Case Series

Candida as an innocent bystander in esophageal ulcers: A case series

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ABSTRACT

Esophageal ulcers are a common endoscopic finding in patients with dysphagia with a broad range of etiologies, including gastroesophageal reflux disease, drug-induced injury, infections, malignancy, corrosive ingestion, etc. *Candida albicans* is the most frequently implicated organism in infectious esophagitis. However, its mere presence on histopathology does not confirm causation, particularly in immunocompetent patients, where it may represent secondary colonization. We report a case series of three patients presenting with esophageal ulcers and histological evidence of *Candida*. In the first two cases, esophageal ulcers resulted from pill esophagitis secondary to doxycycline and non-steroidal anti-inflammatory drugs, while the third case was attributed to herpes simplex esophagitis. Although *Candida*/yeast was identified in esophageal ulcer biopsies of all three patients, the first two cases improved with rabeprazole and sucralfate alone. The third case did not respond to fluconazole; further evaluation confirmed herpes simplex esophagitis and improved following antiviral treatment. This case series underscores that *Candida* is not necessarily the primary cause of esophageal ulcers but may instead represent secondary colonization.

Key words: *Candida*, Colonization, Herpes simplex virus, Esophageal ulcer, Pill esophagitis

Esophageal ulcer is a commonly encountered pathology in patients with dysphagia or odynophagia with diverse etiologies, including gastroesophageal reflux disease (GERD), pill-induced esophagitis, infective esophagitis, caustic ingestion, malignancy, etc. [1,2]. *Candida albicans* is the most frequent fungal pathogen implicated in infectious esophagitis, predominantly in immunocompromised individuals [3]. Nevertheless, the reported prevalence of esophageal candidiasis in otherwise healthy individuals is only 0.35% [4]. Importantly, its detection on histopathology does not necessarily confirm causality, particularly in patients without classical risk factors. *Candida* forms part of the normal mucosal flora and may colonize damaged or inflamed mucosa without causing invasive disease. Pill-induced esophagitis (PE) and viral infections can both produce mucosal ulceration that may become secondarily colonized by *Candida* [5,6].

We describe a case series of three patients with esophageal ulcers in whom *Candida* was identified on histology. Careful clinical correlation, treatment response, and follow-up helped distinguish colonization from true infection. This series emphasizes the need for clinical correlation when *Candida* is detected in esophageal ulcer biopsies. Misattributing *Candida* colonization as the cause of esophageal ulceration may lead to unnecessary antifungal therapy and delayed diagnosis of the true etiology.

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Case 1

A 55-year-old gentleman with no known comorbidities presented to our outpatient department with acute-onset, progressively worsening, severe aching chest pain that was exacerbated by food intake and associated with odynophagia and dysphagia for the past 4 days. He had a history of fever 10 days ago, for which he was prescribed a 7-day course of antibiotics, cefixime 200 mg twice daily, and doxycycline 100 mg twice daily. On examination, his vital signs were stable, and general physical examination revealed no abnormalities. Routine investigations, including hemogram, liver function tests, renal function tests, electrocardiogram

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(ECG), and chest X-ray, were essentially within normal limits. Upper gastrointestinal (GI) endoscopy revealed a large, semi-circumferential ulcer with a whitish coating situated in the upper portion of the lower third of the esophagus (Fig. 1a). Biopsy samples were obtained from both the edge and base of the ulcer for histopathological examination (HPE). On further questioning, he revealed that he had been taking the antibiotics with only a small amount of water. A diagnosis of doxycycline-induced pill esophagitis was considered, and the patient was started on rabeprazole 20 mg sachet twice daily along with sucralfate-oxetacaine syrup 10 mL every 6 h for 2 weeks. His symptoms steadily improved over the next few days, and he became completely asymptomatic within 1 week. He returned to the outpatient department after 2 weeks with a histopathology report showing reactive changes, including basal zone hyperplasia, yeast cells, and epithelial edema, most prominent in the superficial layers (Fig. 2). Despite not receiving antifungal therapy, his repeat endoscopy at 2 weeks showed complete resolution of the ulcer (Fig. 1b).

Case 2

A 35-year-old man with no known comorbidities presented to our outpatient department with a 3-day history of acute-onset, progressively worsening dysphagia, predominantly to solids compared to liquids, associated with odynophagia. He had a history of migraine headache 5 days prior, for which he self-medicated with over-the-counter naproxen 500 mg twice daily for 2 days. Upon examination, his vital signs were stable, and general physical assessment revealed no abnormalities. Routine investigations, including complete blood count, liver and renal function tests, ECG, and chest X-ray, were all within normal limits. Upper GI endoscopy revealed two opposing circular ulcers (kissing ulcers) in the mid-esophagus (Fig. 3a). Biopsy samples were taken from the ulcer for histopathological evaluation. Upon further questioning, he reported taking the tablets in an upright position with an adequate amount of water. A diagnosis of non-steroidal anti-inflammatory drug (NSAID)-induced pill esophagitis was kept, and the patient was started on rabeprazole 20 mg sachet twice daily along with sucralfate-oxetacaine syrup 10 mL every 6 h for 2 weeks. His symptoms steadily improved over the next few days, and he became completely asymptomatic within 1 week. HPE revealed erosive esophagitis pattern of injury with acute inflammation, intraepithelial neutrophilic abscesses, and epithelial edema, along with yeast forms of fungal organism (Fig. 4). Despite not receiving antifungal therapy, his repeat endoscopy at 2 weeks showed complete resolution of the ulcer (Fig. 3b).

Case 3

A 50-year-old gentleman with a history of diabetes

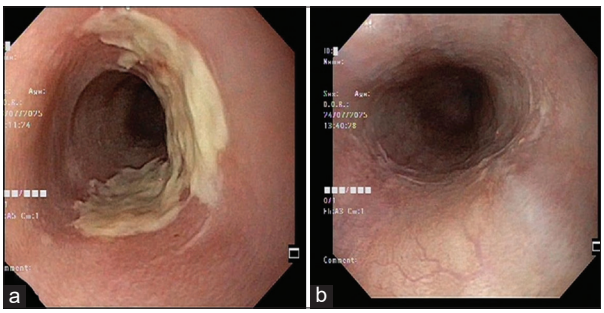

Figure 1: (a) Endoscopic image showing semi circumferential esophageal ulcer with yellowish white coating, (b) showing healed esophageal ulcer (Case 1)

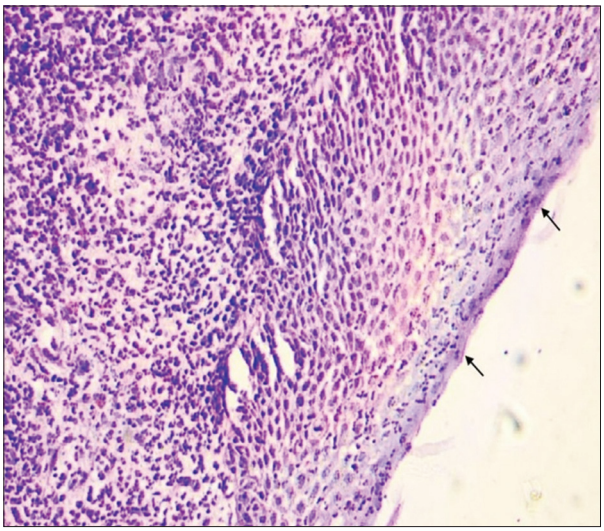

Figure 2: Low power hematoxylin and eosin-stained section showing reactive changes, including basal zone hyperplasia, yeast cells (arrow) and epithelial edema (Case 1)

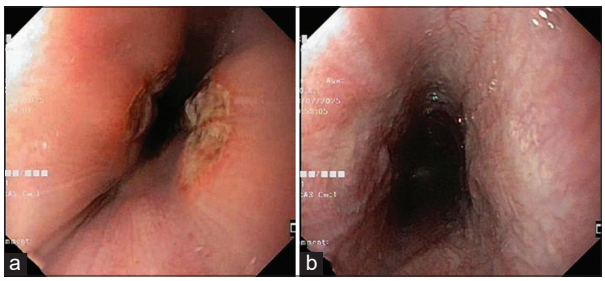

Figure 3: (a) Showing kissing ulcers with exudate at mid esophagus, (b) showing healed esophageal ulcer (Case 2)

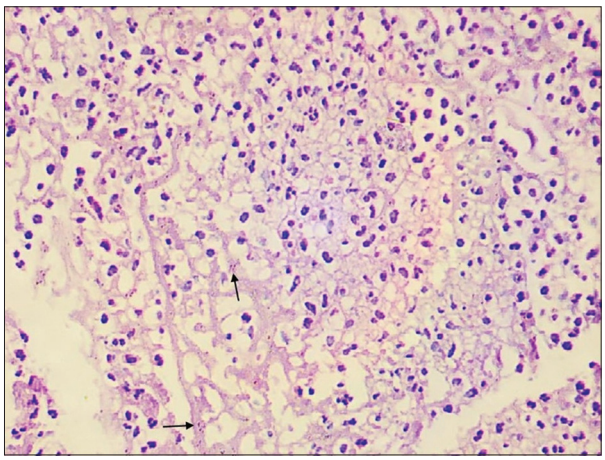

Figure 4: Low power hematoxylin and eosin-stained section erosive esophagitis pattern of injury with acute inflammation along with yeast forms of fungal organism (arrow) (Case 2)

mellitus and coronary artery disease presented to our clinic with a 6-month history of gradually progressive, moderately severe aching chest pain aggravated by food intake, along with a 4-month history of intermittent low-grade fever and progressively worsening dysphagia and odynophagia, more marked for solids than liquids. He also reported an 8 kg weight loss over the past 6 months, accompanied by decreased appetite. There was no history of tuberculosis (TB) contact, cough with sputum production, joint pains, oral ulcers, diarrhea, or skin lesions. He has been on antidiabetic medications (metformin and glimepiride), dual antiplatelet therapy (aspirin and clopidogrel), and atorvastatin. His hemoglobin A1C at the time of admission was 6.8%, compared to 7.2% 10 months earlier. Initially, he consulted multiple practitioners, received antibiotics, proton pump inhibitors, and antacid syrups, but experienced no improvement in his symptoms. His general physical examination was unremarkable. Routine investigations, such as hemogram, liver function test, kidney function test, and viral screening (hepatitis B virus/hepatitis C virus/ human immunodeficiency virus [HIV]) were normal. The upper GI endoscopy suggested multiple whitish plaques of variable sizes throughout the esophagus, along with a longitudinally extended deep ulcer with the base of the ulcer covered with thick yellowish white exudates, extending from 23 cm to 28 cm from the upper incisors, and another small round ulcer with surrounding friable mucosa noted at 20 cm (Fig. 5). Multiple biopsies were taken separately from both the edge and the base of the ulcer for HPE and Gene Xpert. The contrast-enhanced computed tomography chest was done, which suggested edematous wall thickening of the thoracic esophagus with mildly enhancing wall extending from the carina to the retrocardiac region, along with a few mediastinal lymph nodes, the largest measuring about 9 × 6 mm. The tissue gene Xpert from the ulcer came out to be negative. He started on oral fluconazole 400 mg on day 1, followed by 200 mg once daily for 14 days along with rabeprazole 20 mg sachet twice daily and syrup sucralfate-oxetacaine 10 mL every 6 h. HPE suggests prominent ulceration and florid granulation tissue with Candidal infection, with no evidence of dysplasia, granulomas, and inclusion bodies (Fig. 6a). Given the persistent symptoms and concern for a dual pathology, a repeat endoscopy performed after 2 weeks showed resolution of the candidiasis, and a repeat biopsy was obtained from the non-healing ulcer. In view of the nutritional compromise of the patient due to dysphagia and odynophagia, we placed a nasogastric tube under endoscopic guidance. Blood workup was sent for TB, vasculitis, connective tissue disorders, cytomegalovirus (CMV), and herpes simplex virus (HSV). HPE of repeat biopsy showing nuclear molding, margination, and multinucleation of infected cells suggestive of viral (HSV) esophagitis (Fig. 6b). Tissue polymerase chain reaction and immunohistochemistry were not performed

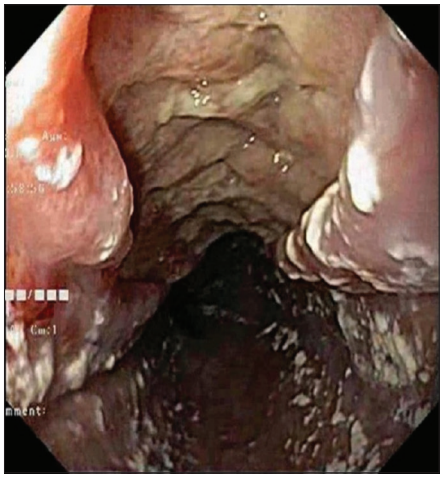

Figure 5: Endoscopic image showing longitudinally oriented deep ulcer and surrounding candidiasis (Case 3)

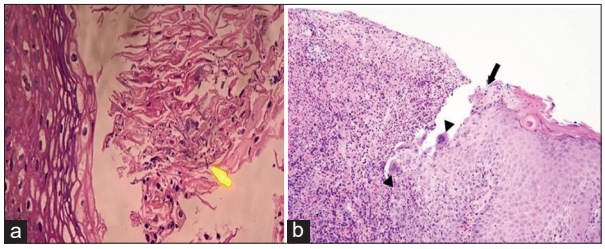

Figure 6: Low power hematoxylin and eosin-stained section showing (a) ulcerated fragment of squamous mucosa with prominent Candidal colonies (arrow), (b) ulcerated epidermis, acantholysis (arrow), nuclear margination, molding and multinucleation (arrowhead) (Case 3)

due to the unavailability of these diagnostic modalities at our center. HSV immunoglobulin G antibody test positive and other workup for TB, CMV, and vasculitis turned out to be negative. Considering the commonality of HSV as a cause of infectious esophagitis, along with supportive histopathological findings and positive HSV antibody results, a diagnosis of HSV esophagitis was made. The patient was started on intravenous acyclovir at a dose of 5 mg/kg every 8 h for 14 days. On day 4, the patient showed significant improvement in fever, chest pain, and odynophagia. The nasogastric tube was removed, and oral intake was resumed. After completing 7 days of intravenous acyclovir, the patient was transitioned to oral acyclovir and subsequently discharged. Follow-up was advised after 1 week; however, the patient was lost to follow-up.

DISCUSSION

An esophageal ulcer is defined as a discrete break in the esophageal mucosa with a clearly circumscribed margin. The etiology of esophageal ulcers included the following: GERD (65.9%), drug induced (22.7%), Candidal (3.4%), caustic injury (2.3%), and HSV, HIV, marginal ulcer, foreign body, and unknown etiology (1.1%) [2]. In this case series, esophageal ulcers in the first two cases were caused by pill-induced esophagitis, while the third case was attributed to HSV infection.

Candida is yeast that normally resides as part of the

normal flora on the surface epithelium of the alimentary and urogenital tracts in healthy individuals. However, in the presence of local or systemic immune compromise, overgrowth of *Candida* can occur, resulting in infection [7]. Risk factors for esophageal candidiasis include recent antibiotics, local or systemic steroids or immunosuppression, malignancy, proton pump inhibitor use, older age, chronic alcohol use, chronic kidney disease, diabetes, and motility disorders that lead to esophageal stasis [8,9]. Esophageal candidiasis is diagnosed based on characteristic endoscopic and histopathological findings. On endoscopy, it typically reveals white plaques or exudates that adhere firmly and cannot be removed with water irrigation. In some severe cases, mucosal ulcerations and stenosis may also be observed along with plaques. HPE of biopsy samples or brushings reveals budding yeast forms and pseudohyphae or hyphae infiltrating the epithelial layer [3,10].

PE typically occurs due to the dissolution of a caustic medication within the esophagus and the subsequent release of its harmful contents, often resulting from delayed transit of the drug to the stomach. Factors contributing to its development include the physical and chemical properties of the pill, such as capsule formulation, large size, and high acidity or alkalinity, as well as patient-related factors, such as body position during ingestion and the amount of water taken with the medication [11]. The most common location is the mid-esophagus, followed by the lower esophagus. Endoscopic findings of PE include kissing ulcers, circumferential ulcers, semi-circumferential ulcers, linear ulcers, erosions, etc. In a retrospective study from India, 6.5% patients with pill-induced esophageal ulcers were covered with *Candida* [5]. In our first two cases, PE was linked to the intake of doxycycline and NSAIDs, both known to cause localized mucosal injury due to their acidic properties and prolonged contact with the esophageal lining.

HSV esophagitis is the second most common cause of infectious esophagitis after candidiasis, typically occurs in immunocompromised individuals, either as a primary infection or due to reactivation of a latent virus. Its occurrence in immunocompetent individuals is uncommon [12]. The gross appearance of lesions can vary based on the timing of endoscopy. In the early stages, vesicles may be observed, which typically rupture and evolve into well-defined, circumscribed ulcers. These ulcers may appear punched-out or volcano-like, and in some cases, may merge to produce a cobblestone or shaggy ulcerative pattern. The disease usually affects the distal or mid-esophagus and, at times, the entire esophagus. Microscopically, biopsies from the edge of ulcers provide the best diagnostic yield [13]. Histological features of HSV esophagitis on Hematoxylin and Eosin staining typically include multinucleated giant cells, with nuclear molding, chromatin margination, and the presence of characteristic Cowdry type A inclusion bodies [14].

In the first two cases, mucosal injury due to doxycycline and NSAIDs created an environment conducive to fungal colonization. However, clinical and endoscopic resolution occurred with only acid suppression and mucosal protection, without antifungal therapy. This supports the hypothesis that *Candida* was an incidental finding rather than the true pathogen. In the third case, a diagnostic challenge, endoscopy revealed a deep longitudinal ulcer along with widespread candidiasis throughout the esophagus, and biopsy from the ulcer showed the presence of inflammation along with *Candida* hyphae. The lack of clinical improvement and persistence of the esophageal ulcer despite 2 weeks of fluconazole therapy, along with repeat biopsy findings and the patient's symptomatic improvement following antiviral treatment, further reinforces that *Candida* was an innocent bystander rather than the true causative agent of the ulcer. Reports of dual esophageal infections in adults suggest that HSV may initially damage the esophageal epithelium, compromise the mucosal barrier, and thereby facilitate secondary colonization or infection by *Candida* species [6,15]. A comparison of baseline characteristics among the three cases is shown in Table 1.

This case series highlights that *Candida* is not always the primary cause of esophageal ulcers. Rather, it may represent secondary colonization, an innocent bystander, resulting from the disruption of the local mucosal barrier due to various underlying factors.

Table 1: Comparison of baseline characteristics among the three cases

Variables	Case 1	Case 2	Case 3
Age (years)	55	35	50
Gender	M	M	M
Diabetes mellitus	No	No	Yes
Hypertension	No	No	No
Coronary artery disease	No	No	Yes
Smoking	No	No	No
Alcohol	No	No	No
Location of ulcer	Lower 1/3rd of the esophagus	Mid-esophagus	Mid-esophagus
Etiology	Pill-induced esophagitis (doxycycline)	Pill-induced esophagitis (doxycycline)	HSV esophagitis
Antifungals	Not received	Not received	Received

HSV: Herpes simplex virus

CONCLUSION

Candida detected in esophageal ulcers does not always imply a primary pathogenic role. In our case series, two immunocompetent patients with drug-induced esophagitis showed complete healing without antifungal therapy, while a third patient, initially treated for Candidal esophagitis, was ultimately diagnosed with HSV esophagitis after failing to respond to fluconazole. These findings emphasize that *Candida* may often be an innocent bystander in the setting of mucosal injury and that over-reliance on histological identification without clinical correlation can lead to misdiagnosis and inappropriate management. Determining the underlying cause is essential for effective and targeted management of esophageal ulcers, guided by a thorough patient history, endoscopic appearance, and treatment response.

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