Nonhealing Gastric Ulcer Caused by Chronic Alendronate Administration

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Introduction

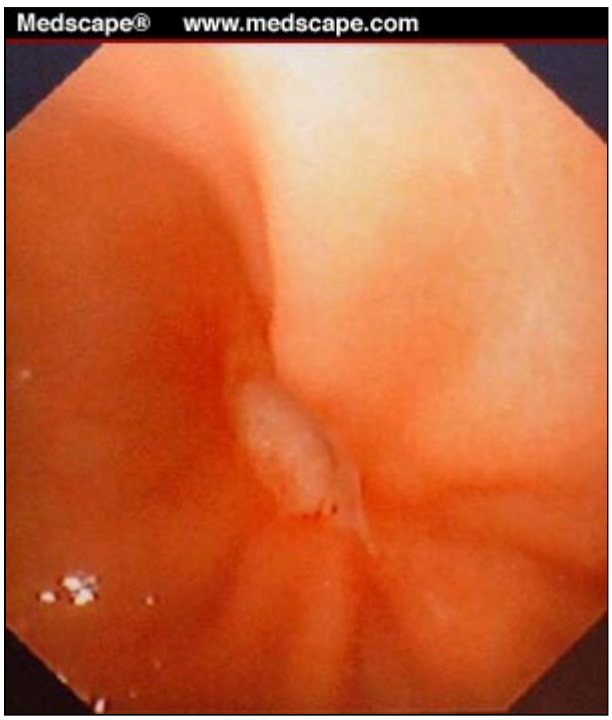
Alendronate is an inhibitor of osteoclast-mediated bone resorption that is widely used for both treatment and prevention of osteoporosis.[1,2] Although clinical trials have shown an adverse event profile similar to placebo, postmarketing reports of gastrointestinal side effects, including ulceration and hemorrhage, have appeared. The incidence of these complications may be increased by concomitant use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs).[3]

A refractory gastric ulcer is defined as one that has not healed after 8 to 12 weeks of therapy.[3] There are several causes, including persistent *Helicobacter pylori* infection, continued use of NSAIDs, smoking, and neoplasia. The basic teaching is "a nonhealing gastric ulcer must be considered cancer until proven otherwise."[4]

We report here a case of a patient with a nonhealing gastric ulcer that had no evidence of malignancy and resolved after stopping treatment with the biphosphonate alendronate.

Case Report

A 68-year-old woman was referred for investigation of epigastric pain. She had epigastric pain for several weeks that was exacerbated after meals. Her weight was stable. Her previous medical history included osteoporosis, hypertension, hypothyroidism, and hyperlipidemia. She was treated with ramipril 5 mg od, amlodipine 5 mg od, atenolol 50 mg od, simavastin 10 mg od, thyroxine 100 mcg od, alendronate 10 mg od, and aspirin 100 mg od. Physical examination revealed epigastric tenderness, no organomegaly, and no signs of bleeding. The rest of the examination was noncontributory. Upper gastrointestinal endoscopy revealed a 1.5-cm ulcer on the greater curvature (Figure 1). Biopsy of this ulcer showed severe chronic active gastritis, with necrotic tissue. *H pylori* was present. Treatment with aspirin was stopped, and the patient received a 7-day course of *H pylori* eradication consisting of omeprazole 20 mg bid, clarithromycin 500 mg bid, and amoxicillin 500 mg bid. The treatment with omeprazole was continued for 1 month. After 5 weeks, a repeat gastroscopy was performed, which revealed a 1-cm ulcer on the greater curvature. Repeat biopsy showed focal ulceration and a fibrino-granulocytic exudate. There was an acute inflammation in the lamina propria and reactive atypia. *H pylori* was not present. Omeprazole was reinstituted and a repeat gastroscopy 1 month later (9 weeks following presentation) showed a 0.3-cm ulcer. Biopsy of the lesion showed partial ulceration and chronic active gastritis with *H pylori* present. A CT scan of the abdomen revealed mild antral thickening but no other abnormalities. A further gastroscopy after 2 months (more than 4 months after presentation) showed a residual small ulcer. *H pylori* was detected by the rapid urease test. The patient received a 4-drug course for *H pylori* eradication consisting of omeprazole 20 mg bid, amoxycillin 1 g bid, metronidazole 500 mg tid, and tripotassium dicitratobimuthate 240 mg bid for 10 days.



Gastric ulcer at intial endoscopy.

Another gastroscopy (number 5) after a further 5 weeks (total of 5 months after presentation)showed that the gastric ulcer was still present and biopsy showed no evidence of malignancy. *H pylori* was not found in biopsies of the antrum and body of the stomach. An endoscopic ultrasound of the stomach showed a normal gastric wall, no enlargement of perigastric lymph nodes, and a normal pancreas.

It was decided to cease treatment with alendronate, and a repeat gastroscopy 2 months later (7 months after initial presentation) showed no evidence of an ulcer. The patient remains well on follow up of several months.

Discussion

We report here a case of a chronic gastric ulcer that persisted despite eradication of *H pylori*. This scenario is suggestive of malignancy but there was no evidence of malignancy on repeat biopsies, nor on accessory investigations including endoscopic ultrasound of the stomach and CT scan of the abdomen. We believe that alendronate administration was responsible for the gastric ulcer and, following its cessation, the ulcer healed.

Alendronate is a biphosphonate and a highly powerful inhibitor of osteoclast-mediated bone resorption.[1] It is widely used for the treatment of osteoporosis and for the prevention of steroid-induced osteoporosis.[1,2] It has been shown to significantly reduce the risk of fracture in osteoporotic postmenopausal women.[1] Alendronate use has been shown to be well tolerated in clinical trials, and the adverse event profile was similar to placebo.[1] Postmarketing reports, however, have shown some side effects on the gastrointestinal tract, especially gastroesophageal inflammation and ulceration[5] as well as hemorrhage.[6] There are reports of gastric ulcers related to alendronate use, although the literature has been conflicting. Following the reports of esophagitis, the manufacturers issued a clear recomendation to take alendronate at least half an hour before a meal, to consume at least 6-8 ounces of water, and to remain upright until the meal.[5] Our patient complied with these recomendations.

Alendronate in a dose of 40 mg per day in healthy volunteers produced a visible gastric mucosal injury in 58% of patients and 1 case of gastric ulceration.[7] In contrast, Lanza and colleagues[8] found no evidence for an increased risk of gastric ulceration in a study of 95 postmenopausal women, both in the 5 mg and 10 mg per day dose. More recently, the same group noted a 13.2% incidence of gastric ulcers in a group of 227 postmenopausal women.[9] The incidence of ulceration was much less (4.1%) in the group of patients receiving risedronate, another biphosphonate.[9] Thus, there are differences between various biphosphonates in regards to the effect on the gastric mucosa.

Another group has reported gastric ulcers in 2 of 25 healthy volunteers receiving alendronate.[10] The combination of NSAIDs with alendronate may increase the degree of mucosal damage.[3] The fact that our patient was treated with aspirin as primary prophylaxis for cardiovascular disease may have contributed to the evolution of the ulcer. Since such use of aspirin is very widespread, as is the use of alendronate, one might expect to encounter an increasing incidence of gastric ulceration as a result of the use of these medications. Recently, the dosing schedule of alendronate has been changed from 10 mg daily to 70 mg weekly.[11] This seems to be equipotent in terms of the effect on osteoporosis and had a similar incidence of upper gastrointestinal adverse effects, although there was a trend toward a lower incidence of esophageal events.[11] More data are required regarding the effect of the 70-mg once-weekly dose of alendronate on peptic ulceration.

The recent paper by Lanza and colleagues[9] showed no correlation between gastrointestinal adverse events and the occurrence of gastric ulcers. An endoscopic study of alendronate also found no linkage between the presence of gastric ulcers and upper gastrointestinal symptoms.[12]

Although our patient had symptoms related to the peptic ulcer, at least initially, many patients with ulcer complications have no previous symptoms.[13] Any nonhealing gastic ulcer raises the specter of malignancy, and initial biopsies may be undiagnsotic due to tissue necrosis. As this case illustrates, a consideration of the ulcerogenic potential of concurrent medication should be made.

In summary, we describe here a case of a refractory gastric ulcer that was related to the use of alendronate. A careful drug history should be taken in any patient with refractory gastric ulcer, as it may reduce the number of invasive and expensive investigations needed to rule out malignancy.

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