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ORIGINAL ARTICLE

Frequent Occurrence of Perianal Disease and Granuloma Formation in Patients with Crohn's Disease and Coexistent Orofacial Granulomatosis

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Abstract

Background Orofacial granulomatosis (OFG) is an inflammatory disorder of the perioral region and oral cavity. Crohn's disease (CD) in conjunction with OFG (CD-OFG), has been suggested to constitute a phenotype of CD with distinct features at diagnosis.

Aims The aim of this project was to investigate whether the distinct phenotypic features of CD-OFG persist in the years following the initial diagnosis of CD.

Methods Clinical data were extracted from medical records covering the first 5 years post-diagnosis for a cohort of patients with CD-OFG, and were compared to those of references with CD without OFG.

Results The clinical characteristics of our cohort of patients with CD-OFG ($N=25$) were evaluated in comparison to references with CD without OFG (ratio 1:2). Five years post-diagnosis, more patients with CD-OFG had a phenotype with perianal disease (cumulative incidence: 16/25, 64% vs 13/50, 26%, $P=0.002$) and intestinal granulomas (cumulative incidence: 22/25, 88% vs 24/50, 48%, $P=0.0009$) than patients in the CD reference group. The patients with CD-OFG were also more likely to have undergone perianal surgery (12/25, 48% vs 4/50, 8%, $P=0.0002$). At the end of the observation period, more of the patients with CD-OFG were receiving combination therapy, i.e., immunomodulators and tumor necrosis factor antagonists, than those in the CD reference group (9/25, 36% vs 5/50, 10%, $P=0.01$).

Conclusion The results support the notion that CD in conjunction with OFG represents a specific phenotype of CD that is characterized by frequent perianal disease, pronounced intestinal granuloma formation and a need for extensive therapy.

Keywords Crohn's disease · Orofacial granulomatosis · Perianal disease · Granuloma formation · Phenotype

Introduction

Crohn's disease (CD) comprises a spectrum of phenotypes [1]. Furthermore, extraintestinal manifestations commonly accompany CD [2]. One of these manifestations is orofacial granulomatosis (OFG), which is a rare chronic inflammatory disorder of the perioral region and oral cavity, alternatively termed 'oral Crohn's disease' when it appears in conjunction with CD [3].

OFG is characterized by perioral manifestations, such as relapsing or persistent lip swelling, erythema of the skin and angular cheilitis, while the oral mucosa may display cobblestone phenomena, tag formation, hyperplastic gingiva and linear ulcers [4]. OFG may appear as a separate disorder or in conjunction with a systemic disease such as sarcoidosis [5] or CD [6]. The coexistence of OFG with CD is most commonly seen in children and young adults [7], although it occurs in adults of all ages [6, 8]. OFG may precede, occur concomitantly with or develop after the onset of the gastrointestinal manifestations of CD [6, 7]. Approximately 40–70% of children and adolescents with OFG have, or will develop CD over time [7, 9, 10], while in a recent report from the UK it was estimated that 1% of patients with CD also suffer from OFG [11], an estimation that is in line with the figure for Sweden of less than 5% (our unpublished observation). In patients with CD and concomitant OFG, the two conditions frequently show different long-term disease

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courses in which the gastrointestinal inflammation usually persists [12], whereas the orofacial inflammation tends to diminish over time [13].

Both CD and OFG are characterized by mucosal granuloma formation. Oral mucosal granulomas occur in 70–100% of patients with OFG, regardless of whether they also have CD [14, 15]. Although intestinal granulomas are considered a hallmark of CD, they can only be found in 40–50% of patients with childhood-onset CD at the time of diagnosis [16, 17], and in only approximately 25% of patients with adult-onset CD [18]. Our research group has previously reported that at the time of CD diagnosis, patients with childhood-onset CD with concomitant OFG (CD-OFG) have a higher prevalence of perianal disease (48% vs 18%) [19], and display intestinal granulomas more than twice as often as patients with CD but without OFG (81% vs 38%) [19]. High prevalence rates of perianal disease have also been reported for patients with CD-OFG in the UK [6], Ireland [20] and France [21], as well as in a recently published multicenter study [8].

The above findings suggest that CD-OFG represents a distinct phenotype of CD [19, 20]. However, studies reporting on the phenotype of CD-OFG have mainly focused on patients who were recently diagnosed with CD [15, 19]. The aim of the present study was to analyze retrospectively the clinical course over the first 5 years following CD diagnosis of children who suffer from CD and concomitant OFG.

Methods

Patients

In this retrospective, descriptive cohort study, all patients with CD and concomitant OFG (CD-OFG) who had a disease duration of CD of at least 5 years and who were diagnosed with CD between 2000 and 2014 were identified at two tertiary care centers of pediatric gastroenterology in Sweden: The Queen Silvia Children's Hospital, Sahlgrenska University Hospital in Gothenburg; and the Astrid Lindgren Children's Hospital, Karolinska University Hospital in Stockholm. All eligible patients agreed to participate in the study. In Sweden, all pediatric patients with CD receive care within the public healthcare system, and a tertiary care center also serves as the county hospital for childhood-onset inflammatory bowel disease (IBD) within its catchment area. This allows the identification of all cases with CD within the catchment areas of these two tertiary care centers and the patients cover the entire clinical spectrum of childhood-onset CD. The presenting clinical picture at diagnosis of CD has previously been reported for 21 of the patients with CD-OFG participating in this study [19].

The reference group comprised randomly selected patients who were diagnosed with CD but not OFG (CD-Ref) in a 2:1 ratio. These patients also received care at either the Queen Silvia Children's Hospital or Astrid Lindgren Children's Hospital. The patients in the CD-Ref group were diagnosed between 2000 and 2013, and were matched according to sex, age at diagnosis (±3 years), and year of diagnosis (±5 years).

CD was diagnosed by pediatric gastroenterologists according to the Porto criteria [22], based on clinical symptoms and findings from endoscopy, histopathology and radiology.

OFG was diagnosed based on established clinical criteria, including lip or facial swelling, mucosal tags, cobblestone phenomenon, stag horning or hyperplastic erythematous gingivae [4], by experienced oral medicine specialists at one of the two tertiary centers for odontology: the Clinic of Oral Medicine, Public Dental Service in Gothenburg; or the Department of Pediatric Dentistry, Eastman Institute, Public Dental Service in Stockholm. To lend further support to the OFG diagnosis, though this is not mandatory, oral biopsies were taken from nearly 2/3 of the patients, all showing a characteristic histologic picture of OFG [4] and in most of the biopsies non-caseating granulomas were found.

Diagnostic work-up and clinical follow-up of the patients with CD were performed according to the Swedish national guidelines, which are based on the Porto criteria [22, 23] and the ECCO-ESPGHAN guidelines (revised consecutively) [24–26], respectively. Thus, the work-up included gastroscopy, colonoscopy and small bowel imaging.

Review of Patients' Charts

Clinical data for the patients in the two diagnostic groups were extracted from medical records covering the time interval from diagnosis of CD and 5 years (±3 months) thereafter. The following variables were registered: clinical symptoms, endoscopic and microscopic disease extension, presence of granulomas in intestinal biopsies, and pharmacologic and surgical treatments. The overall picture of CD disease extension and behavior over the first 5 years from the time of diagnosis was described for each patient using the Paris classification [27], which is the pediatric version of the Montreal classification [28]. The presence of perianal disease was established according to the Paris classification and included fistulas, anal canal ulcers and/or abscesses. Thus, simple fissures and isolated skin tags were not designated as perianal disease.

Statistical Analyses

Univariate statistical analyses were performed with the GraphPad Prism ver. 8 software (GraphPad Software Inc.,

San Diego, CA). Differences in binary data were tested with Fisher's exact test, while numeric data were tested with the Mann–Whitney *U*-test. A *P*-value < 0.05 was considered statistically significant.

Ethical Considerations

This study was performed in line with the principles of the Declaration of Helsinki. Written informed consent was obtained from all study participants and/or their parents. The study was approved by the Swedish Ethical Review Authority (Dnr. 2020-00007). All eligible patients were willing to participate in the study.

Results

Demographic and Basic Clinical Data

In this retrospective study, medical charts from 25 patients with CD-OFG, covering the time from diagnosis of CD until 5 years post-diagnosis, were reviewed. These patients represent all the eligible cases at our two centers, all of whom agreed to participate in the study. The patients were diagnosed with CD at a median age of 12 years (range 8–23 years), whereas OFG was diagnosed over a period of time that ranged from 12 months before to 49 months after the CD diagnosis. In most of the patients (18/25, 72%), CD and OFG were diagnosed within a relatively limited time interval (± 12 months). The patients with CD-OFG had a 4:1 ratio of males to females. A reference group of 50 patients who were suffering from CD without OFG (CD-Ref) was randomly selected from patients who received care at the same pediatric gastroenterology centers, matched for age, sex and year of diagnosis, the latter in order to control for any changes in clinical management during the period. The patients in the reference group had a median age at CD diagnosis of 12 years (range 8–23 years), with 23/25 being diagnosed within the pediatric age interval (< 18 years). In both groups, CD was diagnosed, followed and treated according to national guidelines, based on the Porto criteria [22, 23] and the ECCO-ESPGHAN guidelines [24–26]. There was no significant difference between the two groups regarding the number of endoscopic and radiologic examinations undergone during the 5-year period following the CD diagnosis (Table 1). At the end of the 5-year observation period, 12/25 (48%) of the patients in the CD-OFG had reached 18 years of age, with an overall median age of 17 years (range 13–28 years).

Extension of Inflammation in the Gastrointestinal Tract

No significant differences in intestinal disease location were observed between the CD-OFG and CD-Ref groups 5 years after diagnosis (Fig. 1). The most common inflammatory pattern, found in about 30% of the patients in each diagnostic group, was the "pan-enteric" phenotype defined by the Paris classification (L3 + L4a,b, L3 + L4a and L3 + L4b) [27]. The histologic disease extension was generally in accordance with the endoscopic disease localization.

Perianal Disease

More than half of the patients in the CD-OFG group had perianal disease at the time of diagnosis (14/25, 56%)

Table 1 Endoscopic and/or imaging procedures performed during the first 5 years (including diagnostic work-up)

Section of the gastrointestinal tract	Numbers and % of patients examined			
	Year 1[a]		Years 2–5[b]	
	CD-OFG	CD-Ref	CD-OFG	CD-Ref
Upper gastrointestinal tract [c]	23/25, 92	48/49, 98[d]	15/24, 62	36/50, 72
Small bowel	23/25, 92	44/50, 88	11/24, 46	26/50, 52
Distal ileum	24/25, 96	48/50, 96	17/24, 71	39/48, 81[e]
Colon/rectum	25/25, 100	48/49, 98[d]	17/24, 71	36/49, 73[f]

[a]The numbers of patients who were examined in the different sections of the gastrointestinal tract with an endoscopic and/or imaging procedure at least once during the first year of Crohn's disease, including the diagnostic procedure

[b]The percentages of patients who were examined in the different sections of the gastrointestinal tract with an endoscopic and/or imaging procedure at least once during the 2–5 years following diagnosis

[c]Esophagus, ventricle and duodenum

[d]One patient had an ileocecal resection at debut and was examined during the surgical procedure, but did not undergo endoscopy

[e]Two patients who had an ileocecal resection during the first year of disease are not accounted for here

[f]One patient who had a colectomy during the first year of disease is not accounted for here

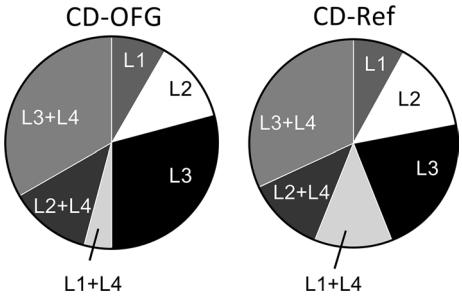

Fig. 1 Endoscopic disease extensions in the gastrointestinal tract according to the Paris classification, registered during the 5-year period after diagnosis of Crohn's disease. Patients with Crohn's disease and concomitant orofacial granulomatosis (CD-OFG, $N=25$) compared with patients with Crohn's disease only (CD-Ref, $N=50$). Paris classification: L1, distal one-third of the ileum with or without limited cecal disease; L2, colonic disease; L3, ileo-colonic disease; and L4, comprising L4a (upper gastrointestinal tract disease above the ligament of Treitz) and L4b (upper gastrointestinal tract disease below the ligament of Treitz and above the distal one-third of the ileum). Due to the low number of patients showing inflammation in the small bowel below the ligament of Treitz and above the distal one-third of the ileum (L4b), we have chosen to report L4a and L4b together as L4

(Fig. 2), while this was true for only 10/50 (20%) of the patients in the CD-Ref group, representing a highly significant difference ($P=0.003$). During the subsequent 5 years, an additional two patients in the CD-OFG group and three patients in the CD-Ref group developed perianal disease. Thus, the majority of the patients with perianal disease had this manifestation already at the time of diagnosis and the difference in 5-year cumulative incidence of perianal disease between the CD-OFG and CD-Ref groups remained highly significant (16/25, 64% vs 13/50, 26%, $P=0.002$).

Disease Behavior

Most of the patients in the two groups had an inflammatory, non-stricturing and non-penetrating disease behavior at the end of the 5-year observation period, with no significant differences between the CD-OFG (18/25, 72%) and CD-Ref (41/50, 82%) groups. During the observation period, four patients in the CD-OFG group developed a stricturing behavior and an additional two patients acquired a penetrating behavior, while one patient developed both stricturing and penetrating disease. In the CD-Ref group, nine patients developed a stricturing disease behavior, two of whom also showed a penetrating disease behavior. Thus, only a minority of the patients in each group showed altered disease behavior, with no significant difference between the groups.

Granuloma Formation

The percentages of patients with granuloma formation from esophagus to rectum at diagnosis and over the first 5 years in the two diagnostic groups are shown in Fig. 3. Consistent with our previous report [19] and the findings of other researchers [6, 20], a high percentage (18/24, 75%)

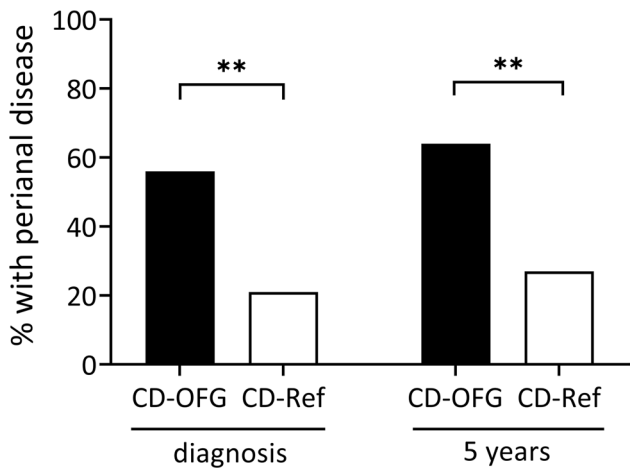

Fig. 2 Prevalence rates of perianal disease in patients with Crohn's disease with or without concomitant orofacial granulomatosis. Patients with Crohn's disease and concomitant orofacial granulomatosis (CD-OFG, $N=25$; black bar) were compared with patients suffering from Crohn's disease only (CD-Ref, $N=50$; white bar) regarding the prevalence of perianal disease at the time of diagnosis, as well as the cumulative incidence of perianal disease up to 5 years after diagnosis. $^{**}P<0.01$ using Fisher's exact test to compare the matched diagnostic groups

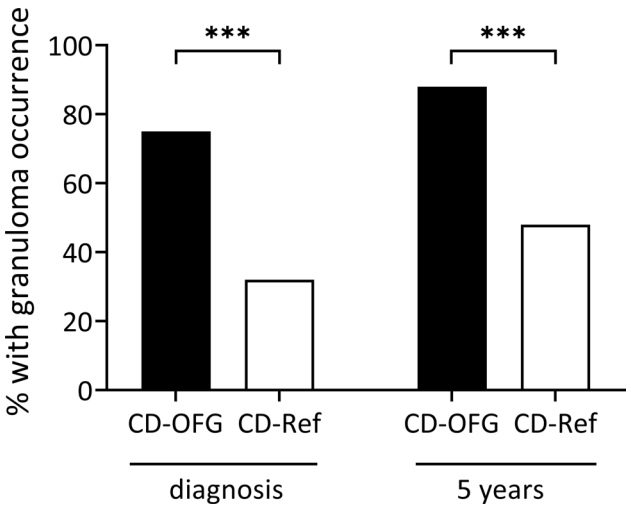

Fig. 3 Frequency of granulomas in intestinal biopsies of patients with Crohn's disease with or without concomitant orofacial granulomatosis. Patients with Crohn's disease and concomitant orofacial granulomatosis (CD-OFG, $N=25$; black bar) were compared with patients suffering from Crohn's disease only (CD-Ref, $N=50$; white bar) regarding the prevalence of granuloma occurrence at the time of diagnosis, as well as the cumulative incidence of granuloma occurrence up to 5 years from diagnosis. $^{***}P<0.001$ using Fisher's exact test to compare the matched diagnostic groups

of patients in the CD-OFG group displayed granuloma in at least one of the biopsies acquired from different sites along the gastrointestinal tract (from esophagus to rectum) at the time of diagnosis. This was significantly higher than the corresponding percentage (16/50, 32%) for the CD-Ref group ($P=0.001$). During the 5-year observation period, granuloma formation was identified in an additional four patients in the CD-OFG group and in eight patients in the CD-Ref group, giving a cumulative incidence at 5 years from CD diagnosis of 22/25 (88%) in the CD-OFG group versus 24/50 (48%) in the CD-Ref group ($P=0.0009$).

The locations of the granulomas did not differ between the two diagnostic groups; in 45/46 (98%) of the patients, granuloma formation was found in the lower gastrointestinal tract (terminal ileum and/or colon). Granulomas in the upper gastrointestinal tract (esophagus, ventricle and duodenum) were detected in 5/21 (24%) of the patients in the CD-OFG group and 8/23 (35%) of the patients in the CD-Ref group ($P=0.7$). A single patient (in the CD-Ref group) had granulomas located exclusively in the upper gastrointestinal tract.

Pharmacologic Treatments

We registered the medications administered to the patients during the first 5 years following diagnosis (Table 2). Immunomodulatory agents (i.e., azathioprine or methotrexate) were administered for some period of time during the 5 years to similar proportions of patients in the two groups (23/25, 92% vs 42/50, 84%, $P=0.5$), as were tumor necrosis factor (TNF) antagonists (i.e., infliximab and adalimumab) (15/25, 60% vs 25/50, 50%, $P=0.5$). However, at the end of the 5-year observation period, immunomodulators were administered significantly more often to the patients in the CD-OFG group than to those in the CD-Ref group (16/25, 64% vs 18/50, 36%, $P=0.03$) (Table 2). Furthermore, at 5 years post-diagnosis, the patients in the CD-OFG group were significantly more often in receipt of combination therapy, i.e., immunomodulators given together with TNF antagonists, than those in the CD-Ref group (9/25, 36% vs 5/50, 10%; $P=0.01$).

Systemic corticosteroids were used less-frequently as induction therapy upon CD diagnosis in the CD-OFG group (11/25, 44%) than in the CD-Ref group (35/50, 70%) ($P=0.04$), while exclusive enteral nutrition therapy tended to be used more often in the CD-OFG group (7/25, 28% vs 6/50, 12%, $P=0.1$). After the induction treatment period, systemic corticosteroids and antibiotics, as well as local treatment with rectal corticosteroids were used intermittently in cases of disease exacerbation. Maintenance therapy with 5-aminosalicylic acid (5-ASA) was prescribed at similar frequencies to patients in the CD-OFG and CD-Ref groups (17/25, 68% vs 27/50, 54%, $P=0.3$). One patient (in the CD-Ref group) was treated with granulocyte apheresis

Table 2 Pharmacologic therapies in the two diagnostic groups during the first 5 years following CD diagnosis

Treatment during the 5-year period	Pharmacologic therapy (number and % of patients)											
	Immunomodulators[a]			Anti-TNF[b]			Combination therapy[c]			5-ASA[d]		
	CD-OFG	CD-Ref	*P*-value	CD-OFG	CD-Ref	*P*-value	CD-OFG	CD-Ref	*P*-value	CD-OFG	CD-Ref	*P*-value
Ever treated	23/25, 92	42/50, 84	0.5	15/25, 60	25/50, 50	0.5				17/25, 68	27/50, 54	0.3
Start at 0–12 months	17/25, 68	32/50, 64	0.8	6/25, 24	7/50, 14	0.3				14/25, 56	24/50, 48	0.6
Treatment at 5 years	16/25, 64	18/50, 36	**0.03**	14/25, 56	20/50, 40	0.2	9/25, 36	5/50, 10	**0.01**	10/25, 40	16/50, 32	0.6

[a]Azathioprine or methotrexate

[b]Anti-tumor necrosis factor agents (infliximab or adalimumab)

[c]Immunomodulators administered together with anti-tumor necrosis factor agents

[d]5-Aminosalicylic acid

and subsequently also received vedolizumab (anti-α4β7 integrin monoclonal antibodies).

Surgical Treatment

Half of the patients with CD-OFG (13/25, 52%) underwent surgery, as compared with 13/50 (26%) of the patients in the CD-Ref group during the 5-year period following diagnosis ($P=0.04$). This difference is attributable to more anorectal surgical procedures, including fistulotomy, seton placement, dilatations and perianal abscess incision, being performed in the CD-OFG group. Twelve patients with CD-OFG (12/25, 48%) underwent such procedures, as compared to only four patients (4/50, 8%) in the CD-Ref group ($P=0.0002$). Furthermore, among the patients with perianal disease in the CD-OFG group, 12/16 (75%) had undergone perianal surgery, as compared with 4/13 (31%) of the patients with perianal disease in the CD-Ref group ($P=0.03$).

Other surgical procedures were distributed equally between the patients in the CD-OFG group and the CD-Ref group as follows: ileostomies due to severe perianal disease ($N=2$ vs $N=1$); ileocecal resections ($N=0$ vs $N=2$); colectomies ($N=0$ *vs* $N=3$); colon resections ($N=1$ vs $N=1$); and gastrostomies ($N=0$ vs $N=2$). The median time from diagnosis to the first surgical intervention was 12 months (range 0–48 months) in the CD-OFG group and 13 months (0–57 months) in the CD-Ref group ($P=0.2$).

The Clinical Course of Orofacial Granulomatosis and the Presence of Other Extraintestinal Manifestations

Although primarily aimed at controlling the CD, the pharmacologic therapies given to the patients (see above) also influenced the orofacial symptoms characteristic of OFG. However, 17/25 (68%) of the patients had orofacial exacerbations that required additional treatment at some point during the observation period. Topical corticosteroids (gel and/or injections) were used most frequently to treat the exacerbations, although some patients also received topical and/or systemic antibiotics or local treatment with tacrolimus. At the end of the observation period, 9/25 (38%) of the patients still reported symptoms from the lips and/or oral cavity, evidencing ongoing OFG.

The percentages of patients who developed extraintestinal manifestations other than OFG during the observation period did not differ between the two diagnostic groups. The most-frequent manifestations registered were from the skin (pyoderma gangrenosum, $N=2$; erythema nodosum, $N=1$; and psoriasis, $N=3$), the joints (arthritis, $N=6$; and sacroileitis, $N=1$), and the liver (autoimmune hepatitis, $N=1$; and primary sclerosing cholangitis, $N=1$).

Discussion

CD with concurrent OFG may represent a distinct phenotype of CD, mainly based on the clinical picture, with perianal disease and intestinal granulomas being frequently present [19, 20]. To investigate whether these distinctive features persist during the years post-diagnosis, we retrospectively followed the clinical course of our cohort of 25 patients with CD-OFG and, for comparison, 50 randomly selected age-matched reference patients with CD without concomitant OFG (CD-Ref). To the best of our knowledge, this is the first systematic study focusing on the clinical picture of CD over time in patients with childhood-onset CD with concurrent OFG.

The high frequency of perianal disease at the time of diagnosis in children with CD-OFG, as we have previously reported [19], persisted after 5 years. Thus, perianal disease was 2.5-times more prevalent in patients with CD-OFG than in the CD-Ref group [16/25 (64%) versus 13/50 (26%)], with the latter percentage being similar to those reported previously in follow-up studies of pediatric CD cohorts [29, 30]. A high prevalence of perianal disease in predominantly adult patients with CD and concomitant OFG was also reported in a recently published multicenter study [8]. Notably, the high prevalence of perianal disease in the CD-OFG group was reflected in the numerous perianal surgical procedures in this diagnostic group, in that about half of the patients with CD-OFG underwent such procedures, as compared to only one-tenth of the patients in the CD-Ref group, with the latter value being in line with that reported in a recent population-based Swedish study [31]. However, we also noted that more than twice as many of the patients with perianal disease in the CD-OFG group underwent perianal surgery than the corresponding patients in the CD-Ref group, which may indicate that patients with CD-OFG have a more-intractable perianal disease that calls for more active surgical treatment.

In general, we found that the patterns of pharmacologic treatment of CD were similar over time in the two diagnostic groups. However, at the end of the 5-year observation period, we found that immunomodulators and combination therapy, i.e., immunomodulators plus a TNF antagonist, were administered significantly more frequently to the patients in the CD-OFG group. This may reflect the preferred strategy for treating active perianal fistulating disease with anti-TNF therapy, as recommended in the consensus guidelines of ECCO/ESPHAN [25]. Alternatively, it may signify a more-complex disease course in the CD-OFG group. When using a step-up strategy for induction treatment in patients with childhood-onset CD, either exclusive enteral nutrition therapy or systemic corticosteroids are usually used as first-line therapy, as these alternatives are considered to have equivalent anti-inflammatory

effects. Notably, patients with CD-OFG tended to receive more often exclusive enteral nutrition, whereas those in the CD-Ref group were treated more frequently with systemic corticosteroids. This may reflect that exclusive enteral nutrition with an amino acid-based formula has been reported to be clinically effective for both CD [25] and OFG [32, 33].

In patients with CD-OFG, a key finding at the time of diagnosis is a high prevalence of intestinal granulomas (from esophagus to rectum) [19, 20]. In this study, we show that granuloma formation as a phenotypic sign is still apparent at least 5 years after diagnosis, with a cumulative incidence of 22/25 (88%) of the patients in the CD-OFG group. The corresponding percentage for the CD-Ref group was 24/50 (48%), which is in line with the percentages reported for other cohorts [16, 17]. Although the follow-up time was set at 5 years, we observed that of the three patients in the CD-OFG group who had not yet developed intestinal granulomas 5 years after diagnosis, two had granulomas at the endoscopic evaluations carried out at 7.5 and 8.0 years, respectively, after diagnosis. We conclude that the almost ubiquitous presence of intestinal granulomas is a distinctive feature of CD in combination with OFG.

Granulomas are aggregates of activated macrophages, which may fuse to form multinucleated giant cells driven by the local Th1 cytokine milieu, which includes TNF and interferon-gamma as the major drivers of granuloma formation [34, 35]. In contrast, interleukin (IL)-10 counteracts granuloma formation in vitro [36]. Mutations in the *NOD2* gene are associated with defective production of IL-10 [37], and it is noteworthy that these mutations appear more frequently in patients with CD than in the general population [38–40]. In a small-scale study, we found *NOD2* mutations to be even more prevalent in Swedish pediatric CD-OFG patients (17%) [9] than in the general pediatric CD population (4.3%) [41]. Therefore, the CD-OFG phenotype may be driven by reduced IL-10 production due to *NOD2* mutations, leading to exaggerated Th1 responses and granuloma formation.

The immunological background to perianal fistulation has not been established. It is possible to speculate that fistula develop due to deficient healing after tissue break-down. Tissue matrix degradation is carried out by metalloprotease enzymes, the production and activation of which are promoted by TNF and Th1-mediated inflammation [42], and counteracted by IL-10 [42, 43]. Thus, increased fistula formation in patients with CD in conjunction with OFG may be another facet of increased Th1-driven inflammation, leading to tissue destruction and healing with fistula formation.

We did not observe any clear differences in the inflammatory extension pattern (assessed according to the Paris classification) along the gastrointestinal tract, i.e., from esophagus to rectum, between the two diagnostic groups 5 years after diagnosis. About one-third of the patients in each group had the maximum extension of inflammation, i.e., L3 + L4a,b, L3 + L4a, and L3 + L4b (Paris classification nomenclature). This is in accordance with the results of a French study, wherein 40% of the children with CD had maximum disease extension (i.e., L3 + L4 according to the Montreal classification) after a median follow-up of 7 years from diagnosis [12]. The disease behavior (assessed according to the Paris classification) was also similar between the two diagnostic groups, with 80% showing an inflammatory disease behavior 5 years after diagnosis. Our data are concordant with the results from a Scottish study of childhood-onset CD with 4 years of follow-up [44], while a report from France has shown higher prevalence rates of stricturing (44%) and penetrating disease (15%) 7 years after diagnosis of CD [12].

As this is a retrospective observational study, the treatment and follow-up given to the patients were based solely on clinical practice, in line with the current ECCO/ESPGHAN's guidelines [26], and did not follow a predetermined study protocol. In line with these guidelines, decisions regarding treatments for the patients were based on clinical parameters, such as extension of inflammation, disease behavior and presence of perianal disease, but not on the presence of granulomas in intestinal biopsies. As the two groups were matched not only for age, but also for year of diagnosis, any revisions made to the treatment protocols over time affected both groups equally. In accordance with this, we found no difference in the numbers of endoscopic and small bowel examinations between the two diagnostic groups during the first 5 years after the diagnosis of CD. Although the two tertiary care centers that contributed the patients to the present study provide coverage for about 4 million inhabitants and for approximately 40% of the Swedish population, we acknowledge that the number of patients in our CD-OFG group is low, as this comorbidity is a rare clinical entity. The results from our CD-OFG cohort in Sweden are supported by previous reports from the UK, Ireland and France showing a high prevalence of perianal disease in children with CD-OFG. Nevertheless, there is a need for a prospective and protocolized study in a larger cohort from other geographic areas, to confirm our results.

Our current observations support and extend the notion that CD in conjunction with OFG is a distinct clinical entity, the phenotype of which is characterized by a high risk of perianal disease and pronounced granuloma formation, as this is apparent not only at the time of diagnosis [19] but also persists over time post-diagnosis. Other extraintestinal manifestations have also been associated with distinctive phenotypes of inflammatory bowel disease (IBD) [2, 3]. For example, ulcerative colitis with concomitant primary sclerosing cholangitis has a unique phenotype that includes features such as extensive colitis and increased risk

of developing colorectal carcinoma [45, 46]. IBD complicated by extraintestinal manifestations in general has been reported to be associated with an IBD disease course that requires intensified therapeutic interventions [2]. If complicated disease is expected, the guidelines recommend early introduction of TNF antagonists in combination with immunomodulators [25]. Thus, the ability to forecast the course of the disease enables individualized treatment, i.e., 'precision medicine' [47].

The clinical implications of our results are that patients with CD-OFG should be carefully monitored for signs of perianal disease, and a rapid step-up strategy may be necessary for many of these patients. Distinguishing the CD-OFG phenotype requires close collaboration with oral medicine practitioners, to ensure that the sometimes subtle lesions of OFG are not overlooked.

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Declarations

Conflict of interest The authors have no conflict of interest or any financial arrangements related to the research to disclose.

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