DIAGNOSTIC PATHOLOGY

Gastrointestinal

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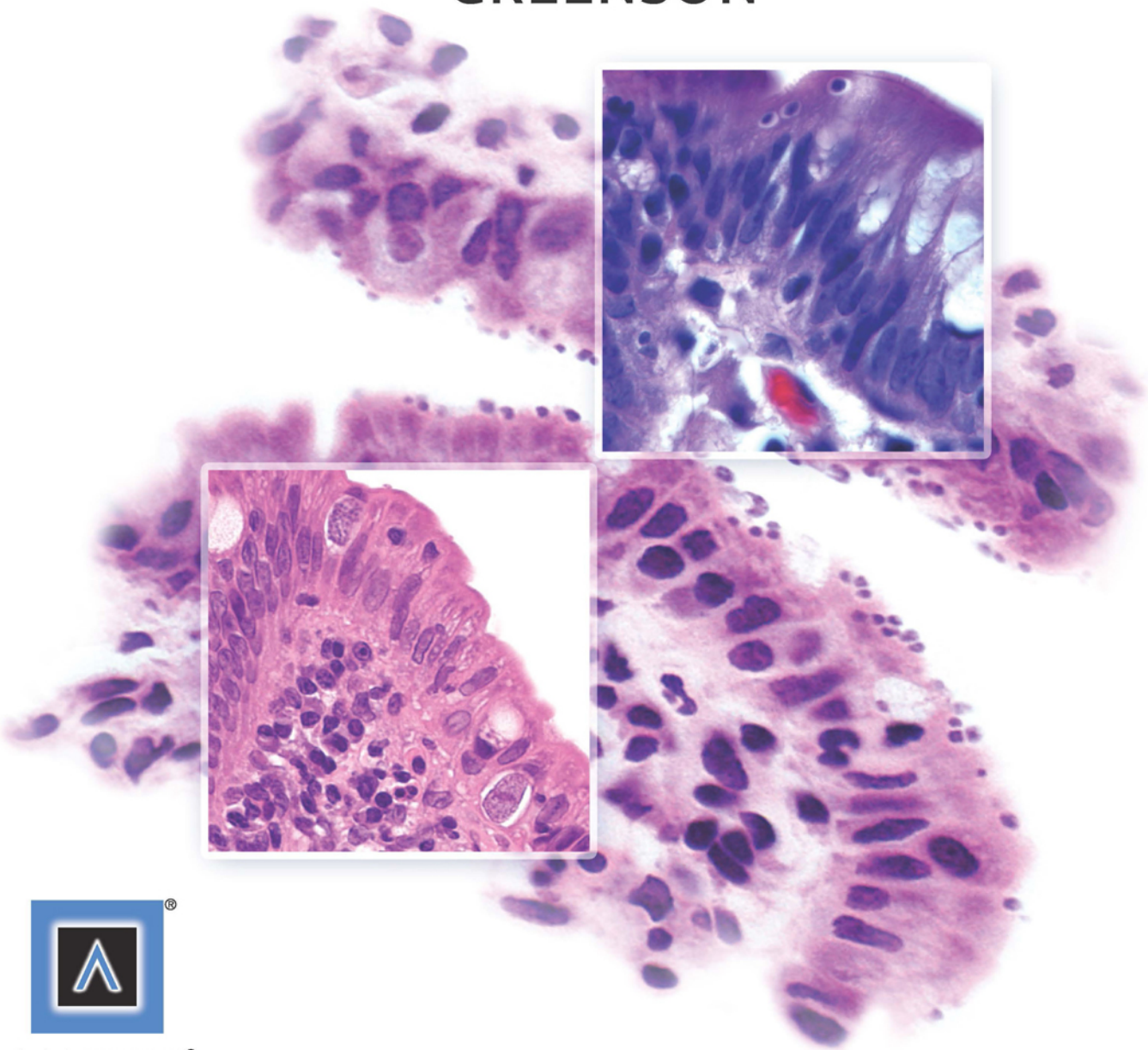

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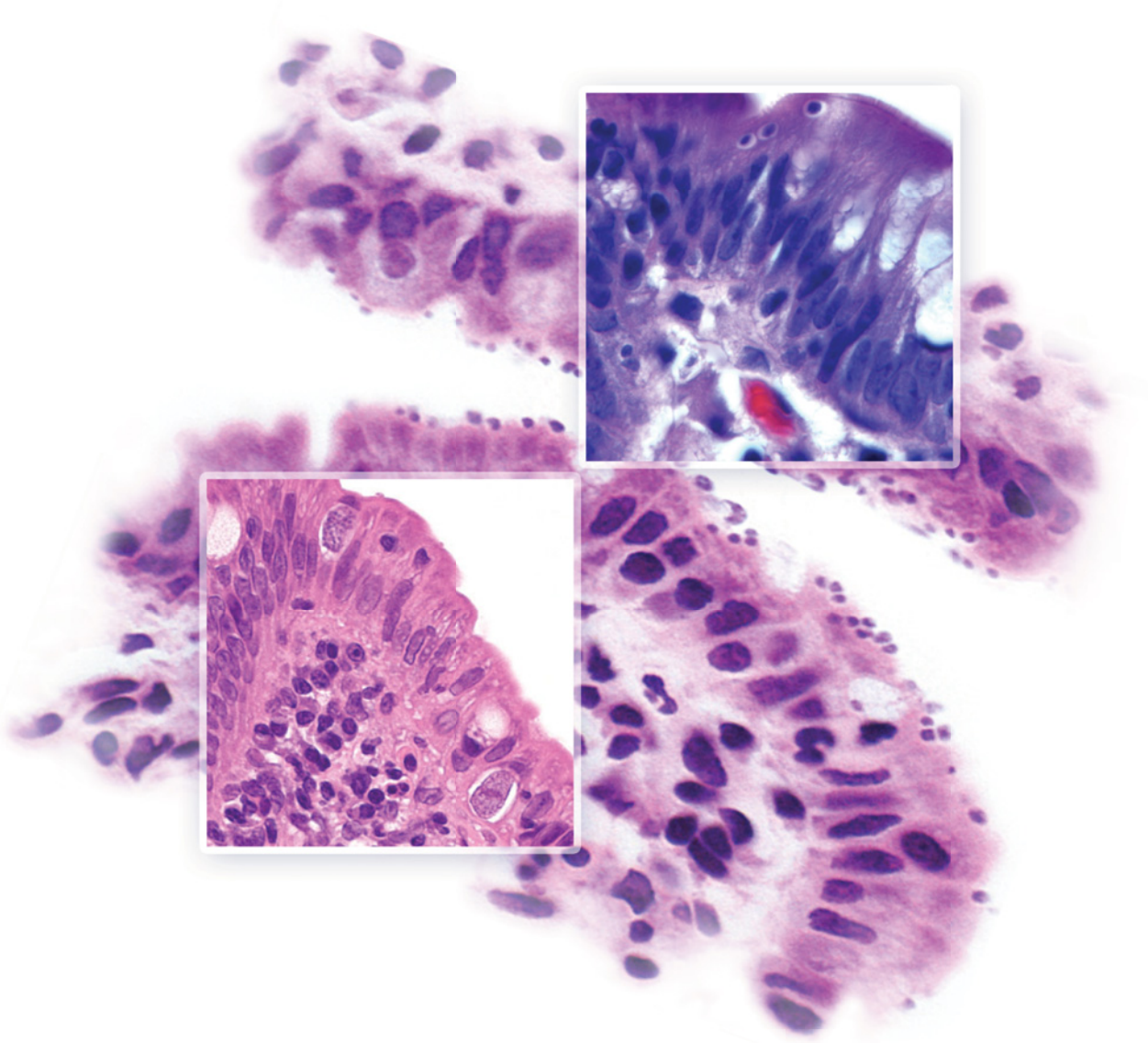

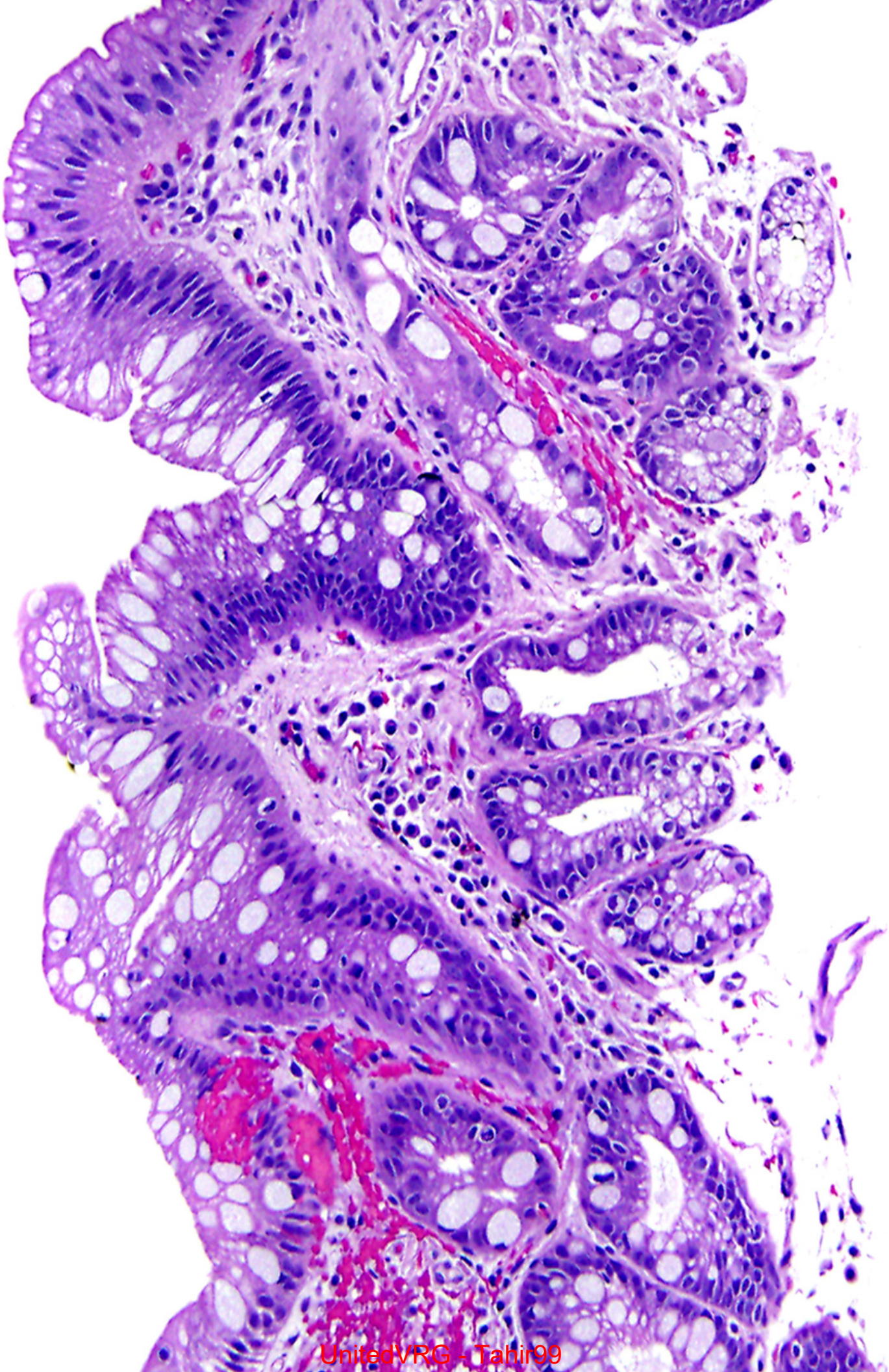

DIAGNOSTIC PATHOLOGY

Gastrointestinal

SECOND EDITION

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Dedications

A project like this is always the result of teamwork on many different levels. I would like to thank my parents, Walter and Louise Greenson, for teaching me the value of a good education and for providing the means for me to get one. I would also like to thank Henry D. Appelman, Stephen A. Geller, and John H. Yardley for being great role models/mentors. I would like to acknowledge the hard work and dedication of all of my coauthors and all the members of the Amirsys team. Lastly, to Jann, Hannah, and Sarah—the three amazing women in my life to whom I owe everything—thank you for putting up with me!

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To my family.

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EAM

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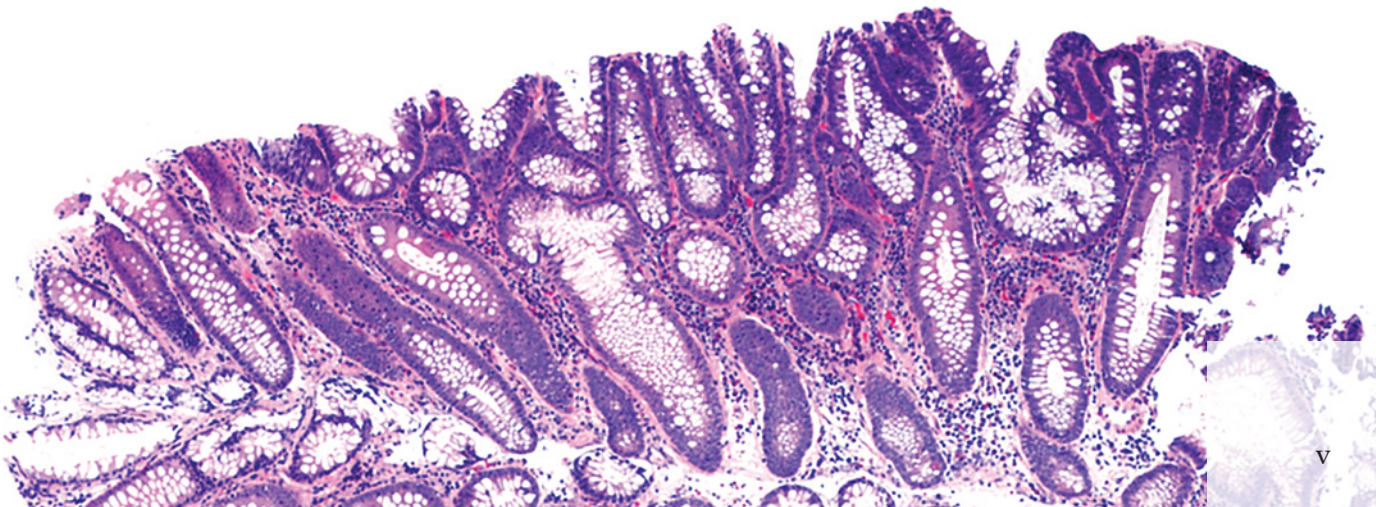
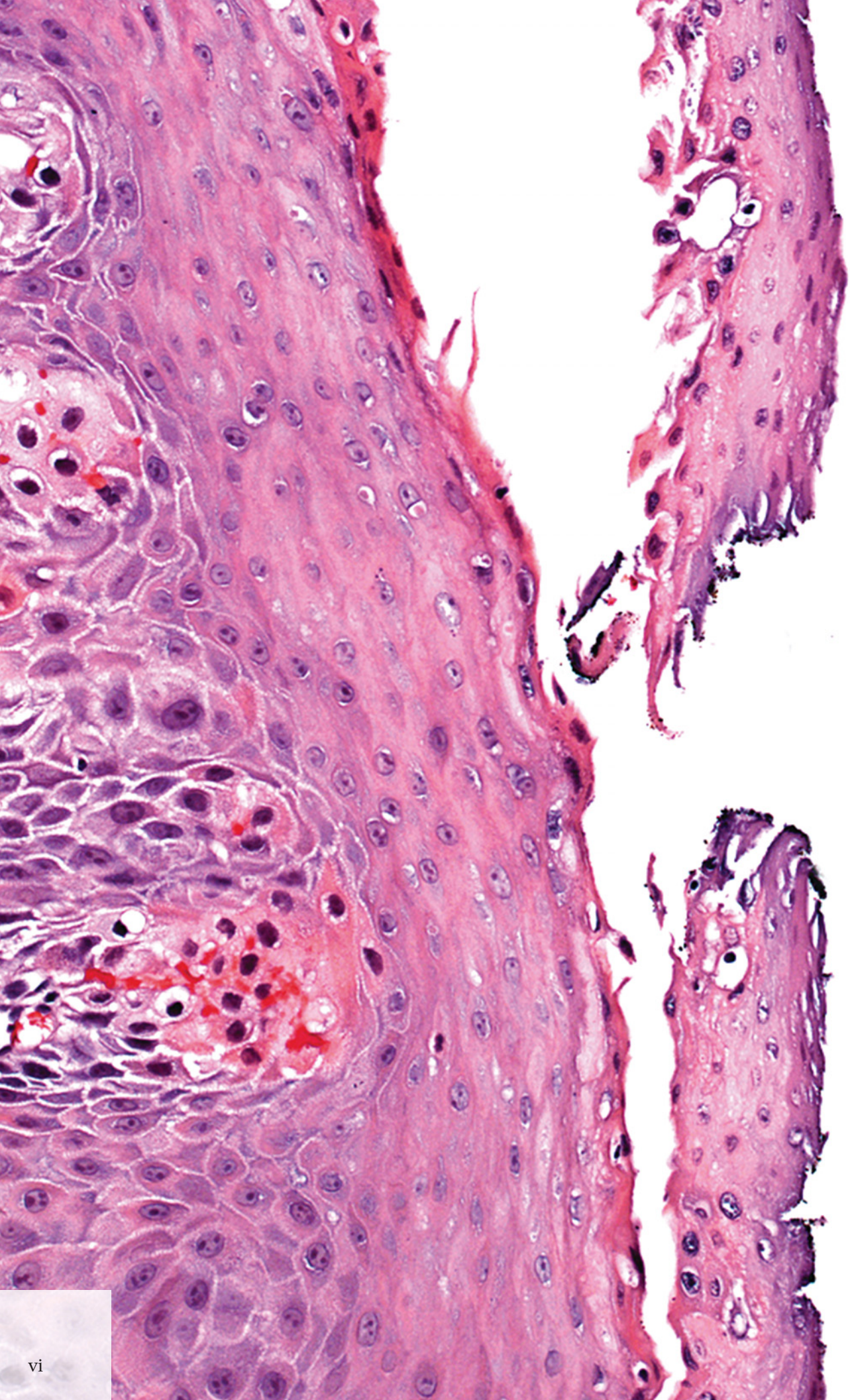
GYL





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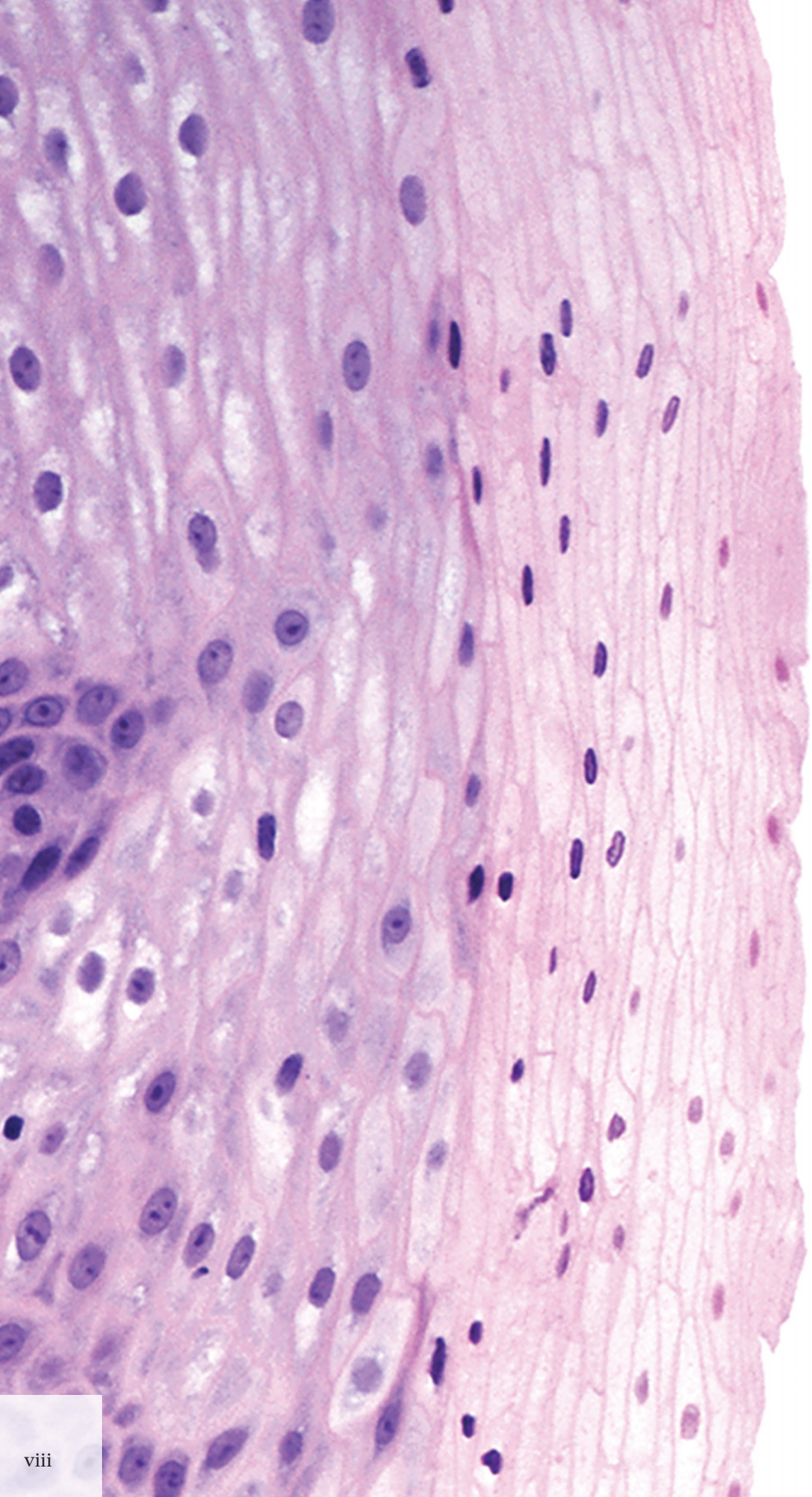

Preface

As we wade deeper into the information age and the database of medical research expands exponentially, it becomes more and more difficult to keep an up-to-date working knowledge of all the things one encounters on a typical day of surgical pathology sign out. Given the number of new immunostains, molecular genetic tests, and the demands of personalized medicine, the surgical pathologist can easily become overwhelmed, both with the amount of material to master and the amount of time required to do so.

The goal of *Diagnostic Pathology: Gastrointestinal, Second Edition* is to provide quick, up-to-date information on gastrointestinal pathology, both visual and factual, to either help the pathologist arrive at the correct diagnosis or refresh his or her memory about the diagnosis itself. Instead of full prose text, we have provided a stripped-down outline format. The key facts regarding each diagnosis are then highlighted in a box for ease of use. Tables highlighting the salient immunostains &/or molecular tests useful in the differential diagnosis of lesions are provided when appropriate, and all diagnoses are illustrated with high-quality color images taken with the intent of mimicking real practice.

We hope that this book is useful as a quick reference at the microscope during sign out, whether to look up something as esoteric as microsporidia or something as common as serrated colorectal polyps. Lastly, owners of *Diagnostic Pathology: Gastrointestinal, Second Edition* will also receive Expert Consult, the eBook version that provides online access to all information and images contained in this text.

We hope you find both the format and the content of this book to be useful in your quest to provide accurate and informative gastrointestinal pathology reports.

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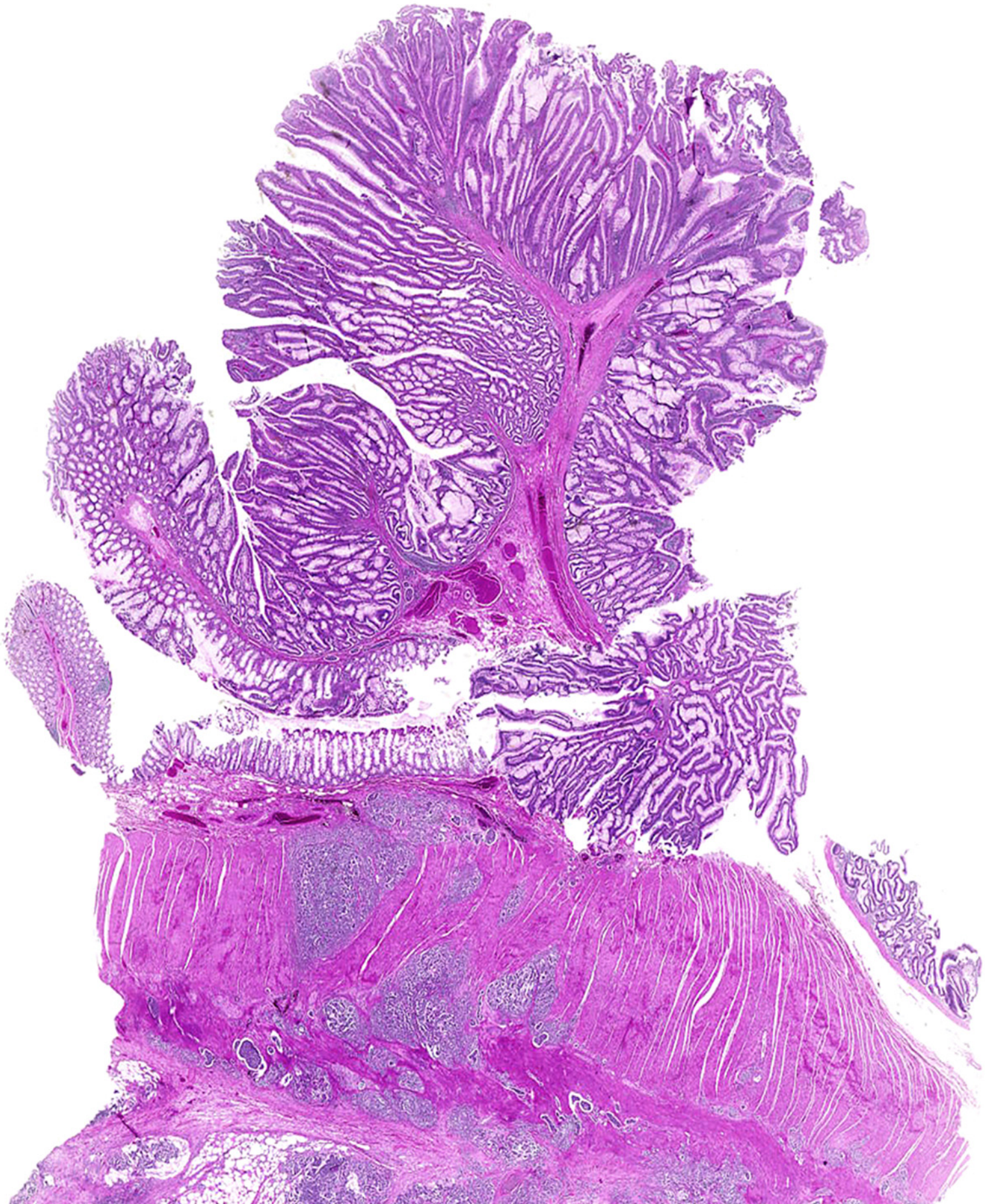

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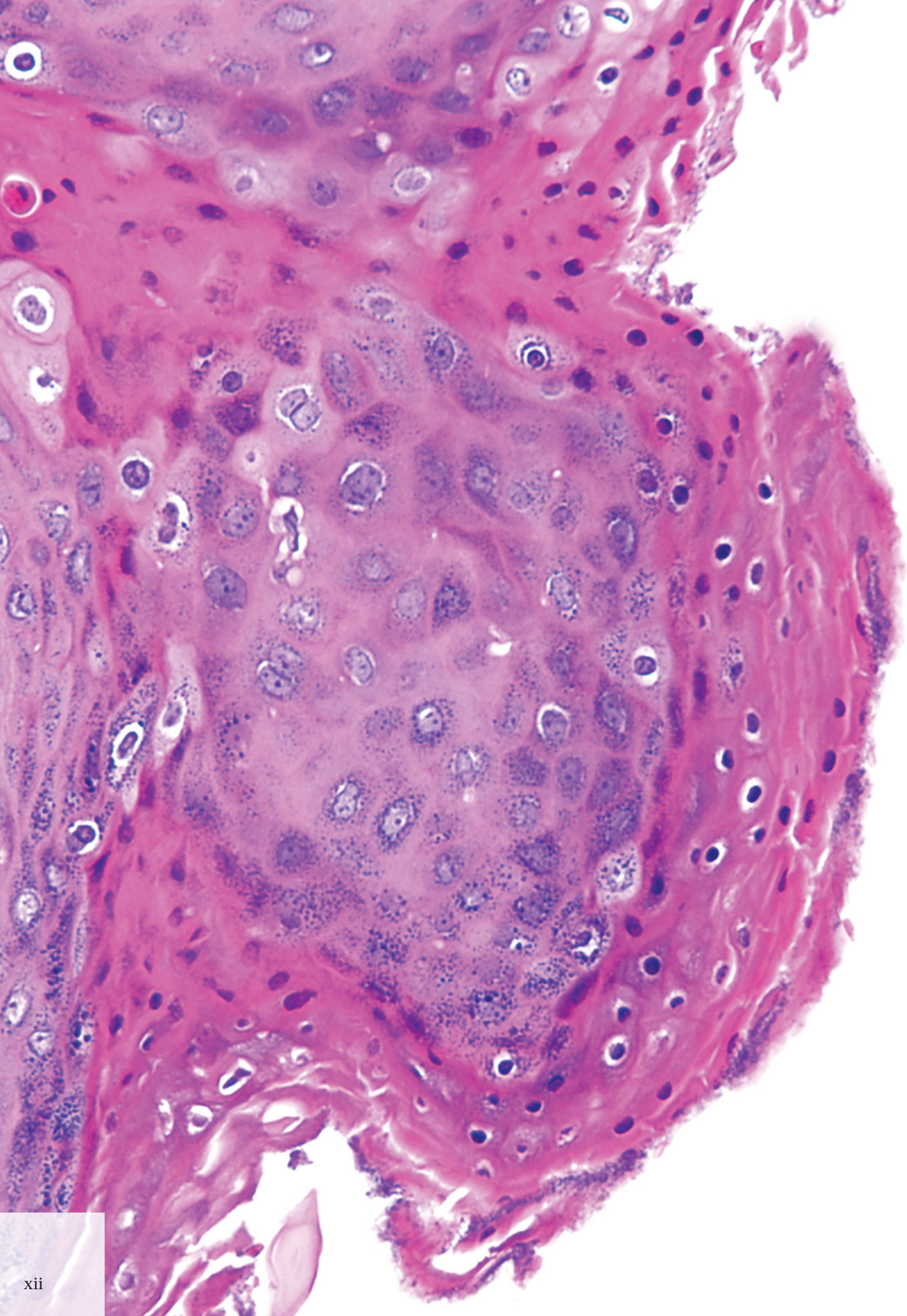

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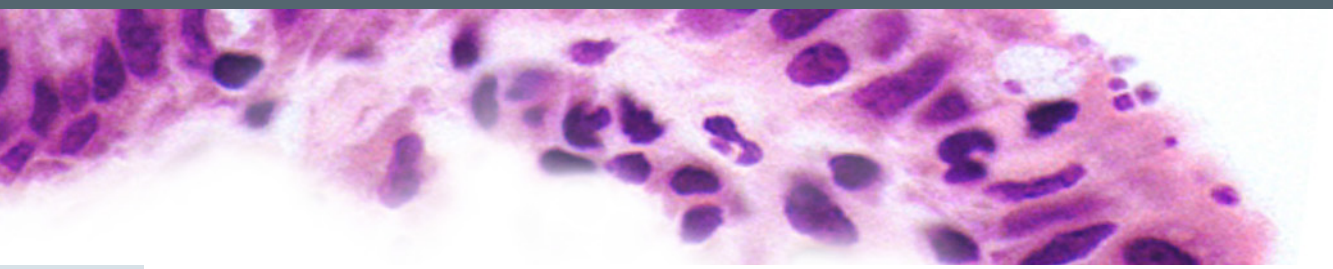

Part I: Esophagus

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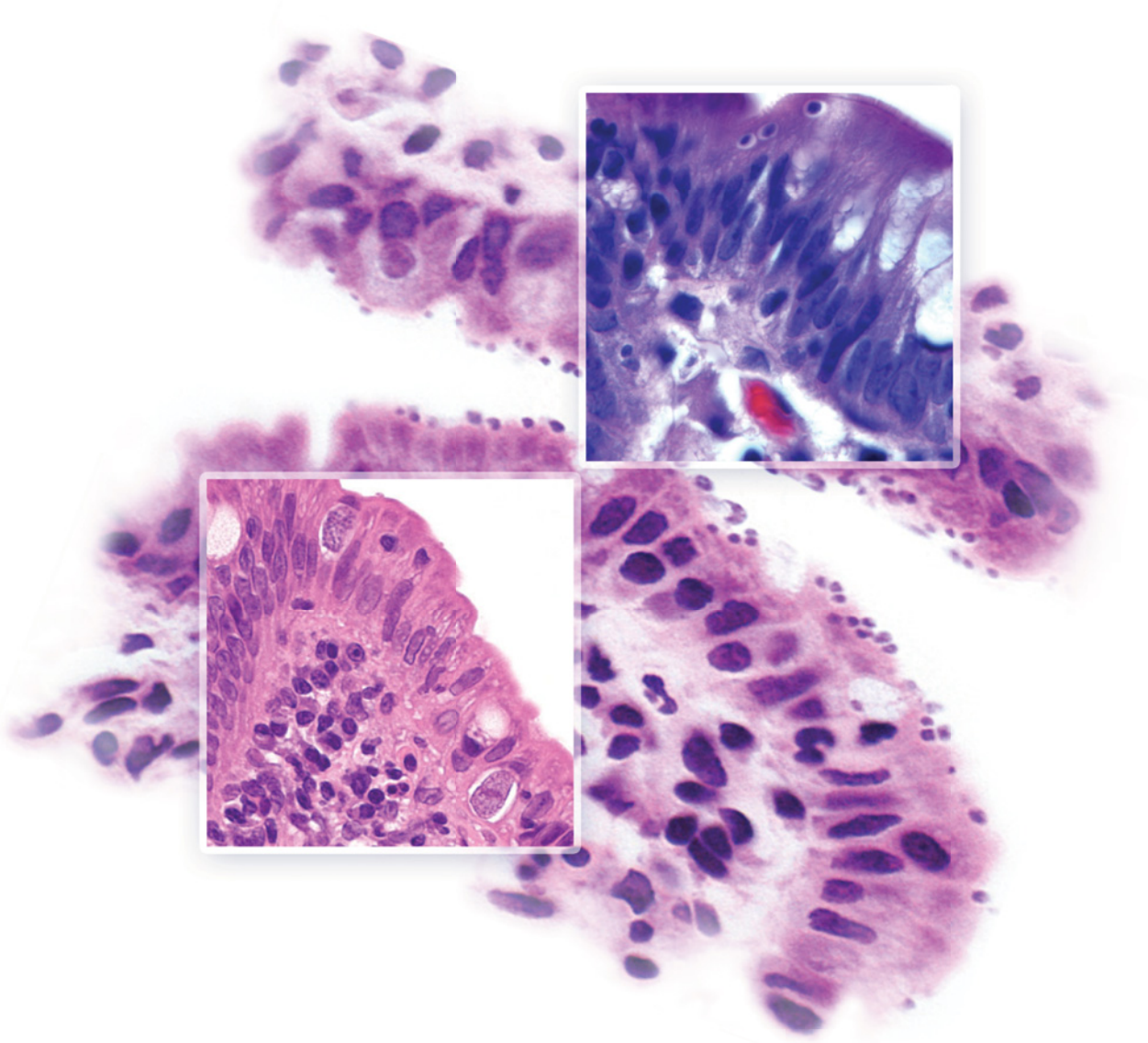

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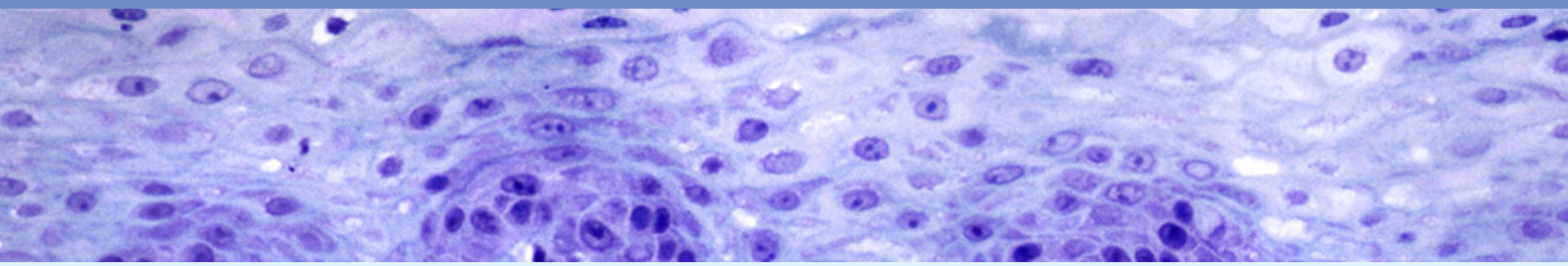
PART I
SECTION 1

Nonneoplastic



Tracheoesophageal Fistula and Esophageal Atresia

KEY FACTS

TERMINOLOGY

- Tracheoesophageal fistula (TEF): Congenital connection between esophagus (proximal &/or distal) and trachea
- Esophageal atresia (EA): Complete interruption of lumen

ETIOLOGY/PATHOGENESIS

- TEF: Incomplete separation of primitive foregut
- EA: Failure of primitive foregut to recanalize
- Associated congenital malformations in ~ 50%
  - Cardiac defects in 30%; trisomy 18, 12, or 21
- Acquired TEF: Neoplasm, trauma, iatrogenic, inflammatory

CLINICAL ISSUES

- Incidence of 0.02-0.04%, usually (98%) with coexistent EA
- Excessive salivation, regurgitation, abdominal distention
- Coughing, choking, aspiration, respiratory distress, cyanosis

IMAGING

- Passed nasogastric tube (NGT) stops at 10-12 cm if EA
- Air in stomach/small bowel confirms a distal TEF
- US: Polyhydramnios, blind esophagus, no gastric bubble

MACROSCOPIC

- Type A (type 2): EA only (5-8%)
- Type B (type 3A): EA with proximal TEF (0.8-1%)
- Type C (type 3B): EA with distal TEF (85-90%)
- Type D (type 3C): EA with both proximal & distal TEF (1-2%)
- Type E (H-type): TEF only (2-6%) ± esophageal stenosis
- Gross type F: Esophageal stenosis only
- Vogt type 1: Esophageal agenesis (complete absence)

MICROSCOPIC

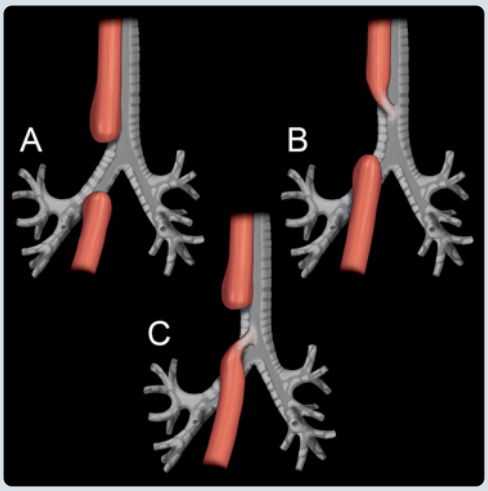
- Epithelium-lined connection (respiratory & digestive tubes)
- Irregular smooth muscle fibers, scar (fibrosis)
- Disrupted Auerbach myenteric plexus

DIAGNOSTIC CHECKLIST

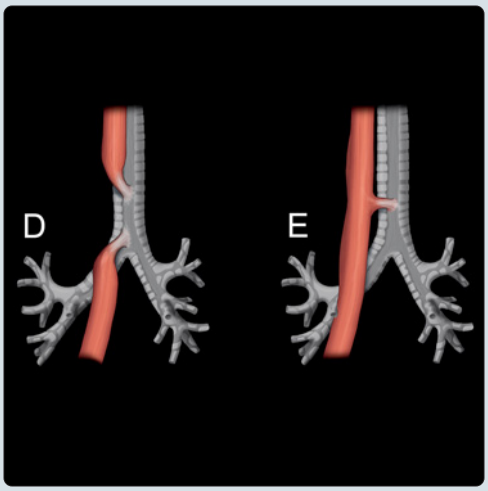
- Tracheobronchial elements in distal esophagus
- Gross appearance determines classification

(Left) *Schematic of the gross classification of EA/TEF types: (A) esophageal atresia only, (B) esophageal atresia and proximal tracheoesophageal fistula, (C) esophageal atresia and distal tracheoesophageal fistula.* **(Right)** *Schematic of gross classification types (continued): (D) esophageal atresia with both proximal and distal tracheoesophageal fistula, (E) tracheoesophageal fistula only, ± additional esophageal stenosis (H-type: No esophageal atresia).*

Gross Classification of TEF

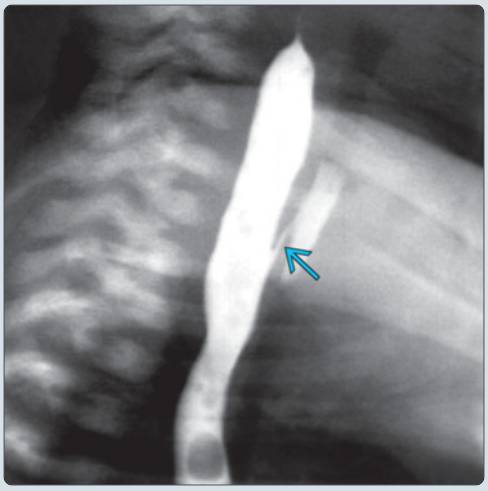


Gross Classification of TEF

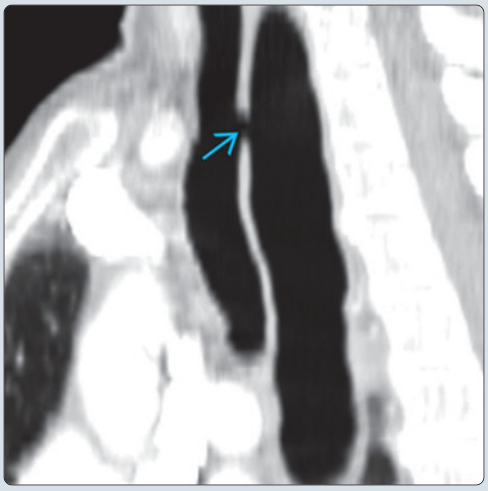


(Left) *Esophagram after barium swallow demonstrates a tracheoesophageal communication ⇨ extending from the esophagus anteriorly and superiorly toward the trachea. In most type B TEFs, the opening in the trachea is usually near the carina.* **(Right)** *Sagittal view of contrast-enhanced CT shows a fistulous connection ⇨ between the trachea and the esophagus. This is an H-type congenital tracheoesophageal fistula. (From ExDDx: Chest.)*

Gross Type B TEF



Gross Type E (H-Type) TEF



TERMINOLOGY

Abbreviations

- Tracheoesophageal fistula (TEF)
- Esophageal atresia (EA)

Definitions

- TEF: Congenital fistulous connection between esophagus (proximal &/or distal) and tracheobronchial tree
- EA: Complete interruption of esophageal lumen continuity
- Coloboma (of the eye), heart defects, choanal atresia (of the nose), growth &/or mental retardation, genital hypoplasia, and ear anomalies (CHARGE association)
- Vertebral anomalies, anal atresia, cardiac defects, TEF &/or EA, renal dysplasia, radial or limb anomalies (VACTERL association)

ETIOLOGY/PATHOGENESIS

Developmental Anomaly

- EA: Failure of primitive foregut to recanalize
- TEF: Incomplete separation of primitive foregut
  - Failure of lung/tracheal bud to completely separate
  - Resulting fistulas vary, depending on amount of epithelium
    - Able to maintain foregut epithelial continuity
- Abnormal proliferation of tracheoesophageal septum
- Premature infants at increased risk
- Associated congenital malformations in ~ 50%
  - Cardiovascular, gastrointestinal, neurologic, genitourinary, or orthopedic
    - Cardiac defects present in 30%
      - Ventriculoseptal defects, tetralogy of Fallot
  - Usually > 1 (often other midline defects)
  - VACTERL association in 20-30% of TEF/EA
    - So-called general foregut malformation
  - 10% of CHARGE patients have TEF/EA
  - 25% of Feingold syndrome patients have TEF/EA

Environmental Exposure

- Risk factors
  - Prenatal exposure to lead, drugs (e.g., methimazole), other physical agents
  - Associated: Maternal diabetes, maternal age < 20 years
- Mostly occurs during 1st trimester
  - Time of major organogenesis

Genetic factors

- Associated with aneuploidy (trisomy 18, 12, or 21) and other chromosomal aberrations
  - Trisomy 18 associated in 6-10% of cases
- Monozygotic twins have higher risk of EA
  - More than 2x higher risk compared to singletons
- Genes implicated: Retinoic acid receptors, *SHH*, and others

Acquired TEF

- Malignancy
  - > 50% of acquired TEFs
- Local injury
  - Blunt or penetrating mechanical trauma
  - Ingestion of caustic material
- Iatrogenic
  - Surgery, stenting, endoscopy
  - Endotracheal intubation, mechanical ventilation
- Inflammatory diseases and infections
  - Tuberculosis, syphilis, herpes, Crohn disease

CLINICAL ISSUES

Epidemiology

- Incidence
  - 0.02-0.04%, usually (98%) with coexistent EA
  - Most common esophageal congenital malformation
- Age
  - 20-30% of babies with TEF/EA are preterm
- Sex
  - EA is more common in males than females

Site

- Majority of TEF (~ 2/3) insert above carina
  - Has practical implications during intubation
- Rest (1/3) are within 1 cm or below carina
- Multiple fistulas can also occur

Presentation

- Single umbilical artery at birth
- Excessive salivation, regurgitation, abdominal distention
  - Coughing, choking, aspiration
  - Respiratory distress, cyanosis
- Reduced weight and height percentiles for age
- Type E (H-type) TEF: More difficult to diagnose clinically
  - Minimal symptoms if long oblique fistula
    - Recurrent pneumonia, aspiration
- Esophageal stenosis may be asymptomatic if milder
  - Usually diagnosed at later age than EA
  - Dysphagia, regurgitation, failure to thrive
    - With introduction of solid foods

Natural History

- Depends on birth weight, esophageal gap length, presence of pneumonia, and ventilator dependence
- Neonatal mortality from associated congenital anomalies
  - Mostly cardiac defects
- Survival has improved from 87% to 94% in last 2 decades
  - Early diagnosis, improved surgical/ventilation techniques
- Impairment reported by 15% of adult survivors

Treatment

- Options, risks, complications
  - Pneumonia, aspiration, foreign body obstruction
    - Disordered peristalsis, impaired sphincter function
  - Structural and functional defects after repair
    - Early pneumothorax, anastomotic leak (20%)
    - Pneumonia, wound infection, perforation
    - Anastomotic stricture (30-50%), recurrence (10%)
    - Tracheomalacia (25%), dysphagia, reflux (50%)
  - Longstanding reflux may lead to Barrett esophagus
    - Adenocarcinoma reported 20 years after repair
    - Long-term endoscopic follow-up advocated
- Surgical approaches
  - Thoracotomy or thoracoscopy
  - Cervical incision (for high or type E TEF)

- Type A TEF: Underdeveloped distal esophageal segment makes surgical correction difficult
- Surgical repair feasible in patients with esophageal stenosis, but restenosis common

Prognosis

- Prognostic classification (Spitz classification)
  - Based on birth weight
  - Presence or absence of cardiac anomalies
  - Predicts long-term outcome (morbidity, mortality)

IMAGING

General Features

- Best diagnostic clue
  - Passed nasogastric tube (NGT) stops at 10-12 cm if EA
    - Chest x-ray shows NGT at superior mediastinum (T2-4)
    - Does not pass into stomach: Confirms diagnosis
  - If air/gas present in the stomach or small bowel
    - Additionally, confirms distal TEF

Ultrasonographic Findings

- Diagnosis on prenatal (3rd trimester) ultrasound
  - Maternal polyhydramnios
  - Prominent fluid-filled or blind-ending esophageal pouch
  - Small or absent gastric bubble

MACROSCOPIC

Gross (Vogt) Classifications (Frequencies)

- Type A (type 2)
  - EA only (5-8%)
  - Complete occlusion (missing mid segment)
- Type B (type 3A)
  - EA with proximal TEF (0.8-1%)
  - Distal esophageal bud
- Type C (type 3B)
  - EA with distal TEF (85-90%)
  - TEF enters close to carina (up to 0.5 cm proximal)
  - Hypertrophied and dilated proximal esophagus
    - Secondary to efforts to swallow amniotic fluid
- Type D (type 3C)
  - EA with both proximal and distal TEF (1-2%)
- Type E (H-type)
  - TEF only (2-6%)
  - No EA present
  - May also have esophageal stenosis
- Gross type F
  - Esophageal stenosis only
- Vogt type 1
  - Esophageal agenesis (complete absence)

MICROSCOPIC

Histologic Features

- Epithelium-lined connection between respiratory and digestive tubes
- Irregular smooth muscle fibers, scar (fibrosis)
- Loss of tracheal ciliated epithelial lining
- Disrupted Auerbach myenteric plexus
- EA: Esophageal and tracheal muscle blend together
  - Hypertrophic muscle with extra myenteric plexus
- Congenital esophageal stenosis
  - Localized muscular hypertrophy
  - Cartilaginous tracheobronchial remnants
  - Membranous diaphragm or web in esophageal wall, obstructing lumen with small central perforation/apperture

Predominant Pattern/Injury Type

- Fibrosis
- Muscle hypertrophy

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Gross appearance
  - Determines classification according to type

Pathologic Interpretation Pearls

- Tracheobronchial elements in distal esophagus
  - Ciliated pseudostratified columnar epithelium, seromucinous glands, or cartilage

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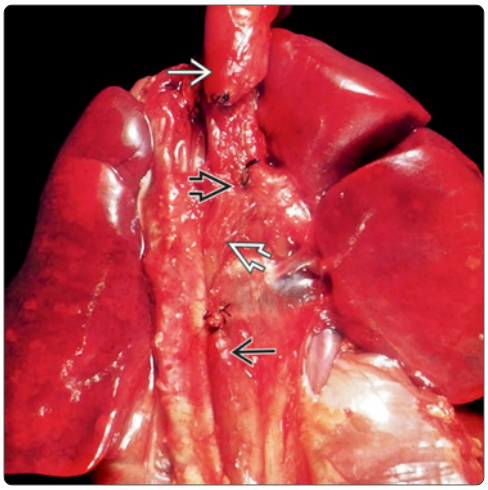
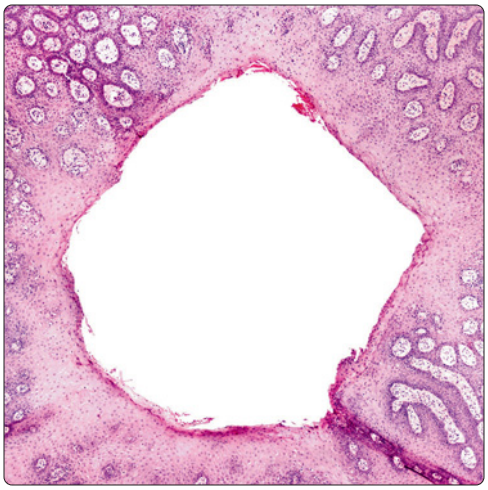
Gross Type C TEF

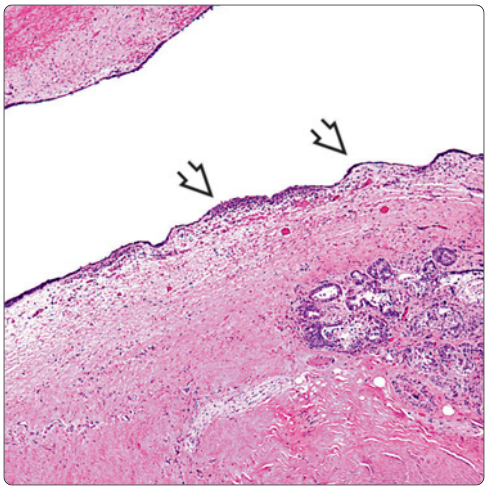


Tracheoesophageal Fistula

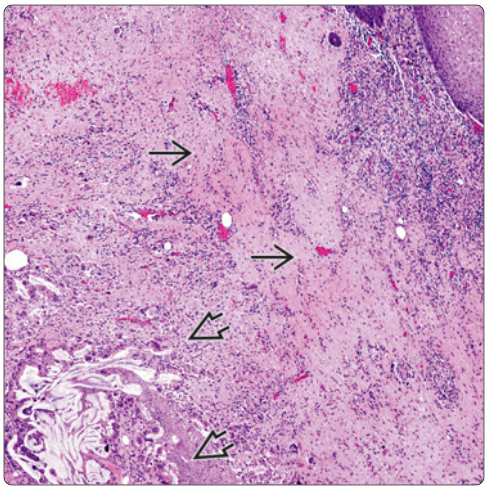


(Left) *Gross image shows EA ➡ with a distal TEF ➡ between the distal esophagus ⇨ and the trachea at the carina ⇨. This gross type C TEF/EA is the most common type, accounting for > 85% of cases.* **(Right)** *This low-power image shows the narrow lumen of a TEF with parakeratotic squamous epithelium.*

Tracheoesophageal Fistula

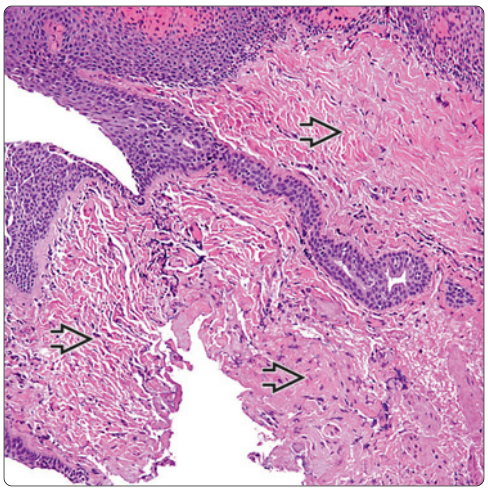


Irregular Smooth Muscle in TEF

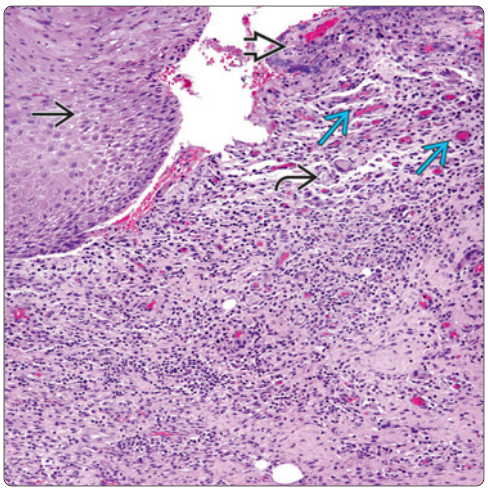


(Left) *Low-power magnification of an H&E-stained section shows a fistulous connection with loss of tracheal ciliated epithelial lining ⇨.* **(Right)** *Low-power magnification of an H&E-stained section shows irregular smooth muscle fibers ⇨ and foreign body giant cell reaction ⇨.*

Submucosal Fibrosis in TEF



TEF With Erosion/Ulcer



(Left) *Medium-power magnification of an H&E-stained section shows fibrotic submucosa ⇨ below squamous epithelium.* **(Right)** *This medium-power magnification of an H&E-stained section shows TEF with associated ulcer. Surface squamous epithelium ⇨ is disrupted by an erosion/ulcer ⇨ with associated capillary proliferation ⇨ (granulation tissue). Multinucleated giant cells can be seen reacting to foreign material ⇨. This should not be misdiagnosed as a malignancy.*

Esophageal Duplication Cyst

KEY FACTS

TERMINOLOGY

- Benign, congenital, primitive foregut-derived, epithelium-lined outpouching or cystic mass of esophagus

ETIOLOGY/PATHOGENESIS

- Foregut duplication cysts: 3 types (bronchogenic, esophageal duplication cyst, neuroenteric)
- Abnormal (incomplete) embryologic/fetal luminal recanalization/obliteration

CLINICAL ISSUES

- ~ 1 in 8,200 live births; 10-20% of all GI duplications
- 2nd most common duplication site in GI tract after ileum
- Most (75%) diagnosed in early childhood; M:F = 2:1
- Majority (60-75%) located in lower (distal 1/3) esophagus
- Symptoms mostly due to mass effect
- Dysphagia, nausea, vomiting, weight loss, anorexia
- Respiratory distress (tracheobronchial tree compression)

MACROSCOPIC

- Single, unilocular, fluid-filled outpouching/cystic mass
- Cystic (80-90%): No communication with esophageal lumen
- Tubular (10-20%): Communicate with esophageal lumen

MICROSCOPIC

- Line by ciliated, pseudostratified, columnar epithelium
- No cartilage or seromucinous glands seen
- 2 perpendicular layers of smooth muscle
- Hemosiderin, chronic inflammation, calcifications common

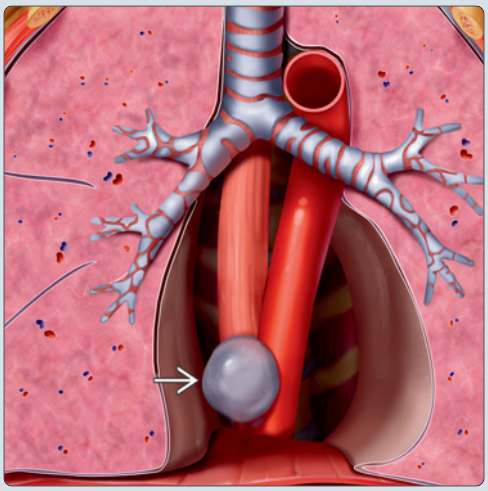
TOP DIFFERENTIAL DIAGNOSES

- Bronchogenic cyst
  - Ciliated mucinous columnar (respiratory) epithelium
  - Intramural cartilage and seromucinous glands

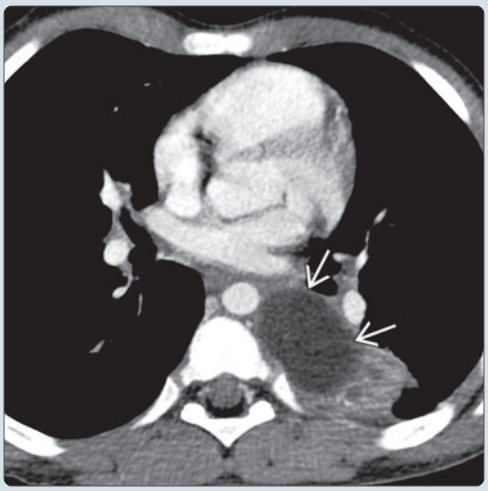
DIAGNOSTIC CHECKLIST

- Located within or attached to esophageal wall, lined by GI epithelium, and has double smooth muscle layer

EDC Location

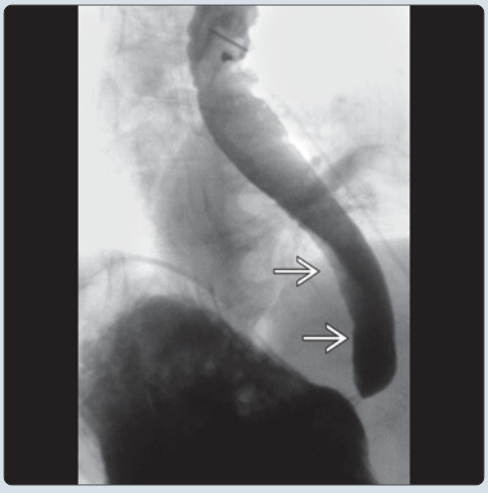


Contrast-Enhanced CT of EDC

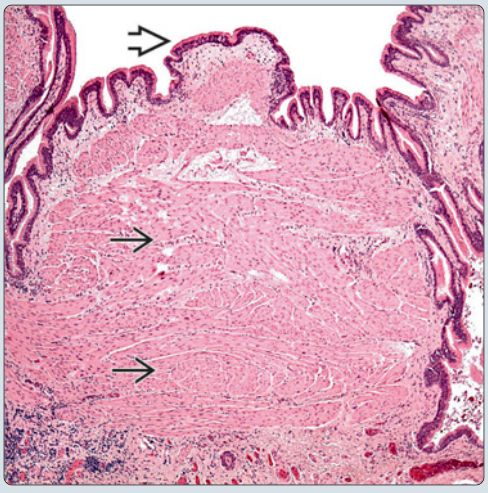


(Left) *Graphic shows the characteristic anatomic location of EDC in the inferior aspect of the middle posterior mediastinum, to the right of the distal esophagus and within or adjacent to the esophageal wall.* **(Right)** *Contrast-enhanced CT shows a cyst within the mediastinum immediately adjacent to the expected location of the esophagus (the esophagus is often not visible on CT scans). This is typical for an EDC, but pathologic confirmation is required.*

Esophagram of EDC



Muscle Layer in EDC



(Left) *Spot film from esophagram in an elderly man with an EDC shows deviation of the distal third of the esophagus, suggesting an extrinsic mass. (Courtesy DI2: Abdomen.)* **(Right)** *Low-power magnification of an H&E-stained section from an EDC shows a well-developed smooth muscle layer and ciliated columnar epithelial lining.*

TERMINOLOGY

Abbreviations

- Esophageal duplication cyst (EDC)

Synonyms

- Intramural esophageal cyst
- Mediastinal gastric cyst
- Neuroenteric/enterogenic cyst
- Tubular duplication

Definitions

- Benign, congenital, primitive foregut-derived, epithelium-lined outpouching or cystic mass of esophagus

ETIOLOGY/PATHOGENESIS

Developmental Anomaly

- Foregut duplication cysts: 3 types
  - Bronchogenic (most common)
  - EDC
  - Neuroenteric
- Proposed theories of pathogenesis
  - Abnormal (incomplete) embryologic/fetal luminal recanalization/obliteration
    - Failure of "coalescence of secretory vacuoles"
    - Timing of budding dictates location of cyst
      - Early errors result in mediastinal cysts
  - Atypical blastogenesis of primitive foregut
    - Sequestration of portions of endoderm
    - Usually in 5th to 8th weeks of gestation
  - "Split notochord" theory
    - Notochord duplication with endoderm herniation
      - Incomplete fusion of vertebral mesoderm
    - EDC associated with other congenital anomalies
      - Intrapulmonary bronchogenic cysts, neuroenteric cysts, sequestrations, bronchiectasis
      - Vertebral anomalies/defects (scoliosis, hemivertebrae, spina bifida)

CLINICAL ISSUES

Epidemiology

- Incidence
  - ~ 1 in 8,200 live births
  - 10-20% of all GI duplications
    - 2nd most common site of duplication in alimentary tract after small intestine (ileum)
  - 0.5-2.5% of all esophageal masses/tumors
  - 2nd most common benign mass in lower esophagus
- Age
  - Most cases (75%) are diagnosed in early childhood
    - Due to symptoms
    - 22% by 2 years old
- Sex
  - M:F = 2:1

Site

- Majority (60-75%) located in lower (distal 1/3) esophagus
  - Generally mediastinal, adjacent to thoracic esophagus
- 2nd most common: Cervical (upper 1/3 of esophagus)
- Few case reports of intraabdominal EDC exist

Presentation

- Common symptoms (in children, usually 1st year of life)
  - Mostly due to mass effect
  - Esophageal wall compression
    - Dysphagia, nausea, vomiting, weight loss, anorexia
  - Respiratory distress from tracheobronchial tree compression
    - Dyspnea, wheezing, coughing, stridor, recurrent pneumonitis
  - Epigastric or substernal pain, fullness, hemorrhage, palpable mass (distention), or even perforation
- Usually asymptomatic in adults
  - Discovered incidentally

Treatment

- Options, risks, complications
  - Cystic: Complete surgical excision for definitive diagnosis
    - Whether symptomatic or incidental
  - Tubular: Surgical reconstruction for definitive repair
  - Surgical resection necessary to prevent complications
  - Benign complications
    - Potential for compression of adjacent organs
      - Symptomatic upper airway obstruction
    - Increased incidence of reflux in adults with EDC
    - Ulcer, hemorrhage, perforation
      - Especially if EDC contains gastric lining
    - Secondary superinfection, life-threatening rupture
  - Squamous cell carcinoma has been reported to arise in EDC
    - Risk is considered very low in general
- Surgical approaches
  - Cervical excision, axillary thoracotomy, median sternotomy, or minimally invasive thoracoscopy

IMAGING

General Features

- Location
  - May mimic submucosal tumor
- Morphology
  - Barium swallow: Extrinsic impression on esophagus
    - Cyst fills with contrast only if in direct communication with lumen

Ultrasonographic Findings

- Endoscopic ultrasound (EUS) increasingly used for preoperative evaluation
  - Preoperative biopsy not recommended as resulting adhesions may complicate subsequent operation
- EDCs often present as anechoic or hypoechoic cysts

MR Findings

- Usually nonenhancing fluid density/cystic mass in posterior mediastinum

CT Findings

- Spherical paraesophageal unilocular cystic lesion
  - Thin cyst wall usually shows contrast enhancement

MACROSCOPIC

General Features

- Usually single, unilocular, ovoid, fluid-filled outpouching/cystic mass
- Cystic (80-90%): No communication with esophageal lumen
- Tubular (10-20%): Communicate with esophageal lumen
  - Generally run parallel to esophagus
  - Best seen on barium swallow, a "true" GI duplication

MICROSCOPIC

Histologic Features

- Usually lined by ciliated, pseudostratified, columnar epithelium
- Scattered mucus-secreting cells may be seen
- Denudation of epithelium is common
- Hemosiderin deposition (indicative of old hemorrhage) is often present
- Chronic inflammation and calcifications are common
- Cytologic atypia or complex architecture of epithelium is generally not observed
- Surrounding wall contains 2 perpendicular layers of smooth muscle (muscularis propria)
- No cartilage or seromucinous glands seen

Predominant Pattern/Injury Type

- Cystic, microscopic or macroscopic

Predominant Cell/Compartment Type

- Epithelial lining
- Muscular wall

DIFFERENTIAL DIAGNOSIS

Bronchogenic Cyst

- Anterior defect in tracheoesophageal separation (aberrant bronchial budding)
- Ciliated mucinous columnar (respiratory) epithelium
  - Ciliated columnar epithelium can also be seen in EDC
- Intramural cartilage and seromucinous glands
  - Not seen in EDC

Cystic Neoplasm

- Need to identify neoplastic epithelial cells

Branchial Cleft Cyst and Thyroglossal Duct Cyst

- Location rather than histology is best way to differentiate lesions from duplication cyst

Esophageal Retention Cyst (Mucocele)

- Small, saccular or flask-shaped dilation of obstructed submucosal glands or excretory ducts
- Usually in lower esophagus; rarely reaches muscularis propria, so not true diverticula

Simple Inclusion Cyst

- Lined by squamocolumnar epithelium

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Organ distribution
  - Classified by anatomic site, embryology, and lining

Pathologic Interpretation Pearls

- Palmer pathologic criteria for diagnosis: EDC must be
  - Located within or attached to the esophageal wall
  - Lined by GI epithelium: Gastric, squamous, intestinal, pancreatic, or respiratory (embryologically related)
  - Covered by well-developed, double smooth muscle layer (muscularis propria)
- Diagnose as "foregut cyst" if
  - Ciliated columnar epithelium present, but
    - No other distinguishing features present, such as
      - Cartilage or respiratory glands (diagnose as bronchogenic cyst)
      - Double smooth muscle layer (diagnose as EDC)
- Cases of intraabdominal EDC have been reported
  - Do not meet Palmer's 1st criterion

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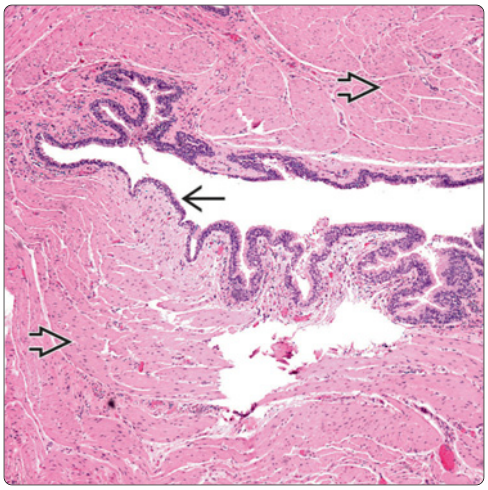
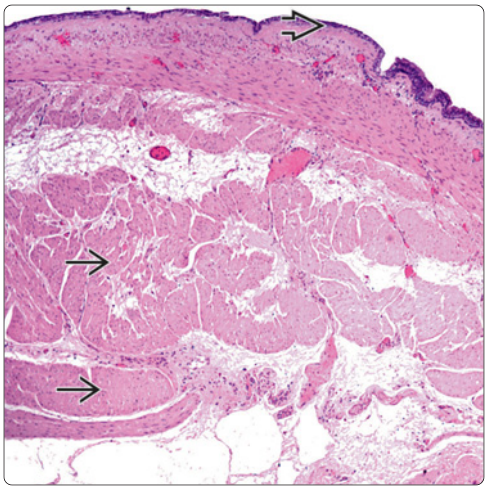
Intramural Esophageal Cyst

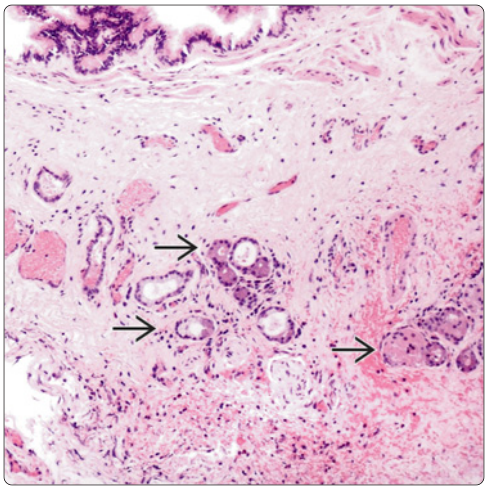


Double Muscle Layer in EDC

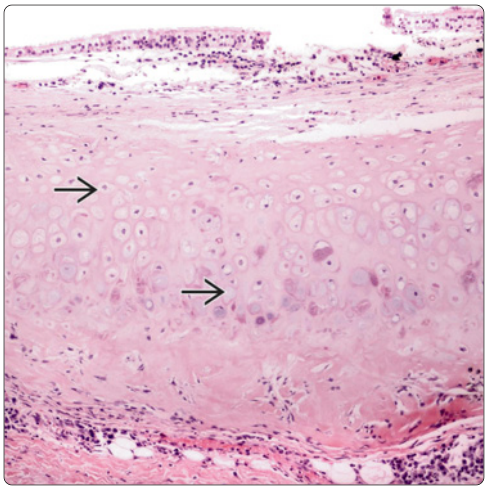


(Left) *Medium-power view of an H&E-stained section shows an intramural esophageal cyst located entirely within the muscularis propria.* **(Right)** *Low-power view of an H&E-stained section from an EDC shows a well-developed double smooth muscle layer (muscularis propria). Note the attenuated epithelium lining the cyst wall.*

Seromucinous Glands in Bronchogenic Cyst

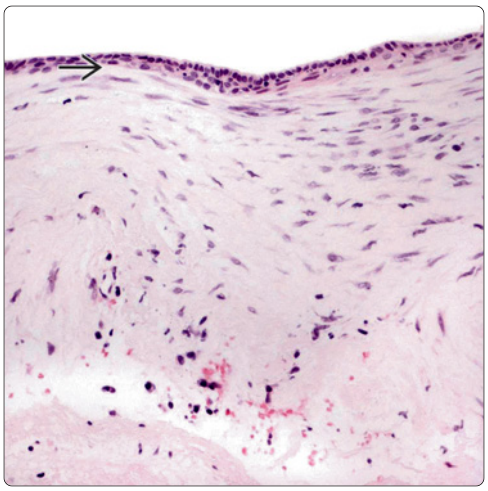


Cartilage in Bronchogenic Cyst

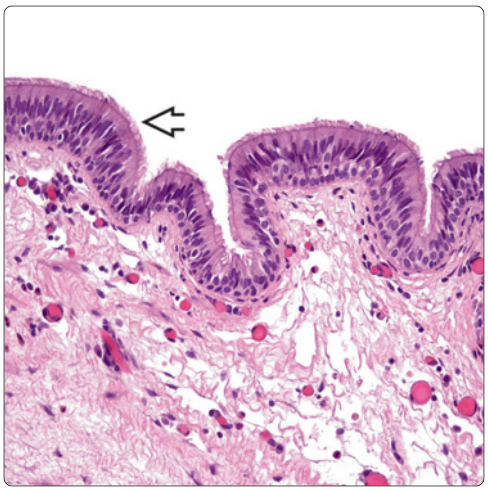


(Left) *Medium-power view of an H&E-stained section shows seromucinous glands in the submucosa, which are diagnostic of a bronchogenic cyst.* **(Right)** *Medium-power view of an H&E-stained section shows cartilage in the wall of this cyst, which is diagnostic of a bronchogenic cyst.*

Simple Inclusion Cyst



Ciliated Epithelium in Foregut Cyst



(Left) *Medium-power view of an H&E-stained section shows squamocolumnar epithelium lining this simple inclusion cyst of the esophagus.* **(Right)** *High-power view of an H&E-stained section shows ciliated columnar mucinous (respiratory) epithelium lining the cyst wall. In the absence of additional diagnostic clues (seromucinous glands, cartilage, or double smooth muscle layer), this is best diagnosed as a "foregut cyst" of the esophagus.*

Inlet Patch

KEY FACTS

TERMINOLOGY

- Gastric columnar mucosa in cervical esophagus
  - Heterotopic gastric mucosa (HGM), microscopically
  - Cervical inlet patch (CIP), macroscopically

ETIOLOGY/PATHOGENESIS

- Congenital: Incomplete squamous re-epithelization

CLINICAL ISSUES

- Incidence: 0.1-18%; most common esophageal heterotopia
- Tends to be clinically underestimated
  - Depends on population, technique, awareness
- In cervical esophagus: At/near upper esophageal sphincter
- Usually asymptomatic; detected incidentally on screening
- Laryngopharyngeal reflux symptoms, treated with drugs
  - Chest pain, dysphagia (often mild), globus sensation
- Acid-related complications
  - Bleeding, ulcer, stricture, stenosis, fistula, perforation
- *Helicobacter pylori* colonization in 5-86% of cases
- Increased risk for Barrett esophagus reported
  - Seen in up to 50% of patients with HGM in some studies
- Dysplasia/adenocarcinoma development exceedingly rare

MACROSCOPIC

- Usually 2-30 mm, well circumscribed, salmon colored
- Single or multiple (twin patches), round or oval
- Flat, raised, depressed, or rarely polypoid

MICROSCOPIC

- Gastric surface/glandular epithelium: Usually fundic type
- Varying degrees of lymphoplasmacytic inflammation

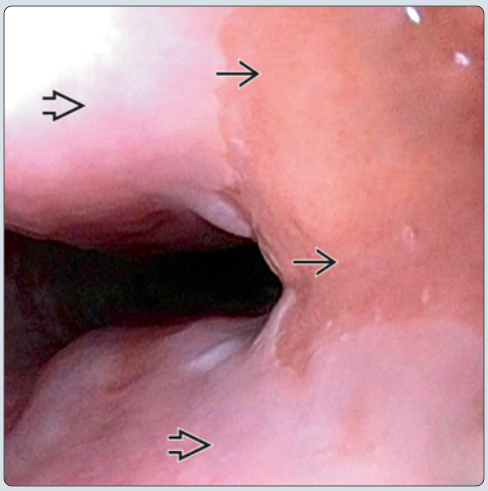
TOP DIFFERENTIAL DIAGNOSES

- Columnar metaplasia/Barrett esophagus
  - HGM can be mistaken for columnar-lined esophagus

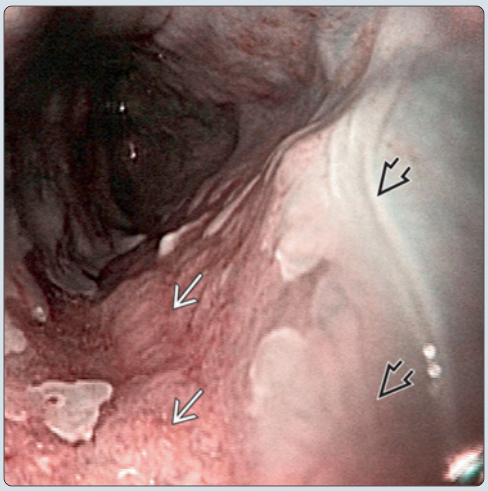
DIAGNOSTIC CHECKLIST

- Specific location of endoscopic biopsy needed for diagnosis
- HGM has been reported in almost any part of GI tract

Endoscopic Appearance of CIP

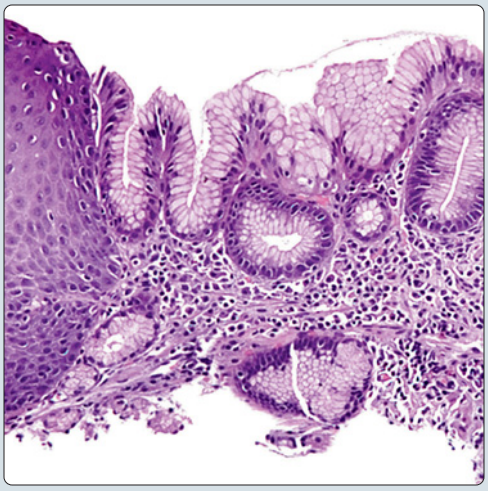


Endoscopic Appearance of CIP (NBI)

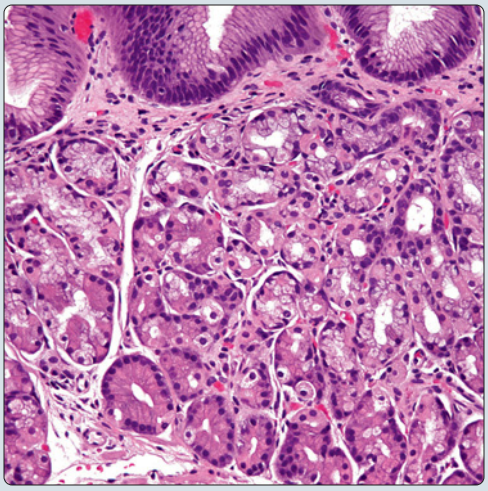


(Left) *Cervical inlet patch (CIP) grossly visible in the cervical esophagus during an upper endoscopy procedure appears as an island of salmon-colored, velvety mucosa ⇨, sharply demarcated from the surrounding pearly white squamous epithelium ⇨. (From DP: GI Endoscopic Correlates.)* **(Right)** *Narrow band imaging (NBI) technique highlights the columnar mucosa of CIP as more red and irregular ➡ than the surrounding smooth, shiny, and whitish squamous mucosa ⇨.*

Antral Gland-Type HGM



Fundic Gland-Type HGM



(Left) *High-power magnification of H&E-stained section shows antral gland-type heterotopic gastric mucosa adjacent to squamous epithelium in a biopsy specimen from the upper esophagus.* **(Right)** *High-power magnification of H&E-stained section shows fundic gland-type heterotopic gastric mucosa with parietal cells in a biopsy specimen from the upper esophagus.*

TERMINOLOGY

Abbreviations

- Cervical inlet patch (CIP)

Synonyms

- Heterotopic (ectopic) gastric mucosa (HGM)

Definitions

- Gastric columnar mucosa in cervical esophagus
  - HGM: Microscopically identified
  - CIP: Macroscopically visible

ETIOLOGY/PATHOGENESIS

Developmental Anomaly

- Considered congenital process by most
  - Incomplete replacement by squamous epithelization, which starts at ~ 5 months gestation
    - Persistence of original columnar epithelium
    - Similar to embryonic-type gastric mucosa
  - Premature migratory arrest of cells destined to differentiate into specialized gastric glands during their descent into future stomach ("cell arrest theory")

Environmental Exposure

- May be metaplastic change ("mixed theory")
  - Following trauma, regurgitation, reflux, or infection
    - Subsequent healing through surfacing of HGM present in lamina propria as a congenital anomaly
  - Tentatively linked to Barrett esophagus
    - Co-incidence, shared mucin/cytokeratin profiles

CLINICAL ISSUES

Epidemiology

- Incidence
  - Most common heterotopia in esophagus
  - Seen in 0.1-18% of published series
    - Prospective series: Endoscopic prevalence 0.3-11%
      - Up to 70% prevalence in autopsy series
    - Tends to be clinically underestimated
    - Depends on population, technique, awareness
      - Often missed due to postcricoid location
      - Additional endoscopy time maybe needed to identify lesion
      - Awareness of lesion may increase prevalence 8x
    - Higher end of range seen in those endoscoped for symptoms of gastroesophageal reflux
- Age
  - Highest prevalence documented between 40-60 years
    - May reflect population undergoing endoscopy
  - Also seen in pediatric population
- Sex
  - No sex predilection established

Site

- Most often in upper 1/3 of esophagus (cervical)
  - At or just below upper esophageal sphincter
    - Within 3 cm (16-18 cm from incisors)
    - Usually in lateral (opposite) walls of esophagus
      - Especially if double ("twin") or multiple lesions

Presentation

- Usually asymptomatic; detected incidentally on screening
- If symptoms are present, they are usually due to laryngopharyngeal reflux
  - Chest pain, dysphagia (often mild), globus sensation
  - Presumably due to acid production by parietal cells
    - Acid suppression achieves symptom resolution
    - Severity has been related to size of HGM
- Cough/spasm, hoarseness, dyspnea/shortness of breath
- Associated lesions reported
  - Reflux esophagitis, duodenal ulcers, hyperplastic polyps in gastric antrum

Natural History

- Clinically significant acid-related complications reported
  - Bleeding, ulcer, stricture, stenosis, fistula, perforation
    - May be serious or even life threatening
  - Chronic peptic esophagitis, esophagotracheal fistula
  - Most are treated endoscopically (dilatation, resection)
- May give rise to or be associated with webs, rings, hyperplastic polyps
  - All probably related to acid secretion
- *Helicobacter pylori* colonization in 5-86% of cases
  - When *H. pylori* also present in stomach
    - Suggests colonization through reflux
    - May function as reservoir of organisms
- Can cause esophageal webs and Plummer-Vinson or Paterson-Kelly syndrome
- Increased risk for Barrett esophagus reported
  - Seen in up to 50% of patients with HGM in some studies
  - Pathogenetic link suggested due to similar cytokeratin protein expression
- Dysplastic changes/malignant transformation reported
  - Biopsy needed to evaluate
  - < 50 cases of adenocarcinoma arising in HGM/CIP have been reported in literature

Treatment

- Options, risks, complications
  - Complete endoscopic mucosal resection of patch
    - Particularly in patients with dysplasia
  - Alternatives: Argon-plasma coagulation, surgical removal, and dilatation of strictures
- Drugs
  - First-line therapy for symptomatic patients
  - Proton-pump inhibitors, H2 receptor antagonists

IMAGING

Specimen Radiographic Findings

- Localized irregularities (high-density barium swallow)
  - Indentations, depressions, serrated outlines
  - Narrowing may represent esophageal stricture
  - Prominent border of CIP may cause rim-like shadows

MACROSCOPIC

General Features

- Usually 2-30 mm, well circumscribed, salmon colored
  - Rarely, lesions up to 5 cm seen
- Single or multiple (twin patches), round or oval

- Flat, raised, depressed, or rarely polypoid
- Longitudinal, transverse, or circumferential
- Heaped margins may be seen
  - Mostly on lateral and posterior surfaces
- Not always easily accessible by endoscopy

MICROSCOPIC

Histologic Features

- Gastric surface and glandular epithelium interposed between esophageal squamous mucosa
  - Usually fundic-type gastric epithelium
  - Less frequently: Antral or transitional type
- Varying degrees of lymphoplasmacytic inflammation but almost always seen
- Esophagitis common in adjacent mucosa, presumably due to acid secretion

Predominant Pattern/Injury Type

- Congenital/metaplastic

Predominant Cell/Compartment Type

- Epithelial, glandular

DIFFERENTIAL DIAGNOSIS

Columnar Metaplasia/Barrett Esophagus

- HGM can be mistaken for columnar-lined esophagus when biopsy site is not indicated as upper esophagus
  - Nevertheless, need to exclude presence of Barrett mucosa between HGM and gastroesophageal junction

Plummer-Vinson or Paterson-Kelly Syndrome

- a.k.a. sideropenic dysphagia
- Rare disease characterized by
  - Difficulty in swallowing
  - Iron deficiency anemia
  - Esophageal web(s)

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- HGM has been reported in almost any part of GI tract
  - Duodenum, jejunum, Meckel diverticulum
  - Tongue, gallbladder, rectum, and anus
- Clinicopathologic classification proposed for CIP
  - Categories I, II, III, IV, and V
  - Based on presence/absence of symptoms, complications, and neoplastic transformation

Pathologic Interpretation Pearls

- Specific location of endoscopic biopsy needed for diagnosis
  - Especially proximal vs. distal esophagus
    - To differentiate from cardia, Barrett mucosa
- Rare intestinal or pancreatic acinar metaplasia in HGM
- Malignant transformation (adenocarcinoma): Very rare
  - Rate less than that seen in Barrett esophagus
  - High-grade dysplasia even more infrequent
  - Therefore, HGM generally not considered premalignant

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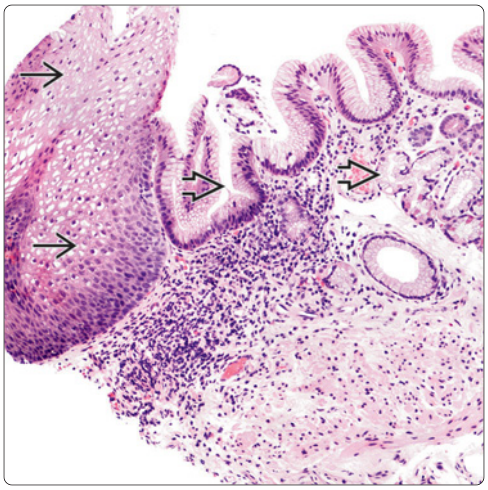
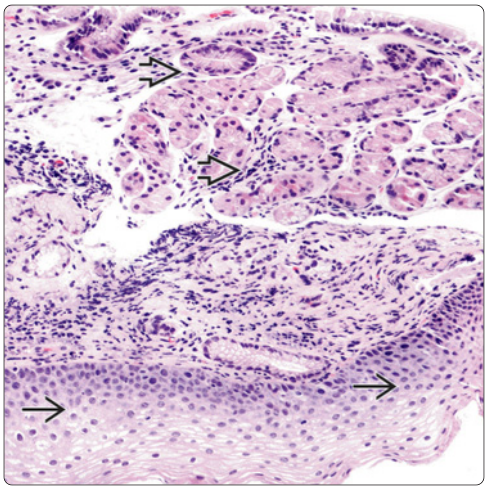
Antral Gland-Type HGM

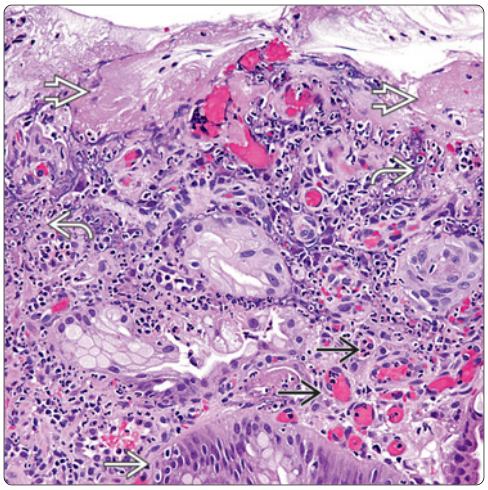


Fundic Gland-Type HGM

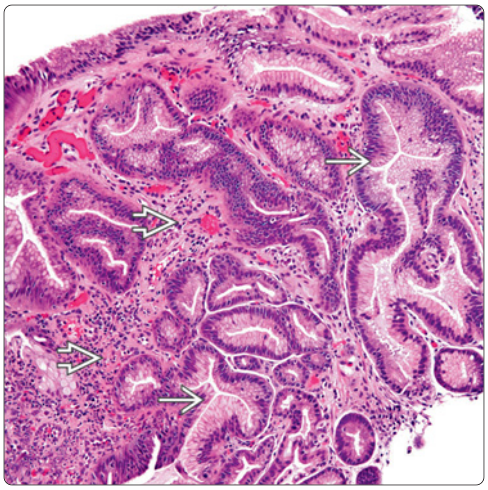


(Left) *Medium-power magnification of H&E-stained section shows HGM with mucinous glands ⇨ resembling gastric antral gland-type mucosa. Squamous epithelium of the cervical esophagus ⇨ can also be seen nearby.* **(Right)** *Medium-power magnification of H&E-stained section shows HGM with fundic-type glands ⇨ featuring parietal cells and resembling gastric fundus/body-type mucosa. The squamous epithelium of the esophagus ⇨ is adjacent.*

Ulcer in HGM

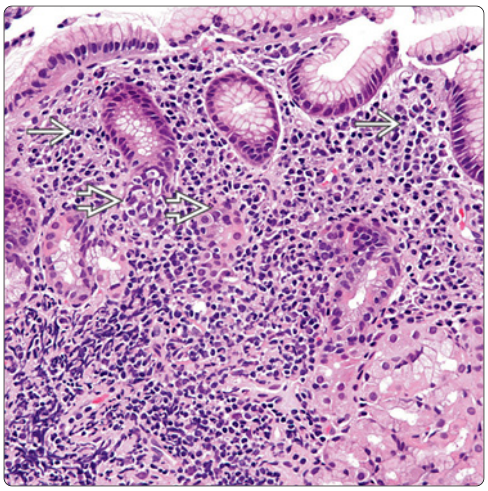


Hyperplastic Polyp in HGM

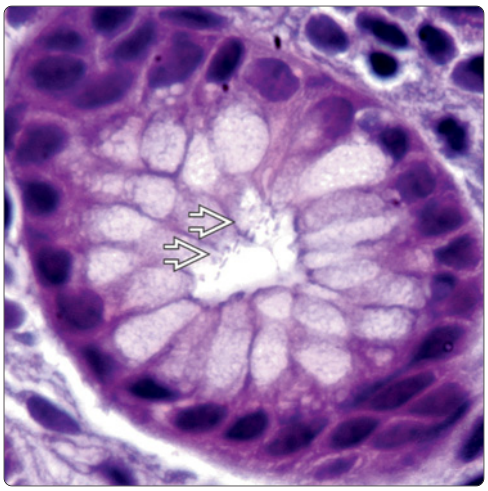


(Left) *High-power magnification of H&E-stained section shows an ulcer in HGM with surface erosion/fibrin deposits ⇨, acute inflammation ⇨, and proliferating capillaries ⇨ in a background of HGM ⇨ in the cervical esophagus.* **(Right)** *Medium-power magnification of H&E-stained section shows a gastric-type hyperplastic polyp with hyperplastic foveolar epithelium ⇨ and an inflamed, expanded lamina propria ⇨ arising in HGM.*

Helicobacter pylori in HGM



Helicobacter pylori in HGM



(Left) *Medium-power magnification of H&E-stained section shows Helicobacter pylori organisms involving heterotopic gastric mucosa. A superficial band of chronic inflammation can be seen ⇨, along with active gastritis ⇨.* **(Right)** *Very high-power magnification (oil immersion) of H&E-stained section shows Helicobacter pylori organisms ⇨ in the superficial mucous layer.*

KEY FACTS

TERMINOLOGY

- Esophageal webs (EW): Eccentric, < 2 mm, **mucosal** membranes at right angle to long axis of esophagus
- Esophageal ring (ER): Concentric, 2-5 mm, distal esophagus
  - Type A = **muscular** ring; type B = **mucosal** (Schatzki) ring
- Plummer-Vinson or Paterson-Kelly syndrome (PVPK): Cervical EW, dysphagia, and iron-deficiency anemia

ETIOLOGY/PATHOGENESIS

- Embryologic remnants vs. result of inflammatory process
- Associations: Reflux, scleroderma, eosinophilic esophagitis

CLINICAL ISSUES

- Incidence: EW = 0.7-16%; ER type A = 4%, type B = 6-14%
- Mostly asymptomatic or solid dysphagia if lumen < 13 mm

IMAGING

- EW: Thin, curvilinear membrane on anterior wall
- ER: Symmetric notches that constrict lumen

MACROSCOPIC

- EW: Mostly proximal esophagus (anterior postcricoid area)
- Type A ER: 2 cm proximal to squamocolumnar junction
- Type B ER: Annular membrane at squamocolumnar junction

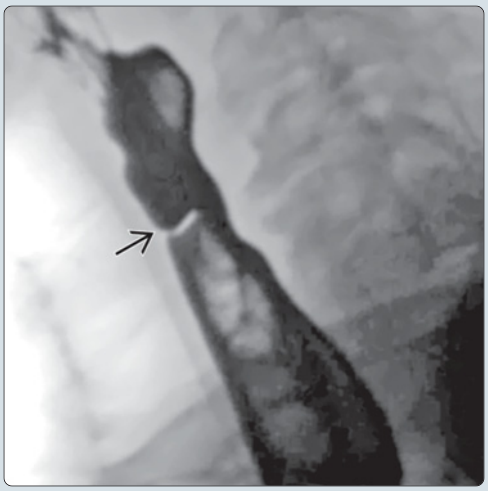
MICROSCOPIC

- EW: Incompletely encircles lumen, no muscle layer
- Type A ER: Squamous epithelium on both surfaces
  - Significant muscular component (in contrast to type B)
- Type B ER: Squamous upper, columnar undersurface
  - Muscularis mucosae fibers, no muscularis propria

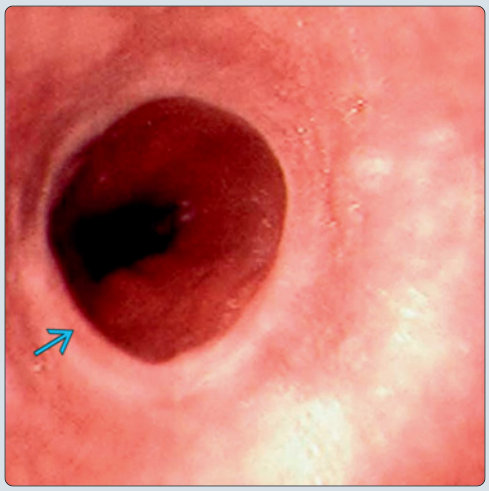
DIAGNOSTIC CHECKLIST

- Multiple/congenital EW with lumen impingement
- Corrugated ringed esophagus (multiple ER)
  - Concentric, evenly spaced ER over long segment
  - Some cases associated with eosinophilic esophagitis
- PVPK: Splenomegaly, glossitis, koilonychia, other autoimmune diseases (sprue, Sjögren syndrome)

Esophageal Web

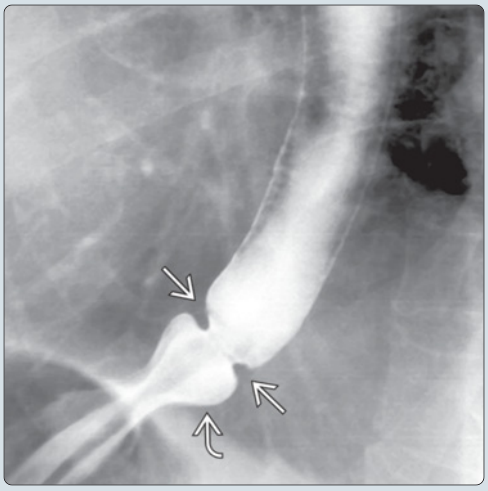


Esophageal Ring (Type B or Schatzki)

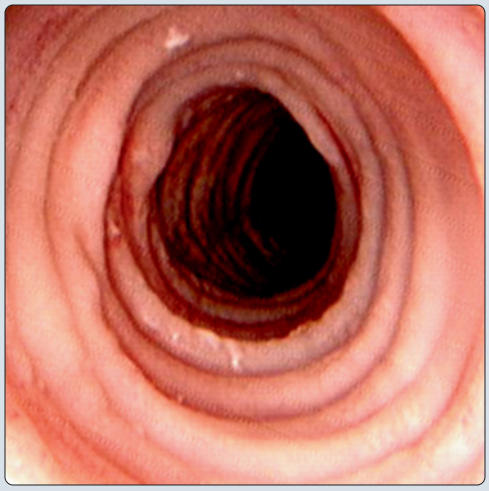


(Left) *Lateral view of barium esophagram with rapid-sequence imaging in a 40-year-old woman with dysphagia shows esophageal web, defined as thin, shelf-like eccentric membrane or indentation projecting from the anterior &/or lateral walls of the pharyngoesophageal junction at the proximal esophagus. (From DI2: Abdomen.)* **(Right)** *Endoscopic image shows view from above a lower esophageal mucosal (type B or Schatzki) ring that encircles the lower esophageal lumen. (Courtesy T. Nostrant, MD.)*

Esophageal Ring (Type B or Schatzki)



Multiple Esophageal Rings



(Left) *Radiograph after a barium swallow shows a small hiatal hernia and an annular ring-like constriction or narrowing at the gastroesophageal junction, known as lower esophageal mucosal (type B) or Schatzki ring.* **(Right)** *Endoscopic image shows multiple concentric esophageal rings, also referred to as "feline esophagus" or corrugated ringed esophagus. This is often seen in patients with eosinophilic esophagitis. (Courtesy T. Nostrant, MD.)*

TERMINOLOGY

Abbreviations

- Esophageal webs (EW)
- Esophageal rings (ER)
- Plummer-Vinson or Paterson-Kelly syndrome (PVPK)

Definitions

- EW: Eccentric, < 2 mm, **mucosal** membranes, at right angle
- ER: Concentric, 2-5 mm, transverse folds in distal esophagus
  - Type A = **muscular** ring; type B = **mucosal** (Schatzki) ring
- PVPK: Cervical EW, dysphagia, and iron-deficiency anemia

ETIOLOGY/PATHOGENESIS

Developmental Anomaly

- EW: Embryologic remnant vs. inflammatory process
  - Chronic graft-vs.-host disease, heterotopic gastric mucosa, blistering skin diseases, radiotherapy, reflux
- Type A ER: Possibly exaggerated normal anatomy
- Type B ER: Thought congenital (but rare before age 40)
  - Associated: Reflux, scleroderma, eosinophilic esophagitis

CLINICAL ISSUES

Epidemiology

- Incidence
  - EW: 0.7-16%
  - ER type A: ~ 4% (autopsy studies), usually children
  - ER type B: 6-14% (0.5% are symptomatic), over age 40

Presentation

- Mostly asymptomatic or solid dysphagia if lumen < 13 mm
- Rarely aspiration, reflux, spontaneous perforation
- Anemia in PVPK ("sideropenic dysphagia")

Natural History

- PVPK associated with oropharyngeal/esophageal cancer

Treatment

- Options, risks, complications
  - Treat underlying condition, lifestyle/dietary changes
  - Severe cases: Endoscopic mechanical disruption
    - Bougienage more successful in type B ER
  - Refractory (last resort): Electrocautery or surgery

IMAGING

Specimen Radiographic Findings

- Best seen on lateral view after barium swallow
- EW: Thin, curvilinear membrane on anterior wall
- ER: Symmetric notches that constrict lumen
  - Type A ER thicker and broader than type B
  - Type "C" ER: Indentation by diaphragmatic crura
    - Asymptomatic, clinically inconsequential

MACROSCOPIC

General Features

- EW: Mostly proximal esophagus (anterior postcricoid area)
  - May be missed or pierced on endoscopy
- Type A ER: 2 cm proximal to squamocolumnar junction
- Type B ER: Annular membrane at squamocolumnar junction
  - Defines proximal border of coexistent hiatal hernia
  - Encircles lumen at level of constrictor cardiae

MICROSCOPIC

Histologic Features

- EW: Incompletely encircles lumen, no muscle layer
  - Normal squamous mucosa, inflamed submucosa
  - Distal EW: Gastric mucosa in undersurface
- Type A ER: Squamous epithelium on both surfaces
  - Significant muscular component (in contrast to type B)
- Type B ER: Squamous upper, columnar undersurface
  - Basal cell hyperplasia, submucosal fibrosis
  - Muscularis mucosae fibers, no muscularis propria

DIFFERENTIAL DIAGNOSIS

Leiomyoma, Neuroma, Carcinoma

- Other lesions that produce ring-like defects

Annular Fibrous Stricture

- Ring-like peptic stricture
  - Inflamed fibrous tissue from healed esophagitis
- Thicker (> 3 mm) narrowing, less easily dilated

Vascular Rings

- Vascular structures encircling trachea and esophagus
- Due to abnormal branchial arch development

"Feline Esophagus"

- Fine transverse folds on double contrast exam
- Probably due to prominent muscularis mucosae
- Incidental or associated with eosinophilic esophagitis

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Multiple/congenital EW with lumen impingement
  - Form of esophageal stenosis
- Corrugated ringed esophagus (multiple ER)
  - Concentric, evenly spaced ER over long segment
  - Congenital, immunologic, or due to reflux
  - Some cases associated with eosinophilic esophagitis
  - Dilation difficult: Mucosal tears and perforations
- PVPK: Splenomegaly, glossitis, koilonychia, other autoimmune diseases (sprue, Sjögren syndrome)

Pathologic Interpretation Pearls

- EW: Proximal, not circumferential, thin membrane
- ER: Distal, concentric, thicker, mucosal, or muscular

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KEY FACTS

TERMINOLOGY

- Esophageal diverticula (ED): Saccular lumen outpouchings
  - Zenker diverticula (ZD): Pharyngoesophageal (proximal)
  - Midesophageal diverticula (MED): Thoracic (middle)
  - Epiphrenic diverticula (EPD): Supradiaphragmatic (distal)
- (Diffuse) esophageal intramural pseudodiverticulosis (EIPD)

ETIOLOGY/PATHOGENESIS

- Pulsion: Mucosal herniation due to ↑ intraluminal pressure
  - Usually false (no muscularis propria); e.g., ZD, EPD
  - Localized point of wall weakness (Killian triangle)
- Traction: Wall pulled outward due to inflammation/scar
  - Usually true (muscle layer present); e.g., MED
  - Tuberculosis, sarcoidosis, histoplasmosis, lung mass
- EIPD: Infection, diabetes, alcohol, reflux, dysmotility
- Congenital diverticula: Rare, true diverticula (all 3 layers)

CLINICAL ISSUES

- Incidence up to 1-2%; mostly elderly; more common in men
  - By ED type: ZD (70%), MED (15-21%), EPD (9-15%)
- Symptoms: Dysphagia, halitosis, regurgitation, obstruction
  - Often can be asymptomatic, incidental (MED, EPD)
- Complications: Diverticulitis, perforation, aspiration
- Malignancy risk: Squamous cell carcinoma in 0.3-0.6%
- Myotomy & diverticulectomy or endoscopic stapling

IMAGING

- Thin-walled, air- or fluid-filled communication with lumen

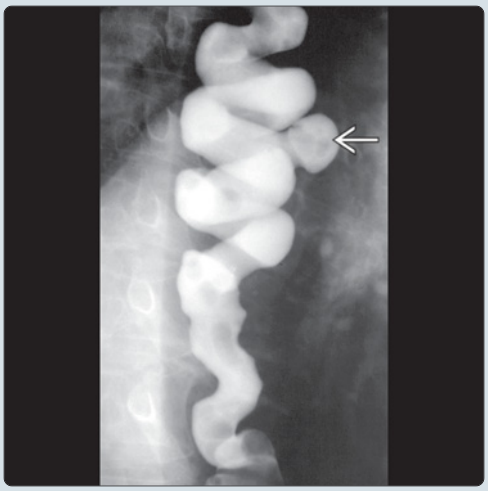
MACROSCOPIC

- ZD: Midline posterior pouch, > 2 cm, left cervical protrusion
- MED: Single or multiple, wide-mouthed, anteriorly at carina
- EPD: Round, wide-mouthed, > 5 cm, right posterolateral
- EIPD: Numerous, flask-like, 1-10 mm, even & linear

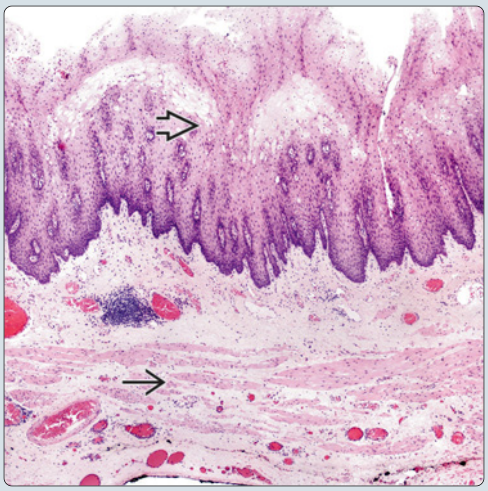
MICROSCOPIC

- Hyperplastic squamous epithelium lines all acquired ED
- Presence/absence of muscularis layer determines ED type
- EIPD: Obstructed, cystically dilated submucosal ducts

Pulsion Diverticulum

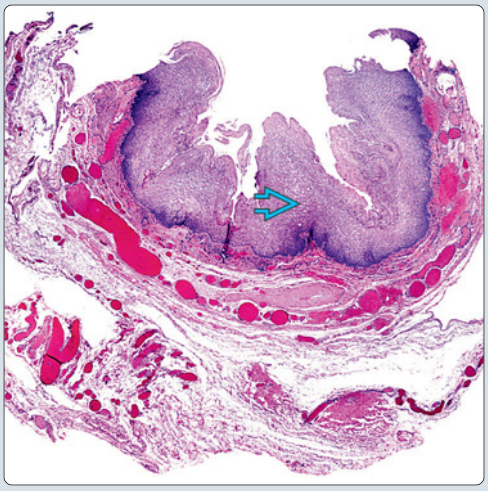


Pulsion Diverticulum

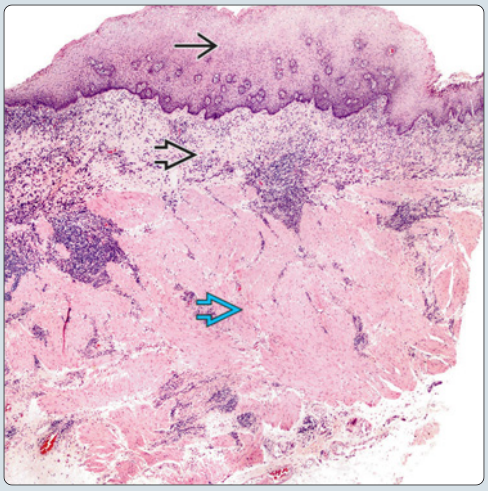


(Left) *Oblique view of barium esophagram shows dramatic appearance of esophageal dysmotility with a "corkscrew" appearance. Motility problems can create high intraluminal pressures and result in pulsion diverticula.* **(Right)** *Medium-power view of an H&E-stained section shows a pulsion diverticulum with acanthotic and edematous squamous epithelium, thickened muscularis mucosae, but no muscularis propria layer (a false diverticulum).*

False Esophageal Diverticulum



True Esophageal Diverticulum



(Left) *Low-power magnification of H&E-stained section shows an ED with hyperplastic squamous epithelium (acanthosis) and absence of muscularis propria, hence a false diverticulum.* **(Right)** *Medium-power view of an H&E-stained section shows a true esophageal diverticulum with all layers of the esophageal wall present: Squamous epithelium, submucosa, and a distinct muscularis propria.*

TERMINOLOGY

Abbreviations

- Esophageal diverticula (ED)
  - Zenker diverticulum (ZD)
  - Midesophageal diverticula (MED)
  - Epiphrenic diverticula (EPD)
- (Diffuse) esophageal intramural pseudodiverticulosis (EIPD)

Synonyms

- ZD: Cervical, pharyngoesophageal, hypopharyngeal
- MED: Thoracic, parabronchial, tracheobronchial
- EPD: Supradiaphragmatic, distal

Definitions

- ED: Saccular outpouchings of epithelium-lined lumen
  - Containing all or part(s) of esophageal wall
- EIPD: Multiple, ectatic, 0.1-1 cm submucosal glands
  - Evenly and linearly distributed along wall

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- ZD: Uncoordinated muscular contractions during swallowing &/or inadequate sphincter relaxation
  - Mucosal outpouching due to high intraluminal pressure
    - Pathogenesis: Pulsion diverticulum
  - Localized point of weakness (Killian triangle)
    - Junction of esophageal wall with pharynx
      - Transverse fibers of cricopharyngeus muscle
      - Oblique fibers of inferior pharyngeal constrictor
  - Association with reflux suggested, not confirmed
  - Can coexist with cervical esophageal web or hiatal hernia
- MED: Necroinflammation in mediastinal lymph nodes
  - Tuberculosis, sarcoidosis, histoplasmosis, lung mass
  - Esophageal wall pulled outward (traction)
  - Alternatively, pulsion MED can also occur
    - Motility disorders (achalasia, esophageal spasm, hypertensive lower esophageal sphincter)
- EPD: Usually due to increased intraesophageal pressure
  - Mucosa pushed out in areas of weak muscle (pulsion)
  - Pathogenesis: Functional or anatomic obstruction
    - Hypertrophic muscle layer distal to EPD
    - Frequently coexistent with hiatal hernia, diaphragm eventration, carcinoma, dysmotility (achalasia)
- EIPD: Unclear etiology, probably acquired
  - Predisposing factors
    - Infectious agents: Candidiasis, herpes esophagitis
    - Diabetes, alcohol abuse, reflux, dysmotility
  - Other associations
    - Squamous carcinoma, chronic granulomatous disease
  - Cyst formation due to duct obstruction

CLINICAL ISSUES

Epidemiology

- Incidence
  - By ED type: ZD (70%), MED (15-21%), EPD (9-15%)
  - ZD: 1-2% of dysphagic patients under radiography
  - EIPD may affect up to 15-17% patients (autopsy series)
- Age
  - ED: More common in elderly (6th and 7th decades)
    - ZD patients slightly older: 7th or 8th decade
  - EIPD: Large age range (8-83 years old)
- Sex
  - ZD: Male predominance (M:F = 2:1)
  - EIPD: Males more commonly affected

Site

- ZD: Midline in posterior wall of proximal esophagus
- MED: Usually anteriorly, at or near tracheal bifurcation
- EPD: Right posterolateral wall, in distal 10 cm of esophagus

Presentation

- ZD: Dysphagia, halitosis, regurgitation of undigested food, cough, choking, obstruction, aspiration, secondary pneumonitis
- MED: Often asymptomatic, almost always incidental
  - Unless there is coexisting diverticulitis
- EPD: Substernal pain, dysphagia, weight loss
- EIPD: Dysphagia, acute bolus obstruction
  - Probably secondary to coexisting esophagitis/stricture

Natural History

- Secondary bacterial colonization may cause diverticulitis
- Perforation may lead to mediastinitis
- Enlarging ZD displaces proximal esophagus anteriorly
  - May lead to esophageal compression
- EPD: Aspiration pneumonia, lung abscess, diverticulitis, esophageal obstruction, perforation, mediastinitis
- EIPD often associated with stricture (75% of patients)
- Malignant transformation
  - Squamous cell carcinoma reported in 0.3-0.6% of ED
    - With up to 7% reported in one series of ZD
    - Secondary to stasis and longstanding inflammation
    - Tend to have poor prognosis due to delayed diagnosis

Treatment

- Options, risks, complications
  - ZD: Follow if small; treat if large &/or symptomatic
    - Surgery: Myotomy plus diverticulectomy
    - Endoscopy: Stapling or incision of wall between diverticulum and esophagus (Dohlman procedure)
  - MED, EPD: Treat motility disorder if symptomatic
    - Esophagomyotomy if refractory or incapacitating
  - EIPD: Treat by dilating underlying stricture
    - Trauma, perforation, colonization by organisms
    - Foreign material: Esophagitis, submucosal fibrosis
    - Strictures and bridging between diverticula
  - Complications (10% of treated ED)
    - Diverticulitis, perforation, mediastinitis, hemorrhage
    - Tracheoesophageal or esophagocutaneous fistula
    - Mucosal ulceration (pill impaction)
    - Obstruction (foreign body, bezoar)
    - Vocal cord paralysis (recurrent laryngeal nerve)

IMAGING

Radiographic Findings

- Best seen on lateral esophagram after barium swallow
  - Characteristic contrast-filled outpouchings from lumen
  - Pulsion diverticula: Smooth rounded contour, wide neck

  - Remain filled after barium emptied (no muscle in wall)
- Usually also evidence of esophageal spasm or dysmotility

CT Findings

- Confirm presence of thin-walled air- &/or fluid-filled structure communicating with esophageal lumen

MACROSCOPIC

General Features

- ZD: Pouches > 2 cm, typically with left cervical protrusion
- MED: Single or multiple, wide-mouthed, cephalad
- EPD: Round/globular, wide-mouthed, can be large (> 5 cm)
- EIPD: Numerous flask-like 1-10 mm lumen outpouchings
  - Evenly, linearly distributed along esophageal wall
  - Most numerous proximally
  - Extend < 3-5 mm into wall, between folds

Endoscopy

- Not indicated for evaluation of ED (risk of perforation)
  - ED may complicate passage of nasogastric tube

MICROSCOPIC

Histologic Features

- Hyperplastic squamous epithelium lines all acquired ED
  - Unless ED develops in Barrett esophagus
- ZD: Lined by acanthotic squamous epithelium
  - Fibrotic wall, inflammation, lymphoid aggregates
  - Muscle layer usually absent or attenuated
  - Mucosa may be ulcerated
- MED: Variably inflamed squamous mucosa and submucosa
  - Muscularis propria may be attenuated
- EPD: Squamous mucosa, submucosa, no muscularis propria
- EIPD: Multiple, cystically dilated submucosal ducts
  - By definition not real diverticula (pseudodiverticulosis)
  - Lumen contains mucin, inflammation, squamous debris
  - Cysts connect to lumen via pin-point ostium
  - Organisms (bacteria, fungi, parasites) can colonize cysts
  - Squamous metaplasia can occur
  - Fibrosis or stricture secondary to inflammation
- Congenital diverticula have all esophageal wall components
  - True diverticula, by definition
  - Lined by columnar, ciliated, or squamous epithelium

Predominant Pattern/Injury Type

- Cystic, macroscopic

Predominant Cell/Compartment Type

- Epithelial, squamous

DIFFERENTIAL DIAGNOSIS

Esophageal Duplication Cyst

- Congenital, usually identified in early childhood
- Most are separate cysts, with no lumen communication
- Mostly lined by columnar epithelium

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- ED classification by location and etiology/pathogenesis
  - Location in esophagus
    - ZD: Pharyngoesophageal (upper esophagus)
    - MED: Thoracic (middle esophagus)
    - EPD: Epiphrenic (lower esophagus)
  - Morphology (wall composition): True vs. false (pseudo)
    - True diverticula contain all 3 esophageal wall layers
    - False diverticula contain mucosa and submucosa only
  - Underlying etiology: Congenital vs. acquired
    - Acquired diverticula usually lack muscularis propria
  - Pathogenesis: Traction vs. pulsion
- ZD, EPD: Usually false diverticula, due to pulsion
  - Mucosa/submucosa herniation through esophageal wall
  - As a result, no intact muscularis propria present
- MED: Usually true (all wall layers), due to traction
- EIPD: Dilated submucosal ducts, not real diverticula

Pathologic Interpretation Pearls

- Congenital ED: Associated with bronchopulmonary-foregut malformations (pulmonary sequestrations)
- EIPD with esophageal stricture: Rule out carcinoma

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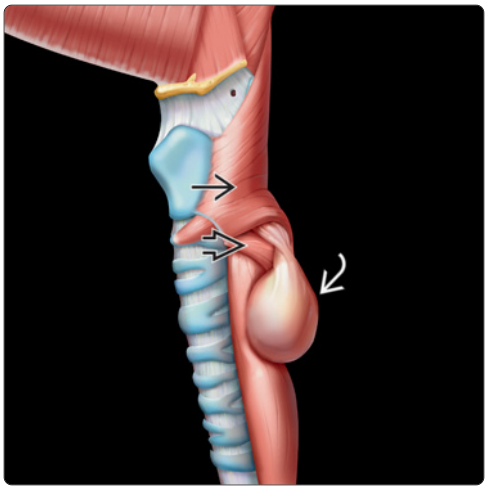
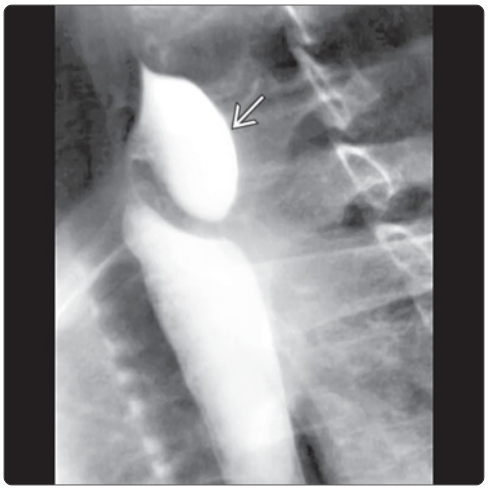
Zenker Diverticulum

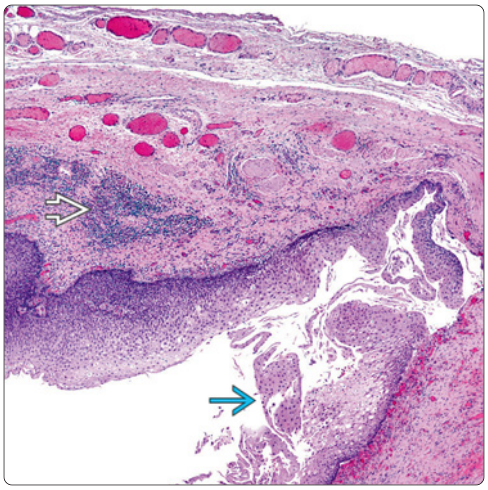


Zenker Diverticulum

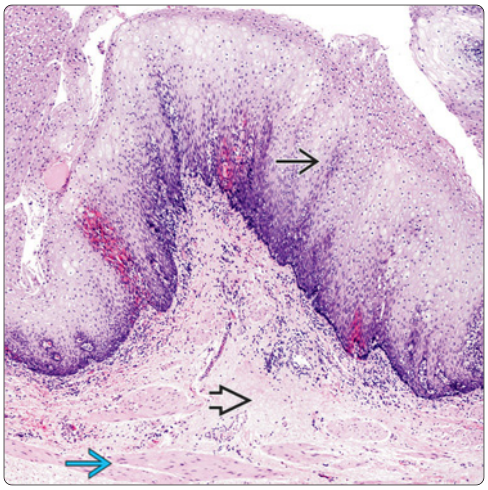


(Left) *Graphic shows Zenker diverticulum (ZD), a false ED resulting from high intraluminal pressure, and outpouching (pulsion) of the esophageal lumen through the oblique fibers of the inferior pharyngeal constrictor and the transverse fibers of the cricopharyngeus muscles.* **(Right)** *Oblique view of barium esophagram shows a classic, moderate-sized ZD originating at the pharyngo-esophageal junction and extending into the upper mediastinum.*

Zenker Diverticulum

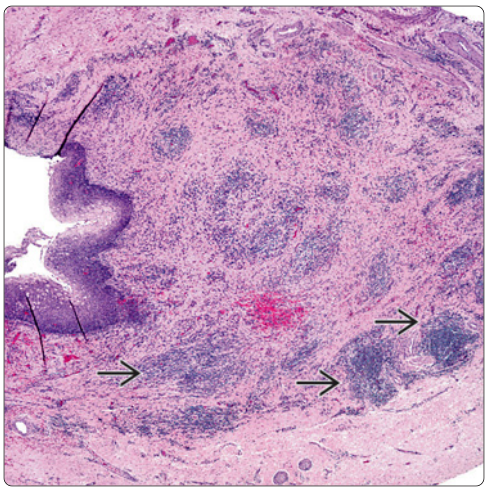


Zenker Diverticulum

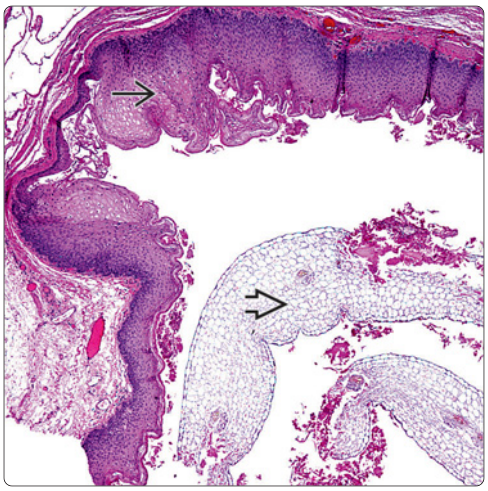


(Left) *Medium-power magnification of an H&E-stained section shows a ZD with acanthosis, chronic inflammation, and absent muscularis propria (false diverticulum).* **(Right)** *High-power magnification of an H&E-stained section shows a ZD with acanthotic surface squamous epithelium, fibrotic lamina propria, and a slightly thickened muscularis mucosae.*

Zenker Diverticulum

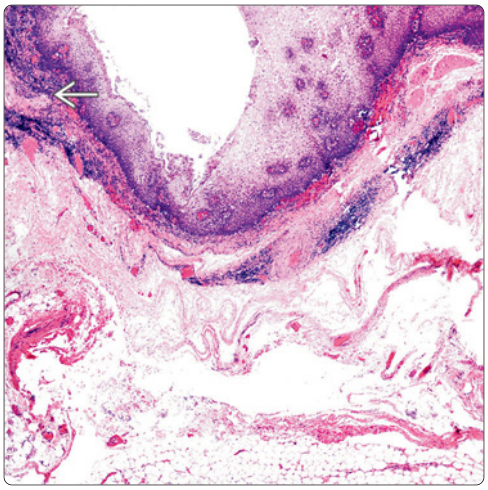


Zenker Diverticulum

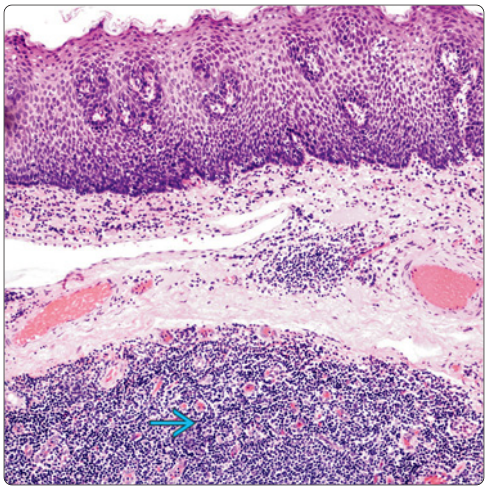


(Left) *Low-power magnification of an H&E-stained section shows inflamed fibrotic wall of a ZD with prominent lymphoid aggregates.* **(Right)** *Medium-power magnification of an H&E-stained section shows a ZD with hyperplastic squamous epithelium and trapped food particles in the lumen.*

Zenker Diverticulum

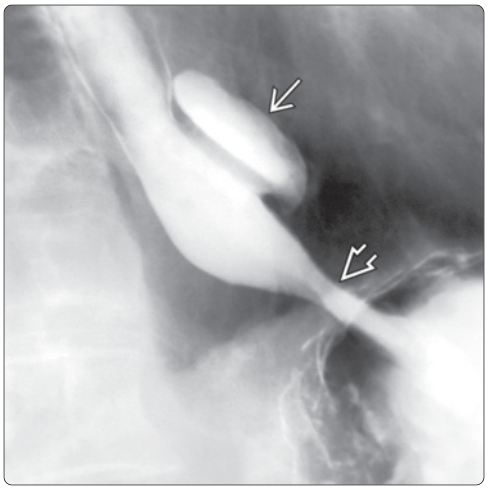


Zenker Diverticulum

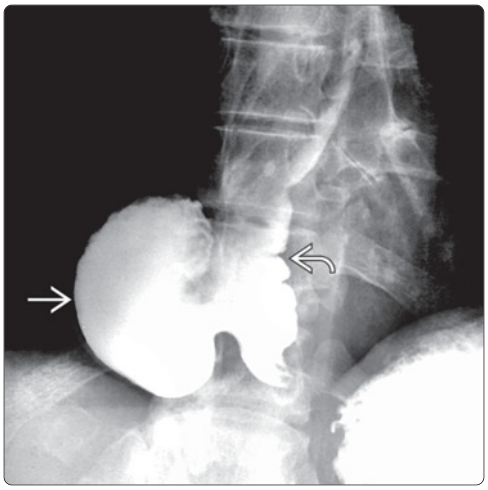


(Left) *Low-power magnification of an H&E-stained section shows the wall of a ZD with prominent chronic inflammatory infiltrates and fibrosis, but no muscularis propria (false diverticulum).* **(Right)** *High-power view of an H&E-stained section shows the wall of a ZD with prominent lymphoid aggregates.*

Epiphrenic Diverticulum

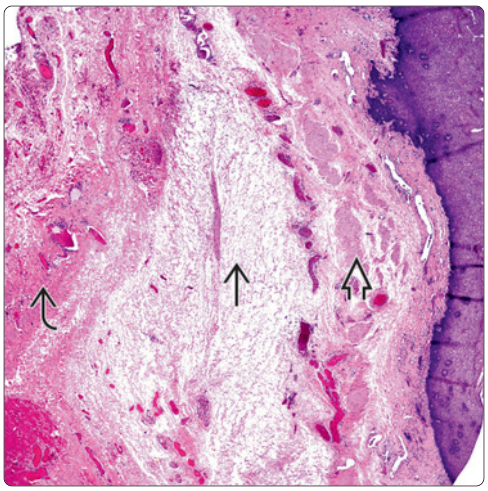


Epiphrenic Diverticulum

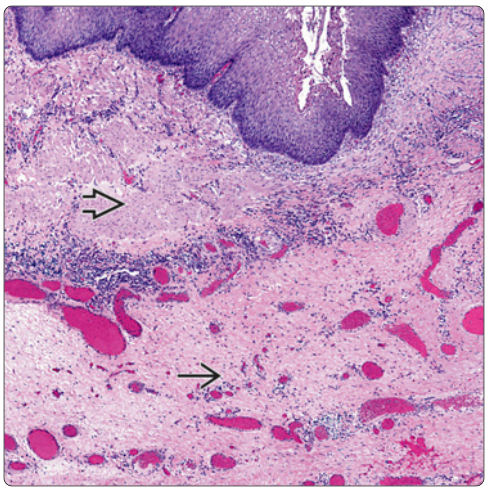


(Left) *Barium esophagram shows an epiphrenic diverticulum just above the gastroesophageal junction.* **(Right)** *Esophagram in an elderly patient with dysphagia and halitosis shows a large epiphrenic diverticulum and esophageal dysmotility with tertiary contractions. (From DI2: Abdomen.)*

Epiphrenic Diverticulum

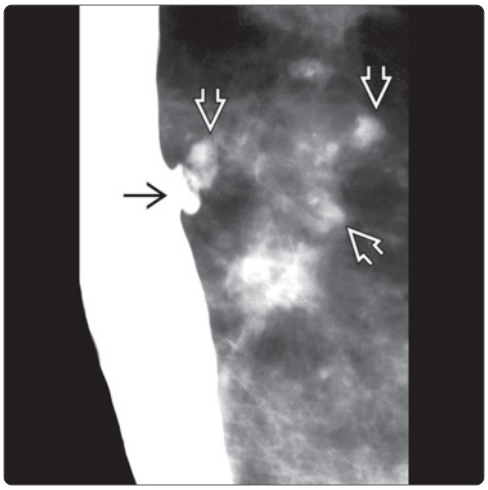


Esophageal Diverticulum

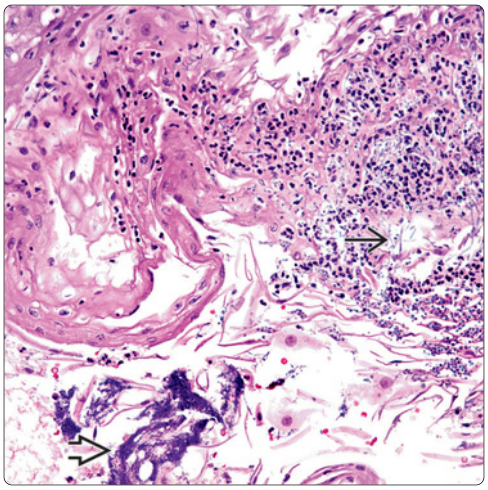


(Left) *Low-power view of an H&E-stained section shows an epiphrenic diverticulum with thickened muscularis mucosae, edematous submucosa, and fibrosis, but absent muscularis propria layer (therefore a false diverticulum).* **(Right)** *Medium-power magnification of an H&E-stained section shows an esophageal diverticulum with thickened muscularis mucosae and fibrotic submucosa.*

Midesophageal Diverticulum

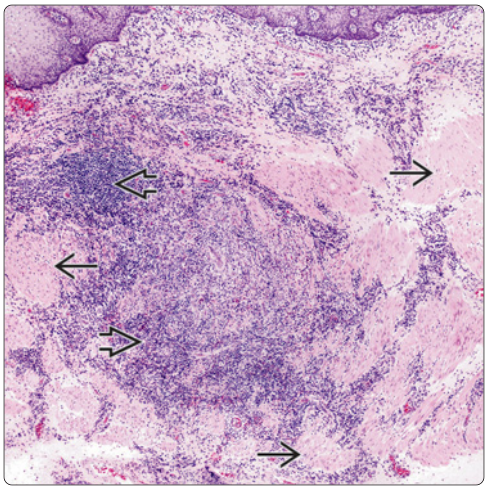


Midesophageal Diverticulum

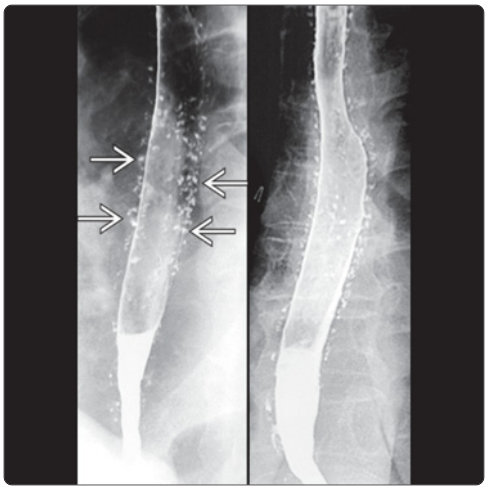


(Left) *Barium esophagram shows a midesophageal diverticulum ⇨ in a patient with tuberculosis. Note the multiple calcified mediastinal lymph nodes ➡, which pulled the esophageal wall outward (traction), creating this true diverticulum.* **(Right)** *High-power magnification of an H&E-stained section shows a midesophageal diverticulum with a very inflamed and partially necrotic squamous epithelium containing bacterial colonies ⇨ and fungal organisms (Candida) ⇨, a common complication in all ED.*

True Esophageal Diverticulum

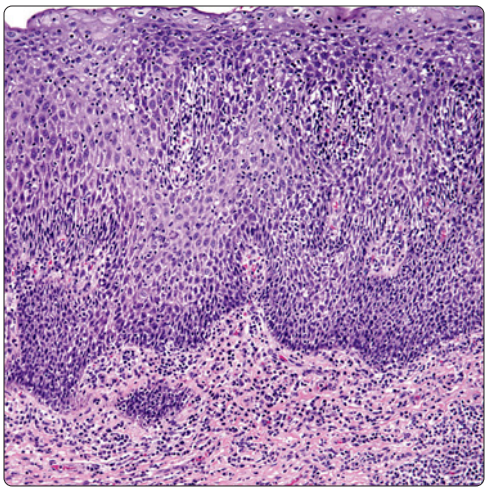


Intramural Pseudodiverticulosis

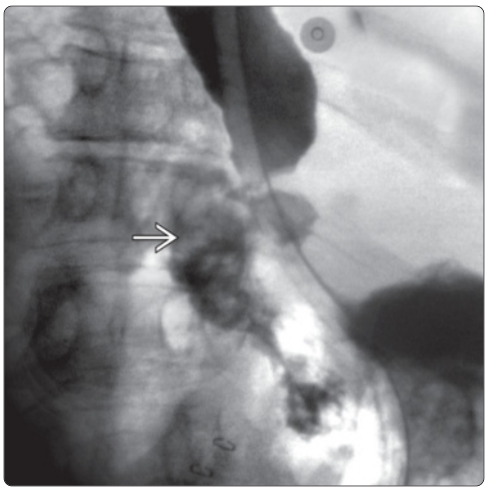


(Left) *Medium-power magnification of an H&E-stained section shows a true esophageal diverticulum with a visible muscularis propria layer ⇨ and prominent inflammation ⇨.* **(Right)** *Barium esophagram shows diffuse esophageal intramural pseudodiverticulosis: Multiple small, flask-shaped outpouchings containing barium ➡ diffusely distributed in the esophageal wall. Not real diverticula, these are ectatic submucosal glands. (From ExDDx: Abdomen.)*

Diverticulitis in Esophageal Diverticula



Boerhaave Syndrome (Mimic)



(Left) *High-power magnification of an H&E-stained section shows diverticulitis in an ED with mostly chronically inflamed mucosa and submucosa.* **(Right)** *Oblique view of barium esophagram shows an irregular paraesophageal collection of contrast material (and gas) ➡ in the lower mediastinum, which has leaked out of the perforated distal esophagus. (From ExDDx: Abdomen.)*

KEY FACTS

TERMINOLOGY

- Spontaneous portosystemic collaterals between vascular channels dilated due to portal hypertension

ETIOLOGY/PATHOGENESIS

- Submucosal plexus receives portal & drains systemic blood
- Occur mostly within 3 cm proximal to GEJ (palisade zone)
- Dilated deep intrinsic veins become subepithelial
- ↑ lumen pressure → ↑ vessel diameter → ↓ wall thickness

CLINICAL ISSUES

- 40-60% of patients with cirrhosis; 1/2 will bleed
  - Responsible for 10-30% of all upper GI bleeding
  - 30-40% initially fatal; up to 50% fatal in 6 weeks
- Asymptomatic until rupture: Massive hematemesis
  - Some patients: Antecedent vomiting, melena
- EV bleeding risk: ↑ size (radius), severe liver dysfunction, red color sign (endoscopy), ongoing alcohol abuse
- Treatment: Prevent initial bleed (1° prophylaxis), control acute hemorrhage, avoid rebleed (2° prophylaxis)
  - Local endoscopic obliteration or ↓ portal pressure
- Most important survival determinant: Liver function

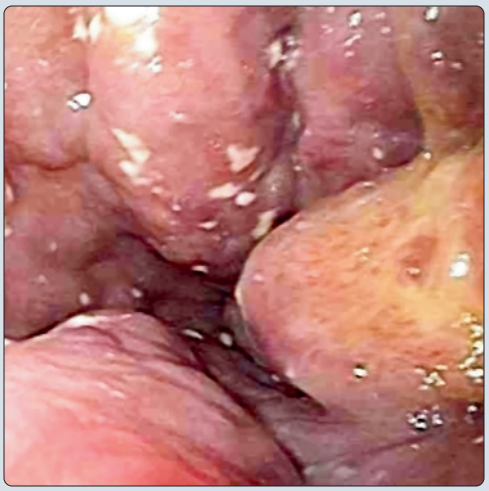
MACROSCOPIC

- Usually collapse after resection (difficult to detect)
- Endoscopic grading (1-4) correlates with risk of bleed
  - Telangiectasias, "red color" signs (cherry red spots): Dilated subepithelial vessels seen through thin mucosa

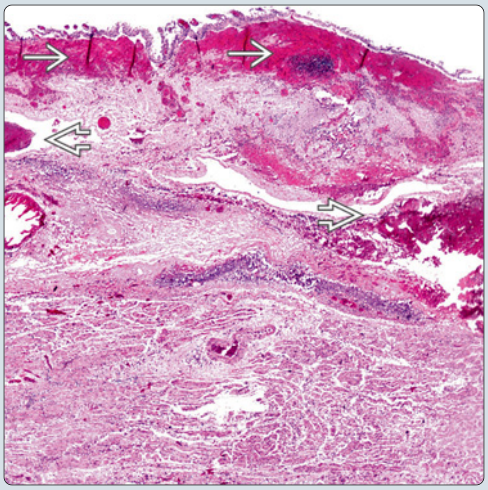
MICROSCOPIC

- Dilated subepithelial blood-filled channels
  - Hemorrhage, rarely intravenous thrombosis
- Edema, epithelial necrosis, inflammation
- Deep esophageal vessels: Thickened and sclerotic
- Organized thrombi can be seen after sclerotherapy
  - Elastic stain can highlight this
- Old thrombosis/hemorrhage in areas of prior rupture

Endoscopic View of Esophageal Varices

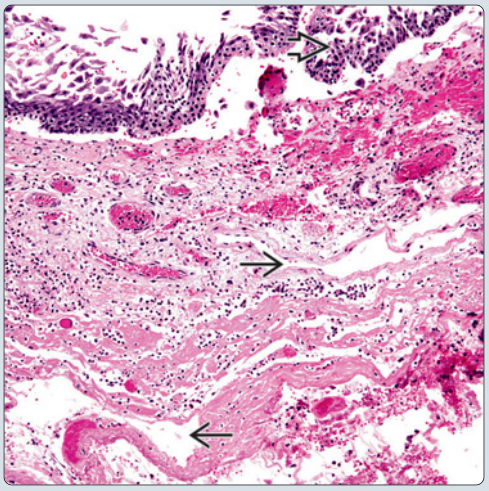


Esophageal Varices

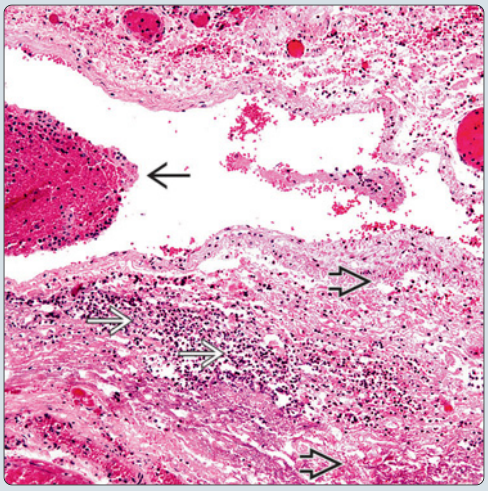


(Left) *Photograph shows the endoscopic appearance of grade 2 esophageal varices. (Courtesy K. Turgeon, MD.)* **(Right)** *Low-power magnification of an H&E-stained section shows subepithelial hemorrhage and dilated, blood-filled vascular channels in the submucosa of the esophagus (esophageal submucosal venous plexus).*

Esophageal Varices



Esophageal Varices After Injection



(Left) *High-power magnification of an H&E-stained section shows attenuated surface epithelium and dilated submucosal vessels.* **(Right)** *High-power magnification of an H&E-stained section shows a thrombus in a submucosal vessel, necrosis, and acute inflammation after paravariceal injection of a nearby esophageal varix.*

TERMINOLOGY

Abbreviations

- Esophageal (gastroesophageal) varices (EV)

Definitions

- EV: Spontaneous portosystemic collaterals between vascular channels dilated by portal hypertension (PH)

ETIOLOGY/PATHOGENESIS

Recruitment of Preformed Channels

- Esophageal submucosal venous plexus
  - Receives (portal) blood: From left coronary gastric vein and short gastric veins (splenic bed)
  - Drains (systemic) blood: Cephalad through azygous vein and intercostal veins into superior vena cava

Lower Esophageal Anatomy (Palisade Zone)

- Sparse submucosal vasculature but numerous thin longitudinal vessels in lamina propria of mucosa
- Mostly within 3 cm proximal to gastroesophageal junction
  - EV most superficial at this site, thin muscularis mucosae

Portal Hypertension and Laplace Law

- Dilated deep intrinsic veins become subepithelial
- ↑ lumen pressure → ↑ vessel diameter → ↓ wall thickness
  - Rupture: Expanding force exceeds wall tension
- Overexpression of nitric oxide synthase in mucosa
  - Development of portosystemic collaterals
- Venous stasis: Anoxia, necrosis, ulceration, ↑ risk of bleed
- EV size depends on severity of liver disease, duration of PH

CLINICAL ISSUES

Epidemiology

- Incidence
  - 40-60% of patients with cirrhosis; 1/2 will bleed
  - Responsible for 10-30% of all upper GI bleeding

Presentation

- Asymptomatic until rupture: Massive hematemesis
- Some patients: Antecedent vomiting, melena
- Splenomegaly, hypersplenism, caput medusa

Natural History

- Bleed: Early morning, late evening (highest pressure)
  - 30-40% initially fatal; up to 50% fatal in 6 weeks
  - 60-70% will stop bleeding, but high risk of rebleed within 1 week

Treatment

- Options, risks, complications
  - Prevent initial bleed (1° prophylaxis), control acute hemorrhage, avoid rebleed (2° prophylaxis)
  - Local endoscopic obliteration
    - Injection sclerotherapy: Intra- or paravariceal
      - Inflammation, fibrosis, venous thrombosis
    - Band ligation: Strangulate EV; safer, ↑ recurrence
      - Necrosis, ulcer, thrombosis, fibrosis
  - ↓ portal pressure (prevent EV formation and growth)
    - Transjugular intrahepatic portosystemic shunt
      - ↓ rebleeds, no survival benefit, encephalopathy
  - Complications: Esophagitis, stenosis, stricture, tear, perforation, dysmotility/reflux, hemolysis
    - Portal vein thrombosis (intravariceal injection)

Prognosis

- EV bleeding risk: ↑ size (radius), severe liver dysfunction, red color sign (endoscopy), ongoing alcohol abuse
  - EV can rupture without triggering event
  - No clear correlation with increased portal pressure
  - Rare if hepatic venous pressure gradient < 12 mm Hg
- Early rebleed: Gastric, large size, high pressure gradient, alcoholic cirrhosis, thrombocytopenia, encephalopathy
- Most important survival determinant: Liver function
- Better prognosis: Noncirrhotic thrombosis, idiopathic PH

IMAGING

Ultrasonographic Findings

- Heterogeneous liver, splenomegaly, collaterals, dilated/thrombosed portal vein, gallbladder thickening

MR Findings

- Angiography: Defines portal anatomy, occlusion site

MACROSCOPIC

General Features

- Usually collapse after resection (difficult to detect)
  - Visualize through transillumination or gelatin filling

Endoscopy: Precise Diagnosis, Initial Therapy

- Telangiectasias, "red color" signs (cherry red spots): Dilated subepithelial vessels seen through thin mucosa
- Red wale marks: Raised longitudinal 1-2 mm streaks
  - "Blowouts" on larger (> 5 mm) submucosal vessels
  - Most advanced grade of EV ("varices on varices")
- Grading (1-4) thought to correlate with risk of bleed
- Well-developed EV: Bluish, sinuous, linear elevations

MICROSCOPIC

Histologic Features

- Dilated subepithelial blood-filled channels
  - Hemorrhage, rarely intravenous thrombosis
- Edema, epithelial necrosis, inflammation
- Deep esophageal vessels: Thickened and sclerotic

DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

- Organized thrombi can be seen after sclerotherapy
  - Elastic stain can highlight this
- May see old thrombosis and old hemorrhage
  - In areas of prior rupture

SELECTED REFERENCES

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