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ORIGINAL CONTRIBUTIONS

Are Ulcers a Marker for Invasive Carcinoma in Barrett's Esophagus? Data From a Diagnostic Variability Study With Clinical Follow-Up

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OBJECTIVES: We correlated follow-up information from 138 patients with Barrett's esophagus and varying degrees of dysplasia with the presence of ulcers.

METHODS: A group of pathologist participants were asked to contribute patients' initial biopsy slides showing Barrett's esophagus (BE) without dysplasia and with epithelial changes indefinite for dysplasia, low grade dysplasia (LGD), high grade dysplasia (HGD), and adenocarcinoma. From the initial 250 cases used for a diagnostic reproducibility study, follow-up information was available for 138 patients.

RESULTS: There were 44 cases submitted as BE, 22 as BE with epithelial changes indefinite for dysplasia, 26 as BE with LGD, 33 as BE with HGD, and 13 as BE with adenocarcinoma. Ulcers were present in 35/138 cases (25%), including 3/44 cases of BE without dysplasia (7%), 2/22 cases of BE with epithelial changes indefinite for dysplasia (9%), 0/26 cases of BE with LGD (0%), 10/33 cases of BE with HGD (30%), and 7/13 cases of BE with adenocarcinoma (54%). On follow-up, there were no invasive carcinomas detected among the BE without dysplasia group (median follow-up = 38.5 months). Adenocarcinomas were detected in 4/22 cases (18%) submitted as BE with epithelial changes indefinite for dysplasia at 19, 55, 60, and 62 months and in 4/26 cases (15%) of BE with LGD at 9, 9, 11, and 60 months. None of these carcinomas occurred in cases in which an ulcer was present in the initial biopsy specimen. Among the 33 HGD cases, 20 (60%) were found to have adenocarcinoma on subsequent resection specimens. The presence of an ulcer with HGD increased the likelihood of finding carcinoma in the resection specimen, as 8/10 biopsies (80%) of HGD patients with ulcers had carcinoma, compared to 12/23 biopsies (52%) of HGD patients without ulcers. All of the cases interpreted as adenocarcinomas on biopsy were found either to have invasive carcinoma on esophageal resection or to have metastases that were demonstrated in unresectable patients.

CONCLUSION: If an ulcer accompanies HGD in a biopsy specimen from a patient with BE, it is likely that invasive carcinoma is also present at that time. (Am J Gastroenterol 2002;97: 27–31. © 2002 by Am. Coll. of Gastroenterology)

INTRODUCTION

When physicians first became aware of the entity now referred to as Barrett's esophagus (BE), the most noteworthy complications were the development of ulcers and strictures (1, 2). As medical therapies directed at acid suppression have considerably reduced these complications, at times to the point of masking carcinomas (3), and as the incidence of esophageal adenocarcinoma has been increasing (4, 5), benign esophageal ulcers and strictures pose lesser threats to patients with gastroesophageal reflux disease. We have revisited the significance of identifying esophageal ulcers in biopsy specimens from patients with BE in the acid suppression era.

MATERIALS AND METHODS

From a cohort of 250 cases that were used to test established criteria for grading dysplasia in BE, we obtained follow-up information on 138 patients. The study was initially a patho-

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Table 1. Barrett's Esophagus and Biopsy Diagnosis: Correlation With Subsequent Detection of Carcinoma by Submitting Diagnoses

Submitting Diagnosis	No. of Cases	Total Follow-Up Period [Median (Range), Months]	Fraction (%) of Ulcerated Cases in Category	Fraction (%) of Ulcerated Cases With Carcinoma on Follow-Up	Total No. (%) in Category of Developing Cancers
No dysplasia	44	38.5 (1–78)	3/44 (7%)	0/3	0 (0%)
Indefinite for dysplasia	22	36 (7–144)	2/22 (9%)	0/2	4 (18%)
LGD	26	24 (2–72)	0 (0%)	0/0	4 (15%)
HGD	33	13 (1–60)	10/33 (30%)	8/10 (80%)	20 (61%)
Carcinoma	13	4.4 (1–22)	7/13 (54%)	7/7 (100%)	13 (100%)

logical one, so patients were not enrolled *per se* and biopsies were initially chosen from participating pathologists' institutional archives to demonstrate histological findings. Consistent information about the endoscopic findings and patients' medication histories were not available. Full results of this follow-up study and results of the intraobserver study from which the data were derived are reported elsewhere (6, 7). Briefly, each of 10 participants from 10 institutions contributed slides, all of which were reviewed by 12 observers (two reviewers did not contribute cases). Each contributor was instructed to supply slides from the *initial* known endoscopic biopsies of patients having the following: 1) BE without dysplasia (goblet cells present above the gastroesophageal junction), 2) BE with inflammation and/or inflammatory atypia, 3) BE with epithelial changes indefinite for dysplasia, 4) BE with low grade dysplasia (LGD), 5) BE with high grade dysplasia (HGD), 6) intramucosal carcinoma in BE, or 7) frankly invasive esophageal adenocarcinoma. However, because many of the biopsies were from referral centers, it is possible that some of the patients could have had prior biopsies and results were unavailable.

All 250 cases were reviewed blindly on two separate occasions by all 12 pathologists, and thus 24 diagnostic opinions were available for each case. Masked slides were circulated with a worksheet that asked participants to assign a grade to each case using the following scale: 0 = BE with no dysplasia, 1 = epithelial changes indefinite for dysplasia, 2 = LGD, 3 = HGD, 4 = intramucosal carcinoma, and 5 = frankly invasive carcinoma. All cases were also separately evaluated by one of the reviewers (E.M.) for the presence or absence of ulcers. Ulcers were defined on strictly histological grounds—namely, by the presence of necroinflammatory exudate extending the full thickness of the mucosa (surface to muscularis mucosae).

Patients did not have their cases followed on rigorous biopsy protocols (8, 9), and thus it was understood that there would be variations in sampling. It was also understood that knowledge of the endoscopic findings and presenting symptoms that led to biopsy would not be uniformly documented. Participants submitted a follow-up worksheet requiring completion of the following data points: patient demographic data (age, gender, race), date of submitted biopsy, follow-up biopsy/specimen date, findings in follow-up biopsy or resection, interval between submitted biopsy and

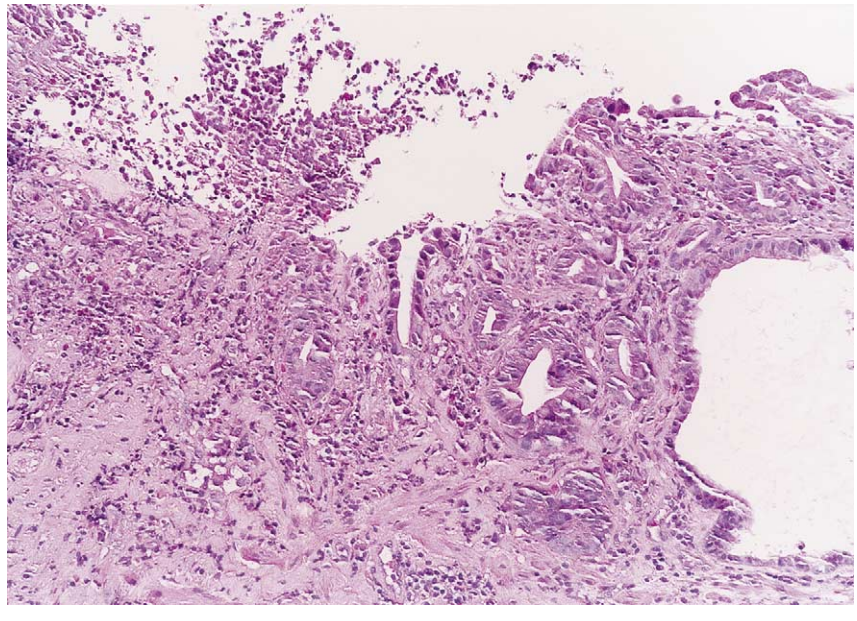


Figure 1. Area of ulcer in a case submitted to the diagnostic variability study as HGD. HGD without invasive carcinoma was found on the subsequent resection specimen.

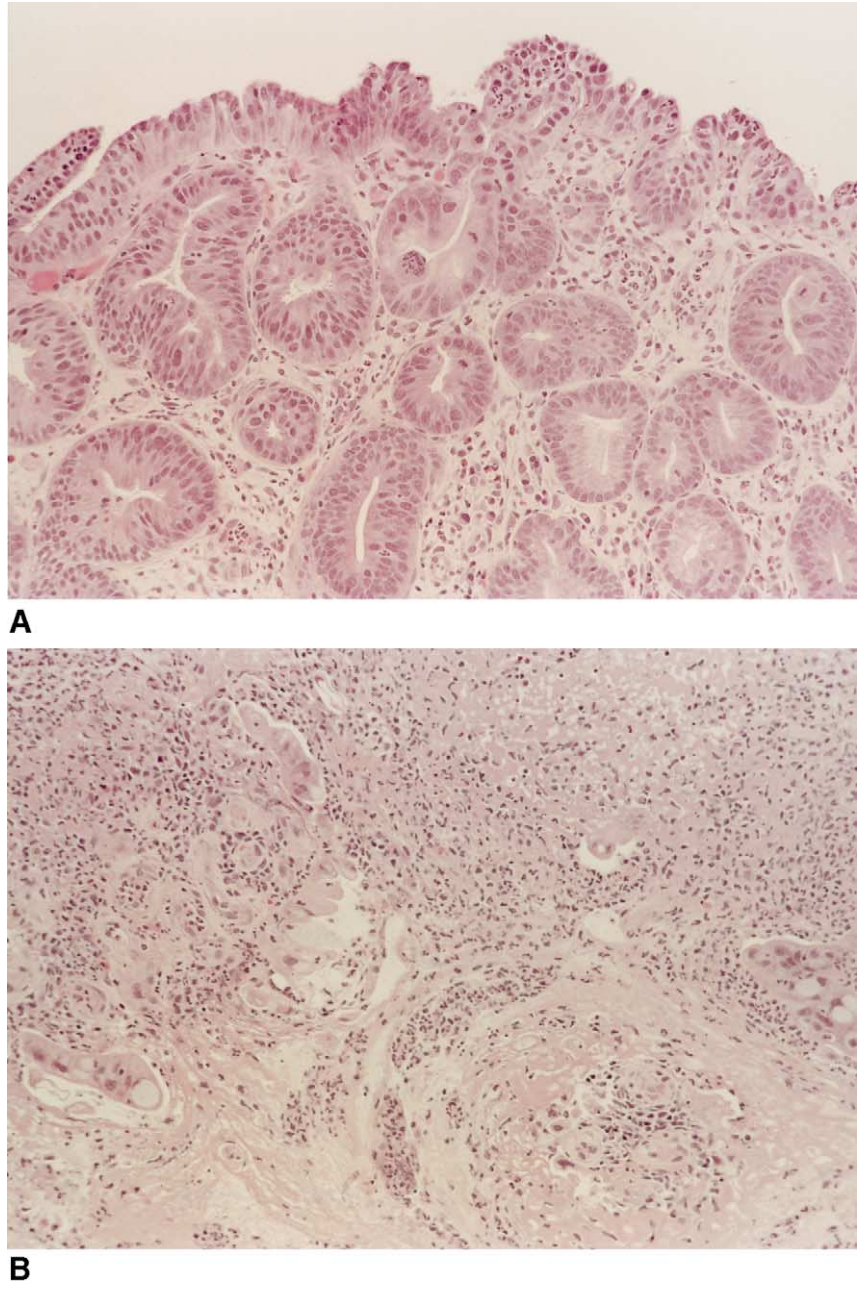


Figure 2. Nonulcerated area *(A)* and ulcerated one *(B)* in specimen submitted as HGD. Invasive carcinoma was detected on the resection specimen.

follow-up biopsy or resection (months), patient status (alive or dead), and last follow-up date. Follow-up information was correlated with the presence of ulcers and categories compared using Fisher's exact test. Full analysis of Kaplan-Meier curves is reported elsewhere (6).

RESULTS (TABLE 1)

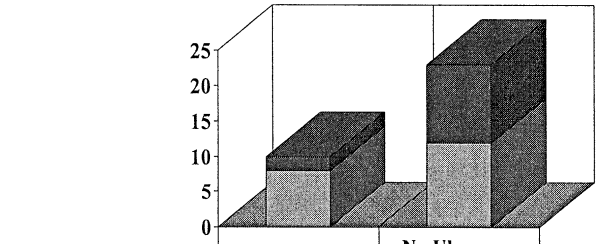
Overall, invasive carcinoma was found in 15/22 (68%) of patients whose biopsy specimens demonstrated an ulcer, but only in 20/116 (17%) cases without.

Summary of Ulcers by Diagnostic Category

Ulcers were only found in 7% of all biopsy specimens interpreted as negative for dysplasia and in 9% of cases of BE with epithelial changes indefinite for dysplasia, and were not identified in the LGD cases. On the other hand, ulcers were found in 30% of HGD and in 54% of carcinoma cases.

Negative for Dysplasia

On follow-up, there were no invasive carcinomas detected among the 44 patients in the BE without dysplasia group during the follow-up period (median follow-up = 38.5



	Ulcers on Biopsy	No Ulcers on Biopsy
No Cancer on Resection	2	11
Cancer on Resection	8	12

Figure 3. Identification of carcinoma in resected specimens from patients with HGD.

months). Three of the 44 patients (7%) in this category had ulcers.

Indefinite for Dysplasia

Adenocarcinomas were detected in 4/22 cases (18%) submitted as BE with epithelial changes indefinite for dysplasia at 19, 55, 60, and 62 months (median follow-up = 36 months). Two of the 22 patients (9%) in the BE with epithelial changes indefinite for dysplasia category had ulcers, but the patients who progressed were not the two with ulcers on their initial biopsies.

Low Grade Dysplasia

Adenocarcinomas developed in 4/26 cases (15%) of LGD at 9, 9, 11, and 60 months (median follow-up = 24 months). No patients diagnosed with LGD had ulcers on their initial biopsies.

High Grade Dysplasia

Among the 33 HGD cases, 20 (60%) were found to have adenocarcinomas on subsequent resection specimens (median follow-up = 13 months). Ten of the 33 (30%) had ulcers. The presence of an ulcer with HGD (Figs. 1 and 2) increased the likelihood of finding carcinoma in the resection specimen, as 8/10 biopsy specimens (80%) with HGD and ulcers had carcinoma in the resection specimen, compared to 12/23 (52%) biopsy specimens with HGD and no ulcers (Fig. 3) ($p = 0.24$, Fisher's exact test).

Adenocarcinoma

All of the cases interpreted as adenocarcinoma on biopsy were found either to have invasive carcinoma on esophageal resection or to have metastases that were demonstrated in unresectable patients. Ulcers were common among patients diagnosed initially with adenocarcinoma (7/13, 54%).

DISCUSSION

Despite its limitations (7, 10), routine histological evaluation remains the major prognostic tool in identifying the subset of BE patients at highest risk for development of invasive esophageal carcinoma (6, 11). Some observers regard HGD as a surveillance endpoint that should prompt esophagectomy (12, 13). However, with intensive endoscopic surveillance including numerous biopsies, some physicians performing endoscopy are willing to observe patients with HGD in whom accompanying invasive carcinoma has been carefully excluded (8, 9), because only about 60% will develop invasive adenocarcinoma within 5 yr (11), usually at an early stage. However, it is well known that patients having *prevalent* HGD, or HGD identified at their initial endoscopies and therefore present for an unknown period of time, are likely to also harbor invasive carcinoma that is detected on further sampling or on resection. This is highlighted in a recent publication by Schnell *et al.* (14). In summarized surgical series, 43% of patients are found to harbor an occult invasive carcinoma upon esophageal resection for HGD (15). However, the frequency with which unsuspected carcinoma is identified in patients undergoing esophagectomy for HGD ranges from 0% to 73% (15).

The current study, derived from a group of patients whose mucosal biopsies were used to test observer variability in grading dysplasia, indicates that the presence of an ulcer accompanying *prevalent* HGD strongly suggests that the patient harbors an invasive lesion. Invasive carcinoma was found in 15/22 patients (68%) whose biopsy specimens demonstrated an ulcer, but only in 20/116 cases (17%) without. Obviously, this summary of our data has no bearing on the true incidence of carcinoma accompanying ulcers in the general Barrett's population because dysplasia and carcinoma occur in a minority of patients and our cases included many examples of dysplasia and known invasive carcinoma. However, the key finding in our study is that 80% of patients with HGD and an ulcer were found to have invasive carcinoma on resection or by documentation of metastases, whereas about 50% of those with HGD without ulcers were found to have adenocarcinomas on resection. Although this difference did not reach statistical significance ($p = 0.24$ by Fisher's exact test), presumably because of relatively small numbers, the figure is alarming and indicates a trend. Other observers have previously noted an association between ulcers and invasive carcinomas in both gastric and esophageal dysplasias resected for the indication of HGD (16).

Although severe erosive esophagitis and strictures were the primary complications of BE in the past (1, 2), in the acid suppression era, ulcers are readily healed. In our group of cases, ulcers were only found in 7% of all biopsy specimens interpreted as negative for dysplasia and in 9% of cases with changes indefinite for dysplasia, and were not identified in the low grade cases. On the other hand, ulcers were found in 30% of our cases with HGD and in over half of the carcinoma cases. BE patients with ulcers warrant close attention and multiple biopsies to exclude occult invasive carcinoma. Patients with HGD and ulceration are highly likely to have synchronous invasive carcinoma.

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