The use of infliximab in X-linked agammaglobulinaemia associated enteropathy

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ABSTRACT

Granulomatous small bowel enteropathy is an unusual presentation associated with X-linked agammaglobulinaemia. We present a rare case of this condition that was further complicated by an enterocutaneous fistula and report our experience managing this condition successfully with infliximab, which has not been documented in the literature previously.

KEYWORDS

Agammaglobulinaemia – Monoclonal antibodies – Enteritis granulomatous

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Case History

A 21-year-old man presented to a district general hospital with crampy abdominal pain and a tender lump in an old laparotomy scar. He gave a past history of X-linked agammaglobulinaemia (XLA) and appendicectomy. As a teenager, he was troubled regularly with diarrhoea, abdominal cramping and weight loss. He had repeated normal upper and lower gastrointestinal endoscopies. On one occasion, colonoscopy confirmed ileitis and ileocaecal inflammation with several large ulcers. Video capsule endoscopy revealed distal small bowel inflammation with ulceration and erythematous areas. He was treated empirically with mesalazine and received some benefit initially although symptoms eventually recurred.

In 2009 the patient presented as an emergency with small bowel obstruction and underwent a laparotomy with resection of a small bowel stricture. Pathological sectioning of the specimen showed mucosal erosion and florid transmural inflammation composed predominantly of large aggregates of histiocytes/granulomas with occasional central neutrophilic abscesses (suppurative granulomas) with reactive lymph nodes. No caseous necrosis was identified. A florid serosal fibroblastic reaction was present. No *Giardia* were seen, and staining for tuberculosis and Whipple's disease was negative. The pathologists concluded that these features in the background of the patient's underlying XLA suggested a diagnosis of XLA associated enteropathy.

The admitting surgical team was concerned about the possibility of an incarcerated incisional hernia and so proceeded to surgical exploration of the lump. The old scar was reopened and the surgeons encountered a large subcutaneous inflammatory mass. A biopsy of the mass was taken and a tube drain was left in situ. The decision was

taken not to proceed further surgically without radiological imaging.

Computed tomography of the abdomen (Fig 1) showed small bowel thickening and oedema in the lower abdomen and pelvis, with surrounding fat stranding. Rectus abdominis and anterior abdominal wall thickening was also noted. On day 2 following the surgery, small bowel content leaked out of the drain site and the patient was transferred to the tertiary unit for further management. The biopsy was reported as inflamed fibro fatty connective tissue and striated muscle, in keeping with inflammation of the rectus sheath.

In the intestinal failure unit, the output from the fistula settled rapidly without the need for parenteral nutrition (Fig 2). The patient was able to recommence an enteral diet. Following discussion between the immunology, gastroenterology and intestinal failure teams, the decision was taken to proceed with a trial of infliximab therapy. The first dose was given while an inpatient, with two further doses performed through the outpatient treatment unit. At review at four weeks, following his third dose of infliximab, the enterocutaneous fistula was healed, the patient had gained 10kg in weight and stool consistency had markedly improved.

Discussion

XLA is a primary immunodeficiency caused by mutations in the gene for Bruton's tyrosine kinase that result in the deficient development of B cells and hypogammaglobulinaemia.¹ The disease was first elucidated by Bruton in 1952, for whom the gene is named. The diagnosis of XLA is suspected in male patients with early onset bacterial

Figure 1 Computed tomography showing thickening of small bowel loops and inflammation of the anterior abdominal wall

Figure 2 Midline laparotomy scar and wound with fistula

infections, marked reduction in all classes of serum immunoglobulins and absent B cells (CD19⁺ cells); the decrease in the number of B cells is the most consistent and distinctive feature. The incidence is 1 in 100,000 live births. A prevalence of 1 case per 250,000 individuals has been estimated in the US, compared with 1 per 1,399,000 individuals in Eastern and Central Europe.

The diagnosis is usually made after four months of age as the maternal antibodies are degraded. Primary presentations can be extremely varied and include otitis, pneumonia, sinusitis, chronic or recurrent diarrhoea, conjunctivitis,

pyoderma, cellulitis, meningitis or encephalitis, septic arthritis, hepatitis and osteomyelitis.¹

The gastrointestinal tract is the largest lymphoid organ in the body containing T and B cells, macrophages and dendritic cells. Patients with antibody deficiency syndromes such as combined variable immunodeficiency syndrome and XLA can present with a spectrum of abnormalities in the gastrointestinal tract although gastrointestinal symptoms are less frequent in XLA than in other antibody deficiency syndromes. This is presumably because the T cell function is preserved in XLA. The most common presentations in XLA are diarrhoea (57%),¹ malabsorption states and failure to thrive. Some patients also present with recurrent small bowel strictures with fissuring necrosis, resulting in fistula formation. Infectious diarrhoea in XLA is well reported including *Giardia*, *Salmonella*, *Campylobacter* and rotaviruses.¹

Biopsies from the gastrointestinal tract can resemble graft-versus-host disease, inflammatory bowel disease and Whipple's disease but they often lack some of the diagnostic features of the diseases. Rare Crohn's disease-like pathology occurring in the small bowel has been reported in patients with XLA,² with some even regarding Crohn's disease as a consequence of immunodeficiency.³

Infliximab, a chimeric antitumour necrosis factor alpha monoclonal antibody, is now a well recognised and valuable treatment in Crohn's disease and ulcerative colitis. The use of infliximab has been reported in cases of other immunodeficiency syndromes to treat granulomatous disease in both extraintestinal⁴ and intestinal locations.⁵

Conclusions

On review of the literature, we believe this to be the first documented case of granulomatous small bowel enteropathy in a patient with XLA treated successfully with infliximab.

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