in the authors' practices are described, together with a review of the pertinent literature.

CASE 1

A 24-year-old married woman was seen in February 1998; her chief complaint was odynophagia. She had suffered from prolonged heartburn. Treatment with H₂-receptor blockers, and later with proton pump inhibitors, produced only minor symptom relief. Subsequently, odynophagia developed, brought on by swallowing any food or even saliva. Avoidance of spicy foods produced minimal benefit. Past medical history recalled by the patient included 'functional' gastrointestinal problems in 1986, when the patient was 12 years old. Unrelated events also recalled included bouts of cystitis, and asthma treated with oral prednisone and an albuterol inhaler. On physical examination, the patient appeared well developed and nourished, vital signs were normal and general examination failed to show any abnormalities. Because of the odynophagia, EGD was performed. EGD revealed three distinct esophageal ulcers, each appearing as a sharply demarcated, red, approximately 5 mm round area in the lower esophagus surrounded by normal-appearing mucosa (Figure 1). The Z-line was distinct without clinically apparent esophagitis or stricture. The stomach and duodenum appeared normal. Biopsies from the lower esophagus revealed dense lymphocytic infiltrates in several areas and ulcerations in others. Granulomas were not found.

The patient's mother recalled that her daughter had been suspected of having CD in 1986. Records and x-rays were retrieved. The patient had presented in 1986 with diarrhea and abdominal pain. Barium contrast studies of the gastrointestinal tract were reviewed and showed a distinct segment of ileocolitis involving about 6 cm of the terminal ileum and 3 cm of the adjacent cecum. The EGD in

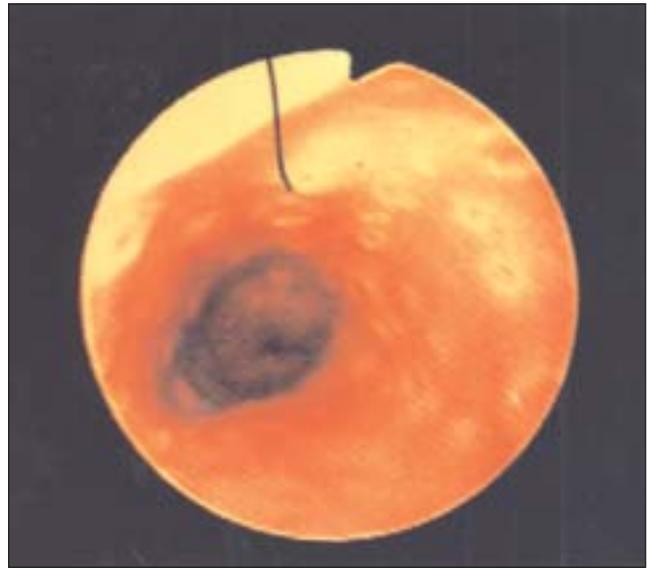


Figure 2) Multiple aphthous ulcers in the mid- and distal esophagus of the patient described in case 2

1986 also showed antral gastritis, with biopsies confirming nonspecific inflammation of the prepyloric area with *Helicobacter pylori* positivity. Treatment with ampicillin seemed to help. Follow-up radiographs in 1989 showed partial improvement of the ileal changes. Repeat radiographs obtained in 1998 showed minimal residual scarring of the terminal ileum. Treatment was initiated with mesalamine, but the patient was lost to follow-up before the response to treatment could be evaluated.

The interpretation of events from 1986, 1989 and 1998 suggests that they were due to CD, and that the recent predominant problem is esophageal CD with multiple ulcers and corresponding symptoms.

CASE 2

A 28-year-old married woman presented in April, 1991 with three weeks of abdominal cramps and up to six watery stools per day. Five days before her visit, she developed a sore throat, and her husband, who was a physician, noted aphthous ulcers in her mouth. The patient developed dysphagia and odynophagia by the time of her evaluation. She had fevers with temperatures of up to 102°C. Past medical history included uveitis treated at a university clinic with steroid eye drops.

On examination, the patient's blood pressure was 100/70 mmHg and her pulse was 112 beats/min. On the hard palate and buccal surfaces, multiple white papules – some ulcerated – were noted. The remainder of the examination was unremarkable, except for a grade 2 systolic murmur at the apex and mild, lower to mid-abdominal tenderness. On the EGD, multiple small aphthous ulcerations on slightly elevated bases were noted, which were similar to the ones in the mouth and measured from 2 mm to 6 mm in diameter (Figure 2). Similar lesions were also found diffusely distributed in the stomach and proximal duodenum. The duodenal loop was normal. Biopsies and brushings taken from the

ulcers failed to show viral inclusions but did show acute and chronic superficial gastritis and esophagitis, with some granulation tissue and scattered ulcerations. Flexible sigmoidoscopy, done at the same time, showed erythema and shallow irregular ulcerations scattered over the distal 35 cm. Biopsies revealed acute and chronic inflammation with crypt abscesses, consistent with inflammatory bowel disease. Granuloma formation in submucosal lymphoid aggregates was suggested.

The patient was treated with sulfasalazine 2 g/day and prednisone 40 mg/day, followed by a dramatic response – the disappearance of dysphagia within a few days and improvement in the diarrhea. When the patient was seen in the office three weeks later, the aphthous ulcerations of the mouth were no longer seen, and she reported to be free of dysphagia and diarrhea. Stool cultures and examinations for ova and parasites were reported to be negative. Prednisone was tapered to nothing over a 10-week period, but sulfasalazine was continued. Pancolonoscopy, done in this healing phase, showed mild erythema in the right colon and nodularity in the distal 30 cm of the left colon. Biopsies from the right colon showed acute and chronic colitis, while biopsies from the left colon showed focal lymphoid aggregates with early changes of granuloma.

The patient became pregnant shortly after going into remission and delivered healthy twins in January, 1993. Sulfasalazine was stopped seven months later, and the patient remained well for another 10 months, when she developed recurrent diarrhea. She again responded to sulfasalazine and prednisone, the latter being tapered over the next two months. With sulfasalazine alone, the patient remained in remission for two years. Sulfasalazine was again stopped, followed by another relapse four months later. Both prednisone and sulfasalazine were restarted with a prompt response. After tapering prednisone again, the patient continued in remission while on sulfasalazine alone for the next eight months of observation. None of the relapses were accompanied by esophageal symptoms.

CASE 3

A 42-year-old man was evaluated in a gastrointestinal clinic for a 20-year history of Crohn's disease, initially involving the terminal ileum. The diagnosis was established with exploratory laparotomy for what was thought to be acute appendicitis in 1979, at age 22 years. His initial presentation was severe right lower quadrant pain, with elevation of his white blood cell count to 14,000. After a period of observation, it was thought that he had acute appendicitis and, at the time of laparotomy, was found to have congestion and thickening of the terminal ileum with a large thickened mesentery and an enlarged mesenteric lymph node. Pathology revealed increased lymphocytes with no granulomas in the mesenteric lymph nodes and a normal appendix. A subsequent small bowel series revealed 5 cm to 6 cm of terminal ileal narrowing, consistent with Crohn's disease.

In 1984, the patient developed perianal burning and pain with defecation. He had recurrent fissures involving

the anal sphincteric region and was seen by his attending gastroenterologist; he was subsequently referred to a colorectal surgeon. A fissure from the Crohn's disease was noted, and local care, incision and drainage were judiciously performed over the next several years.

In 1985, an air contrast barium enema revealed scarring of the ileocecal valve with aphthous ulcerations consistent with Crohn's disease.

In 1986, the patient described dysphagia, particularly with solid foods, and was evaluated by a gastroenterologist with upper endoscopy. Findings at that time revealed an exudative distal esophageal mucosa with multiple small ulcerations. The amount of esophageal involvement was approximately 2 cm to 3 cm in length. He was treated with high dose H₂-receptor antagonists without improvement. His esophageal ulcerations were re-evaluated by two subsequent gastroenterologists – all within an 18-month period. Despite intensive antisecretory therapy, the esophageal ulcerations persisted. Several biopsies of the area revealed lymphocytic infiltrate with occasional eosinophils. No granulomas were identified. He initially required balloon esophageal dilation, and periodically since 1986, he has required Maloney bougienage therapy for recurrent dysphagia and odynophagia. His esophageal ulcerations persisted despite proton pump inhibitor therapy in the form of omeprazole 40 mg bid, H₂-receptor antagonists in the form of ranitidine or famotidine 40 mg bid, and antacids. The dysphagia and perianal discomfort with defecation improved with azathioprine therapy 300 mg/day. However, he developed severe leukopenia, and this medication was withdrawn.

Intermittent therapy with metronidazole, ciprofloxacin, corticosteroids and 5-aminosalicylic acid preparations have not significantly altered the patient's recurrent symptoms of odynophagia and dysphagia for solids. He requires periodic esophageal dilations with Maloney tapered bougies. Successful dilations are completed to an approximately 1.6 cm esophageal lumen, performed approximately every three to six months, in conjunction with therapy to decrease acid secretion in the form of proton pump inhibitors, H₂-receptor antagonists and sucralfate suspension.

He is relatively asymptomatic from a lower gastrointestinal viewpoint, having approximately one or two formed bowel movements per day.

LITERATURE REVIEW

Review of the English language literature using a computer search of MEDLINE for the years 1967 to 1998 yielded reports for 72 patients with esophageal CD (1,3-40). After adding the present three cases, data of all 75 patients were tabulated by age, sex, whether CD at other sites predated the esophageal presentation and which sites, in addition to the esophagus, were involved. Data were also tabulated on the endoscopic and radiographic appearance of the esophagus, and whether granulomas were found in biopsies and other tissue specimens. Finally, available data on medical and surgical treatments and clinical outcome were analyzed.

TABLE 1
Distribution of Crohn's disease with initial presentation of esophageal disease

Distribution of Crohn's disease	No previous history of Crohn's disease (n=41)*	Previous history of Crohn's disease (n=33)
Colon	22	24
Small bowel	22	26
Gastroduodenal	12	7
Oral	11	9

*One case history indeterminate for additional Crohn's disease

RESULTS

Among the 75 patients reviewed, including the three present cases, 34 were male and 41 female – an insignificant difference. The average age of the patients at diagnosis of esophageal CD was 34 years; this average masks a substantial number of patients diagnosed in childhood, most of whom were reported relatively recently. In 13 patients (17.5%), the initial diagnosis of CD was made by the presence of esophageal manifestations alone. In an additional 28 patients (37.8%), esophageal involvement, together with involvement more distally in the gut, was present on initial diagnosis. Among the 13 patients with esophageal disease only on presentation, two developed more distal bowel involvement during the four years of follow-up (9,25). With the short follow-ups available in many cases, it was not possible to determine whether subsequent flare-ups were associated with more distal bowel disease.

The distribution of involved segments of the gut in patients with and without prior diagnosis of CD showed no significant differences in disease distribution (Table 1). Extraintestinal manifestations (not listed) were present in 20 patients (27%), and involved the eyes, joints and skin.

The coexistence of oral and esophageal lesions was striking. Of the 20 patients with oral disease, 11 had similarly appearing aphthous ulcers in the esophagus. The remaining nine patients had variable esophageal lesions ranging from deeper ulcerations to strictures. Table 2 lists the combined endoscopic and radiographic appearance of the esophageal CD in the group of 75 patients. The largest number of patients presented with aphthous or deeper ulcerations; smaller numbers presented with nodularity or erythema, strictures, fistulas and, in two instances, pseudopolyps (13,19).

The histology of esophageal tissue recovered from 69 patients showed acute and chronic inflammation, ulcerations, and occasional fibrosis and transmural involvement in patients who had surgical, full-thickness biopsies. Classic granulomas were found in 27 patients (39%).

Esophageal complications in the form of stenosis, fistula or both were present in 27 patients; their mean age was 47 years – considerably older than the mean age of the entire group. This suggests that these patients had longstanding disease progressing to the complications listed. In four

TABLE 2
Gross appearance of esophageal Crohn's disease in 75 patients*

Category [†]	Patients with characteristic (n)
Aphthous ulcers	32
Deep ulcerations	20
Nodularity and erythema	15
Pseudopolyps	2
Stricture	24
Fistula	9

*Total of more than 75 indicates that there was more than one gross characteristic in the same patient; [†]Categories based on endoscopic and radiological appearance

patients, fistulous drainage was documented to a pleural cavity or bronchus (15,16,25,32). Seventeen of the 27 patients with fistulas and/or stenosis required surgery. Of these, 13 were improved while four failed to improve, including three who died (34,40). Of the 10 remaining patients treated medically, five improved and five failed to improve, including two deaths (16,32). Among the 75 patients (total) there were nine deaths, and only four were due to causes other than esophageal complications, including fulminant disease with bowel perforation (34), multiple resections and their nutritional consequences (28,31), and sepsis (10).

Seventeen of the 75 patients were treated with surgery alone. Fourteen additional patients underwent surgery together with various medical interventions. Thirty-five were treated with medical or pharmacological therapy alone. In nine cases, no details of therapy were provided. Among the 49 patients treated medically, 43 received corticosteroids alone or in combination with aminosaliculates, and six received aminosaliculates only. Ten patients were also treated with other modalities including bougienage, acid suppressants or 6-mercaptopurine (five patients). Steroid treatment generally produced short term improvement, but long term results could not be noted. Responses to drugs other than steroids or immunomodulators were usually poor, although, in case 2 in the present report, sulfasalazine seemed to provide some benefit. Some patients showed symptomatic improvement with acid suppression and/or bougienage, but no esophageal healing could be seen.

Eighteen patients had bowel surgery either before or after the discovery of esophageal disease. Resolution of bowel disease and improvement in unresected esophageal disease was reported in one patient (30). Another (18) had esophageal improvement while on steroids, which were tapered four months postoperatively. In 16 other patients, esophageal disease developed after bowel resection or esophageal disease progressed despite segmental resection of intestinal CD (8-10,13,16,19,20,25,28,29,31-34).

DISCUSSION

The esophagus is among the least common segments of the digestive tube involved in CD. We were able to find only 72 cases reported in the literature and added the three present

cases. Very few cases were reported before 1967, although the initial description of esophageal CD is attributed to Franklin and Taylor in 1950 (41). Undoubtedly, many more cases encountered have not been reported. With the wider use of upper gastrointestinal endoscopy in recent years, and with prospective studies in patients with CD, esophageal involvement has been observed in up to 43% of children with CD (2). Lenaerts et al (42) surveyed 230 children and adolescents with CD for an average of 6.6 years. Thirty per cent of these had disease of the esophagus, stomach or duodenum. Although 69 of the 230 patients had upper gastrointestinal symptoms, 13 had normal x-rays, and only endoscopy revealed lesions compatible with CD. Korelitz et al (43) performed routine upper endoscopies and biopsies of the esophagus, stomach and duodenum in 45 patients with CD, and normal upper gastrointestinal x-rays. They found diagnostic biopsies in 11 patients and nonspecific microscopic changes in 19 patients; among the patients with abnormal biopsies were 11 patients with endoscopically normal-appearing mucosa. These studies illustrate the frequent presence of upper gastrointestinal lesions in the absence of symptoms and sometimes in the absence of endoscopic abnormalities. There seems to be a major difference in the prevalence of esophageal CD between children and adults. Because CD is a chronic, often lifelong disease, the difference in the frequency of esophageal involvement between children and adults invites speculation as to the cause of this discrepancy. Many patients with esophageal CD were reported to have aphthous ulcerations, generally regarded as very early manifestations of CD and often observed at onset of the disease. With later progression of the disease, the aphthous ulcers of the esophagus may disappear. However, in the present literature review, CD of the colon, ileum or gastroduodenal segment preceded esophageal involvement in 33 patients by up to 24 years, perhaps showing in yet another way the wide range of manifestations of this baffling disease. When esophageal CD was observed in adults, it often presented with stenoses and fistulas, which are generally considered complications of longstanding CD.

Most patients with esophageal CD present with odynophagia and/or dysphagia. Bleeding and fistulization occur rarely; however, when present, they indicate a more threatening aspect of the disease. Fistulas to bronchi or pleural spaces usually require surgical intervention, and carry a substantial risk of morbidity and mortality. Three deaths occurred in the group of 17 patients who were operated on for esophageal fistulas and/or stenosis, and two deaths occurred in patients treated medically for this complication. Only four additional deaths occurred among the entire group of 75 patients reviewed. The use of the newer expandable metal stents may decrease the need for surgery, and complications could perhaps be reduced.

The diagnosis of esophageal CD can be suspected if dysphagia or odynophagia is present, but these are not specific for CD. In patients with CD known to exist in other gastrointestinal segments, the right diagnosis should be sug-

TABLE 3
Differential diagnosis of Crohn's disease

Carcinoma
Reflux esophagitis
Viral esophagitis (herpes simplex, cytomegalovirus)
Other granulomas (sarcoidosis, fungal disease, tuberculosis)
Behçet's syndrome
Epidermolysis bullosa acquisita
Drug-induced ulcer
Intramural diverticulosis

gested but needs confirmation by means of endoscopy and tissue examination. In most cases, endoscopic findings alone are not specific; histological changes, more likely than not, fail to show granulomas and can only be considered compatible with CD. Yet with the exclusion of other specific diagnoses, and in the proper clinical setting, the diagnosis reasonably can be made with these tests.

The differential diagnosis of CD of the esophagus is tabulated in Table 3. In the presence of stenosis, severe reflux esophagitis or carcinoma ranks high among diagnostic possibilities. The additional presence of fistulas would especially suggest malignancy. Aphthous or other superficial ulcerations would require differentiation from viral infections, especially the herpes simplex virus and the cytomegalovirus; single or multiple ulcers would also have to be differentiated from drug-induced lesions. Behçet's syndrome would pose diagnostic difficulties in areas where this disease is common (eg, Turkey – it is rarely encountered in the United States). In this syndrome, overlapping involvement of the eyes, mouth, skin, joints and gastrointestinal tract occurs. Two cases of Behçet's syndrome involving the esophagus and ileum were reported by Vlyman and Moskowitz (44). Two other cases of colonic disease indistinguishable from CD were also reported (45,46). Epidermolysis bullosa acquisita is another autoimmune disease that can be associated with esophageal strictures. Thirteen cases have been reported in association with CD (47). The diagnosis is made by immunoelectron microscopy of the skin lesions demonstrating immunoglobulin G and C-3 deposits.

There is little information on appropriate treatment. No controlled therapeutic trials have been reported dealing with esophageal CD, and its relative infrequency would make such trials difficult to perform. Observational data suggest therapeutic benefits primarily from corticosteroids given over short periods of time. Virtually all pharmacological agents used for inflammatory bowel disease have been used in the treatment of CD, including aminosalicylates and immunomodulators. Removal of a stenotic segment of esophagus refractory to medical treatment and frequent bougienage were the most common reasons for surgery among the patients reviewed. The relative frequency of surgery and its high complication rate are noted. Surgical resections of diseased distal gut segments failed to affect the course of esophageal CD in 16 of 18 patients.

Prognosis on medical therapy was addressed by D'Haens et al (3), who followed 14 patients for an average of six years. Twelve patients were treated with prednisone and two were treated with aminosalicylates plus antibiotics. In eight patients, there was complete healing of the esophageal disease despite further exacerbations of CD elsewhere. These data, as well as the higher prevalence of esophageal CD in children compared with adults, suggest that spontaneous improvement of esophageal CD occurs commonly.

Analysis of the collected data suggests that esophageal CD should be categorized into three broad clinical presentations. The most common presentation is dysphagia or odynophagia accompanied by aphthous or deeper ulcerations, usually associated with acute exacerbations of the CD. Patients may also present with strictures (stenosis) with or without fistula, usually at an older age and with a history of chronic disease. Patients with esophageal CD may be asymptomatic but frequently have symptomatic CD in more distal gut segments. This would include patients with normal endoscopy but abnormal histology. This presentation would explain the high prevalence of esophageal CD reported in children with symptomatic CD distally, but undergoing EGD and biopsy.

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