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Genital Granulomatosis in Male and Female Patients With Crohn's Disease: Clinical Presentation and Treatment Outcomes

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Abstract

Background: Genital granulomatosis [GG] is a metastatic form of Crohn's disease [CD], characterised by granulomatous inflammation of the genital skin without contact with the gastrointestinal tract. Little is known about GG, as most publications are case reports or small series, and only sporadic in male cases.

Methods and Aims: Cases of GG were retrospectively collected through the Collaborative Network For Exceptionally Rare case reports project of the European Crohn´s and Colitis Organisation.

Results: A total of 43 patients [9 males, 34 females] were diagnosed as having GG, mostly as oedema and/or ulcers. Histological confirmation of granulomas was obtained in 70% of the cases. CD location was colonic or ileocolonic in 97% and perianal disease was documented in 57%. There was no significant difference between males and females in CD phenotype or genital lesions. GG was the first manifestation of inflammatory bowel disease [IBD] in one-third of the patients; these patients were younger at the time of GG occurrence and they all were non-smokers. GG occurred in the absence of gastrointestinal disease activity in 30% of the cases. Ten out of 11 patients [91%] responded to systemic corticosteroid treatment, 5/9 patients responded to immunomodulators, and 9/11 patients responded to anti-tumour necrosis factor alpha [TNF-α] agents.

Conclusions: GG is a rare extraintestinal manifestation of CD. It mainly occurs among women, in the setting of colonic involvement of CD, and perianal disease is often associated. Most cases are successfully managed with systemic corticosteroids or anti-TNF agents.

Key Words: Crohn's disease; genital granulomatosis; vulvar; penile; scrotal

1. Introduction

Extraintestinal manifestations of Crohn's disease [CD] have been reported in up to 35% of patients. Between 22% and 44% of patients with extraintestinal manifestations present with mucocutaneous symptoms, which may be categorised as: fissures and fistulas arising through direct extension of the gastrointestinal disease; cutaneous changes secondary to nutritional deficiencies [eg acrodermatitis enteropathica-like syndrome secondary to zinc deficiency]; and cutaneous disorders that have been associated with CD [eg pyoderma gangrenosum, erythema nodosum].[1] The most common cutaneous manifestations of CD are perianal, peristomal, and perifistular inflammatory lesions.

Parks *et al*. were the first to describe the presence of sterile, non-caseating, granulomatous lesions of the skin without contact with the gastrointestinal tract in patients with CD.[2] In 1970, this condition was named 'metastatic CD' by Mountain.[3] Those cutaneous manifestations of CD are infrequent and can potentially occur at any location of the body. Genital granulomatosis [GG] is one of them, and it is defined as granulomatous genital inflammation occurring independently from fistulising CD. Hence, a contact with the gastrointestinal tract has to be ruled out. This is sometimes difficult, especially when a simultaneous perianal disease is present. Typical histopathological findings in GG are superficial and deep non-caseating granulomas with giant cells, granulomatous vasculitis, massive oedema of the dermis and a rich eosinophilic infiltration.[4] GG can be encountered as genital swelling or oedema, 'knife-cut' ulcers, fissures, hypertrophic lesions, abscesses or chronic suppuration. These lesions are non-specific and have numerous differential diagnoses including allergic contact dermatitis, angioedema, sexually transmitted diseases [eg herpes simplex, gonorrhea, or *Chlamydia* infections], sarcoidosis, tuberculosis, Behcet`s disease, foreign body reactions, lymphogranuloma venereum, and many others. Therefore, an interdisciplinary work-up might be necessary in many cases. Since 1965, 123 cases of GG have been reported, mostly in female patients. Recently, a systematic review reporting on 86 cases[5] and a French case series including 22 female patients were published by Laftah *et al*.[6] However, GG has been described significantly less frequently in male patients and only 37 cases of male GG cases have been published to date, with only one publication including more than one patient, and no comparison between male and female cases has been addressed to date.[7–25] In 2014, Mirheydar *et al*. published a literature review on prepubertal male GG including 17 cases.[8] Beyond clinical presentation, scarce data on treatment efficacy are available, leading to a lack of treatment algorithms in this clinical setting.

The primary aim of this study was to extensively describe GG in patients with CD, with particular attention to male cases. The secondary aim was to provide data on the response to treatments in GG.

2. Materials and Methods

In this European Crohn's and Colitis Organisation [ECCO] observational multicentre study, cases of GG were retrospectively collected through the CONFER [Collaborative Network For Exceptionally Rare case reports] project. The CONFER project was initiated by ECCO in order to specifically identify and report together rare inflammatory bowel disease [IBD] associations, which otherwise are under-reported due to their exceptional rarity. Once a specific topic is selected by the Steering Committee as a CONFER project, ECCO launches a call to identify similar cases encountered by IBD physicians worldwide. The call to physicians was made through announcements at the ECCO annual congress and in national and international IBD meetings across Europe. Furthermore, the call for similar cases was disseminated by direct emails to all ECCO members and affiliated physicians and on the ECCO website and eNews. Physicians were then prompted to report their cases to the CONFER database using pre-determined standardised Case Reporting Forms [CRF].

The ECCO CONFER Cases project was centrally approved by the Institutional Research Board [IRB] of the Sheba Medical Center, Israel. All cases included are anonymous, to protect confidentiality and respect patients' privacy. For investigators in need of a local institutional review board [IRB] approval in their own institution to participate in this retrospective project, the project protocol, CRF, and central site IRB approval could be downloaded at the ECCO CONFER website to facilitate this process.

2.1. Patients and procedures

CD patients who ever suffered from GG were eligible for inclusion in this project. GG was defined as genital swelling, oedema, ulcer, fissures, hypertrophic lesions, abscesses, or chronic suppuration without contact with gastrointestinal tract Figure 2 and 3. As in most previous reported series GG was not confirmed histologically in all cases [range 69%-93%],[5,6,26] we decided to include also patients with typical presentation of GG [even not confirmed histologically] if the diagnosis of gastrointestinal CD was established by conventional criteria. Fistulas should have been excluded clinically, by magnetic resonance imaging [MRI] or by an endoanal ultrasonography. In case of histologically confirmed granulomas, tuberculosis had to be ruled out by a chest X-ray, interferon-gamma-release assay [IGRA], or tuberculin skin test. Sexually transmitted diseases [HIV, herpes simplex, syphilis, or *Chlamydia trachomatis* infection] also had to be ruled out.

The CRF was divided into two sections, one that included patients' and CD characteristics and another that described the details of the GG clinical presentation and treatment outcomes. The phenotype of CD [including age at diagnosis, disease location and behaviour, and perianal involvement] was described using the Montreal classification.[27]

Treatment response was assessed retrospectively when reduction in symptoms, healing of fissures and ulcers, or improvement of genital swelling were reported. Primary failure was defined as lack of clinical response and the secondary failure was defined as loss of an initial clinical response.

2.2. Statistical analysis

Continuous variables were described as a mean in the case of normal distribution and as a median with range in the case of non-normal distribution. Fisher's exact test was applied to compare the frequencies and the Mann-Whitney test was applied in the case of non-normal distribution for continuous variables. A value of $p < 0.05$ was considered statistically significant [SPSS version 21.0].

3. Results

In all, 43 patients [9 males, 34 females] diagnosed with GG were identified from 21 centres. Three cases were excluded because of concomitant rectovaginal or rectolabial fistulas. Only one case of a male patient from the present cohort has been published previously.[8]

The presence of granulomas was confirmed histologically in 28 cases [70%]. Histological features are shown in Figure 1. Gastrointestinal CD was confirmed in all cases either at the time of

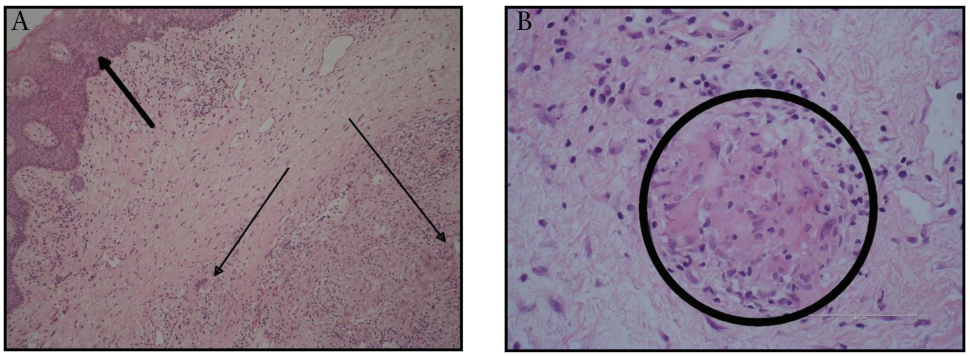

Figure 1. [A] Regular squamous cell epithelium at the surface [thick arrow] and a granulomatous inflammation including giant cells [thin, long arrows] [haematoxylin-eosin staining, x40 magnification]; [B] close-up view of a typical non-caseating granuloma [circle] in a patient with Crohn's type granulomas [haematoxylin-eosin staining, x400 magnification].

GG diagnosis, before it, or later. Tuberculosis was ruled out by chest X-ray, IGRA, or tuberculin skin test in all cases.

The main phenotypic characteristics of CD, as well as the time interval between the two diagnoses and the previous exposure to immunosuppressants or anti-tumour necrosis factor [TNF] agents, are described in detail in Table 1. Twenty patients [46%] were aged younger than 17 years at the time of CD diagnosis, 18 patients [42%] were between 17 and 40 years, and five patients [12%] were older than 40 years. Colonic involvement was almost constant, with 19 patients [47%] having isolated colonic disease and a further 20 patients [50%] having ileocolonic disease. Perianal disease manifestations were documented in 23 patients [57%]; in all but one, perianal disease occurred before GG. The mean age at the time of GG occurrence was 25.5 years [range, 7 to 61 years]. At the time of genital manifestations, 28 [70%] patients had non-stricturing/non-penetrating disease behaviour, four patients [10%] had a stricturing pattern, and eight patients [30%] presented with penetrating disease. Extraintestinal manifestations other than GG were present in 37% of the cases. Thirteen patients [30%] had had some kind of IBD surgery before the occurrence of the GG. There was no significant difference between male and female patients in age at disease onset, localisation, behaviour, prevalence or type of extraintestinal manifestations, and prevalence of perianal manifestations [Table 2].

There were some differences between patients in whom GG was confirmed histologically and patients without histological confirmation. The former patients were significant older at the time of GG diagnosis and also older at the time of Crohn's disease diagnosis. None of the patients without histological confirmation was a smoker or former smoker. Perhaps this is connected to the young age of this group. Anal fistula was present more frequently in patients without histological confirmation. Also, mere colonic as opposed to ileocolonic disease was present more often in patients with histological confirmation of GG. But these differences between both groups were not statistically significant [Table 3].

GG was the first manifestation of CD in 13 patients [30%]. In these patients, GG preceded occurrence of other CD manifestations by a median time of 2 months [range, 0 to 12 months]; seven patients presented with GG within 1 year before IBD diagnosis and six patients developed GG simultaneously with gastrointestinal manifestations. In six patients, GG occurred within the first year after CD diagnosis. In the remaining 21 patients, GG occurred 12 to 422 months after IBD diagnosis. Of note, patients in whom GG was the first IBD manifestation were younger at the time of genital manifestations as opposed to patients in whom GG occurred later [mean age at the time of genital manifestations was 21 years vs 29 years, respectively; $p = 0.056$]. However, no differences in age at the time of IBD diagnosis were found between both groups [median of 29 years in each group]. Furthermore, all patients with GG as the first disease manifestation were non-smokers, as opposed to eight current smokers and two former smokers in patients with GG occurring later during the course of disease [$p = 0.022$].

The main characteristics of GG are summarised in Table 2. Most frequent clinical manifestations of GG were swelling with oedema or skin infiltration in 75% [30 of 40 patients with pertinent information], and ulcers in 35% [14/40]. There was no significant difference in type of lesions between female and male patients; however, clinical presentation as a solid mass was reported in only two female patients.

Intestinal disease was judged to be clinically active by the treating physician in 20 of 33 patients [60%] with known CD at the time of genital manifestation. Endoscopic activity was found in 14 of the 20 [70%] patients, with available data, and radiological activity in eight of 14 patients [57%] at the time of genital manifestation. C-reactive protein level was raised [> 5 mg/dL] in 13 of 25 patients [52%] at the time of GG occurrence.

After median follow-up period of 30 months [range, 9 to 154 months], clinical response to applied treatment was documented in all but one patient; 26 patients received some kind of monotherapy as first-line treatment attempt. A combination of two or three immunosuppressant drugs was used in 14 patients as first-line therapy. To figure out which was the most potent drug in first-line therapy of GG, we categorisedfive treatment groups from the least to the most potent, as follows: mesalazine [5-ASA; 5-aminosalicylic acid], antibiotics, corticosteroids, immunosuppressant drugs, and anti-TNFs [Table 4]. In cases of combination therapies, we matched the patients to the most potent drug group. One patient had a spontaneous remission and one patient had a surgical remission after vulvoplasty. Only one patient out of three with 5-ASA first-line therapy responded, but had a secondary treatment failure. A monotherapy with antibiotics led to one response out of four cases. However, a treatment response was induced by combining antibiotics [mostly ciprofloxacin or metronidazole] with corticosteroids, immunosuppressants, and/or anti-TNFs in 11 of 13 documented cases. Ten out of 11 patients [91%] responded to initial systemic corticosteroid treatment. Treatment with immunosuppressants [azathioprine, 6-mercaptopurine, or methotrexate] led to response in 10 out of 14 cases. In most cases, azathioprine was used initially in combination with systemic corticosteroids. After stopping corticosteroids, long-term response was achieved in two cases. Eleven patients were treated primarily with anti-TNFs, nine of them achieving response [82%]. Altogether, anti-TNF agents were used in 26 patients during

Table 1. Characteristics of the included patients.

Age [years]	Sex	Familial IBD	Smoking	Montreal-classification				Time to GG [months]	Previous surgeries	Previous use of IMs or anti-TNFs	Other EIMs
				A	l	B	P				
40	F	No	Never	2	2	1	1	-1	NA	No	Yes
25	F	No	Never	2	2	1	0	-3	NA	No	Yes
51	F	No	Never	2	2	1	1	52	No	No	No
54	F	No	Never	3	1	1	1	87	No	No	No
38	F	No	Yes	2	3	1	1	9	No	No	No
38	F	No	Never	1	3	2	0	78	Ileocaecal resection, ileal resection	Yes	No
28	F	No	Never	2	3	3	0	-12	No	No	No
30	F	No	Never	2	3	3	1	52	No	Yes	No
28	F	No	Never	1	2	1	0	0	No	No	No
38	F	No	Never	1	3	1	0	130	Ileocaecal resection	No	No
34	F	No	Never	1	2	1	0	69	Proctocolectomy	No	No
41	F	No	Yes	2	3	3	1	132	Subtotal colectomy + ileal resection with ileostomy, ileal resection and new ileostomy	Yes	No
55	M	No	Former	2	2	1	1	249	No	No	No
38	F	No	Yes	2	2	1	1	38	No	Yes	Yes
52	M	Yes	Yes	2	2	1	1	368	Colonic resection and subtotal colectomy with ileo-colic anastomosis	Yes	Yes
64	F	Yes	Never	3	2	3	1	-7	NA ano-vaginal fistula	No	No
26	F	No	Yes	1	3	3	1	125	Ileostomy	Yes	Yes
11	F	No	Never	1	3L4	1	1	6	Abscess drainage	Yes	Yes
19	F	No	Never	1	3	2	1	59	No	Yes	No
16	F	No	Never	1	2	1	1	19	NA	Yes	Yes
13	F	No	Never	1	2	1	1	0	NA	No	No
16	M	No	Never	1	3	1	1	3	No	Yes	Yes
15	M	No	Never	1	3	1	1	0	NA anal tag excision	No	No
24	F	No	Never	1	2	1	0	3	No	No	No
32	M	No	Unknown	2	2	2	1	77	Transient ileostomy, perianal abscess, colostomy	No	No
54	M	No	Unknown	3	3	1	1	42	Multiple abscess drainages	No	No
22	M	Yes	Never	2	3	1	0	-6	NA	No	No
16	F	No	Never	1	2	1	1	-6	NA	No	Yes
15	F	Yes	Never	1	3	1	0	14	No	Yes	No
32	F	No	Yes	2	3	3	1	59	Fistulectomy, setons	Yes	Yes
54	F	No	Yes	1	3	2	0	416	No	No	Yes
23	F	No	Never	2	2	1	0	0	No	No	Yes
33	F	No	Yes	2	2	1	0	12	No	Yes	No
16	M	No	Never	1	3	1	0	-9	Na	No	No
18	F	No	Never	1	3	1	0	80	No	Yes	No
18	F	No	Never	1	2	1	1	0	No	No	Yes
47	M	No	Former	2	2	1	0	172	No	Yes	Yes
44	F	No	Never	3	2	3	0	2	No	No	No
62	F	No	Never	2	3	1	0	262	No	Yes	Yes
70	F	No	Never	3	3	3	1	0	No	No	No

F, female; M, male; IBD, inflammatory bowel disease; GG, genital granulomatosis; EIM, extraintestinal manifestations; NA, not applicable.

the course of GG. There was an initial response in 22 cases [85%], with a secondary treatment failure in four cases [15%] and a long-term response in 12 cases [46%]. Overall, treatment response was achieved after a median of two treatment attempts [range, 1–7 treatments]. There was only one patient with a primary treatment failure to any treatment he received.

Table 2. Genital granulomatosis characteristics and gender.

	Female [*n* = 31]	Male [*n* = 9]	*p*
Crohn's disease phenotype			
A1/A2/A3	15/12/4	3/5/1	0.92
Ileal/colonic/ileocolonic	1/15/15	0/4/5	0.58
Inflammatory/stricturing/ penetrating	20/3/8	8/1/0	0.65
Perianal disease [ever]	17	6	0.45
Previous exposure to			
Immunosuppressants	11	3	0.72
Anti-TNF agents	9	1	1.0
Age at genital granulomatosis diagnosis	25 [7–61]	26 [10–53]	0.84
GG occurring before diagnosis or within 1 year after Crohn's disease diagnosis [%]	15 [48]	4 [44]	1.0
Location of lesions [%]			
Vulvar	31 [100]	-	
Penile	-	6 [75]	
Scrotal	-	8 [89]	
Foreskin	-	1 [11]	
Type of lesions [%]			
Oedema	23 [75]	7 [78]	1.0
Ulcer	13 [42]	2 [22]	0.69
Solid mass	2 [6]	0	1.0
Current medical therapy at the time of GG [%]			
No treatment	11 [35]	4 [44]	0.85
5-ASA	7 [23]	5 [55]	0.1
Corticosteroids	4 [13]		0.56
Immunosuppressants	7 [23]	1 [11]	0.65
Anti-TNF agents	6 [19]		0.31

GG, genital granulomatosis; TNF, tumour necrosis factor; 5-ASA, 5-aminosalicylic acid.

Table 3. Comparision of cases with and without histological confirmation.

Variable	Patients with histological confirmation [*n* = 28] *N*, %	Patients without histological confirmation [*n* = 12] *N*, %	*p*
Male sex	5 [18%]	4 [33%]	0.41
Age at diagnosis of Crohn's disease			
0–16 years	8 [29%]	9 [75%]	
17–40 years	16 [57%]	3 [17%]	0.023
> 40 years	4 [14%]	1 [8%]	
Age at diagnosis of genital granulomatosis, years	32.5	17.6	0.004
Genital granulomatosis as a first manifestation of the disease	10 [36%]	3 [25%]	0.72
Presence of perianal fistula	15 [56%]	11 [85%]	0.09
Smoking	10 [36%]	0 [0%]	0.038
Disease localisation			
Colonic	15 [58%]	4 [33%]	0.17
Ileocolonic	10 [38%]	9 [67%]	0.17
Family history of Crohn's disesae	3 [11%]	1 [8%]	1.0
Type of lesion			
- ulcer	11 [39%]	4 [33%]	0.73
- oedema	21 [75%]	9 [75%]	1.0
- solid mass	1 [4%]	1 [8%]	0.53

Table 4. Genital granulomatosis treatment outcomes.

	Initial response	Secondary treatment failure	Long-term response
Antibiotics	11/13	1/13	1/13
Steroids	14/15	2/15	2/15
5-ASA	1/3	0/3	1/3
AZA/MP	10/14	1/14	2/14
TNF-alpha	22/26	4/26	12/26

5-ASA,5-aminosalicylic acid; AZA, azathioprine; MP, mercaptopurine; TNF, tumour necrosis factor.

4. Discussion

GG is a rare extraintestinal manifestation of CD. Most publications on that subject are case reports or small case series, the two largest being published very recently. The first of these larger publications was a single-centre retrospective study of 22 female patients with vulvar CD, although intestinal CD was only demonstrated in 14 of them.[6] The second one was a literature review on vulvar CD including 86 patients treated between 1965 and 2013. Both publications focused on female GG and, therefore, did not include male patients. Until now, only 37 male cases had been reported. Mirheydar *et al.* recently published a case report with literature review describing 17 prepubertal boys with GG.[8] Thus, the present study is the largest original series and it also provides the highest number of adult male GG cases.

GG preceded CD diagnosis in one-third or occurred within the first year of disease in further 20% of our cases. Similar findings had been reported in literature reviews of female GG, with 25% of GG patients without previous intestinal symptoms.[5,26] Apparently GG tends to occur at an early age, with a median age at diagnosis of GG in our study of 25 years and only one patient being diagnosed with CD when aged over 40 years, in accordance with previous studies.[6,26] Interestingly, Mirheydar reported that only 29% of prepubertal boys [mean age 10 years] had known CD at the time of GG presentation. In three adolescent boys included in our study, GG preceded CD diagnosis in one, and occurred simultaneously with gastrointestinal symptoms in another one. Of note, perianal disease has been reported in a high proportion of CD patients with GG. In the above-mentioned literature review, 75% of boys with no previous diagnosis of CD had a past history of anal fissures, perianal fistulas or abscesses, anal skin tags, crampy abdominal pain, or rectal bleeding. In our series, 22 patients [55%] had a previous history of perianal disease at the time of GG occurrence. Thus, clinicians should of course be aware of potential GG in young CD patients with unexplained genital swelling, but they should also seek to rule out luminal CD in children or young adults with these symptoms, particularly if there is a past history of perianal fistulas or fissures.

Beyond presentation at an early age [even preceding CD diagnosis] and its association with perianal disease in a high proportion of patients, we found that GG occurs almost exclusively in CD patients with colonic involvement. In our study, colonic involvement of CD [exclusive or together with ileal disease] was present in 97% of the whole cohort and in all those cases with genital symptoms preceding gastrointestinal manifestations. Laftah *et al*., in a smaller series of 14 female patients with vulvar CD, reported 72% colonic involvement.[6] Regarding luminal CD phenotype, it is noteworthy that 70% had an inflammatory disease behaviour and only five patients had a history

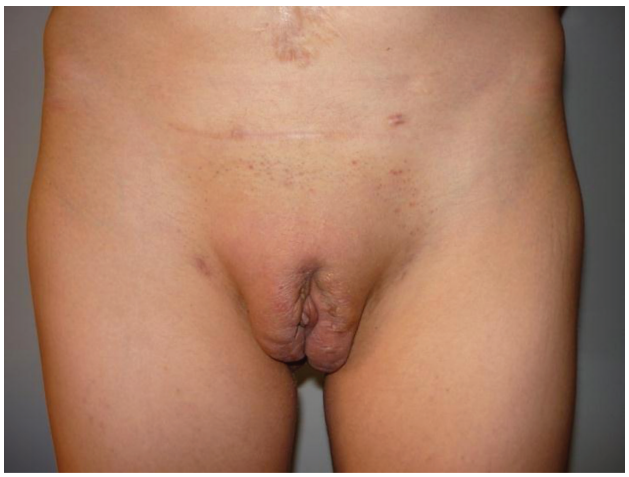

Figure 2. Labial oedema and swelling in a 28-year old Caucasian woman with Crohn's disease.

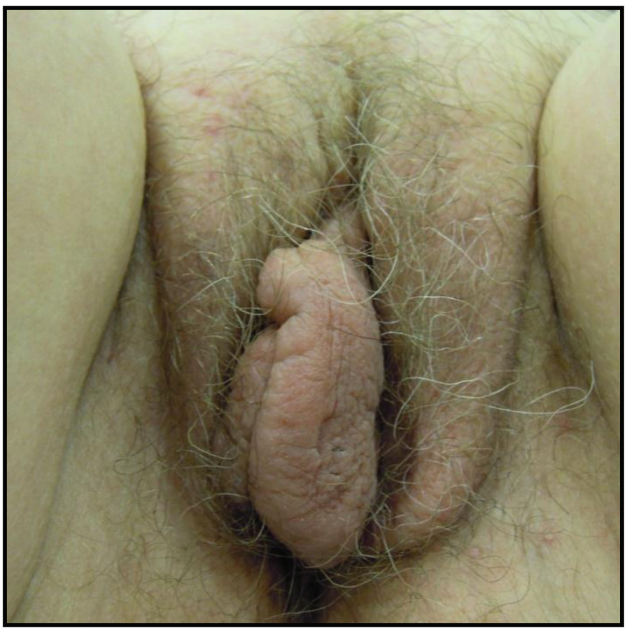

Figure 3. Hypertrophic lesion of the labia minora in a 54-year old woman with Crohn's disease.

of intra-abdominal penetrating complications, regardless of perianal disease. No other large series or literature reviews had addressed phenotypic features of CD. Lebwohl *et al*. had already suggested a relationship between dermal extraintestinal manifestations [EIM] and colonic disease localisation,[28] whereas Graham *et al*. reported vulvo-vaginal symptoms in 81% of female patients who had active colonic and perianal disease.[29]

Finally, from our results it could be concluded that GG development is not necessarily associated with luminal disease activity, as 30% of patients were in clinical or endoscopic/radiological remission. This is comparable to the study of Karmiris *et al*., who found an association between active IBD and presence of EIM in 61.1% of the patients.[30]

No large series of male GG are available and, to date, only one literature review focused on male GG has been published. Mirheydar *et al*. recently reviewed a total of 17 paediatric [prepubertal] male cases of genital CD.[8] As in our nine male cases, most of them had penile and scrotal disease, and only a minority had foreskin involvement. Contrary to what it might be thought from that review, none of our male cases had a prepubertal onset of GG, and only one-third presented during adolescence. Although we specifically assessed if there were phenotypic differences in CD between male and female cases, we did not find any.

To date, the natural history of GG has not been well documented; apparently the course of disease ranges from spontaneous healing[31] to lesions refractory to medical therapy, requiring surgery.[32–35] The present retrospective study also focused on treatment results. A prompt response to conventional CD treatment was observed in most cases. The treatment choice was mostly affected by gastrointestinal symptoms. However, a very good response rate to systemic corticosteroids of up to 91% could be observed. Antibiotics, especially ciprofloxacin and metronidazole, were also effective in 85%, but mostly in combination with corticosteroids or immunosuppressants. On the other hand, we documented clinical response to antibiotic monotherapy in only 25% of the cases. For metronidazole, there seems to be some evidence of clinical efficacy in acute flares due to secondary infection causing cellulitis and abscess formation, but with no effect on the genital oedema. Also, there is no evidence that GG symptoms could be improved by antibiotics in the long term.[6,8] Therefore, the combination of corticosteroids, azathioprine, and metronidazole could be an effective first-line therapy, especially in cases of secondary infections. We also found a high response rate to anti-TNF therapy, with only 15% of primary failures. In fact, response to anti-TNFs has also been reported after failure of antibiotics, corticosteroids, or immunosuppressants in some cases.[5]

As in previous large series, the main limitations of the present study come from its retrospective design. This led to histological corroboration of only 70% of cases. The presence of subacute or chronic inflammatory infiltrate, epidermal ulceration, together with non-caseating tuberculoid granulomas, strongly supports the diagnosis and therefore some authors pose that biopsy samples for histological study are mandatory.[5] But these histological features do not confirm GG because, for example, sarcoidosis or foreign body reactions might have the same histological presentation. On the other hand, in the recently published study of Laftah, histological features of CD were found in only 69% of the biopsies of the vulva and non-caseating granulomas were found in 89% of these cases.[6] All of our cases had histologically confirmed gastrointestinal CD and typical clinical presentation of GG. Comparing the cases with [28] and without [12] histological confirmation of genital manifestation, the main difference in both groups was the age at onset of GG. The group without histological confirmation was younger at diagnosis of GG. Perhaps this is the reason why biopsies were taken less. No significant difference was seen in phenotype of CD or treatment outcome. However, our series excluded those patients with concomitant active perianal disease, as well as those in whom gastrointestinal CD involvement was never demonstrated. The study design also made it difficult to evaluate the best therapeutic approach to these patients, as there was not a preestablished treatment algorithm or a standardised way to measure response.

In conclusion, GG is a rare extraintestinal manifestation of CD that occurs predominantly in young females with colonic involvement and perianal disease. In almost half of the patients, GG precedes or develops early after CD diagnosis. Systemic corticosteroids in combination with azathioprine or, in case of concomitant infection

with metronidazole, could be recommended as a first-line treatment, although anti-TNF agents seem also to be an effective treatment option in most cases.

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Conflict of Interest

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Author Contributions

FD initiated the study, analysed and interpreted the data, and drafted the manuscript; ED interpreted the data and drafted the manuscript; all the other authors on the title page contributed more than one case and critically revised the manuscript. All other collaborating authors of the 'ECCO CONFER genital CD project', who contributed a case to the study, are mentioned below:

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References

1. Burgdorf W. Cutaneous manifestations of Crohn's disease. *J Am Acad Dermatol* 1981;**5**:689–95.
2. Parks AG, Morson BC, Pegum JS. Crohn's disease with cutaneous involvement. *Proc R Soc Med* 1965;**58**:241–2.
3. Mountain JC. Cutaneous ulceration in Crohn's disease. *Gut* 1970;**11**:18–26.
4. Ishida M, Iwai M, Yoshida K, Kagotani A, Okabe H. Metastatic Crohn's disease accompanying granulomatous vasculitis and lymphangitis in the vulva. *Int J Clin Exp Pathol* 2013;**6**:2263–6.
5. Barret M, de Parades V, Battistella M, Sokol H, Lemarchand N, Marteau P. Crohn's disease of the vulva. *J Crohns Colitis* 2014;**8**:563–70.
6. Laftah Z, Bailey C, Zaheri S, Setterfield J, Fuller LC, Lewis F. Vulval Crohn's disease: a clinical study of 22 patients. *J Crohns Colitis* 2015;**9**:318–25.
7. Fikrele T, Lomicova H, Szakos H, Pizinger K. Anogenital granulomatosis: report of two cases. *Clin Dermatol* 2015; **40**: 149–51.
8. Mirheydar HS, Friedlander SF, Kaplan GW. Prepubertal male genitourinary metastatic Crohn's disease: report of a case and review of literature. *Urology* 2014;**83**:1165–9.
9. Foley CC, McMenamin M, Gordon KD, Irvine AD. An unusual case of genital swelling. *Clin Exp Dermatol* 2013;**38**:946–8.
10. Gordon KD, Brice G, Walker Y, Pollok R, Mortimer P, Slater C. Genital lymphoedema due to ano-genital granulomatosis. *Int J STD AIDS* 2013;**24**:149–51.
11. Weinberg AE, Hazard FK, Hsieh MH. A case of genitourinary Crohn's disease. *Urology* 2012;**80**:1132–4.
12. Sackett DD, Meshekow JS, Figueroa TE, Napoli JA. Isolated penile lymphedema in an adolescent male: a case of metastatic Crohn's disease. *J Pediatr Urol* 2012;**8**:e55–8.
13. Vaid RM, Cohen BA. Cutaneous Crohn's disease in the pediatric population. *Pediatr Dermatol* 2010;**27**:279–81.
14. Lopez V, Alonso V, Monteagudo C, *et al.* Penile and scrotal edema as a manifestation of Crohn's disease. *Int J Dermatol* 2009;**48**:1136–7.
15. Okotie OT, Maizels M, Cheng EY. Metastatic Crohn's of the genitalia in a child. *J Pediatr Urol* 2007;**3**:253–4.
16. Savino A, Pelliccia P, Breda L, *et al.* Genital swelling in an adolescent patient. *Eur J Pediatr* 2006;**165**:76–9.
17. Macaya A, Marcoval J, Bordas X, Moreno A, Vázquez S, Peyrí J. Crohn's disease presenting as prepuce and scrotal edema. *J Am Acad Dermatol* 2003;**49**:S182–3.
18. van de Scheur MR, van der Waal RIF, Stoof TJ, van Deventer SJH. Anogenital granulomatosis: the counterpart of oro-facial granulomatosis. *J Eur Acad Dermatol Venereol* 2003;**17**:184–9.
19. Saadah OI, Oliver MR, Bines JE, Stokes KB, Cameron DJ. Anorectal strictures and genital Crohn disease: an unusual clinical association. *J Pediatr Gastroenterol Nutr* 2003;**36**:403–6.
20. Poon KS, Gilks CB, Masterson JS. Metastatic Crohn's disease involving the genitalia. *J Urol* 2002;**167**:2541–2.
21. Acker SM, Sahn EE, Rogers HC, Maize JC, Moscatello SA, Frick KA. Genital cutaneous Crohn disease: two cases with unusual clinical and histopathologic features in young men. *Am J Dermatopathol* 2000;**22**:443–6.
22. Phillips SS, Baird DB, Joshi VV, Rosenberg AJ, Janosko EO. Crohn's disease of the prepuce in a 12-year-old boy: a case report and review of the literature. *Pediatr Pathol Lab Med* 1997;**17**:497–502.
23. Neri I, Bardazzi F, Fanti PA, Guidetti MS. Penile Crohn's disease: a case report. *Genitourin Med* 1995;**71**:45–6.
24. Slaney G, Muller S, Clay J, Sumathipala AH, Hillenbrand P, Thompson H. Crohn's disease involving the penis. *Gut* 1986;**27**:329–33.
25. Cockburn AG, Krolikowski J, Balogh K, Roth RA. Crohn disease of penile and scrotal skin. *Urology* 1980;**15**:596–8.
26. Andreani SM, Ratnasingham K, Dang HH, Gravante G, Giordano P. Crohn's disease of the vulva. *Int J Surg* 2010;**8**:2–5.
27. Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut* 2006;**55**:749–53.
28. Lebwohl M, Fleischmajer R, Janowitz H, Present D, Prioleau PG. Metastatic Crohn's disease. *J Am Acad Dermatol* 1984;**10**:33–8.
29. Graham DB, Tishon JR, Borum ML. An evaluation of vaginal symptoms in women with Crohn's disease. *Dig Dis Sci* 2008;**53**:765–6.
30. Karmiris K, Avgerinos A, Tavernaraki A, *et al.* Prevalence and characteristics of extra-intestinal manifestations in a large cohort of Greek patients with inflammatory bowel disease. *J Crohns Colitis* 2016;**10**:429–36.
31. Shen RN, Cybulska BA, Thin RN, McKee PH. Vulval Crohn's disease mimicking genital herpes. *Int J STD AIDS* 1993;**4**:54–6.
32. Kao MS, Paulson JD, Askin FB. Crohn's disease of the vulva. *Obstet Gynecol* 1975;**46**:329–33.
33. Baker VV, Walton LA. Crohn's disease of the vulva. *South Med J* 1988;**81**:285–6.
34. Fenniche S, Mokni M, Haouet S, Ben Osman A. [Vulvar Crohn disease: 3 cases]. *Ann Dermatol Venereol* 1997;**124**:629–32.
35. Reyman L, Milano A, Demopoulos R, Mayron J, Schuster S. Metastatic vulvar ulceration in Crohn's disease. *Am J Gastroenterol* 1986;**81**:46–9.