Rapid Recovery of a Rectovaginal Fistula with Infliximab in a Patient with Crohn’s Disease

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Abstract

We present the case of a female patient diagnosed with colonic Crohn’s disease, having a clinical evolution with many recurrences and in whom conventional therapy had failed. The patient was admitted in our department 4 years after the onset of the disease, with an altered general state, diarrhea, malnutrition, fever and fecaloid vaginal discharge. Investigations classified the patient in a severe activity flare of Crohn’s disease (CDAI 329), complicated with a rectovaginal fistula. Infliximab therapy was initiated. The evolution was rapidly favorable and the fistula closed after 4 weeks of therapy.

Key words


Introduction

During the past decades since Crohn’s Disease (CD) was diagnosed by its clinical manifestation, researchers have faced many problems, from defining the etiopathogenetic mechanisms to the extending of the range of diagnostic tools and subsequently to finding new therapeutic solutions in order to improve the evolution and prognosis of these patients [1].

In order to diagnose CD, a broad range of investigations have been used, from biochemical and serologic examinations, upper and lower digestive endoscopy, histopathological examination, ultrasonography, enteroclysis and newer acquisitions such as capsule endoscopy, endoscopic ultrasound, CT and MRI [2].

The clinical presentation of CD is heterogeneous, and during the evolution complications such as stenoses and bowel obstructions, fistulas, abscesses or perianal lesions may occur. Therapy depends on the clinical aspect, extension and presence of the complications and includes antiinflammatory agents, antibiotics, corticosteroids, immunosuppressants, and biological agents [3].

Tumor necrosis factor alpha (TNFα) is a proinflammatory mediator that plays a key role in CD pathogenesis. Introduction of Infliximab, an anti TNFα agent, in the therapy has demonstrated favorable results for obtaining and maintaining remission in selected cases of CD. In addition, it has contributed to the reduction of the number of hospitalizations and the need for surgery and to the improvement of the quality of life in these patients [4].

Case report

A 24-year old female patient was diagnosed with colonic CD. For 4 years, her evolution was fluctuating, with periods of remission and recurrence, increasing in frequency over the last 2 years. During the evolution, the treatment evolved from 5-ASA (5-aminosalicylic acid) and corticosteroids in maximal doses to azathioprine. Nevertheless, the remission periods became shorter and the flares more severe, so that the patient herself decided to stop therapy.

About 6 months after ceasing the treatment, she came to our clinic for 8-10 diarrheic stools/day with mucus, diffuse abdominal and perianal pain, disuria, vaginal secretions with fecaloid content, dispareunia, fever 37.9-38.5°C, important weight loss, poor general state.

At the physical examination, the patient was depressed, with marked denutrition (BMI=13.67 kg/m²), pale skin, fever 37.8°C. She presented sensitivity on abdomen palpation, and no pathological findings of the perianal region. Laboratory examination revealed dyselectrolitemia, leucocytosis with fecaloid content, dispareunia, fever 37.9-38.5°C, important weight loss, poor general state.

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The conventional abdominal ultrasound was completed by high resolution ultrasound focused on the digestive tract. A thickening of the colonic wall was found,
which was hypoechogeneous and presented intraparietal hypervascularization at Doppler color examination (Fig. 1). These changes were present in the whole colon, and numerous pericolonic lymph nodes and a small quantity of liquid in the pelvic cavity were also found.

The endovaginal ultrasound revealed the presence of a fistula between the rectum and vagina, enlarged lymph nodes (Fig. 2), hypoechogenicity and thickening of the colonic wall (Fig. 3). The colonoscopy with terminal ileoscopy showed aphthoid ulcerations in the terminal ileum, longitudinal deep ulcerations, segmentary “cobblestone” lesions in the entire colon, and a fistulous opening on the lateral right wall of the rectum. Histopathological examination of the biopsy samples from the colon showed mixed diffuse inflammatory infiltrations, focal cryptic abscesses, deep ulcerations, fibrosis and granulomas formed by epitelioid cells and multinuclear giant cells (Fig. 4).

Upper digestive endoscopy and enteroclysis did not evidence extension to other digestive tract segments.

The severity of the flare was assessed by the CDAI score, obtaining 329 points, which confirmed an active severe form. According to the Vienna classification, the patient was classified as type A1L2B3 [5].

Taking into account the history of the patient, with numerous recurrences during the first two steps of maximal therapy (corticotherapy, 5-ASA, immunosuppressants) and the severe fistulising form diagnosed during the current hospitalization, the decision was made to administer a biological therapy, namely Infliximab. Prior to starting Infliximab, an epidemiological inquiry, intradermoreaction to PPD and the chest Xray excluded a present or antecedent tuberculosis.

The recommended treatment consisted of three doses of Infliximab 5 mg/kg/dose, gradual reduction of the corticosteroid, broad-spectrum antibiotic treatment and supportive treatment to correct the existent mineral and protein deficits.

After 4 weeks of treatment, the clinical state of the patient improved, the number of the stools diminished to 2-3/day, without pathological products in the stools. The vaginal discharge disappeared, the rectovaginal fistula (evaluated by ultrasonography) was sealed and the patient had a weight gain of 4 kg. She was followed-up at 6 and 12 months after treatment. She remained in remission, with a good nutritional status, free of symptoms, no biological and imaging pathological findings, and has been reintegrated in her professional milieu.
Discussion

Fistulas as complications of CD are in 54% of cases perianal, 24% enteroeenteric, 9% rectovaginal and 13% with other locations. They are more frequent in the colonic location of the disease [6-8]. Fistulas can be internal or external. The contrast radiological examinations (barium enema, enteroclysis, CT) visualize the trajectory of the fistula [9-11]. Endoscopy with biopsies can evaluate the strictures and assess the severity and the extension on the inflammatory process. Preoperatively, in enterocolonic fistulas, endoscopy has a role in establishing the type of surgery and in the future might also have a role in the topical administration of anticytokines or biological products [12].

Abdominal ultrasound has a sensitivity and specificity comparable to those of the radiologic methods in diagnosing fistulas, stenoses and abscesses that complicate CD [13, 14].

Treatment of the fistulas is a therapeutical challenge in CD. Assessment of the whole digestive tract is required to establish the best therapeutic management. The treatment starts with conservative medical methods for moderate or severe forms and ends with surgery for cases complicated with ulcers, strictures or in case of failure of a previous surgical treatment [15]. Fistulas are generally associated with active forms of Crohn’s disease, with chronic evolution, and are rarely spontaneous, in 6-13% [16-19].

Administration of 5-ASA, corticosteroids and budesonide is not efficient, and recent trials using Rh interleukin 10 or 11, beta7 monoclonal antibodies, molecules of intercellular adhesion did not report positive results. Azathioprine, 6-mercaptopurine, cyclosporine and methotrexate can have favourable, but inconstant effects. Only Infliximab and tacrolimus have proved efficacy [6, 16, 20].

Crohn’s disease is characterized by an increase of the TH1 response, that induces production of inflammatory cytokines (TNFα, IFNγ, IL-18, IL-12). Production of TNFα is augmented in the intestinal mucosa in CD and it has a role as proinflammatory mediator with multiple actions: a) it stimulates the production of other cytokines IL1 and 6; b) stimulates growth; c) enhances the expression of the adhesion molecules; d) amplifies leucocyte migration.

Through all these actions it has a key role in mediating the acute and chronic inflammation. Infliximab is an anti-TNFα factor (chimeric monoclonal antibody) that acts upon the pathogenetical mechanisms induced by TNFα in CD, being recommended for moderate or severe forms that do not respond to conventional treatment in necessary or maximal doses (corticosteroids, immunosuppressants), for situations when corticosteroid or immunosuppressant treatment is not indicated or produces severe adverse events, and for fistulizing forms that do not respond to conventional therapy [21]. Treatment with Infliximab is performed in two steps: induction therapy (3 doses of 5mg/kg body in weeks 0, 2 and 6) and maintenance therapy, at an interval of 8 weeks.

One of the first studies, published in 1997, demonstrated the role of Infliximab in obtaining remission as compared to a placebo: 41% versus 12% [22]. In another study that referred to the utility of Infliximab in treating the fistulizing forms of Crohn’s disease, more than 50% of Infliximab treated patients presented a reduction of the fistulas output and 30% were cured, as compared to 26%, respectively 13% of those given a placebo [17].

Two large trials evaluated the role of maintenance therapy with Infliximab in CD. The results of the Accent I trial showed that therapy with a single dose of Infliximab 5 mg/kg is significantly inferior to a successive 8 week administration of a 5 mg/kg or 10 mg/kg Infliximab dose. Clinical remission at 54 weeks was achieved in 25% of the group with Infliximab compared to 11% in the case of a single dose (placebo), mucosa healing in 13 of 43 patients as compared to 1 of 28 (placebo). Reduction of the corticosteroid was obtained after 22 weeks vs 46 and antibody presence was reported in 10% vs 30% of patients [23]. The Accent II trial showed that treatment with Infliximab in a single dose is inferior to that of maintenance in fistulizing forms of CD. At the 54th week of follow-up, the reduction of the fistulas output was noted in 46% (Infliximab group) compared to 23% (placebo) and complete healing in 36% vs 19% [24, 25]. Thus, the advantages of maintenance therapy versus induction therapy are a higher health-related quality of life, including a reduction of hospitalization and of surgery need.

Conclusions

Rectovaginal fistula is a relatively frequent and disabling complication of Crohn’s disease; this type of complication can be accurately diagnosed by endovaginal ultrasonography. Treatment with Infliximab significantly improves the patient’s clinical evolution and prognosis.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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