Esophageal Adenocarcinoma Arising from Barrett’s Epithelium in Taiwan

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The prevalence of Barrett’s esophagus (BE) in Eastern countries is rising to match the prevalence in the West. However, a corresponding trend of BE-associated adenocarcinoma has yet to be observed in Asia. Historically, adenocarcinoma complicating BE has been considered a rare event in Taiwan. In the present report, we collected three Taiwanese cases of esophageal adenocarcinoma arising from BE. The first case was a 37-year-old man with an advanced cancer that developed on pre-existing BE after a 3-year interval without endoscopic surveillance. The second case was a 63-year-old man who presented with odynophagia and was found to have an ulcerative tumor centered on the characteristic Barrett’s mucosa. The final case was a 44-year-old man who presented with gradual-onset dysphagia and weight loss, without typical reflux symptom. Our report emphasizes the need for an updated epidemiologic study to determine the incidence of BE-associated adenocarcinoma in Taiwan. [J Formos Med Assoc 2007;106(8):664–668]

Key Words: Barrett’s esophagus, esophageal adenocarcinoma, gastroesophageal reflux disease

Case Reports

Case 1
A 37-year-old man who did not smoke or drink alcohol presented with gradual-onset dysphagia. Three years earlier, he had undergone esophagogastroduodenoscopy (EGD) at National Taiwan University Hospital because of typical GERD symptoms. At that time, the squamocolumnar junction was located 4 cm proximal to the upper ends of the gastric mucosa and had an appearance typical of BE (Figure 1A). A biopsy specimen proved the presence of intestinal metaplasia. For unknown reasons, the patient failed to receive regular endoscopic surveillance afterwards. The EGD performed...

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Received: April 10, 2006
Revised: May 9, 2006
Accepted: February 6, 2007

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3 years later showed a nodular creeping tumor of the lower esophagus arising from the pre-existing Barrett's territory (Figure 1B). Pathology proved adenocarcinoma. After multiple liver, bone and brain metastases were identified, the patient underwent intensive systemic chemotherapy with palliative irradiation.

Case 2
A 63-year-old man with chronic GERD symptoms for 6 months visited Taipei Medical University Hospital with gradual-onset odynophagia of roughly 1 month's duration. He denied the habits of alcohol, tobacco, and betel quid consumption. EGD found a bulging tumor with central ulceration at the lower esophagus, 33–36 cm below the incisors (Figure 2A). The squamocolumnar junction was displaced 4 cm proximal to the esophagogastric junction; velvety pink mucosa with wave-like projections coursed across the ulcerated tumor. Biopsies confirmed adenocarcinoma arising from BE. The patient was treated with radical esophagectomy and proximal gastrectomy with esophagogastric anastomosis. Examination of the surgical specimen showed that the malignant ulcer was located near the proximal end of the distinctive Barrett’s mucosa (Figure 2B). Microscopically, the tumor was moderately to poorly differentiated adenocarcinoma in glandular structures, infiltrating as solid nests into the desmoplastic stroma. The surrounding Barrett’s mucosa contained intestinal metaplasia. Eight months after surgery, the patient was free of recurrent disease, but he has since undergone two endoscopic dilation procedures for anastomotic stricture.

Case 3
A 44-year-old man without a history of reflux symptoms visited National Taiwan University Hospital because of a 6-week history of progressive dysphagia and weight loss. He did not smoke, but had limited amount of alcoholic beverages. Barium swallow examination revealed an irregular narrowing of the lower esophagus (7 cm in length) that was continuous with the gastroesophageal junction (Figure 3A). A subsequent EGD showed an eccentric tumor of the lower esophagus that extended longitudinally from the gastroesophageal junction to the level of 33 cm below the incisors. The tumor was nodular, with a friable surface (Figure 3B). The gastric cardia was partially involved. The underlying mucosa surrounding the tumor was composed of pink velvety-like epithelium that extended to the upper end of the tumor, a typical picture of BE. Biopsies confirmed an adenocarcinoma and surrounding BE (Figure 3C). Endoscopic ultrasound

Figure 1. Case 1: (A) esophagogastroduodenoscopy reveals a proximal extension of the squamocolumnar junction (arrow), typical of Barrett’s esophagus; (B) 3 years later, a repeat examination shows that an irregular exophytic tumor had developed on the territory of Barrett’s mucosa.
showed that tumor depth was limited to the adventitia and that there was regional lymphadenopathy (disease stage T3N1M0). The patient was referred for concurrent cisplatin-based chemoradiotherapy.

**Discussion**

This report has described three Taiwanese men of middle to old age (range, 37–63 years) with lower esophageal adenocarcinoma. Each of the three
malignant tumors was morphologically proven to have concomitant BE. All three patients came to medical attention only after developing symptoms of an advanced lesion due to lack of surveillance or adequate follow-up.

BE is an incomplete form of intestinal metaplasia resulting from chronic GERD, in which the normal squamous epithelium of the esophagus is replaced by intestinal-type epithelium. In Western countries, it is found in approximately 6–12% of patients with reflux symptoms who have undergone endoscopy. It generally affects older people, with a peak incidence at around 55–65 years, and has a male-to-female ratio of 7:1.7,8 Although approximately 50% of cases of esophageal adenocarcinoma arise from BE, reflux symptoms alone can be associated with an increased risk. In a Swedish study, Lagergren et al9 reported that 60% of 189 patients with esophageal adenocarcinoma had previous histories of heartburn or acid regurgitation. Other putative risk factors include duration of GERD symptoms, presence of nocturnal reflux symptoms, hiatus hernia, and the absence of *Helicobacter pylori* infection.10

Although a causal relationship between BE and esophageal adenocarcinoma is well-established, the precise mechanism of progression remains elusive. It is believed that carcinogenesis may progress through the sequence of metaplasia-dysplasia-adenocarcinoma, with possible pathogenic roles for repeated exposure to acid and cyclooxygenase (COX)-2 related pathway activity.11 Chemoprevention with proton-pump inhibitors, COX-2 inhibitors, and aspirin has been proposed to arrest or delay progression to adenocarcinoma.12,13 However, available regimens have not convincingly decreased the likelihood of developing cancer. Current efforts are emphasizing endoscopic detection of small cancer foci by using magnification, chromoendoscopy, and/or optical devices to identify or delineate the margin.14,15

Long-segment BE, defined as a length of intestinal epithelium ≥ 3 cm, deserves intensive endoscopic surveillance because it is associated with higher esophageal acid exposure and subsequent rate of malignant transformation.16,17 In our report, all three patients had long-segment BE; two of them had typical reflux symptoms. Based on the recently validated Prague C & M criteria,18 all of their BEs can be described as C2-3 M4-7, which confirm the clinical utility of measurement of circumferential and maximum extents. A relatively young age of onset (mean age, 48 years) in our series deserves special attention. Liou et al9 reviewed 17,894 dyspeptic patients screened by upper endoscopy in Taiwan and found that 13.7% and 7.6% of patients were aged less than 45 and 40 years old, respectively. They suggested that 40 years might be an optimal age threshold for screening endoscopy for uninvestigated dyspepsia in Taiwan. Our report may strengthen their findings in making the optimal screening strategy specific for Taiwanese patients with functional gastrointestinal disorder.

We assumed that there may be an increase in BE-associated adenocarcinoma in Taiwan, corresponding to the 18.4% prevalence of endoscopic esophagitis reported from a cross-sectional survey.4 Other supportive evidence is the 2% prevalence of BE among a Taiwanese population of 464 self-referred subjects, a rate that potentially matches up with the range of rates (5–10%) reported in Western countries.3 However, the reported incidence of BE-associated adenocarcinoma may be difficult to distinguish with cardiac gastric cancer, especially when the tumors are disclosed in advanced stages. The misclassification can be substantial when we estimate the incidence based on the crude database of the National Cancer Registry. In fact, the World Health Organization classification uses the proximal end of gastric folds to define distal esophageal tumor, junctional tumor, and cardiac tumor.20 El-Rifai et al21 also detected specific genetic alterations that may be helpful in distinguishing BE-associated adenocarcinoma from cardiac gastric cancer. Further validation of morphologic and histopathologic diagnoses is a worthwhile endeavor.

In summary, we report three Taiwanese men with advanced esophageal adenocarcinoma with concomitant BE. In discordance to the common thought of disease rarity in Eastern countries, these
cases show similar characteristics to those reported in Western countries. Although the evidence remains limited, our report emphasizes the importance of risk assessment and follow-up surveillance in patients with reflux symptoms. Updated epidemiologic data are therefore warranted.

References