

# Educational Case: Esophageal Carcinoma

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*The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see <http://journals.sagepub.com/doi/10.1177/2374289519897383>.*<sup>1</sup>

## Keywords

pathology competencies, organ system pathology, gastrointestinal tract, gastrointestinal neoplasia, esophageal carcinoma, neoplasia, environmental influences, Barrett esophagus

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## Primary Objective

*Objective GT3.3: Esophageal Carcinoma.* Describe the location of adenocarcinomas versus squamous cell carcinomas of the esophagus and list the major risk factors for each.

Competency 2: Organ System Pathology; Topic: Gastrointestinal tract (GT); Learning Goal 3: Gastrointestinal Neoplasia.

## Secondary Objective

*Objective N2.1: Prevalence and geographic impact on Neoplasia.* Describe the prevalence of neoplastic diseases and discuss the environmental factors that influence patients as they move between geographical regions.

Competency 1: Disease Mechanisms and Processes; Topic: Neoplasia (N); Learning Goal 2: Environmental Influences on Neoplasia.

## Patient Presentation

A 64-year-old man presents to his primary care physician with a chief complaint of progressive difficulty swallowing over the past 4 months, as well as an unintentional 25 pound weight loss. At first, the difficulty was only with swallowing solids but this progressed to liquids as well. He states, he had been feeling well prior to this, with only a past medical history of heartburn he treats with over-the-counter medications. He reports mild alcohol intake

(2 beers per week), with no tobacco or illicit drug history. He is married with 3 healthy adult children. A retired accountant, he spends his time gardening, playing golf, and traveling.

## Diagnostic Findings, Part I

Vital signs are all within normal limits. Review of systems is only positive for dysphagia. Physical examination reveals a well-nourished man with no apparent distress. His body mass index is 30, despite his reported recent weight loss.

## Question /Discussion Points, Part I

*What Is Your Differential Diagnosis Based on Clinical Presentation Alone?*

Dysphagia has many etiologies, including a benign structural obstruction, a functional issue, esophagitis, or neoplasia. Benign obstructions include esophageal webs, rings, and

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stenosis. As these conditions often progress slowly, the patient may modify his or her diet to make swallowing easier. Appetite and weight are relatively maintained.

Functional conditions causing dysphagia include nutcracker esophagus and diffuse esophageal spasm. These conditions are due to uncoordinated or dysfunctional contractions of the smooth muscle.

Esophagitis can be infectious or noninfectious. Infectious esophagitis mostly affects immunocompromised hosts and usually presents with pain with swallowing (odynophagia). Common infections of the esophagus include candidiasis, herpes simplex, and cytomegalovirus. Noninfectious esophagitis includes eosinophilic esophagitis and gastroesophageal reflux disease (GERD). Eosinophilic esophagitis often presents in young, male, atopic patients with a history of food or environmental allergies; biopsies show eosinophils throughout the entire length of the esophagus. Gastroesophageal reflux disease, the most prevalent esophagitis in the United States, is caused by the reflux of gastric contents into the lower esophagus secondary to relaxation of the lower esophageal sphincter. This may be triggered by certain foods, increased abdominal pressure (obesity), pregnancy, increased gastric volume, and alcohol and tobacco. Lastly, neoplasia must always remain a diagnostic possibility when dealing with dysphagia, especially in the clinical setting of a significant unintended weight loss.

## Diagnostic Findings, Part 2

An upper endoscopy is performed and biopsies taken from lesional tissue.

## Question/Discussion Points, Part 2

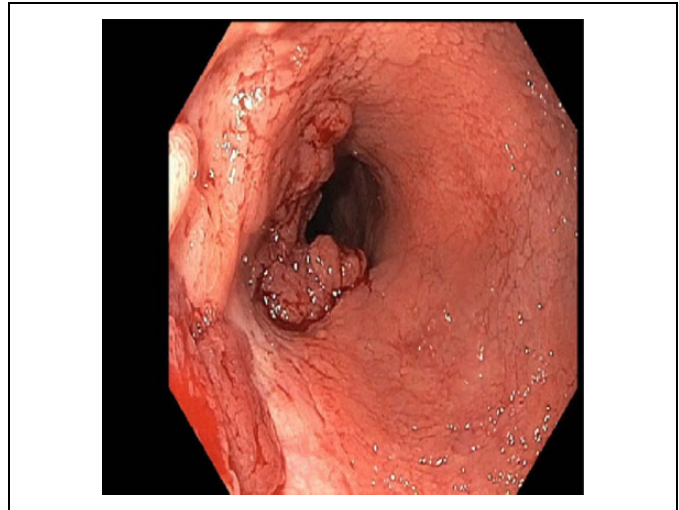
### What Are the Pertinent Findings on the Endoscopy Image? Figure 1

Located at the gastroesophageal junction (GEJ) is a fungating mass measuring up to 4 cm in greatest dimension. Proximal to this mass, there are salmon-colored patches.

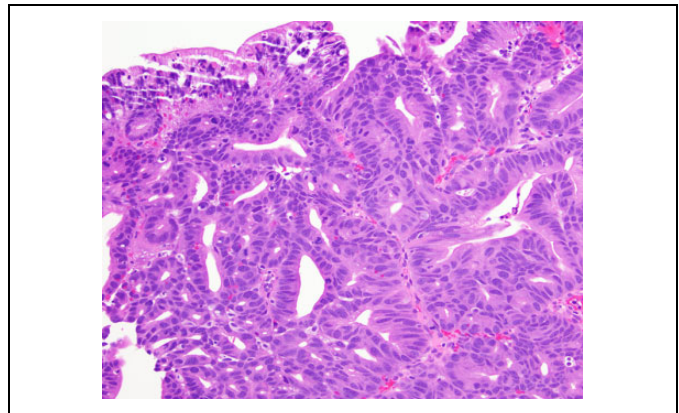
### What Are the Pertinent Histologic Findings Seen in Figures 2 and 3?

Figure 2, a biopsy of the mass, shows irregular, angulated, infiltrating back-to-back glands with minimal intervening stroma. The glandular proliferation is composed of cells with enlarged hyperchromatic nuclei with irregular nuclear contours. There are a high nuclear-to-cytoplasmic ratio and scattered atypical mitoses.

Figure 3A shows a biopsy of the salmon-colored mucosa at least one centimeter proximal to the GEJ. There is transition of squamous epithelium to glandular epithelium. The glandular epithelium is not the gastric foveolar type as expected for the stomach; rather there are goblet cells. This is intestinal metaplasia of the lower esophagus consistent with Barrett esophagus (BE). Figure 3B is a higher power image of the same area



**Figure 1.** Endoscopy shows a fungating mass at the gastroesophageal junction (GEJ) with salmon-colored mucosa proximal to the mass.



**Figure 2.** Biopsy of esophageal mass, hematoxylin and eosin (H&E) stained section,  $\times 200$  magnification. Adenocarcinoma characterized by irregular, infiltrating glands.

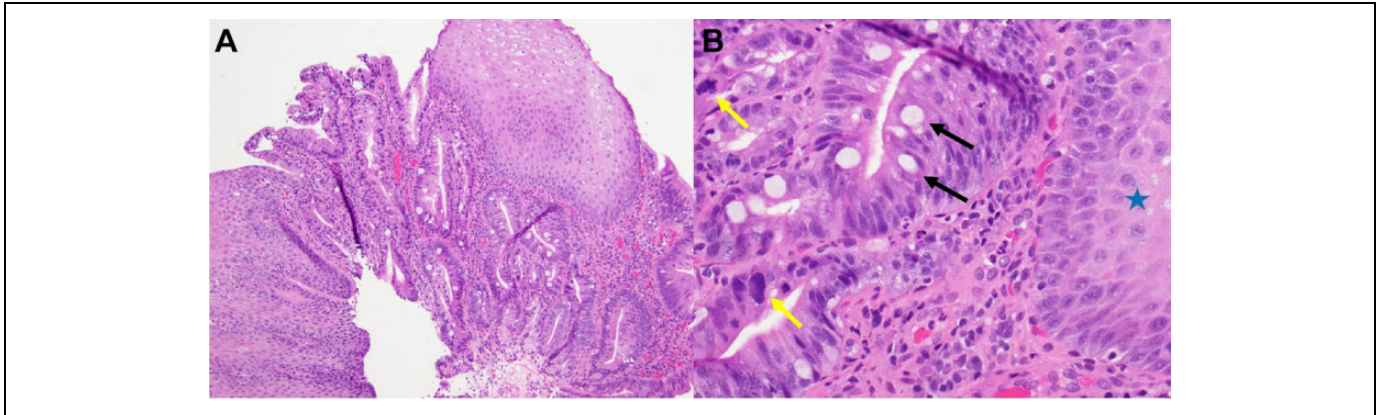
of BE. The squamous epithelium is marked with a star. Black arrows point to goblet cells. Yellow arrows point to the evidence of dysplasia including enlarged, hyperchromatic nuclei and atypical mitotic figures.

### What Is the Diagnosis?

Adenocarcinoma arising in BE. Adenocarcinoma is an invasive neoplasm of epithelial tissue of glandular origin. The histology seen in Figure 2 of infiltrating back-to-back glands is typical of adenocarcinoma.

### Describe the Pathophysiology of the Progression of Esophageal Mucosa to BE and Ultimately Esophageal Adenocarcinoma

Barrett esophagus results from the exposure of the squamous epithelium to the acidic contents of the stomach, as



**Figure 3.** A, Biopsy of salmon-colored mucosa adjacent to gastroesophageal junction, hematoxylin and eosin (H&E) stained section,  $\times 100$  magnification. B, Same area,  $\times 400$  magnification showing dysplastic features. Black arrows indicate goblet cells. Yellow arrows point to dysplastic features including hyperchromatic, enlarged nuclei, and mitotic figures. The star overlies the squamous epithelium.

occurs in the setting of GERD. Barrett esophagus is diagnosed when intestinal metaplasia of the squamous mucosa of the esophagus is seen on biopsy in correlation with endoscopic findings. The presence of goblet cells in columnar mucosa is the key feature that defines intestinal metaplasia. With continued acid exposure, the intestinalized epithelium may accumulate genetic abnormalities, including chromosomal abnormalities, TP53 mutations, and alterations of the *CDKN2A*, *EGFR*, and cyclin genes.<sup>2</sup> The accumulation of these genetic abnormalities correlates with histopathologic observation of low-grade dysplasia, high-grade dysplasia, and ultimately invasive adenocarcinoma.

#### Discuss the Risk Factors of Esophageal Adenocarcinoma

Esophageal adenocarcinoma is the most common cancer of the esophagus in the United States, though not worldwide, and its incidence has greatly increased in the past half century. The most important risk factor for the development of adenocarcinoma is BE. Patients with BE have at least a 30-fold increased risk of developing adenocarcinoma in comparison to the general population. However, the absolute risk of these patients developing adenocarcinoma is still low, estimated at 0.5% per year.<sup>3</sup> Risk factors for the development of BE include the same risk factors for GERD, including obesity. There is a strong gender and racial predilection with Caucasian males being significantly more affected than females or other races.

#### Describe the Common Clinical Presentation of Esophageal Adenocarcinoma

Because of its association with BE, esophageal adenocarcinoma arises in the distal third of the esophagus. It may be fungating or ulcerating and clinically presents with dysphagia, odynophagia, and weight loss. At the time of clinical presentation, esophageal adenocarcinoma is usually diagnosed at a high stage. It typically has a poor prognosis.

#### Describe the Histology of Esophageal Adenocarcinoma

The histology usually shows infiltrating mucinous glands (as in Figure 2), and less commonly diffuse signet ring cells.

#### What Is the Other Major Histologic Type of Carcinoma of the Esophagus? Discuss the Risk Factors

The majority of neoplasms in the esophagus fall into 2 types: squamous cell carcinoma (SCC) and adenocarcinoma. Worldwide, SCC is the more prevalent esophageal tumor. Although the presentation is similar, the epidemiology and risk factors vary considerably (see Table 1).

Squamous cell carcinoma has a significant variation in incidence, up to 180-fold difference, among geographic regions (see ‘What is the Geographic Impact on Esophageal Neoplasia’). These geographic differences suggest environmental or cultural risk factors associated with esophageal SCC. Poverty and nutritional deficiencies in general are considered risk factors. Specific dietary factors include foods containing nitrosamines, fungus-contaminated foods, and consuming extremely hot beverages. Exposure to polycyclic hydrocarbons, found in burning coal gasoline, trash, and other materials, is also a risk factor.<sup>4</sup>

In developed countries, smoking tobacco and consuming alcohol are the most significant risk factors. There is an 8-fold increase in the incidence of SCC in African Americans than in Caucasians, which is partially explained by the differences in tobacco use.<sup>5</sup> Similarly to adenocarcinoma, SCC affects males more frequently than females (4:1).

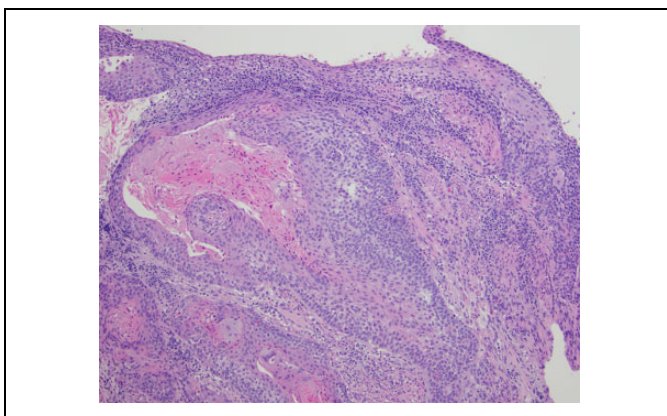
An important risk factor for SCC worldwide is human papillomavirus (HPV). Human papillomavirus infection has been linked to SCC of multiple body organs. There is wide variation in reported associations of HPV infection with esophageal SCC, ranging from 0% to 78%.<sup>6</sup> These associations vary geographically, with regions with a high incidence of esophageal SCC tending to have a high incidence of HPV infection. In the United States, esophageal SCC is only



**Table 1.** Comparison of Esophageal Adenocarcinoma and Squamous Cell Carcinoma.

Clinical Factors	Esophageal Adenocarcinoma	Esophageal SCC
Presentation	Progressive dysphagia (solids to liquids), unintentional weight loss	Progressive dysphagia (solids to liquids), unintentional weight loss
Epidemiology	Most common esophageal cancer in the United States. Incidence in the United States has increased greatly over the past 50 years.	Most common esophageal cancer worldwide. More common in developing countries, and incidence is highly geographic dependent. Disproportionately affects African Americans in comparison to Caucasians in the United States.
Risk factors	<ul style="list-style-type: none"> <li>- Barrett esophagus</li> <li>- Obesity</li> </ul>	<ul style="list-style-type: none"> <li>- Diet rich in nitrosamines, red meat, and very hot beverages</li> <li>- Environmental exposure to polycyclic hydrocarbons</li> <li>- Poverty</li> <li>- Smoking tobacco</li> <li>- Consuming alcohol</li> <li>- HPV infection</li> </ul>

Abbreviations: HPV, human papillomavirus; SCC, squamous cell carcinoma.



**Figure 4.** Biopsy of esophageal squamous cell carcinoma, hematoxylin and eosin (H&E) stained section, × 100 magnification.

infrequently associated with HPV infection. A clear etiologic role of HPV in the development of esophageal SCC has not been established.<sup>6</sup>

Squamous cell carcinoma arises predominantly in the upper and middle third of the esophagus. Histologically, esophageal SCC looks the same as SCC found elsewhere in the body. It is composed of dysplastic squamous cells with

hyperchromatic nuclei, so-called paradoxical maturation, and squamous pearls (Figure 4). Similarly to adenocarcinoma, SCC often presents at an advanced stage and, given the rich lymphatic network within the esophageal wall, distant spread is often seen.

### What Is the Geographic Impact on Esophageal Neoplasia?

Squamous cell carcinoma is more common in underdeveloped countries with a particularly high incidence across Iran and central northern China, known as the esophageal “cancer belt.”<sup>4</sup> There are also pockets within individual countries, including Brazil, South Africa, and Kenya, with a high incidence of esophageal SCC. These geographic differences likely reflect dietary or environmental exposures. Diets rich in nitrosamines, red meat, and hot beverages, and low in fruits and vegetables have been implicated in the development of esophageal SCC. Environmental exposures such as polycyclic hydrocarbons are also more prevalent in these geographic hotspots.

### Teaching Points

- There are 2 major types of esophageal carcinoma—SCC and adenocarcinoma.
- Adenocarcinoma is the most common type of esophageal cancer in the United States and the most important risk factor is BE. Adenocarcinoma occurs in the distal third of the esophagus.
- Barrett esophagus is caused by chronic GERD and is defined histologically by intestinal metaplasia (goblet cells) of the squamous epithelium of the esophagus.
- Squamous cell carcinoma is the most common type of esophageal cancer worldwide. Squamous cell carcinomas arise in the upper and middle third of the esophagus.
- There are significant geographic hotspots for esophageal SCC and risk factors include nutritional deficiencies, poverty, tobacco, and alcohol.

### Declaration of Conflicting Interests

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