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EDITORIAL

Perianal Crohn's disease: Is there something new?

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Abstract

Perianal lesions are common in patients with Crohn's disease, and display aggressive behavior in some cases. An accurate diagnosis is necessary for the optimal management of perianal lesions. Treatment of perianal Crohn's disease includes medical and/or surgical options. Recent discoveries in the pathogenesis of this disease have led to advances in medical and surgical therapy with good results. Perianal lesions in Crohn's disease remain a challenging aspect for both gastroenterologists and surgeons and lead to a greatly impaired quality of life for all patients affected by this disease. A multidisciplinary approach is mandatory to obtain the best results.

Key words: Crohn disease; Diagnosis; Biologic therapy; Surgery; Rectal fistula

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INTRODUCTION

Perianal lesions are common in patients with Crohn's disease (CD); these may consist of anal skin tags, hemorrhoids, anal fissures and ulcers, anorectal strictures, perianal fistulas and abscesses, rectovaginal fistulas or ultimately carcinoma[1].

In the literature, the incidence of perianal inflammation in patients with CD ranges from 25% to 80%[2]. Risk factors for the development of disabling disease in CD patients are an initial need for steroids, an age below 40 years, and the presence of perianal disease[3]. Perianal lesions show a more aggressive CD phenotype, especially if perianal disease is present at the initial diagnosis[3-5].

In approximately 10% of patients perianal fistulization is the initial manifestation, usually preceding the diagnosis by several years[6]; less than 5% of patients have perianal disease as a unique manifestation of disease[7]. In a population-based study of fistulizing CD the incidence of perianal fistulas was 26%[8]. Perianal fistulizing CD should be considered as a distinct disease phenotype from luminal fistulizing disease, and it has a greater association with colonic and upper gastrointestinal rather than small bowel disease[9].

The pathogenesis of perianal fistulas, despite the prevalence of fistulas in CD, is poorly understood. There are 2 theories: the first suggests that fistulas begin as deep penetrating ulcers, and the second that fistulas result from an anal gland abscess[10]; but it is believed that the etiology of perianal CD involves microbiological, genetic (susceptibil-

ity locus on chromosome 5) and immunological factors[11]. This could explain the aggressive and chronic behavior of perianal lesions.

CYTOKINES

The success of antibodies towards tumor necrosis factor (TNF)-α has led to recent studies investigating other cytokines in perianal CD. In one study[12], the serum levels of TNF-α, interleukin (IL)-12, IL-1β, and IL-6 were analyzed in 12 patients with chronic perianal CD and a CD activity index (CDAI) score < 150 to exclude active intestinal disease, in 7 patients with indeterminate colitis (IC) after restorative proctocolectomy with perianal complications, in 7 patients with active intestinal CD without perianal manifestations, and in 19 healthy controls. Serum TNF-α levels were significantly higher in patients with IC than perianal CD patients and healthy controls. Serum TNF-α levels significantly correlated with perianal CDAI score and with the presence of anal fistulas. Serum IL-12 levels correlated with the presence of anal strictures and were similar in all groups. Serum IL-6 levels were significantly higher in the presence of perianal fistulas and lower in the presence of anal strictures. This study found that the efficacy of anti-IL-12 antibodies appeared doubtful in chronic perianal CD or IC without anal strictures while the role of IL-6 as a systemic mediator for active chronic inflammation was confirmed.

In a subsequent study[13], the cytokine profile was assessed in the rectal mucosa of patients affected by perianal CD in order to understand its relations with the systemic cytokine profile and inflammatory parameters and the need for surgery. Seventeen patients affected by perianal CD, 7 affected by CD without perianal involvement, and 17 healthy controls were enrolled and underwent blood sampling and endoscopy. During endoscopy rectal mucosal samples were taken and the expression of TNF-α IL-6, IL-1β, IL-12, and transforming growth factor (TGF)-1 was quantified by enzyme-linked immunosorbent assay. Local cytokine levels were compared and correlated with diagnosis, therapy, phenotype (fistulizing and stenosing), and disease activity parameters. In the group with perianal CD, rectal mucosal IL-1β, IL-6, and serum IL-6 and TNF-α were higher than in patients with small bowel CD and healthy controls. IL-12 and TGF-1 mucosal levels did not show any differences among the 3 groups. Mucosal IL-6 significantly correlated with the perianal disease activity index (PDAI) and mucosal TNF-α and IL-1. Mucosal TNF-α and IL-1β showed a direct correlation with the histological grade of disease activity. Furthermore, mucosal levels of IL-6 and IL-12 seemed to be predictors of recurrence and of need for surgery in perianal CD patients.

Further prospective and randomized studies are necessary to evaluate the use of these cytokines in this complex disease.

CLASSIFICATION

In 1998, the Vienna classification categorized CD phenotypes, considering age at onset, location and behavior[14], but only in the Montreal modification (2005) of this classification was perianal disease added as a subclassification of behavior; perianal fistulizing disease is not necessarily associated with intestinal fistulizing disease, and it was felt that perianal disease alone required separate subclassification[15].

At the present time, there are different classification systems for perianal CD, but no one has achieved a widespread agreement. In 1976 Parks *et al*[16] proposed a classification of perianal fistulas that uses the external sphincter as a landmark, describing 5 types: intersphincteric, trans-sphincteric, supra-sphincteric, extrasphincteric, and superficial. However, the value of this classification is limited because it does not consider the connection with other organs such as the bladder or the vagina. In 1978, Hughes proposed the Cardiff classification, an anatomic and pathologic classification in which each major manifestation of perianal CD (ulceration, fistula and stricture) is graded on a 2-point scale. This classification has never been globally accepted because it is considered of limited clinical relevance and difficult to use in daily practice[17,18]. In 2003, the American Gastroenterological Association (AGA) technical review[1] proposed an empiric approach that included: physical examination of the perianal area, endoscopic evaluation and a classification of fistulas as simple or complex: simple fistulas are low (superficial, low inter-sphincteric or low intra-sphincteric origin) with a single external opening and are not associated with perianal abscess, rectal stenosis or macroscopic proctitis and have no connection to the vagina or bladder; complex fistulas are high (high intersphincteric, high trans-sphincteric, supra-sphincteric or extra-sphincteric origin) and may have several external openings associated with perianal abscess, rectovaginal fistula, anorectal stenosis or macroscopic proctitis.

In 1995, Irvine described an index to evaluate perianal disease morbidity in CD patients, the PDAI, comprised of 5 categories: presence of fistula discharge, pain, restriction of daily activity, restriction of sexual activity, type of perianal disease, and degree of induration. Each category is graded on a 5-point scale, ranging from no symptoms to severe symptoms. It is widely used but it has never been compared with a reference standard[19,20]. Another method proposed to measure perianal disease activity is the Fistula Drainage Assessment: the presence of purulent drainage from the cutaneous opening after compression is considered an index of activity, but it does not consider the morbidity of the patient and the association with an abscess[20].

DIAGNOSIS

An accurate diagnosis is necessary for the optimal management of perianal lesions. Recently, the goal of treatment has changed from symptomatic improvement to cessation of drainage or even fistula healing. Therefore, the priority of diagnostic tools is to define the anatomy and the number of the fistulas, their complexity, and complicating features such as abscess and anal stenosis[6].

Besides physical examination (findings of skin tags, ulcers, fissures, abscesses, fistulas or anorectal stenoses), there are several other diagnostic modalities. Endoscopic examination is important to identify macroscopic inflammation or stenosis in the rectum; furthermore AGA and the European Crohn's and Colitis Organization (ECCO) agreed on the need to complete the study of perianal disease with other diagnostic methods such as examination under anesthesia (EUA), magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS)[21].

EUA is considered the gold standard for assessing fistulas; it has an accuracy of up to 90 for diagnosis and classification of fistulas and abscesses[22]. At the same time, it is possible to perform several surgical procedures to treat fistulas. However, as suggested by one author, anesthesia can produce a loss of tone and could compromise precise identification of underlying muscles[23]. MRI, an expensive modality, has an accuracy of between 76% and 100% and, combined with EUA, can obtain additional information in 15%-21% of patients; in contrast, EUS, known to be operator-dependent, has a diagnostic accuracy of between 56% and 100% and its findings can alter the surgical approach in 10%-15% of cases[21]. When any 2 modalities are combined, the accuracy is 100%, suggesting that EUA in combination with either EUS or pelvic MRI is the best approach for evaluating and classifying perianal fistulas[22]. The diagnostic accuracy of conventional fistulography and computed tomography (CT) does not exceed 50%-60%, which is considered too low to be clinically useful[1]. Even though fistulography was the first technique used to assess perianal fistula, nowadays it is rarely performed because of several weak points: extensions from the primary track may fail, the sphincter muscles are not directly imaged, the levator plane cannot be visualized, and there is dissemination of septic fistula contents and discomfort for patients[6,21]. Since CT exposes patients to not inconsiderable amounts of ionizing radiation, it may only be used for the diagnosis of fistulas associated with pelvic abscesses if other techniques are unavailable or cannot be tolerated[23,24].

THERAPY

Treatment of perianal CD includes medical and/or surgical options. The primary aim is to heal perianal lesions, but in many cases, because of the aggressiveness of the disease, the physician's role is to relieve symptoms and treat complications of the disease to improve the patients' quality of life. The percentage of spontaneous healing for perianal fistulas is very low, ranging from 6% to 13% in the placebo arm of 2 controlled studies[25,26].

MEDICAL THERAPY

Drugs with definite or potential efficacy for treating perianal CD include antibiotics (metronidazole and ciprofloxacin), immunosuppressors (azathioprine and 6-mercaptopurine), calcineurin inhibitors (cyclosporine and tacrolimus) and biologic agents (infliximab, adalimumab and certolizumab)[1,6].

Antibiotics

Antibiotics are used as first-line treatment for fistula healing, and also for abscesses and infection associated with fistulas. Despite the widespread use of antibiotics for the treatment of perianal CD, there is a lack of controlled studies in the literature and usually data consist of small sample size trials[27,28]. In these studies, the clinical response generally occurs after 6 to 8 wk, as a decreased drainage, while fistula closure is uncommon and symptoms may recur after the end of treatment. Recently, Thia *et al*[29] performed a randomized, double-blind, placebo-controlled trial to evaluate ciprofloxacin and metronidazole for the treatment of perianal CD, concluding that remission and response occurred more frequently in patients treated with ciprofloxacin, but the difference between the treatment arms was not significant. The limit of this study was probably the small sample size. Antibiotics are also used as a bridge to immunosuppressive therapy with azathioprine. In a prospective open-label trial, the use of metronidazole and/or ciprofloxacin at week 8 induced fistula closure in 25% of cases[30]. At week 20, patients treated with additional azathioprine had a better mid-term response (48% *vs* 15%). Antibiotics can be also used as an adjuvant to other drugs. In a recent placebo-controlled study, all patients received infliximab and were randomized to receive either 500 mg ciprofloxacin twice daily or a placebo for 12 wk. The response at week 18 showed a better result of ciprofloxacin in combination with infliximab compared to infliximab alone[31]. Recently, in a randomized controlled study[32], 74 patients with perianal CD received 0.7 g 10% metronidazole ointment or placebo ointment applied perianally 3 times daily. Metronidazole ointment was not effective in reducing the perianal DCAI score, but some secondary outcomes showed improvement, suggestive of a treatment effect and it was well tolerated, with minimal adverse effects.

Immunosuppressants

Azathioprine and 6-mercaptopurine are immunosuppressive agents that, as demonstrated in the literature, successfully treat intestinal CD inflammation[33]. A meta-analysis of 5 randomized controlled studies, in which the closure of various fistulas was considered, showed a complete closure or decreased drainage in 54% of the patients treated with azathioprine or 6-mercaptopurine compared with 21% in the placebo group[34]. However, in this meta-analysis the fistula response was a secondary endpoint in all of the studies considered and at the moment there are no controlled trials in which fistula closure is the primary endpoint. Azathioprine or 6-mercaptopurine could be used as a second-line treatment in patients in whom immediate surgery is not mandatory, and when other pharmacological treatments have already been initiated[6].

Cyclosporine selectively blocks T-helper and cytotoxic lymphocytes through the inhibition of the transcription of IL-2. Several uncontrolled case series reported the use of intravenous cyclosporine in perianal CD patients resistant to traditional therapy, but the initial response was rapidly lost on drug withdrawal[35]. The effects of tacrolimus,

which has a similar mechanism, on fistulizing CD have been evaluated in a randomized, double-blind, placebo-controlled, multicenter study: 43% of the tacrolimus-treated patients had fistula improvement compared with only 8% of the placebo group; however fistula remission was comparable in the 2 groups[36]. More studies are warranted and at the moment the use of cyclosporine and tacrolimus for treatment of fistulizing CD is not recommended[6].

Methotrexate is used as a third-line therapeutic agent for CD patients intolerant to azathioprine and 6-mercaptopurine. No prospective studies have investigated its use for the treatment of fistulizing CD; however, in a retrospective study, 44% of patients treated with methotrexate had partial or complete fistula closure after 6 mo[37].

Studies evaluating therapies such as sargramostim (a granulocyte-macrophage colony-stimulating factor), mycophenolate mofetil (an antimetabolite agent) and thalidomide concluded that these could be considered as potential treatments for perianal CD[38-40].

Biologic therapy

The use of anti-TNF-α agents has changed the approach to CD, especially in patients with severe and refractory disease; in fact TNF-α is believed to play a key role in the pathogenesis of this disease[41].

Infliximab is a murine/human chimeric monoclonal antibody directed toward soluble and membrane-bound TNF-α[42]. There are 2 randomized, double-blind, placebo-controlled trials that demonstrated the efficacy of infliximab in fistulizing CD[25,43]. Present *et al*[30] assessed infliximab induction therapy and reported that 3 infusions of infliximab, 5 or 10 mg/kg, at weeks 0, 2, and 6 resulted in complete perianal fistula closure in 46% of patients. The median length of time the fistula remained closed was 12 wk, and the response rate was higher with the 5 mg/kg dose. The ACCENT Ⅱ (Adjuvant Colon Cancer End Points) study evaluated infliximab as maintenance therapy with 5 mg/kg infliximab at weeks 0, 2 and 6[43]. Of those patients, 64% had a response to therapy at weeks 10 and 14. At week 14, responders were randomized to receive placebo or infliximab 5 mg/kg every 8 wk for 54 wk. The time to loss of response was 40 wk in the infliximab maintenance group *versus* 14 wk in the placebo group. Cessation of drainage at week 54 was maintained in 36% of the patients in the infliximab group compared with 19% of the placebo group. The regime proven to be efficacious in clinical studies comprises induction therapy with 5 mg/kg infliximab at weeks 0, 2 and 6; maintenance therapy can then be continued at 5 mg/kg every 8 wk and the dose may be increased to 10 mg/kg if loss of response is seen at the lower dose. Adverse events of infliximab include infusion reactions, an increased rate of infections, delayed hypersensitivity reactions, formation of antibodies to infliximab, formation of anti-double-stranded DNA antibodies and drug-induced lupus[1].

Adalimumab is a fully humanized monoclonal antibody directed toward TNF-α and has proven effectiveness and efficacy in CD[44]. Its effects have been evaluated in 2 randomized, double-blind, placebo controlled, short-term (4 wk) induction trials. In the CLASSIC-1 trial (Clinical Assessment of Adalimumab Safety and Efficacy Studied as an Induction Therapy in Crohn's Disease), adalimumab was administered at 2 different doses during weeks 0 and 2; instead in the GAIN study (Gauging Adalimumab Efficacy in Infliximab Nonresponders), adalimumab was administered at a high dose and all participants were intolerant to infliximab or had experienced loss of response during week 4 of treatment[45]. In both studies, fistula closure was not significantly higher in patients treated with adalimumab compared with placebo. In the CHARM (Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance) study, adalimumab was associated with an increased fistula closure compared with placebo. Closure of all fistulas that were draining at baseline was achieved in 30%-33% of adalimumab-treated patients compared with 13% of placebo-treated patients[46]. CD patients, including those with a fistula, should receive an induction dose of adalimumab (160 mg in the USA and 80 mg in Europe), with a second dose (80 mg in the USA and 40 mg in Europe) during week 2; the recommended maintenance dose in both the USA and Europe is 40 mg every other week, beginning at week 4 and the dose frequency can be increased to once weekly if there is no response[6].

Two randomized, double-blind, placebo-controlled trials that investigated the efficacy of certolizumab on fistula closure, for comparison with infliximab and adalimumab[47], were not sufficiently powered[48,49], and its effects require further study. Ng *et al*[50] evaluated CD perianal fistula closure after anti-TNF-α using MRI: even though fistulas appeared clinically healed, MRI demonstrated the persistence of the fistulous tracks as already demonstrated by previous studies[51]; so MRI fistula resolution could be useful to determine the duration of anti-TNF-α therapy.

A recent Japanese study investigated the effects of adsorptive carbon in fistulizing CD patients[52]. Thirty-seven percent of patients treated with an oral adsorptive carbon agent (AST-120) showed an improvement compared to 10% of the placebo group; the former group also had a significantly lower rate of remission (29.6% *vs* 6.7%). Probably adsorptive carbon reverses abnormalities in the luminal environment and gut microflora. In the ECCO consensus statement antibiotics and azathioprine or 6-mercaptopurine are considered the first-line therapy in complex perianal disease, and infliximab or adalimumab are reserved as a second-line treatment in case of failure[53]. In the AGA technical review infliximab is recommended for the treatment of complex perianal disease along with azathioprine or 6-mercaptopurine and antibiotics for the induction phase[1]. Maintenance is recommended with azathioprine or 6-mercaptopurine, and just in some cases in association with infliximab.

Surgical therapy

In the literature the incidence of perianal CD fistulas that require surgery ranges from 25% to 30%[54,55]. The primary goal of surgery is fistula healing and avoidance of sphinc-

ter damage. Patients with superficial or low perianal fistulas without proctitis can be treated by fistulotomy, which has reported healing rates of up to 85%[56,57]. Surgical treatment of complex perianal fistulizing disease requires abscess drainage and usually placement of non-cutting setons[58] before biologic therapy. Setons can be removed after 3 mo in the presence of fistula healing or can remain if the healing process has not been established. However, patients who were assessed 10 years after placement of a seton showed that complete healing was obtained in only 20% of patients[59]. Fistulectomy or fistulotomy are rarely indicated in complex fistulas because of the high rate of subsequent proctectomy due to closure failure or incontinence caused by the transection of both anal sphincters[53,58]. Endorectal flaps are useful when there are severe cases of high fistulas[58,60]. An advancement flap consists of incising a flap of tissue (mucosa, submucosa, circular muscle) around the internal opening of a fistula, excising the internal opening of the fistula tract, and pulling the flap down to cover the opening[61].

Makowiec *et al*[62] reported an initial healing rate of 89% in patients treated with an advancement-flap procedure, but fistulas recurred in 34% of cases during follow-up. If a second flap fails, the failure rate of subsequent flaps increases up to 75% and a temporary stoma might be necessary[63]. In patients with severe refractory disease, fecal diversion (loop ileostomy or end colostomy) is necessary and has an early response rate of 70%-80%[64,65]. Quality of life in symptomatic patients is rapidly improved by fecal diversion[53]. A recent study showed that patients with complicated perianal CD, colonic involvement, and a high rate of abdominal procedures carried a significant risk for a permanent stoma; the incidence of patients requiring a permanent stoma was 31%[66]. In another series of 86 patients with perianal CD disease, 49% of patients finally required permanent fecal diversion[67]. In the literature, proctocolectomy is necessary in only 18% of patients[66].

Primary closure after extended resection can be limited by scar tissue and healing can be impaired by contamination and immunosuppressive medication. Thus, myocutaneous flaps such as the gracilis and the distally based rectus abdominis muscle are used to repair perineal and vaginal defects that are too big to be closed directly.

The use of myocutaneous flaps are well described after proctectomy for cancer and there are only a few reports focusing on CD patients undergoing proctocolectomy and primary closure with myocutaneous flaps[68-70]. Schaden *et al*[69] concluded that a combined proctocolectomy and a perineal single-stage myocutaneous flap closure technique can reduce recovery time, obtain complete healing and improve patients' quality of life.

The treatment of rectovaginal fistulas in CD patients remains challenging. Rectovaginal fistulas seem to be a negative prognostic indicator for successful anti-TNF-α therapy[71]. In a study evaluating a series of 52 CD patients undergoing surgery for a rectovaginal fistula the outcome of surgery and the effect of anti-TNF therapy on healing were assessed[72]. Fistula closure was achieved in 81% of patients. Primary and secondary surgical success rates were 56% and 57% respectively. The primary healing rate was similar in patients who received anti-TNF treatment before the first operation (12 of 18 patients) and those who did not (19 of 34). In univariate analysis, duration of CD and previous extended colonic resection were significantly related to failure of primary surgery, but only the latter remained significant in multivariate analysis The authors concluded that fistula closure was achieved in most patients, but more than one operation was often required.

A recent systematic review was performed including 11 observational studies with a total of 219 flap procedures for rectovaginal fistulas in CD[73]. The pooled primary fistula closure rate was 54.2% after rectal advancement flaps and 69.4% after vaginal advancement flaps. Four studies were eligible for direct comparison between the 2 procedures. Although limited by the small number of studies at a low clinical evidence level, no significant difference in terms of outcome between rectal and vaginal advancement flaps was observed. The risk of recurrence after rectal advancement flaps compared with vaginal advancement flaps also seemed similar.

New therapies

New therapies include laser and adhesive treatment. In an uncontrolled study in perianal CD patients carbon dioxide laser ablation is considered an alternative treatment[74]. The injection of fibrin glue into fistulas is a simple and safe procedure[75]. The first series studies regarding this treatment reported good healing rates (52%-60%), while recent trials have not achieved the same success[76].

Fibrin glue variants include human granulocyte colony-stimulating factor[77] and autologous mesenchymal adult stem cells. Adult stem cells are obtained from adipose tissue with liposuction and initial studies have shown a complete response in 75% of perianal CD patients with complex fistulas[78,79].

More recently bioprosthetic plugs, incorporating porcine intestinal submucosa, have been used in the treatment of patients with anal fistulas[80], but in a retrospective review the use of anal fistula plugs was associated with a lower success rate (15%) than previously reported[81]. Finally, there are other local therapies which are under development. Tacrolimus is a macrolide compound isolated from *Streptomyces tsukubaensis*. Hart *et al*[82], in a randomized, double-blind, placebo-controlled trial showed that, although complete healing was not observed, improvement occurred rapidly, but there was no clear clinical indication that tacrolimus was helpful for fistulizing disease. Topical tacrolimus may have a role in patients who do not respond to infliximab. Similarly, infliximab[83,84], and more recently adalimumab[85], injected directly into the fistula seem to result in healing in some patients resistant to systemic therapy; the rationale of this approach is to avoid systemic toxicity.

CONCLUSION

Perianal lesions in CD remain a challenge for both gas-

troenterologists and surgeons and they lead to a greatly impaired quality of life for all affected patients. A multidisciplinary approach is mandatory to obtain the best results.

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