

# **Esophagitis from A to Z-line**

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The objectives of this presentation are:

Review the endoscopic and histologic features of reflux esophagitis and compare and contrast them to other forms of esophagitis, specifically: primary eosinophilic esophagitis, pill-induced esophagitis, CMV esophagitis, herpes esophagitis, and candidal esophagitis,

In the past, the differential diagnosis of esophagitis and esophageal ulcers in the immunocompetent host was fairly simple and straightforward. The vast majority of such cases were due to gastroesophageal reflux (GERD), while a few may have been iatrogenic (pills, capsules, NG tubes, etc.). In the past several years, however, primary eosinophilic esophagitis has emerged as an important entity that has considerable histologic overlap with GERD. The latest studies on differentiating these entities will be discussed in detail.

The differential diagnosis in the immunocompromised host is much broader, as a number of infectious pathogens may involve the esophagus, either alone or in combination.

## **Gastroesophageal Reflux (GERD):**

Reflux typically involves the distal esophagus from the gastroesophageal junction proximally. If the endoscopic impression is that of a more proximal based lesion, then infectious and/or iatrogenic etiologies are more likely. The histologic features of reflux may include both reactive epithelial changes as well as inflammation. The presence of basal cell hyperplasia and elongation of the vascular papillae are non-specific markers of increased epithelial turnover which often correlate with the clinical symptoms of reflux. Other reactive findings which may also be seen in reflux include balloon cells and capillary dilatation (vascular lakes). The inflammatory changes which may be seen in reflux can mimic those seen in infectious esophagitis. The presence of neutrophils in the superficial layers of the epithelium is something often seen in both reflux and Candidal esophagitis. Of course the inflammatory cell which gets the most press as being specific for GERD is the eosinophil. Unfortunately, eosinophils are typically seen in pill-induced esophagitis as well as eosinophilic esophagitis and hence are not specific for GERD at all. Distinguishing pill-induced esophagitis from GERD requires clinical/endoscopic information from the clinician. Pill-induced lesions tend to be in the mid-esophagus where the aortic arch and left ventricle may impinge on the lumen and allow medications to get hung up. While GERD is probably hundreds of times for common than pill-induced ulcers, the later can prove problematic. Some common causes of pill-induced esophagitis include; Doxycycline, Fosamax, Emepromium bromide, KCL, Quinidine – (forms mass-like lesions), iron and NSAIDs.

## **Eosinophilic Esophagitis:**

Eosinophilic esophagitis (EE) is an increasingly recognized disease entity typified by dysphagia in patients who often have asthma/atopy. It has been described clinically as “asthma of the esophagus”. There is a male predominance of between 2-4 to 1. The disease affects both children and adults, many of whom are incorrectly diagnosed and treated for GERD. Patients may present with multiple food impactions. Endoscopically the esophagus often shows multiple rings, furrows or strictures that require dilatation. Some cases also show pinpoint white exudates that seem to correlate with sloughing partially necrotic squamous mucosa microscopically. Histologically biopsies shows marked numbers of intraepithelial eosinophils with basal zone hyperplasia and elongated vascular papillae. Distinction from severe reflux-type changes can be problematic. Several studies have reported that finding >15,20 or 25 eos per high power field is strongly suggestive of EE. In my experience, the presence of mid level or superficial eosinophilic microabscesses is a strong finding in favor of EE. In addition, the presence of marked basal zone hyperplasia (>50% thickness) is also strongly suggestive of EE. Biopsies from the upper or mid esophagus can be very helpful as they are usually involved in EE but not in GERD. Unfortunately the histologic changes of EE can be very patchy, so that one or two biopsies may miss the disease entirely. While an esophageal biopsy with 50 to 100 eosinophils per high power field is most certainly EE, we really don't know what the minimal number that can be seen in EE. In my own practice I have seen one patient with the classic clinical features of EE who only had 7 eos/hpf.

Some patients may have both EE and GERD. Many EE patients take medications for asthma, and many of these compounds are thought to induce GERD. Since EE is treated with oral steroid preparations and other anti-asthma medications rather than PPI, it is important to make the diagnosis. In children, EE may also be treated by avoidance of foods that the patient is allergic to. Some patients may also have increased eosinophils in the rest of their GI tract (eosinophilic gastroenteritis) but most have only esophageal involvement.

### **Candidal Esophagitis:**

Several species of *Candida* organisms are part of the normal flora of the gut, including the oropharynx. In immunocompetent hosts, these organisms may gain a selective advantage after broad-spectrum antimicrobial therapy, particularly if mucosal defects are present from reflux or another predisposing factor. Immunosuppressed patients are at even greater risk; with AIDS, and leukemia/lymphoma patients appearing to have the highest incidences of infection.

Patients with *Candida* esophagitis often present acutely with odynophagia and/or dysphagia. Endoscopically, *Candida* esophagitis has the appearance of white-yellow plaques that resemble cottage cheese. These shaggy exudates may be seen radiographically as longitudinally oriented plaques with a cobblestone appearance. Sub-acute and chronic forms of *Candida* esophagitis do exist, but are much less common. The subacute form of the disease is associated with strictures and intramural pseudodiverticulosis. Chronic *Candida* esophagitis is often associated with cell-mediated immunodeficiency states.

### **Histopathology:**

There can be a variety of findings in *Candida* esophagitis. Ulcers, erosions, or intact epithelium may be seen. Often clumps of necrotic squamous cells with a mummified appearance are present. Close scrutiny of these necrotic clumps on H&E stained sections will often yield yeast and

pseudohyphae. The pseudohyphae often grow straight down perpendicular to the plane of the epithelium. If no yeast are seen on H&E stained sections use of either a PAS (one can use a PAS/alcian blue) or methenamine silver stain (GMS) is recommended. As this necrotic squamous debris may detach from the underlying mucosa, only small fragments may be present in a set of endoscopic biopsies. It is easy to ignore these small pieces of necrotic junk while screening the tissue at low power. If a fungal stain is employed, your attention will quickly be focused on the small fragment of ignored “junk” as it will be crawling with yeast and pseudohyphae. Infiltration of the superficial squamous mucosa by neutrophils (active esophagitis) is another feature often seen in Candida esophagitis. This finding is also seen frequently in reflux esophagitis. In cases without necrotic squamous debris, it can be very difficult to identify Candida without special stains. I have a very low threshold for using fungal stains in cases of active esophagitis, particularly if the patient is immunosuppressed and/or the endoscopist is suspicious of an infectious lesion.

In ulcerated lesions of the esophagus, the type of inflammatory cells present in the exudate can help point one towards the etiologic agent. Candida esophagitis cases tend to have large amounts of neutrophils in their exudates while herpes and CMV esophagitis cases have a predominance of macrophages. Occasionally, however, Candida esophagitis will have large aggregates of lymphocytes which may appear partially necrotic. In such cases, the pathologist may even contemplate the diagnosis of lymphoma.

Occasionally one may encounter a few yeast forms on a special stain of an esophageal biopsy and wonder about their clinical significance. Yeast forms can easily be a contaminant from the oropharynx, where they are part of the normal flora. In general, the presence of pseudohyphae in the esophagus is a sign that the organism is a “real pathogen” that has invaded tissue. When I encounter pseudohyphae in a case of esophagitis I have no problem making the diagnosis of “Candida esophagitis”. When only a few yeast are found on the edge of a specimen, I tend to mention their presence but state “no tissue invasion or pseudohyphae identified”.

### **Herpes Virus Esophagitis:**

Herpes simplex virus is so ubiquitous that nearly all adults have serologic evidence of previous infection. Herpes esophagitis can be caused by either herpes simplex virus type 1 (HSV 1) or herpes simplex virus type 2 (HSV 2). In adults, most cases of herpes esophagitis occur in immunocompromised hosts and represent reactivation of latent HSV type 1. HSV esophagitis has been reported in immunocompetent hosts, in which the infection is presumed to be a primary event. The virus probably gains entry into the esophagus via infected saliva. In neonates, herpes esophagitis may occur as part of disseminated intrapartum infection from HSV 2.

Patients with HSV esophagitis typically present with odynophagia, dysphagia, and/or chest pain. GI bleeding and hematemesis may also occur. Autopsy studies have reported that up to 25% of esophageal ulcers were due to HSV, however, most of these lesions were not diagnosed pre-mortem. The radiographic appearance of HSV esophagitis in barium swallow studies is that of multiple 2 to 3 mm shallow ulcerations present in the middle or lower third of the esophagus. Endoscopically HSV may appear as multiple grouped vesicles, erosions, and/or ulcers, as well as single ulcers, depending on the stage of the disease. Because of the wide variety of endoscopic findings and the high incidence of coinfection with other pathogens, biopsy, brushings and/or cultures are needed to establish the diagnosis.

### **Histopathology:**

The histologic diagnosis of HSV esophagitis depends upon the identification of viral inclusions within the squamous epithelium. These inclusions are intranuclear and vary from large inclusions that completely fill the nucleus to smaller ones that have a clear halo between them and the nuclear membrane (Cowdry type B and A respectively). The inclusions often have a blue-gray color with a ground-glass texture. The nuclear membrane of infected cells are often prominent and irregular. Multinucleated cells with dark smudgy nuclear inclusions are also present. These diagnostic inclusions are usually located at the edge of a vesicle or ulcer, and may not form until relatively late in the infection. Because of this, sampling error may cause the diagnosis to be missed. One diagnostic feature which may aid pathologists in finding diagnostic inclusions is the observation that nearly all ulcerated HSV esophagitis cases have a prominent population of macrophages in their exudates. These macrophages tend to form aggregates in endoscopic biopsy specimens, possibly as a result of the biopsy forceps forcing them together. In some cases, these aggregates can get so large that the pathologist may worry about the possibility of a large cell lymphoma. In general, infected epithelial cells can be found closely adjacent to these macrophage aggregates, often with a small zone of neutrophils between the mucosa and the macrophages. Similar, yet smaller aggregates have been noted in the exudates and granulation tissue from cases of CMV esophagitis. Biopsies from Candida and reflux esophagitis do not contain these macrophages. Hence, the presence of these macrophages in a biopsy that does contain diagnostic viral inclusions warrants additional studies (either deeper H&E stained sections, immunoperoxidase stains, or molecular testing - see ancillary studies section).

### **Cytomegalovirus esophagitis:**

Cytomegalovirus (CMV) is another ubiquitous virus which, similar to HSV, reactivates in the face of immunosuppression. AIDS patients and organ transplant patients seem to be at particularly high risk of developing CMV esophagitis. Unlike HSV, CMV esophagitis is often accompanied by systemic CMV infection.

The clinical presentation of CMV esophagitis is nearly identical to that of Candida and HSV. The radiologic findings in CMV esophagitis often show a single distal esophageal ulcer. Endoscopically, a single distal ulcer is the most common finding with CMV, however, multiple erosions or small ulcers have also been described. As there is no pathognomonic endoscopic finding in CMV, a tissue diagnosis is required. While the identification of CMV viral inclusions on H&E stained sections remains the diagnostic gold standard, viral culture, immunoperoxidase stains, in-situ hybridization, and PCR detection methods may all help increase our diagnostic yield.

### **Histopathology:**

Cytomegalovirus infection can be detected via identification of nuclear and/or cytoplasmic viral inclusions. Cells infected with the virus are greatly enlarged (cytomegaly) and may contain the "classic" Cowdry type A intranuclear inclusion. This classic inclusion has amphophilic (purple) staining with a clear halo surrounding it, giving it an "owl's eye" appearance. The nuclear membrane is often irregularly thickened. Recently, Schwartz and Wilcox described atypical or non-classic cellular abnormalities associated with CMV infection. These authors found many enlarged cells that lacked the classic nuclear inclusion were positive with in-situ hybridization studies. These changes included the lack of halo around the inclusion, the presence

of an enlarged perinuclear amphophilic zone in cells without inclusions, and the presence of smudgy densely eosinophilic nuclei in smooth muscle cells. Cytoplasmic inclusions are also often seen in CMV, however, these occur after the development of the intranuclear inclusions, and hence may not be present in a small biopsy sample.

Unlike HSV, CMV does not appear to infect squamous epithelium. Viral inclusions are often easiest to find in endothelial cells, however, they may also be seen in macrophages, stromal cells, and smooth muscle cells. Because of this, the best place to biopsy for CMV is usually the middle of an ulcer, and the deeper the better. Similar to HSV, the presence of aggregates of macrophages are a marker of CMV esophagitis. The aggregates tend to be smaller than in HSV, and are often centered around blood vessels within granulation tissue.

### **Bacterial Esophagitis:**

While bacteria may be seen in esophageal biopsies for a number of reasons, primary bacterial esophagitis is uncommon. Bacteria may be a secondary pathogen in cases of CMV, HSV, or Candida esophagitis. Bacterial colonization may also be seen secondary to obstruction from tumors, strictures, or diverticula. The presence of dyskeratotic cells with lots of bacteria always makes me worry that the biopsy came from the top of particularly necrotic squamous cancer. When bacteria are primary pathogens, it is nearly always in immunocompromised patients. Occasionally, bacterial esophagitis may lead to bacteremia, particularly when the bacteria are gram positive.

#### **Histopathology:**

Large numbers of bacteria present on the surface of the esophagus or on top of ulcer exudates most likely represent colonization. Primary bacterial infections should show tissue invasion by bacteria. In some cases, no host inflammatory response will be present secondary to the patients' granulocytopenia. Tissue gram stains may help identify tissue invasion as well as sub-classify the organisms.

### **HIV associated Esophagitis:**

AIDS patients have a high incidence of esophagitis and esophageal ulcers. While many are due to combinations of HSV, CMV, and/or candidiasis, a proportion of HIV+ patients have giant esophageal ulcers for which no pathogen other than HIV has been found. These ulcers tend to be located in the middle or distal esophagus and are often deep and greater than 1 cm in diameter. The histologic findings are that of a chronic ulcer without other identifiable pathogens. Some studies have identified HIV RNA and antigens within these ulcers, however, it is still unclear whether HIV causes the virus directly, or secondarily via local immune dysregulation. Treatment with steroids has been effective, but patients frequently relapse once the steroids are withdrawn. Epstein-Barr virus, Cryptosporidium, Pneumocystis carinii, and MAI have also been reported to cause esophageal pathology in AIDS patients.

### **Other infectious agents:**

#### **Fungi:**

Immunocompromised hosts may develop fungal esophagitis from a number of pathogens other than Candida. **Aspergillus**, **Mucor**, **Rhizopus**, and **Absidia** can all involve the esophagus, either

primarily or via disseminated infection. Reports of esophageal involvement by disseminated deep fungal infections such as **Histoplasma** and **Blastomyces** have occurred in both immunocompetent and immunocompromised hosts.

**Mycobacteria:**

Esophageal involvement by *M. tuberculosis* is very uncommon, but may occur from contiguous spread from involved mediastinal lymph nodes. Involvement by atypical mycobacterial species (MAI) in AIDS patients is more common.

**Parasites:**

While very uncommon in the United States and Canada, parasitic infections of the esophagus do occur in developing countries. The most common parasitic infection of the esophagus is **Chagas' disease**. Destruction of the nerve ganglia leads to a megaesophagus and secondary stasis type changes. The infecting organisms are not seen in biopsy specimens.

## The Red Goose Blues

I went to see the doctor cause I had some heartburn  
He said I was suffering from a bad case of GERD  
He gave me purple pills that I could not afford  
And put me on a diet that sure made me bored  
No more chocolate and no more alcohol  
I'm hungry and I'm sober and I'm climbing the wall

He said the squamous mucosa that lines my goose  
Its all inflamed from too much gastric juice  
My esophageal sphincter doesn't seem to function  
I've got erythema above my GE junction  
My big beer belly gives the acid a push  
And leads to dyspepsia just like good old president Bush

I've had enough of this pain in my neck  
I can't stand the taste of this antacid dreck  
Reflux esophagitis running around my brain  
This stuff's enough to make you go insane  
My goose is red so now I have the blues  
My baby done left me and my kids all need new shoes

I've got asthma, allergies and excematous skin  
I guess its something I got from inbred kin  
Been having trouble swallowing so I had endoscopy  
It seemed like torture and they charged me quite a fee  
The doc saw some rings and a stricture too  
He took lots of biopsies and he sent them off to you

The pain in my throat makes me crazy as a loon  
If I don't get relief I won't finish this tune  
Payin all this money to a bunch of rich quacks  
If they don't get me better I'll have em all whacked

I've had enough of this choking sensation  
I need a GI pathologist you know the best in the nation  
To look at my biopsies and tell me what's wrong  
Better read them stat so I can finish this song

My goose is red so now I have the blues  
Better figure out what's wrong with me before I sue

Lots of eosinophils were in my mucosa  
My papillae went up and down like a roller coaster  
Basal zone hyperplasia was easy to see  
This wasn't no reflux it was classic EE  
Forget that awful diet and those PPIs  
I need topical steroids and lots of bourbon over ice

Eosinophilic esophagitis running round my brain  
Pour those nasty antacids right on down the drain  
Don't have no reflux bothering me  
It's just a complication of my atopy  
My goose ain't red, but I still got those blues  
Can't pay my path bill and my kids still need new shoes

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