

Acute Infusion Reaction to Infliximab in a Case of Crohn's Disease with Recto-Scrotal Fistula

Hoduț A, Simedrea I, Belei Oana, Militaru Andrea, Bojinescu Raluca, Brad Giorgiana

First Pediatric Clinic, Faculty of Medicine, University of Medicine and Pharmacy, Timișoara, Romania

Crohn disease is an inflammatory bowel disease that involves any region of the alimentary tract from the mouth to the anus and it is transmural. Children with early onset are more likely to have colonic involvement. Infliximab constitutes today one of major therapeutic approaches in severe and fistulising cases of Crohn disease.

We present the case of a 16 year-old boy who was admitted to our department presenting recto-scrotal fistula, fever, tenesmus, red-bloody stools, pain during and after defecation. In order to induce remission of the disease, we administrated Infliximab. The initial response to therapy was good, but he developed an acute infusion reaction during the administration of the 3rd dose, which forced us to quit this therapy.

Keywords: Crohn's disease, fistula, Infliximab, acute infusion reaction

Introduction

Inflammatory bowel disease includes two distinctive disorders (Crohn's disease and ulcerative colitis) of idiopathic chronic intestinal inflammation, characterized by unpredictable exacerbations and remissions. Crohn's disease involves any region of the alimentary tract from the mouth to the anus and it is transmural. Children with early onset are more likely to have colonic involvement [1]. Its evolution may be local or with systemic, sometimes severe complications. The occurrence of fistulas represents one of the more dangerous local complications, because of therapeutic difficulties [2].

Infliximab represents today one of the major therapeutic approaches in severe and fistulising cases of Crohn's disease [3,4]. It is a chimerical monoclonal antibody (75% human and 25% mouse) directed against tumoral necrosis factor alpha (TNF- α), a cytokine with important role in the inflammatory activity of the disease [3]. The use of Infliximab is associated with a significant reduction of intestinal inflammation and a favorable clinical response [2].

Case presentation

We present the case of a 16 year-old boy, from urban environment, with a particular onset and evolution of Crohn's disease.

In 2006 the patient discovered the presence of a small perianal formation, following an acute episode of enterocolitis with bloody stools. During the next 10 months several other similar formations appeared and the patient losted 3 kg, with no diarrhea or bloody stools. Surgical and dermatological examination led to the diagnosis of perianal condylomatosis and surgical excision was performed. Three weeks later the patient had diarrhea, red bloody stools, severe abdominal pain and fever (39°C). Local examination showed perianal lesions after electrocauterisation, and a bleeding ulcer at 3 o'clock, without local inflammation. Histological examination of the resected fragment revealed anal mucosa with extensive ulceration (the base of ulceration consisted of granulation

tissue with a rich vessel network, lympho-plasmocytic infiltrate); chronic inflammatory infiltrate with gigantic cells and lymphocytic aggregates were also present, findings that were suggestive for Crohn's disease. He was advised to refer to the Pediatric Gastroenterology department of the Cluj Napoca Children's Hospital. There the investigations established the diagnosis of Crohn's disease with duodenal and ileo-colic involvement. He was prescribed a specific treatment with Prednisone (2 mg/kg/day), Mesalazine [Salofalk] 2 g/day, as well as antibiotic and antifungal therapy. With this therapy the evolution was favorable with weight gain, normalized acute phase reactants and macroscopic aspect of colic mucosa, and improved endoscopic appearance of eso-gastro-duodenal lesions. The treatment was continued with Mesalazine, the Prednisone dose was reduced (to 0.5 mg/kg/day). In July 2007 Azathioprine [Imuran] (75 mg/day) was associated. No digestive symptoms were present, but cortisone's side effects started to appear (full moon face, acne, hypertrichosis). Until December 2007 the amount of Prednisone was reduced to 10 mg/day. It was then when the symptoms rebounded with pain during defecation, anal ulceration. Diarrhea and red bloody stools with blood drops after defecation also reappeared. Fever (over 39°C), painful scrotum, tumefaction were present too. The diagnosis of scrotal abscess was established and surgical drainage was performed. Culture from scrotum exudate showed *Proteus mirabilis*. The patient received antibiotic therapy according to the antibiogram, but an other surgical drainage was necessary.

The patient was admitted at the end of January 2009 to First Pediatric Clinic Timișoara, for fever, tenesmus, bloody stools, pain during and after defecation, and ongoing fistula.

Physical examination revealed a poor general condition, short stature (1.55 m – 5th percentile), height velocity less than 3rd percentile (3 cm/year) and small weight (39 kg) with a BMI less than the 5th percentile (16.23 kg/m²). Data were pertained to 2007 WHO growth standards.

Auscultation detected a systolic heart murmur. Exami-



Fig. 1. Aspect of fistula

nation of the anal region found a 2 cm large fistula, located in the lateral right position of the anus (at 11 o'clock) with thickened clear-cut edges, painful at palpation (Figure 1.) Anoscopy allowed visualization of a linear anal ulceration with ano-scrotal fistula and inflamed mucosa around the ulceration.

Blood sample analysis revealed a discrete increase in the number of leukocytes (12.240 WBC/mm^3), neutrophilia (72.4%), inflammation (erythrocytes sedimentation rates [ESR] 60 mm/h, C-reactive protein [CRP] 75.75 mg/l and normal fibrinogen). All other analyses were normal. Abdominal ultrasound showed thickening of the intestinal wall. Immunological markers such as anti-neutrophil cytoplasmic antibodies (ANCA), anti-saccharomyces cerevisiae antibody (ASCA), antibodies to tissue transglutaminase (ATA or anti-tTG) and anti-streptolysin O antibody (ASLO) were all negative. Gastroscopy revealed a normal esophagus and stomach, but some small (1–2 mm) superficial ulceration around the ampulla of Vater was observed.

Colonoscopy showed linear anal ulcers with ano-scrotal fistula and inflamed mucosa around the ulcerations; the sigmoid mucosa was pale. The rest of colon was normal.

Computer tomography (CT) scan of the abdomen (performed in January 2009) was normal – no intra-abdominal collection, abscess or inflammatory lymph nodes.

Cardiological ultrasound for the systolic murmur showed a ventricular septal defect.

Radiography of the pelvis showed grade 1 sacroiliitis. (based on New York grading criteria).

We established the diagnoses of: Crohn's disease with recto-scrotal fistula, ventricular septal defect and severe growth failure.

The Pediatric Crohn Disease Activity Index (PCDAI) calculated in January 2009 counted 60 points (normal value <15) (Figure 2.)

We intended to induce remission and decided to administer Infliximab, which has been approved for the initial treatment and subsequent maintenance therapy in adults with Crohn's disease, but it is also commonly used

Australian Government
Medicare Australia

PBS

Paediatric Crohn's Disease Activity Index

1 Week ending 1/1 for (patient's full name) _____

Age 14, 7/12 years Sex Male Female

Each parameter in this table must be assigned a value.		Score	Subtotal
Abdominal pain	No abdominal pain	0	10
	Mild, no interference with Activities of Daily Living (ADL)	5	
	Moderate/severe, daily, nocturnal, interferes with ADL	10	
Stools/day	0–1 liquid, no blood	0	5
	≤ 2 semi-formed + small blood or 2–3 liquid	5	
	> 3 loose stools, gross blood, or nocturnal diarrhoea	10	
General function	Well, no limitations of activities	0	5
	Below par, occasional difficulty with activities	5	
	Very poor, frequent limitation of activities	10	
Examination			
Weight	Weight gain (or voluntarily stable/reduction)	0	5
	Weight loss < 10% (or involuntarily stable)	5	
	Weight loss ≥ 10%	10	
Height* (at diagnosis)	< 1 channel decrease from previous percentile	0	5
	1 to < 2 channel decrease from previous percentile	5	
	≥ 2 channel decrease from previous percentile	10	
Height velocity**	< -1 standard deviation from normal	0	10
	-1 to < -2 standard deviation from normal	5	
	≥ -2 standard deviation from normal	10	
Abdomen	No tenderness or mass	0	5
	Tenderness, or mass without tenderness	5	
	Tenderness, involuntary guarding, definite mass	10	
Peri-rectal disease	None, asymptomatic tags	0	10
	1–2 isolated fistula, scant drainage, non-tender	5	
	Active fistula, drainage, tenderness, or abscess	10	
Extra-intestinal***	None	0	0
	1 manifestation	5	
	≥ 2 manifestations	10	
Laboratory			
Haematocrit (%)	M/F 6–10 years: > 35	0	0
	M 11–14 years: > 30		
	F 11–19 years: > 34		
	M 15–19 years: > 37		
	M/F 6–10 years: 38–52		
	M 11–14 years: 35–54		
	F 11–19 years: 29–53		
	M 15–19 years: 32–56		
	M/F 6–10 years: < 28		
	M 11–14 years: < 30		
F 11–19 years: < 39			
M 15–19 years: < 32			
ESR (mm/hr)	< 20	0	5
	20–50	2.5	
	> 50	5	
Albumin (g/L)	≥ 35	0	0
	31–34	5	
	≤ 30	10	
TOTAL PCDAI SCORE			60

* Height channel represents lines on the standard percentile chart up 10 → 25 → 50 percentiles & 2 channels reference.
** Height velocity is calculated from measurements over last 6–12 months in cm / year compared to standard deviation below (minus 1σ) normal.
*** Extra-intestinal includes fever of > 38 °C over 3 days over last week, arthritis, uveitis, Erythema nodosum or Pyoderma gangrenosum

Prescriber's declaration

2 I declare that:
the information provided on this form is correct.

Name of prescriber _____ Signature of prescriber _____ Date: 29/Jan/2009

Print full name in BLOCK LETTERS

Fig. 2. PCDAI score, January 2009

in children. Uncontrolled studies suggest marked symptom improvement in 50–70% of patients. It is initially administered in three infusions over a six-week period (at 0, 2, and 6 weeks) [1]. Maintenance therapy is usually necessary and it is administered as 5 to 10 mg/kg/dose every 8 weeks.

We managed to administer only two doses. Two minutes after the 3rd infusion was started, the patient presented generalized cutaneous rash, dyspnea and vertigo. The infusion was immediately.

Four weeks after we started Infliximab therapy PCDAI was significantly reduced (27.5 points) and after 8 weeks it was still decreased (22.5 points), although the third dose of Infliximab wasn't administered (Figure 3).

After quitting Infliximab, we continued the treatment with Azathioprine [Imuran] (75 mg/day). Antibiotic therapy was also continued, as well as gastric acid proton pump inhibitor.

Results

Due to an acute infusion reaction we had to stop the administration of Infliximab. More infusions would have been necessary to close the fistula. With two Infliximab infusions PCDAI decreased based on the general function, there was no abdominal pain or fistula drainage, the patient presented normal stools, reduced ESR and a slight weight gain.

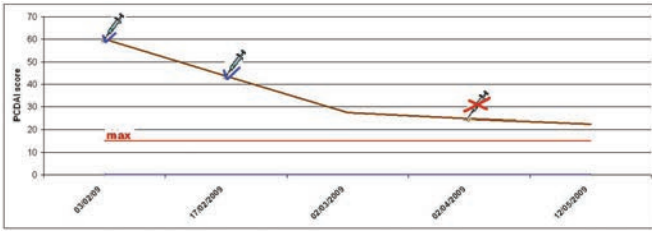


Fig. 3. PCDAI score after Infliximab infusions

Soon after quitting Infliximab the first relapse occurred and we were forced to reintroduce Prednisone in May 2009. Other relapses occurred in July and August 2009. For blood sample analysis and PCDAI in evolution see Figures 3–6.

Discussions

Among children with Crohn’s disease, the initial presentation most commonly involves the ileum and the colon (ileo-colitis) [1], the disease having a predilection for the distal small bowel and proximal colon. Perianal disease is another common presentation for 20–80% of cases, depending on the inclusion criteria, the quality of the examination and the degree of specialization of the clinic [4]. Children may present with growth failure as the only manifestation of Crohn’s disease and that may precede other symptoms by 1–2 years. Our patient was diagnosed with Crohn’s disease after perianal lesions appeared and he also had growth failure at that moment.

Acute infectious enteropathies are the most common diagnoses to be distinguished from Crohn’s disease. The patient had two such events (diarrhea, bloody stools and abdominal pain) which might have been the first manifestation of his Crohn’s disease, but at that moment it was considered acute colitis.

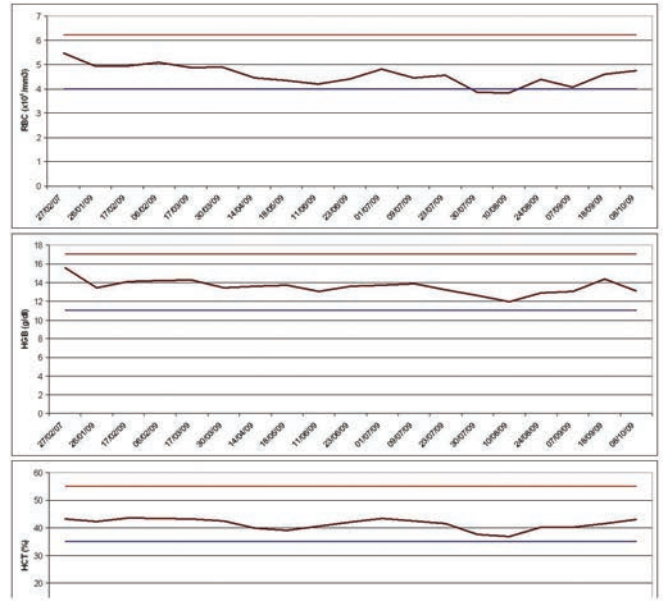


Fig. 4. RBC, Hb, Hct

Typically, therapy for pediatric Crohn’s disease is administered in a step-up approach [5]. More recently, adult data have supported the use of biological therapy earlier in the course of the disease (a "step-down" approach) as a more effective treatment method [6]. It is essential to consider the adverse consequences of therapy, particularly with regard to any durable consequences of short-term treatment and adverse effects of maintenance therapy [4].

In a prospective, open-label trial, Kugathasan S et al. intended to determine whether Infliximab treatment would be of benefit for pediatric patients with medically refractory Crohn’s disease. 94% of the patients improved after Infliximab infusion, with a significant decrease of both PCDAI and daily steroid use by 4 weeks, and 67% achieved complete remission by 10 weeks. The authors

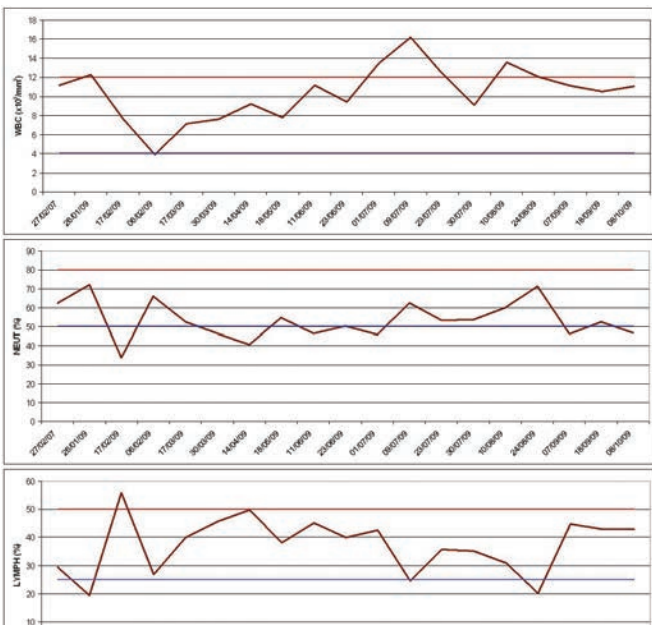


Fig. 5. WBC

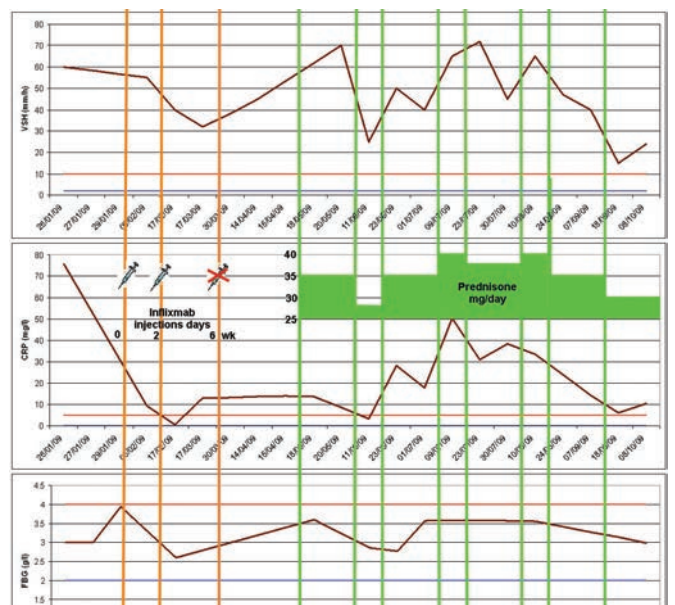


Fig. 6. Inflammatory tests and treatment

also assessed the duration of response: 50% of the children with early disease maintained clinical response through the 12-month trial period without late disease.

There are several acute reactions described in literature: anaphylactic and anaphylactoid reactions, serum sickness-like reactions or antibody to Infliximab (ATI). In most patients these antibodies develop soon after the initiation of treatment [7]. ATI are especially associated with mild to moderate infusion reactions, not with the severe reactions [8]. ATI have been demonstrated in 7–61% of patients [9,10].

Typical symptoms of serum sickness are rash, fever, and polyarthralgias or polyarthritis. These symptoms begin 1–2 weeks after the first exposure to the responsible agent and resolve within a few weeks after discontinuation. A delayed infusion reaction to Infliximab clinically imitates serum sickness [11,12].

An anaphylactic reaction is defined as an acute systemic reaction caused by the massive release of histamine and other cytokines from mast cells, mediated by IgE [13]. Bronchospasms and urticaria are typical symptoms of an IgE-mediated anaphylactic reaction, or type I hypersensitivity reaction [14]. Similarly to anaphylactic reactions, anaphylactoid reactions are serious and potentially life threatening [13].

The most difficult question is whether treatment with Infliximab can be continued. We decided to stop further infusions. Possibilities for prevention of infusion reactions are premedication, desensitization, immunosuppressants, adjustment of schedule and dosage or switching to another biologic therapy [15].

Premedication is often routinely given before infusions, consisting of Paracetamol, antihistamines and/or corticosteroids, to prevent the occurrence of infusion reactions [15]. We administered Levocetirizinum [Xyzal] and Paracetamol before each Infliximab infusion. Should we have given corticosteroids too? However, solid evidence that prophylactic medication can prevent infusion reactions is lacking [15]. For betamethasone there was no significant difference compared to placebo. And for intravenous hydrocortisone there was a lower percentage of infusion reactions (24% vs. 15% for placebo), but these results were also not significant [16].

In a retrospective cohort study with 28 children with Crohn disease Candon et al. [17] showed that with a loading schedule (weeks 0, 2 and 6) ATI were formed in 16% vs. 78% when only one initial infusion was administered. Similar conclusions were reached by Farrell [16] and Kugathasan [12].

Switching from Infliximab to Adalimumab without complication has been described after the occurrence of an infusion reaction [10,18]. Adalimumab could be a solution for our patient.

Conclusions

The case we presented is particular by the appearance of skin lesions and fistula in the early stages of the disease.

Perianal condylomatosis can be the initial appearance of Crohn's disease.

Conventional therapy could not fully control the disease. We had a good response to biologic agents (Infliximab), but the appearance of side effects limited its use and relapse occurred soon after the discontinuation of treatment. We also had a poor compliance to treatment protocols. Surgical therapy for fistula closing was refused several times by surgeons because of the high risk of recurrence.

Adalimumab would be necessary for this patient to close the fistula with biological therapy. Several studies in Europe and USA prove Adalimumab's efficacy in children, but in Romania this biologic agent is not approved for pediatric use, narrowing future therapeutic possibilities for this patient.

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