

Timing and pharmacological support in the surgical treatment of multiple perianal fistulas in Crohn's Disease

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Abstract. We present a case report on the management of a young woman affected by Crohn's Disease ever since childhood, complicated by complex, multiple perianal fistulas. In literature, there is increasing evidence to support the treatment of perianal fistulas using a combined association of medical and surgical strategies. In the case of our patient, the choice of surgery in association with pharmacological treatment was supported by the consideration of the fact that intervening during a quiescent phase of the disease, from the symptomatic, clinical-biohumoral and endoscopic standpoint, would have reduced the risk of complications and thus promoted healing. (www.actabiomedica.it)

Key words: Crohn's Disease, I.B.D., perianal fistular surgery, mesatazine, beclometasone dipropionate

Introduction

Perianal fistulas in patients affected by Crohn's Disease are a pathological condition that can be extremely difficult to treat and that can have a strong negative impact on the patient's quality of life. The cumulative incidence of perianal fistulas in patients affected by Crohn's Disease is between around 20 and 25% (1), so it is a problem of considerable dimensions. The American Gastroenterological Association (AGA) has developed a clinical classification of perianal fistulas that includes only two categories: simple fistulas and complex fistulas (2). The first are low, they usually have a single external fistulous opening, they are not associated with the presence of a perianal abscess or with macroscopic proctitis, the fistula tract itself is small and not, in any case, connected with the bladder or the vagina, and they are generally susceptible of medical treatment alone. Complex perianal fistulas, on the other hand, are high, they can have multiple external fistulous openings, they are associated with perianal abscesses and macroscopic proctitis with

rectal stenosis, and the fistulous tracts can extend to the bladder or the vagina. Complex perianal fistulas are extremely difficult to manage. They require a synergy of aggressive treatments, both medical and surgical, which sometimes fail to bring about complete healing or which can present recurrences within a short space of time (3).

Case Report

The case involves M.B., a 41-year old woman with a known medical history of Crohn's Disease, clinically and histologically documented since the age of 12, who reported to us roughly a year ago asking us to "resolve her extremely troublesome problem of perianal fistulas". We were already familiar with the patient as she had been treated, on reaching adulthood, both by the gastroenterology team and by the surgical team of our Department. In actual fact, we lost track of her for a few years because, since she was feeling well, she decided, of her own free will, to suspend all

the treatments and not to report for any more check-ups. The worsening of a situation characterised by multiple chronic abscesses with multiple branching fistulizations on both sides of the anal opening and at the front towards the vulva prompted our patient to report to our centre on April 2010. Her recent medical history showed a situation of general well-being apart from continuous discomfort in the perianal and perineal region which had persisted for several years and which severely limited her in physical and relational activities; her general state of health was, however, very good. The physical objective examination proved negative with the exception of the perineum which presented a clinical picture of chronic inflammation with purulent secretions from multiple fistulous openings. This induced us to carry out an MR fistulography which produced the following result (Fig. 1): “in the right perianal region, fistulous tract (...) that branches into two parts, one of which is posterior and continues superiorly in an abscessual collection (...) and a frontal part that extends to the *labium ma-*

jus. A fistulous tract starts at the left perianal region and extends in a superior-anterior direction for a length of 51 mm until it reaches the floor of the levator ani muscles but remains below them (...)”.

Prior to suggesting a course of treatment, we subjected the patient to a re-evaluation of the underlying disease by means of blood chemistry tests which revealed a slight neutrophilic leukocytosis (WBC 11,780) associated with increased levels of anti-ASCA antibodies (IgA 144.0 KU/L, IgG 123.0 KU/L), and a colonoscopy which revealed the integrity of the colonic mucosa and the last ileal loop, further confirmed by the histological examination of the serial biopsies, both ileal and colonic. Cultural analyses of the fistulous secretions repeatedly excluded the presence of germs – other than the common bacterial flora of the perianal region – both in terms of morphology and in terms of sensitivity to antibiotics.

The apparent systemic remission of the disease prompted us to suggest the possibility of surgical treatment for the severe perineal disease. But we

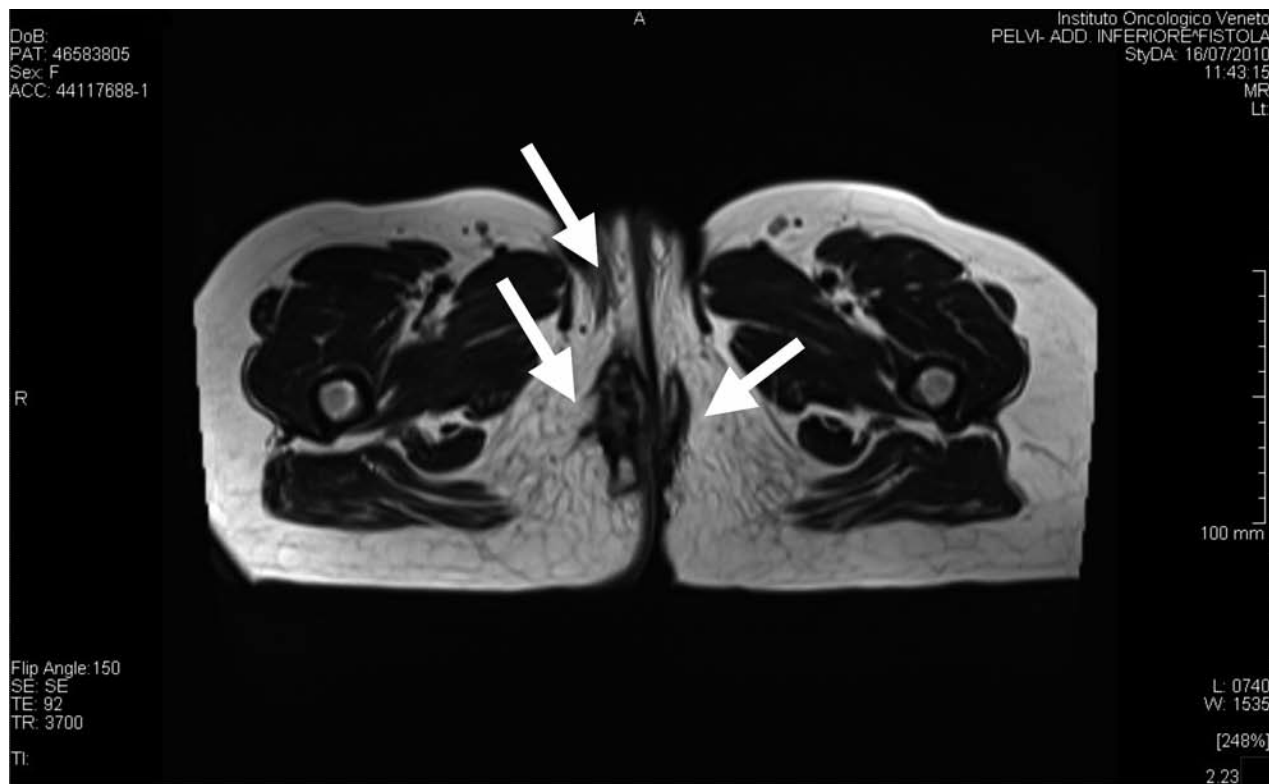


Figure 1. MR image of the perineal floor showing the complex fistulous picture of our patient (Arrows)

nonetheless started treatment with Mesalazine capsules at 800 mg x 3/day and Beclomethasone Dipropionate enemas, first daily and then on alternate days for two months. With this treatment, the inflammatory picture and the subjective symptomatology improved. Given the good therapeutic control and the approach of the summer season, we decided to continue the medical treatment for a further three months.

On 23/09/2010, after a check-up that confirmed the existence of a perfectly localized clinical picture, a surgical operation was performed to extensively remove the fistulous network and which involved opening of the abscess sacs, which reached beyond the floor of the levator muscles on both sides, placing of a suprasphincteric seton on the left and another on the right which also affected some fibres of the levator muscle. After extensive washing, drainage plugs were positioned bilaterally. The postoperative phase passed without particular complications, although for the first week dressings had to be changed on alternate days under anaesthetic and the patient was also admitted to hospital on the ninth day after surgery due to a hemorrhage, resolved by a simple tamponade. Twenty days after surgery, the patient's dressings were changed twice a week and the setons were subjected to traction after the first month. They fell off after a further 8 weeks on the left side and after 10 weeks on the right. Five months after surgery, the left perianal wound closed up completely, while the right one had re-epithelialized completely after almost 7 months. Throughout this period, the patient had continued with the Mesalazine treatment which, as of the second month after surgery, had been reduced to 800mg x 2, while the Beclomethasone Dipropionate enemas, suspended for obvious management reasons during the postoperative period, were resumed on alternate days for a month after the setons had fallen off.

The blood chemistry tests carried out after the successful completion of the postoperative period, show slight polyclonal hypergammaglobulinemia with persistent and increased levels of anti-ASCA antibodies (IgA 1300.0 kU/L; IgG 124.0 kU/L) which prompted us to continue with the Mesalazine treatment.

The patient is, nonetheless, fully satisfied with the results of the surgery. She has experienced complete remission of the subjective symptomatology, and has already asked us to perform plastic surgery on the perineal scars.

Discussion

The treatment of perianal fistulas in patients affected by Crohn's Disease is particularly difficult and complex, and is still considered a highly controversial challenge, firstly, due to the many and varied therapeutic options available and secondly due to the impact on quality of life not only of the disease itself but also of its treatment and the potential complications of the same.

In the pharmacological treatment of perianal fistulas in patients affected by Crohn's Disease, therapeutic strategies involve the use of antibiotics, immunosuppressants and biological drugs. Antibiotic therapy is the front-line pharmacological treatment and generally involves the use of metronidazole, sometimes in association with ciprofloxacin. A recent review reports the closing of fistulous tracts in 34-83% of patients affected by Crohn's Disease (4). Antibiotics are, however, associated with a high recurrence rate on discontinuation of the therapy. In the pathogenic hypothesis of perianal fistulas associated with Crohn's Disease, in addition to superinfection by anaerobic bacteria, a key role is also played by mediators of inflammation and, in particular, by TNF-alpha. This aspect justifies the introduction in therapeutic procedures of monoclonal antibodies, such as infliximab or adalimumab. Present et al. (5) report 46% of closures of fistulous tracts after 12 weeks of treatment with infliximab. However, treatment with anti-TNF alpha presents a number of intrinsic disadvantages. Some studies, among which that of Sands (6), demonstrate better results by implementing continuous, long-term treatment with infliximab, but this is associated with a series of major systemic adverse effects, such as an increased rate of opportunistic infections or the risk of lymphoproliferative diseases, not forgetting the extremely high costs of these treatments. The role of corticosteroids and immunosuppressants, on the other

hand, appears to be somewhat limited. Among the immunosuppressants, azathioprine and 6-mercaptopurine promote the closure of the fistulas in a small minority of patients, resulting in a significant improvement in subjective symptomatology, such as a reduction in the degree of pain or discomfort suffered, while the clinical response to the intravenous administration of cyclosporine or the oral administration of tacrolimus manifests itself rapidly in the course of the first week of treatment, so these drugs are used, for the most part, as "bridging therapy" (3).

Our patient presented with a chronic perianal fistulous disease, without signs of superinfection. For this reason, we opted for steroidal, anti-inflammatory support therapy. The general state of well-being of the patient did not, in our opinion, justify the use of drugs that would be more difficult to manage and with more severe adverse effects, such as the most widely used immunosuppressants (azathioprine or 6-mercaptopurine), not to mention immunomodulators, the results of which do not yet enjoy a consolidated consensus.

In the past, surgery tended only to be considered in the most serious, acute cases in order to treat or avoid clinical pictures of sepsis. This approach was justified by the risk of complications, such as incontinence or lack of healing, with worsening of the perianal disease to such an extent as to require a proctectomy with a stoma upstream. Such serious complications unquestionably raised doubts about recommending a treatment that could have an impact on quality of life that was even worse than the disease itself. It is currently a consolidated fact that the best results in the management of patients with Crohn's Disease and perianal fistulas, especially complex ones, are obtained through combined medical and surgical treatment (7). Infliximab, for example, promotes the closure of fistulous tracts, but sometimes the closure of the external openings is too rapid with respect to the deep healing so, over the course of time, this can lead to the formation of abscesses which can, in turn, be effectively avoided through the placement of a slow-cutting seton. Our patient responded positively to a traditional type of surgical treatment with extensive removal of the fistulous network and seton placement with drainage plugs. Moreover, the subsequent re-assessments, carried out under sedation in order to be able

to examine and medicate the patient with all the attention and precision required, were of fundamental importance. Among the new strategies in the surgical field, it is important to mention the topical administration of tacrolimus, fibrin glue and the use of adipose (fat) stem cells (4); these are also, however, experimental options for which valid study protocols do not yet exist.

In conclusion, the clinical case that we have presented offers a valid basis for discussion, i.e. the concept of the therapeutic window. Scientific literature is, in fact, rich in studies that examine the various therapeutic possibilities, be they medical or surgical, but very few indications are to be found regarding timing. In our case report, the surgical indication was contemplated primarily because the disease was in a quiescent phase. The interesting data therefore emerges from the consideration that, in the management of patients with perianal fistulas and Crohn's Disease, the efficacy of the therapies is not only linked to the pathogenesis of the clinical picture, but it is also strongly conditioned by the moment in which they are applied, hence in relation to the phase of activity of the disease itself. In this respect, a new and stimulating line of research is to be hoped for, both for gastroenterologists and for surgeons, first and foremost because the serious and troublesome problem of perianal fistulas strikes, on average, one Crohn's Disease sufferer out of four and the treatment available today still does not offer fully satisfactory results.

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