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Histologic Subtyping of Gastric Intestinal Metaplasia: Overview and Considerations for Clinical Practice

Shailja C. Shah¹, Andrew J. Gawron^{2,3}, Reem Mustafa⁴, M. Blanca Piazuelo¹

¹Division of Gastroenterology, Hepatology, and Nutrition, Vanderbilt University Medical Center, Nashville, Tennessee

²Salt Lake City Specialty Care Center of Innovation and Gastroenterology Section, VA Salt Lake City Health Care System, Salt Lake City, Utah

³Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City, Utah

⁴Division of Nephrology and Hypertension, University of Kansas Medical Center, Kansas City, Kansas

Gastric cancer remains the third leading cause of cancer-related mortality and the fifth most common cancer worldwide, responsible for an estimated 1 million new cases and more than 780,000 deaths in 2018 alone.¹ Gastric adenocarcinoma is the most common form of gastric cancer, of which there are 2 histologic subtypes: intestinal-type and diffuse-type. Intestinal-type gastric adenocarcinoma is the final stage of the chronic inflammation to dysplasia-carcinoma sequence, known as the Correa cascade, with *Helicobacter pylori*-induced gastritis as the most common initial trigger.^{2–4} Atrophic gastritis and gastric intestinal metaplasia (GIM) are established pre-neoplastic lesions for intestinal-type gastric adenocarcinoma.^{2,5} As reported in the American Gastroenterological Association Technical Review informing the guidelines for GIM surveillance, the pooled incidence rate for the progression of GIM in the absence of dysplasia to gastric cancer was 12.4 (95% confidence interval, 10.7–14.3) per 10,000 person-years; this was based on 10 cohort studies that included nearly 26,000 patients with non-dysplastic GIM.^{6,7} Currently, we are neither able to predict who will develop pre-neoplasia nor who will subsequently have neoplastic progression. As such, focused efforts on identifying and further defining predictive determinants are needed immediately.

That said, the slow, stepwise progression of gastric pre-neoplasia to neoplasia does at least allow for targeted surveillance and the opportunity for early detection and resection of neoplastic lesions. Although there are no established predictive biomarkers routinely used clinically, histologic subtyping of GIM into incomplete and complete types is one biomarker for further stratifying this already at-risk group. Based on a meta-analysis of 7 studies that included 2014 individuals with GIM and no concomitant neoplasia (929 with incomplete

Address correspondence to: Shailja C. Shah, MD, MPH, Division of Gastroenterology, Hepatology, and Nutrition, Vanderbilt University Medical Center, 2215 Garland Avenue, Medical Research Building IV, 1030-C, Nashville, Tennessee 37212. shailja.c.shah@vumc.org; fax: 352-251-0126.

GIM, 1112 with complete GIM) who developed 74 gastric cancers during 3–12.8 years of follow-up, incomplete GIM was associated with a 3.33-fold (95% confidence interval, 1.96–5.64) higher risk of incident gastric cancer compared to individuals with complete GIM.^{6,7}

Despite data demonstrating a differential risk of gastric cancer and pathologists' ability to discriminate GIM histologic subtypes using routine stains, histologic subtyping remains vastly underutilized, particularly in the United States. The underutilization is most certainly multifactorial, with a sizeable contribution from the lack of awareness of the clinical utility and the heterogeneous and relatively limited body of literature supporting the prognostic value of GIM subtyping.^{6,7} The objective of this brief report, which is tailored for clinicians, is to: (1) provide a foundational background of histologic subtyping of GIM; (2) highlight considerations for incorporating subtyping into routine clinical practice; and (3) delineate potential barriers and their solutions to facilitate inclusion of GIM subtyping as one “best-practice” component of endoscopic GIM surveillance.

Histologic Subtyping of Gastric Intestinal Metaplasia

GIM is the replacement of normal gastric epithelium with epithelium resembling the intestine as an adaptive response to chronic injury, such as chronic inflammation due to *Helicobacter pylori* infection. As early as the 1970s, investigators not only recognized that there were variants of GIM that differed based on morphology and the enzymes and mucins secreted, but they also demonstrated that some of these variants were more strongly associated with intestinal-type gastric adenocarcinoma.^{8–13}

Assuming adequate tissue processing conditions, most cases of GIM can be classified into complete and incomplete types on H&E-stained sections (Figure 1). The complete type resembles small intestinal epithelium and is characterized by well-developed goblet cells interspersed between columnar absorptive cells, with a characteristic-appearing brush border. Paneth cells are frequently observed at the base of the crypts.² The incomplete type displays goblet cells of variable size and intervening columnar mucin-secreting cells without a brush border. Table 1 details other distinguishing features. Mixed characteristics of complete and incomplete types are sometimes observed, even in a single biopsy. These cases may be classified as “mixed,” “mixed, predominantly complete,” or “mixed, predominantly incomplete”^{14,15} acknowledging some level of subjectivity on the part of the reviewing pathologist.

Another classification system suggested by pathologists Filipe and Jass was based on the type of mucins secreted.^{16,17} This system recognizes 3 types of GIM and requires the special stains Alcian blue pH 2.5 (AB)/periodic acid-Schiff (PAS) and high iron diamine (HID)/AB for discrimination between types I, II, and III.^{18,19} AB/PAS differentiates neutral mucins, which stain magenta and are normally present in the stomach, from acid mucins, which stain blue and are normally present in intestinal mucosa; acid mucins are not typically identified in gastric mucosa except in very small quantities in mucous neck cells in the oxyntic mucosa. The HID/AB stain, in turn, differentiates acid mucins into sialomucins, which stain blue and are present in the small intestine and colon, and sulphomucins, which stain brown and predominate in the colon. Type I corresponds to complete GIM and types II and III are

subclassifications of incomplete GIM. Characteristics of each type are included in Table 1 and Figure 2. The AB/PAS technique is performed frequently in histopathology laboratories and thus is a useful adjunct to H&E for differentiating complete vs incomplete types. The HID/AB technique has been used extensively in the past in cross-sectional and longitudinal studies, showing an association between GIM type III and gastric cancer.^{17,20–22} However, this stain is technically challenging and involves potentially toxic diamine reagents, which has led to its discontinuation in many laboratories worldwide. Distinguishing between the incomplete types II and III using HID/AB might have clinical value based on limited data, but currently is reserved for research for the stated reasons.

Considerations for Clinical Practice

Ultimately, there is an unmet need for standardization of endoscopic surveillance protocols for gastric pre-neoplasia. In addition to careful examination of the adequately cleaned and insufflated gastric mucosa, best practice should, at a minimum, include: (1) multiple nontargeted biopsies from the greater and lesser curvatures of the antrum and the fundus/corpus, separated into 2 containers labeled “antrum/incisura” and “corpus” in order to define the extent of preneoplastic involvement; (2) targeted biopsies of any concerning lesions; and (3) histologic subtyping as complete or incomplete- or mixed-type GIM. Furthermore, promoting a standardized, efficient protocol that includes histologic subtyping will generate rich data sources and catalyze clinical and translational research efforts in this area, which are direly needed.

Based on limited epidemiologic data, the prevalence of complete vs incomplete GIM varies across studies, with higher prevalence of complete GIM in specimens with benign conditions, in populations with low gastric cancer risk, and in younger individuals.^{3–5,17,22,23} The body of literature comparing the clinical outcomes of incomplete- vs complete-type GIM consistently reports a higher risk of gastric cancer among individuals with incomplete GIM relative to the baseline elevated risk still associated with the complete type.^{6,7} This observation provides at least indirect evidence for the prognostic value of histologic subtyping. It is worth noting that studies have shown a significant association between the prevalence of incomplete-type GIM and GIM extent, which is reflected in increasing stages of the Operative Link on Gastritis Assessment (OLGA) and Operative Link on Gastritis/Intestinal Metaplasia Assessment (OLGIM) staging systems.^{23,24} This evidence supports the argument that incomplete types of GIM carry a prognosis similar to advanced OLGA/OLGIM stages (stages III and IV), further underscoring the clinical utility of histologic subtyping. Although not commonly used in the United States, the OLGA/OLGIM staging systems are routinely used in clinical practice in some other countries, and are a major component of the European Society of Gastrointestinal Endoscopy (ESGE) guidelines for the management and endoscopic surveillance of gastric pre-neoplastic lesions.²⁵ Both systems evaluate the extension of atrophic changes of the gastric mucosa, recognizing that the risk of progression to gastric cancer increases as the atrophic lesions become more extensive. The OLGA system includes the assessment of both metaplastic (GIM and pseudopyloric metaplasia) and non-metaplastic atrophy.²⁶ The diagnosis of non-metaplastic atrophy is difficult because it: (1) requires the observation of the complete thickness of the mucosa, with the mucosa properly oriented perpendicular to the sectioning plane during

paraffin embedding; and (2) has demonstrated high inter-observer variability.^{27,28} The OLGIM staging system was then proposed because histologic scoring of GIM alone is more consistent than that of the aggregate scoring of the whole spectrum of atrophy variants.²⁸ In addition, observation of the complete thickness of the mucosa is not required for the diagnosis of GIM. As a caveat, both OLGA and OLGIM systems require a 5-biopsy protocol of the antrum, incisura, and corpus, which is not routine practice globally, although we acknowledge the need to standardize endoscopic protocols in the United States. Consistent with the current AGA guidelines, 29 recent ESGE guidelines also recognize the prognostic value of histologic subtyping of GIM into incomplete or complete, which is in contrast to the earlier 2012 iteration of the ESGE guidelines recommending against GIM subtyping.^{25,30}

With the recommendation for histologic subtyping, one key consideration is that while the identification of incomplete GIM is useful for its presence as a marker of an even higher risk of incident gastric cancer compared to complete GIM, its absence is less useful for clinical risk stratification. 20 Indeed, its absence could relate to sampling error, given the patchy nature of GIM, but it might also represent true biological absence in some individuals who remain at heightened risk for gastric neoplasia. Thus, the absence of incomplete GIM in people with other risk factors cannot be used for lowering the degree of surveillance but, based on current evidence, its presence is sufficient indication for surveillance.^{6,29} These data highlight the need for more research investigating etiologies for the observed discrepancies. In the current era focused on advancing precision medicine, it is essential that the gastroenterology field prioritize the identification of histologic or molecular markers that might prove to be clinically useful adjuncts for precisely identifying individuals with pre-neoplastic lesions who are at highest risk for neoplastic progression and who would benefit from surveillance and intervention. As an example, recent molecular profiling of GIM from cancer-free individuals identified determinants (shortened telomeres and chromosomal alterations) associated with subsequent dysplasia or cancer.³¹ These same authors also compared the molecular profiles of GIM histologic subtypes. They detected somatic copy number aberrations in 13% of incomplete GIM vs none in complete GIM or normal gastric tissues, and reported a trend for incomplete GIM to have shorter telomeres; however, they did not identify statistically significant differences in mutational burden, *H pylori* density, or DNA methylation levels between the subtypes, which might relate to insufficient power for these secondary analyses, among other reasons.³¹ Until more precise tools become available, the presence of incomplete GIM is a clinically useful marker of increased risk for gastric cancer. Other recognized risk factors are certain ethnic/racial backgrounds.^{6,7,32} Perhaps the case in which subtyping is most clinically valuable is in someone identified as having localized antral GIM and no other risk factors for gastric cancer, but histologic subtyping shows incomplete GIM. Based on the histologic subtype, this individual might benefit from endoscopic surveillance.

Barriers to Clinical Implementation

There is limited awareness on the part of gastroenterologists and pathologists of the potential prognostic value of histologic subtyping of GIM, which is conceivably driven and propagated by limited robust evidence-based data. The current literature, while generally consistent for the overall conclusion that incomplete GIM is associated with higher gastric

cancer risk, is heterogeneous with respect to study design and populations, baseline risk of gastric cancer, time period, endoscopic and biopsy protocol, quality of outcome assessment, variable follow-up, and variable efforts in adjusting for confounders, among other considerations. Practice pattern variability for GIM management is one consequence of the heterogeneous evidence base.^{33,34} This is perhaps compounded by the misperception that histologic subtyping is time-consuming, costly, or that the techniques or interpretation require additional expertise above that of an appropriately trained gastrointestinal pathologist. Instead, histologic subtyping adds minimal time and negligible or minimal cost—AB/PAS specialized stain, if even needed, costs approximately \$20. In contrast to non-metaplastic gastric atrophy, inter-observer agreement for GIM diagnosis is strong, ranging from 85% to 90% in most studies.^{27,28} Furthermore, the level of inter-observer agreement for GIM histologic subtype is likely similarly high,¹⁵ because the histologic features and interpretation of the respective stains are not subtle in their differentiating characteristics for complete and incomplete GIM. In support, one study reported 91% inter-observer agreement for GIM histologic subtypes.¹⁵

Overcoming barriers to GIM subtyping will require: (1) close collaboration among pathologists, gastroenterologists, and their governing societies; (2) promoting the clinical prognostic value and importance of GIM subtyping based on current data; (3) achieving consensus on endoscopic and histopathologic protocols and definitions (eg, establishing threshold percentage cutoffs for what qualifies as mixed type, predominantly complete vs incomplete, which is currently mostly arbitrary¹⁵); and (4) collaborative research efforts to generate high-quality evidence profiles so that our gastric neoplasia screening and surveillance efforts can continue to be refined. With the support of the respective gastroenterology and pathology societies, some modalities to facilitate these efforts include online training modules, publication and distribution of standardized protocols and metrics, educational sessions at national and regional conferences, and focused symposiums.

Conclusions

Although we acknowledge the heterogeneous body of literature related to GIM histologic subtyping and clinical outcomes, the data consistently support differential risks of intestinal-type gastric adenocarcinoma according to GIM histologic subtype. When the potential prognostic value and the opportunity to generate a more robust body of clinical and epidemiologic evidence are considered alongside the minimal cost and invested effort for pathologists, the recommendation for routine subtyping in cases of GIM is palatable. With time, we will be able to iteratively refine our clinical management of GIM based on evidence that is more substantial, less heterogeneous, and more applicable to the contemporary, diverse United States population. As stated, it is important for clinicians to recognize that the absence of incomplete GIM or the presence of only complete GIM in the specimens examined should not be used as grounds to downgrade someone who might otherwise benefit from surveillance.^{6,7,29} Moreover, while there are established endoscopic protocols and quality metrics for colorectal and esophageal neoplasia screening and surveillance in the United States, this is not yet the case for gastric neoplasia. There is an immediate need to establish and disseminate best-practice endoscopic and histologic protocols for gastric pre-neoplasia, as well as rubrics for GIM histologic subtyping, to ensure that practices are

consistent among individuals for whom shared decision-making favors surveillance. Collectively, this would be a critical step in advancing gastric cancer prevention and early detection efforts in the United States.

Abbreviations used in this paper:

AB	Alcian blue pH 2.5
ESGE	European Society of Gastrointestinal Endoscopy
GIM	gastric intestinal metaplasia
HID	high iron diamine
OLGA	Operative Link on Gastritis Assessment and Gastritis/Intestinal Metaplasia Assessment
OLGIM	Operative Link on Gastritis/Intestinal Metaplasia Assessment
PAS	periodic acid-Schiff.

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Figure 1.

(A) GIM, complete type, with straight crypt architecture, well-developed goblet cells, eosinophilic enterocytes with brush border (*arrow*), and Paneth cells at the crypt base (*arrowheads*). (B) GIM, incomplete type, showing more irregular architecture, greater variation in goblet cell size, and presence of intermediate columnar cells in various stages of differentiation containing intracytoplasmic mucin (*arrowhead*). H&E, $\times 200$.

Figure 2.

GIM subtypes by Jass and Filipe classification. With the AB/PAS technique, GIM type I shows a mixture of neutral (*magenta*) and acid (*blue*) mucins in goblet cells (yielding a *violet color*); in this image, a few normal gastric glands are observed (*magenta; asterisks*). With HID/AB staining, GIM type I shows only sialomucins (*blue*) in goblet cells. GIM types II and III with AB/PAS staining present a mixture of neutral (*magenta*) and acid (*blue*) mucins in goblet and columnar cells. With HID/AB, GIM type II shows only sialomucins

(*blue*) in goblet and columnar cells, and GIM type III presents predominantly sulfomucins (*small brown mucin droplets*) in columnar cells. AB/PAS, HID/AB, ×200.

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Table 1.

Features of Gastric Intestinal Metaplasia According to Histologic Subtype

Histologic subtype	Morphology and cell types (H&E staining)				Mucin types (special stains)		Associated cancer risk ^a
	Crypt architecture	Goblet cells	Columnar cells	Paneth cells	AB/PAS stain pink: neutral mucins blue: acid mucins	HID/AB stain blue: sialomucins brown: sulfomucins	
Complete, Type I	Organized, straight crypts	Round, well developed	Absorptive, with well-defined brush border	Often present at the crypt base	Acid mucins in goblet cells. No mucins in columnar cells.	Sialomucins in goblet cells. No mucins in columnar cells.
Incomplete, Type II	Variable degree of architectural distortion, with branched crypts at the base more commonly observed in type III.	Variable sizes	Mucous, "intermediate" cells, with mucin droplets of variable size Few or absent absorptive cells	Occasional	Acid mucins in goblet cells. Acid and/or neutral mucins in columnar cells.	Sialomucins in goblet and columnar cells. Sulfomucins in goblet cells or absent.	
Incomplete, Type III						Sulfomucins predominate in columnar cells. Goblet cells may contain sialo- or sulfomucins.	

NOTE. If mixed type, there will be a combination of complete and incomplete features.

^aincomplete, type III is associated with the highest risk of gastric cancer (incomplete, type III > incomplete, type II >> complete, type I).