BMJ Case Reports

BMJ Case Reports: publishing, sharing and learning through experience

BMJ Case Reports 2010; doi:10.1136/bcr.04.2009.1739

Novel treatment (new drug/intervention; established drug/procedure in new situation)

Anti-TNFα antibody infliximab treatment for an infant with fistulising Crohn's disease

Omar I Saadah

- Author Affiliations

King Abdul-Aziz University Hospital, Department of Pediatrics, Jeddah, 21589, Saudi Arabia

Omar Ibrahim Saadah, saadaho@hotmail.com

Published 13 January 2010

Summary

A female infant presented at the age of 4 weeks with dyschezia and bloody streaking of stools which did not improve on elemental formula for proposed cow's milk protein allergy. At 6 months of age perianal ulceration appeared which evolved into multiple fistulas opening into the perineum. A diagnosis of infantile Crohn's disease was made after colonoscopy and histopathology examination and exclusion of other conditions. An 8 week trial of total parenteral nutrition, in addition to corticosteroids, salazopyrine, metronidazole, and azathioprine failed to arrest deterioration of the perianal fistulas. Treatment with the anti-TNFα antibody infliximab was started at 5 mg/kg/dose at 9 months of age. She was given three doses at 0, 2, and 6 weeks, respectively. This resulted in significant healing of her fistulas and cessation of fistula output. This improvement was sustained at the time of last follow-up 10 months after treatment.

Background

Crohn's disease, primarily a disease of older children and young adults, is very rare in the first year of life where it is usually a severe illness with poor prognosis.[1] Data regarding the best therapeutic approach in such infants are scant. Anti-tumour necrosis factor α (anti-TNFα) has been reported to be effective in adult patients with fistulising Crohn's disease,[2] but no data are available to support its use in infants. Here we describe the successful use of the anti-TNFα antibody infliximab in an Arab infant with infantile Crohn's disease with severe perianal fistulas and perineal destruction.

Case presentation

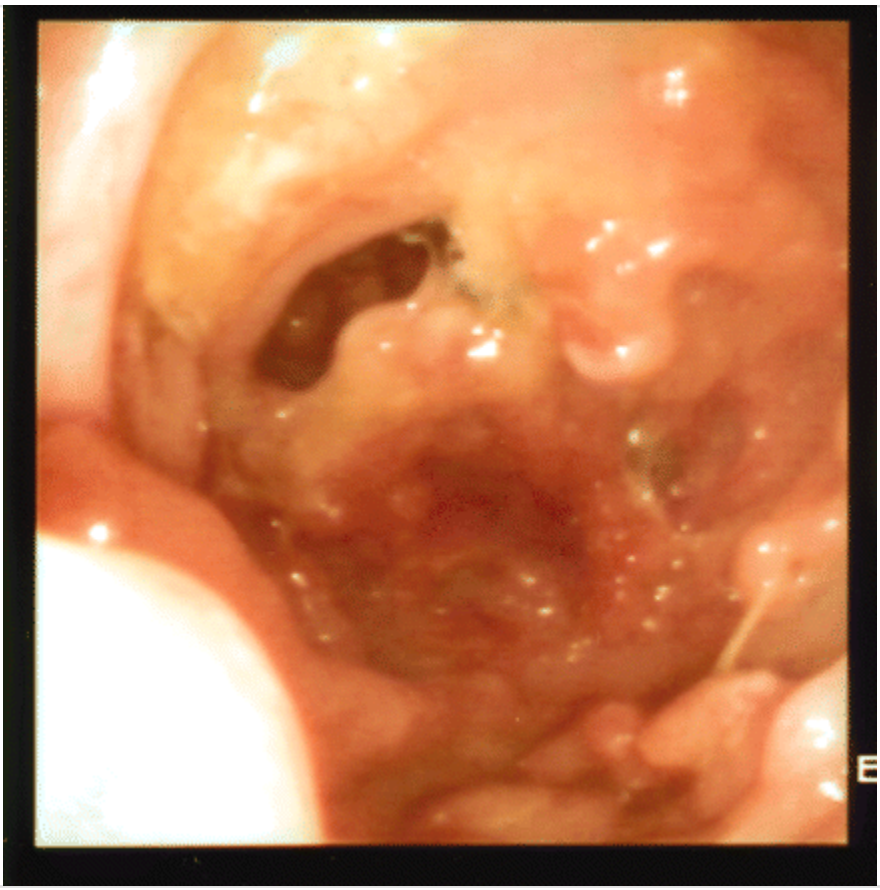
This female infant was born at term with birth weight of 2.3 kg. She was breast fed with infant formula supplement. At 4 weeks of age she started to have dyschezia and bloody streaking of stools. Parents were first degree cousins with no family history of inflammatory bowel disease (IBD). Stool analysis revealed numerous pus cells, blood and mucus, but stool culture was negative. Flexible sigmoidoscopy performed at 3 months of age showed ulcerated rectal mucosa which was attributed to cow's milk protein allergy. She was put on elemental formula but continued to pass blood and mucus with her stool, and was not gaining weight.

On physical examination she was pale and malnourished with cradle cap and eczematous lesions on the face. At 6 months of age, a fleshy skin tag appeared around the anus, and skin ulcers appeared in the right labia majora and over the sacrum. She was treated with antibiotics and the parents were instructed how to care for the ulcers. One month later the sacral ulcer had healed but the right labia majora ulcer was revealed as the end of a fistula.

Investigations

Laboratory investigations showed haemoglobin of 8.6 g/dl, white blood cell count of $14\times10^3/mm^3$, and C reactive protein (CRP) of 89 mg/l. Serum albumin was 13 g/l. Stool analysis for culture, *Clostridium difficile* toxins, and parasite examination was negative. Mantoux test for tuberculosis was negative. Immune studies including total immunoglobulin, serum complement, total lymphocytes and lymphocyte subset were within normal limits. Allergy tests (radio allegro sorbent test, RAST) for cow's milk protein, soya, and wheat were negative.

Colonoscopy to the terminal ileum showed severe patchy inflammation with inflammatory pesudopolyps, deep linear ulcerations and cobblestone appearance throughout the whole colonic mucus and the terminal ileum (fig 1).



View larger version: In a new window Download as PowerPoint Slide

Figure 1

Mucosal inflammation of the caecum and ileocaecal valve at colonoscopy

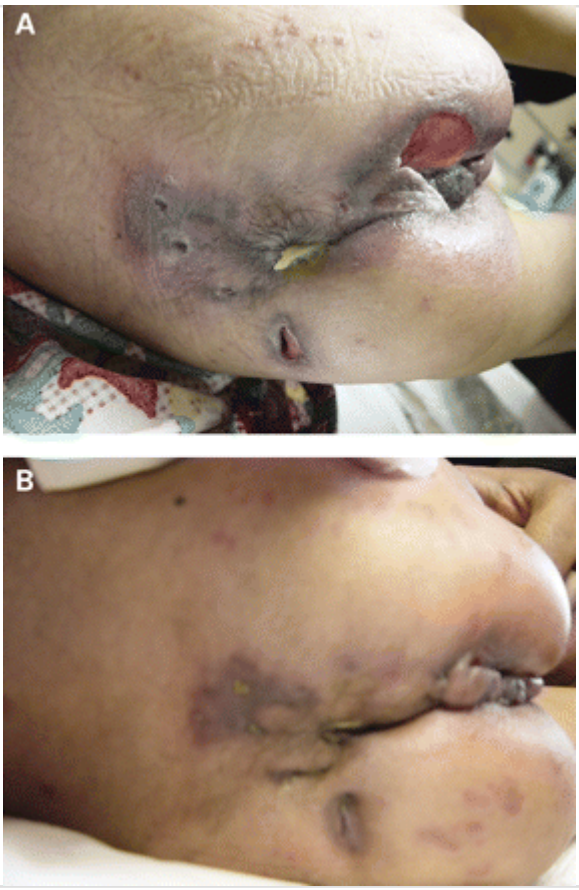
Histopathology of the mucosal biopsy taken from the terminal ileum and different parts of the colon showed moderate increase in the lamina propria of mononuclear inflammatory cells and neutrophils indicating cryptitis and crypt abscess. No granulomata were seen.

Barium meal and follow through showed mild narrowing with irregular outline at the middle of the jejunum and terminal ileum.

Treatment

The patient was treated with total parenteral nutrition for 8 weeks in addition to corticosteroids, salazopyrine, metronidazole, and azathioprine.

After 2 months of treatment with conventional treatment, perianal disease was getting worse. More fistulas appeared and there was more perineal destruction (fig 2A).



View larger version: In a new window Download as PowerPoint Slide

Figure 2

Figure 2 (A) Perianal fistulas before treatment with infliximab. (B) Perianal fistulas after treatment with infliximab.

The chimeric anti-TNFα antibody infliximab was started after discussion with the parents. An intravenous infusion at a dose of 5 mg/kg was given at 0, 2, and 6 weeks, respectively. It was well tolerated apart from mild allergic skin rash after the second dose. The rash improved after treatment with antihistamine and hydrocortisone. The third dose of infliximab was tolerated.

Outcome and follow-up

After the induction with infliximab, the stool became formed with no blood or mucus. This was followed by gradual and slow reduction in the output from the fistulas with evidence of healing and improvement in the perianal disease (fig 2B).

The patient's general condition improved with less irritability and better weight gain. The improvement in her condition was sustained when she was last reviewed at 20 months of age. She gained 4 kg over a 10 month period. During her follow-up she was admitted twice at the age of 12 and 16 months with sepsis secondary to *Escherichia coli* and *Staphylococcus aureus*, respectively, for which she was treated.

Discussion

Crohn's disease in infancy is extremely rare. In one Swedish study of 639 children with IBD, only one child had Crohn's disease before the age of 2 years.[1] In a study from Denmark of 103 children with IBD, only five children including one with Crohn's disease were younger than 2 years.[3]

Several case reports of young children with Crohn's disease have been published.[4–8] However, reports of neonatal onset are limited.[4,5,7] They include all 12 patients reported by Miller and Larsen,[7] one of seven patients reported by Marx *et al*,[5] and two of the four cases reported by Cohen *et al*.[4]

The diagnosis of Crohn's disease in this infant was made on clinical grounds confirmed by the presence of chronic histological changes in the colon and terminal ileum and endoscopic features compatible with Crohn's disease.

The aetiology of Crohn's disease remains unknown, but the interaction between genetic and environmental factors plays a role. Cohen *et al*[4] reported infantile Crohn's disease occurring in three siblings and their first degree cousin in an Arab Bedouin family, highlighting the importance of genetic factors, especially in early onset disease.

The differential diagnosis of infantile Crohn's disease should include allergic colitis as the main cause of non-infectious colitis in this age group[9]; however, this patient did not respond to elemental formula, and there were no histological changes to suggest allergy.

All infants with non-infective colitis with a proposed diagnosis of Crohn's disease need to be investigated for immunodeficiency since it can mimic the presentation of Crohn's disease,[10,11] and could result in lethal consequences following treatment with immunosuppressive therapy. Immune abnormality was excluded in our case by finding normal immunoglobulin, serum complement, total lymphocytes and lymphocyte subset. Nitroblue tetrazolium test was also

performed and excluded the possibility of chronic granulomatous disease in this infant.

In the presence of recurrent mouth ulcers and chronic diarrhoea, especially if the diarrhoea is unresponsive to oral prednisolone and sulfasalazine, with the characteristic ulcers in biopsy, Behçet's syndrome should always be considered.[12] Absence of mouth ulcers in this patient and the presence of perianal disease make this possibility unlikely.

Perianal fistulas in infants with Crohn's disease was reported in four infants by Cohen *et al*[4] and in two infants by Marx *et al*.[5] Infants can have severe perianal disease even with mild bowel involvement.[8] Extension of the perianal disease to involve the genitalia, whether direct or metastatic through possible microfistulae, can be complicated by anal stricture, which has been reported by the author in older children with Crohn's disease involving the genitalia.[13]

Management of perianal disease in Crohn's patients has always been difficult. Some improvement can occasionally be achieved by the use of metronidazole and azathioprine; however, this improvement is not usually sustained. The reported outcome of surgical intervention in fistulising disease in children is variable.[4,7,8] Thus conservative treatment is usually recommended. The new biological therapy anti-TNFα has been very successful when used in fistulising disease in adults with Crohn's disease.[2] But experience with this new therapy in young infants is lacking, and there is concern about the immunomodulatory aspects in a young child whose T cell repertoire is developing. This child has normal immune function 10 months following the last dose of infliximab.

It is also important to consider the infection risk of infliximab in this population, since TNFα is an important component of the immune system's response to a variety of infections. TNFα inhibitors can cause serious infections.[14] These infections have included bacterial sepsis,[15] tuberculosis,[16] invasive fungal[17] and other opportunistic infections.[18,19] This infant had two episodes of bacterial sepsis with *E coli* and *S aureus* that were treated with appropriate antibiotics. Failure to recognise early symptoms and signs of infection can result in fatal outcome.[20,21] Parents should be educated about the recognition of signs and symptoms of infection during and after treatment with infliximab, and should have access to appropriate medical care. This risk of infection must be interpreted in the context of the potential benefits and of the possible adverse effects of conventional therapies. Repair of the fistulas and improvement of the severe skin damage appears so far to justify its use in the case presented here.

Learning points

- Crohn's disease should be considered in infants with bloody stools unresponsive to elemental formula.
- Infliximab was effective in this young infant with perianal fistulas.
- Infliximab is probably safe in the short term, although long term safety is not known.
- There is a potential risk for infections in individuals treated with infliximab that needs to be balanced against the potential benefits.

Acknowledgments

Professor Grame Barnes, University of Melbourne, Australia for reviewing the manuscript

Footnotes

Competing interests: None.

Patient consent: Patient/guardian consent was obtained for publication.

REFERENCES

1. Lindberg E, Lindquist B, Holmquist L, *et al*. Inflammatory bowel disease in children and adolescents in Sweden, 1984-1995. *J Pediatr Gastroenterol Nutr* 2000; : 259–64. [CrossRef] [Medline] [Web of Science]
2. Present DH, Rutgeerts P, Targan S, *et al*. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med* 1999; : 1398–405. [**Abstract**/**FREE Full text**]
3. Langholz E, Munkholm P, Krasilnikoff PA, *et al*. Inflammatory bowel diseases with onset in childhood. Clinical features, morbidity, and mortality in a regional cohort. *Scand J Gastroenterol* 1997; : 139–47. [Medline] [Web of Science]
4. Cohen Z, Weizman Z, Kurtzbart E, *et al*. Infantile colonic Crohn's disease: a report of four cases in one family. *J Pediatr Gastroenterol Nutr* 2000; : 461–3. [CrossRef] [Medline]
5. Marx G, Seidman EG, Martin SR, *et al*. Outcome of Crohn's disease diagnosed before two years of age. *J Pediatr* 2002; : 470–3. [CrossRef] [Medline]
6. Mezoff AG, Cohen MB, Maisel SK, *et al*. Crohn disease in an infant with central nervous system thrombosis and protein-losing enteropathy. *J Pediatr* 1990; : 436–9. [CrossRef] [Medline] [Web of Science]
7. Miller RC, Larsen E. Regional enteritis in early infancy. *Am J Dis Child* 1971; : 301–11. [**Abstract**/**FREE Full text**]
8. Pashankar D, Schreiber RA, Israel DM. Perianal Crohn's disease in infancy. *J Pediatr Gastroenterol Nutr* 2000; : 80–2. [CrossRef] [Medline]
9. Jenkins HR, Pincott JR, Soothill JF, *et al*. Food allergy: the major cause of infantile colitis. *Arch Dis Child* 1984; : 326–9. [**Abstract**/**FREE Full text**]
10. D'Agata ID, Paradis K, Chad Z, *et al*. Leucocyte adhesion deficiency presenting as a chronic ileocolitis. *Gut* 1996; : 605–8. [**Abstract**/**FREE Full text**]
11. Ojuawo A, St Louis D, Lindley KJ, *et al*. Non-infective colitis in infancy: evidence in favour of minor immunodeficiency in its pathogenesis. *Arch Dis Child* 1997; : 345–8. [**Abstract**/**FREE Full text**]
12. Chong SK, Wright VM, Nishigame T, *et al*. Infantile colitis: a manifestation of intestinal Behcet's syndrome. *J Pediatr Gastroenterol Nutr* 1988; : 622–7. [Medline] [Web of Science]
13. Saadah OI, Oliver MR, Bines JE, *et al*. Anorectal strictures and genital crohn disease: an unusual clinical association. *J Pediatr Gastroenterol Nutr* 2003; : 403–6. [CrossRef] [Medline]
14. Crum NF, Lederman ER, Wallace MR. Infections associated with tumor necrosis factor–alpha antagonists. *Medicine (Baltimore)* 2005; : 291–302. [CrossRef] [Medline]
15. Kroesen S, Widmer AF, Tyndall A, *et al*. Serious bacterial infections in patients with rheumatoid arthritis under anti-TNF-

15. alpha therapy. *Rheumatology (Oxford)* 2003; : 617–21. [**Abstract**/**FREE Full text**]
16. Gomez-Reino JJ, Carmona L, Valverde VR, *et al*. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. *Arthritis Rheum* 2003; : 2122–7. [CrossRef] [Medline] [Web of Science]
17. Wallis RS, Broder M, Wong J, *et al*. Reactivation of latent granulomatous infections by infliximab. *Clin Infect Dis* 2005; (Suppl 3): S194–8. [CrossRef] [Medline] [Web of Science]
18. Kaur N, Mahl TC. Pneumocystis jiroveci (carinii) pneumonia after infliximab therapy: a review of 84 cases. *Dig Dis Sci* 2007; : 1481–4. [CrossRef] [Medline]
19. Seddik M, Meliez H, Seguy D, *et al*. Pneumocystis jiroveci (carinii) pneumonia following initiation of infliximab and azathioprine therapy in a patient with Crohn's disease. *Inflamm Bowel Dis* 2004; : 436–7. [CrossRef] [Medline]
20. Herrlinger KR, Borutta A, Meinhardt G, *et al*. Fatal staphylococcal sepsis in Crohn's disease after infliximab. *Inflamm Bowel Dis* 2004; : 655–6. [CrossRef] [Medline]
21. Rijkeboer A, Voskuyl A, Van Agtmael M. Fatal Salmonella enteritidis septicaemia in a rheumatoid arthritis patient treated with a TNF-alpha antagonist. *Scand J Infect Dis* 2007; : 80–3. [CrossRef] [Medline]