

# CLINICAL MANAGEMENT

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## Intestinal Metaplasia at the Gastroesophageal Junction

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### Clinical Case

A 52-year-old man has a 10-year history of typical heartburn several times a week. His heartburn responds well to antacids and over-the-counter H<sub>2</sub>-receptor antagonists. Recently, he read a newspaper article warning of an association between heartburn and cancer of the esophagus, and he became concerned. He called his primary care physician, who referred him to a gastroenterologist. The patient had no weight loss, dysphagia, or gastrointestinal bleeding. Physical examination and routine laboratory tests were unremarkable. An endoscopic examination was normal except for a slightly irregular squamocolumnar junction (Z-line) at the end of the esophagus. Two biopsy specimens were taken at the Z-line: one showed gastric cardiac-type epithelium with mild inflammation and *Helicobacter pylori* organisms, and the other showed moderately inflamed squamous epithelium abutting specialized intestinal metaplasia, typical of Barrett's esophagus, with prominent goblet cells.

### Background

When discussing the management of the patient described in this report, physicians often focus on the semantic issue of what to call the condition. Does this patient have short-segment Barrett's esophagus, intestinal metaplasia at the gastroesophageal junction (GEJ), or intestinal metaplasia of the gastric cardia? The debate over terminology often obscures the key clinical issues, which are: (1) Does this patient have a condition that predisposes to malignancy and, (2) If so, what can the clinician do to prevent cancer?

**The squamo-columnar and gastroesophageal junctions: What is normal?** Stratified squamous epithelium normally lines the body of the esophagus, whereas the normal gastric body is lined by an oxyntic (acid-producing) columnar mucosa whose glands contain nu-

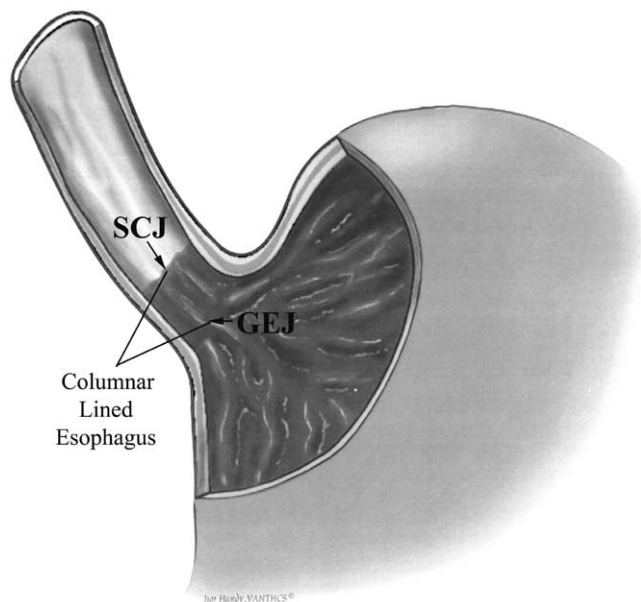
merous parietal and chief cells. There is normally an abrupt transition from squamous to columnar epithelium in the distal esophagus that can be identified both grossly and histologically.<sup>1</sup> This squamo-columnar mucosal junction (the Z-line) may or may not coincide with the GEJ, the anatomical level at which the esophagus ends and the stomach begins. Endoscopically, the GEJ is recognized as the level of the most proximal extent of the gastric folds when the stomach is partially inflated with air (overinflation can obscure this landmark) (Figure 1).<sup>2,3</sup> When the squamo-columnar junction (SCJ) is located proximal to the GEJ, there is a columnar-lined segment of esophagus.

Both the histological type and the precise anatomical location of the columnar epithelium at the normal Z-line are disputed. Traditional teaching holds that the normal Z-line is a junction between squamous epithelium and cardiac epithelium, a columnar lining characterized by tortuous, tubular glands comprised almost exclusively of mucus-secreting cells.<sup>4</sup> Authorities have claimed that cardiac epithelium can line up to 2 cm of the most distal esophagus, and may extend several centimeters below the GEJ to line the most proximal stomach (the gastric cardia).<sup>4,5</sup> However, the evidence on which these claims are based is scanty and dubious. Endoscopically, the gastric folds that delimit the stomach are dynamic structures whose proximal extent may vary with respiration and gagging, and with the degree of gastric distention. Surgical and autopsy specimens of the esophagus and stomach can be manipulated mechanically so that the landmarks used to identify the GEJ (e.g., the proximal

*Abbreviations used in this paper:* CK, cytokeratin; GEJ, gastroesophageal junction; GERD, gastroesophageal reflux disease; NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, proton-pump inhibitors; SCJ, squamo-columnar junction.

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0016-5085/04/\$30.00

doi:10.1053/j.gastro.2003.11.061



**Figure 1.** Endoscopic landmarks for identifying Barrett's esophagus. The squamo-columnar junction (SCJ or Z-line) is the visible line formed by the juxtaposition of squamous and columnar epithelia. The gastroesophageal junction (GEJ), the imaginary line at which the esophagus ends and the stomach begins, is identified as the level of the most proximal extent of the gastric folds when the stomach is partially inflated with air. When the SCJ is located proximal to the GEJ, there is a columnar-lined segment of esophagus. If biopsy specimens of the columnar-lined segment show specialized intestinal metaplasia, the patient has Barrett's esophagus. (Reprinted with permission from Spechler SJ. The role of gastric carditis in metaplasia and neoplasia at the gastroesophageal junction. *Gastroenterology* 1999;117:218–228).

extent of gastric folds, the angle of His) vary considerably in location. Without a fixed and precise marker for the GEJ, it is difficult to establish whether the Z-line normally is located precisely at or slightly proximal to the junction of esophagus and stomach. Thus, it is not clear whether it is normal to have a short segment of columnar-lined esophagus.

Pathologists also dispute fundamental histological characteristics of the cardiac epithelium. Some feel that the presence of any parietal cells in the glands precludes a histological diagnosis of cardiac epithelium,<sup>6</sup> whereas others contend that cardiac epithelium can have occasional parietal cells provided that other architectural features are typical of cardiac mucosa.<sup>7</sup> Some pathologists recommend the terms "oxyntocardiac mucosa" or "transitional mucosa" to describe a cardiac-type epithelium that has occasional parietal cells.<sup>6</sup> Finally, authorities dispute whether cardiac epithelium is even a normal structure.<sup>6,8</sup>

Tissues exposed chronically to agents that induce injury and inflammation may change into other types of tissue that are less susceptible to damage by those

agents.<sup>1</sup> This process is called metaplasia. Recent studies have shown that both the squamous and columnar epithelia at the GEJ are exposed repeatedly to noxious agents capable of inducing injury and inflammation including acid, pepsin, bile, and nitric oxide.<sup>9</sup> Furthermore, many individuals, like the patient described at the beginning of this report, are infected with *H. pylori*, an organism that causes chronic gastritis, which also predisposes to metaplasia of columnar mucosa at the GEJ.<sup>10</sup> It has been proposed that cardiac epithelium is a metaplastic mucosa acquired as a consequence of the chronic inflammation induced by repeated exposure to noxious agents.<sup>6,8</sup>

A recent study of 40 patients who had subtotal esophagectomy with esophagogastrostomy, an operation frequently complicated by severe reflux esophagitis in the esophageal remnant, supports the notion that cardiac epithelium is metaplastic.<sup>11</sup> Endoscopic examinations performed at a median of 36 months postoperatively showed that 19 of the 40 patients had developed columnar metaplasia in the esophageal remnant (10 cardiac epithelium, 9 intestinal metaplasia). Seven patients who had serial endoscopic examinations showed progression from cardiac epithelium on the initial postoperative endoscopy to specialized intestinal metaplasia (typical of Barrett's esophagus) on subsequent studies. The median time to the development of cardiac epithelium was 14 months, whereas specialized intestinal metaplasia was found at a median of 27 months postoperatively. These findings suggest that cardiac epithelium is not only metaplastic, but also the precursor of intestinal metaplasia in the esophagus.

Although it might seem that the issue of whether cardiac epithelium is a normal structure could be settled by a careful study of autopsy and surgical specimens of the GEJ (especially specimens from fetuses and children), such studies have yielded contradictory results. Table 1 summarizes the results of 5 recent studies on the histology of the GEJ that have focused on the prevalence of cardiac epithelium.<sup>12–16</sup> The explanation for the enormous disparity among these studies in the frequency of finding "pure" cardiac mucosa (with no parietal cells) at the Z-line is not clear. All 3 studies that found a low frequency of pure cardiac mucosa did describe a high frequency of oxyntocardiac mucosa at the Z-line.<sup>14–16</sup> Despite the disparate results, it is clear that the extent of cardiac epithelium is considerably shorter than that suggested by traditional texts. Cardiac epithelium, if present at all, rarely extends more than a few millimeters below the Z-line. One group reported that cardiac mucosa always was located on the gastric side of the GEJ,<sup>12</sup> but

**Table 1.** Results of Studies on Frequency of Cardiac Mucosa at the Gastroesophageal Junction

Study Author	Number (type) of specimens	Age of subjects	% of Subjects with "pure" cardiac mucosa <sup>a</sup>	Length of cardiac mucosa (range)
Kilgore <sup>12</sup>	33 (autopsy)	6.3 years <sup>b</sup>	100%	1.8 mm <sup>b</sup> (1.0–4.0 mm)
Sarbia <sup>13</sup>	36 (surgical)	55 years <sup>c</sup>	97%	5.0 mm <sup>c,d</sup> (1–15 mm)
Chandrasoma <sup>14</sup>	18 (autopsy)	24 years <sup>b</sup>	44%	1.3 mm <sup>b,d</sup> (0.25–2.75 mm)
Zhou <sup>15</sup>	31 (autopsy)	fetal	6%	NS
	46 (autopsy)	children 1 wk–17 yrs	48%	NS
Park <sup>16</sup>	23 (autopsy)	fetal and children	0%	–

<sup>a</sup>Only mucus cells, no parietal cells.

<sup>b</sup>Mean.

<sup>c</sup>Median.

<sup>d</sup>Length of maximal extent of cardiac mucosa.

NS, Not stated.

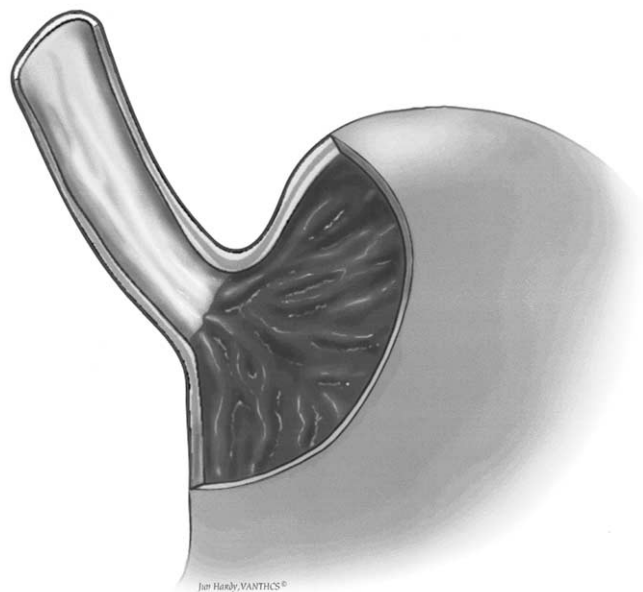
it is not clear that the gross landmarks used to identify the GEJ have the precision necessary to localize a structure whose extent is measured in millimeters. Thus, it remains unclear whether this tiny band of cardiac mucosa is a normal structure, and whether it lines the esophagus, the proximal stomach, or both.

**Intestinal Metaplasia at the GEJ.** Although authorities dispute the normal features of the GEJ, all seem to agree that it is abnormal to find intestinal metaplasia in this region.<sup>1</sup> If biopsy specimens from a columnar-lined esophagus show specialized intestinal metaplasia, then the patient has Barrett's esophagus (Figure 1). If the distance between the Z-line and the GEJ is  $\geq 3$  cm then the patient has long-segment Barrett's esophagus, whereas the condition is deemed short-segment Barrett's esophagus if that distance is  $< 3$  cm.<sup>3</sup> Substantial diagnostic difficulties result when there are very short segments of intestinal metaplasia (spanning millimeters rather than centimeters) in the region of the GEJ, however, as there were in our patient.

Intestinal metaplasia can develop in the stomach, the esophagus, or both. Histologically, intestinal metaplasia in the stomach can be indistinguishable from intestinal metaplasia in the esophagus. Since the GEJ cannot be identified with great precision, it can be difficult to determine whether short segments of intestinal metaplasia found in the GEJ region are lining the esophagus (short-segment Barrett's esophagus) or the proximal stomach (intestinal metaplasia of the gastric cardia).<sup>3</sup> The term "intestinal metaplasia at the GEJ" has been used to describe the condition in which intestinal metaplasia is found at a Z-line that appears to coincide precisely with the GEJ (Figure 2). Rather than constituting an independent condition, however, intestinal metaplasia at the GEJ almost certainly represents either short-segment Barrett's esophagus or intestinal metaplasia of the cardia.

Intestinal metaplasia in the stomach often develops as a consequence of chronic *H. pylori* gastritis, whereas

intestinal metaplasia in the esophagus develops as a sequela of chronic gastroesophageal reflux disease (GERD).<sup>17</sup> For some patients, therefore, intestinal metaplasia at the GEJ is merely part of a diffuse *H. pylori* gastritis whereas, for others, the condition results from GERD that causes intestinal metaplasia in segments of esophagus so short that they cannot be distinguished from the serrations of a normal Z-line. Some studies even have shown a negative association between *H. pylori* and complicated GERD, suggesting that the infection may protect against Barrett's esophagus.<sup>18</sup> Unfortunately,



**Figure 2.** The SCJ and GEJ coincide. If biopsy specimens at the Z-line reveal intestinal metaplasia, the condition is called intestinal metaplasia at the GEJ. Intestinal metaplasia at the GEJ represents either short-segment Barrett's esophagus or intestinal metaplasia of the gastric cardia, but these conditions cannot be distinguished because the gross landmarks used to identify the GEJ are imprecise. (Reprinted with permission from Spechler SJ. The role of gastric carditis in metaplasia and neoplasia at the gastroesophageal junction. *Gastroenterology* 1999;117:218–228).

testing for *H. pylori* is not a reliable way to distinguish short-segment Barrett's esophagus from intestinal metaplasia of the gastric cardia. *H. pylori* gastritis is not rare in patients with Barrett's esophagus, even though they have a lower prevalence of infection than patients without GERD complications. Furthermore, one recent study found that intestinal metaplasia at the GEJ was not clearly associated either with *H. pylori* infection or GERD symptoms in more than one-third of cases.<sup>19</sup> Our patient has both classic GERD symptoms and *H. pylori* infection, and it is not clear whether his intestinal metaplasia at the GEJ represents short-segment Barrett's esophagus or intestinal metaplasia of the gastric cardia.

If intestinal metaplasia in the esophagus had the same malignant potential as intestinal metaplasia in the stomach, then distinguishing short-segment Barrett's esophagus from intestinal metaplasia of the gastric cardia would have no impact on patient management and little practical importance. However, circumstantial evidence suggests that the risk of malignancy is substantially higher for intestinal metaplasia in the esophagus. Sharma et al. found dysplasia (the precursor of malignancy) in 20 of 177 patients (11.3%) with short-segment Barrett's esophagus, but in only 1 of 76 patients (1.3%) with intestinal metaplasia in the gastric cardia.<sup>20</sup> Authorities recommend endoscopic cancer surveillance routinely for patients with Barrett's esophagus, but not for patients with intestinal metaplasia in the stomach.<sup>21,22</sup> Therefore, the distinction between these 2 conditions has clear-cut clinical implications.

Cytokeratin (CK) staining has been proposed as a means to differentiate intestinal metaplasia of the cardia from short-segment Barrett's esophagus. The specialized intestinal metaplasia of Barrett's esophagus frequently exhibits strong immunoreactivity for CK7 in its superficial and deep glands, and immunoreactivity for CK20 in superficial glands and surface epithelial cells.<sup>23</sup> In contrast, intestinal metaplasia in the gastric body infrequently shows this so-called "Barrett's CK7/20 pattern." In one recent study of 34 patients with biopsy specimens showing intestinal metaplasia at the GEJ, immunostaining revealed a Barrett's CK7/20 pattern in 16.<sup>19</sup> These patients had a low prevalence of *H. pylori* infection and frequent symptoms of GERD, whereas the 18 patients with a CK7/20 pattern typical of gastric intestinal metaplasia usually had *H. pylori* gastritis. The sensitivity and specificity of the CK7/20 immunoreactivity pattern as a marker for Barrett's esophagus remains disputed, however,<sup>24-26</sup> and it is not clear that immunostaining for cytokeratins has advantages over other proposed biomarkers for Barrett's esophagus such as reactivity with mAb

Das-1 (a monoclonal antibody raised against colonic epithelial cells) and expression of colonic-type sulfomucins.<sup>25,27</sup> A recent review has concluded that the utility of biomarkers in distinguishing short-segment Barrett's esophagus from intestinal metaplasia of the gastric cardia has not been established, and the authors advised against basing clinical decisions on the presence of these biomarkers.<sup>28</sup>

#### **Cancer risk for intestinal metaplasia at the GEJ.**

There are few prospective data on the incidence of adenocarcinoma for patients with intestinal metaplasia at the GEJ and, consequently, their risk of malignancy is not known. As discussed above, intestinal metaplasia at the GEJ likely represents either intestinal metaplasia of the stomach, which has a low risk of progression to malignancy, or short-segment Barrett's esophagus, which is more worrisome. Therefore, the risk of cancer for intestinal metaplasia at the GEJ should be less than or equal to that for Barrett's esophagus. Published estimates on the annual incidence of cancer in patients with long-segment Barrett's esophagus have ranged from 0.2% to 2.9%, but modern studies suggest that their cancer risk is approximately 0.5% per year.<sup>29-32</sup> The risk for cancer in short-segment Barrett's esophagus is disputed.

Cancers in Barrett's esophagus evolve through the accumulation of genetic mutations that endow the cells with growth advantages.<sup>33</sup> Mutations are to some extent chance events, and it seems logical to assume that the risk of cancer in Barrett's esophagus should vary with the extent of metaplastic epithelium. Patients with longer segments of metaplasia have more cells at risk for DNA damage and, therefore, should be more likely to acquire the critical mutations that cause malignancy. Although data from a number of observational studies support this hypothesis,<sup>31,34-38</sup> there is yet no proof that the risk of cancer varies with the extent of the metaplastic lining. In one recent report of 235 patients with Barrett's esophagus, furthermore, the cancer risk was not found to vary significantly with the extent of metaplasia.<sup>39</sup> For our patient, therefore, the maximum annual risk for adenocarcinoma is approximately 0.5%, and his real risk probably is substantially lower than that.

#### **Potential Management Strategies**

Intestinal metaplasia at the GEJ causes no symptoms. Therapies might be aimed at treating associated conditions like GERD and *H. pylori* gastritis, and at reducing the risk of malignancy. However, no studies have addressed specifically the efficacy of antireflux and cancer-preventive treatments for patients with intestinal

metaplasia at the GEJ. In these patients, data on the treatment of Barrett's esophagus may provide insights into therapeutic options for those whose condition is really short-segment Barrett's esophagus, whereas data on the treatment of gastric intestinal metaplasia may provide guidance for those whose condition is part of a diffuse *H. pylori* gastritis.

**Antireflux therapy.** For patients, like ours, who have intestinal metaplasia at the GEJ associated with GERD, acid-suppressing medications should be administered at least in dosages sufficient to control the symptoms of reflux disease. Many patients with intestinal metaplasia at the GEJ have few or no clinical manifestations of GERD, however, and it is not clear that any antisecretory therapy is indicated in those cases.<sup>40</sup> Some authorities have proposed that the ultimate goal of medical therapy for patients with Barrett's esophagus should be the virtual elimination, rather than the mere reduction, of acid reflux through the administration of antisecretory medications in dosages and combinations beyond those required just to eliminate GERD symptoms.<sup>41</sup> This proposal is based on indirect evidence, summarized below, that such aggressive acid suppression might have a cancer-protective effect in Barrett's esophagus. If intestinal metaplasia at the GEJ is really short-segment Barrett's esophagus in many cases, then should patients with intestinal metaplasia at the GEJ receive aggressive acid suppression therapy regardless of GERD symptoms?

Biopsy specimens of specialized intestinal metaplasia maintained in organ culture exhibit hyperproliferation when exposed briefly to acid,<sup>42,43</sup> and such acid exposure has been shown to activate the mitogen-activated protein kinase pathways that increase proliferation and decrease apoptosis in Barrett's esophagus.<sup>44</sup> In a study of patients treated with proton-pump inhibitors (PPIs), esophageal biopsy specimens from those with normal acid exposure exhibited decreased expression of PCNA (a proliferation marker), whereas no such decrease was observed in patients with persistently abnormal acid reflux.<sup>45</sup> Furthermore, PPI therapy has been shown to cause partial regression of specialized intestinal metaplasia.<sup>46</sup> These studies all suggest that aggressive acid control might be beneficial for patients with Barrett's esophagus. However, it is not clear that the acute effects of acid on tissues in organ culture reflect the chronic effects of GERD on Barrett's esophagus, nor is it clear that effects on protein kinases and proliferation markers reflect important changes in cancer risk. Moreover, the areas of partial regression induced by PPI therapy may exhibit underlying intestinal metaplasia and worrisome proliferative abnormalities.<sup>47,48</sup> Thus, the role of aggressive antisecre-

tory therapy for patients with intestinal metaplasia in the esophagus remains unclear. For patients whose intestinal metaplasia at the GEJ is part of a diffuse *H. pylori* gastritis, moreover, some data suggest that aggressive acid suppression may accelerate the progression of gastric atrophy.<sup>49</sup>

It has been proposed that fundoplication might be more effective than antisecretory therapy for preventing deaths from cancer in Barrett's esophagus,<sup>50</sup> but little direct evidence supports this contention. A recent report of a randomized trial of medical and surgical therapies for 247 patients with complicated GERD explored this issue.<sup>32</sup> During 10 to 13 years of follow-up, 4 of 165 patients (2.4%) in the medical group and 1 of 82 (1.2%) in the surgical group developed esophageal adenocarcinoma. The difference between the groups in the incidence of this tumor was not statistically significant, and any potential cancer-preventive benefit of surgery was offset by an unexplained (but significant) decrease in survival for the surgical patients due to excess deaths from heart disease. In a Swedish population-based cohort study, in which patients with GERD were followed for up to 32 years, the relative risk for developing esophageal adenocarcinoma (compared with the general population) among 35,274 men who received medical antireflux therapy was 6.3 (95% CI, 4.5–8.7), whereas the relative risk for 6406 men treated with fundoplication was 14.1 (95% CI, 8.0–22.8).<sup>51</sup> These reports do not support a strong cancer-preventive effect for antireflux surgery in Barrett's esophagus.

***H. pylori* treatment.** Chronic *H. pylori* infection is a well-established risk factor for adenocarcinoma of the gastric body.<sup>17</sup> For patients whose intestinal metaplasia at the GEJ is part of a diffuse *H. pylori* gastritis, therefore, eradication of the infection might be expected to protect against gastric cancer. Data on how *H. pylori* treatment affects cancer risk for patients with intestinal metaplasia of the stomach are inconclusive and contradictory, however.<sup>52,53</sup> Some investigators have found that *H. pylori* eradication causes regression of intestinal metaplasia in the stomach,<sup>54–58</sup> whereas others have not.<sup>59–63</sup> Some reports have suggested that *H. pylori* eradication may decrease the incidence of gastric cancer,<sup>58,64</sup> but available studies are difficult to interpret because of deficiencies such as small sample size, lack of randomization, and absent or inappropriate control groups.<sup>53</sup> Furthermore, the risk of gastric cancer for Western patients with nondysplastic intestinal metaplasia of the stomach appears to be so small that there is little reason to initiate any treatment solely for the purpose of cancer prevention.<sup>22</sup>

*H. pylori* eradication would not be expected to benefit patients whose intestinal metaplasia at the GEJ is really short-segment Barrett's esophagus, because the infection plays no apparent role in the pathogenesis or progression of this lesion. There are even data to suggest that the treatment of *H. pylori* might exacerbate the GERD that underlies the development of esophageal intestinal metaplasia, although this issue remains highly controversial.<sup>65</sup> Thus, there is little reason to routinely test or treat for *H. pylori* infection in patients who have intestinal metaplasia at the GEJ.

#### **Nonsteroidal anti-inflammatory drugs (NSAIDs).**

Epidemiological studies suggest that aspirin and other NSAIDs, which inhibit cyclooxygenase (COX), might protect against cancer in Barrett's esophagus.<sup>66</sup> Moreover, the specialized intestinal metaplasia of Barrett's esophagus exhibits increased expression of COX-2,<sup>67</sup> and inhibition of COX-2 has antiproliferative and pro-apoptotic effects in Barrett's-associated esophageal adenocarcinoma cell lines.<sup>68</sup> Nevertheless, prospective clinical studies are needed before NSAIDs can be recommended for chemoprevention for patients with Barrett's esophagus in general, and specifically for patients with intestinal metaplasia at the GEJ. Even if efficacy in cancer prevention can be demonstrated, it is not clear that the high cost of the COX-2 selective NSAIDs will be justified for routine clinical use. Aspirin, an inexpensive, nonselective NSAID that can prevent cardiovascular, as well as neoplastic complications, might be a useful drug if its protective effects can be shown to outweigh its risk of gastrointestinal complications.

**Endoscopic surveillance.** Endoscopic surveillance for curable neoplasia is not recommended routinely for patients with nondysplastic intestinal metaplasia of the stomach because their risk of cancer appears to be too low to justify an expensive and potentially hazardous procedure with no proved efficacy in reducing gastric cancer mortality.<sup>22</sup> In contrast, regular endoscopic surveillance is recommended for patients with Barrett's esophagus despite the lack of proof that this practice decreases mortality from esophageal adenocarcinoma.<sup>21</sup> Small, observational studies have documented that endoscopic surveillance can detect curable neoplasms in Barrett's esophagus, and that cancers discovered during surveillance are less advanced than those found in patients who present with cancer symptoms like dysphagia and weight loss.<sup>69–71</sup> However, these studies are susceptible to a number of biases (e.g., lead-time and length-time biases) that could substantially inflate the value of surveillance programs.<sup>72</sup>

Some computer models have suggested that endoscopic surveillance can be beneficial under certain conditions.<sup>73,74</sup> In one Markov model that assumed an annual cancer incidence rate of 0.4%, for example, endoscopic surveillance performed every 5 years was the preferred strategy for patients with Barrett's esophagus, costing \$98,000 per quality-adjusted life year gained.<sup>73</sup> However, these models are highly sensitive to variations in a number of key assumptions (e.g., the incidence of cancer in Barrett's esophagus, the quality of life after esophagectomy) that can alter the conclusions substantially. A recent cost-utility analysis contradicted the conclusions of earlier models, finding that whereas screening for Barrett's esophagus appeared to be cost-effective, surveillance did not.<sup>75</sup> None of these computer models can be considered definitive, however, because all incorporate numerous layers of soft data and questionable assumptions.

The American College of Gastroenterology has recommended surveillance endoscopy at an interval of every 3 years for patients with Barrett's esophagus who have had 2 consecutive endoscopies that show no dysplasia.<sup>21</sup> Although this societal recommendation can be considered "standard of care," it is not entirely clear why this surveillance interval was chosen. As discussed, one computer model suggests that the optimal interval for endoscopic surveillance is every 5 years.<sup>73</sup>

### **Recommended Management Strategy**

For patients who have intestinal metaplasia at the GEJ associated with GERD, like the patient presented at the beginning of this report, acid-suppressing medications should be administered in dosages sufficient to control the reflux disease. The indirect evidence that aggressive acid suppression might prevent cancer in Barrett's esophagus does not seem strong or compelling enough to warrant the routine administration of antisecretory medication beyond that necessary to control the symptoms of GERD. Furthermore, fundoplication cannot be recommended solely as a cancer-preventive procedure even for patients with verified Barrett's esophagus, and certainly should not be recommended for this purpose in patients who have intestinal metaplasia at the GEJ.

Patients with intestinal metaplasia at the GEJ should not have routine testing for *H. pylori* infection unless there is a clear indication, such as a verified history of peptic ulcer disease. In our patient, *H. pylori* organisms were identified incidentally in biopsy specimens taken at the Z-line. In this situation, antibiotic treatment may be

recommended with the rationale that the infection is both a risk factor for peptic ulcer disease and a potential gastric carcinogen. Data suggesting that *H. pylori* eradication may exacerbate GERD are weak and unconvincing, and any potential exacerbation could almost certainly be controlled by adjusting the antisecretory therapy. Furthermore, there is no established role for the routine prescription of NSAIDs for chemoprevention in patients who have intestinal metaplasia at the GEJ.

Endoscopic surveillance using the guidelines established for Barrett's esophagus can be considered for patients with intestinal metaplasia at the GEJ, but there is no proof that this practice prolongs survival or improves quality of life even for patients with verified Barrett's esophagus. Both observational studies and computer models suggest that surveillance can decrease mortality from cancer in Barrett's esophagus, but at considerable expense. Surveillance is associated with risks including complications that result both from the endoscopy and from the invasive procedures used to treat lesions found by endoscopy, but no study has shown an overall survival disadvantage for patients in surveillance programs. It has been proposed that, in this murky situation where most of the indirect evidence available suggests that surveillance is beneficial, it is better to err by performing unnecessary surveillance than by missing curable esophageal neoplasms.<sup>76</sup> This same reasoning can be applied to the management of patients like ours who have intestinal metaplasia at the GEJ. In this situation, regular endoscopic surveillance can be considered at intervals of every 3 to 5 years.

## Conclusions

This discussion should not be construed as a recommendation for endoscopists to take biopsy specimens routinely from a normal-appearing Z-line to seek intestinal metaplasia at the GEJ. Indeed, considering the paucity of data on the natural history of the condition and on the efficacy of management strategies, I feel that routine biopsy sampling of the Z-line should be discouraged. This report is intended merely to help guide the management of patients who, appropriately or not, are found to have intestinal metaplasia at the GEJ.

Intestinal metaplasia at the GEJ likely is either short-segment Barrett's esophagus, which has a cancer risk of at most 0.5% per year, or intestinal metaplasia of the proximal stomach which appears to have a substantially smaller risk for malignancy. These conditions cannot be distinguished reliably because the morphological and histochemical features of gastric and esophageal intestinal metaplasia are similar, and because the gross land-

marks used to identify the GEJ do not have the precision necessary to localize a mucosa whose extent may be measured in only millimeters. For patients found to have intestinal metaplasia at the GEJ, therefore, a conservative approach is to assume a worst-case scenario in which the condition is short-segment Barrett's esophagus, and to manage patients according to established guidelines for Barrett's esophagus.

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