

ORAL CANCER

- I. MAIN FORM: Squamous cell carcinoma arising in oral mucosa; tends to grow slowly and spread late; floor of mouth and tongue worse than buccal mucosa; usually easy to detect.
- II. OTHER FORMS:
 - Adenocarcinomas arising from minor salivary glands.
 - Odontogenic tumors arising from dental structures in jaw.
 - Malignant melanoma, sarcomas and other very rare lesions.
- III. PRECANCEROUS LESIONS:
 - Leukoplakia
 - Erythroplakia/erythroplasia
 - Dysplasia
- IV. POSSIBLE ETIOLOGIC AGENTS: smoking; chewing tobacco, betel, etc; strong alcohol; chronic irritation.
- V. MARKED GEOGRAPHIC VARIATIONS IN INCIDENCE: Southeast Asia highest.

PATHOLOGY OF THE ESOPHAGUS

INTRODUCTION

The esophagus is a simply constructed organ: a straight muscular tube 10 inches (25 cm) long (15 to 40 cm from the teeth) with a squamous epithelial lining.

There is a limited range of lesions that can occur: obstruction to flow, perforation, rupture, surface alterations and loss of propulsion.

The number of microscopic lesions is also limited due to the small number of tissues present.

Therefore it is paradoxical that esophageal disease is serious disease: cancer of the esophagus has about the worst prognosis of any organ even though one might imagine that early cancers would produce signs and symptoms at stages compatible with cure; hemorrhage and perforation in the esophagus are generally more lethal than similar lesions occurring in the remainder of the GI tract; obstruction is much more difficult to deal with than in other portions of the GI tract.

Because of its location, next to the trachea, left bronchus, aortic arch, descending aorta and left atrium, and its lack of a serosa, it is difficult to manipulate, remove, replace, repair and reconstruct. Unlike the gut, there is nothing to spare; it needs all of its 10 inches.

I. DEVELOPMENTAL ANOMALIES.

These can be grouped generally into focal narrowing, focal dilatation and displaced tissues.

The following apply to most GI sites as well:

Atresia - No lumen

Stenosis - Narrow lumen

Fistula - Abnormal communication between 2 hollow organs

Duplication - Extra lumen with enteric-type wall

Cyst - Closed sac with lining

Diverticulum - Outpouch of lumen

Hernia - Protrusion of organ outside normal cavity

A. ~~Atresia, stenosis and tracheoesophageal fistula.~~ These are relatively common congenital malformations (1 per 1000 births). The gut and respiratory tract start as a single tube between which a septum forms. The second month of pregnancy is the critical time of separation. The most frequent form of anomaly (80-90%) is: the upper end of the esophagus forms a blind sack and the lower end enters the trachea within 2 cm of the bifurcation. Usually a gap of 1-5 cm is between the upper and lower ends; these may be connected by a cord.

Pure atresia is rare and associated with hydramnios. Esophageal atresia is often associated with other congenital anomalies, e.g. imperforate anus and lesions of the small bowel and heart. The signs and symptoms depend on the defect, e.g. air in the stomach, regurgitation, excessive salivation, pneumonia.

B. ~~Duplication, diverticula and cysts.~~ Duplication, an extra segment, is very rare compared to such lesions in the intestines. Cysts are more common. Most occur posteriorly and can be associated with vertebral anomalies. They can be lined by ciliated epithelium or gastric mucosa with a muscular wall. Anterior mediastinal esophageal cysts

are less common than posterior ones and contain respiratory elements such as ciliated epithelium, bronchial glands and cartilage. Congenital diverticula are rare compared to acquired lesions (see below; also for pulsion vs traction diverticula).

C. Heterotopia. Gastric mucosa in the esophagus is rarely congenital; usually is acquired metaplasia (see Barrett esophagus).

D. Diaphragmatic Hernia. Left posterolateral: common site of congenital hernia; stomach, gut and spleen may enter left chest; may compress lung and prevent its maturation in utero.

Hiatal Hernia: Hernias through the diaphragm are mostly acquired and occur at the hiatus; stomach enters. Most hiatal hernias occur in late adulthood. There are three types: (1) sliding hh: the stomach slides above the diaphragm due to a hiatus which is too large; comprises 80-90% of acquired hiatal hernias. Associated with chronic cough, kyphosis and obesity; (2) rolling hh: paraesophageal herniation of the stomach; less than 10%; (3) traumatic hh: due to perforation. About 5% of the population has some form of hiatus hernia, most without symptoms. Heartburn and regurgitation due to gastric reflux occur in only 10% of these patients. Bending and lying down increase symptoms.

II. MUSCULAR AND MURAL DISORDERS.

A. Achalasia (cardiospasm). A neuromuscular disorder characterized by obstruction at the cardia due to failure of the lower sphincter to relax and loss of normal coordinated peristalsis. The proximal tube dilates progressively, elongates and becomes tortuous. There is a reduction in the number of ganglion cells in the myenteric plexus in the dilated portion and the spastic area may contain ganglion cells (unlike Hirschsprung disease of rectum). Pain, regurgitation, aspiration and squamous carcinoma are associated with this lesion. Chagas disease leads to achalasia: trypanosomes destroy the myenteric ganglion cells. Achalasia may occur in Parkinson disease.

B. Scleroderma; progressive systemic sclerosis. Part of a generalized systemic disease or of a more localized one involving primarily the GI tract. Gradual atrophy of smooth but not striated muscle with fibrosis. Eventually results in reduced competence of the lower esophageal sphincter leading to reflux esophagitis and stricture.

C. Acquired diverticula. Out-pouchings of the lumen are mostly acquired and of two types:

1. Pulsion diverticula: Due to raised intraluminal pressure, often related to weakened wall especially in areas proximal to sphincter; above the upper sphincter (Zenker diverticulum) or above the lower sphincter.
2. Traction diverticula: Due to external scarring and inflammation, especially at the area of tracheal bifurcation following tuberculosis. These lesions lead to regurgitation, aspiration, inflammation, hemorrhage, perforation or there may be no symptoms.

D. Rings and webs. Rings are annular constrictions, ledges. Webs are eccentric, thin membranous rims. Both may be congenital or acquired. Rings in the lower esophagus are usually near the esophagogastric junction and are due to inflammatory scarring. Upper esophageal webs and rings occur at the level of the cricopharyngeal muscle and are associated with the Plummer-Vinson syndrome (hypochromic anemia, atrophic glossitis and dysphagia) (sideropenic dysphagia). In this location, the web or ring may develop a carcinoma.

E. Lacerations, perforations and rupture.

1. Foreign bodies: bones and endoscopes.

2. Mallory-Weiss syndrome: linear, irregular lacerations resulting from vomiting, usually occurring at or near the gastroesophageal junction, leads to massive hemorrhage.
 3. Trauma: following intra-abdominal blow.
- F. Varices. Dilated tortuous veins. The submucosal venous plexus of the esophagus connects the portal and systemic systems. Portal hypertension (from cirrhosis) leads to their dilatation. These tortuous veins are typically in the distal third of the esophagus. They project into the lumen, are prone to rupture and are a major source of hemorrhage and death in cirrhotics.

III. INFLAMMATORY LESIONS - ESOPHAGITIS

Infection is unusual due to tough smooth surface. Occurs in debilitated, immunosuppressed, etc. Inflammation is frequent due to acid reflux.

A. Acute

1. Acute esophagitis.
 - a. Herpes simplex virus. Most common cause of viral esophagitis. Patients with visceral herpes generally have esophageal involvement. Occurs primarily in immunosuppressed patient often after chemotherapy for cancer. Intranuclear viral inclusions, ground glass nuclei, multinucleated giant cells and ballooning degeneration of infected cells are best seen in the squamous epithelium at the ulcer margin.
 - b. Cytomegalovirus. Occurs in ulcers throughout GI tract. Immunosuppression predisposes. CMV inclusion bodies are in large endothelial cells and fibroblasts of ulcer base.
 - c. Candida albicans (Monilia). The most common cause of fungal esophagitis. Usually in diabetic, immunosuppressed or antibiotic treated patients. Endoscopically there are white plaques or umbilicated mucosal lesions with little inflammatory response. A fibrinopurulent exudate contains the organisms. Pseudohyphae should be seen in tissue sections because yeast forms are common surface contaminants.
 - d. Corrosive esophagitis. Lesion due to accidental or suicidal ingestion of agents such as lye, phenol, lysol, acids, alkalis, hot foods and alcohol. Diffuse ulceration and extensive hemorrhage can lead to complete separation of the mucosa so that a cast is regurgitated. Lesion may heal with extensive scar formation leading to obstruction, rings and strictures. Squamous cell carcinoma is increased among these patients.
 - e. Intubation - A common cause of esophagitis amongst hospitalized patients.
 - f. Nonspecific esophagitis. Lesions associated with upper respiratory infections, allergy and uremia among others. Associated with dysphagia, pain and hematemesis. Can mimic myocardial infarction.
 - g. Drug-induced esophagitis. Usually result of physical entrapment of undigested pills or capsules (taken at bedtime with too little water) leading to ulcer, typically at level of tracheal bifurcation. Allergy to drugs can also cause esophagitis.

B. Chronic esophagitis. This typically follows corrosive and reflux esophagitis.

1. ~~Tuberculosis~~. Secondary to pulmonary disease due to swallowed sputum or penetration from a hilar lymph node. Rare.
2. ~~Radiation esophagitis~~. This follows therapeutic radiation to the thorax and is associated with edema and ulcers in the acute stage and strictures later due to ischemia from vessel damage.
3. ~~Chagas disease~~: Trypanosoma cruzi transmitted by Triatoma. Leishmanial forms cause cysts in infected cells in smooth and cardiac muscle. Leads to cardiomegaly, achalasia, megaesophagus and megacolon. A neurotoxin damages the ganglion cells. When 90% are destroyed aperistalsis results. This leads to reflux and chronic inflammation.

C. ~~Reflux (peptic) esophagitis~~. The most important and most common form of esophagitis. Reflux of gastric juices occurs most frequently in hiatus hernia but also in alcoholism, scleroderma, recurrent vomiting, and diseases affecting the muscular tone of the lower esophageal sphincter. Squamous mucosa is not resistant to a low pH, particularly below 5.8. (Bile regurgitation into the esophagus after gastric resection is even more damaging). Reflux esophagitis is important because it is chronic and frequent. Reflux results in:

1. Inflammation: polys and eosinophils in the epithelium.
2. Hyperplasia: thickening of the basal layer (over 15%); elongation of the papillae of the lamina propria (above the 50% level)
3. Ulceration: peptic; can lead to perforation and bleeding
4. Scarring: narrowing with strictures, rings and webs
5. Glandular metaplasia - Barrett esophagus: sequel to long standing reflux esophagitis. About 10% of patients with symptomatic reflux esophagitis have Barrett esophagus. Patchy or diffuse glandular tissue replaces the squamous epithelium; a mixture of gastric and intestinal type cells. It is a precancerous lesion because dysplasia develops in the metaplastic tissue and can become adenocarcinoma (in up to 10% of Barrett cases). The majority of adenocarcinomas of the esophagus arise in Barrett epithelium. Whites have a much higher incidence of Barrett metaplasia and adenocarcinoma than blacks, though reflux occurs in both groups.

IV. TUMORS

A. ~~Epithelial~~

1. Benign
 - a. ~~Squamous cell papilloma~~: rare in the esophagus
 - b. ~~Adenomas~~: rare
2. Malignant
 - a. ~~Squamous cell carcinoma~~. Over 75% of esophageal malignancies are squamous cell carcinomas. Over 80% occur in the distal two-thirds of the esophagus. In the distal two-thirds, there is a marked predilection for males, 4 or 5:1. It is associated with achalasia, chronic esophagitis, strictures, alcohol and tobacco use. Blacks have incidence rates over 4 times that of whites. The typical radiographic and endoscopic appearance is an ulcerated mass with an overhanging margin; may be flat or annular, polypoid, nodular or diffuse. Microscopically, squamous cell carcinomas are generally

differentiated and may show submucosal infiltration laterally that is beyond what is visible grossly. They tend to invade the lung, but lung tumors do not tend to invade the esophagus.

Symptoms: late; progressive obstruction leads to dysphagia (difficult swallowing)

Tracheoesophageal fistulas occur in up to 10% of esophageal carcinoma.

- b. ~~Adenocarcinoma~~: about 15% of esophageal malignant tumors; most are located in the lower third of the esophagus, comprising over 40% of cancers there. Whites have incidence rates over 4 times greater than blacks (the reverse of squamous cell carcinoma). Males have much higher incidence than females. Most arise in Barrett esophagus. The adenocarcinomas have the same histologic features as do gastric carcinomas: form glands, frequently are papillary, may be mucinous, and can be signet ring cell in type. Dysplasia appears to precede carcinoma in a situation analogous to dysplasia and carcinoma in atrophic gastritis and ulcerative colitis.

Adenocarcinomas of submucosal glands are rare.

Survival strongly depends on anatomic extent of tumor, i.e. stage, but overall, esophageal carcinoma has the poorest prognosis of all digestive tract cancers: less than 10% 5-year survival.

TNM classification of esophageal carcinoma

T1	Lamina propria, submucosa
T2	Muscularis propria
T3	Adventitia
T4	Adjacent structures
N1	Regional

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