

EDUCATION PRACTICE

How to Manage a Barrett's Esophagus Patient With Low-Grade Dysplasia

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Clinical Scenario

A 52-year-old Caucasian man with a 12-year history of heartburn requiring daily therapy with proton pump inhibitors undergoes an upper endoscopy for screening of Barrett's esophagus (BE). His symptoms of gastroesophageal reflux disease are well controlled on once-daily proton-pump inhibitor therapy. His physical examination is unremarkable except for mild obesity. Upper endoscopy performed at an outside facility revealed a 5-cm-long segment of BE. In addition, a single small area of mucosal irregularity was reported within this segment. A biopsy specimen obtained from this area was reported as having "acute and chronic inflammatory changes with atypical cells, cannot rule out high-grade dysplasia (HGD)" whereas the remaining random biopsy specimens revealed intestinal metaplasia without dysplasia. Repeat upper endoscopy revealed a 3-cm hiatal hernia and the squamocolumnar junction was displaced 5 cm above the most proximal extent of the gastric folds (circumferential segment, 3 cm; maximal extent, 5 cm; Prague C3M5). The previously mentioned nodule was identified within the Barrett's segment. The presence and extent of the small area of mucosal irregularity (approximately 7-8 mm) was well defined using narrow band imaging and was removed by endoscopic mucosal resection (EMR). Random surveillance biopsy specimens were obtained from the remaining Barrett's segment. The specimen obtained by EMR revealed low-grade dysplasia (LGD) that was confirmed by an expert pathologist, whereas the random biopsy specimens showed intestinal metaplasia with no dysplasia. How should this patient be managed? How should you counsel this patient with BE and LGD regarding progression to esophageal adenocarcinoma? What is the role of advanced imaging techniques and ablative therapies in the management of patients with BE and LGD?

The Problem

BE, a condition resulting from chronic gastroesophageal reflux disease, is a well-established premalignant condition for the development of esophageal adenocarcinoma (EAC). It is defined as displacement of the squamocolumnar junction proximal to the gastroesophageal junction with the presence of intestinal metaplasia. The development of EAC occurs as a multistep process in which patients are believed to progress from intestinal metaplasia with no dysplasia to invasive cancer, a progression that occurs in a probabilistic rather than deterministic manner. Despite the progress made in endoscopic imaging technology and identification of molecular biomarkers as risk factors for progression, the conventional histologic classification of dysplasia based on endoscopic biopsies is still the

single most predictive biomarker for progression of BE patients to EAC. The degree of dysplasia has been shown in several studies to correlate with the risk of developing cancer, and HGD clearly is associated with the greatest risk. The degree of dysplasia is one of the most important determinants for surveillance intervals and further management of BE patients. Unfortunately, data regarding the progression to EAC risk in the setting of LGD are scant and management strategies are based mainly on expert opinions.

Histologic Interpretation of Low-Grade Dysplasia

LGD is characterized by crypts with relative preservation of simple glandular architecture (Figures 1 and 2). Epithelial cell nuclei are oval or elongated and generally retain polarity. The nuclei are hyperchromatic with mild irregularity of nuclear membrane contour. Nuclear stratification is present and usually occupies the lower half of the thickness of the epithelium; full-thickness stratification is not present. Other features include mucin depletion, decreased number of goblet cells, and increased epithelial mitotic figures. Importantly, there is lack of maturation at the surface such that these changes are present on surface epithelium. A biopsy specimen that lacks well-represented surface epithelium should be interpreted with great caution to prevent overdiagnosis of LGD because changes resembling LGD can be seen in the bases of crypts in regenerating epithelium. There is also a significant degree of interobserver variability in the diagnosis of dysplasia, even among expert gastrointestinal (GI) pathologists, with the highest degree of variability occurring at the lower end of the spectrum (ie, differentiating no dysplasia, indefinite for dysplasia, and LGD). Montgomery et al, in a reproducibility study that assessed agreement using kappa statistics, showed that the interobserver agreement was only fair for LGD ($\kappa = 0.32$) and slight for indefinite dysplasia ($\kappa = 0.15$). To compound the difficulties, the interpretation of dysplasia by community pathologists can be subject to even greater interobserver variations. A recent study showed that LGD in BE patients was overdiagnosed among community pathologists and review by 2 expert pathologists resulted in downgrading of diagnosis from LGD to

Abbreviations used in this paper: AMACR, α -methylacyl coenzyme A racemase; BE, Barrett's esophagus; EAC, esophageal adenocarcinoma; EMR, endoscopic mucosal resection; GI, gastrointestinal; HGD, high-grade dysplasia; LGD, low-grade dysplasia.

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1542-3565/09/\$36.00

doi:10.1016/j.cgh.2008.08.014

Figure 1. LGD characterized by simple glandular architecture with nuclear stratification and lack of maturation at the surface (hematoxylin-eosin: original magnification, 100×).

nondysplastic BE in 77% of the cases; fortunately none of the patients with LGD were upgraded to HGD. These data add credence to the current recommendations that require expert pathologist confirmation for a diagnosis of dysplasia in BE.

Clinical Course of Patients With Low-Grade Dysplasia

The data on the natural history of LGD are highly variable (Table 1). Sharma et al, in a prospective, multicenter, clinical, and endoscopic outcomes project involving a single large database of BE patients, identified 156 patients with LGD who were followed up for a mean period of 5 years (range, 1–15.5 y). On follow-up evaluation of these LGD patients, 103 (66%) patients had nondysplastic BE, 32 (20.5%) had persistent LGD, 16 (10.3%) developed HGD, and 5 (3.2%) developed EAC. The incidence of cancer was 1 in 156 patient-years of follow-up evaluation or 0.6% per year, a rate similar to the risk of cancer in patients with nondysplastic BE. A retrospective analysis reported a crude incidence rate of 1 in 78 patient-years (annual incidence risk, 1.28% per year) for HGD/cancer in LGD patients. In another retrospective cohort of 357 patients with BE, more patients with LGD progressed to HGD/cancer in comparison with patients with nondysplastic BE (hazard ratio, 5.9; 95% confidence interval, 2.6–13.4). More recently, a systematic review reported the natural history of LGD patients and incidence of EAC in this group of patients. Sixteen studies (1512 patients) met inclusion criteria and the weighted-average incidence rate of EAC in LGD patients was 1.69 per 100 patient-years (95% confidence interval, 1.3–2.08). However, significant publication bias was identified in the LGD patients undergoing follow-up evaluation.

There are several explanations for the highly variable data on the natural history of LGD. The number of patients with LGD in most studies is limited. In addition, analyses frequently do not distinguish prevalent (defined as the proportion of the population who have the disease at a given point in time) from incident (defined as the proportion of the population who get the disease over a period of time) dysplasia cases. Prevalent LGD has been associated with a higher rate of neoplastic progression compared with incident LGD. That is, prevalent cases of LGD

are more likely to progress to HGD/cancer compared with patients with incident LGD. The data on survival analyses are sparse and HGD instead of cancer frequently is used as the study end point. Finally, the interobserver agreement in these studies is not assessed and few used an expert/central reading pathologist.

Another noteworthy feature in the natural history data of LGD patients is the phenomenon of regression. This is most likely related to sampling error, the interobserver variability among pathologists, misdiagnosis, removal of the dysplastic focus by biopsy, and perhaps even true regression of the dysplastic area. This transient diagnosis of LGD can have significant negative implications in daily clinical practice. This potentially could increase anxiety levels, increase health care costs and potential morbidity owing to an increased number of endoscopies and biopsies, increase health insurance premiums, and, finally, negatively impact a patient's quality of life. In a recent study, Shaheen et al showed that the majority of BE patients with dysplasia (LGD and HGD) reported a substantial impact on their quality of life irrespective of their baseline grade of dysplasia.

Management Strategies and Supporting Evidence

The Role of an Expert Gastrointestinal Pathologist

Because of the problem of interobserver variability among pathologists, a diagnosis of LGD should be confirmed by an expert GI pathologist. In addition, it also has been suggested that a consensus diagnosis of LGD among expert GI pathologists is associated with an increased risk of progression to HGD or cancer. In a retrospective analysis, biopsy specimens from 43 BE patients with LGD were reviewed by 3 GI pathologists along with cases diagnosed as BE without dysplasia, indefinite for dysplasia, and HGD. Follow-up data were available on 25 patients and progression was defined as a subsequent diagnosis of HGD or cancer. Seven patients (28%) developed HGD or cancer during a mean follow-up period of 26 months (range, 2–84 mo). The individual GI pathologists' di-

Figure 2. Stratified nuclei in LGD occupy the lower part of the epithelium and retain some degree of polarity (hematoxylin-eosin: original magnification, 400×).

Table 1. Publications Reporting the Incidence of Esophageal Adenocarcinoma in BE Patients With LGD

Study	Year	No. of patients with LGD	Follow-up period, y	Patient years in follow-up	No. of incident cancers
Hameeteman et al	1989	6	5.2	31	3
Miros et al	1991	10	3.6	36	1
Ferraris et al	1997	5	3	15	1
Reid et al	2000	43	3.9	168	3
Montgomery et al	2001	26	2	52	4
Schnell et al	2001	738	7.3	5387	10
Weston et al	2001	48	3.4	163	1
Skacel et al	2002	16	1.9	30	2
Murray et al	2003	171	3.7	633	7
Conio et al	2003	16	5.5	88	1
Hage et al	2004	11	12.7	140	1
Dulai et al	2005	134	3.21	430	1
Sharma et al	2006	156	5	780	5
Srivastava et al	2007	31	3.1	96	14
Lim et al	2007	34	8	272	9
Vieth et al	2007	67	2.33	156	23

agnosis did not correlate with progression but when at least 2 GI pathologists agreed on LGD, there was a significant association with progression (7 of 17 patients, 41%; $P = .04$). When all 3 pathologists agreed, 4 of 5 LGD patients progressed ($P = .012$). However, these conclusions are drawn from a relatively small number of patients with LGD and hence need validation in large prospective studies.

Recent Advances in Histopathologic Evaluation

A recent study by Srivastava et al examined the significance of the extent of LGD as a risk factor for progression to cancer in BE patients. Seventy-seven patients with a worse pathological diagnosis of LGD ($n = 31$) or HGD ($n = 46$), of which 44 progressed to cancer, were examined. The total number of LGD and HGD crypts were determined separately by counting all crypts and the extent of LGD, HGD, and total dysplasia were correlated with cancer outcomes. The mean proportion of LGD crypts/patient was significantly higher in progressors (46.4% vs 26%; $P = .03$). However, at the present time, the utility of counting the number of crypts in patients with LGD is uncertain. Studies have shown α -methylacyl coenzyme A racemase (AMACR) to be a highly specific marker in Barrett's neoplastic lesions. A retrospective study analyzed the role of AMACR expression in reactive and neoplastic lesions and noted that nondysplastic BE and indefinite for dysplasia lesions ($n = 30$) did not show AMACR immunoreactivity, whereas 91% of cases with LGD were AMACR positive and 96% of cases with HGD and early EAC were positive for AMACR. The role of this new diagnostic marker for dysplasia carcinoma sequence in BE merits further study.

Surveillance Endoscopy, Biopsy Protocol, and the Role of Endoscopic Mucosal Resection

Endoscopy should be performed in patients whose reflux symptoms are controlled with proton pump inhibitor therapy and biopsy specimens should not be obtained in the setting of active inflammation. If changes of erosive esophagitis are identified at the endoscopy when LGD is diagnosed, the patient should be treated aggressively with high-dose proton pump inhibitor therapy and repeat endoscopy should be performed

within 3 to 6 months to ensure healing of erosive esophagitis, to exclude the possibility of higher grades of dysplasia and cancer, and, finally, to overcome the likelihood of inflammatory changes interfering in the interpretation of dysplasia (overdiagnosis). A recent study showed that in patients with erosive esophagitis undergoing treatment with acid-suppressive therapy, BE is detected in approximately 12% of patients on repeat endoscopy. Thus, patients with reflux symptoms undergoing endoscopy for screening or surveillance of BE should be treated with acid-suppressive therapy and should be asymptomatic (on proton pump inhibitor therapy) before endoscopy and biopsy specimens should not be obtained in the presence of erosive esophagitis to enhance the yield of BE and associated dysplasia. The grading of the Barrett's segment should be performed using the Prague C&M endoscopic grading system. Four-quadrant biopsies every 1 to 2 cm of the endoscopically recognized area of BE should be obtained. Because biopsy specimens obtained every 1 cm in HGD patients detects more cancers than biopsies taken every 2 cm, a similar biopsy protocol may be applied to LGD patients.

EMR has become increasingly important in recent years as a curative treatment option and as a diagnostic/staging tool for BE-associated dysplasia and mucosal EAC. Recent studies have shown that EMR is superior to endoscopic mucosal biopsies as a diagnostic tool and results in a change in diagnosis in approximately 25% of the patients, which includes upstaging and downstaging of the lesions. In addition, EMR also may enhance the diagnostic reproducibility compared with mucosal biopsy specimens. This is largely owing to significantly larger specimens obtained by EMR, allowing a more precise assessment of histologic landmarks. Thus, all patients with mucosal abnormalities should undergo EMR as a complete mode of dysplasia assessment. Random and target biopsies and EMR specimens should be submitted in separate jars with appropriate labeling based on their location of sampling.

The initial finding of LGD, when confirmed, warrants a follow-up endoscopy within 6 months to ensure that it is the highest-grade lesion within the BE segment. Further surveillance, based on published guidelines, mandates surveillance endoscopies on a yearly basis until no dysplasia is present on 2 consecutive annual endoscopies. However, data supporting this

specific interval are lacking and given the low rates of progression of LGD to EAC, future prospective studies should assess if surveillance intervals can be extended in patients with LGD. One potential strategy is performing endoscopy within 6 months, followed by yearly endoscopies for 2 years, followed by endoscopy every 2 years in patients with persistent LGD.

Advanced Imaging Techniques

The distribution of dysplasia or early EAC within a BE segment is patchy and focal and hence standard endoscopy with random biopsies may not detect dysplastic changes. In patients undergoing surgery for HGD or early EAC, Cameron and Carpenter found the median surface area of the total BE segment to be 32 cm², LGD to be 13 cm², HGD to be 1.3 cm², and EAC to be 1.1 cm². The development of emerging novel endoscopic techniques such as magnification/high-resolution endoscopy, narrow band imaging, autofluorescence imaging, confocal endomicroscopy, and optical coherence tomography may improve evaluation of patients with BE and associated neoplastic lesions. These techniques potentially could provide an in vivo diagnosis of the lesion and improve the detection of dysplasia. Narrow band imaging is at the forefront, using blue light with narrow band filters that enable detailed imaging of the mucosal and vascular surface patterns within the BE segment with a high level of resolution and contrast without the need for chromoendoscopy. Although it has been shown to detect HGD with a high sensitivity and specificity, the data showing its efficacy in differentiating LGD from nondysplastic BE or HGD are limited. Small-area imaging techniques such as confocal microendoscopy provide a real-time/optical diagnosis by magnifying the mucosa and allow subsurface imaging of cellular structures. A single-center study that recruited 63 BE patients showed that BE and associated neoplasia could be predicted with a sensitivity of 98.1% and 92.9% and a specificity of 94.1% and 98.4%, respectively (accuracy, 96.8% and 97.4%) using confocal laser endomicroscopy. Their role specifically in LGD patients has not been evaluated. The role of miniprobe-based confocal laser microscopy is being assessed. Large, multicenter, well-designed, randomized, controlled trials using validated and standardized terminologies are needed for these techniques to make substantive inroads into routine clinical practice.

The Role of Biomarkers

Recent times have seen an explosion in the number of studies reporting on various biomarkers of BE progression with a few studied in a prospective manner. Detection of DNA content abnormalities by flow cytometry (aneuploidy or increased 4N fraction) and mutation or loss of heterozygosity of the p53 and p16 genes are markers that have been evaluated prospectively. In addition, several biomarkers of dysregulated cell proliferation, impaired apoptosis, angiogenesis, and cell cycle abnormalities have been studied. However, these biomarkers, among others, are not widely available and need to be validated further in large prospective multicenter studies before their routine use in the risk stratification of BE patients with LGD can be advocated. It appears that LGD will be the group in which it would be the most applicable.

Treatment Options in Low-Grade Dysplasia Patients

There is epidemiologic and experimental evidence to suggest that chemoprevention using nonsteroidal anti-inflammatory drugs, aspirin, and selective cyclooxygenase-2 inhibitors may reduce the risk of cancer in BE patients. However, a recent phase IIb, multicenter, randomized, placebo-controlled trial of celecoxib (200 mg twice daily) for 48 weeks in BE patients with dysplasia (LGD, 64; HGD, 36) showed no difference in the proportion of biopsy specimens with dysplasia or cancer between treatment groups. Results of well-designed, prospective, clinical studies such as the ongoing Aspirin Esomeprazole Chemoprevention Trial (AsPECT) study in the United Kingdom still are needed to establish the efficacy of aspirin and proton pump inhibitor therapy in the prevention of EAC. There are no prospective data showing that proton pump inhibitor therapy reduces the likelihood of dysplasia in BE patients.

Several ablative therapies have been developed in attempts to reverse BE and reduce cancer risk. Modalities include argon plasma coagulation, multipolar electrocoagulation, laser ablation, photodynamic therapy, radiofrequency ablation, cryotherapy, and EMR. These techniques are based on the hypothesis that injury of the metaplastic epithelium combined with vigorous acid suppression would lead to reversion of the BE to squamous epithelium and reduce the risk of progression to cancer. However, most studies have reported on a limited number of patients with LGD. There has been an increased interest in the role of radiofrequency ablation and cryotherapy in BE patients with dysplasia (HGD and LGD). Interim results of a randomized, multicenter, sham-controlled trial of radiofrequency ablation for BE patients with dysplasia showed that complete clearance of dysplasia and intestinal metaplasia occurred in 96% and 83%, respectively, of the LGD patients. Given the limited available data and low likelihood of progression to cancer, ablative therapies cannot be recommended in patients with LGD outside the research arena.

Areas of Uncertainty

The area of greatest uncertainty is the rate of development of cancer in BE patients with LGD. This can be attributed to the highly variable natural history data of LGD patients frequently reported in small numbers of patients with a short duration of follow-up evaluation. Other significant confounding variables include high interobserver variability among pathologists, difficulty in differentiating between prevalent and incident cases, and selection and referral bias. It is unclear if surveillance intervals can be extended (eg, every 2 years in patients with LGD) and multicenter randomized controlled trials of surveillance intervals are sorely needed to assess the validity of current surveillance protocols. The role of advanced imaging techniques, both broad-based and small-area imaging, needs further clarification before these technologies are ready for primetime. It is uncertain if LGD patients should be treated using ablative techniques and results of ongoing studies are awaited. Finally, risk stratification, that is, identification of LGD patients at risk for progression to HGD/cancer (using clinical and endoscopic features with biomarkers) should be a priority.

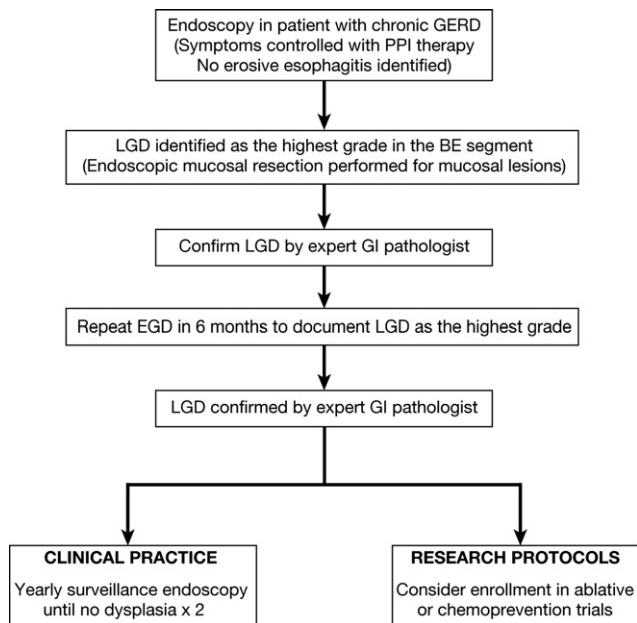


Figure 3. Algorithm for the management of BE with LGD.

Published Guidelines

The most updated guidelines recommend that the finding of LGD warrants a follow-up endoscopy within 6 months to ensure that no higher grade of dysplasia is present within the BE segment. If none is found, then yearly endoscopy is warranted until no dysplasia is present on 2 consecutive annual endoscopies. LGD always should be confirmed by an expert gastrointestinal pathologist because of the problem of reading variability. These guidelines do not recommend ablative therapies for BE patients with LGD. Similarly, no recommendation was made to use proton pump inhibitors or other therapies as chemopreventive agents.

Recommendations

An algorithm highlighting the current approach to a BE patient with LGD is shown in Figure 3. The patient presented earlier in this article sheds light on many of the issues surrounding the management of BE patients with LGD. The patient underwent repeat endoscopy in approximately 6 months and no mucosal abnormalities were identified. Random biopsy specimens showed the presence of intestinal metaplasia with no dysplasia. The patient was counseled regarding the low likelihood of progression to EAC and has been enrolled in a surveillance endoscopy program.

Conclusions

LGD is a poor histologic marker for progression of BE to cancer. The data on the natural history of LGD are highly variable and the incidence of EAC ranges from 0.6% to 1.6% per year. Interpretation frequently is fraught by the small number of patients with a relatively short duration of follow-up evaluation, high interobserver variability among pathologists, selection and referral bias, and difficulty in differentiating between prevalent and incident cases. More recently, significant publication bias has been reported in studies describing the natural

history of LGD patients. The future lies in risk stratification and identification of those LGD patients most likely to progress to HGD/EAC. This is most likely to be achieved by the use of advanced imaging techniques and biomarker studies. Patients with LGD and abnormalities noted on advanced imaging and/or biomarkers are the group of patients most likely to progress and hence may be treated aggressively, whereas the majority may be managed as nondysplastic BE.

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