CASE REPORT

Crohn disease or intestinal fistulising tuberculosis? Diagnosis difficulties in a case treated with Infliximab and corticosteroids

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Abstract
Crohn disease represents an idiopathic inflammatory bowel disorder with possibility of local and extra intestinal complications. Infliximab therapy is one of major therapeutic alternatives but this treatment may by followed by several possible infections, especially the reactivation of a latent tuberculosis. We present a case of a 28-year-old patient who was admitted in our hospital with clinical signs of bowel obstruction. Colonoscopy revealed close stenosis at the level of splenic flexure. Surgery was soon performed for the imminence of occlusion and pathology has revealed chronic inflammatory infiltrate with lymphocytes and plasma cells, interpreted as Crohn disease complicated with stenosis. A treatment with prednisone 30 mg/day, ciprofloxacin 1000 mg/day administrated intermittently and sulphasalasine 3 g/day for one year was indicated but the patient develop external abdominal fistula. Infliximab therapy 5 mg/kg/dose was administered at two weeks interval, with initial good results after two doses. At two weeks after the second dose, the patient has presented fever and weight loss; abdominal CT-scan has revealed inflammatory adherences of right flexure of the colon with external fistula, resolved by surgery. The evolution was later complicated by right tibio-tarsian involvement, which imposed orthopedic intervention. Pathology has revealed bone tuberculosis and antibacillary therapy was initiated with good results. Conclusions: Bone tuberculosis may represent a rare evolutive modality at a patient with Crohn disease treated by Infliximab and corticoids. Infliximab therapy in a patient with immunosuppressant (previous corticotherapy, splenectomy) may activate a latent center of tuberculosis. Ciprofloxacin therapy may explain insidious modality of evolution by minor antibacillary effect.

Keywords: Crohn disease, intestinal tuberculosis, bone tuberculosis, Infliximab.

Introduction
Crohn disease represents an idiopathic inflammatory bowel disease with possibility of evolution to local and systemic complications, sometimes severe. The occurrence of intestinal fistulas represents one of dangerous local complications because of therapeutic difficulties. Although Crohn disease and intestinal tuberculosis are distinct and rare clinical entities, the differential diagnosis may be very difficult in some patients [1].

Infliximab use (TNF-α antagonist) constitutes today one of major therapeutic approaches in severe and fistulising cases of Crohn disease [2, 3]. Infliximab is a chimirical monoclonal antibody (75% human and 25% mouse) directed against tumoral necrosis factor alpha (TNF-α), cytokine with important role in inflammatory activity of disease [2].

The use of Infliximab is associated with significant reduction of intestinal inflammation and clinical favorable response. Infliximab therapy may be followed by several infections and reactivation of latent tuberculosis.

Patient and methods
We present the case of a 28-year-old male, from rural habit, with slow onset of symptoms with diffuse abdominal pain, anorexia, weight loss of 4–5 kg and recent constipation.

Anamnesis fails to reveal any medical history of personal or familial disease. After many presentations into the Emergency Department, the patient was admitted with clinical signs of bowel obstruction (severe constipation, abdominal flatulence); blood sample analysis has revealed mild anemia (11.3 g%), the number of leucocytes and platelets being normal, and moderate inflammation (erythrocytes sedimentation rates 45/86 mm, C-reactive protein present).

Colonoscopy has revealed a close stenosis at the level of splenic flexure, the presumed diagnosis being tumor of left large bowel (Figure 1).

Although pathology from colonic biopsies obtained at the level of stenosis has show only inflammatory aspect, surgery was performed for imminence of intestinal occlusion, with segmental
colectomy, anastomosis between transverse bowel and rectum, associated with splenectomy (imposed by splenic involvement into the tumoral mass).

Pathology exam from resected bowel specimen has showed chronic inflammatory infiltrate with gigantic cells and lymphocytic aggregates at the level of interface between mucosa and submucosa (Figure 2, a and b); Ziehl-Nielsen stain fails to reveal the presence of Koch bacillus.

The case was therefore considered as stenosing Crohn disease, and postoperative treatment with sulphasalasine 3 g/day, ciprofloxacinum 1000 mg/day intermittently and prednisone 30 mg/day was performed for one year. During this treatment, the patient develop three external enteric fistulas that were refractory on conventional therapy; Infliximab therapy, 5 mg/kg, was administered in two doses scheduled at two weeks interval; the evolution was initially favorable after two doses, with closure of two fistulas, improvement of symptoms and quality of life. Colonoscopy exam performed for the reevaluation of colonic mucosa after second Infliximab dose has revealed persistence of colonic inflammation with multiple pseudopolyps with diffuse disposition at all bowel segments (Figure 3), and internal colonic anastomosis has showed inflammatory persistence signs despite therapy with Infliximab and conventional associated treatment.

Pathology exam has revealed abundant chronic inflammatory infiltrate with the dissociation of muscularis mucosae (Figure 4, a and b). After two weeks following second dose of Infliximab the patient was readmitted into the hospital for fever and weight loss (4 kg in two weeks interval). Paraclinical exams has show moderate anemia (10 g%) with biological inflammatory syndrome (erythrocyte sedimentation rates 90/124 mm, C-reactive protein present), and clinical exam has show the persistence of one external orifice of the fistula. Abdominal CT-scan has revealed inflammatory adherences between hepatic flexure of the colon and abdominal wall, external fistula with visualization of fistula trajectory (epigastric external orifice and internal prehepatic), infiltration of sub hepatic region, mesocolon, second part of the duodenum with gastric distension (Figure 5, a and b).

Surgery was again performed with fistula closure, by fistula trajectory excision and suture of internal and external orifices, but the persistence of fever has imposed the continuation of paraclinical investigations for the exclusion of localized infection, because Infliximab use may be associated with some severe infection, especially with Koch bacillus.
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CT-scan of the thorax and culture of the sputum has excluded a pulmonary tuberculosis, urine culture was negative; serology for lues and HIV were also negative. After four months, the patient was complaining about tumefaction and erythema at the level of right leg, considered as enteropathic right tibio-tarsian arthritis or reactive arthritis. Two successive radiographies of the joint has revealed only diffuse osteoporosis. Later, patient has developed small periarticular septic collection of about 4 cm diameter, located at the level of external maleola of the right leg, which was resolved by local aspirative puncture with remission of pain and fever. The local joint involvement was progressive through functional disability and orthopedic surgery was performed. Pathology has revealed the presence of granuloma with caseum necrosis, epitheloid cells and infiltrate with lymphocytes and plasma cells, and the diagnosis of bone tuberculosis was made (Figure 6, a–c).

**Figure 4** – (a) Abundant chronic inflammatory infiltrate with the dissociation of muscularis mucosae: pathological aspect (HE stain, ×100); (b) Abundant chronic inflammatory (detail): pathological aspect (HE stain, ×200).

**Figure 5** – (a) CT-scan: abdominal external fistula, prehepatic communication, with the visualization of gas; (b) CT-scan: abdominal external fistula, prehepatic communication, with the visualization of gas, multiple adenopathies.

**Figure 6** – (a) Pathological aspect of bone tuberculosis with some confluent tuberculosis foliculae (HE stain, ×100); (b) Epitheloid granuloma and gigantic cells (HE stain, ×100); (c) Multinucleate gigantic cell: detail (HE stain, ×200).
Antibacillary therapy was initiated, with isoniazide 10 mg/kg/dose, rifampicine 10 mg/kg/dose, pyrazinamide 35 mg/kg/dose, and ethambutol 30 mg/kg/dose, three times/week scheduled, nine months, with favorable clinical evolution and disappearance of fever, maintaining also sulphasalasine therapy, 3 g/day.

During antibacillary therapy, in the first month the patient was complaining about bilateral lumbosacral pain, with presumed diagnosis of sacroileitis associated with Crohn disease.

CT-scan of the pelvis was performed, without any destructive lesion. Lab exams has shows also severe anemia of 3.6 g% associated with significant thrombocytosis of 2 000 000/cmm; bone marrow aspirate was normoreactive.

A detailed medical history has showed that patient has use excessive non-steroidal anti-inflammatory drug use without medical advice, associated with rectal bleeding.

Anemia was considered as related to bleeding and incomplete controlled inflammation, and thrombocytosis as related to splenectomy and rectal bleeding. Anemia, thrombocytosis and lumbosacral pain were complete remitted during antibacillary and sulphasalasine therapy; at six months after finishing antibacillary therapy symptoms were absent, without any fistula, osteoarticular manifestations were also absent with complete functional recovery; biological inflammatory syndrome and hemogram were normal.

The patient has decided, without medical advice, to stop also sulphasalasine therapy, but after three months, the recurrence of intestinal symptoms was noted, with multiple stools, fact which has demonstrated the accuracy of the first initial diagnosis of Crohn intestinal disease. Clinical evolution was favorable after sulphasalasine therapy.

Discussion

The differential diagnosis between Crohn disease and intestinal tuberculosis represent an important problem, especially in developing countries where the prevalence of tuberculosis remains high [4].

This distinction between those two diseases is very important because the therapeutic approach is different. Diseases involve the gut, both are granulomatous diseases, caseum necrosis and Koch bacilli are characteristic but rare on biopsy fragments.

They are some colonoscopic features who suggested Crohn disease (ano-rectal lesions, longitudinal or aphthoid ulcers, cobblestone appearance) and intestinal tuberculosis (involvement of less than four segments, involvement of ileo-cecal valve, deformation of ileo-cecal valve, transverse ulcers, scars or pseudopolyps), and one study who analyzed the difference between these two diseases show the correct diagnosis in 87.5% of cases if many suggestive signs for Crohn than for tuberculosis were found [5].

Accuracy of diagnosis increased with the number of biopsies [6]. The frequency of granuloma visualization is higher in intestinal tuberculosis than in Crohn disease (78% vs. 28%) [4] and the medium number of granuloma are also higher. The size of Crohn granuloma is smaller than in tuberculosis and is predominant into the mucosa, and in tuberculosis is larger and with submucosal dominance, frequently confluent [4, 6]. Caseum necrosis was notated in 22% of cases at patient with intestinal tuberculosis and never in Crohn disease [4].

The presence of conglomerates of epitheloid cells and disproportionate submucosal inflammatory infiltrate are more frequent in intestinal tuberculosis. Intestinal tuberculosis involve more frequent right bowel and ileo-cecal valve, is exceptionally fistulising but may determine perforation and intestinal obstruction.

Radiological techniques may help to differential diagnosis, with the appearance of mural stratification and large adenopathies with central necrosis (in 33% of cases) in intestinal tuberculosis, who may determine the displacement of bowel loops [7].

Because pathology and clinical-endoscopic signs cannot certainly establish the diagnosis, the use of PCR from biopsy tissue seem to represent the method of election [8, 9], especially because the presence of Koch bacilli at microscopic exam is infrequent (35–60%) [1].

PCR may show the presence of Koch bacillus unrelated to the presence or absence of granuloma or caseum necrosis [9].

In medical literature, several cases of intestinal tuberculosis mimicking Crohn disease were reported [1, 10–14].

The exact diagnosis was very important because of therapeutic implications in case of wrong diagnosis of Crohn disease. Most treatments used in Crohn disease (corticosteroids, immunosuppressants, biological therapies) are associated with risk of favoring tuberculosis dissemination because of immune response depression. In addition, they are some implications linked to possibility of reactivation of latent tuberculosis because of immunosuppressant therapy use.

Anti-TNF-α therapy represents a recent approach into the treatment of Crohn disease and an increasing number of rheumatismal diseases. It is also one of the most studied medications linked to the possibility of TBC reactivation.

In one evaluation published in 2002 [15], 70 cases of tuberculosis were noted of above 140 000 cases treated with Infliximab. Although the risk of tuberculosis is relative small (below 1:2000), it is almost seven time higher than in general population [2], and up to 50% of cases who appear at patients treated with Infliximab were extra pulmonary tuberculosis (17 disseminated, 11 ganglionar, four peritoneal, two pleural, meningéal, enteric, paravertebral, bone, genital and urinary bladder) [16].

Another report who evaluated the rate of tuberculosis at patients treated with Infliximab in France showed an incidence of 23/10 000 in 2000, and 8/10 000 patients in 2002, above eight times higher than in general population [17].

Another review published in 2003 reported 175 000 patients treated with Infliximab and 101 cases of tuberculosis, pulmonary and extra pulmonary [18].
In Romania, one study published in 2003 on 24 cases of Crohn disease treated with Infliximab show no case of tuberculosis; this result may be explained by low prevalence of 1:2000 cases into the world [19].

The exact mechanism through TNF-α inhibitors may favor reactivation of latent tuberculosis is not known; one of explanation imply the reduction of infected macrophage apoptosis, which reduce natural antibacillary defense. Other mechanisms are reduction of buciclat-responsive T-cells by 70% and of gamma interferon production antigen-dependant by 70% [20].

Today most authors recommend an IDR to PPD and thoracic radiography prior to Infliximab therapy [17, 21], and in subjects with prior inadequate antibacillary therapy, chemoprophylaxis was also recommended [21].

The presented case has showed many difficulties related to positive and differential diagnosis. The association between corticosteroids and Infliximab therapy may represent a favorable context for bone tuberculosis, especially at a patient with immunosuppression post-splenectomy.

Differential diagnosis between Crohn disease and intestinal tuberculosis was very difficult. IDR to PPD was negative before Infliximab use, but the patient was already on immunosuppressant therapy.

We considered that initial diagnosis of Crohn disease was correct because the lesions were predominant on the left side of the colon (which is atypical in intestinal tuberculosis), resected bowel granuloma, caseum necrosis or Koch bacillusses are not present, the evolution was favorable initially, and with Infliximab therapy we succeed to close most of the fistulas.

In these conditions, the later unfavorable evolution was probably related to reactivation of latent tuberculosis as a result of combining immunosuppresant therapy (corticoids, Infliximab) and post-splenectomy status, and orthopedic surgery with antibacillary therapy were followed by favorable evolution.

**Conclusions**

The appearance of bone tuberculosis at a patient with Crohn disease and splenectomy, treated with Infliximab and corticoids represent a very rare evolutive possibility that impose many problems of diagnosis. The use of Infliximab therapy and corticoids may favor the activation of latent tuberculosis, and ciprofloxacín therapy may explain the torpid clinical evolution because of minor antibacillary effect of this drug.

**References**


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