Primary antibody deficiency and Crohn's disease

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Summary

Five patients with primary antibody deficiency were investigated because of intermittent but persistent diarrhoea of several years duration despite immunoglobulin replacement therapy. We found no evidence of *Giardia lamblia* or other intestinal pathogens to explain their gastrointestinal symptoms. All five had definite radiological evidence of small bowel Crohn's disease and three had histological specimens available with abnormalities consistent with Crohn's disease. One patient had a non-caseating granuloma in an oral ulcer. A second patient with stricturing disease in the small bowel had a mucosal inflammatory infiltrate with non-caseating granulomas. A third had transmural inflammation but no granulomas. All five patients were diagnosed as having Crohn's disease and have responded symptomatically to steroid therapy.

Keywords: antibody deficiency; Crohn's disease

Some patients with primary antibody deficiency have an enteropathy. Infection is common and although immunoglobulin replacement therapy seems to have reduced the incidence of some bowel pathogens such as *Giardia*, *Salmonella* and *Campylobacter*, 10% have diarrhoea, abdominal pain or weight loss which defies explanation.¹

There is a broad spectrum of histological abnormality in these patients. In the stomach there is a high frequency of gastric atrophy and a predisposition to gastric carcinoma,²⁻⁴ whilst in the small bowel, lymphoid nodular hyperplasia is common.²⁻⁵ In those with common variable immunodeficiency, there are well-documented cases of jejunal villous atrophy which may or may not respond to gluten withdrawal; however, the diagnosis of coeliac disease has only been reliably proved in one patient after gluten withdrawal and challenge.⁶

There have been several case reports showing radiological appearances compatible with Crohn's disease in patients who have presented with diarrhoea and intestinal strictures, although the histology has generally not shown granulomas or transmural inflammation.⁷⁻¹¹ Teahon and Webster,¹¹ in their series of patients with primary antibody deficiency, proposed the existence of an enteropathy distinct from Crohn's disease. The radiology was consistent

with Crohn's disease but the histology was apparently distinctive with the presence of microscopic colitis, increased intra-epithelial lymphocytes and an intact crypt architecture in the colon. Any inflammation in the small bowel was not transmural and there were no granulomas.

We investigated the cause of diarrhoea in five patients with primary antibody deficiency who were referred with refractory diarrhoea.

Methods

We investigated five patients who were referred with intermittent but persistent diarrhoea of several years duration from a cohort of 100 patients with primary antibody deficiency from the Department of Immunology at Hope Hospital in Manchester over a period of 8 years. There were four men (19-65 years) and one woman (54 years). One had X-linked agammaglobulinaemia (Bruton's disease), the others had common variable immunodeficiency. All five patients had been shown to have a primary immunological deficiency by their repeated failure to generate responses to common antigens such as pneumococcus, tetanus and pokeweed nitrogen. All were on regular immunoglobulin replacement therapy with Sandoglobulin (Sandoz Pharmaceuticals) at a dose of 0.3-0.4 g/kg/month with regular assessment of their immunoglobulin trough levels.

Two sets of three fresh stool specimens from each patient were examined for evidence of parasitic involvement or other pathogens. Each patient had a gastroscopy with duodenal biopsy, full colonoscopy and a small bowel enema. The specimens obtained were examined histologically for parasites.

Patients were commenced on steroid therapy and their response assessed according to improvements in their symptoms. They were then followed up over a 5-year period.

Results

The main findings are shown the table. No pathogens were identified from several stool examinations specifically looking for *Salmonella*, *Shigella*, *Campylobacter*, ova and cysts. All of the patients had radiological evidence of small bowel abnormalities compatible with Crohn's disease. Patient 1 had nodular thickening throughout the jejunum and ileum (figures 1 and 2). Patient 2 showed stricturing disease in the duodenum and small bowel (figure 3). Patient 3 had a stenotic lesion in the terminal

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Table 1

Patient	Age	Sex	Presentation	Radiological abnormalities	Histological abnormalities	Other features	Other sites of infection	
1	X-linked agammaglobulinaemia	19	M	Weight loss, loss of appetite, abdominal pain	Jejunum, ileum = nodular thickening	Mouth-granulomas, non-caseating S - not done D - duodenitis, no atrophy SB - none available C - normal	Has developed a protein losing enteropathy	Bronchiectasis
2	CVID	60	M	Oral ulcers, abdominal pains, weight loss	Duodenum, jejunum, ileum = stricturing 2nd & 4th parts of the duodenum & mid small bowel	S - not done D - not done SB - granulomas, inflammatory infiltrate, not transmural C - not done	Stricturing disease in mid small bowel requiring resection	Nil
3	CVID	36	M	Diarrhoea, abdominal pain	Terminal ileum = skip lesions & ulceration with stenotic lesions	S - normal D - total villous atrophy, crypt hyperplasia, intraepithelial lymphocytes SB - none available C = non-specific inflammation	Has developed spondyloarthopathy affecting large joints	One episode of meningitis
4	CVID	33	M	Diarrhoea, right iliac fossa pain	Terminal ileum = oedematous, with rose thorn ulcerations	S - normal D - normal SB - none available C - non-specific inflammation		Bronchiectasis
5	CVID	52	F	Bloating, diarrhoea, abdominal pain	Terminal ileum = ulceration and stricturing disease	S - gastritis, no atrophy D - not done SB - mild transmural inflammation, patchy inflammatory cells, no granulomas C - normal	Required terminal ileum resection	Recurrent chest infection

CVID = common variable immunodeficiency, S = stomach, D = duodenum, SB = small bowel, C = colon.

ileum with skip lesions and ulceration. Patient 4 had rosethorn ulceration of the terminal ileum. Patient 5 also had stricturing disease in the terminal ileum (figure 4).

There was a wide spectrum of histological abnormality. Patient 1 had granulomatous ulceration in the mouth and duodenitis. Patient 3 had total villous atrophy on duodenal biopsy with increased intra-epithelial lymphocytes and crypt hyperplasia. Patient 5 had gastritis. Patients 2 and 5 needed resections for obstructive symptoms. One resected terminal ileal

specimen revealed an inflammatory non-transmural lymphocytic infiltrate, fibrosis and two non-caseating granulomas. The other resected ileal specimen showed transmural lymphocytic inflammation without granulomas. In the colon of patients 3 and 4 the specimens demonstrated a mild non-specific inflammation restricted to the mucosa which was mainly lymphocytic with some neutrophils, infiltration, no crypt abscesses, and without

Figure 1 Film on barium follow-through study (patient 1). There is mild thickening and nodularity of the jejunum. In addition in this case more diseased loops of bowel are seen within the pelvis where the nodularity is more marked (open white arrow) and there is associated luminal narrowing with bowel loop separation (black arrow)

Figure 2 Film from small bowel enema (patient 2). Note the small bowel enema tip in third part of duodenum. Strictures are evident: the first (white arrow) is at the junction of the second and third part of the duodenum. A second stricture is seen in the region of the DJ flexure (curved open arrow). This is causing pre-stenotic dilatation of the third part of the duodenum which contains a filling defect/food residue. Contrast has, however, passed beyond this point into the proximal jejunum

Figure 3 Film from small bowel follow-through series (patient 2). There is mild, diffuse nodular thickening of the jejunum and proximal ileum. No structuring disease is identified. The appearances are non-specific but can be seen in diffuse Crohn's jejunal ileitis as well as many other conditions such as Giardiasis.

Figure 4 Cone view of right iliac fossa during small bowel enema (patient 5). The distal terminal ileum shows stricturing in several places (white arrows). The folds are thickened and there is nodularity with several adverse ulcers. These are most prominent between the two labelled strictures.

intra-epithelial lymphocytes. There was no evidence of parasites in any of the specimens examined.

Patients 1 and 3 who had particularly severe symptoms were treated with budesonide but did not respond and were controlled on regular prednisolone. The other three patients responded to short courses of prednisolone following commencement of steroids, a clinical improvement was documented by a significant reduction in stool frequency.

Discussion

The five patients described had Crohn's disease. We found no evidence to support the existence of a separate enteropathy associated with primary antibody deficiency. One might have expected that infection would explain these patients relapsing and remitting gastrointestinal symptoms. After all, the majority had

evidence of infection in other body systems, but despite looking for pathogens in stools and histological specimens none was ever implicated. It could be argued that we did not look aggressively enough for micro-organisms. *Microsporidia* and *Cyclospora* are difficult to detect on haematoxylin and eosin sections; electron micrographs would perhaps have been preferable. It is also difficult to attain a perfect plateau of immunoglobulin replacement, even with frequent monitoring of trough levels, and Sandoglobulin contains predominantly IgG with only small amounts of IgA, the principal bowel immunoglobulin.

All of our patients had radiological evidence of small bowel involvement varying from stricturing disease requiring surgical resection in two patients to nodular thickening in the jejunum and ileum or rosethorn ulceration. The histological abnormalities were very diverse. Two patients had non-caseating granulomas; in one, this was present in a lesion in the mouth and the other in a resected terminal ileal specimen. This latter patient, however, had a predominantly mucosal rather than transmural lymphocytic infiltrate. The other patient who needed a terminal ileal resection for stricturing disease had a mild transmural lymphocytic infiltrate without granulomas.

Total villous atrophy with increased intra-epithelial lymphocyte infiltration was found in one patient on duodenal biopsy but he showed no improvement in histological appearance with gluten withdrawal. Another had lymphocytic infiltration in the duodenum but no other abnormalities. In colonic specimens, two patients had mild inflammation restricted to the mucosa, with an intact crypt architecture and no increase in intra-epithelial lymphocytes.

We would argue that the pattern of histological and radiological findings demonstrate these patients to have Crohn's disease rather than belonging to a different grouping as originally proposed by Teahon and Webster.¹¹

Patients 2 and 5 needed small bowel resections for stricturing disease in the early part of their clinical course; their subsequent gastrointestinal symptoms have responded well to short courses of prednisolone, as have those of patient 4. Two other patients (1 and 3) were tried on 9 mg of budesonide but did not respond and have better disease control on regular prednisolone therapy, with one of these also tolerating and responding to an elemental diet. Patient 1 with x-linked agammaglobulinaemia has recently developed a protein-losing enteropathy initially suggested by rising requirements for immunoglobulin therapy. Interestingly, this problem appears to have been controlled with steroid therapy.

The aetiology of Crohn's disease is still unknown. A variety of hypotheses exist but none have been proved. Immune function has been extensively tested in Crohn's patients. There have been studies suggesting mild defects in neutrophil functions, both in ability to phagocytose¹² and in chemotaxis on 'skin

windows¹³ (serum-filled perspex windows placed over abraded skin). Others, however, have shown normal neutrophil oxidative ability^{14, 15} and normal chemotaxis in vitro. All in all, these probably add up to mild defects in phagocyte function. Lymphocyte function is thought to be normal in Crohn's disease; although there is a specific increase in IgG2

immunocytes.¹⁶ It is not known how many patients with Crohn's have primary antibody deficiency.

In conclusion, we report five patients with primary antibody deficiency who also have Crohn's disease defined radiologically and histologically, and whose symptoms are controlled on steroid therapy.

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Brain parenchymal, subarachnoid racemose, and intraventricular cysticercosis in an Indian man

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Summary

The coexistence of brain parenchymal cysts at various stages of evolution, both intraventricular and subarachnoid racemose, is reported in a patient with neurocysticercosis. The condition has a variety of presentations, depending on the location of the cyst. This case is of particular interest because of the rarity of this condition in India.

Keywords: brain parenchymal cyst; cysticercosis; albendazole

Cysticercosis is caused by cysticercus larvae of *Tenia solium*. The most common manifestation of neurocysticercosis is seizure due to brain parenchymal cysts at various stages of evolution.¹ Subarachnoid and intraventricular cysts are rarely seen in India. In Mexicans, however, they are more common (up to 10% of all cases).² Subarachnoid cysts are of the racemose type, as are the majority of intraventricular ones. A combination of cysticercus cysts in these locations is rather uncommon, especially in the Asian subcontinent. Considering the varied presentations of neurocysticercosis, de-

pending on the location of the cysts, it was felt to be worthwhile reporting this case. Some of the varied presentations and their pathogenesis are also discussed.

Case report

A 50-year-old man presented to the neurology out-patient department with history of left-sided sensorimotor seizures for the last 3 years with a frequency of once every one or two months. There was secondary generalisation at times. There was also a history of complex partial seizures for the last 6 months. These were characterised by episodic altered behaviour, aimless running around, and complete amnesia for the events. He had suffered from recurrent, nonthrobbing left parieto-occipital headaches, each lasting for a few hours, for the last 18 months. Accompanying the headache, he experienced tinnitus in both ears and vertigo, but there was no vomiting or visual symptoms. He gave a history of pork ingestion. He was on a maintenance of dose of phenytoin. He had received albendazole for a month in November 1994.

His general examination was normal. Systemic examination was unremarkable. The

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