Transient protein losing enteropathy associated with acute gastritis and campylobacter pylori

I D HILL,* C SINCLAIR-SMITH,† A J LASTOVICA,‡ M D BOWIE,* AND M EMMS†

*Department of Paediatrics and Child Health, †Department of Pathology, and ‡Department of Medical Microbiology, University of Cape Town and Red Cross War Memorial Children's Hospital, Cape Town

SUMMARY Three children presented with acute protein losing enteropathy and were found to have acute gastritis associated with *Campylobacter pylori* infection. Recovery from protein losing enteropathy was accompanied by resolution of the gastritis and the disappearance of *C pylori* from the gastric mucosa. Their clinical course suggested that the *C pylori* had caused the gastritis and the protein losing enteropathy. The association between gastritis caused by *C pylori* and protein losing enteropathy in children has not to our knowledge been previously described.

Organisms resembling campylobacter have been reported in association with active chronic gastritis and gastric and duodenal ulcers in adults.^{1,2} Recently this association was described in children with symptomatic gastritis.³ As these organisms are rarely found in normal gastric mucosa it has been suggested they may be the cause of the inflammatory changes.^{3,4}

This report describes three children presenting over a period of four months with acute protein losing enteropathy. They were found to have an acute gastritis associated with *Campylobacter pylori*. Recovery from the protein losing enteropathy was accompanied by a return to normal of the gastric mucosa and disappearance of the organisms.

Case reports

CASE 1

A 4½ year old girl presented with a week's history of periorbital swelling and pitting oedema of her legs and sacrum. The rest of the clinical examination yielded normal results and she had no skin changes or other features of malnutrition. Her serum protein concentration was 35 g/l and serum albumin concentration 17 g/l. Microscopy and culture of her stool specimen did not show any parasites or bacterial pathogens. A ⁵¹Cr labelled albumin study confirmed protein losing enteropathy; in a four day stool collection 6.2% of the injected isotope was recovered (normal <1%). At gastroscopy swollen gastric rugae were seen with pronounced hyperaemia of the mucosa in the body and (to a lesser extent) in the antrum of the stomach. The duo-

denum was macroscopically normal. Biopsy specimens of gastric mucosa showed oedema of the lamina propria with an increased number of inflammatory cells that were mainly plasma cells and

Fig 1 Gastric mucosal biopsy specimen showing numerous *C pylori* in superficial mucus (single arrow) and penetrating between cells (double arrow) (Warthin-Starry stain).

lymphocytes. Histology of the duodenal biopsy specimen showed only a slight increase in the number of plasma cells. Fig 1 shows that numerous organisms resembling campylobacter were found on the surface of the gastric mucosa on Warthin-Starry staining. These were confirmed by electron microscopy to be *C pylori* (fig 2). She was given antacids for the gastritis but no other treatment. The oedema gradually resolved and her serum protein concentration rose; 19 days after admission her serum protein concentration was 53 g/l and that of albumin 27 g/l. Gastroscopy was repeated and showed a macroscopically normal gastric mucosa; histology of biopsy specimens showed a residual mild inflammatory cell infiltrate with scanty organisms resembling campylobacter on Warthin-Starry staining. Culture of a biopsy specimen grew *C pylori*. Two months after admission she had completely recovered and her serum protein concentrations were

normal. The gastric mucosa was normal both macroscopically and histologically. *Campylobacter* could neither be seen on staining nor grown on culture.

CASE 2

A boy aged 2 years and 3 months presented with a history of a self limiting episode of diarrhoea two weeks previously that had been followed one week later by generalised swelling. On admission he had pitting oedema of his legs and sacrum, and ascites. He had no skin changes or clinical features of malnutrition and the remainder of the examination yielded normal results. Microscopy and culture of a stool specimen did not show any parasites or bacterial pathogens. His serum protein concentration was 28 g/l and serum albumin concentration 10 g/l. Protein losing enteropathy was confirmed, as 7.8% of injected ^{51}Cr labelled albumin was recovered

Fig 2 Low power electron micrograph showing numerous *C pylori* (cp) in contact with cell membranes and microvilli (mv) and concentrated at intercellular tight junctions (arrows). Inset: high power view of *C pylori* showing characteristic sheathed flagellae (arrow) and association with intercellular junction (double arrow).

from a four day stool collection. At gastroscopy pronounced hyperaemia of the mucosa of the body of the stomach was found, the antrum being normal. The duodenum also looked normal. Histology of the gastric biopsy specimens showed oedema of the lamina propria with an increased number of plasma cells, lymphocytes, and neutrophils. On Warthin-Starry staining numerous organisms resembling campylobacter could be seen on the mucosal surface, and electron microscopy confirmed these as *C pylori*. Culture of a gastric biopsy specimen failed to grow the organism. He was treated with erythromycin and within 48 hours the oedema began to subside. After 10 days of treatment with erythromycin the oedema had completely resolved and his serum protein concentration was 72 g/l, that of albumin being 39 g/l. Gastroscopy showed normal gastric and duodenal mucosa. Histology of biopsy specimens of the body of the stomach was normal, and no organisms resembling campylobacter were detected on Warthin-Starry staining. Culture of the biopsy specimen produced a scanty growth of *C pylori*.

CASE 3

A 3 year old boy presented with a one week history of diarrhoea and generalised swelling for one day. He seemed well nourished but had periorbital swelling and pitting oedema of his legs and sacrum. The rest of the clinical examination yielded normal results. By the time he was admitted to hospital his diarrhoea had resolved and a stool specimen sent for microscopy and culture did not show any parasites or bacterial pathogens. His serum protein concentration was 26 g/l and albumin concentration 12 g/l. Protein losing enteropathy was confirmed by recovery of 8.4% of the injected ^{51}Cr labelled albumin from a four day stool collection. At gastroscopy swollen gastric rugal folds were seen and there was intense hyperaemia of the mucosa of the body of the stomach. The duodenum was macroscopically normal. Histology of gastric biopsy specimens showed oedema of the lamina propria with increased plasma cells and lymphocytes. The duodenal biopsy specimen showed only a slight increase in the number of chronic inflammatory cells in the lamina propria. On Warthin-Starry staining numerous organisms resembling campylobacter were seen along the surface of the gastric mucosa. Electron microscopy and culture confirmed these to be *C pylori*. He was treated with erythromycin and improved considerably. The oedema resolved within three days and by 10 days his total serum protein concentration was 66 g/l, that of albumin being 33 g/l. Gastroscopy at this time showed normal appearances both macroscopically and histologically,

and no organisms resembling campylobacter were seen on Warthin-Starry stain. Culture of biopsy specimens from the body of the stomach did not grow *C pylori*.

Methods

At least eight gastric biopsy specimens were taken under direct vision through the gastroscope on each occasion. Specimens for light microscopy were immediately fixed in Carson's fluid and sections subsequently stained with haematoxylin and eosin and by the Warthin-Starry method. Specimens for electron microscopic examination were fixed in 4% S-collidine buffered glutaraldehyde (pH 7.2-7.4), washed in S-collidine buffer (0.1 M), fixed again in 1% S-collidine buffered osmium tetroxide (pH 7.4), block stained with uranyl acetate, dehydrated in graded alcohols, and embedded in Spurr's resin. Ultrathin sections were stained with uranyl acetate and lead citrate and viewed in a Phillips 201 electron microscope.

Specimens for culture were placed in sterile tubes and taken to the laboratory immediately. Fresh biopsy specimens were moistened with tryptic soy broth and rubbed over the surface of plates of tryptose blood agar base (CM 233, Oxoid Ltd, Basingstoke, Hants, United Kingdom) containing unlysed horse blood 7% v/v. The plates were incubated in a microaerophilic environment at 37°C for up to six days in both a Carbon-dioxide incubator and a Gaspak system (BR 56, Oxoid). The organisms were identified as *C pylori* by their morphological appearances and using accepted biochemical criteria.⁵

Discussion

These patients all had severe hypoproteinaemia due to protein losing enteropathy that was confirmed by the amount of ^{51}Cr labelled albumin excreted in the stools. There are many causes of protein losing enteropathy in childhood but the history, age, and manner of presentation of these children suggested the diagnosis of Menetrier's disease (giant hypertrophic gastritis). This is characterised by giant gastric rugal hypertrophy seen on barium swallow examination or at gastroscopy.⁶ There are typical histological features in the biopsy specimens and usually peripheral eosinophilia as well.⁶ The cause of Menetrier's disease is uncertain but it may be due to infections with certain viruses such as cytomegalovirus.⁷

The gastroscopic and histological findings in these patients were unlike those described in Menetrier's disease. None had peripheral eosinophilia and

no intranuclear inclusion bodies suggestive of cytomegalovirus were seen. Although there was some oedema of the gastric folds, the most striking feature was a severe acute gastritis predominantly affecting the body of the stomach. This contrasts with reports in adults in whom the antrum of the stomach is usually the worst affected. The duodenum was macroscopically and histologically normal in all cases. Histological examination of biopsy specimens of gastric mucosa confirmed the macroscopic appearances of acute gastritis. All had oedema of the lamina propria with increased numbers of inflammatory cells, mainly plasma cells and lymphocytes. Neutrophil polymorphs were prominent in one case and none had eosinophils. Examination by light microscopy showed numerous organisms resembling campylobacter, easily seen using the Warthin-Starry stain, on the surface of the

gastric mucosa. The organisms were short, thick 'sea-gull' shaped spiral rods (fig 1). They were lying free in the superficial mucus or attached horizontally to the surface of the gastric mucosal cells where they were often so numerous that they seemed to form a lining sheet. They were also lying between epithelial cells, both surface and glandular, having penetrated the intercellular spaces.

Organisms resembling campylobacter found on examination by light microscopy may be identified as *C pylori* either by recognising the characteristic morphology and sheathed terminal flagellae on electron microscopy⁸ or by bacterial culture.⁵ All three patients had *C pylori* identified by one or both of these methods. The initial negative culture in Case 2 was probably due to technical problems in the culture method.

Clustering of the *C pylori* around the tight

Fig 3 High power electron micrograph showing *C pylori* embedded in cell junction (arrow). Second organism is associated with disrupted and widely separated intercellular space (double arrows) containing amorphous material streaming into the lumen of the stomach. Inset: *C pylori* that has penetrated to base of parietal cell canaliculus; C=subepithelial collagen.

junctions between the cells was noted on electron microscopic examination. Concentration of the organisms in this area has been described previously, and it was postulated that this represented the site through which preferred metabolites and growth factors diffuse.⁹ In all three cases electron microscopic examination showed that some cells were clearly separated from each other with amorphous material lying in the widened space (fig 3). In addition to disruption of the intercellular junctions, there was cellular degeneration with nuclear pyknosis, increased lysosomal activity, and loss of cell membranes. This disruption of the cellular structure could be the site of the protein loss.

The association between organisms resembling campylobacter and symptomatic gastritis is well known in adults^{1,2} and has been described more recently in children.³ The additional finding of an acute, severe protein losing enteropathy with this association, however, has not to our knowledge been previously reported. It has been postulated that the organisms are the cause of the gastritis as they are not usually found in normal gastric mucosa.^{3,4} In addition, clearance of the organisms from the gastric mucosa led to improvement of the gastritis in a series of adult patients.¹⁰ The findings in our patients are in keeping with this, and also suggest that protein losing enteropathy may be a consequence of the gastritis. In each case recovery from the protein losing enteropathy was accompanied by a return to normal of the gastric histology and disappearance of the organisms. In view of the transient nature of the illness and negative clinical findings on admission it is unlikely that any of the other known causes of protein losing enteropathy in childhood were responsible for the disease in these patients. Case 1 was not given antibiotics, and complete recovery from the protein losing enteropathy and gastritis and eradication of the organisms took a long time. In contrast, cases 2 and 3 were treated with erythromycin to which *C pylori* has been shown to be sensitive in vitro¹¹ and they recovered rapidly in all respects within 10 days. The

apparent response to treatment may have been coincidental as others have not found *C pylori* to be sensitive to erythromycin in vivo.¹⁰

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Correspondence to Dr ID Hill, Institute of Child Health, Red Cross Children's Hospital, Rondesbosch 7700, South Africa.

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