Non-*Helicobacter pylori*, Non-NSAID Peptic Ulcer Disease: An Important Consideration in the Evaluation of Patients with Gastric or Duodenal Ulcers

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

Review Article

ABSTRACT

Peptic ulcers are common although the pattern of aetiology is changing. The traditionally most frequent causes of *Helicobacter pylori* infection and non-steroidal anti-inflammatory toxicity are likely to assume less relative importance as the proportion of cases attributed to other causes rises. Primary care physicians should be aware the pathogenesis of peptic ulceration in non-*H. pylori* non-NSAID induced disease. This article considers the various less prevalent causes of peptic ulcers and outlines their evaluation and management. Greater awareness of such conditions will improve patient care when traditional causes and remedies are absent.

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ABBREVIATIONS

PUD: peptic ulcer disease; NSAID: non-steroidal anti-inflammatory drug; PPI: proton pump inhibitor; H.pylori: Helicobacter pylori.

1. INTRODUCTION

Peptic ulcer disease (PUD) embodies both gastric and duodenal ulcers. Ulcers are defined as breaks in the mucosal surface of 5mm or more which penetrate into the submucosa (Fig. 1). Mucosal damage smaller than 5mm in size or which involves mucosal disruption but does not breach the submucosa is known as an erosion (Fig. 2) [1,2]. Peptic ulceration occurs as a consequence of an imbalance between protective and destructive influences acting on the gastroduodenal mucosa [3].

PUD is a common condition with a worldwide prevalence of approximately 1.5% [4]. *Helicobacter pylori* (*H. pylori*) infection and the use of non-steroidal anti-inflammatory medications (NSAIDs) account for the large majority of PUD in developed areas [5]. Although PUD remains common its incidence in the western world is declining, primarily reflecting the falling proportion of ulcers caused by *H. pylori* or NSAID use [6]. The drop in rates of *H. pylori* induced disease is probably associated with improved hygiene and living conditions while the smaller relative contribution of NSAID toxicity is possibly because of a combination of growing proton pump inhibitor (PPI) use and the advent of COX-2 selective anti-inflammatory agents [7-10].

Approximately 12% of cases of PUD are not associated with *H. pylori* or NSAID ingestion [11,12]. It is therefore important that general practitioners are able to identify alternative explanations for peptic ulceration when patients test negative for *H. pylori* or deny NSAID ingestion and have at least some knowledge on how to approach such cases.

1.1 Initial Approach to Suspected Peptic Ulcers

Patients with peptic ulceration commonly complain of upper abdominal pain or discomfort which varies with meals. The pain of gastric ulcers is classically worsened by meals while duodenal ulcer pain is classically relieved by eating and worsened during the night. PUD is also an important cause of hematemesis and must be considered in any patient with that presentation. Physical examination may reveal epigastric tenderness but is regularly unremarkable.

The differential diagnosis for a patient with dyspeptic symptoms is wide. Common problems include PUD, gastro-oesophageal reflux, malignancy, infectious gastritis or functional dyspepsia. In addition, there is a host of non-gastrointestinal pathologies which may mimic the symptomatology of PUD.

Fig. 1. gastric ulcer on endoscopy [48]
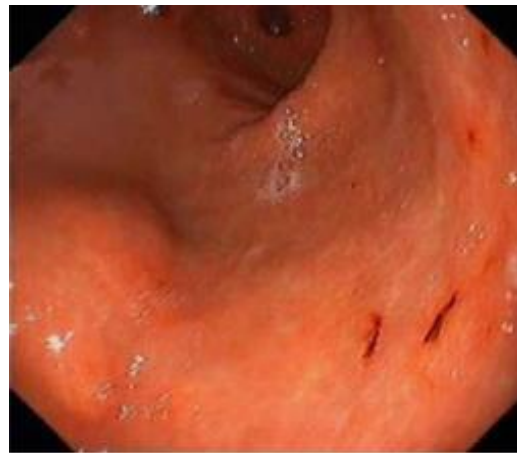
Fig. 2. gastric erosions on endoscopy [49]

Individuals with ulcer pain do not always require further investigation. If younger than 55 years of age and accompanied by no alarm features patients may receive sufficient treatment simply with lifestyle changes and acid suppression. Urgent upper endoscopy is mandated in the presence of alarm features such as anaemia, weight loss, gastrointestinal bleeding or first presentations in patients older than 55 years of age.

A definitive cause should be sought for those younger patients who remain symptomatic with dyspepsia after four weeks of antisecretory treatment. Exclusion of *H. pylori* or NSAID overuse is the first step. Non-invasive methods in the workup of *H. pylori* include stool antigens, serology and the urea breath test, all of which are more than 90% sensitive [13]. Patients with confirmed infection or acknowledgement of NSAID consumption can then be managed accordingly.

In patients testing negative for *H. pylori* or denying NSAID intake, the clinician's initial consideration should be that *H. pylori* testing was falsely negative or that the patient's recollection of NSAID consumption is misleading. These aetiologies remain the most significant causes PUD and identifying them can avoid further unnecessary workup or treatment. Concealed NSAID use or false-negative *H. pylori* tests are probably the most common reasons for apparently *H. pylori*-negative, NSAID-negative PUD. Patients should be questioned directly about NSAID intake and should be retested for *H. pylori*, preferably with two or more different modalities given that no one test is completely sensitive. Regarding workup for *H. pylori* it should be recognised that current or recent use of PPIs or antibiotics may render non-invasive tests falsely negative [14,15].

Patients who are negative for *H. pylori* with non-invasive methods need referral for upper gastrointestinal endoscopy to either confirm *H. pylori* colonisation formally or establish an alternative diagnosis. The provisional diagnosis of peptic ulcer should also be revisited given that the list of causes of dyspeptic symptoms is broad.

1.2 Evaluation of Non-Nsaid Non-*H. pylori* Disease

Not all cases of dyspepsia can be explained by peptic ulcers produced by *H. pylori* or NSAID ingestion. There are various atypical causes of PUD and in many cases dyspepsia is not related to PUD at all. Depending on the clinical impression other gastrointestinal or non-gastrointestinal diagnoses might be contemplated or investigated.

Patients with suspected *H. pylori*-negative NSAID-negative PUD should receive acid suppression therapy while they await examination with upper endoscopy. Identification of peptic ulceration on endoscopy should prompt the general practitioner to search for a causative agent, with the assistance of a gastroenterologist if necessary. Failure to discover a cause is associated with frequent ulcer recurrence and a significantly higher mortality from ulcer bleeding [16].

A careful history and physical examination may identify clues to an underlying diagnosis. At minimum a diagnostic workup should include a serum gastrin level. Further investigations depend on clinical circumstances and what diagnoses appear plausible.

2. OTHER CAUSES OF PEPTIC ULCER DISEASE

2.1 Infection

Both herpes simplex virus type 1 (HSV-1) and cytomegalovirus (CMV) have been implicated in the aetiopathogenesis of PUD. This is supported by several studies showing a presence of both HSV-1 and CMV antibodies in ulcer biopsy specimens, mostly in immunosuppressed patients, without systemic evidence of infection [17,18]. Although there appears to be a convincing causative relationship the mechanisms of ulcer formation by these pathogens is not established [17].

HSV-1 and CMV infections account for a very low number of PUD cases overall. There is no placebo-controlled data to guide treatment and management decisions are largely empirical. Immunocompetent hosts typically recover without the need for intervention; however ulcer healing can be aided with the prescription of an antisecretory agent for four weeks, such as omeprazole 20 mg daily or ranitidine 300mg daily. In immunosuppressed patients or those with severe disease intravenous antiviral therapy is usually required.

2.2 Medications Other than NSAIDs

There are a number of common drugs other than NSAIDs which may rarely be responsible for gastritis and subsequent ulcerogenesis. Although these relationships exist NSAIDs remain by far the most significant medication class associated with peptic ulceration.

2.2.1 Paracetamol

In the dose range used by most patients paracetamol does not increase the risk of peptic ulceration. However, consumption in excess of 2 grams per day is associated with moderately elevated risk of upper gastrointestinal haemorrhage and perforation [19,20]. This association appears to be independent of any confounding factors.

2.2.2 Spironolactone

Spironolactone has been found in several case-control studies to be linked with peptic ulcer formation. The relationship seems to be causative with a relative risk of upper gastrointestinal haemorrhage or peptic ulcer of 2.7 in patients taking spironolactone versus randomly selected controls [21]. Risk of PUD rises proportionally with increasing spironolactone dose. The mechanism of gastroduodenal toxicity is probably related to inhibition of fibrous tissue formation, a process that relies on mineralocorticosteroids [22].

2.2.3 Selective serotonin reuptake inhibitors (SSRIs)

SSRIs are known to cause gastroduodenal ulcers. The intake of SSRIs also exacerbates bleeding in patients with *H. pylori* or NSAID-induced ulcers [23]. In a recent meta-analysis SSRI use raised the likelihood of upper gastrointestinal haemorrhage overall by an odds ratio of 2.36 and by an odds ratio of 6.11 in patients taking concomitant NSAIDs [24]. A proposed mechanism for this trend is that inhibition of serotonin reuptake impairs platelet aggregation. The highest risk is seen with fluoxetine, paroxetine and sertraline [24].

2.2.4 Bisphosphonates

Bisphosphonates occasionally cause peptic ulceration, mostly in the stomach. This finding has been observed in several blinded randomised trials [25,26]. Alendronate is the agent most implicated with gastric ulcers demonstrable endoscopically in approximately 10% of patients after just 2 weeks of treatment [26]. Risedronate and pamidronate have also proven ulcerogenic although to a lesser extent [26-28]. Patients in these studies were screened with endoscopy and presence of ulcers was not shown to correlate with symptoms or gastrointestinal haemorrhage so the clinical importance of this finding is uncertain.

2.2.5 Corticosteroids

The association between glucocorticoid use and PUD is controversial. Although most physicians continue to consider corticosteroids ulcerogenic based on clinical experience, such a relationship has not been established in the literature [29-31]. Most major studies have demonstrated no statistically significant risk of peptic ulcer associated with corticosteroid use alone with elevated risk only appreciable in patients also consuming NSAIDs [30,31]. One meta-analysis did identify an increased risk of gastrointestinal bleeding or perforation with corticosteroid use at an odds ratio of 1.42 in hospitalised patients [32]. Such problems in this setting were more likely a result of comorbidities or medical treatments which may have been potentiated by corticosteroid use, as opposed to direct injury and ulceration by corticosteroids alone.

2.3 Gastrinoma

Gastrin-secreting adenomas, or 'gastrinomas', secrete excessive gastric acid which can produce gastric or duodenal ulcers. This represents the classic entity known as Zollinger-Ellison syndrome. The commonest location of gastrinomas is the duodenum followed by the pancreas. These tumours account for less than 1% of PUD cases and have an overall prevalence of 1-2 patients per million, so are exceptional, but should be considered in patients with a family history of ulcers [13,33]. In general practice the possibility of gastrinoma is usually raised by measuring fasting serum gastrin. Formal diagnosis and treatment is complex and should ideally be overseen by a specialist.

Management of gastrinomas is both medical and surgical. Medical therapy comprises high dose PPIs which are generally effective at controlling symptoms and peptic ulceration. For example, the patient could be commenced on omeprazole 60mg daily for several weeks followed by dose adjustment according to response. Maximum

treatment should not exceed 360mg daily in divided oral doses. The PPI should be tapered in the longer term to a minimal level necessary to control gastric acid output. Gastrinomas are malignant and metastatic disease leads to death in many patients. Therefore, in combination with pharmacotherapy patients also require follow up and prompt consideration for surgical resection which may be curative in early disease.

2.4 Carcinoid Syndrome

Carcinoid syndrome is a constellation of symptoms produced by a carcinoid tumour, a neuro-endocrine neoplasm typically found in the gastrointestinal tract. Carcinoid tumours are capable of producing an array of hormones, of which histamine and gastrin most likely bring on peptic ulceration. The secretion of vasoactive substances by carcinoid tumours elicits a diverse range of possible clinical manifestations with classic clues including diarrhoea or cutaneous flushing.

The diagnostic test most useful to the general practitioner is measurement of urinary 5-hydroxyindoleacetic acid (5-HIAA). 5-HIAA is a breakdown product of serotonin metabolism. Performing this test involves a 24-hour urine collection with subsequent measurement of total 5-HIAA content. It is both highly sensitive and specific for carcinoid syndrome. In most laboratories a normal total 5-HIAA excretion is less than approximately 8mg in 24 hours.

The management of carcinoid syndrome as a whole is a complex and specialised area however the ulcer element of this syndrome can be effectively controlled with antacids and histamine H_2 receptor blockers such as ranitidine. An appropriate course of ranitidine would be 300 mg once daily, taken in the evenings. Acid suppression can be stepped down empirically according to the individual patient, once systemic control of carcinoid syndrome is achieved. Regarding the disease in general, treatment with somatostatin analogues such as octreotide are usually highly effective in controlling symptoms while surgical resection of the tumour is often necessary for cure.

2.5 Radiotherapy

Irradiation directed at the abdomen or pelvis can result in peptic ulceration. The incidence of radiation ulcers is not insignificant. In a retrospective chart analysis of 100 patients receiving radiotherapy for liver tumours, 5% subsequently developed gastroduodenal ulcers within 5 months of treatment. In this series only patients with suggestive symptoms underwent endoscopy to confirm the diagnosis. One of the five patients to develop an ulcer was taking regular NSAIDs [35].

Radiation ulcers are usually located in the proximal duodenum. Symptoms begin in the first several months following cessation of radiation therapy [34]. Irradiation therapy for gynae-cological tumours or rectal cancer are the most frequently associated treatments. Management of radiation-induced ulceration is challenging as it tends to be unremittent to acid suppression and most cases will require surgery [34,36].

2.6 Sarcoidosis

Sarcoidosis can affect virtually any organ and the gastrointestinal tract is not exempt. Gastrointestinal sarcoidosis is very rare with granulomatous gastritis being the most frequent finding in this setting [37]. Gastritis alone tends to be asymptomatic but erosive gastritis may progress to ulcer at which point most patients present with symptoms. A clue to this diagnosis is that gastroduodenal disease almost exclusively occurs in patients demonstrating pre-existing pulmonary manifestations of sarcoidosis [38].

Trial data on the management of gastric or duodenal sarcoidosis is scant. In general, asymptomatic patients probably do not require treatment and may be monitored for development of symptoms. If intervention is indicated, patients should be commenced on PPI therapy and glucocorticoids and continued on a tapering course for between six and twelve months. Case reports have described minimal response from antacids or ranitidine [38-40].

2.7 Crohn's Disease

Discovery of Crohn's disease (CD) in the stomach or duodenum is relatively frequent. A retrospective study of patients with known CD found histological evidence of gastric disease in 41.5% of cases and duodenal lesions in 12% [41]. Nonetheless, upper gastrointestinal CD is usually subclinical and gastroduodenal involvement is the primary complaint in less than 1 in 20 patients with CD [42,43]. Even fewer patients will experience progression of their disease to peptic ulceration.

Treatment of upper tract CD is similar in principle to more distal disease. The medicinal regimen may comprise acid-suppression, glucocorticoids and immunomodulatory therapy if necessary. Sulfasalazine and mesalamine are ineffective options for this purpose because their principal site of action is the distal ileum and colon [44,45].

2.8 Stress Ulcer

Stress ulcers are the third commonest cause of PUD, accounting for 3-5% of cases overall [46]. Stress ulcers arise in patients with critical illness such as those hospitalised in the intensive care environment or in the post-operative state. They form principally due to splanchnic hypoperfusion. General practitioners are less likely than hospitalists to face this problem in routine practice but having an awareness of the condition remains important.

2.9 Idiopathic Ulcer

There remains a small group of patients with truly idiopathic ulcers. Idiopathic PUD is a diagnosis of exclusion. The pathogenesis of idiopathic PUD is uncertain but identified risk factors include smoking and psychological stress [47]. There is no definite management strategy however patients usually require long-term treatment with acid suppression agents to achieve and maintain symptom control.

3. RISK FACTORS FOR PEPTIC ULCERATION

Several medical comorbidities or environmental risk factors increase susceptibility to peptic ulceration without being capable of producing ulcer disease alone (Table 1). The mechanisms responsible for ulcer diathesis in these cases are not well known. Importantly, although these risk factors are not causative they do increase the likelihood of developing PUD and increase the likelihood of disease complications by impairing ulcer healing.

Table 1. Non-causal risk factors for peptic ulceration

- Smoking
- Alcohol
- Psychological stress
- Organ transplantation
- Diabetes mellitus
- Cirrhosis
- Chronic kidney disease

A number of risk factors, such as alcohol or smoking, are widely believed to independently cause PUD although evidence in the literature to substantiate this belief is absent.

3. CONCLUSION

Peptic ulcers are common and are typically attributable to *H. pylori* infection or NSAID use. While these aetiologies remain the most frequent causes of PUD their relative incidence compared with other less common pathologies is declining. This is explained in part by the falling incidence of *H. pylori* infection and the availability of NSAIDs with lower gastroduodenal toxicity.

Causes of non-*H. pylori* non-NSAID peptic ulceration are unfamiliar to many clinicians. Primary care physicians should be aware of how to approach patients with ulcer disease that is negative for *H. pylori* or unassociated with NSAIDs. In most instances repeat evaluation for undetected NSAID use or *H. pylori* will identify one of these two causes as the underlying reason for peptic ulceration. Occasionally, however, further testing is required for more obscure causes of PUD which account for approximately 10% of cases overall. Possessing at least some knowledge of the various conditions implicated in the pathogenesis of PUD will enable improved patient care when traditional causes and remedies are absent.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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