Lesions Indefinite for Intraepithelial Neoplasia and OLGA Staging for Gastric Atrophy

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Abstract

Gastric intraepithelial neoplasia (IEN; formerly dysplasia) is an advanced precancerous lesion. Lesions indefinite for IEN mimic the IEN phenotype but lack some morphologic attributes of IEN. Indefinite for IEN lesions may arise in native foveolae (atypical foveolar hyperproliferation [aFH]) or intestinalized glands (hyperproliferative intestinal metaplasia [HIM]). The clinicopathologic outcome of such lesions is debated. We retrospectively studied the clinicopathologic behavior of 129 consecutive indefinite for IEN lesions (HIM, 98; aFH, 31; median follow-up, 31 months) and correlated outcome with the extent and topography of mucosal atrophy (assessed by OLGA staging) at the initial endoscopy/biopsy. At enrollment, aFH never coexisted with severe/extensive atrophy (all cases were in low-risk OLGA stages [0-II]), whereas HIM associated with low- and high-risk OLGA stages (0-II, 73; III-IV, 25). At follow-up, IEN was never documented among cases enrolled as aFH, while follow-up endoscopy/biopsy documented 6 neoplastic intraepithelial lesions among 98 cases of HIM (6%, all high-risk OLGA stages at initial biopsy). OLGA staging can stratify indefinite for IEN lesions into different risk classes, potentially contributing to decisions for a patient-specific follow-up strategy.

Gastric cancer is the second cause of cancer-related death worldwide, and its incidence closely overlaps the prevalence of Helicobacter pylori.1-5 According to Correa and Houghton,2 intestinal-type gastric cancer is the final step in a sequence of genotypic disruptions and phenotypic alterations involving long-standing gastritis, gastric atrophy, neoplastic intraepithelial transformation (intraepithelial neoplasia [IEN]; formerly known as dysplasia), and invasive gastric cancer.2,4-13

The distinction on phenotypic and molecular grounds between neoplasia-mimicking hyperplastic lesions and IEN is controversial. When it is histologically difficult to distinguish atypical hyperplasia from IEN (low-grade), a provisional diagnostic label of indefinite for IEN has been suggested. From a clinical standpoint, such a diagnostic category means reconsidering cases after leaving aside any potential confounding agent responsible for regenerative changes (such as H pylori or nonsteroidal anti-inflammatory drugs).13,14

Two variants of indefinite for IEN lesions have been described: atypical foveolar hyperproliferation (aFH) and hyperproliferative intestinal metaplasia (HIM). The former affects native (IE, nonintestinalized) gastric glands, usually coexisting with erosions or ulcers; the latter consists of adenomatous-like foci of back-to-back intestinalized glands with a moderate to high mitotic rate.13,14 Little is known about the neoplastic risk associated with indefinite for IEN lesions. Published information suggests that they carry a low risk of progression, but no long-term follow-up studies are available; this incomplete picture results in inconsistent clinical-endoscopic follow-up strategies.15-22

Gastric mucosal atrophy is considered the “cancerization field” in which gastric cancer most frequently develops. The
OLGA system (Operative Link for Gastritis Assessment, developed by an international group of pathologists and gastroenterologists) for staging gastritis is based on assessing the extent and location of gastric atrophy, and it stratifies gastritis in different stages of gastric cancer risk (low risk, stages 0-II; high risk, stages III-IV).

This study concerns a series of consecutive patients initially diagnosed with indefinite for IEN lesions whose OLGA-staged gastritis was assessed retrospectively. The clinicopathologic outcome for lesions indefinite for IEN was ascertained from long-term follow-up and correlated with the gastritis stage established on the initial biopsy set.

**Image 1** Representative examples of lesions indefinite for intraepithelial neoplasia (IEN). A and B, Lesions indefinite for IEN (ie, dysplasia) in native foveolar epithelia (ie, foveolar hyperproliferation): abnormal architecture of glandular structures in a slightly raised lesion of the antral mucosa (A, H&E, ×20; B, H&E, ×40). There is no intestinal metaplasia, as confirmed by appropriate mucin staining (C, high iron diamine, ×40). The indefinite histologic pattern raises concern for architectural and cytologic abnormalities (B, arrows, typical and atypical mitoses). The lesion coexisted with Operative Link for Gastritis Assessment (OLGA) stage I gastritis, and no further lesions were documented at endoscopic follow-up 3 years later. D and E, Lesions indefinite for IEN (ie, dysplasia) in intestinalized glands (ie, hyperproliferative intestinal metaplasia): pseudoadenomatous growth pattern of intestinalized glands; the superficial metaplastic epithelia reveal no cytologic markers of IEN (D, H&E, ×20; E, H&E, ×40), and high iron diamine confirmed the presence of type II intestinal metaplasia (F, goblet cells secreting sialomucins and sulfomucins, ×40).
Materials and Methods

Cases

All cases of indefinite for IEN gastric lesions (including the equivalent definitions of “indefinite for dysplasia” and/or “indefinite for noninvasive neoplasia”) reported between January 2003 and March 2009 were retrieved from the archives of the Surgical Pathology & Cytopathology Unit, Department of Diagnostic Medical Sciences & Special Therapies, Padua University, Padua, Italy. During the study period, a total of 30,127 gastric biopsy sets were examined in the department.

Of the 268 consecutive cases of indefinite for IEN initially identified, 139 were not considered for the purposes of this study for 1 or more of the following reasons: (1) incomplete clinical or demographic details, 9 cases; (2) lost to follow-up or followed up for less than 12 months, 38 cases; (3) biopsy sampling protocol inconsistent with the OLGA staging system requirements, 63 cases; and (4) history of esophageal/gastric surgery and/or esophagogastroduodenal endoscopic resection or submucosal dissection, 27 cases.

Informed consent was obtained from the patients involved in all but 2 cases (which were also ruled out). The institute’s ethical regulations on research on human tissues were followed.

The study included 129 cases that met the inclusion criteria. (All patients were Caucasians living in the Veneto region.) All endoscopy procedures were performed at the same institution (Padua University Hospital, Padua) according to a previously reported biopsy sampling protocol. Patients’ latest biopsy sets were used to ascertain the status of the lesions consisted of low-grade (dysplasia-like) cell architecture and were termed indefinite for IEN (i.e., dysplasia). In native gastric glands, indefinite for IEN status had been assessed at the time of each patient’s enrollment (Table 1); all H pylori–positive cases were treated to eradicate the infection.

Histologic Assessment

Three pathologists (M.F., M.P., and M.R., who were unaware of all endoscopic and clinical information) with specific expertise in gastrointestinal diseases reassessed all histologic specimens, and reached consensus on the score for each pertinent histologic variable. OLGA staging was applied according to the current recommendations.

Briefly, the OLGA staging system ranks gastric cancer risk according to the extent and severity of gastric atrophy and includes 5 stages: 0, I, and II, or low-grade atrophy associated with a low risk of gastric cancer, and III and IV, or high-grade atrophy associated with a high risk of gastric cancer. The OLGA approach recommends that at least 5 biopsy samples be obtained from the following areas: (1) the greater and lesser curvatures of the distal antrum (2 samples); (2) the lesser curvature at the incisura angularis, where the earliest atrophic-metaplastic changes tend to occur (1 sample); and (3) the anterior and posterior walls of the proximal corpus (2 samples). Gastritis is staged by combining the extent of atrophy (scored histologically) with its topographic location (resulting from the mapping protocol).

Nonneoplastic and neoplastic lesions (documented at the end of the follow-up) were assessed according to internationally validated criteria. Gastric IEN lesions were further classified as low- or high-grade IEN.

The diagnostic label of indefinite for IEN lesions (as proposed by the International Padua Classification and the World Health Organization Blue Book) was applied to cases in which the pathologist was unable to state with certainty whether a lesion represented a nonneoplastic or a neoplastic intraepithelial transformation. Previous studies recommended applying specific immunohistochemical markers to make this distinction, but the differential diagnosis still relies on subjective criteria. In native gastric glands, indefinite for IEN lesions consist of low-grade (dysplasia-like) cell architecture anomalies, with foveolar elongation and an expanded proliferative compartment. Atypical mucus-depleted epithelial cells...
with hyperchromic nuclei, thickened nuclear membrane, and prominent nucleoli tend to decrease from the deepest mucosal portion toward the superficial epithelial layers, usually coexisting with high-grade inflammation. A similar situation may be seen in intestinalized gastric glands, in which a pseudoadenomatous growth coexists with elongated or pseudostratified nuclei showing an increased mitotic index. These 2 particular gastric variants of indefinite for IEN lesions are aFH and HIM.

**Statistical Analysis**

The strength of the association between OLGA stage and demographic and pathologic features of the cases was calculated by applying the Wilcoxon signed-rank test and the modified Kruskal-Wallis nonparametric test for trend (KW), as appropriate. Stata software (Stata, College Station, TX) was used for all calculations. A P value of less than .05 was considered significant.

**Results**

The demographic and pathologic features of the considered cases are summarized in Table 1. The male/female ratio was 1/1.15, and the mean age of the sample was 63.8 years (range, 32.7-81.3 years). The mean age of patients with OLGA stage III or IV (high-risk) gastritis was significantly higher than for patients with OLGA stage 0, I, or II (low-risk) gastritis (mean, 63.1 vs 66.6 years; P < .001; Kruskal-Wallis).

At initial biopsy, *H pylori* was detected histologically (by Giemsa staining) in 49 (38.0%) of 129 cases; at final biopsy, only 19 (14.7%) of 129 cases were still *H pylori*–positive.

Among the 129 indefinite for IEN cases, 98 (76.0%) were HIM, and 31 (24.0%) were aFH. Significant differences were found in the mean ages of patients with aFH and HIM (59.7 and 66.0 years, respectively; P < .001; Wilcoxon). None of the 31 aFH cases were in high-risk OLGA stages. The prevalence of cases of HIM among the low-risk OLGA stages was 73/104 and 25/25 among the high-risk OLGA stages.

At the end of the follow-up (median, 30.8 months; mean, 31.2 months; range, 12.0-70.8 months), none of the cases diagnosed as aFH at initial endoscopy showed neoplastic (intraepithelial or invasive) lesions. In the HIM cases, 6 cases of IEN (5 low-grade; 1 high-grade) emerged at the end of the follow-up (6/98 [6%]; mean follow-up, 32.3 months); all 6 patients had disease in high-risk OLGA stages (stage III) at the time of enrollment.

**Discussion**

The extent of gastric mucosal atrophy correlates with the degree of gastric cancer risk, and different gastritis staging systems have been proposed based on this rationale. In different epidemiologic settings, the OLGA staging system has been consistently shown to carry prognostically useful information on the gastric cancer risk associated with gastritis. This correlation should result in endoscopic follow-up being recommended for high-stage cases.

For this study, we reviewed all cases diagnosed as indefinite for IEN among 30,127 gastric biopsy sets obtained at the Padua University Hospital between 2003 and 2009. The prevalence of indefinite for IEN was 0.89%. The vast majority (98/129) of indefinite for IEN lesions arose in intestinalized epithelium.

This long-term follow-up study strongly suggests that even severely atypical nonintestinalized epithelium has no neoplastic potential. On this point, it is worth noting that our selection criteria ruled out any cases with a history of gastric surgery, which meant excluding patients in whom aFH has been reported most frequently (ie, patients with gastric stumps).

The clinicopathologic outcome of patients with indefinite for IEN gastritis significantly correlated with OLGA staging at enrollment, a finding consistent with the well-established association between gastric atrophy (as a cancerization field) and the clinicopathologic outcome of gastric IEN. It is impossible to state with certainty that the IEN detected in the considered patients at the end of the follow-up was missed at the time of their enrollment. In our opinion, at least, this would not affect the clinical impact of the results achieved; in the setting considered here, OLGA staging helps in the identification of patients who are likely to benefit from closer clinical attention (ie, stricter endoscopy/biopsy follow-up).

It has been claimed that the diagnostic category indefinite for IEN is somewhat overused and that it is more a matter of pathologists being “indefinite,” rather than the histologic lesions concerned. Riddell and Riddell et al made the point and this study likewise assumed that in the gastric mucosa (as in the setting of inflammatory bowel disease), the indefinite category underscores the difficulty of distinguishing nonneoplastic “atypia” from low-grade IEN; in this gray zone, the indefinite for IEN label responds to the need to keep following the patient and eventually results in a more definite diagnosis.

aFH affects the native foveolar gastric epithelium and usually stems from direct mucosal injuries. In the present study, aFH was significantly associated with the low-risk OLGA stages (mainly OLGA stage 0), and the lesion was never seen again after long-term endoscopic follow-up using an extensive, standardized biopsy sampling protocol.

By definition, HIM develops in intestinalized mucosa. Morphologic and immunohistochemical criteria have been used to help distinguish between neoplastic and nonneoplastic phenotypes arising in intestinalized glands. If “adenoma-like” intestinalized glands are identified, the following can be
considered valid discriminating criteria: (1) mature columnar cells on the surface layer, (2) an uneven distribution of cell architecture anomalies, (3) the absence of any proliferative activity (Ki-67 expression) in the superficial nuclei, and (4) bc12 restricted to the nuclei of the proliferative compartment.\textsuperscript{15} In a number of cases, however, even pathologists with specific expertise in gastrointestinal tract diseases may be in doubt, and this situation negatively affects patient management.\textsuperscript{15,19,20}

In the present series of cases indefinite for IEN, only cases involving HIM coexisting with high-risk OLGA stages correlated with the subsequent detection of IEN. These results further support the clinical impact of OLGA staging for the purposes of patient-tailed clinical and endoscopic follow-up.

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References


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