Title

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Educational Case: Infectious Esophagitis

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.[1]

Keywords
pathology competencies, organ system pathology, gastrointestinal tract, mechanical disorders of bowel, dysphagia, infectious esophagitis, candida esophagitis, Herpes simplex virus esophagitis, cytomegalovirus esophagitis

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Primary Objective

Objective GT8.1: Dysphagia. Describe the pathophysiology and clinicopathological features of disorders presenting with dysphagia.

Competency 2: Organ System Pathology; Topic GT: Gastrointestinal Tract; Learning Goal 8: Mechanical Disorders of Bowel.

Secondary Objective

Objective GT7.1: Bowel Infections. Compare the underlying mechanism and clinicopathologic features of gastrointestinal tract involvement by common bacterial, fungal, and parasitic pathogens.

Competency 2: Organ System Pathology; Topic GT: Gastrointestinal Tract; Learning Goal 7: Bowel Infections.

Objective FECT2.3: Histopathologic Features of Viral Infection. Compare and contrast the histopathological features of herpes virus, cytomegalovirus, human papilloma virus, and adenovirus in terms of nuclear features, inclusions, size of cells, and other unique characteristics; recognize these histopathological features of viral infections in images of different tissues.

Competency 1: Disease Mechanisms and Processes; Topic FECT: Infectious Mechanisms; Learning Goal 2: Pathogenic Mechanism of Infection.

Objective FECT2.9: Histopathologic Features of Fungal Infection. Recognize histopathologic evidence of fungal infections and compare and contrast the histopathological features and staining characteristics of the following fungi: *Candida albicans*, *Cryptococcus neoformans*, *Aspergillus*, *Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomyces dermatitis*, *Pneumocystis jiroveci*, and *Zygomycetes*.

Competency 1: Disease Mechanisms and Processes; Topic FECT: Infectious Mechanisms; Learning Goal 2: Pathogenic Mechanism of Infection.

Patient Presentation

A 45-year-old female presents to her primary care physician with a 2-week history of odynophagia, dysphagia, dry mouth, and retrosternal pain. She reports limited intake of solid food due to the pain, as well as an unintentional weight loss of 10 lbs

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during the past month. The patient has been HIV positive for over 10 years. She is not taking her antiretroviral therapy and has not seen a physician regularly. Her most recent CD4 count was 150 over 1 year ago.

Diagnostic Findings Part I

Physical examination is notable for a cachectic female, with white lesions on the tongue and buccal mucosa. These lesions are easily scraped off with a tongue depressor.

Questions/Discussion Points Part I

What Is the Differential Based on Clinical Presentation and Physical Examination Findings?

The differential diagnosis for a patient presenting with esophageal dysphagia and odynophagia includes esophagitis secondary to infection with cytomegalovirus (CMV), herpes simplex virus, and/or *Candida* spp. Additionally, medication-induced esophagitis, reflux esophagitis, eosinophilic esophagitis, and idiopathic HIV ulcers should be considered.[2]

It can be difficult to distinguish between these entities; however, there are key differences in clinical presentation and physical examination findings. Patients who present with medication-induced esophagitis are typically elderly patients who swallow several large pills without enough liquid and do so in a suboptimal position.[3] They can present with dysphagia and odynophagia. This is less likely for our patient, as she does not report any current medication use. Patients with reflux esophagitis frequently have a history of heartburn or regurgitation that is worse after consuming fatty meals. They may also report a worsening of symptoms with changes in posture, such a lying down or bending forward. It is unlikely that the patient has reflux esophagitis, as she does not report any history of heartburn, regurgitation, or a postural relationship to her odynophagia. Lastly, patients with eosinophilic esophagitis can present with symptoms, such as upper abdominal pain, dysphagia to solid foods, and food impaction.[4] Patients with this condition typically have a history of allergic conditions such as asthma and eczema. Although our patient does present with dysphagia to solid foods, eosinophilic esophagitis is less likely given the acute onset of symptoms and no history of allergic conditions.

Additionally, physical examination findings of a cachectic female with scrapable white lesions are concerning for a patient with an immunodeficiency, consistent with our patient's history of HIV. Patients who have severely depressed cell-mediated immunity are often susceptible to infections from opportunistic organisms, such as *Candida spp*, which can manifest as oral thrush.

What Are the Next Steps in Working Up This Patient's Condition?

Because the patient has a history of HIV and is presenting with two weeks of odynophagia and dysphagia, the next step is to perform an upper endoscopy with biopsies of any esophageal lesions.

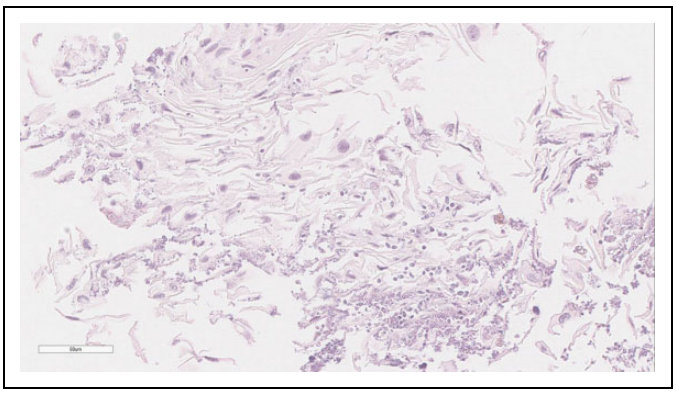

Figure 1. Candida esophagitis with yeast forms amidst the "shredded wheat" like appearance of squamous epithelium (hematoxylin and eosin, ×40. Bar = 50 μm.).

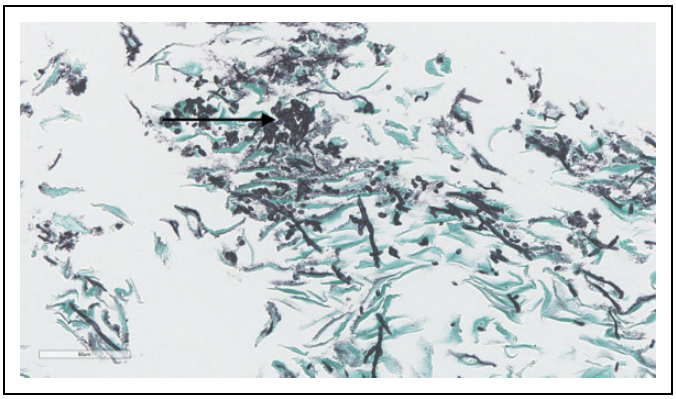

Figure 2. Candida esophagitis with an abundance of pseudohyphae and yeast amidst squamous cells, arrow pointing toward the yeast forms (Gomori Methenamine-Silver, ×40. Bar = 60 μm.).

Diagnostic Findings Part II

Upper endoscopy reveals several raised, white plaques throughout the esophagus, which are biopsied (Figure 1). The surrounding mucosa is erythematous and edematous.

Questions/Discussion Points Part II

Describe the Histologic Features Seen in Figures 1 and 2

Figure 1 shows superficial squamous epithelium that is disrupted due to the biopsy giving a "shredded wheat" appearance. Between the squamous cells multiple small oval yeast forms can be identified. Figure 2 is a Gomori Methenamine-Silver (GMS) special stain, which is often used to visualize fungal elements and other opportunistic organisms. The oval yeast forms (arrow) and other fungal elements are stained black, as the GMS stain highlights the fungal cell wall polysaccharide elements. Lastly, neutrophilic inflammation accompanies this infection.

Based on the Clinical and Pathologic Features, What Is Your Diagnosis?

This patient has Candida esophagitis. The diagnosis is suspected on direct endoscopic visualization of the esophagus, which reveals classic diffuse white mucosal plaques.[5] Confirmatory biopsies show histologic evidence of tissue invasion by Candida spp. It is essential to find evidence of spores or hyphae invading the squamous epithelium, or within the necrotic, inflammatory debris.

What Are the Clinical Features of Candida Esophagitis?

Candida esophagitis is the most common type of infectious esophagitis in adults, and *C. albicans* is the most common organism identified.[5] In contrast to eosinophilic esophagitis or reflux esophagitis, candida esophagitis presents with a rapid onset of symptoms. These include dysphagia, odynophagia, retrosternal chest pain, vomiting, and fever.[5] Patients may also present with chest pain or gastrointestinal (GI) tract bleeding. Some patients may be entirely asymptomatic.

What Is the Pathophysiology of Candida Esophagitis?

Candida species are part of the normal flora in the oropharynx and esophagus. Candida esophagitis results from a combination of factors, including fungal overgrowth and impaired cell-mediated immunity.[5] Overgrowth of *Candida* species can be secondary to broad-spectrum antibiotic therapy, poorly controlled diabetes mellitus, abnormal esophageal motility, or mechanical abnormalities (esophageal stricture).[5] Additionally, individuals who have AIDS, receive chemotherapy/radiation, or take immunosuppressant medication have impaired cell-mediated immunity, and are therefore more susceptible to opportunistic infections. It is estimated that 10% to 15% of patients with AIDS will develop this condition over their lifetime.[2] In fact, the development of candida esophagitis may be the first indication that an HIV-positive patient has developed AIDS.[2]

What Is the Treatment for Candida Esophagitis?

Candida esophagitis is treated with systemic therapy for 2 to 3 weeks.[6] Intravenous medications are given to those who cannot tolerate oral intake. Although fluconazole is the recommended agent due to efficacy and low cost, other medications include echinocandins or amphotericin B.[6]

Notably, patients with HIV are less responsive to antifungal therapy and may take longer to improve. This group is also prone to reinfection, as opportunistic pathogens are difficult to eliminate in immunosuppressed individuals.[5]

What Are the Clinical Features of Herpes Simplex Virus Esophagitis?

Herpes simplex virus (HSV) esophagitis presents similarly to Candida esophagitis; the main features are dysphagia, odynophagia, chest pain, fever, extra-esophageal herpetic lesions, nausea, vomiting, and GI bleeding.[7] Patients may also present with oropharyngeal ulcers or herpes labialis.

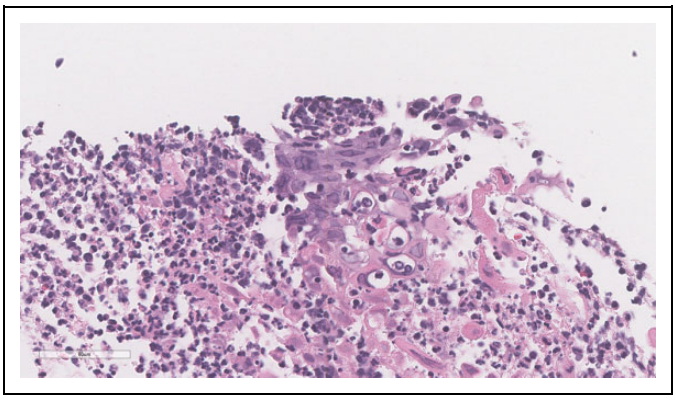

Figure 3. Herpes simplex virus esophagitis with infected squamous cells demonstrating multinucleation, nuclear molding, and chromatin margination (hematoxylin and eosin, ×40. Bar = 60 μm.).

The main risk factor for HSV esophagitis is immunodeficiency, and impaired cellular immunity in particular.[7] Thus, patients who have T-lymphocyte deficiency, such as those with HIV, are at particularly increased risk. Lastly, the use of chemotherapeutic agents and steroids are established risk factors for HSV esophagitis. In addition to immunosuppression, certain chemotherapy drugs compromise the esophageal mucosa integrity, making infection with opportunistic organisms more likely.[7] Steroids are also involved in downregulation of T-cell proliferation, contributing to immune dysfunction.

What Is Seen on Endoscopy for Patients With Herpes Simplex Virus Esophagitis?

The diagnosis of HSV esophagitis requires endoscopy with biopsy and histologic confirmation. Endoscopy typically reveals lesions in the distal esophagus. The early stage of HSV esophagitis is characterized by vesicles or "volcano ulcers" that are up to 2 cm in size.[7] Later stages show coalescing ulcers with friable mucosa.[7] Biopsies and brushings are typically taken from the margins of the ulcers, where viral cytopathic activity is seen in the squamous epithelium.[7]

Describe the Histologic Features Seen in Herpes Simplex Virus Esophagitis (Figures 3 and 4)

Figure 3 reveals squamous epithelial cells with nuclei that have a "ground glass" appearance, marginated chromatin, multinucleation, and nuclear molding, characteristics of HSV esophagitis.[7] Additionally, eosinophilic intranuclear and cytoplasmic inclusion bodies within squamous epithelial cells at the ulcer margins may be seen, referred to as Cowdry type A inclusions.[7] Further, biopsies taken from the ulcer bed may reveal an abundance of inflammatory cells and necrotic debris.[7] Figure 4 is an immunohistochemical stain used to detect HSV-infected cells. This is done using antibodies that specifically bind to the HSV

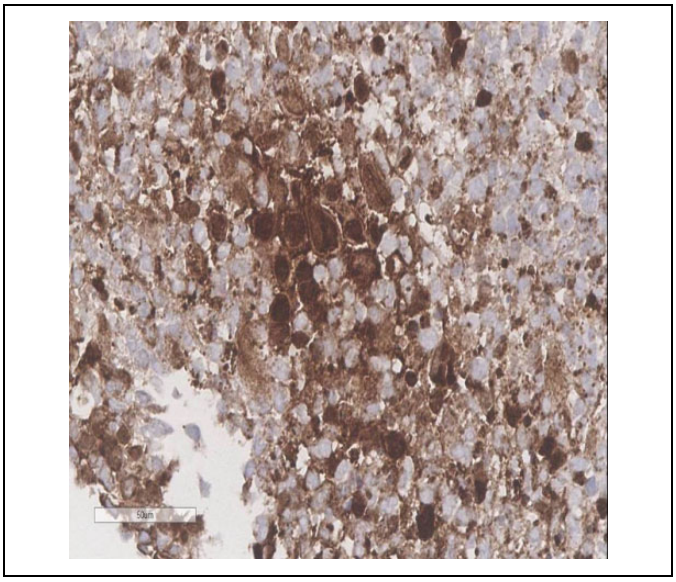

Figure 4. Herpes simplex virus esophagitis with nuclear and cytoplasmic staining, confirming infection within cells (Immunohistochemical, ×40. Bar = 50 μm.).

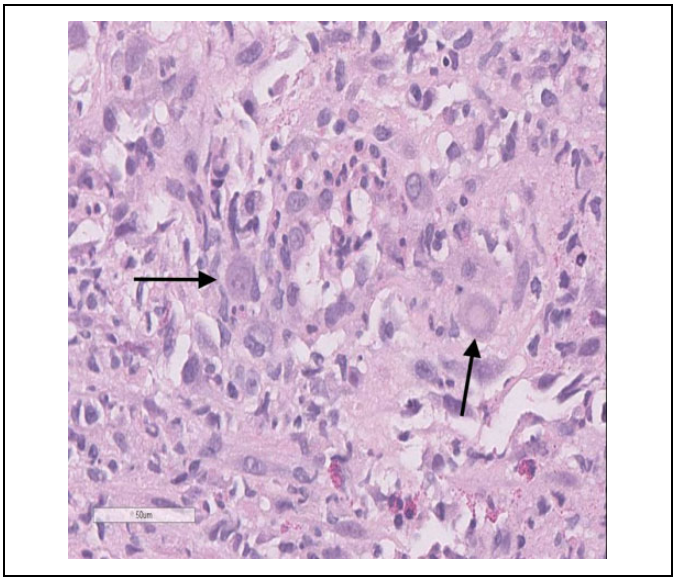

Figure 5. Cytomegalovirus esophagitis with enlarged mesenchymal cells containing basophilic nuclei and pale perinuclear regions. Arrows pointing to "owl's eye" appearance of cells (hematoxylin and eosin, ×40. Bar = 50 μm).

antigens and subsequently visualizing the antigen–antibody complex, with a colored stain. Figure 4 shows significant nuclear and cytoplasmic staining, or immunoreactivity, suggesting an infection of HSV within the squamous cells.

What Is the Pathophysiology of Herpes Simplex Virus Esophagitis?

Herpes simplex virus-1 is a large, double-stranded DNA virus in the *Herpesviridae* family that is implicated in HSV esophagitis. The HSV-1 is transmitted through oral-to-oral, oral-to-genital, or genital-to-genital contact. This occurs when an unaffected individual comes into contact with skin, mucosal secretions, or lesions that are infected with HSV-1.[8] A significant majority of individuals with primary HSV-1 infection are asymptomatic. Individuals with symptomatic primary infection present with painful oral ulcers, lymphadenopathy, fever, malaise, or headache.[8] Recurrent HSV-1 infections occur in approximately 20% to 40% of infected individuals. This typically occurs due to immunodeficiency, stress, or fever.[8] The HSV esophagitis is most commonly due to reactivation of a latent HSV-1 virus in the sensory ganglia. Occasionally, reactivation of a latent HSV-2 infection can also result in esophagitis. The virus is thought to spread to the esophagus via the vagus nerve or directly from the oral cavity into the esophagus during an infection.[9] Less commonly, HSV esophagitis can result from a primary herpes infection.

What Are Clinical Features of Cytomegalovirus Esophagitis?

Cytomegalovirus is frequently identified in individuals who are HIV-positive, have a CD4 count below 200 cells/mm^3, and/or do not take antiretrovial therapy. Other individuals who are particularly vulnerable to CMV esophagitis include organ transplant recipients, dialysis participants, or those taking immunosuppressive medications.[9] Clinical manifestations include odynophagia, fever, nausea, and substernal pain.

What Is Seen on Endoscopy for Patients With Cytomegalovirus Esophagitis?

Endoscopic findings can be variable for CMV esophagitis. Typically, there are several, well-circumscribed shallow ulcerations found in the distal esophagus.[9] However, deep ulcers or diffuse erosions may be seen. Additionally, ulcers tend to be linear or longitudinal in shape.[10] It is essential to take biopsies from the ulcers or erosions to diagnosis CMV esophagitis.

Describe the Histologic Features of Cytomegalovirus Esophagitis (Figures 5 and 6)

Figure 5 is a hematoxylin and eosin image of CMV-infected cells. The viral cytopathic effect of CMV is typically seen within endothelial and stromal cells at the base of the ulcer.[11] Characteristic features seen on histology include cytomegaly, often eccentrically positioned basophilic nuclei with inclusions surrounded by a clear halo (similar to an "owl's eye"), and a paler perinuclear region.[11] Arrows in Figure 5 point to this "owl's eye" appearance. Additionally, basophilic cytoplasm with intracytoplasmic granules may be seen. Figure 6 is an immunohistochemical stain used to detect CMV-infected cells. Specific antibodies bind to the CMV antigens within cells, and the antigen–antibody complex is visualized with special

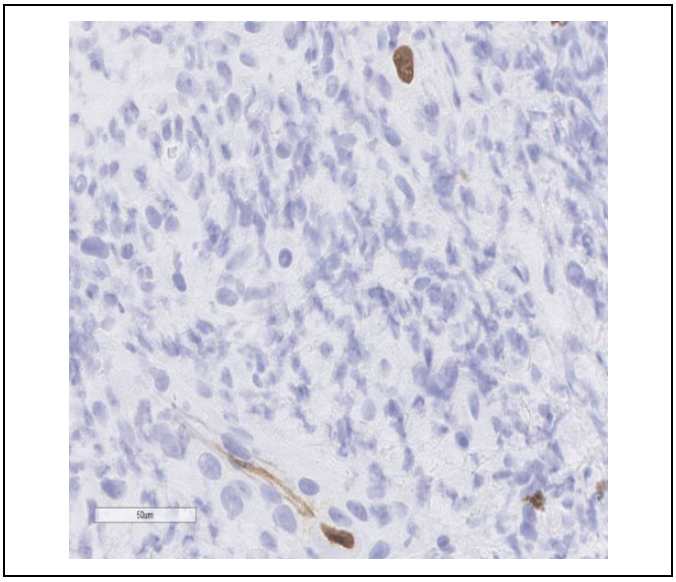

Figure 6. Cytomegalovirus esophagitis with nuclear staining, confirming infection within cells (immunohistochemical, ×40. Bar = 50 μm).

staining. In Figure 6, there is pronounced nuclear staining, confirming CMV infection within the cells.

What Is the Pathophysiology of Cytomegalovirus Esophagitis?

Like HSV-1, CMV belongs to the *Herpesviridae* family and is a double-stranded DNA virus. The pathophysiology of CMV esophagitis is similar to that of HSV esophagitis. The virus is transmitted through several routes, including perinatal, sexual, and blood or tissue exposure.[12] Additionally, individuals with close contact to those infected with CMV are at a greater risk of developing infection because the virus can be shed from the upper respiratory tract and urine.[12] Cytomegalovirus infection is quite common, an estimated 90% of adults older than 80 are infected.[12] The majority of individuals who are infected with CMV are immunocompetent and asymptomatic. Healthy individuals may develop an illness similar to mononucleosis, with fever, tonsillitis, lymphadenopathy, and dermatologic manifestations.[12] Because CMV can remain in a latent form in several organs, immunosuppression allows the latent virus to become activated.[13] Reactivation of the virus results in a systemic disease with viremia that can colonize several organs, such as the GI tract.[13] Patients who have evidence of CMV infection in the GI tract frequently also have CMV retinitis; therefore, it is imperative for patients to be evaluated with ophthalmologic examinations.[13]

What Are the Key Differences Between Candida, Herpes Simplex Virus, and Cytomegalovirus Esophagitis?

Although the various types of infectious esophagitis have similar risk factors and clinical presentations, they can be differentiated by endoscopic and histologic findings as shown in Table 1.

Table 1. A Comparison of *Candida*, HSV, and CMV Esophagitis.

Pathogens	Endoscopic Findings	Histologic Features
Candida	White mucosal plaques dispersed throughout the esophagus, with an underlying erythematous mucosa.	Pseudohyphae and yeast among patches of necrotic squamous cells. Pseudohyphae invading GI tissue.
HSV	Diffuse, superficial ulcers typically in the distal esophagus. Early endoscopic findings include vesicles up to 2 cm. Later findings are coalescing ulcers with friable mucosa.	Nuclear molding, multinucleation, and chromatin margination. Eosinophilic or basophilic inclusion bodies in squamous epithelial cells at ulcer margins (Cowdry type A inclusions).
CMV	Multiple linear or longitudinal ulcers that are found in the distal mucosa. The ulcers are well circumscribed and can be shallow or deep.	Infection of mesenchymal and stromal cells at the base of the ulcer. Cytomegaly, intranuclear basophilic inclusions (owl's eye), granular cytoplasmic inclusions.

Abbreviations: CMV, cytomegalovirus; GI, gastrointestinal; HSV, Herpes simplex virus.

Teaching Points

- The main clinical manifestations for infectious esophagitis include dysphagia, odynophagia, chest pain, fever, nausea/vomiting, and GI bleeding.
- Risk factors for all types of infectious esophagitis include AIDSs, chemotherapy/radiation, and immunosuppressant medications.
- Endoscopic findings for candida esophagitis are raised white plaques throughout the esophagus, with edematous and erythematous mucosa.
- Histology for candida esophagitis includes pseudohyphae and yeast invading viable tissue, often with associated neutrophilic inflammation.
- Endoscopic findings for HSV esophagitis include vesicles or "volcano ulcers" in the early stage and coalescing ulcers with friable mucosa in later stages.
- Histology for HSV esophagitis shows nuclear molding, margination, and multinucleation of infected cells. Eosinophilic intranuclear and cytoplasmic inclusion bodies within squamous cells, referred to as Cowdry type A inclusions, may be seen.
- Endoscopic findings for CMV esophagitis are multiple well-circumscribed shallow ulcerations found in the distal esophagus. Cytomegalovirus ulcers typically are linear or longitudinal in shape.
- Histology for CMV esophagitis reveals enlarged cells with basophilic nuclei, intranuclear, basophilic inclusions surrounded by a clear halo, and perinuclear paler

regions. Basophilic cytoplasm with intracytoplasmic granules may also be present.

Declaration of Conflicting Interests

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References

1. Knollmann-Ritschel BEC, Regula DP, Borowitz MJ, Conran R, Prystowsky MB. Pathology competencies for medical education and educational cases. *Acad Pathol*. 2017:4. doi:10.1177/2374289517715040.
2. Vazquez J. Optimal management of oropharyngeal and esophageal candidiasis in patients living with HIV infection. *HIV/AIDS—Research and Palliative Care*. 2010. https://www.academia.edu/13746998/Optimal_management_of_oropharyngeal_and_esophageal_candidiasis_in_patients_living_with_HIV_infection. Accessed April 23, 2019.
3. Castell DO. Medication-induced esophagitis. 2018. *UpToDate*. https://www.uptodate.com/contents/medication-induced-esophagitis. Accessed November 2, 2019.
4. Bystrom J, O'Shea NR. Eosinophilic oesophagitis: clinical presentation and pathogenesis. *Postgrad Med J*. 2014;90:282-289. doi:10.1136/postgradmedj-2012-131403.
5. Baig MA, Rasheed J, Subkowitz D, Vieira J, Gerges S. Severe esophageal candidiasis in an immunocompetent patient. *Int J Infect Dis*. 2005;5. doi:10.5580/a1. f.
6. Kauffman CA. Treatment of oropharyngeal and esophageal candidiasis. 2018. *UpToDate*. http://www.uptodate.com/contents/treatment-of-oropharyngeal-and-esophageal-candidiasis?.search=candidaesophagitis&source=search_result&selectedTitle=1～78&usage_type=default&display_rank=1. Accessed April 27, 2019.
7. Généreau T, Rozenberg F, Bouchaud O, Marche C, Lortholary O. Herpes esophagitis: a comprehensive review. *Clin Microbiol Infect*. 1997;3:397-407. doi:10.1111/j.1469-0691.1997.tb00275.x.
8. Johnston C, Wald A. Epidemiology, clinical manif estations, and diagnosis of herpes simplex virus type 1 infection. 2019. *UpToDate*. https://www.uptodate.com/contents/epidemiology-clinical-manifestations-and-diagnosis-of-herpes-simplex-virus-type-1-infection. Accessed November 4, 2019.
9. Rosołowski M, Kierzkiewicz M. Etiology, diagnosis and treatment of infectious esophagitis. *Prz Gastroenterol*. 2013;8:333-337. doi:10.5114/pg.2013.39914.
10. Hashimoto R, Chonan A. Esophagitis caused by cytomegalovirus infection in an immune-competent patient. *Clin Gastroenterol Hepatol*. 2016;14:e143-e144. doi:10.1016/j.cgh.2016.06.016.
11. Grin A, Streutker CJ. Esophagitis: old histologic concepts and new thoughts. *Arch Pathol Lab Med*. 2015;139:723-729. doi:10.5858/arpa.2014-0132-ra.
12. Friel TJ. Epidemiology, clinical manifestations, and treatment of cytomegalovirus infection in immunocompetent adults. 2019. *UpToDate*. https://www.uptodate.com/contents/epidemiology-clinical-manifestations-and-treatment-of-cytomegalovirus-infection-in-immunocompetent-adults. Accessed November 5, 2019.
13. Jacobson MA. AIDS-related cytomegalovirus gastrointestinal disease. 2017. *UpToDate*. https://www.uptodate.com/contents/aids-related-cytomegalovirus-gastrointestinal-disease. Accessed May 5, 2019.