Coeliac disease and Crohn's disease: an association not to be forgotten

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CASE REPORT

A 10-month-old girl presented with a 2-month history of diarrhoea, 5–6 times a day. She was otherwise healthy, had a good appetite, and was thriving on a normal infant diet. She was born at full term by normal delivery, birth weight being 3.29 kg (25th centile). Immunizations were up to date and the development was normal. There was no other relevant past history. Her father had Crohn's disease, her maternal grandmother had coeliac disease and her maternal grandfather had ulcerative colitis. She did not improve after changing to a soya-based milk formula. Given the family history, her mother was anxious that she might have coeliac disease and began a gluten-free diet before any formal investigations. This diet led to resolution of her symptoms and she thrived. After medical review, a gluten-free diet was continued and it was decided that a dietary gluten challenge to confirm the diagnosis would be performed at a later date.

A gluten challenge was performed at 18 months of age. Duodenal biopsy by Crosbie capsule after 4 weeks showed some normal villi, but was poorly oriented. Gluten intake was not formally assessed. Her diarrhoea recurred and her parents recommenced gluten exclusion, which again led to resolution of her symptoms. A second gluten challenge was arranged when she was 4 years old. This time she tolerated gluten. She did not have a repeat biopsy or serological testing and was discharged from medical follow up on a normal diet. The presumption was that her enteropathy had resolved. Soon after this, however, her parents restarted the gluten-free diet because her symptoms had returned. They did not re-present to her physician and her subsequent compliance with the diet was poor. Thus she remained undiagnosed but on a mostly gluten-free diet.

She was referred for reassessment at the age of 12 years with 4 months history of recurrent abdominal pain and profuse diarrhoea. She had lost weight and had developed a secondary amenorrhoea, having started her periods at the age of 11 years. Her recent symptoms had responded, at least in part, to avoiding milk and gluten. Neither the gluten nor the milk exclusion was complete. Her height and weight were between the 25th and 50th centile. Physical examination was unremarkable. Her mother had been diagnosed with coeliac disease 3 years earlier.

Investigations showed a normal full blood count, erythrocyte sedimentation rate, C-reactive protein and serum immunoglobulins. Her immunoglobulin A (IgA) anti-endomysial antibody was moderately positive. IgG and IgA anti-gliadin antibodies were negative. IgE RASTs (radioallergosorbent test) to wheat and milk were negative. Barium studies of the small bowel were normal. Three separate stool specimens were negative for bacterial and viral pathogens.

She was kept on a strict gluten-free diet for 6 months and improved symptomatically, gaining weight and restarting her periods. Repeat IgA anti-endomysial antibody testing was negative. She had a third gluten challenge in order to formalize the diagnosis of coeliac disease. This was supervised and gluten intake was good. Her symptoms worsened while on the gluten-containing diet. Duodenal biopsy, done after 3 months, showed partial villous atrophy consistent with coeliac disease (*Figure 1a*).

Although she went back to a strict gluten-free diet, there was only moderate improvement in her clinical state. She deteriorated, developing symptoms typical of colitis. Sigmoidoscopy with biopsy showed granulomatous changes in her sigmoid colon consistent with Crohn's disease. She started to improve without additional treatment and her parents were therefore keen to defer further investigation until a relapse. Repeat upper gastrointestinal endoscopy and colonoscopy done after 2 months, while excluding milk and gluten, showed healing of the duodenum (*Figure 1b*) but a severe colitis consistent histologically with Crohn's disease (*Figures 2a* and *b*). Some biopsies showed transmural inflammatory changes and there was a marked inflammatory infiltrate, with granulomata.

Her colitis responded well initially to corticosteroids. Milk was successfully reintroduced. She is treated with azathioprine, commenced after a symptomatic relapse, and has remained well for over 12 months. Coeliac antibody titres are normal. She is HLA-DQ2 positive.

INTRODUCTION

Coeliac disease and Crohn's disease have been reported rarely in the same patient in the paediatric literature. Their co-existence may complicate the diagnostic process. This article presents the progress of a girl who presented at the age of 10 months, with a family history of coeliac disease and inflammatory bowel disease, whose coeliac disease was undiagnosed for over 10 years. She had a negative duodenal biopsy after gluten challenge at 18 months of age, but was intolerant of wheat and was kept on a mostly gluten-free diet.

She re-presented with diarrhoea at the age of 12 years. Investigations revealed a normal full blood count and inflammatory markers with a moderately positive immunoglobulin A (IgA) anti-endomysial antibody. Duodenal biopsy was consistent with coeliac disease. However, her symptoms persisted after full gluten exclusion. Subsequent upper gastrointestinal endoscopy showed duodenal healing but colonoscopy revealed Crohn's disease. After treatment with corticosteroids, she remains well on a gluten-free diet and azathioprine.

DISCUSSION

Coeliac disease and Crohn's disease are inflammatory conditions and often present in childhood with predominantly gastrointestinal symptoms. Both have an increased incidence in fami-

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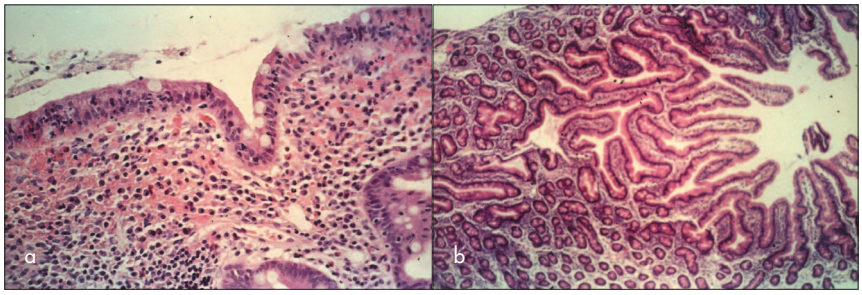

Figure 1. a. Duodenal biopsy showing villous atrophy and large number of intraepithelial lymphocytes. b. Repeat biopsy following gluten exclusion showing healing of the duodenum and restoration of normal architecture.

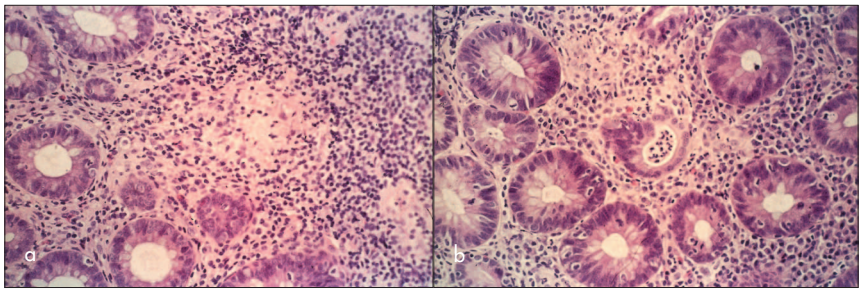

Figure 2. Rectal biopsy showing (a) granuloma in the background of severely inflamed lamina propria and (b) a small crypt abscess surrounded by glands showing good preservation of normal architecture.

lies. They have, however, only rarely been documented in the same patient during childhood.

The first paediatric association was reported in a 19-year-old patient. This adolescent male with known Crohn's disease had extreme wasting, growth retardation, intractable diarrhoea, and delay in sexual development. Subsequent jejunal biopsy was found to be compatible with coeliac disease (Euler and Ament, 1977).

The second case was a 2-year-old boy with peritoneal miliary Crohn's disease with coexistent coeliac disease. He presented with ascites in addition to vague gastrointestinal symptoms and was found at laparotomy to have serosal miliary Crohn's disease. The jejunal mucosa was markedly atrophic, compatible with a diagnosis of co-existent coeliac disease (Glasgow et al, 1983). In adult literature this association, although uncommon, is recognized more often, as reviewed by Kitis et al (1980).

Immunopathogenesis is of central importance in both coeliac and Crohn's disease. T-cell activation leading to small intestinal enteropathy is common to both diseases. Such enteropathy is related to T-cell activation with the release of interferon-gamma, tumour necrosis factor-alpha and other cytokines (Walker-Smith, 2000). Over 95% of patients with coeliac disease express the HLA haplotype HLA-DQ2 or HLA-DQ8, which preferentially presents gluten-derived gliadin peptides on its antigen-presenting groove to stimulate intestinal mucosal T cells (Farrell and Kelly, 2002). However, coeliac disease only manifests in around 1 in 50 of those who carry these HLA types. The presence of HLA-DQ2, as in this case, supports the diagnosis of coeliac disease. The diagnosis is confirmed by the biopsy and serology results, particularly with their response after completely removing gluten.

The immunopathogenesis of Crohn's disease is complex. Experimental and observational data suggest that the intestinal inflammation mediated by T cells is caused by abnormal immune reactivity to usually commensal enteric bacteria in genetically susceptible individuals (Shanahan, 2002). A higher than expected prevalence of inflammatory bowel disease has been noted in the first-degree relatives of patients with coeliac disease. This supports the possible genetic predisposition of patients with coeliac disease to inflammatory bowel disease (Shah et al, 1990). Although false-positive IgA anti-endomysial antibodies can be detected in duodenal Crohn's disease, the possibility of the coexistence of both diseases should always be considered in those patients not showing the expected therapeutic response to immunosuppression (Weber et al, 1998).

For the case presented, the presumption is that she has had undiagnosed coeliac disease since infancy and the Crohn's disease manifested later. The difficulties in diagnosis at the age of 18 months reflect her poor gluten intake and that biopsy after gluten challenge was poorly oriented. When she re-presented tests for coeliac disease was complicated by the dietary restriction of gluten. After the diagnosis had been made her symptoms did not resolve with full gluten exclusion, prompting further investigations. These led to the additional diagnosis of Crohn's colitis. This case illustrates that the diagnosis of coeliac disease remains problematic in certain patients, particularly in the context of inflammatory bowel disease. **HM**

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