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Diagnosis and Outcome of Oesophageal Crohn's Disease

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Abstract

Background and Aims: Crohn's disease [CD] can involve any part of the gastrointestinal tract. We aimed to characterize the clinical, endoscopic and histological features and treatment outcomes of CD patients with oesophageal involvement.

Methods: We collected cases through a retrospective multicentre European Crohn's and Colitis Organisation CONFER [COllaborative Network For Exceptionally Rare case reports] project. Clinical data were recorded in a standardized case report form.

Results: A total of 40 patients were reported (22 males, mean [±SD, range] age at oesophageal CD diagnosis: 25 [±13.3, 10–71] years and mean time of follow-up: 67 [±68.1, 3–240] months). Oesophageal involvement was established at CD diagnosis in 26 patients [65%] and during follow-up in 14. CD was exclusively located in the oesophagus in two patients. Thirteen patients [32.2%] were asymptomatic at oesophageal disease diagnosis. Oesophageal strictures were present in five patients and fistulizing oesophageal disease in one. Eight patients exhibited granulomas on biopsies. Proton-pump inhibitors [PPIs] were administered in 37 patients [92.5%]. Three patients underwent endoscopic dilatation for symptomatic strictures but none underwent oesophageal-related surgery. Diagnosis in pre-established CD resulted in treatment modifications

in 9/14 patients. Clinical remission of oesophageal disease was seen in 33/40 patients [82.5%] after a mean time of 7 [±5.6, 1–18] months. Follow-up endoscopy was performed in 29/40 patients and 26/29 [89.7%] achieved mucosal healing.

Conclusion: In this case series the endoscopic and histological characteristics of isolated oesophageal CD were similar to those reported in other sites of involvement. Treatment was primarily conservative, with PPIs administered in the majority of patients and modifications in pre-existing inflammatory bowel disease-related therapy occurring in two-thirds of them. Clinical and endoscopic remission was achieved in more than 80% of the patients.

Key Words: Crohn's disease; oesophagus

1. Introduction

Crohn's disease [CD] is a lifelong disease arising from an interaction between genetic and environmental factors. It can involve any part of the gastrointestinal tract, but the most common locations are the terminal ileum and colon. Oesophageal involvement is not usual. Nevertheless, more than 100 cases of oesophageal CD have been published since the first report of Franklin and Taylor in 1950.[1–3] A prevalence of 0.3–10% is suggested in adults but population-based studies are lacking.[3–7] More frequent oesophageal involvement has been implicated in studies reporting on paediatric CD patients [4.2–42%].[8,9] The wide variations are generally attributed to whether asymptomatic patients with histological involvement are included in the analysis. Gastroduodenoscopy is not considered a prerequisite for CD mapping in most guidelines and especially in asymptomatic adults.[9,10]

Oesophageal CD can present as an erosive–ulcerative oesophagitis, oesophageal stricture or fistula, thus sharing many features of other more common diseases of the oesophagus [reflux oesophagitis, infection, drug-induced, related to malignancy or autoimmune diseases]. The histological features of oesophageal CD may be non-specific further adding to diagnostic challenge. The optimal treatment of oesophageal CD is unknown because controlled trials are lacking. Most physicians use proton pump inhibitors [PPIs] as an add-on regimen to conventional therapy and have a lower threshold for starting anti-tumour necrosis factor [anti-TNF] therapy compared to disease located elsewhere, given the expected poor prognosis.[10]

We aimed to describe diagnostic work-up, interventions and outcome of a series of patients with CD located in the oesophagus.

2. Materials and Methods

2.1. Study design

The European Crohn's and Colitis Organisation [ECCO] CONFER [COllaborative Network For Exceptionally Rare case reports] projects are based on an initiative introduced by ECCO to support individual investigators in identifying, assembling and reporting together rare inflammatory bowel disease [IBD] cases of clinical relevance, which are otherwise seldom reported. The core of CONFER methodology is selecting certain topics worthy of investigation out of case proposals submitted by physicians involved with IBD. The Steering Committee makes an initial selection, identifying those cases with the highest scientific interest and being closest to the purpose of CONFER project. A Feasibility Network, consisting of 30–35 high-volume IBD centres around the globe, is asked to identify similar cases and the final decision is again taken by the Steering Committee based on the outcome of networking. This topic then becomes a CONFER project. ECCO supports dissemination of a call to identify similar cases encountered by IBD physicians worldwide using several tools: announcements in the ECCO annual congress and in national and international IBD meetings across Europe, e-mailing to all ECCO members, posting on the ECCO website and ECCO eNews, flyers and personal communication between ECCO members. Physicians are then prompted to report their case[s] using a predetermined standardized case report form. The call for the present case series was entitled 'Oesophageal Crohn's Disease'. No financial support or input in the collection of data, the analysis or the publication of the data collected is provided by ECCO. ECCO and/or any of its staff members may not be held liable for any information published in good faith in the ECCO CONFER articles.

2.2. Patients and procedures

All CD patients with oesophageal involvement diagnosed either throughout the course of CD or at diagnosis were eligible for inclusion in this study. A diagnosis of oesophageal CD was based on clinical presentation, endoscopic appearance and histological findings.[10] Oesophageal involvement was histologically supported in all patients reported in this case series. Data were collected using a case report form, which was divided into two main sections. Section 1 included patient [epidemiological data, past medical history, alcohol consumption/smoking, family history] and disease [date of diagnosis, Montreal classification, extraintestinal manifestations and treatment] characteristics. Section 2 included a description of oesophageal CD: disease location, endoscopic and histological findings, treatment of CD at oesophageal diagnosis, interventions, treatment modifications and course of disease. Relevant laboratory and radiological tests were also recorded. Data were collected and analysed anonymously and handled according to local regulations. Informed consent was obtained, where obligatory.

2.3. Statistics

All statistical analyses [frequencies, descriptive statistics] were done with the SPSS 20.0 software package [IBM SPSS Statistics].

3. Results

3.1. Patients' background information

A total of 15 centres responded to our call and 50 cases were initially reported. Ten patients were excluded due to a lack of compatible histological data and thus 40 cases were included in the analysis. Patients' characteristics are shown in Table 1. Mean [±SD, range] age at CD diagnosis was 23 years [±12.6, 3–71]. Only two patients [5%]

Table 1. Patient demographics and Crohn's disease characteristics.

Characteristic	Patients [*n* = 40]
Mean [±SD, range] age at diagnosis [years]	23 [±12.6, 3–71]
Sex	
Male	22 [55%]
Female	18 [45%]
Race	
Asian/Oriental	6 [15%]
Caucasian/White	34 [85%]
Ethnicity	
Hispanic or latino	5 [12.5%]
Non-Hispanic or non-latino	35 [87.5%]
Geographical spread	
Poland	8 [20%]
China	3 [7.5%]
The Netherlands	4 [10%]
Portugal	3 [7.5%]
Spain	2 [5%]
Greece	6 [15%]
Switzerland	4 [10%]
Germany	3 [7.5%]
Italy	2 [5%]
Malta	2 [5%]
UK	2 [5%]
Israel	1 [2.5%]
Positive family history of IBD	3 [7.5%]
Smoking	
Current	2 [5%]
Former	2 [5%]
Non-smoker	36 [90%]
Montreal Classification—age	
≤16 years	18 [45%]
17–40 years	20 [50%]
>40 years	2 [5%]
Montreal Classification—location	
L1	9 [22.5%]
L2	3 [7.5%]
L3	24 [60%]
Isolated L4	4 [10%]
Montreal Classification—behaviour	
B1	22 [55%]
B2	8 [20%]
B3	10 [25%]
Perianal disease	18 [45%]
Extra-intestinal manifestations	14 [35%]
Ocular—uveitis/episcleritis	1/1
Osteoarticular—peripheral arthropathy	5
Skin—erythema nodosum	6
Oral granulomatosis	3
Prior IBD treatment	
5-Aminosalicylic acid	14 [35%]
Systemic corticosteroids	12 [30%]
Anti-TNF	13 [32.5%]
Thiopurines	16 [40%]
Methotrexate	3 [7.5%]
Surgery	6 [15%]

Abbreviations: IBD, inflammatory bowel disease; TNF, tumour necrosis factor.

were current smokers. A family history of IBD was reported in 7.5% of patients. CD was exclusively located in the upper gastrointestinal [GI] tract in four patients and solely in the oesophagus in two, while in the rest, ileal disease was present in nine [22.5%], colonic in three [7.5%] and ileo-colonic in 24 [60%] patients. Gastric involvement was generally seen in 15 patients [37.5%]. Of those, only two had active *Helicobacter pylori* infection. Thirteen patients [32.5%] had received at least one anti- TNF agent and six [15%] had undergone a CD-related surgery [partial small bowel resection, stricturoplasty, partial colectomy, ileo-caecal resection or rectal abscess drainage] prior to a diagnosis of oesophageal involvement.

Table 2. Characteristics of oesophageal Crohn's disease.

Characteristic	Value [*n* = 40]
Age [±SD, range] at diagnosis [years]	25 [13.3, 10–71]
Course of disease	
Oesophageal disease at diagnosis	26 [65%]
Oesophageal disease at follow-up	14 [35%]
Symptoms	
Dysphagia/odynophagia	19 [47.5%]
Heartburn	8 [20%]
Vomiting	3 [7.5%]
Chest pain	8 [20%]
Weight loss	8 [20%]
Asymptomatic—incidental finding at endoscopy	13 [32.5%]
Location	
Proximal	6 [15%]
Mid	9 [22.5%]
Distal	15 [37.5%]
Entire oesophagus	10 [25%]
Endoscopic findings	
Erosions or small ulcers	31 [77.5%]
Deep ulceration	7 [17.5%]
Patchy erythema	6 [15%]
Multiple focal erythematous spots	6 [15%]
Stricture	5 [12.5%]
Fistula	1 [2.5%]
Oesophageal histology	
Presence of granulomas	8 [20%]
Acute and chronic inflammation	17 [42.5%]
Chronic inflammation	12 [30%]
Acute inflammation	2 [5%]
IBD disease activity at oesophageal CD diagnosis	
Clinically active	33 [84.6%]
Endoscopically activity	35 [89.7%]
CT or MR enterography evidence of disease	21 [53.8%]
Treatment after diagnosis of oesophageal CD	
Proton pump inhibitor	37 [92.5%]
5-Aminosalicylic acid	16 [40%]
Systemic corticosteroids	21 [52.5%]
Anti-TNF	23 [57.5%]
Thiopurines	19 [47.5%]
Enteral nutrition	6 [15%]
Endoscopic dilatation	3 [7.5%]

Abbreviations: CD, Crohn's disease; IBD, inflammatory bowel disease; TNF, tumour necrosis factor; CT, computed tomography; MR, magnetic resonance.

3.2. Oesophageal CD diagnosis

Oesophageal disease characteristics are summarized in Table 2. Mean IBD duration until oesophageal disease diagnosis was 2.9 [±5.7, 0.0–27.9] years, with a mean age at diagnosis of 25 [±13.3, 10–71] years. Oesophageal involvement was established at CD diagnosis in 26 patients [65%] and during follow-up in 14 [35%]. Most patients had at least one additional test to exclude more common diagnoses [*n* = 35, 87.5%]: contrast oesophageal examination in 12 patients [30%], interferon gamma release assay [IGRA] in 27 [67.5%], tuberculin skin test in 18 [45%], oesophageal brushing for

Candida species in 11 [27.5%], an angiotensin converting enzyme test in five [12.5%], antibodies against human immunodeficiency virus [HIV] in 29 [72.5%], mycological infection staining on biopsy in 19 [47.5%], Ziehl–Nielsen stain in 11 [27.5%], polymerase chain reaction for *Mycobacterium tuberculosis* in four [10%], chest computed tomography in 12 [30%], chest X-ray in 28 [70%], oesophageal manometry in five [12.5%] and 24-h oesophageal pH test in five [12.5%]. Laboratory testing was abnormal in most of the patients at oesophageal disease diagnosis, with elevated C-reactive protein in 23 patients (mean 2.9 [±1.9, 1.0–7.0] mg/dL) and elevated erythrocyte sedimentation rate in 24 (mean 44 [±18.4, 26.0–94.0] mm/h). Sixteen patients [40%] had anaemia (mean haemoglobin value 9.8 [±2.3, 6.0–12.0] g/dL).

The most common symptom was dysphagia or odynophagia in 19 patients [47.5%]. Thirteen patients [32.5%] were asymptomatic at oesophageal disease diagnosis. As mentioned before, oesophageal CD was diagnosed during follow-up in 14 patients. Upper GI endoscopy was performed in these patients due to: dysphagia and/or odynophagia in six, weight loss in two, heartburn in one, iron deficiency anaemia in two, and reassessment of pre-existing upper GI CD in two and in a paediatric patient with active disease.

Distal oesophagus was the most common site of involvement, either alone [*n* = 15, 37.5%] or as part of involvement of the entire oesophagus [*n* = 10, 25%]. There were several endoscopic findings, but erosions and small ulcers were more frequently seen [*n* = 31, 77.5%]. Interestingly, one patient presented with an oesophageal fistula. Representative pictures of endoscopic findings are shown in Figure 1.

On histology, 17 patients [42.5%] had acute and chronic inflammation while 12 [30%] were found to have chronic inflammation with predominantly lymphocytes and plasma cells. Non-caseating granulomas were less frequently seen [*n* = 8, 20%].

3.3. Oesophageal disease treatment and outcomes

Thirty-four patients [85%] had an inflammatory phenotype of oesophageal CD and were treated with a variety of medications [Table 2]. Treatment was decided not only upon oesophageal CD activity but also on extra-oesophageal involvement. Most patients were treated with more than one drug [*n* = 33, 82.4%]. PPIs (*n* = 37, 92.5%] were administered in the majority of patients, but only three were treated with a PPI as monotherapy. Three patients underwent endoscopic dilatation for symptomatic strictures but none for CD-related oesophageal surgery. CD was active either clinically and/or endoscopically in the majority of patients at oesophageal involvement diagnosis [>80%].

Interestingly, oesophageal disease diagnosed during CD follow-up [14/40] resulted in treatment modifications in 9/14 patients, excluding PPI use, six of them also with extra-oesophageal clinical activity: five started systemic corticosteroids, two topical steroids [fluticasone], one anti-TNF and one methotrexate. Thirty-three patients [82.5%] were successfully treated with first-line therapy

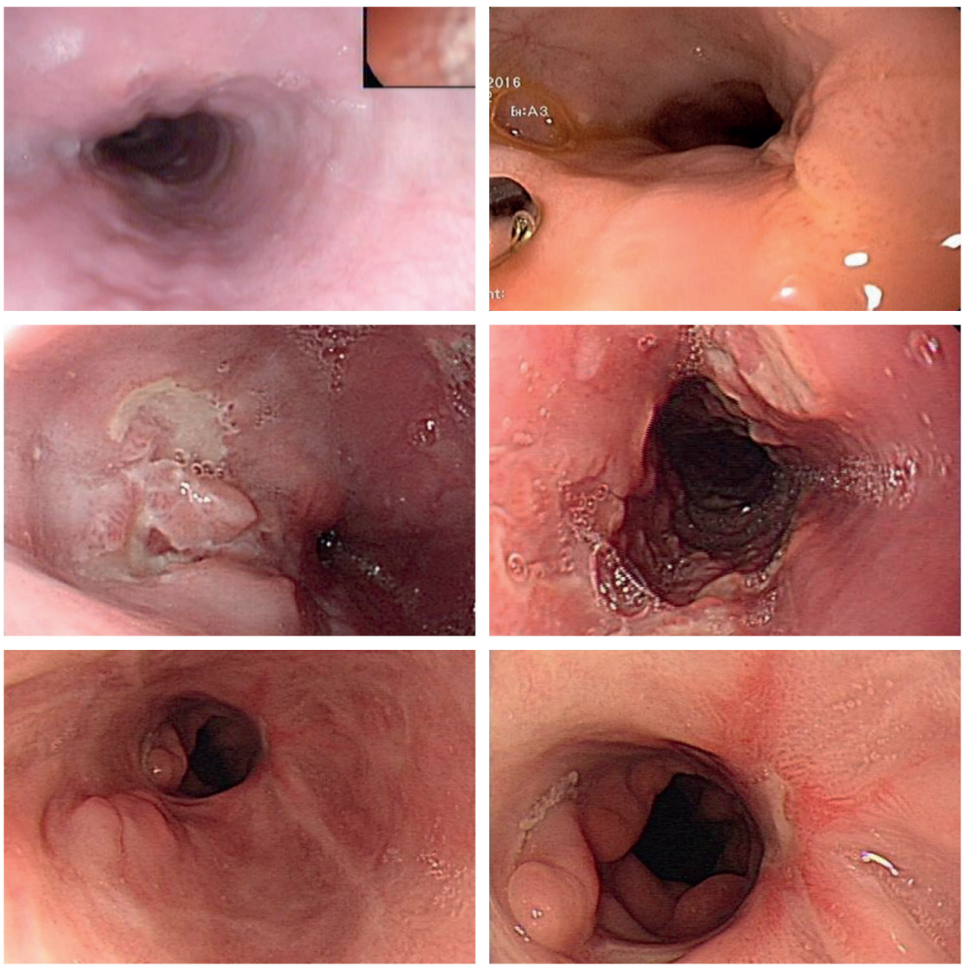

Figure 1. Endoscopic findings: A, focal erythematous spots; B, erosions; C and D, deep ulcerations; E and F, stenosis and pseudopolyps.

and complete resolution of symptoms occurred after a mean time of 7 [±5.6, 1.0–18.0] months. Three patients required second-line therapy for sustained clinical activity [two endoscopic interventions and one initiation of thiopurines]. Three patients had symptomatic recurrence after initial clinical response, all beyond the first year after diagnosis, and regained remission after starting systemic corticosteroids, anti-TNF and undergoing oesophageal dilatation, respectively. On last follow-up, one patient had not achieved remission after multiple therapies and active extra-oesophageal disease. Follow-up endoscopy was performed in 29 patients and 89.7% achieved mucosal healing. Of the two patients with isolated oesophageal disease, one was treated only with PPIs with complete symptomatic resolution while the other required combined endoscopic and medical therapy initially with PPIs and systemic corticosteroids and subsequently administration of thiopurine and anti-TNF; both had achieved mucosal healing at last follow-up.

4. Discussion

This is a retrospective, international study reporting a series of CD patients with oesophageal involvement. Although this study was not designed to assess the prevalence of oesophageal CD, we can infer that the onset of this presentation may be under-recognized due to the infrequent performance of upper GI endoscopy in asymptomatic individuals with CD, especially adults.

Diagnostic work up includes a combination of oesophageal-specific symptoms, a history of extra-oesophageal CD, and endoscopic and histological features that are supportive but not specific for CD. Almost one-third of the patients in our series were asymptomatic while the rest complained of non-specific symptoms such as dysphagia/odynophagia, heartburn, vomiting, chest pain and weight loss, resembling gastro-oesophageal reflux disease [GERD], similar to previous reports.[3,5,7] Most patients had at least one additional test to exclude more common diagnoses [87.5%]. CD of the oesophagus is not difficult to diagnose in cases in which other segments of the digestive tract are simultaneously involved or in patients with a prior history of CD, but isolated oesophageal disease requires exclusion of more common diseases, so we suggest that in the absence of a previous diagnosis of CD, an exclusion of GERD [based on pH impedance study], infectious oesophagitis [based on specific stains at least for *Candida* and *Cytomegalovirus*] and granulomatous diseases such as tuberculosis and sarcoidosis [based on imaging and laboratory tests] should be made.

Endoscopic features are not pathognomonic. Wang *et al.* proposed that oesophageal CD progresses through three phases. The initial phase involves inflammation, oedema, erosions and linear ulcers without significant symptoms, then there is a progression to stenotic lesions with mucosal bridges and finally patients present with progressive dysphagia, odynophagia, vomiting and weight loss, and severe complications due to fibrotic strictures and fistulae.[11] Distal superficial ulcers, erosions and/or erythema were common in our cohort as described in other reports.[3,5,7] However, stenotic lesions necessitating interventions were uncommon and only one patient developed a fistula.

Histological features are also not always compatible with CD. In our cohort, chronic inflammation was the most common presentation; eight patients [20%] had non-caseating granulomas in the setting of chronic inflammation, a higher rate than the one reported in the literature [7–9%], perhaps due to the inclusion of paediatric patients as granuloma formation is more often seen in younger patients, and mainly in severe, active penetrating disease.[12,13]

CD limited to the oesophagus is rare but has been described in case reports.[6,11,14,15] In our cohort there were only two cases. Oesophageal involvement was established at CD diagnosis in two-thirds of the patients [65%] and during follow-up in one-third [35%]. Almost half of the patients demonstrated perianal disease, which is also in line with previous reports.[16] One-third of the cohort had extra-intestinal manifestations, slightly less than global data for CD, which can also be justified by the inclusion of paediatric patients.[17]

There are limited data on the most suitable management of oesophageal CD due its rarity and the frequent coexistence of distal disease, which leads to the use of standardized therapeutic protocols. ECCO guidelines suggest treating mild oesophageal CD with PPIs only and more severe or refractory disease with systemic corticosteroids or an anti-TNF-based strategy.[10] PPI-induced acid suppression is thought to play a facilitating role in oesophageal mucosal healing, similar to what happens with ulcers resulting from endoscopic submucosal dissection. De Felice *et al.* suggested treating oesophageal CD based on disease behaviour.[3] This cohort confirms this strategy with the vast majority of patients being treated with a PPI, and fewer patients with more complicated or persistently active disease at oesophageal involvement diagnosis requiring step-up therapies. Oesophageal disease diagnosed during follow-up resulted in medical treatment modifications in 64.3% of patients, two-thirds of whom [66.7%] also had extra-oesophageal clinical activity.

The limitation of the CONFER methodology should be acknowledged, as it relies on voluntary submission of cases by physicians responding to ECCO calls, which could introduce geographical and other selection biases. However, we believe this caveat is offset by the benefits of this methodology for identifying and reporting larger case series of rare events, which are otherwise seldom reported in a single case-report format. The sample size is relatively small and thus no risk factors or predictors can be investigated. Follow-up endoscopy was not available in all patients.

In conclusion, oesophageal involvement can be detected either at CD diagnosis or during follow-up, manifesting as the only site of CD location in rare cases. Characteristics are similar to those of other sites of involvement and diagnosis can be challenging and performed even with CD in remission. Optimal treatment is conservative but not consensual, depending also on extra-oesophageal sites of involvement, with PPIs administered in the majority of patients and treatment modifications occurring frequently, when diagnosed at a later phase. Properly designed, ideally prospective studies are needed to identify more reliable diagnostic criteria and phenotypes of oesophageal CD that predict response to specific medical therapies. However, until further data are available, this needs to be a case-by-case decision.

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Conflict of Interest

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Author Contributions

R.V.R. and K.K. conceived the study, analysed and interpreted the data and drafted the manuscript; M.S., K.K., C.J.W., J.W., S.V., N.T., P.E., E.S., M.C., D.B., A.M.O., M.F., A.B.G.S. and L.R. contributed the cases and critically revised the manuscript.

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