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# The Diagnosis of Clinically Significant Esophageal *Candida* Infections: A Reappraisal of Clinicopathologic Findings

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**Abstract**

Aims: Distinguishing true esophageal *Candida* infections from oral contaminants is a common diagnostic issue. Historically, histologic features believed to indicate true infection included epithelial invasion by pseudohyphae and intraepithelial neutrophils. Whether or not these features correlate with endoscopic lesions, symptoms, and response to therapy has never been tested in a large cohort. Our goal was to determine if specific histologic features correlate with clinical and endoscopic findings when *Candida* is found in esophageal biopsies.

Methods: We reviewed 271 biopsies in which *Candida* was detected. Cases were evaluated for the presence of desquamated epithelial cells, location/type of fungal forms, neutrophils, and ulceration. Medical records were reviewed for clinical history, endoscopic lesions, and response to antifungal therapy. Statistical analysis was used to determine whether any histologic features significantly correlated with clinical variables.

Results: There were 120 males and 151 females with mean age of 42 years. Fifty-nine percent had symptoms referable to the esophagus, particularly dysphagia (36%). Most (73%) patients had abnormal endoscopic findings with plaques, ulcers, or macroscopic evidence of esophagitis. Seventy-one percent of patients with documented antifungal therapy showed symptomatic improvement. Overall, there was no statistically significant correlation between any histologic feature and presenting symptoms, endoscopic findings, or response to therapy. Importantly, the lack of pseudohyphae, demonstrable invasion of intact epithelium, or neutrophilic infiltrates did not exclude clinically significant infection.

Conclusions: We conclude that detection of *Candida* in esophageal biopsies is always potentially clinically significant. Treatment decisions should be made based on an integration of clinical, endoscopic, and histologic findings.

**Keywords: Candida, esophagitis, infection**

## Introduction

Infectious esophagitis is the third leading cause of esophagitis, following gastroesophageal reflux and eosinophilic esophagitis[1]. *Candida* infection, particularly *C. albicans*, is the most common cause of infectious esophagitis, with an overall prevalence of 0.8-7.3%[2–11]. *Candida* is generally considered to be an opportunistic infection, causing disease in patients with altered immunity due to immunodeficiency, diabetes mellitus, pregnancy, advanced age, and a number of other disorders associated with alterations in the normal components of the gastrointestinal flora. Affected patients typically present with odynophagia and/or dysphagia accompanied by endoscopically apparent white plaques and exudates; ulcers and strictures can occur in severe cases[2,3,11–13]. Although exudates are fairly characteristic of esophageal candidiasis, they are not uniformly present in infected patients, nor are they entirely specific for this diagnosis. In fact, the specificity of upper endoscopic findings for *Candida* esophagitis is only slightly more than 80%, with a positive predictive value of 89%[14]. For this reason, definite diagnosis relies on pathologic confirmation with cytologic brushings, mucosal biopsy, and, in some cases, fungal cultures.

Oropharyngeal colonization by *Candida* occurs in 31-60% of healthy individuals, with highest rates among those with co-morbidities, recent antibiotic use, and underlying malignancy[15–18]. Distinction between true esophageal infection and contaminants from colonized oropharyngeal mucosal is clinically important, and several histologic findings have been passed down through generations of trainees as indicators of clinically significant esophageal infection. These include the presence of pseudohyphae, epithelial invasion by fungi, and detection of intraepithelial neutrophils, particularly when clustered in the superficial epithelium[7,11,19]. However, the significance of these histologic features has never been rigorously evaluated in a systematic fashion, nor has there been any attempt to correlate their presence or absence with clinical symptoms, endoscopic lesions, or response to antifungal therapy in a large cohort. We performed this study to determine whether any specific histologic features correlate with clinical symptoms, underlying conditions, endoscopic findings, or treatment response when esophageal samples contain *Candida*.

## Materials & Methods

### *Case Selection*

We retrospectively identified esophageal biopsy samples containing *Candida* from three participating institutions located on the east coast of the United States, in the midwestern United States, and South Africa. The electronic medical records and endoscopy reports of 271 patients were reviewed for information regarding comorbidities, presenting symptoms, endoscopic findings, therapeutic interventions, and follow-up data, when available. Permission for the study was obtained from the Institutional Review Boards of each of the participating groups.

*Histopathologic Evaluation*

Routinely processed, hematoxylin and eosin (H&E)-stained tissue sections from all cases were evaluated by a pathologist at each institution. Each case was assessed for specific histological features that were defined and agreed upon by all participating reviewers. These included the presence of desquamated epithelial cells and/or keratin debris, reactive epithelial changes (i.e., basal cell hyperplasia, rete peg elongation, and intercellular edema) location of fungi in intact epithelium or desquamated debris, morphology of fungal forms (i.e. budding yeast and/or pseudohyphae), the presence of neutrophils in the intact epithelium, and ulceration. When available, Gomori methenamine-silver (GMS) nitrate and/or periodic acid–Schiff–diastase (PAS-D) stains were reviewed when available with the case, but the determination of the presence or absence of Candida was made on H&E. Histologic findings were compared with clinical and endoscopic findings as well as treatment and outcome data.

*Statistical analysis*

Fisher's exact test was used to evaluate the associations between clinical and histologic features. Associations with a p value $<0.05$ were considered to be statistically significant. All analyses were conducted using JMP, Version 14.1 (SAS Institute Inc., Cary, NC, 1989-2019).

**Results**

The study group consisted of 271 biopsy samples from unique patients, including 120 men and 151 women. Most patients were adults with a mean age of 42 years (range: 1-91). Clinical and endoscopic features are summarized in Table 1. Approximately half (48%) of the study patients had underlying

conditions predisposing them to *Candida* infection, most commonly autoimmune diseases (n=51, 19%) managed with immunosuppressive therapy, followed in frequency by concurrent cancer (14%) and diabetes mellitus (11%). Most (59%) patients presented with esophageal symptoms, particularly dysphagia (36%). Thirteen (5%) patients complained of odynophagia and 103 (38%) showed no symptoms directly referable to the esophagus. The majority (n=199, 73%) of patients had abnormal endoscopic examinations with plaques, ulcers, or macroscopic evidence of esophagitis (Figure 1). The frequency of endoscopic abnormalities did not differ between patients with and without symptoms. Therapeutic interventions with antifungal therapy were documented in 209 (77%) patients. Of these, 149 (71%) experienced complete resolution of symptoms or symptomatic improvement after treatment with antifungal agents. *Candida* was superimposed on a pre-existing or concurrent esophageal disease in a minority (~ 30%) of patients. The most common coexisting esophageal disease was a history of reflux (24% of all patients). 20 patients with both *Candida* and a history of reflux were treated with antifungals; of those, 45% responded to antifungal therapy, and only two patients had simultaneous changes made to their antireflux therapy dosages. Thus, for at least the vast majority of cases, symptom resolution, when documented, clinically appeared to be due to antifungal therapy.

The histologic features of the study cases are listed in Table 2. Desquamated epithelial cells (n=243, 90%) and pseudohyphae (n=262, 96%) were most commonly detected (Figure 2). Ulcers and/or erosions were identified in 41 (15%) cases. Invasive yeast were observed in intact squamous epithelium in 100 (37%) cases, but this feature did not significantly correlate with the presence of clinical symptoms or any endoscopic findings. The only histologic finding that was associated with the presence of clinical symptoms was reactive epithelial changes, including basal cell hyperplasia, rete peg elongation, and/or intercellular edema, findings similar to that seen in reflux-related injury (78%, p=0.01). Similarly, reactive epithelial changes was the only histologic parameter that showed statistically significant association with endoscopy findings or response to treatment. Moreover, there was no relationship between the histologic identification of epithelial invasion by fungi and a clinical response to antifungal agents (Figure 2). In fact, 64% of patients with a documented response to antifungal therapy did not have fungal invasion of the epithelium in their biopsy samples. Only nine

(4%) patients had biopsy samples that featured budding yeast without pseudohyphae. Six of these patients had esophageal symptoms accompanied by endoscopically apparent plaques (n=3), ulcers (n=1), and esophagitis (n=2), including five patients who experienced symptomatic relief with antifungal therapy. The relationships between histologic findings, presenting esophageal symptoms, endoscopic abnormalities, and documented response to antifungal treatment are summarized in Table 3.

**Discussion**

To our knowledge, this is the first study of its size that tests widely held notions regarding the clinical significance of various histologic findings encountered in esophageal samples harboring *Candida,* and reassesses the diagnostic criteria for esophageal candidiasis. We did not find any correlation between specific histologic features and presenting symptoms or comorbidities, endoscopic findings, or response to antifungal therapy. Importantly, the lack of pseudohyphae or demonstrable invasion of intact epithelium, long touted as morphologic indicators of "true" *Candida* infection, did not exclude the possibility of clinically significant esophageal infection. Six (4%) of our study patients experienced symptomatic relief with antifungal therapy even though their biopsy samples contained only budding yeast and/or lacked invasive fungi in the epithelium. We conclude that detection of fungal forms in esophageal biopsy material should always be considered as potentially clinically significant. In other words, pathologists should not disregard isolated budding yeast in detached debris as oral contamination, nor should they require the presence of neutrophilic inflammation to establish a diagnosis of fungal infection. In fact, only slightly over half of the biopsies (68%) included in this study contained a neutrophilic infiltrate, and 23% of biopsies with demonstrable invasion of mucosa did not have associated neutrophils. Interestingly, patients with neutrophils were more likely to be immunosuppressed, most commonly due to an autoimmune condition.

*Candida* esophagitis is an important cause of morbidity, particularly among immunocompromised patients. Although this disease once showed a predilection for HIV-infected individual and developed in up to 42% of these patients, improved retroviral therapy has resulted in decreased infection rates in this population[20]. Other risk factors for *Candida* esophagitis include

heavy alcohol consumption, hepatitis C viral infection, syphilis, and medications such as corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and proton pump inhibitors[6]. Recent use of antibiotic agents, motility disorders, uncontrolled diabetes mellitus, malnutrition, and any process that diminishes host immunity, alters pH, or modifies the microbial flora of the mucus membranes can also predispose to esophageal candidiasis[1,3,5,14–16,21].

The mainstay of therapy for *Candida* esophagitis is oral fluconazole, with resolution rates of greater than 90% in treated patients[10,21–26]. However, emerging data suggest that not all patients require therapeutic intervention[27,28]. Lee et al. evaluated 141 asymptomatic patients with *Candida* esophagitis and found that 81% showed resolution of esophageal inflammation on follow-up endoscopy, even though most were not treated with antifungal therapy[28]. Hoversten et al. reported similar findings. In their study of 218 patients with *Candida* in esophageal biopsy samples, 92% of untreated patients showed resolution of lesions at interval endoscopy. Of the 74 asymptomatic patients who did not receive a therapeutic intervention, most (91%) remained asymptomatic, and all patients (n=12) who underwent follow-up endoscopy showed resolution of esophageal inflammation[29]. Although these data suggest that asymptomatic *Candida* esophagitis is of little clinical significance in some patients, criteria for distinguishing patients who require therapy from those who do not remain unclear; asymptomatic patients can certainly have endoscopically apparent esophagitis with exudates and fungi in esophageal biopsy samples. Esophageal biopsies with *Candida* infection are usually described as containing budding yeast and/or pseudohyphae, variably present neutrophilic and/or lymphocytic infiltrates, superficial exudates of desquamated epithelial cells, and reactive squamous epithelial changes that may mimic other types of esophagitis[5,19,30]. Historically, many pathologists have required the presence of pseudohyphae and/or fungal invasion of intact epithelium to establish a diagnosis of clinically significant infection, but our data show that patients with clinically significant infections often lack these features. In addition, desquamated tissue fragments and detached yeast may be lost as a result of prior cytologic brushings or during tissue processing[11,31]. In these situations, other histologic changes, such as reactive epithelial changes or intraepithelial neutrophils, may be helpful diagnostic clues[2,30,32]. However, roughly one fourth of the patients in our study had esophageal biopsies that showed fungal invasion of the squamous epithelium unaccompanied by neutrophil-rich inflammation.

The results of this study indicate that the histologic features of esophageal *Candida* infection are variable and do not correlate well with either clinical or endoscopic findings. They also suggest that the historic question regarding the distinction of clinically significant infection from oral flora is likely not within the sole purview of pathologists. Our data show that detection of *Candida* is rarely a clinically insignificant finding, even if only budding yeast are identified in esophageal biopsy samples. For this reason, pathologists should determine whether yeast are present in esophageal biopsy samples, but they cannot confirm or exclude clinically significant *Candida* infection, particularly among immunocompromised patients. The ultimate decision to treat *Candida* infection with antifungal therapy should be made based on the integration of clinical, endoscopic, and histologic findings.

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Table 1: Clinical features of patients with Candida esophagitis.

| | Total patients (N=271) |
|---|---|
| Mean age | 42 years (range: 1-91) |
| Male:Female ratio | 120:151 |
| Comorbidities | |
| Cancer | 38 (14%) |
| Autoimmune disease | 51 (19%) |
| Immunosuppressive therapy | 43 (16%) |
| Transplant | 16 (6%) |
| HIV | 10 (4%) |
| HCV | 6 (2%) |
| Diabetes mellitus | 31 (11%) |
| Indication for endoscopy | |
| Abdominal pain | 37 (14%) |
| Dysphagia | 97 (36%) |
| Esophageal reflux | 47 (17%) |
| Anemia | 18 (7%) |
| Barrett's disease | 11 (4%) |
| Odynophagia | 13 (5%) |
| Bleeding | 12 (4%) |
| Follow up (other) | 17 (6%) |
| Nausea/vomiting | 17 (6%) |

Table 2: Histologic findings identified in all esophageal biopsies with Candida.

| Histologic findings | All biopsies (N=271) |
|---|---|
| Presence of budding yeast | 219 (81%) |
| Presence of pseudohyphae | 262 (96%) |
| Epithelial neutrophilic infiltrate | 184 (68%) |
| Yeast in intact squamous epithelium | 100 (37%) |
| Desquamated epithelial cells and keratin | 243 (90%) |
| Reactive epithelial changes | 195 (72%) |
| Ulceration | 41 (15%) |

Table 3: Histologic findings identified in esophageal biopsies of symptomatic patients, those with endoscopic abnormalities, and/or those who responded to antifungal therapy.

| Histologic findings | Symptomatic patients (N=157) | Endoscopic abnormalities present (N=199) | Response to antifungal treatment (N=149) |
|---|---|---|---|
| Presence of budding yeast | 126 (80%) | 159 (80%) | 117 (79%) |
| Epithelial neutrophilic infiltrate | 114 (73%) | 142 (71%) | 94 (63%) |
| Yeast in intact squamous epithelium | 60 (38%) | 76 (38%) | 53 (36%) |
| Presence of pseudohyphae | 151 (96%) | 192 (96%) | 133 (89%) |
| Desquamated epithelial cells and keratin | 143 (91%) | 184 (92%) | 125 (84%) |
| *Reactive epithelial changes | 122 (78%) | 152 (76%) | 126 (85%) |
| Ulceration | 25 (16%) | 25 (13%) | 22 (15%) |

* This was the only histologic finding found to show a statistically significant association with clinical symptoms (p=0.013), endoscopic abnormalities (p=0.035) or response to antifungal treatment (p=0.014).

**Figure Legends:**

**Figure 1:** Most patients with abnormal endoscopic findings had yellow-white exudates in a focal (A) or diffuse, circumferential distribution; the latter were frequently associated with ulcers (B).

**Figure 2:** Samples from four symptomatic patients with endoscopically identified esophageal plaques and a response to antifungal therapy feature variably severe abnormalities. Some cases featured squamous hyperplasia with intraepithelial neutrophils, desquamation, and budding yeast with pseudohyphae in both desquamation and intact epithelium (A). Others displayed superficially invasive yeast unaccompanied by inflammation (B). Some patients with yeast confined to desquamated keratin debris did respond to antifungal therapy (C). Another patient with endoscopically apparent plaques had mostly unremarkable squamous mucosa (D); a few budding yeast without pseudohyphae were limited to desquamated epithelium (see inset).

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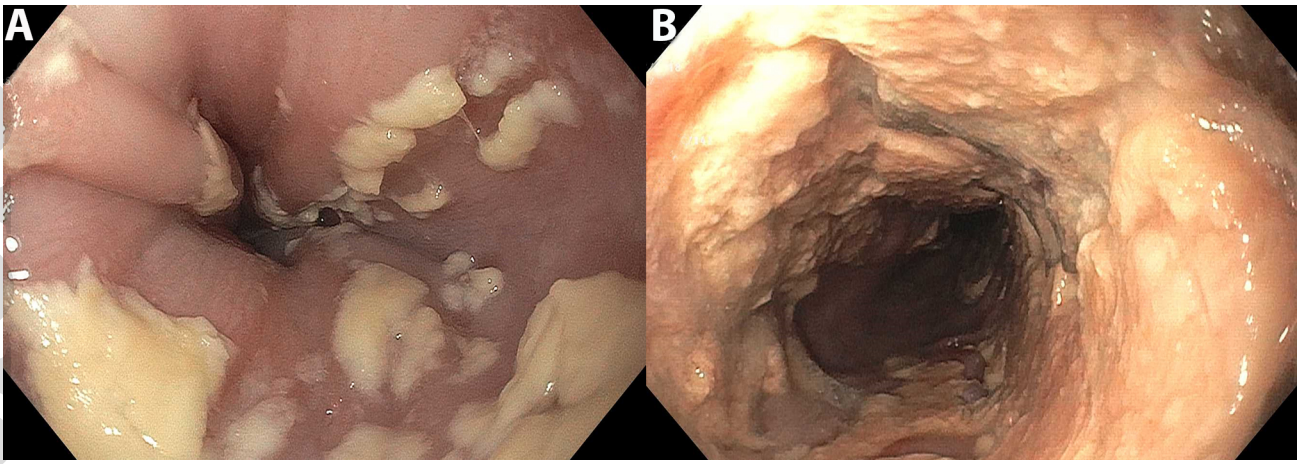


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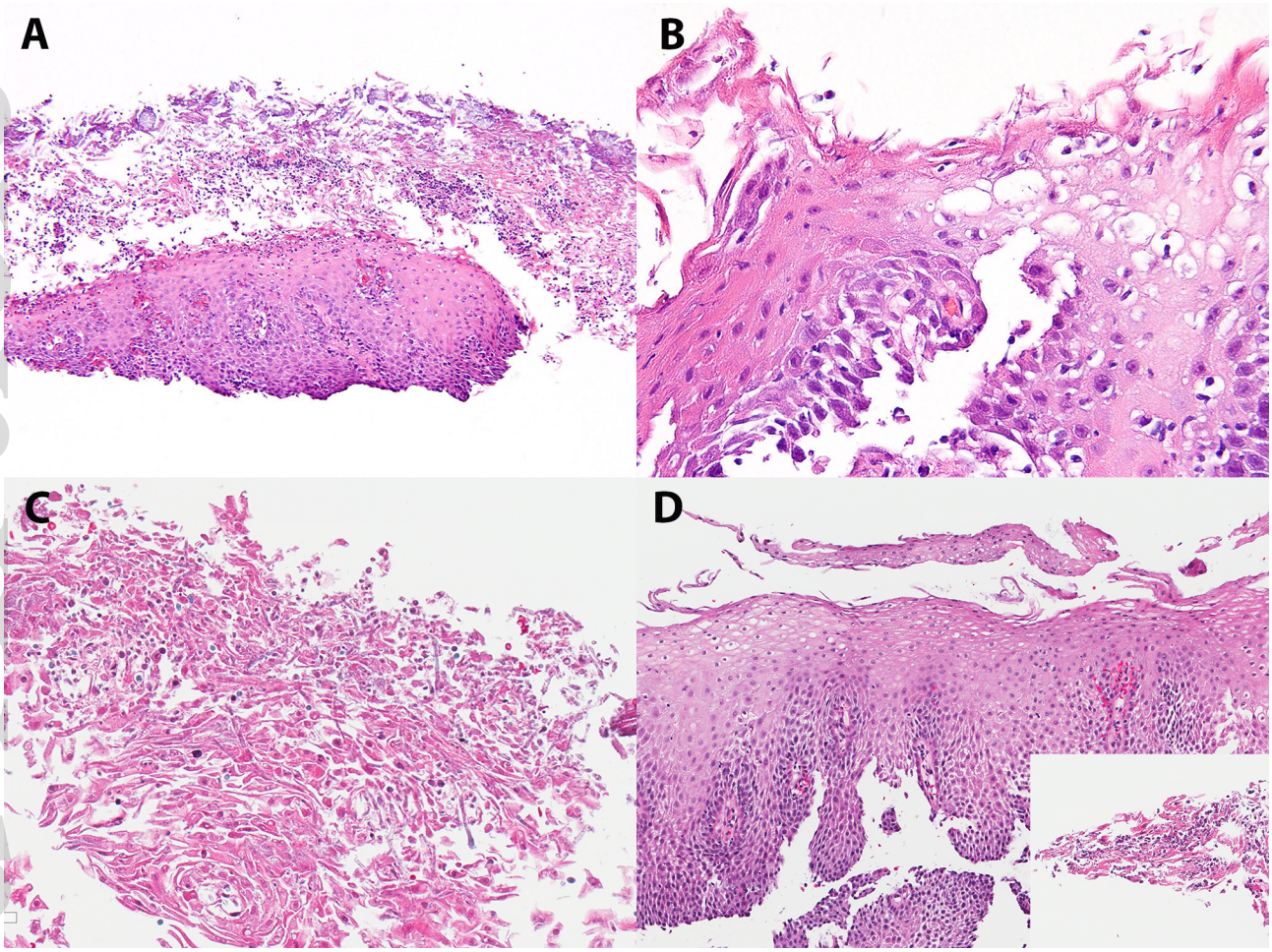


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