Modern Pathology (2015) 28, S1–S6

Current issues in Barrett's esophagus and Barrett's-related dysplasia

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Surgical pathologists frequently encounter biopsies in patients with Barrett's esophagus (BE), defined as replacement of the normal stratified squamous epithelium of the distal esophagus by metaplastic columnar epithelium containing goblet cells. Thus, one of the primary roles of the pathologist is to definitively identify goblet cells, best done on routine stained sections. It has recently been questioned as to whether goblet cells should be absolutely necessary to render a diagnosis of BE, given immunohistochemical and flow cytometric similarities between columnar-lined esophagus with and without goblet cells. Once a diagnosis of BE is rendered, the pathologist must state, using a simple classification, whether the biopsy is negative for dysplasia or shows dysplasia (low-grade dysplasia or high-grade dysplasia). However, there are a number of known pitfalls in distinguishing dysplasia from reactive epithelium, and it can be similarly difficult to distinguish low-grade dysplasia from high-grade dysplasia. In addition, there are some cases in which the distinction of high-grade dysplasia from intramucosal adenocarcinoma can be challenging. All of these issues are summarized in this paper.
Modern Pathology (2015) **28,** S1–S6; doi:10.1038/modpathol.2014.125

Biopsies of the distal esophagus and gastroesophageal junction (GEJ) are among the most commonly encountered specimens seen by general surgical pathologists and gastrointestinal pathologists. Most often, the pathologist is asked to determine whether Barrett's esophagus (BE) or BE-related dysplasia is present, given the known association between BE and the development of esophageal adenocarcinoma.[1,2]

This discussion will focus on three major issues. First, there has been recent interest in reassessing the current definition of BE. Although not widely appreciated, this definition varies in different parts of the world, and given the attendant implications of this diagnosis on endoscopic surveillance, the impact of the quality of life and even insurances rates, it is critically important to reassess this definition. Second, it is not uncommon to counter a biopsy labeled 'GEJ, rule out Barrett's esophagus' and, as such, it becomes important to understand whether intestinal metaplasia (IM) in biopsies procured from this location necessarily imply a diagnosis of BE. Finally, this discussion will focus on the difficulties in recognizing BE-related dysplasia and touch upon the concept of crypt dysplasia.

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Received 5 May 2014; accepted 16 May 2014

The evolving definition of BE

The recent guidelines provided by the American Gastroenterological Association and American College of Gastroenterology define BE as a condition in which the normal stratified squamous epithelium of the distal esophagus is replaced by metaplastic columnar epithelium containing morphologic evidence of IM (goblet cells).[3,4] Thus, using this definition, the role of the pathologist is very clear—to identify the presence or absence of IM (Figure 1). This itself can, on occasion, be difficult, as columnar cells may be distended with neutral mucin, thereby acquiring a shape that may mimic a true goblet cell (so-called pseudogoblet cells). However, as these distended cells may also contain some acidic mucins (which are characteristic of true goblet cells) and, therefore, can stain with Alcian blue, the use of histochemical stains is discouraged. In the end, recognition of unequivocal goblet cells filled with blue-gray-tinged mucin on routine hematoxylin and eosin-stained sections is what is required for this diagnosis.

It should be acknowledged that IM is not required for a diagnosis of BE in all parts of the world. For example, both the UK and parts of Asia only require the presence of columnar-lined esophagus (CLE) identified on endoscopy, without the necessity of identifying goblet cells.[5–7] As stated by Riddell and Odze,[8] 'the basis for this definition (requirement of IM) rests mainly on the fact that

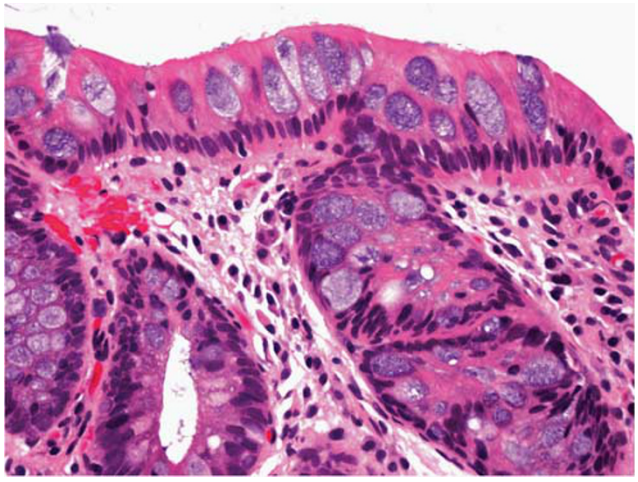

Figure 1 Barrett's esophagus is characterized by the presence of unequivocal intestinal metaplasia (goblet cells), best seen on routine stained sections. The goblet cells show cytoplasmic distention filled by mucin with a blue-gray tinge on hematoxylin and eosin-stained sections.

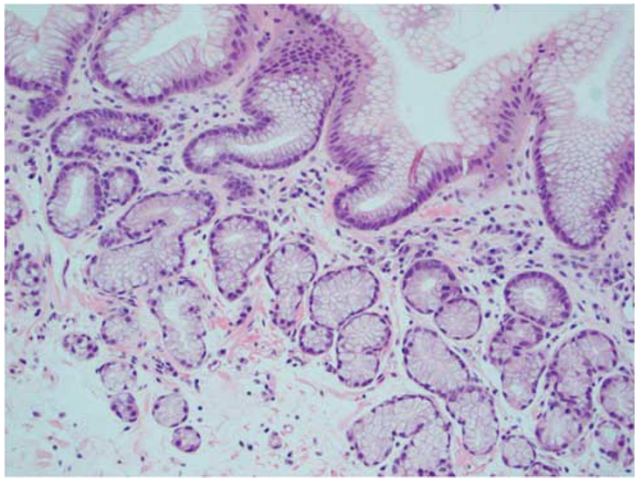

Figure 2 Not uncommonly, biopsies of the distal esophagus show metaplastic columnar epithelium with mucus glands resembling the native gastric cardia. Goblet cells are not identified in this biopsy.

most adenocarcinomas of the esophagus develop in BE mucosa with IM in retrospective cohort studies.' For example, US and German studies found IM in mucosa adjacent to esophageal adenocarcinomas in 79% and 85% of cases, respectively.[9,10] Given this close association, the definition of BE in the United States has required the identification of IM. This would, therefore, imply that nongoblet cell-containing CLE does not impart a similar risk of progression to esophageal adenocarcinoma as does intestinalized mucosa (Figure 2).

There are, however, several lines of evidence to suggest that nongoblet cell-containing CLE may not be completely benign (as previously believed). Immunohistochemical studies have found that nongoblet cell-containing CLE shows phenotypic similarities to intestinalized mucosa, including the expression of CDX2, DAS1, villin and HePAR1.[11–14] Even more compelling are the studies showing DNA content abnormalities in nongoblet cell-containing CLE, which are similar to those typically found in esophageal intestinalized mucosa.[11,15,16]

Several recent studies have found a similar risk of progression of high-grade dysplasia or adenocarcinoma in patients with and without goblet cells in CLE. Gatenby *et al*[17] found no significant difference in rates of progression to low-grade dysplasia, high-grade dysplasia or adenocarcinoma in patients with (19.8%) and without (13.2%) goblet cells in their index biopsies. However, it could be reasonably argued that sampling error could account for the apparent risk of progression in patients with non-goblet cell-containing CLE. In contrast, in a study of a large group of patients who underwent extensive sampling of their CLE, Chandrasoma *et al*[18] found no risk of progression for those patients with nongoblet cell-containing CLE.

What are the implications of changing the diagnostic criteria for BE to require only the presence of CLE and not goblet cells? A recent study from the University of Chicago found a 150-fold increased prevalence of BE if goblet cells are not required for this diagnosis.[19] Balasubramanian *et al*,[20] studied 1058 patients with gastroesophageal reflux disease and found a prevalence of CLE on index endoscopy of 23.3%, whereas CLE with IM was found in only 14.1%. On multivariate analysis, heartburn duration for >5 years, Caucasian race and the presence of a hiatal hernia were found to be independent predictors for CLE, and CLE length was significantly associated with the presence of IM. CLE lengths <1 cm, 1–3 cm and ≥ 3 cm were associated with a prevalence of IM in 29, 58.7 and 87.8% of patients with CLE, respectively. The authors concluded that this expanded definition of BE (that is, not requiring the presence of goblet cells) would have enormous ramifications on healthcare resources in the USA.

IM of the GEJ

Pathologists are often faced with the difficulty of determining whether IM in a biopsy procured from the GEJ represents BE. Although beyond the scope of this discussion, it is clear that IM at this location can be related to multiple factors, including gastroesophageal reflux disease, *Helicobacter pylori* infection and possibly simply as a manifestation of aging ('wear and tear') of the GEJ. Etiology aside, if the risk of progression to adenocarcinoma was the same for the IM on the esophageal side of the junction as the cardia side, then the exact location of the IM would be a moot point. Although a number of published studies have obscured this evaluation by virtue of a lack of details of the anatomic and biopsy landmarks

used in these studies, the meticulous studies that have been published suggest a significant increased risk of progression to high-grade dysplasia or adenocarcinoma for IM on the esophageal side of this junction when compared with the cardia side.[21] Given this apparent difference in the risk of progression, it would be important for the pathologist to attempt to determine the exact location of the IM in biopsies procured from the GEJ. Histochemical stains have not been found to be useful in this regard. Although innumerable studies have evaluated the utility of immunohistochemical markers in this setting (including CK7/20, MUC1, MUC6, DAS1, CDX2 and HepPAR1, among others), most of them have been found to lack sufficient sensitivity and specificity to be used as a clinical test.[22] In the end, careful morphologic evaluation seems to be the most useful way to determine the origin of IM near the GEJ. Srivistava *et al*[23] found IM subjacent to the squamous epithelium, IM confined to the superficial mucosa and the presence of IM adjacent to esophageal glands or ducts to be helpful indicators of esophageal origin. From a practical standpoint, it seems reasonable to diagnose the biopsy described above as 'intestinal metaplasia of the GEJ,' with a comment on the presence or absence of the aforementioned histologic features that are indicative of esophageal origin. Ultimately, it is the gastroenterologist with knowledge of the clinical symptoms and endoscopic appearance who is responsible for determining whether the IM is indicative of BE, thereby necessitating endoscopic surveillance.

BE-related dysplasia

In our GI pathology consultation practice, by far the most frequent consult is the presence (and degree) or absence of dysplasia in patients with BE. Although dysplasia can be rather difficult to define, the IBD-Morphology Study Group defined dysplasia as the presence of neoplastic epithelium that is confined within the basement membrane of the gland within which it arises (intraepithelial neoplasia).[24] The type of dysplasia that most often arises in BE does not entirely resemble a colonic adenoma (unlike that seen in IBD-related dysplasia, which very commonly resembles a sporadic adenoma). Very often, cytologic atypia, characterized by nuclear hyperchromasia and enlargement, arises in glands that retain their normal configuration and often lack nuclear stratification, as is seen in adenoma-like dysplasia. BE-related dysplasia can be classified as either low-grade or high-grade on the basis of the degree of cytologic atypia present. As such, all biopsies with BE should be diagnosed using the following classification scheme: negative for dysplasia, positive for dysplasia, either low-grade or high-grade or epithelial alterations indefinite for dysplasia.

Low-grade dysplasia typically shows preservation of the crypt architecture, and the cytologic atypia is generally limited to the basal half of the dysplastic crypts (Figure 3). The nuclei show variable hyperchromasia with overlapping of cell borders, some nuclear crowding and irregular nuclear contours. Occasionally, one encounters dystrophic goblet cells. Typically, the goblet cell numbers are reduced when compared with the surrounding BE, and, in fact, there are cases of BE-related dysplasia that lack identifiable goblet cells. High-grade dysplasia shows more severe cytologic and architectural changes than are present in low-grade dysplasia (Figure 4). Architecturally, there tends to be more glandular distortion, often with the development of a villiform surface configuration and/or branched or cribriform glands. From a cytologic standpoint, the nuclei show a greater degree of pleomorphism and hyperchromasia than is seen in low-grade dysplasia, and there may be nuclear stratification to the crypt luminal surface. In some cases, the distinction of regenerative epithelial changes from true dysplasia, particularly in a background of ulceration or active inflammation, can be difficult, if not impossible. A diagnosis of indefinite for dysplasia is entirely appropriate if the pathologist is unsure as to whether the epithelial alterations are regenerative or dysplastic in nature (Figure 5). Because BE is itself a metaplastic epithelium, there is always a 'baseline atypia' present at the base of the mucosa, which does not involve the surface epithelium (Figure 6). Thus, the low-magnification appearance of the mucosa is extremely important, as cytologic alterations at the base of the mucosa are often within the confines of this 'baseline atypia.' As a general rule, cytologic alterations on the surface epithelium are extremely useful in making a definitive diagnosis of dysplasia. Certainly, there are exceptions in which one does not definitively identify dysplasia

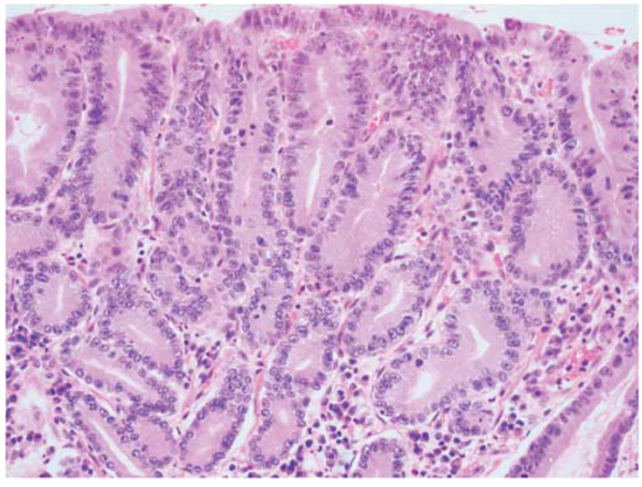

Figure 3 Barrett's esophagus with low-grade dysplasia. Cytologic atypia extends to the surface, but the degree of cytologic atypia is less than that seen in Figure 4.

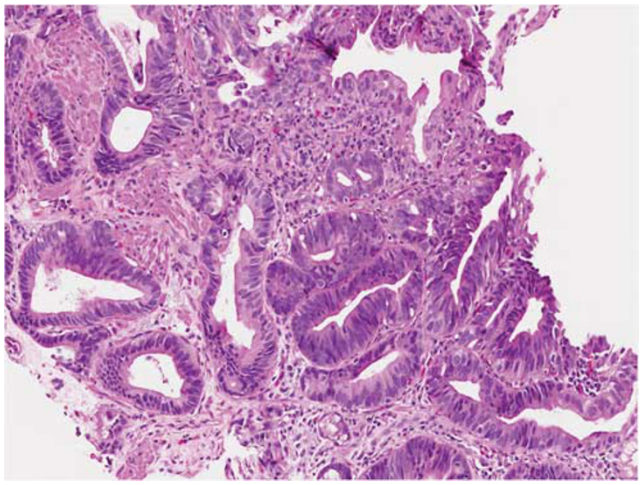

Figure 4 Barrett's esophagus with high-grade dysplasia characterized by marked cytologic atypia, as well as architectural complexity with rare cribriform glands.

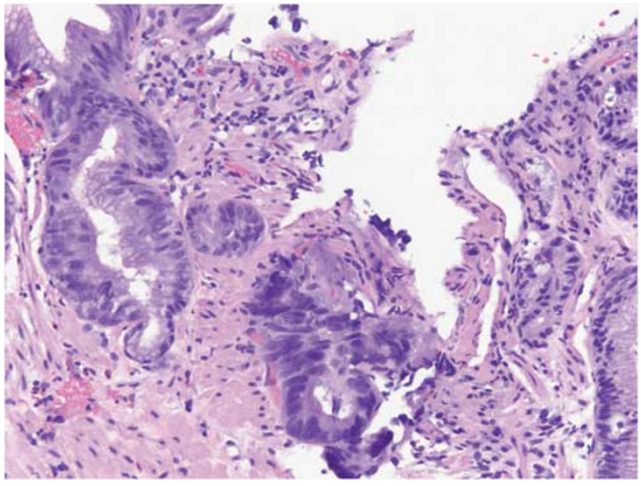

Figure 5 Barrett's esophagus with cytologic alterations considered indefinite for dysplasia. Although there is glandular atypia present, there is an absence of definitive atypia on the surface epithelium.

on the surface epithelium but in which the cytologic alterations in the glands still warrant a diagnosis of dysplasia, often high-grade dysplasia. However, it is important to note the emerging concept of crypt dysplasia, as described by Lomo *et al*.[25] These authors suggest that dysplasia begins in the crypt bases and progresses to involve the full length of the crypts and surface epithelium, and thus crypt dysplasia can be recognized before surface involvement (in the face of surface maturation). Morphologically, crypt dysplasia has all the features of traditional low-grade dysplasia but is limited to the crypt bases and is devoid of active inflammation, which might explain the cytologic alterations. In the study of Lomo *et al*,[26] 47% of cases of crypt dysplasia were associated with full-thickness dysplasia elsewhere, and molecular studies have found similar alterations in crypt dysplasia when compared with traditional dysplasia, which are distinct from those found in nondysplastic epithelium.

Although distinguishing regenerative epithelial changes from dysplasia can be extremely difficult, dysplastic epithelium tends to show variable nuclear hyperchromasia and nuclear pleomorphism. In other words, some cells look different from their neighbors, with some showing nuclear hyperchromasia and pleomorphism when compared with the surrounding cells within the same crypt. In contrast, nuclear hyperchromasia and pleomorphism tend to be less severe and more uniform in the regenerative epithelium, with cells often resembling their neighbors within the same crypt or in adjacent crypts. Dysplastic cells also tend to have a higher nuclear-to-cytoplasmic ratio, as well as irregular nuclear contours. Although regenerative epithelial cells may have similar nuclear size to those seen in dysplasia, there is a commensurate increase in cytoplasm such that the nuclear-to-cytoplasmic ratio is normal or at most only mildly increased. In addition, regenerative epithelial cells tend to have round and regular nuclear contours.

Interestingly, more of our consults in recent years have been focused on separating BE-related high-grade dysplasia from 'early adenocarcinoma' (Figure 7). As treatment options broaden for patients with BE-related HGD or intramucosal/superficial submucosal adenocarcinoma, the distinction of these two diagnoses may have clinical significance. In fact, some authors have proposed that esophagectomy be reserved only for those patients in whom cancer can be documented by a biopsy,[27] but these recommendations rest on the assumption that pathologists can reliably distinguish high-grade dysplasia from intramucosal adenocarcinoma in biopsy specimens. Given the fact that lymphatic channels are present within the esophageal mucosa, there is still a small risk of lymph node metastasis, even in patients with intramucosal adenocarcinoma.

Recently, several studies have focused on the distinction of these diagnoses in biopsy specimens. Downs-Kelly *et al*[28] found only moderate agreement in distinguishing among these diagnoses, and, as such, the authors called into question management decisions based upon the distinction of these diagnostic categories in pretreatment biopsy specimens. Zhu *et al*[29] attempted to ascertain the prevalence of carcinoma in esophagi resected for high-grade dysplasia or high-grade dysplasia 'suspicious for carcinoma' diagnoses in pretreatment biopsy specimens. On the basis of the original diagnoses, adenocarcinoma was found in 17% of cases diagnosed as high-grade dysplasia and 74% of cases diagnosed as high-grade dysplasia with changes suspicious for carcinoma. These authors then attempted to more precisely define these categories, with the latter category including those

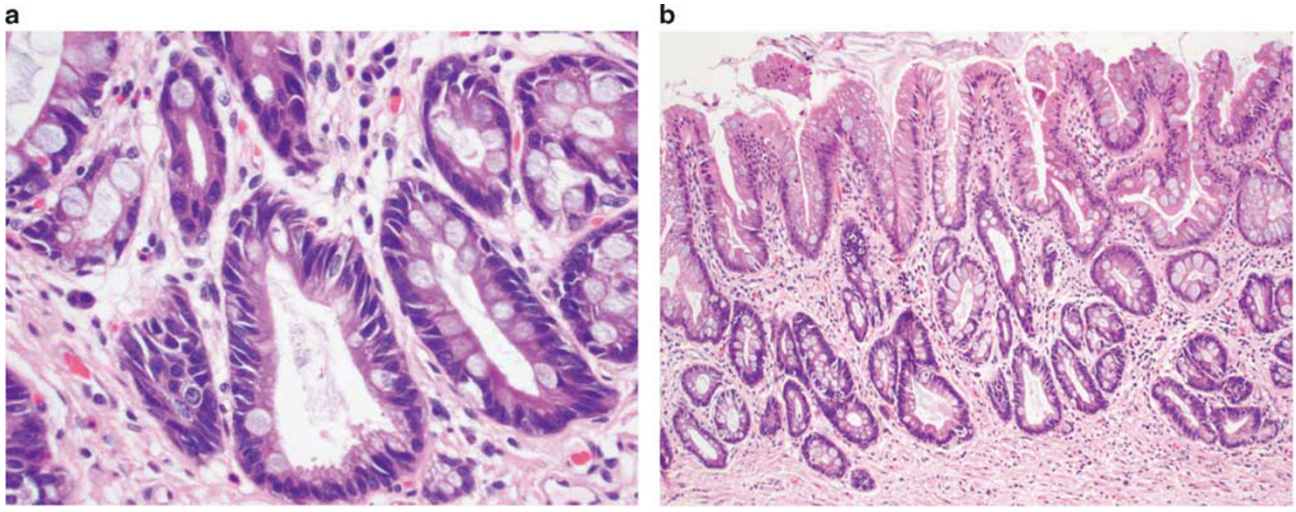

Figure 6 (**a**) These glands were found at the base of a Barrett's segment and represent the 'baseline atypia' that one typically sees at the base of the mucosa. (**b**) At low magnification, there is clearly surface maturation with an absence of cytologic atypia on the surface epithelium.

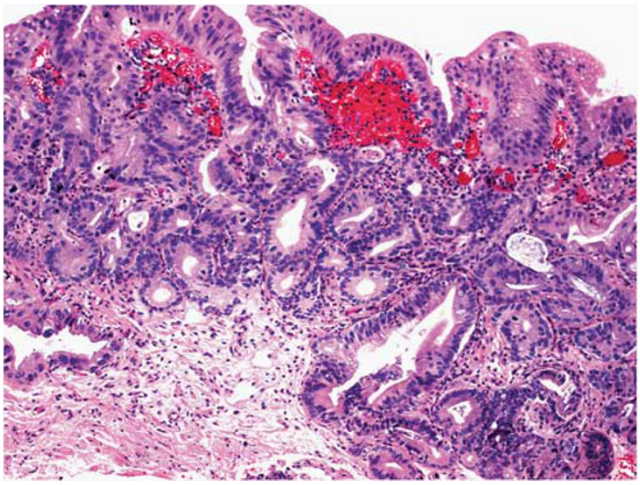

Figure 7 Barrett's esophagus with at least high-grade dysplasia. At low magnification, there is architectural complexity with back-to-back glands, but definitive invasion into the lamina propria characteristic of intramucosal adenocarcinoma could not be identified.

cases with solid or cribriform arrangements, ulcers occurring within the high-grade dysplastic epithelium, dilated dysplastic tubules containing necrotic debris, large numbers of neutrophils within the high-grade dysplastic epithelium and dysplastic tubules that were incorporated into the overlying squamous epithelium. After reclassification of these biopsy specimens, only 5% of cases with high-grade dysplasia were found to harbor a carcinoma in the resection specimen, whereas 72% of cases reclassified as high-grade dysplasia with changes suspicious for carcinoma showed adenocarcinoma in the resection specimen. Thus, the authors concluded that it is rare to find an invasive lesion in an esophagectomy specimen performed for high-grade dysplasia, provided that rigorous histologic criteria are used. High-grade dysplasia with changes suspicious for carcinoma is a biopsy diagnosis that is much more likely to be associated with an invasive lesion in the resection specimen. In a study by Patil *et al*[30] comparing the criteria defined by Downs-Kelly *et al*[28] with those defined by Zhu *et al*,[29] the authors found the presence of an endoscopic lesion, a 'never-ending' glandular pattern, sheet-like growth, angulated glands, three or more dilated glands with intraluminal debris and one or more foci of single-cell infiltration of the lamina propria to be predictors of adenocarcinoma in the resection specimen. The latter two variables remained independent predictors of invasion by multivariate analysis.

In summary, the pathologist frequently encounters biopsies to either diagnose BE or to determine the presence of absence of dysplasia in a patient with known BE. This review summarizes some of the more common difficulties encountered by pathologists when assessing these biopsy specimens.

Disclosure/conflict of interest

The author declares no conflict of interest.

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