EDITORIAL

Shining a light on the monsters under the bed

In the fight against esophageal adenocarcinoma, endoscopists confront the precursor lesion, Barrett's esophagus. We diagnose Barrett's esophagus with screening endoscopies, monitor for signs of neoplastic progression with surveillance endoscopies, intervene with organ-sparing endotherapy, and keep close vigil during postendotherapy surveillance for signs of recurrence. Our repertoire includes high-resolution endoscopy, optical imaging technologies, and a variety of tools for endoscopic resection and ablation. However, uncertainty about buried Barrett's may provoke unease about our reassuring endoscopic examination or successful treatments. Buried Barrett's is the presence of specialized intestinal metaplasia beneath squamous epithelium. The debate about the significance of buried Barrett's persists as a thorn in our robust success on the management of Barrett's esophagus–associated neoplasia. Although some in the field worry about buried Barrett's that may be missed on endoscopic surveillance and lead to disease recurrence, others deem it largely trivial and unworthy of further concern. Are these subsquamous glands like the monsters that children fear are hiding under the bed after the lights go out?

Buried Barrett's is present in naïve Barrett's and after treatment and may be due to a variety of possibilities, including residual disease after inadequate treatment, or it may reflect the development of Barrett's—which itself has unclear origins. Buried Barrett's has significant implications for treatment, surveillance, and tissue sampling. A histologic study of samples from patients who underwent circumferential endoscopic resection without prior endoscopic therapy for the treatment of Barrett's–associated neoplasia demonstrated buried Barrett's under squamous epithelium within the proximal squamocolumnar junction in 28% of cases, with most of the cases displaying buried glands harboring advanced pathologic changes of high-grade dysplasia (HGD) or intramucosal carcinoma.[1] This study supports that treatment should extend to 1 cm beyond the squamocolumnar junction to capture possible subsquamous extension of disease. Among those patients treated with radiofrequency ablation, the rate of reported buried Barrett's esophagus is seemingly low, at 0.9%.[2] However, insufficient depth of the biopsy specimens and sampling errors based on biopsy protocol may limit our detection of buried disease. A study of biopsy depth reported that forceps biopsies in patients who had undergone radiofrequency ablation contained subepithelial structures in 79% of patients, suggesting that we capture sufficient depth most of the time.[3] Although we believe biopsies to be able to reach an adequate depth, biopsy protocol still seems be of low yield and inherently limited by sampling error. Optical coherence tomography–based imaging modalities have raised the question of buried Barrett's detected after treatment, but there remain challenges in distinguishing subsquamous intestinal metaplasia from normal submucosal structures.[4,5]

Collectively, investigations examining subsquamous intestinal metaplasia bring to our attention that many cases may be endoscopically apparent, whether they show discoloration on white-light or narrow-band imaging, raised areas, artifacts from performance of biopsy on small islands, or subsquamous extension near the squamocolumnar junction.

During postendotherapy surveillance, a careful endoscopic examination with high-definition white-light endoscopy and ideally with optical chromoendoscopy is recommended to detect any areas of mucosal irregularity or nodularity or any residual columnar lined epithelium.[6] In the absence of any of these visible irregularities, 4-quadrant random biopsies throughout the neosquamous epithelium and gastric cardia are typically performed to exclude disease histologically.

The diagnosis of buried Barrett's requires a histologic interpretation, whereby the pathologist identifies squamous epithelium overlying specialized intestinal metaplasia. We often imply that buried Barrett's is hidden endoscopically if we assume that these areas are not seen, targeted specifically, and designated as such. However, it may be that many areas that called buried Barrett's histologically may be apparent endoscopically. In a study evaluating small Barrett's islands and report of histologic analysis, Pouw et al[7] suggest that often a small columnar island that may be endoscopically apparent may appear under squamous epithelium on histologic examination

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because of orientation issues and crush artifact and then reported as buried.

In this issue, Yang et al[8] report their retrospective study of a cohort of 506 patients with Barrett's-associated neoplasia. They identified that 7% of their population had buried Barrett's on histologic analysis. Almost two-thirds of the patients had been previously treated with EMR and radiofrequency ablation, 10% received a single modality of treatment, and 18% had received no prior treatment. The authors suggest that the majority of patients (79%) had indeed been suspected of having buried Barrett's at the time of endoscopy. They report that endoscopic features include either darker pink or darker brown mucosa under squamous epithelium on narrow-band imaging or raised areas under squamous mucosa. These features were associated with buried Barrett's in almost half of these cases. These suspected areas were noted to be next to a columnar-lined island in 48% of cases. Sampling of suspected areas was performed with either forceps biopsy (50%) or EMR (50%). Among the 44 cases of endoscopically suspected areas, buried Barrett's was confirmed in 26 cases, leading to a sensitivity of 79% and positive predictive value of 59%. Neoplasia was identified in 12 of the cases, with 5 cases of intramucosal carcinoma, 1 HGD, and 6 low-grade dysplasia, and the endoscopic features of buried Barrett's were present in all cases of neoplasia but 1 case. The other patients had no buried Barrett's and often experienced inflammation or reflux. The limitations of this study include its retrospective nature and a tertiary care population of patients with Barrett's-associated neoplasia.

Collectively, investigations examining subsquamous intestinal metaplasia bring to our attention that many cases may be endoscopically apparent, whether they show discoloration on white-light or narrow-band imaging, raised areas, artifacts from performance of biopsy on small islands, or subsquamous extension near the squamocolumnar junction. After attention and recognition, the follow-through steps would be sampling either by forceps or by EMR and appropriate designation to correlate endoscopic findings and histologic examination, followed by treatment, if appropriate.

Although future studies are needed to prospectively track the targeting of the endoscopic features in patients undergoing surveillance for Barrett's esophagus to validate these recognizable endoscopic features, ultimately any irregularity should be targeted. More importantly, additional investigation is still needed to identify the genetic and molecular features to explore the pathogenesis of residual or recurrent Barrett's that arises after treatment. There may be a potential to uncover pathways to recurrent disease or patterns of residual disease that may be more resistant to treatment.

This study underscores that oftentimes buried Barrett's lesions are not "invisible." Just as we have recognized that most instances of HGD and early cancer are subtle rather than occult, many cases of buried Barrett's may be subtle and endoscopically suspected as well. As part of a rigorous evaluation, it is warranted to pay more attention, target any discolorations on white-light or narrow-band imaging, identify any raised areas, and sample any areas of subtle irregularity throughout the previously treated segment. Validation of these endoscopic features would support a more targeted biopsy approach and improve our yield of postsurveillance biopsy protocols. High-definition white-light endoscopy, optical chromoendoscopy, attentiveness, and a trained eye have the potential to shine a light on the monsters under the bed, whether they are inflammation, overlapping squamous and columnar epithelium, subsquamous intestinal metaplasia, or perhaps the monster we most fear: recurrent neoplasia.

DISCLOSURE

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Abbreviation: HGD, high-grade dysplasia.

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