Aggressive *Helicobacter pylori*-negative peptic ulceration as the initial manifestation of Crohn's disease

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Abstract

Peptic ulceration is a recognised feature of Crohn's disease, but the characteristics of this manifestation are rather poorly described. Furthermore, most reports in the literature relate to ulcer disease in cases of established Crohn's disease.

The authors report a series of four cases in which the diagnosis of Crohn's disease was preceded by peptic ulceration. Potential confounding factors were as far as possible excluded, implying a true association. Characteristics of the ulcer disease included (1) a multifocal distribution, (2) *Helicobacter pylori* negativity and (3) an unusually aggressive clinical course despite proton pump inhibitor therapy, necessitating endoscopic or surgical intervention in three cases.

Crohn's-related peptic ulceration is a relatively common manifestation which may precede the diagnosis of Crohn's disease itself. Recognition of the underlying diagnosis may be hampered by non-specific histology, but is important in view of the aggressive course of the ulceration, which may respond to medical therapy for Crohn's disease.

Introduction

Peptic ulceration (PU) is an inflammatory process resulting from focal tissue destruction extending through the muscularis layer of mucosa exposed to gastric acid. PU is commonly caused by *Helicobacter pylori* infection, exposure to non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin, or a combination of these risk factors.¹ The falling population prevalence of *H. pylori* infection, the more cautious prescribing of NSAIDs and the increasingly widespread use of acid-suppressing therapy have probably all contributed

to the falling incidence of PU disease over recent years,² and so other causes now account for a greater proportion of cases.¹

The overwhelming majority of peptic ulcers heal rapidly with the appropriate combination of *H. pylori* eradication, drug withdrawal and acid-suppressing therapy. However, in a small minority of cases the ulcer runs a more refractory and/or aggressive course failing to respond to conventional treatments and leading to complications including strictures and haemorrhage.¹

Crohn's disease (CD) is a form of inflammatory bowel disease (IBD) characterised by chronic, granulomatous, transmural inflammation of the bowel wall.³ CD may affect anywhere in the gastrointestinal tract (GI) tract from mouth to anus, typically in a patchy distribution—so-called 'skip' lesions. CD can cause a range of clinical manifestations depending on the location, extent and severity of the underlying lesions, but abdominal pain, diarrhoea, weight loss and anaemia are common features. The diagnosis of CD is made on the basis of a characteristic set of clinical, radiological, endoscopic and histological appearances.³ The symptoms of CD may in some cases be present for years before the diagnosis is established.

The aetiology and pathogenesis of CD are not fully understood.⁴ However, recognised risk factors include predisposing genes and environmental factors including cigarette smoking and hygienic living conditions in childhood.^{5–7}

PU has long been recognised as a feature of CD, with a reported lifetime

prevalence of up to 10%.^{8–10} There is evidence that Crohn's-related PU may be relatively refractory to conventional therapy and require more intensive medical or surgical intervention.^{11–13} However, the literature relates primarily to cases of established CD, and most reports do not include data regarding *H. pylori* status. Furthermore, the possibility remains of spurious association due to a confounding factor, in particular cigarette smoking (a risk factor for both PU¹ and CD⁴) and NSAID usage (a risk factor for PU¹, and likely to be more common in patients with CD due to the associated arthropathy³).

Case reports

Case 1

This 60-year-old woman, with a history of dyspepsia and weight loss, was referred for an open access gastroscopy in October 2007. The initial examination revealed multiple small ulcers within the pyloric canal. Subsequent gastroscopies showed poor healing with proton-pump inhibitor (PPI) therapy, and by October 2009 she had developed an inflammatory stricture of the pylorus. She denied taking NSAIDs or aspirin, and had never smoked. Serial biopsy histology revealed non-specific inflammatory changes only, with no evidence of granulomata, malignancy or *H. pylori* infection.

At review she reported ongoing weight loss, with intermittent episodes of colicky abdominal pain and rectal bleeding, and blood tests showed mild iron deficiency anaemia with raised inflammatory markers. She therefore underwent colonoscopy, which revealed multiple small aphthoid ulcers in the terminal ileum, caecum and rectum—the appearances were characteristic of CD, and biopsy histology was entirely consistent with this diagnosis.

Her symptoms eased with the combination of a reducing course of prednisolone and continued PPI therapy, but a month after the introduction of mercaptopurine she developed overt gastric outflow obstruction, confirmed on MR enterography. At endoscopy there was a tight pyloric stricture but no residual ulceration—the stricture was successfully treated by endoscopic balloon dilatation, allowing her to resume a normal diet. She subsequently settled well on mercaptopurine and lansoprazole, her laboratory parameters normalised and she regained some 10 kg in weight over the following 6 months.

Case 2

This 59-year-old woman presented to another hospital in 2006, with abdominal pain, vomiting and weight loss, set against a long background history of duodenal ulcer disease. Investigations revealed a tight inflammatory stricture of the duodenal bulb and she went on to have a Polya partial gastrectomy. She denied taking NSAIDs or aspirin and had never smoked. Examination of the resection specimen revealed

non-specific inflammatory changes only, with no evidence of underlying malignancy or *H. pylori* infection.

She presented to our hospital in 2008 with chronic low-grade diarrhoea, colicky abdominal pains and recurrent, transfusion-dependent iron deficiency anaemia. Colonoscopy was unremarkable, but capsule endoscopy revealed a series of inflammatory strictures and serpiginous ulcers in the mid and lower ileum. The appearances (figure 1) were characteristic of Crohn's ileitis. Her symptoms eased with a reducing course of oral prednisolone. She settled following the introduction of immunosuppressive therapy, and her anaemia resolved.

Figure 1 Capsule endoscopy views of the ileum of case 2, showing (A) an inflammatory stricture and (B) a serpiginous ulcer.

Case 3

This 34-year old gentleman presented in March 2006, with a short history of melaena, having taken a few aspirin tablets for a headache a few weeks earlier. Gastroscopy revealed an antral ulcer and a larger chronic ulcer in the duodenal bulb with a visible vessel, which was successfully treated with epinephrine injection and heater probe ablation. PPI therapy was commenced and the importance of avoiding NSAIDs and aspirin was stressed. Despite adhering to this advice and continuing PPI therapy he represented in July 2007 and again in January 2010 with further acute upper GI bleeds. On both occasions he had endoscopic evidence of recurrent duodenal ulceration. Antral biopsy histology was *H. pylori* negative throughout, and revealed no other specific abnormalities. He had never been a regular cigarette smoker. His fasting serum gastrin concentration (off PPI) was normal, and his *Helicobacter* serology was negative.

Meanwhile, in January 2008 he had presented with a 4-month history of low-grade bloody diarrhoea. Colonoscopy revealed appearances of moderately active Crohn's colitis with sparing of the terminal ileum and rectum. Having settled on corticosteroids initially, he proved to be intolerant of thiopurines and methotrexate. His response to infliximab was disappointing, and in July 2009 he underwent subtotal colectomy. Examination of the resection specimen revealed appearances characteristic of Crohn's colitis, with multiple non-caseating granulomata.

Case 4

This 79-year-old woman, with a history of dyspepsia and weight loss, was referred for open access gastroscopy in early 2008. Serial gastroscopies over the next 2 years revealed multifocal antral ulceration, which

failed to heal despite multiple courses of acid-suppressing therapy including high dose PPI. She denied taking NSAIDs or aspirin, and had never smoked. Repeated biopsy histology revealed non-specific inflammatory changes only, with no evidence of underlying malignancy or *H. pylori* infection. Her fasting serum gastrin concentration (off PPI) was normal, and her *Helicobacter* serology was negative.

On review in early 2010, she admitted to some intermittent low-grade diarrhoea and occasional crops of mouth ulcers, and so went on for further investigation. Colonoscopy to the terminal ileum was normal, but capsule endoscopy revealed mild, patchy inflammatory changes throughout the small bowel but most marked in the proximal ileum, with focal hyperaemia, scattered tiny aphthoid ulcers and mucosal oedema. Gastroscopy in April 2010 revealed a large chronic antral ulcer with a couple of smaller satellite lesions (figure 2).

She was treated with a reducing course of prednisolone and commenced on mercaptopurine; PPI therapy was continued. On this regime, her symptoms resolved and her weight stabilised. Repeat gastroscopy in July 2010 showed complete healing of her antral ulceration with some residual radial scarring at the site of her largest ulcer.

Upper GI tissue samples from all four cases were subsequently reviewed by an independent histopathologist, who confirmed that none of them revealed evidence of *H. pylori* infection or diagnostic features of CD. The key features of the four cases are summarised in table 1.

Discussion

The cases reported here demonstrate an association between CD and PU in the absence of potential

Figure 2 Endoscopic view of the gastric antrum of case 4, showing a large deep ulcer above the pylorus, and smaller lesions below and to the left of it.

Table 1 Case Summary

	Case 1	Case 2	Case 3	Case 4
Year of birth	1947	1947	1971	1928
Diagnosis of PU	2007	2006	2006	2008
Ulcer location	Pyloric canal	Duodenal bulb	Antrum and duodenal bulb	Antrum
Ulcer type	Multifocal	Not known	Multifocal	Multifocal
Course of ulcer	PPI-resistant: dilatation for stenosis	Resection for stenosis	PPI-resistant: recurrent haemorrhage	PPI-resistant
<i>H. pylori</i> status	Negative	Negative	Negative	Negative
Smoking	Never	Never	Never	Never
NSAIDs/aspirin	No	No	Few aspirin initially only	No
Diagnosis of Crohn's disease	2009	2009	2008	2010
Crohn's location	Ileocolonic	Small bowel	Colonic	Small bowel

NSAID, non-steroidal anti-inflammatory drugs; PPI, proton-pump inhibitor; PU, peptic ulceration.

confounding factors—cigarette smoking and NSAID exposure—and illustrate the point that the peptic ulceration may predate the diagnosis of CD. Seven other cases of CD and PU seen in recent years were excluded from the report because they did not fulfil all of these criteria. The obvious question that arises is whether the purported association reflects anything more than the simple coincidence of CD and PU in the same individuals. Three lines of evidence support the contention that the association is a genuine one, and we would like to suggest the term CPU (Crohn's-related peptic ulceration) for this distinct entity.

First, while this is not a formal epidemiological study, the association appears to be more common than would be expected by chance alone. This district general hospital has seen about 160 new cases of CD over the last 4 years, giving a prevalence of CPU in this cohort of 2.5%, and this is a conservative estimate due to the selection criteria outlined above. Recent population incidence data for PU disease in the UK would predict a figure for the cohort of <0.3%.² Furthermore, the local incidence of ulcerative colitis (UC) is similar to that of CD, yet we saw no cases of UC-related PU in the same time frame.

Second, CPU appears to have some characteristic features that distinguish it from conventional peptic ulcer disease, tending to be multifocal, and to run an aggressive course despite conventional medical therapy, with a high risk of ulcer complications. It is not unduly surprising that CPU is typically *H. pylori*-negative, since several studies have now confirmed that the prevalence of *H. pylori* infection is substantially lower in CD than in control groups.^{14–17} This observation may reflect the reduced risk of *H. pylori* infection resulting from the

hygienic childhood conditions which appear to predispose to the later development of CD.^{6,17}

Third, while Crohn's related PU appears refractory to conventional acid-suppressing therapy alone, our findings would suggest that it responds well to immunosuppressive therapy directed at the treatment of CD. This is obviously of practical importance. It is interesting that the ulcer disease went into sustained remission in cases 1 and 4, who tolerated therapy, but caused recurring problems in case 3, who did not. We interpret the development of symptomatic gastric outflow obstruction in case 1 shortly after starting treatment as a manifestation of effective ulcer healing with scarring.

Our data does not reveal the pathogenesis of CPU, and it remains to be established if it reflects direct involvement of the upper GI tract by the disease process underlying Crohn's, or whether CPU is a systemic manifestation, analogous to anterior uveitis, for example. Unfortunately, biopsy histology is unlikely to distinguish these possibilities, as it is typically non-specific in CD lesions of the upper GI tract. The prevalence of granulomata for example may be as low as 10%.^{18–20}

A reasonable criticism of this paper would be that we have failed to prove that our subjects were not surreptitiously exposed to confounding factors - notably exposure aspirin, NSAIDs and tobacco. We did not, for example, go as far as measuring salicylate levels - but negative salicylate levels would not necessarily exclude low dose or intermittent ingestion, or use of non-salicylate-based NSAIDs. Ultimately of course, proving a negative is impossible, but we feel that latent confounding factors are unlikely to be the explanation for our findings. Over and above the absence of a relevant history, one might expect ulcers due to these confounders to respond to some degree to PPI therapy - but not to immunosuppression (cases 1 and 4).

In summary, we report four subjects in whom PU preceded the diagnosis of CD by several years. Having, as far as possible, excluded potential confounding factors, the evidence would suggest that this was the initial manifestation of CD. The ulcer disease was characterised by being *H. pylori*-negative, often multifocal and refractory to conventional acid-suppressing therapy, with a high risk of progression to ulcer complications. We would suggest that CPU is an important differential in patients presenting with peptic ulcers with these features. The particular importance of this observation is that the ulcer disease may respond to immunosuppressive therapy.

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Competing interests None.

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References

1. Malfertheiner P, Chan FK, McColl KE. Peptic ulcer disease. *Lancet* 2009;374:1449–61.
2. Cai S, García Rodríguez LA, Massó-González EL, *et al.* Uncomplicated peptic ulcer in the UK: trends from 1997 to 2005. *Aliment Pharmacol Ther* 2009;30:1039–48.
3. Baumgart DC, Sandborn WJ. Inflammatory bowel disease: clinical aspects and established and evolving therapies. *Lancet* 2007;369:1641–57.
4. Baumgart DC, Carding SR. Inflammatory bowel disease: cause and immunobiology. *Lancet* 2007;369:1627–40.
5. Gaya DR, Russell RK, Nimmo ER, *et al.* New genes in inflammatory bowel disease: lessons for complex diseases? *Lancet* 2006;367:1271–84.
6. Tobin MV, Logan RF, Langman MJ, *et al.* Cigarette smoking and inflammatory bowel disease. *Gastroenterology* 1987;93:316–21.
7. Gent AE, Hellier MD, Grace RH, *et al.* Inflammatory bowel disease and domestic hygiene in infancy. *Lancet* 1994;343:766–7.
8. Harary AM, Rogers AI. Gastroduodenal Crohn's disease. Differential diagnosis and treatment. *Postgrad Med* 1983;74:129–33, 137.
9. Greenstein AJ, Janowitz HD, Sachar DB. The extra-intestinal complications of Crohn's disease and ulcerative colitis: a study of 700 patients. *Medicine (Baltimore)* 1976;55:401–12.
10. Fielding JF, Cooke WT. Peptic ulceration in Crohn's disease (reional enteritis). *Gut* 1970;11:998–1000.
11. Yamamoto T, Allan RN, Keighley MR. An audit of gastroduodenal Crohn disease: clinicopathologic features and management. *Scand J Gastroenterol* 1999;34:1019–24.
12. Poggioli G, Stocchi L, Laureti S, *et al.* Duodenal involvement of Crohn's disease: three different clinicopathologic patterns. *Dis Colon Rectum* 1997;40:179–83.
13. Valori RM, Cockel R. Omeprazole for duodenal ulceration in Crohn's disease. *BMJ* 1990;300:438–9.
14. Ando T, Watanabe O, Ishiguro K, *et al.* Relationships between *Helicobacter pylori* infection status, endoscopic, histopathological findings, and cytokine production in the duodenum of Crohn's disease patients. *J Gastroenterol Hepatol* 2008;23 Suppl 2:S193–7.
15. Matsumura M, Matsui T, Hatakeyama S, *et al.* Prevalence of *Helicobacter pylori* infection and correlation between severity of upper gastrointestinal lesions and *H. pylori* infection in Japanese patients with Crohn's disease. *J Gastroenterol* 2001;36:740–7.
16. Halme L, Rautelin H, Leidenius M, *et al.* Inverse correlation between *Helicobacter pylori* infection and inflammatory bowel disease. *J Clin Pathol* 1996;49:65–7.
17. Feeney MA, Murphy F, Clegg AJ, *et al.* A case-control study of childhood environmental risk factors for the development of inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2002;14:529–34.
18. Wright CL, Riddell RH. Histology of the stomach and duodenum in Crohn's disease. *Am J Surg Pathol* 1998;22:383–90.
19. Jaśkiewicz K, Lemmer E. Histological findings in gastroduodenal mucosa in patients with Crohn's disease. Any diagnostic significance? *Pol J Pathol* 1996;47:115–8.
20. Korelitz BI, Wayne JD, Kreuning J, *et al.* Crohn's disease in endoscopic biopsies of the gastric antrum and duodenum. *Am J Gastroenterol* 1981;76:103–9.