

## Case report

# Chronic colitis after *Aeromonas* infection

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**SUMMARY** Three patients with an acute colitis in which the only pathogen detected was either *Aeromonas hydrophila* or *A sobria* progressed to a chronic phase after the infection had been eliminated by antibiotic treatment in two and had resolved spontaneously in the third. The final diagnosis in each case was ulcerative colitis. Two of the patients have responded to anti-inflammatory medication but one has required panproctocolectomy. The sequence of symptoms and observations in these cases, as well as in others from the literature involving more familiar pathogens, suggests that bacterial infection may contribute to the development of chronic colitis. This supposition could be tested by extending the follow up of patients with acute infective colitis in a prospective multicentre trial.

Pathogens implicated in exacerbations of chronic inflammatory bowel disease include *Shigella*<sup>1,2</sup> and *Salmonella*<sup>1-4</sup> spp, *Campylobacter jejuni*,<sup>5,6</sup> *Clostridium difficile*,<sup>7-9</sup> cytomegalovirus,<sup>10</sup> and *Giardia lamblia*.<sup>6</sup> Evidence for a causal relationship between infection with such organisms and the disease itself has been considered at best inconclusive, although in one follow up study of patients from an epidemic of bacillary dysentery it was observed that an unexpectedly large number had subsequently contracted either ulcerative colitis or Crohn's disease.<sup>11</sup>

Vibrios of the genus *Aeromonas* are Gram negative non-sporulating rods, motile with a single polar flagellum. They are not considered part of the normal human faecal flora, though isolation of *A hydrophila* from as many as 3-2% of subjects without signs of intestinal infection has been reported.<sup>12</sup> Heavy growths of *A hydrophila* in the stool are obtained only from patients with diarrhoea.<sup>13</sup> Support for its pathogenic role in such cases has been gained

through the identification of both an enterotoxin<sup>14-17,19</sup> and up to three distinct cytotoxins<sup>18-20</sup> among the many strains studied. When populations with and without diarrhoea are compared a significantly higher proportion of the former excrete enterotoxigenic<sup>21</sup> or cytotoxigenic<sup>22</sup> strains. While the ability to cause diarrhoea seems chiefly dependent on enterotoxin production, an additional invasive property may be required to induce the blood loss which implies dysenteric pathology.<sup>23</sup>

We have described a case of acute distal colitis caused by *A hydrophila*.<sup>24</sup> A series of children infected with this organism included some displaying clinical features suggestive of ulcerative colitis,<sup>21</sup> and elsewhere among 19 adults with *Aeromonas* positive diarrhoea submitted to sigmoidoscopy only two gave a history of chronic colitis yet nine showed obvious colitic change.<sup>25</sup> The following case histories record the development of a chronic colitis in two patients, infected respectively with *A hydrophila* and *A sobria*, one the subject of our previous report who relapsed clinically after cure of the infection by antibiotic treatment. In a third patient microscopic abnormalities of the rectal mucosa persisted for at least seven months after spontaneous elimination of *A sobria*.

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## Case reports

### PATIENT 1

A 35 year old Indian doctor contracted bloody diarrhoea with abdominal cramps during a visit home in December 1979. One of two stools examined on his return to UK a week later yielded a moderate growth of *A hydrophila*, and the same organism was grown from rectal fluid at a sigmoidoscopy which showed haemorrhagic proctitis. Biopsy displayed chronic inflammatory change consistent with ulcerative colitis. Negative results were obtained in routine haematological and liver function tests. A barium enema was normal. Within six days of starting co-trimoxazole the patient was passing normal stools without blood. Repeat sigmoidoscopy was normal.

Slight rectal bleeding recurred after six weeks, but it was not until another 12 weeks had passed that the patient reported back. Then sigmoidoscopy showed a granular, oedematous mucosa oozing blood, with some adherent pus. Biopsy findings were similar to those during the original infection, but no subsequent stool contained *A hydrophila*. During the next year gradual improvement followed treatment with oral sulphasalazine and intrarectal steroids, and by July 1981 sigmoidoscopy was again normal. Sulphasalazine was then stopped, and the patient has remained well since.

### PATIENT 2

While travelling in the USA during the summer of 1981 a 24 year old Englishman suffered diarrhoea, with five loose blood tinged stools a day, and bouts of severe upper abdominal pain. He presented after two months, well in general but with a mild proctitis. Microscopic changes of a chronic, relatively quiescent, colitis were seen in the rectal biopsy. Four stools grew *A sobria*. Routine blood tests were normal. Barium enema showed fine ulceration and disturbance of the haustral pattern at several points up to the hepatic flexure.

The previous summer this patient had contracted a brief gastroenteritis in the Canary Islands. Some months later he had been admitted to hospital overnight with suspected appendicitis.

During a 10 day course of co-trimoxazole the stool became negative for *A sobria*, and remained so four and six weeks later. As symptoms continued a course of oxytetracycline was given, but with no better result. Combined treatment with sulphasalazine and intrarectal hydrocortisone foam was substituted, but after brief improvement the frequency of the blood stained stools doubled, so oral prednisolone was added and the hydrocortisone was given in retention enemas. This change resulted in formation and much reduced frequency of the stools. Two months later

colonoscopy showed rectum and sigmoid colon to be macroscopically normal, but from here to mid-transverse colon the mucosa was oedematous, with a segment of 'cobblestoning' and ulceration just distal to the splenic flexure. Microscopically all biopsies gave evidence of a severe chronic colitis.

Diarrhoea and bleeding increased at doses of prednisolone below 10 mg daily. Additional oral and intrarectal treatments were prescribed, with modest improvement in the stools, although the patient remained unable to work. Azathioprine was added, but one month later he suffered a severe relapse, with stools still negative for pathogens, and in September 1982 panproctocolectomy with ileostomy was carried out. The resected colon was inflamed and ulcerated throughout, with gross and microscopic appearances typical for ulcerative colitis. The patient made an uneventful recovery and has remained well since.

### PATIENT 3

A 39 year old schoolmaster developed diarrhoea at the same time as his wife and son in June 1983. He passed four loose stools (some containing blood) each day. There was lower abdominal pain and tenesmus, but apart from some weight loss his general health was unaffected. Because he still required medication after one month, culture of three stools was arranged, and all grew *A sobria*. No antibiotic was given, yet two further stools cultured 10 days later were free of the organism despite persistent diarrhoea. When the patient was examined seven weeks after stool cultures became negative the only external abnormality was perianal inflammation with oedematous skin tags. Sigmoidoscopy showed a uniformly haemorrhagic proctosigmoiditis. Microscopically there was severe chronic inflammation without epithelioid granulomas. Normal results were obtained in routine blood tests. In the barium enema the colon and terminal ileum were normal.

No anti-inflammatory treatment was given, but the diarrhoea gradually diminished, and after six months the patient reported a near normal bowel habit, with weight increase of 6 kg. Repeat sigmoidoscopy in March 1984 detected only mild erythema and loss of vascular pattern. Microscopically the changes were those of a quiescent chronic colitis. Three months later the patient was passing one formed stool a day and had gained a further 5 kg in weight.

Nearly three years later, in January 1987, the patient again reported diarrhoea with blood, and at flexible sigmoidoscopy was found to have ulcerative colitis of moderate severity as far as the splenic flexure. The histology was consistent with this diagnosis. No pathogen was grown from the stools. He responded well to sulphasalazine and is currently symptom free.

## MICROBIOLOGICAL DATA

*Aeromonas* in North Herts Health District

Lister Hospital, Stevenage, provides the only gastroenterology service for the district (population 190 000), so it is unlikely that any other patients with chronic colitis were among the 84 subjects recorded here during the past 10 years as yielding stools positive for *Aeromonas spp.* Most specimens came from patients with acute self-limiting diarrhoea referred by their general practitioners. Few isolates were submitted for speciation, but the fact that all these were obtained by direct plating onto solid media and proved to be of either *A hydrophila* or *A sobria* argues strongly for the pathogenicity of the strains identified.

*Methods of isolation*

Most isolations during the acute phase of a diarrhoeal disease have been made on layered blood agar plates containing 10 mg/l of ampicillin. All oxidase positive (and particularly haemolytic) colonies require further identification, which has been feasible for routine laboratories only since 1986 when commercial kits, such as AP1 20E, were introduced. When culture is attempted later in the clinical course of a colitis enrichment in alkaline peptone water, with subculture onto blood agar or xylose sodium desoxycholate solid media, may be needed.

*Findings in present cases*

*Aeromonas* was the only putative pathogen isolated from these patients. Routine tests for parasites, attempted virus isolation, and tests for *Clostridium difficile* and its toxin were negative in all cases.

The Table shows details of isolation and characteristics of the *Aeromonas spp.* Speciation and assays for enterotoxin and haemolysin production were carried out by Professor M Gracey, Princess Margaret Children's Medical Research Foundation, Perth, Western Australia. Enterotoxin production was tested by the suckling mouse method.<sup>26</sup> Invasiveness was determined in Dr Barbara Chang's laboratory using HEp-2 cells.<sup>27</sup> The isolates were sensitive to all commonly used antimicrobials against aerobic Gram

negative organisms except ampicillin, cephaloridine, and ticarcillin.

**Discussion**

The clinical picture in *Aeromonas* infection of the bowel is usually one of an enteritis, with acute self-limiting diarrhoea of about two weeks' duration, commonly accompanied by abdominal pain and fever, occasionally by vomiting.<sup>22, 28</sup> A search of the English literature has failed to reveal any case history relating the onset of a chronic colitis to infection with *Aeromonas spp.*, although bloody diarrhoea persisting for more than three months prompted a provisional diagnosis of ulcerative colitis in one of the children of the Australian series,<sup>21</sup> and the closely related organism, *Plesiomonas shigelloides*, has been isolated from one patient with ulcerative colitis.<sup>13</sup> Infection with *A hydrophila* was almost certainly the initial event in our patient 1. Patient 2 had suffered two episodes of possible relevance in the previous year: a self-limiting non-bloody diarrhoea contracted during a holiday in the Canary Islands and a brief attack of abdominal pain simulating appendicitis. The former was characteristic of intestinal infection, the latter severe enough to merit hospital admission, yet neither had sufficed to precipitate colitis. In patient 3 a non-toxicogenic non-invasive strain of *A sobria* was eliminated spontaneously within days of its detection more than a month after symptoms began, suggesting that its presence might have been irrelevant to what in retrospect could be interpreted as a mild first attack of chronic ulcerative colitis. The simultaneous onset of diarrhoea in the patient and two family members, however, followed by his seemingly complete recovery, gives this the stamp of an infective episode, and until the criteria for pathogenicity in *Aeromonas spp.* are more firmly established we would see the relationship of acute infection with *A sobria* and the subsequent development of typical ulcerative colitis in this man as a variant of the sequence in patient 1.

These cases of infection accompanying a chronic colitis are not the first to be reported in which the timing might be considered to implicate the infection as the principal cause of the colitis.<sup>1-4, 11, 29</sup> A few case histories selected by the authors from 525 they

Table Particulars of *Aeromonas spp.* isolated

Case	Species	Positive stools (n)	Time between first and last isolation (wk)	Haemolysin titre	Enterotoxin	Invasiveness
1	<i>A hydrophila</i>	5	7	1/16	+	+
2	<i>A sobria</i>	4	3	<1/4	+	+
3	<i>A sobria</i>	3	1	<1/4	-	-

examined in a survey of colitis among men of the United States Army<sup>2</sup> included one in which chronic ulcerative colitis followed typical *Shigella flexneri* dysentery and another in which 10 years of colitis were preceded by four weeks of gastroenteritis ascribed to *Salmonella oranienberg*. In a study of the relationship between *Salmonella* and ulcerative colitis<sup>3</sup> the bloody diarrhoea of two patients yielding *Salmonella spp* at the onset of their illness continued despite elimination of the pathogen and resolved only after treatment with corticosteroids. It was concluded that in these patients the infection was more likely to have precipitated than complicated the chronic disorder. One of six cases described as examples of *Salmonella* induced relapse in ulcerative colitis<sup>4</sup> concerned a patient whose stools grew *S agona* after three weeks of diarrhoea and abdominal pain. Only when the infection had responded to an antibiotic did bleeding occur, and at 18 months a barium enema showed extensive colitis. An acute ileocolitis in a young woman, diagnosed at laparotomy and accompanied by serological evidence of recent infection with *Yersinia pseudotuberculosis*, underwent complete clinical and radiological remission.<sup>29</sup> After a year the patient reported recurrent diarrhoea and was found to have developed Crohn's disease. The history here resembles that of our patient 1, who presented with all the clinical features of an infection, confirmed by laboratory tests and responsive to antimicrobial treatment. In both instances there followed a period of total quiescence before the onset of a relapse in which the subsequent course was typical of idiopathic chronic inflammatory bowel disease. Whether or not these and the other patients discussed above were predisposed to the development of chronic inflammation there can be little doubt that in most, if not all, an infection was the event which triggered the pathogenetic sequence.

Infection has always been recognised as a logical candidate for the role of inducing agent in chronic idiopathic colitis, although the paucity of cases in which a convincing association could be shown has recently favoured the study of other environmental factors. If the genetic predisposition to a colitis confers adequate specificity, however, there need be no limit to the variety of potential inducing agents. The two species of *Aeromonas* which have supplied the only three examples in our experience of a chronic colitis after acute infection may have special properties in this respect, but in theory almost any bacterial pathogen of the gastrointestinal tract could be similarly implicated. We believe that the cases we have collected provide sufficient circumstantial evidence for a role of infection in chronic colitis to warrant a prospective multicentre study of outcome

related to bacteriological findings in patients with less than a month's history of colitis.

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