COMPLICATED COURSE OF A CROHN'S DISEASE CASE, PRESENTING WITH ABDOMINAL PAIN AND DIAGNOSED WITH ILEAL FISTULA AND ABSCESS

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Abstract

About one fifth of cases with Crohn's disease (CD) are diagnosed in people less than 18 years. Although most of pediatric patients present with inflammatory behaviour, penetrating CD is increasingly seen. We report a case of an adolescent female, whose main complain was abdominal pain and who was diagnosed with ileal fistula and abscess. Even if surgery was initially planned, she has been treated with steroids and Sulphasalazine. She developed peritonitis and underwent ileo-cecal resection. Shortly after, an ileal fistula developed, requiring the second surgery. After the operation, she was given Sulphasalazine. In our service, she was found with active disease in the remnant ileum. She was switched to Mesalazine and Azathioprine. Currently, 13 months after starting the new therapy, she is in clinical and endoscopic remission. We emphasize the current concepts in managing fistulizing disease and preventing the post-surgical recurrence.

Key words: Crohn's disease, fistula, surgery, post-surgical recurrence, children

Introduction

Crohn's disease (CD) is diagnosed in about 20% of patients before the age of 18 years[1]. Its phenotype is more complicated than in adult-onset CD patients[2] and requires a more aggressive therapy, including surgery[3,4]. Although the inflammatory behaviour (B1) predominates at the onset (68%), the penetrating (B3 – 18%) and stricturing (B2 – 11%) disease is also described in children[5]. The cumulative incidence of fistula formation in patients with Crohn's disease is 17–50% in population-based studies[6-8]. We present a case of an adolescent female, whose main complain was abdominal pain and who was diagnosed with ileal fistula and abscess at the disease onset. Since the course of the disease was more complicated during and after the therapy, we emphasize the current concepts in managing fistulizing disease and preventing the post-surgical recurrence.

Case report

A 14-year 5-month-old girl, without any significant personal medical history, presented at our hospital in March 2010, with pain, mainly in the epigastrum, rarely also in the right iliac fossa, heartburn, nausea, and poor appetite, for about 5 months. During this period, she has lost approximately 2 kg, mainly due to the appetite loss. Three months before, she had been treated with Omeprazole for 10 days, without any effect. The parents mentioned that she has always been slim. Her mother and grand-father were treated for gastro-duodenal ulcer, in their childhood.

At admission, the physical examination revealed pathologically an adolescent female with cachexia (weight 33 kg, height 152 cm, BMI 13.8 kg/m^2 < p5), pallor and slight tenderness at the abdominal palpation in the epigastric area, without any sign of acute surgical abdomen.

Upper digestive endoscopy showed only some erythema and erosions in the antral area; urease test for Helicobacter pylori was negative. The histopathology report (a few days later) showed no pathologic features in the antral and duodenal mucosa. Basic blood tests have shown hypochromic microcytic hyposideremic anemia (Hb 11.3 g%, VEM: 79.5 fl, HEM: 24.5 pg, Fe=9 μg/dl); liver, pancreatic and urinary tests were normal, as was serology for celiac disease. A treatment with Pantoprazole and antacids was started, associated with diet and partial parenteral nutrition. Over the next days, the abdominal pain worsened, especially in the lower right quadrant, with indefinite palpable mass, requiring analgesics. Inflammatory markers were elevated: ESR=50 mm/h [n <20 mm/h], fibrinogen=560 mg% [n 200-400 mg%], CRP: 2.8 mg% [n <0.8 mg%] and albuminemia was 3.7g/dl [n 4-5 mg%]. There was no leukocytosis (leucocytes 6900/mm^3) [n 4000-10.000/mm^3), with a percentage of neutrophils of 66.2%.

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Abdominal Doppler hydrosonography showed pathologically: inhomogeneous thickness of the ascendant colonic wall (5.5 cm), with hypervascularisation and a terminal ileum with thickened wall and stenosis on the last 4 cm, (wall thickness of 7 mm), loss of stratification and hypervascularisation. On the ileal area, 3.5 cm from the ileocaecal valve, a fistula was identified, which continued with a small hypoechogenic collection, 1.5 cm in diameter (possible abscess). Lateral from the collection, the appendix was normal. Numerous lymph nodes were identified within this area, up until 14 mm in diameter. A marked suspicion of complicated ileo-colonic Crohn's disease was raised, but other diagnoses had to be ruled out (intestinal tuberculosis, yersiniosis, anisakiasis). Lower endoscopy was contraindicated. Immunologic panel (including antinuclear antibodies, antiDNA, serum immunoglobulins, pANCA, cANCA, ASCA) was normal. HIV and cytomegalovirus Ig M antibodies were negative. Hemocult test was only slightly positive, without any pathologic infectious agents or dysbiosis in the stool. Tuberculin intradermoreaction was negative, as was the chest X-ray.

A discussion with the adult-patients surgeon concluded on the necessity of surgery. Until the transfer, the girl was given intravenously Ceftazidime, Ciprofloxacine and Metronidazole (the last one not tolerated), associated with probiotics and partial parenteral nutrition. After a slight improvement over the first 2 days, her condition worsened, with insupportable abdominal pain, without any answer to analgesics, total loss of appetite, nausea and vomiting. Transferred to the adult surgery department after 1 week, it was considered that she did not need surgery anymore; the abscess was questioned since she did not experience fever or leukocytosis. She was treated with Prednisone 0.75 mg/kg/day and Sulphasalazine, in the medical section of the adult hospital and after 1 week she was dismissed. Nine days later, she presented to the adult clinic with paroxysmal abdominal pain, nausea, vomiting and marked weight loss (3 kg). Abdominal sonography showed perihepatic fluid collection, liquid collection in Douglas and between the loops, bilateral pleural effusion. An emergency surgery was performed, while the patient's weight was 27 kg. An inflammatory abscessed lump comprising the terminal ileum, the caecum and the proximal ascendant colon was found. The affected segments were resected (Fig 1) with latero-lateral anastomosis. The pathology report concluded that the microscopic features were consistent with Crohn's disease.

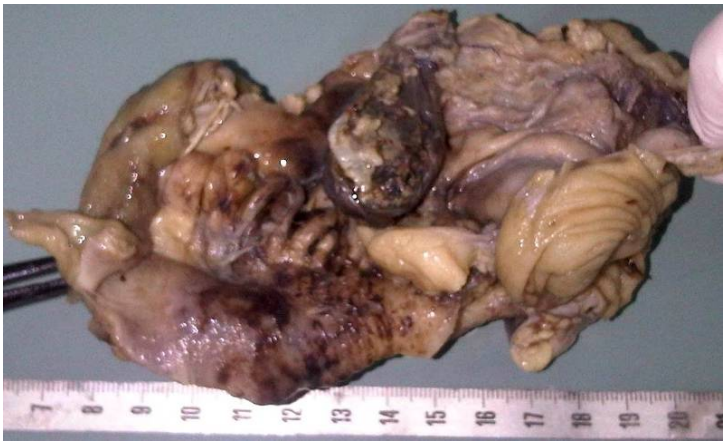

Fig. 1. Macroscopical aspect of the resected area.

The post-surgical course of the disease was eventful, with fever and leukocytosis. Ultrasound showed new ileal fistula and right subphrenic abscess, and another surgery was required. After surgery, the abdominal incision became dehiscent 3 times, requiring repeated sutures.

To prevent the recurring disease, the girl was treated with Mesalazine for 2 weeks and after, switched to Sulphasalazine. Two months after, in July, she was asymptomatic but returned to our clinic, because of cachexia (weight 34 kg, BMI 13.8 kg/m^2 << pc 5) and pallor. Laboratory analyses showed only a slight leukopenia (L 3500/mm3), probably as result of Sulphsalazine. Ultrasonography detected a slight inhomogeneous thickness of the terminal ileum, above the anastomosis. We raised the hypothesis of a recurrence or of an incomplete resection of the previously affected area. We decided to use Modulen, in addition to the normal food, as she did not accept exclusive enteral nutrition. Also, we switched the medication to Mesalazine and Imuran (2 mg/kg/day), closely monitoring the hematologic, liver, renal and pancreatic functions. Five months later, the ileal aspect was normal at ultrasonography.

Last follow-up in July 2011 (15 months after the surgery) showed no symptoms, weight of 43 kg, height of 156 cm, with a BMI of 17.7 kg/m^2 (pc 5-10), normal results of the blood tests, normal hydrosonography and endoscopy with biopsies. She did not develop any severe infection and no side effects related to the therapy.

Discussions

Given the complicated presentation and the course of the CD in this child, we consider important to discuss the following points: the optimal management in patients presenting with fistula and abscess, the best post-surgical approach in order to prevent the recurrence and the gold

standard methods for detecting the relapse.

The current approach in the management of complicated CD states that surgery should be considered for fistulae, abscess and stenosis; an abscess must be drained. Close collaboration between gastroenterologists and a surgeon experienced in pediatric inflammatory bowel disease (IBD) is essential, as stated in the literature[9]. In our region, given the relatively recent emergence of the childhood-IBD, pediatric surgical experience is rather limited. This is the reason why we usually resolve our cases with adult-patient surgeons. Maybe fever and leukocytosis are required to diagnose an abscess in adults; however, in children its signs may be rather atypical. Not considering that this child had an abscess ended up in treating her with steroids. According to the current guidelines, glucocorticoids are not an effective treatment for fistulas in patients with CD. Moreover, studies showed that patients with CD who received prednisolone for the treatment of fistulas had a more deleterious outcome than patients not receiving steroids[10,11]. It is possible that, in our case, steroid treatment and the absence of the abscess drainage favored the peritonitis. Giving the poor nutritional state of this patient, a fistula developed after the first surgery and the wound healing was problematic as well.

Approximately 75% of patients with CD will eventually undergo surgery[12]. Unfortunately, surgery for CD is not curative. Recurrence of disease following a primary resection for CD is a common phenomenon. Approximately 30% of patients who require surgery for CD will experience symptomatic recurrence within 3 years, and as high as 60%, within 10 years, in the absence of prophylactic therapy[13]. Endoscopic recurrence is more common than symptomatic relapse, approaching 90% one year after surgery[14,15]. Early recurrence of symptoms is particularly undesirable in adolescents, as prolonged disease activity in this patient group can lead to significant morbidity and permanent stunting (education, socialization and particularly growth). Currently, there are reports of pediatric surgery for ileo-cecal resection performed for fistula and abscess and/or stenosis, either classically, by laparotomy[16] or by laparoscopy[17], with the latter having the best outcomes (reducing complications from adhesions). Some retrospective data in adults suggests that laparoscopic techniques may reduce the need for further surgery to < 10% in patients having a laparoscopic ileo-cecal resection[18]. There are still only very limited reports of laparoscopic resections in children with CD. A very recent study on 30 children has shown that laparoscopic ileocecectomy, both single-incision laparoscopic approach and standard laparoscopy, is safe and effective[17].

How to prevent the recurrence? There are no formal guidelines for the prevention of postoperative CD. A recent Cochrane review (until February 2009) has shown that probiotics, corticosteroids (systemic and rapidly metabolized steroids - like Budesonide) are probably of little benefit in preventing postoperative recurrence[19]. Budesonide could have been efficacious to heal the active ileal inflammation, but not in this patient with cachexia and wound healing troubles. A systematic review and meta-analysis of all randomized controlled trials conducted until April 2010 in adults with luminal CD in remission after a surgical resection showed that Sulphasalazine was of no benefit in preventing relapse in 448 patients[20]. Mesalazine compounds are of modest benefit, but they are widely used, given their safety profile[9], as it was proved in a recent meta-analysis[20]. The agents of choice, according to the ECCO Consensus, are currently the thiopurines, even if they are not ideal in preventing the relapse and have important side effects[10,19]. A recent meta-analysis found purine analogs to be more effective than either placebo or mesalamine in preventing 1-year clinical recurrence and severe endoscopic recurrence, although the numbers needed to treat were 13 and 7, respectively[21]. In a recent Cochrane review (until February 2009), the use of nitroimidazole antibiotics appeared to reduce the risk of clinical and endoscopic recurrence relative to placebo. However, these agents were associated with higher risk of serious adverse events[19]. We could not use Metronidazole in our patient, since it was not tolerated. The experience with Infliximab (IFX) is very limited; however excellent results have recently been published. The endoscopic recurrence with IFX 1-year after surgery was 9% vs 84.6% with placebo[22]. In another study, a dose of 3 mg/kg of IFX, every 8 weeks, was sufficient to avoid disease recurrence, determined by endoscopy, in all patients at 1 year[23].

Which patients require therapy? According to the recent ECCO Consensus, there are predictors of early post-operative recurrence after ileocolonic resection: smoking, prior intestinal surgery, penetrating disease behavior (as in our patient), perianal location and extensive small bowel resection[10]. Other risk factors have also been associated: early age at initial surgery, short duration of disease prior to initial surgery, both ileal and colonic disease distribution, use of corticosteroids prior to surgery[24], all being found in our patient. Moreover, Swoger et al classified the risk of recurrence according to the risk factors. A very low risk of recurrence is considered in those with a longstanding history of CD (> 10 years) who come to their first surgery for a short stricture (< 10 cm). No maintenance medication may be necessary in these patients. A low-to-moderate risk of disease recurrence appears in those naive to immunomodulators with less than 10 years of disease duration, a long stricture (>10 cm), or significant inflammation. In this category of patients, the authors suggest thiopurines, with or without a 3-month course of Metronidazole. The high risk for recurrence include penetrating disease (e.g., abscess, perforation or internal fistula), smokers, patients with a prior surgery for Crohn's disease, and those who progressed to surgery despite treatment with an immuno-modulator. In these patients, an anti-TNF agent within 2–4 weeks of surgery should be started[24]. With all these data, our choice was to use Mesalazine in association with Azathioprine. However, in our patient we had to do more than prevent the recurrence of the disease, since the disease was already active in the terminal ileum, whatever it was - early recurrence or incomplete resection. We had first to induce the remission and after to maintain it. Our main concern was the

impossibility of dosing the thiopurine methyltransferase activity or the levels of the metabolites 6-thioguanine and 6-methylmercaptopurine, in order to ensure maximal benefit, with minimal toxicity. However, considering the results of the new studies and our patient having a high risk of recurrence, it is possible that IFX therapy could be required.

How to asses the recurrence? The relapse of the disease should not be assessed by clinical signs or biological markers. According to the recent ECCO consensus[10], ileocolonoscopy is the gold standard in the diagnosis of post-operative recurrence by defining the presence and severity of morphologic recurrence and predicting the clinical course (by the Rutgeerts's score[15]). Ileocolonoscopy is recommended within the first year after surgery, where treatment decisions may be affected. Trans-abdominal ultrasound, magnetic resonance enterography, small bowel capsule endoscopy are less invasive diagnostic methods, emerging as alternative tools for identifying post-operative recurrence[10]. Endoscopic findings that indicate recurrence include small aphthous ulcers, deep linear ulcers, mucosal inflammation, fistulae, and strictures. These varying degrees of endoscopic disease activity may be seen within 3 months of surgery in more than 70% of patients. The most common site of recurrence is the surgical anastomosis, especially the proximal side of the anastomosis[14]. In low- and moderate-risk-factor patients, if there is no endoscopic recurrence, some authors do not modify the previous regimen, and repeat a colonoscopy 1–3 years later[25]. If there is evidence of early endoscopic recurrence, they recommend an immunomodulator or anti-TNF agent. In high-risk patients, if there is significant endoscopic recurrence, they check anti-TNF antibodies and serum trough levels and escalate anti-TNF dosing when appropriate and/or add an immunomodulator. In our patient, whatever caused the active inflammation in the remnant ileum (incomplete resection or recurrence), the absence of relapse was demonstrated by abdominal ultrasound and endoscopies with biopsies.

In *conclusion,* we have presented a CD case, with a severe complicated onset, contrasting with the paucity of symptoms and blood tests results. The course of the disease was also complicated during the medical and surgical therapy. The presence of poor prognostic factors requires a close follow-up of this patient, given the impossibility of a post-surgical optimum therapy and monitoring. We emphasize the necessity of knowing the current management of CD, before taking major therapeutic decisions and also the importance of a close collaboration between the gastroenterologists and surgeons specialized in IBD.

References

1. IBD Working Group of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition. Inflammatory bowel disease in children and adolescents: recommendations for diagnosis – the Porto criteria. J Pediatr Gastroenterol Nutr 2005; 41: 1-7.
2. Van Limbergen J, Russell RK, Drummond HE, et al. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. Gastroenterology 2008; 135(4): 1114-22.
3. Vernier-Massouille G, Balde M, Salleron J, et al. Natural history of pediatric Crohn's disease: a population-based cohort study. Gastroenterology 2008; 135: 1106-13.
4. Turunen P, Ashorn M, Auvinen A, et al. Long-term health outcomes in pediatric inflammatory bowel disease: a population-based study. Inflamm Bowel Dis 2009; 15: 56-62.
5. Orel R, Kamhi T, Vidmar G, Mamula P. J Pediatr Gastroenterol Nutr 2009; 48: 579-86.
6. Hellers G, Bergstrand O, Ewerth S, Holmström B. Occurrence and outcome after primary treatment of anal fistulae in Crohn's disease. Gut 1980; 21: 525–7.
7. Schwartz DA, Loftus EV Jr, Tremaine WJ, et al. The natural history of fistulizing Crohn's disease in Olmsted County, Minnesota. Gastroenterology 2002; 122: 875–80.
8. Solomon MJ. Fistulae and abscesses in symptomatic perianal Crohn's disease. Int J Colorectal Dis 1996; 11: 222–226
9. Sandhu BK, Fell JME, Beattie RM, et al. Guidelines for the Management of Inflammatory Bowel Disease in Children in the United Kingdom. J Pediatr Gastroenterol Nutr 2010; 50: S1–S13.
10. Van Assche G, Dignass A, Reinisch A, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Special situations. J Crohn's Colitis 2010; 4: 63–101.
11. Nielsen OH, Rogler G, Hahnloser D, Thomsen OO. Diagnosis and management of fistulizing Crohn's disease. Nature Clin Pract Gastroenterol Hepatol 2009; 6: 92-106.
12. Bennell O, Lapidus A, Hellers G. Risk factors for surgery and postoperative recurrence in Crohn's disease. Ann Surg 2000; 231: 38–45.
13. Sachar DB. The problem of post operative recurrence of Crohn's disease. Med Clin North Am 1990; 74: 183–8.
14. Olaison G, Smedh K, Sjodahl R. Natural course of Crohn's disease after ileocolic resection: endoscopically visualized ileal ulcers preceding symptoms. Gut 1992; 33: 331-5.
15. Rutgeerts P, Geboes K, Vantrappen G, et al. Predictability of the postoperative course of Crohn's disease. Gastroenterology 1990; 99: 956-63.
16. Cook L, Al-Hendawi E, Bates AW, et al. Limited ileo-caecal resection for localised Crohn's disease in childhood: Clinical outcome and predictors of further surgery. J Crohn's Colitis 2007; 1:82-86.
17. Laituri CA, Fraser JD, Garey CL, et al. Laparoscopic ileocecectomy in pediatric patients with Crohn's disease. J Laparoendosc Adv Surg Tech A 2011; 21(2): 193-5.
18. Lowney JK, Dietz DW, Birnbaum EH, et al. Is there any difference in recurrence rates in laparoscopic ileocolic resection for Crohn's disease compared with

conventional surgery? A long-term, follow-up study. Dis Colon Rectum 2006; 49: 58-63.
19. Doherty G, Bennett G, Patil S, et al. Interventions for prevention of postoperative recurrence of Crohn's disease. Cochrane Database Syst Rev 2009; 7: CD006873.
20. Ford AC, Khan KJ, Talley NJ, Moayyedi P. 5-Aminosalicylates prevent relapse of Crohn's disease after surgically induced remission: systematic review and meta-analysis. Am J Gastroenterol 2011; 106: 413-20.
21. Peyrin-Biroulet L, Deltenre P, Ardizzone S, et al. Azathioprine and 6-mercaptopurine for the prevention of postoperative recurrence in Crohn's disease: a meta-analysis. Am J Gastroenterol 2009; 104: 2089-96.
22. Regueiro M, Schraut W, Baidoo L, et al. Infliximab prevents Crohn's disease recurrence after ileal resection. Gastroenterology 2009; 136: 441–50.
23. Sorrentino D, Paviotti A, Terrosu G, et al. Low-dose maintenance therapy with infliximab prevents postsurgical recurrence of Crohn's disease. Clin Gastroenterol Hepatol 2010; 8: 591-9.
24. Swoger JM, Regueiro M. Postoperative Crohn's disease: how can we prevent it? Expert rev. Clin. Immunol 2010; 6: 501-4.
25. Cho SM, Cho SW, Regueiro M. Postoperative management of Crohn's disease. Med Clin North Am 2010; 94: 179-88.

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