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Genital fistulas in female Crohn's disease patients. Clinical characteristics and response to therapy

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Abstract

Background: Genital fistulas (GF) can arise in the course of Crohn's disease (CD), are difficult to manage and determine a significant alteration of the quality of life.
Aims: To review the joint experience of the Inflammatory Bowel Disease Units in six University Hospitals in the management of GF in Crohn's disease on female patients.
Results: A total of 47 patients with GF were identified, affecting 3.8% of women with CD treated in our centers. A 47.5% of patients were smokers. The median of time from the diagnosis of CD reached 102 months. According to anatomical type, GF were classified as rectovaginal (74.5%), anovaginal/anovulvar (21.3%) and enterovaginal (4.3%). Main symptoms were vaginal discharge of fecal material (55.3%), vaginal passage of gas (40.4%), or both. Fistulas were treated with antibiotics in 59.6% of patients, without any lasting success. Thiopurines were used in 80.9% of cases, with 13.2% of complete and 23.7% of partial responses. Anti TNF-alpha therapy was applied in 63.8%, with a 16.7% of complete and a 30% of partial responses (all responding patients received infliximab). Surgery was indicated in 38.3% of patients, with a 22% of complete responses after a first operation and 38.8% after reintervention. In all, definitive closure after one or more of these therapies was achieved in only 31.9% of cases.

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Conclusion: Genital fistulas are a significant problem in female Crohn's disease patients. Therapy is not well defined and only partially effective (one in three cases). Surgical therapy stands out as the most effective treatment.

1. Introduction

Fistulas are a well recognized component of the spectrum of Crohn's disease (CD); approximately 35% of patients develop this condition during the first 10 years of disease, reaching 50% during the next 10 years.[1] More than half of the fistulas are located in the perianal area. Their importance is such, that the presence or absence of this condition must be independently stated when classifying a patient according to the Montreal system.[2]

Ano-vaginal or recto-vaginal fistulas account for just a 9% of all fistulas in CD, [1] and affect approximately 5 to 10% of female patients [3,4]; they are more frequent whenever the colon is affected.[5] According to their anatomical situation in respect to the anal sphincter, they can be subdivided into anovaginal (if the internal orifice is in the anal canal) or rectovaginal (if fistula opens above the anal sphincter).[5] Enterogenital and anovulvar fistulas are less frequent. Any fistula originating in the rectum, above the anal sphincter, is generally associated to rectal disease and will frequently be multiple.

Clinical manifestations of GF include vaginal passage of air or fecal material, as well as recurrent vaginal infections. However, up to one fifth of all patients are asymptomatic.[6] Available diagnostic tools include careful surgical examination under anesthesia (including the use of dyes), anorectal ultrasonography and magnetic resonance. However, most cases are diagnosed only on clinical grounds.[7]

Management of GF is hazardous, of moderate efficacy and not clearly protocolized. Current guidelines are based on short patient series. This and other factors explain the difficulty in designing clinical studies, so case collection and reporting are the only source of knowledge on their response to different therapies.

These considerations moved us to design a retrospective case series to assess the incidence of GF on Crohn's disease patients, to explore any patterns in their appearance, and to define clinical presentation and risk factors. Moreover, we wished to evaluate response to therapy, surgical or otherwise, and the long-term evolution of this condition.

2. Materials and methods

The study was undertaken as a collaboration between the IBD Clinics in six University Hospitals in the Community of Madrid, Spain. Clinical charts of female patients with CD, according to the Lennard–Jones' criteria [8] were retrospectively reviewed from February 2009 to May 2010. Exclusion criteria were: diagnosis of ulcerative colitis or non-classified colitis, fistula secondary to obstetric trauma, or patient's refusal to participate in the study.

Diagnosis of fistula mainly relied on clinical presentation, and confirmation by imaging studies was not required in clinically evident cases or whenever the fistula was identified during surgical exploration.

Following data were collected: demographic data, time from diagnosis of CD, Montreal classification, months elapsed between CD diagnosis and the appearance of GF, smoking habit, time of appearance of GF relative to menopause, type of fistula (recto-vaginal, ano-vaginal, entero-vaginal, other), clinical symptoms of GF, and therapy indicated for the resolution of GF and its results.

The use of Montreal classification deserves a comment. Rectovaginal and anovaginal fistulas are part of the spectrum of perianal CD.[9] Therefore, such patients could be classified with a "+P" according to their disease behavior.[2] However, the European Crohn and Colitis Organization (ECCO) specifically designated these GF as "non-perianal".[10] We decided to classify disease behavior without taking into account the presence of GF.

The evaluation of response to therapy was done through clinical follow-up, generally considering cessation of symptoms as evidence of fistula closure, and it was subdivided into complete response, partial response (clinical alleviation but persistence of symptoms), absence of response or recurrence (symptoms reappearing after a complete response).

Statistical analysis was done with SPSS 17.0 software. Fisher's test was used to assess causality of basal qualitative variables (smoking habit, menopause, Montreal phenotype) and Mann–Whitney's test to analyze the influence of time since diagnosis of CD until the appearance of the GF. We did not statistically analyze the association of the different therapeutic options, given that they were frequently used in succession or in combination.

3. Ethical considerations

Informed consent was obtained in all cases, and the protocol was evaluated and approved by the Ethical Committee of the steering center (Hospital "Ramón y Cajal", Madrid).

4. Results

4.1. Basal characteristics (Table 1)

A total of 47 women with GF were identified in this cohort of 1215 female CD patients, representing a 3.8% of cumulative incidence.

Phenotype according to Montreal's classification and main clinical characteristics are shown in Table 1. According to their topography, 35 fistulas (74.5%) were recto-vaginal, 6 (12.8%) were ano-vaginal, 4 (8.5%) ano-vulvar and 2 (4.3%) entero-vaginal.

The mean time from the diagnosis of CD to the appearance of the GF was 102 ± 96.8 months, with a very wide

Table 1 Basal characteristics of patients.

Montreal classification		N	%
A1	16 years or younger	6	12.8
A2	17–40 years	35	74.5
A3	Over 40 years	6	12.8
L1	Ileon/ileocecal	6	12.8
L2	Colon	14	29.8
L3	Ileocolon	25	53.2
L unknown/unavailable		2	4.3
B1	Nonstricturing/nonpenetrating	16	34.0
B2	Stricturing	10	21.3
B3	Penetrating	21	44.7
P	No	12	25.5
	Yes	35	74.5
Type of fistula			
Recto-vaginal		35	74.5
Ano-vaginal		6	12.8
Entero-vaginal		2	4.3
Ano-vulvar		4	8.5
Symptoms			
Passing gas	No	28	59.5
through vulva	Yes	19	40.4
Passing heces	No	21	44.7
through vulva	Yes	26	55.3
Infection	No	33	70.2
	Yes	14	29.8
Dyspareunia	No	46	97.8
	Yes	1	2.1

range (60 months before to 348 months after the diagnosis of CD).

4.2. Response to therapy (Table 2)

Antibiotics were administered at some time in 28 patients (more than half of cases, 59.6%). Thiopurines were used in 38 cases (80.9%), 30 patients received infliximab (63.8%) and 4 patients received adalimumab (8.5%). Surgery aimed at the correction of the GF was indicated in 18 patients (38.3%).

The most frequently used antibiotic combinations involved ciprofloxacin and metronidazole (78.6%), or metronidazole monotherapy (21.4%). In all, 13/28 (46.4%) patients treated with antibiotics failed to show any response, a partial response was observed in 9/28 cases (32.1%) and a complete response was achieved in just 5/28 patients (17.9%). All fistulas recurred after antibiotic withdrawal (Table 2).

A majority of patients (80.9%) was treated with thiopurines at some time, with intestinal activity being the indication in about half of cases (52.7%) and management of the fistulous disease in the remaining. Therapy was maintained for 64.5 ± 53.4 months; a complete response was obtained in 5 patients (13.2%), a partial response in 9 (23.7%) and a temporal response in 4 (10.5%), while 15 (39.5%) did not show any positive effect of therapy (Table 2). The results were not dependent on dosage of the medication.

Infliximab was prescribed in 30 patients, 80% for the treatment of fistulous disease. Patients received a mean of 12 ± 11.7 infusions. A complete response was observed in 5 cases (16.7%), a partial response in 9 (30%) and a temporal response in 4 (13.3%); 10 patients failed to show any effect of this therapy (33.3%) (Table 2).

Only four patients were treated with adalimumab. Three could be evaluated, all were treated for the fistula itself. No one of them showed response (Table 2).

Other therapies included aminosalycilates (3 cases), glucocorticoids (1 case) and methotrexate, tacrolimus and certolizumab (1 case each), without any response.

Surgical therapy was attempted in 18 patients. Five were treated with seton placement and drainage of associated abscesses, five patients with fistuloraphia or fistuloplastia, four with advancement flaps, and two with a definitive ileostomy. Specific details of surgery were lacking in two cases. Globally, a complete response was achieved in 4 out of 18 patients (22.2%), three patients experimented a partial response (16.7%) and four a temporal response. No response was observed in 33.3% (6 patients). A second surgery was indicated in four patients (22.2%), and this resulted in three more closures, one in combination with thiopurines and another with infliximab (Table 2). The rest of patients did not receive a medical maintenance treatment for the enterogenital fistulae itself. Thus the percentage of complete response after surgical therapy reaches 38.8% (seven of 18 patients, three after a second intervention). The small number of patients treated surgically precludes any statistical analysis.

In spite of all the therapies attempted, just 15/47 fistulas (31.9%) finally closed.

4.2.1. Influence of basal characteristics of fistula on response to therapy

Only two clinical variables were associated to a better response to therapy. Firstly, younger age at diagnosis significantly correlated with treatment success in our series ($p = 0.006$). Patients with Montreal A1 phenotype (age at

Table 2 Response of fistulas to therapy.

	Antibiotics	Thiopurines	Infliximab	Adalimumab	Surgery	Second surgery
Closure	0	5/38 (13.2%)	5/30 (16.7%)	0	4/18 (22%)	3/4 (75%)
Improvement	9/28 (32.1%)	9/38 (23.7%)	9/30 (30.0%)	0	3/18 (16.7%)	0
Non response	13/28 (46.4%)	15/38 (39.5%)	10/30 (33.3%)	3/4 (75%)	6/18 (33.3%)	0
Recurrence	5/28 (17.9%)	4/38 (10.5%)	4/30 (13.3%)	0	4/18 (22.25)	1/4 (25%)
Unknown	1/28 (3.6%)	5/38 (13.2%)	2/30 (6.7%)	1/4 (25%)	1/18 (5.6%)	0

diagnosis <16 y), were the ones in which a therapeutic success was more frequently observed (83.3% of fistula closure), whereas this was not achieved in any patient with Montreal A3 phenotype (age at diagnosis >40 y).

The other variable that was associated to a better outcome, was a negative history of tobacco use. The probability of fistula closure in current or previous smokers was halved, compared to that in patients who never smoked (22.1% vs. 43.8%, p=0.08).

No significant differences were found, as regards response to therapy, according to the different localizations of CD, nor to the clinical pattern (parameters "L" and "B" of Montreal classification).

Other variables that did not influence success of therapy were the presence of additional perianal disease (other than the fistula itself), the time elapsed between CD diagnosis and the appearance of the fistula, and the fact of the fistula developing after the menopause. However, there was a tendency of fistulas diagnosed late in the course of the disease and fistulas developing before menopause to respond better to therapy.

5. Discussion

The presence of a GF significantly conditions quality of life in women with CD, with a severe interference both in the psychosocial and sexual spheres. Diagnosis of genital fistulas is problematic: imaging procedures are frequently falsely negative, and sometimes the only positive finding is an unmistakeable description by the patient; however, specific recall of signs of symptoms possibly related to GF is not unfrequently omitted in the anamnesis of patients with CD.

Scientific evidence on the management of GF in CD is scarce, probably due to their clinical heterogeneity. Medical treatment is seen as difficult and without much success, and surgery does not offer a guarantee of fistula closure.

There has never been a randomized trial looking into the usefulness of antibiotics in the management of GF. However, short non-controlled series have shown that a symptomatic improvement can be achieved, as well as temporary closure, with ciprofloxacin, metronidazole or both. Fistula almost inevitably recurs after cessation of therapy.[11–13] This is in complete agreement with our results: only half of our patients responded to antibiotics, and a definitive closure was never achieved.

A complete healing of GF has been described under thiopurine therapy in 33–50% of cases, with the drawbacks of a long latency between therapy start and fistula closure (3–4 months) and the frequent recurrence after treatment withdrawal.[14,15] In our experience, 38 patients received thiopurines, with some temporary improvement in 14, but only five cases of complete success, one of them in combined infliximab therapy. Parenteral cyclosporin (never used in our series) has been described to heal fistulas in up to 100% of cases, after a median of 7 days, but with poor results after switching to oral cyclosporin maintenance; thiopurines have been used to extend in time the effects of cyclosporin.[16–18]

Infliximab (together with thiopurines or alone) is the only drug that has been evaluated in a controlled fashion in randomized studies. It has shown its efficacy attaining fistula closure in CD, both acutely and as a maintenance agent. Although no trial has specifically addressed the case of GF, analysis of subsets of patients included in trials on fistulous disease, showed that its efficacy is lower in genital than in perianal fistulas, with closure being observed in 0 to 45% of cases.[19–24] In our series, a 16.7% of complete and a 43.3% of partial responses were observed, somewhere in between the 45% of complete responses observed in the subgroup with GF discussed in the ACCENT II trial,[19] and the 0% communicated by Van Bodegraven in a short series where, however, mainly ultrasonic criteria and not clinical criteria were used.[21]

Surgery is reserved for GF that are anatomically complicated or refractory to medical therapy. Initial management generally includes the placement of Setons and drainage of associated collections. In low fistulas (anovaginal and anovulvar), a fistulotomy could be performed, always exerting special care in preserving continence. Therapy is much more complex in the case of rectovaginal fistulas, in which different procedures have been used, such as primary closure, endorectal or transvaginal advancement flap, among others. Any of these procedures is condemned to failure if performed in the presence of active rectal disease. Recurrences are sometimes treated with muscle interposition. A temporary ileostomy is frequently indicated, to protect the surgical site and promote healing. Sometimes, proctectomy and permanent ileostomy is the only choice.[9,25] This surgical "solution" is sometimes complicated by presacral sinusoidal inflammation, which is often as debilitating as usual fistulae.[26] With this heterogeneity of approaches, and the many degrees of severity in fistulas and in the structural damage they condition, success of surgical therapy is varied, oscillating between 25 and 93%, [25] and always lower than success rates in the surgical therapy of perianal disease. The evaluation of diverse surgical procedures performed in different centers and accompanied by a variety of medical therapies is surely complicated. Nevertheless, surgery has been the best performer in our series (38.8% of fistula closure, although a second surgery was needed in almost half of cases). Better results have been observed in the experience of dedicated surgical groups, such as a recent communication, in which a 44% initial success rate, improved up to 78% after a second surgery, in a series of 45 patients with CD, after a median of 1.8 surgeries.[7] These and other data support the recommendations of the European Crohn and Colitis Organization (ECCO), to surgically approach symptomatic GF when conservative and medical therapy fails.[10]

We observed better results in patients with a younger age at CD diagnosis, and worse outcome in older patients. This probably reflects the hormonal influence on genital trophism.

As regards tobacco use, its deleterious effects on CD outcomes are well known: smokers are subject to a higher incidence, more flares, more hospital admissions and a generally more aggressive course of their disease.[27] Moreover, in a recent series, tobacco use was the only factor associated to GF recurrence in CD patients.[7] As expected, and although a statistical significance was not achieved (probably due to the small sample), tobacco also seems to halve the rates of fistula closure observed in our series.

Our work surely has significant weaknesses and biases: it studies a short retrospective series, and response to therapy is evaluated by subjective clinical changes in a majority of cases. However, we think that our results are of great

clinical interest, and that the relative rarity of GF, their variability and the wide array of therapeutic options available make it difficult to obtain better data. In Crohn's disease, GF are fortunately rare, but imply a difficult personal challenge for the patients and a complicated therapeutic decision for the attending physicians. Although infliximab and, possibly, thiopurines deserve a chance in their management, surgery appears still the best management option.

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References

1. Schwartz DA, Loftus EV, Tremaine WJ, Panaccione R, Harmsen WS, Zinsmeister AR, Sandborn WJ. The natural history of fistulizing Crohn's disease in Olmsted County, Minnesota. *Gastroenterology* 2002;**122**:875–80.
2. Silverberg MS, Satsangi J, Ahmad T, Arnott ID, Bernstein CN, Brant SR, Caprilli R, Colombel JF, Gasche C, Geboes K, Jewell DP, Karban A, Loftus Jr EV, Peña AS, Riddell RH, Sachar DB, Schreiber S, Steinhart AH, Targan SR, Vermeire S, Warren BF. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a working party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* 2005;**19**(Suppl A):5–36.
3. Platell C, Mackay J, Collopy B, Fink R, Ryan P, Woods R. Anal pathology in patients with Crohn's disease. *Aust N Z J Surg* 1996;**66**:5–9.
4. Radcliffe AG, Ritchie JK, Hawley PR, Lennard-Jones JE, Northover JM. Anovaginal and rectovaginal fistulas in Crohn's disease. *Dis Colon Rectum* 1988;**31**:94–9.
5. Andreani SM, Dang HH, Grondona P, Khan AZ, Edwards DP. Rectovaginal fistula in Crohn's disease. *Dis Colon Rectum* 2007;**50**: 2215–22.
6. Moles JR, Minguez M. Tratamiento de situaciones clínicas especiales: fistulas no perianales y masa abdominal/absceso. Conductas de actuación en la enfermedad inflamatoria crónica intestinal, Manual práctico. 4ª edición. Madrid: Adalia farma SL; 2007. p. 119–35.
7. Pinto R, Peterson T, Shawki S, Davila W, Wexner S. Are there predictors of outcome following rectovaginal fistula repair. *Dis Colon Rectum* 2010;**53**:1240–7.
8. Lennard-Jones JE. Classification of inflammatory bowel disease. *Scand J Gastroenterol Suppl* 1989;**24**:2–6.
9. American Gastroenterological Association. American Gastroenterological Association Medical Position Statement: perianal Crohn's disease. *Gastroenterology* 2003;**125**:1503–7.
10. Caprilli R, Gassull MA, Escher JC, Moser G, Munkholm P, Forbes A, Hommes DW, Lochs H, Angelucci E, Cocco A, Vucelic B, Hildebrand H, Kolacek S, Riis L, Lukas M, de Franchis R, Hamilton M, Jantschek G, Michetti P, O'Morain C, Anwar MM, Freitas JL, Mouzas IA, Baert F, Mitchell R, Hawkey CJ. European Crohn's and Colitis Organization European evidence based consensus on the diagnosis and management of Crohn's disease: special situations. *Gut* 2006;**55**(Suppl 1):i36–58.
11. Turunen U, Farkkila M, Seppala K. Long term treatment of perianal or fistulous Crohn's disease with ciprofloxacin. *Scand J Gastroenterol* 1989;**24**:144.
12. Wolf JL. Ciprofloxacin may be useful in Crohn's disease. *Gastroenterology* 1990;**98**:A212.
13. Solomon MJ, Mc Leod RS, O'Connor BI, Steinhart A, Greenberg G, Cohen Z. Combination ciprofloxacin and metronidazole in severe perianal Crohn's disease. *Scand J Gastroenterol* 1993;**7**:571–3.
14. Present DH, Korelitz BI, Wisch N, Glass JL, Sachar DB, Pastermack BS. Treatment of Crohn's disease with 6-mercaptopurine. A long-term randomized double blind study. *N Engl J Med* 1980;**302**: 981–7.
15. O'Brien J, Bayless T, Bayless J. Use of azathioprine in the treatment of Crohn's disease. *Gastroenterology* 1991;**101**:39–46.
16. Present DH, Lichtiger S. Efficacy of cyclosporine in treatment of fistula of Crohn's disease. *Dig Dis Sci* 1994;**39**:374–80.
17. Hanauer SB, Smith MB. Rapid closure of Crohn's disease fistulas with continuous intravenous cyclosporine A. *Am J Gastroenterol* 1993;**88**:646–9.
18. Egan LJ, Sandborn WJ, Tremaine WJ. Clinical outcome following treatment of refractory inflammatory and fistulizing Crohn's disease with intravenous cyclosporine. *Am J Gastroenterol* 1998;**93**:442–8.
19. Sands BE, Blank MA, Patel K, van Deventer SJ. Longterm treatment of rectovaginal fistulas in Crohn's Disease: response to infliximab in the ACCENT II study. *Clin Gastroenterol Hepatol* 2004;**2**:912–20.
20. Parsi M, Lashner B, Achkar JP, Connor JT, Brzezinski A. Type of fistula determines response to infliximab in patients with fistulous Crohn's Disease. *Am J Gastroenterol* 2004;**99**:445–9.
21. Van Bodegraven AA, Sloots CE, Felt-Bersma RJ, Meuwissen SG. Endosonographic evidence of persistence of Crohn's disease associated fistulas after infliximab treatment, irrespective of clinical response. *Dis Colon Rectum* 2002;**45**:39–45.
22. Ricart E, Panaccione R, Loftus EV, Tremaine WJ, Sandborn WJ. Infliximab for Crohn_s disease in clinical practice at the Mayo Clinic: the first 100 patients. *Am J Gastroenterol* 2001;**96**: 722–9.
23. Bell SJ, Halligan S, Windsor AC, Williams AB, Wiesel P, Kamm MA. Response of fistulating Crohn's disease to infliximab treatment assessed by MRI. *Aliment Pharmacol Ther* 2003;**17**: 387–93.
24. Topstad DR, Panaccione R, Heine JA, Johnson DR, MacLean AR, Buie WD. Combined seton placement, infliximab infusion, and maintenance immunosuppressives improve healing rate in fistulizing anorectal Crohn's disease: a single center experience. *Dis Colon Rectum* 2003;**46**:577–83.
25. Ciga MA, Oteiza F, Marzo J, Armendáriz P, De Miguel M, Ortiz H. Tratamiento de la enfermedad de Crohn perianal. *An Sist Sanit Navar* 2006:29367–86.
26. Yamamoto T, Allan R, Keighley M. Audit of single-stage proctocolectomy for Crohn's disease: postoperative complications and recurrence. *Dis Colon Rectum* 2000;**43**:249–56.
27. Mahid SS, Minor KS, Soto RE, Hornung CA, Galandiuk S. Smoking and inflammatory bowel disease: a meta-analysis. *Mayo Clin Proc* 2006;**81**:1462–71.