The Significance of “Indefinite for Dysplasia” Grading in Barrett Metaplasia

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Context.—For a confident diagnosis of dysplasia in Barrett metaplasia, the epithelial atypia should also involve the surface epithelium. However, pathologists are often faced with biopsies where the crypts show dysplasia, but the surface epithelium is either uninvolved or unevaluable. We previously grouped these cases with indefinite for dysplasia (IND).

Objective.—To determine the clinical significance of IND grading in Barrett metaplasia.

Design.—All biopsies from 276 prospectively followed patients with Barrett metaplasia, who did not have high-grade dysplasia (HGD) or esophageal adenocarcinoma (EAC) on initial biopsy, were graded as negative for dysplasia (ND), IND, low-grade dysplasia (LGD), HGD, and EAC. Biopsies with multifocal IND or LGD were graded as IND or LGDM, respectively.

Results.—Only 3 of 193 patients (2%) with an initial diagnosis of negative for dysplasia and only 1 of 48 patients (2%) diagnosed with IND progressed to HGD or EAC. By contrast, 1 of 7 patients (14%) with INDM, 2 of 21 (10%) with LGD, and 1 of 7 (14%) with LGDM progressed to HGD or EAC. There was no significant difference in progression rate between patients with an initial diagnosis of negative for dysplasia and those diagnosed IND nor were there significant differences among patients with initial diagnoses of INDM, LGD, or LGDM. Kaplan-Meier analysis showed that patients with INDM, LGDM, or LGDM on initial biopsy (group 1) were more likely to progress to HGD or EAC than were those patients who were diagnosed negative for dysplasia or IND (group 2; log-rank test, P < .001).

Conclusions.—Multifocal IND in an esophageal biopsy from a patient with Barrett metaplasia has the same clinical implication as LGD.

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Histopathologic diagnosis of dysplasia is the cornerstone of current surveillance programs aimed at detecting esophageal adenocarcinoma (EAC) at an early stage in patients with Barrett metaplasia.1 For a confident diagnosis of dysplasia, the epithelial abnormalities characteristic of dysplasia should not only be present in the crypts but also involve the surface epithelium.2 However, pathologists are often faced with biopsies where the crypts show dysplastic changes, but the surface epithelium is either uninvolved, denuded, or replaced by squamous epithelium, making a confident diagnosis of dysplasia in these cases impossible. We have been grading such biopsies as indefinite for dysplasia (IND),3 a diagnosis previously rendered on cases that fulfilled the criteria for dysplasia but had significant active inflammation. The clinical significance of this expanded diagnosis of IND is currently unknown.

MATERIALS AND METHODS

Hematoxylin-eosin–stained sections of formalin-fixed and paraffin-embedded tissue from initial and follow-up biopsies from 276 patients with histologically confirmed Barrett metaplasia, without high-grade dysplasia (HGD) or EAC on the initial biopsy and with a mean follow-up of 41 months (median, 35), were evaluated for dysplasia using standard criteria.2 All patients were treated with proton pump inhibitors during the course of the study. Because a confident diagnosis of dysplasia cannot be rendered on biopsies when dysplastic changes involve the crypts but involvement of the surface epithelium cannot be documented,2 these cases were prospectively graded as IND. Slides were evaluated in a blinded fashion and separately by 2 experienced gastrointestinal pathologists, then cases with discrepant grading were resolved by joint review of the slides in question. Initially, the grading of dysplasia was performed independently by 2 authors (M.Y. and J.L.). However, after the unfortunate and untimely death of Dr Lechago, the slides that he did not have the time to grade were graded by G.Y.L. Biopsies were graded as negative for dysplasia (ND), IND, low-grade dysplasia (LGD), HGD, and EAC. Biopsies with multifocal IND or LGD were graded as IND or LGDM, respectively. Multifocal involvement refers to the presence of dysplasia in biopsies from 2 or more levels in the esophagus (from 24 cm and 26 cm from the incisors, for example). Kaplan-Meier analysis was used to determine the rate of progression according to the initial dysplastic classification.
to the grade of dysplasia on initial biopsy, with progression to either HGD or EAC considered an end result (failure).

**RESULTS**

Examples of cases graded IND because of failure to document involvement of the mucosal surface by dysplasia present in the crypts are shown in Figure 1. In Figure 1, A, LGD is present in the crypts; the mucosal surface, however, is lined by nondysplastic columnar epithelium. In Figure 1, B, the crypts also show features of LGD, but the surface epithelium is denuded. Multiple deeper levels were cut from this biopsy, but still no surface epithelium was visualized. In Figure 1, C, a biopsy from a patient on long-term proton pump inhibitor treatment, the crypts, seen at higher magnification in Figure 1, D, also show changes consistent with LGD, but the surface epithelium is squamous; obviously, the dysplastic changes do not extend to the mucosal surface. Using the standard criteria for grading dysplasia, a confident diagnosis of dysplasia cannot be reached in any of these cases.

Of the 276 patients entered in the study, 193 (70%) had ND on initial biopsies, and of those, 3 (2%) progressed to HGD or EAC. Similarly, only 1 of 48 patients (2%) with IND progressed. By contrast, 1 of 7 patients (14%) with INDM, 2 of 21 patients (10%) with LGD, and 1 of 7 patients (14%) with LGDM progressed to HGD or EAC. The difference in progression between patients with initial diagnoses of ND and those diagnosed IND was not significant (Fisher exact test, \( P > .99 \)). Similarly, there were no differences in progression among patients with initial diagnoses of INDM, LGD, or LGDM. Kaplan-Meier analysis showed that patients with INDM, LGD, or LGDM on initial biopsy (group 1) were more likely to progress to HGD or EAC than those with ND or IND (group 2; log-rank test, \( P < .001 \); Wilcoxon \( P < .001 \) ) (Figure 2, A and B).

**COMMENT**

Using the established criteria for grading dysplasia in mucosal biopsies of the esophagus from patients with Barrett metaplasia, we could not reach a confident grading of dysplasia in 20% of the initial biopsies in this series. This is a significantly large proportion of the biopsies and, in clinical practice, probably represents patients with ND, IND, and, possibly, LGD. With the advent of modern...
treatments for Barrett metaplasia, with and without dysplasia, we are increasingly encountering such cases, especially following ablation therapy and treatment with proton pump inhibitors, where a significant number of biopsies have been reported with surface re-epithelialization with squamous epithelium.4-7

When we started our prospective study on Barrett metaplasia and encountered biopsies with dysplastic changes limited to the crypts, we suspected they may have malignant potential, despite the lack of surface involvement, so we decided to grade those biopsies as IND4 in our database, pending final analyses to determine the significance of the changes. Lomo and colleagues,8 using microdissection, immunohistochemical, molecular techniques, showed that what they called basal crypt dysplasia-like atypia was similar to conventional LGD and HGD rather than to nondysplastic Barrett epithelium. However, clinical follow-up was not available for the patients in that article, so the clinical significance remained unknown. Our findings show that most cases of crypt dysplasia without documented surface involvement, which we initially graded as IND, have a malignant progression potential similar to that of LGD, complementing the results of the study by Lomo and colleagues.8 These findings suggest that, at least for the time being, these cases should be regarded with caution and graded at least as IND, and not as ND, and as warranting closer follow-up.

The findings in this study, in spite of the large number of patients and its prospective nature, should be regarded as preliminary, and the decision to grade such cases as LGD or HGD, based on the severity of the dysplastic changes in the crypts, should await further studies. Currently, there is no clear guideline or consensus on how to grade these cases. The morphologic grading of dysplasia in Barrett metaplasia is known to have significant interobserver and intraobserver variability.9,10 We suspect that variability is even greater in the grading of this type of dysplasia, and we hope to see additional studies addressing this subject soon. Although we initially called these cases IND, we like the name crypt dysplasia with surface maturation coined by Lomo et al; unfortunately, many of the cases included in our IND grading had no columnar epithelium-lined mucosal surface. Future studies are needed to determine whether the biological differences between this type of dysplasia and LGD (eg, longer time to progression) are sufficient to warrant keeping them as separate entities. Such studies could help determine whether these cases should be given a universally accepted and simple name or be categorized with LGD or HGD, based on severity of the dysplastic changes in the crypts. Additional studies are needed to confirm our findings—that these cases have a malignant potential similar to conventional cases of dysplasia—and to determine whether the distinction in prognosis between single IND and multifocal IND can be supported.

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References

CORRECTION

In the article by Younes et al that appeared in the April 2011 issue (The Significance of “Indefinite for Dysplasia” Grading in Barrett Metaplasia. Arch Pathol Lab Med. 2011;135[4]:430–432), the y-axis text in Figure 2, A and B, is shown as “Percent progression.” This text should have read “Percent Without Progression.”