A Retrospective Study of Esophageal Candidiasis in Jordan, a non-HIV Endemic Area

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Abstract

Background: *Candida albicans*, which inhabits the esophagus in approximately 20% of healthy individuals, is the most common causative organism of fungal esophagitis. Although esophageal candidiasis is considered an acquired immunodeficiency syndrome (AIDS) defining illness in human immunodeficiency virus (HIV) infected patients, it is increasingly reported in healthy people. We aimed to investigate the prevalence and risk factors of esophageal candidiasis among Jordanians and increase awareness about its pathology in HIV uninfected individuals.

Methods: This a retrospective study of all cases of esophageal candidiasis admitted to King Abdullah University Hospital, between June 2005 and December 2016. All patients diagnosed with esophageal candidiasis based on cytological evaluation of esophageal biopsies, were included. Patients were considered immunocompromised, if they had impaired cell mediated immunity, diabetes, active malignancy, connective tissue disease, or if they were treated with cytotoxic medicines or corticosteroids within 2 weeks of diagnosis of esophageal candidiasis.

Results: Between June 2005 and December 2016, 20826 patients underwent upper endoscopy at King Abdullah University Hospital, of which 16 (0.0007%) were diagnosed with esophageal candidiasis. All patients were adults, with an age range of 20-70 years. Three patients were females (19%). In all patients, Candida albicans was the causative organism. Six (38%) of the patients were considered immunocompetent.

Conclusion: The prevalence of esophageal candidiasis in the studied population was markedly lower than in other countries. Future studies to elucidate mechanisms of esophageal candidiasis in healthy individuals and to investigate protective factors in low prevalence populations are needed.

Keywords: Esophageal candidiasis, Esophagoscopy, HIV, Jordan.

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Introduction

Candida species are considered part of the normal flora of the gastrointestinal tract; they inhabit the esophagus in approximately 20% of healthy individuals[1, 2]. *Candida albicans* is the most common causative organism of fungal esophagitis[3].

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Esophageal candidiasis (EC), an acquired immunodeficiency syndrome (AIDS)-defining illness, is common among human immunodeficiency virus (HIV) infected patients[4]. This is because approximately 10% of HIV infected patients will develop EC during their lifetime, and another 90% of all HIV infected patients will develop oropharyngeal candidiasis[5]. Among HIV uninfected individuals, other predisposing factors, have been elucidated in many studies[6,7]. These include the use of antacids (mainly proton pump inhibitors and histamine-2-blocker)[8], radiation, chemotherapy[6,7], systemic and inhaled corticosteroids[3], broad-spectrum antibiotics[9], alcoholism[10], diabetes mellitus[11], malnutrition, abnormal esophageal motility (achalasia or scleroderma)[12,13], and advanced age[14]. With the frequent use of endoscopy that helps to identify white candida plaques on mucosa and to take biopsies, an increasing number of immunocompetent patients with esophageal candidiasis are being detected.

The diagnosis of esophageal candidiasis depends on endoscopy which usually shows white candida plaques on erythematous mucosa, and biopsy to confirm the presence of yeast and pseudohyphae invading mucosal cells[15,16]. Increasing numbers of immunocompetent patients with EC are being detected using these diagnostic methods.

Data on the prevalence of EC in the Middle East are scarce. In this study, we investigated the prevalence and etiology of EC in Jordanians. We also compared our data to those from other countries[11, 17, 18]. The results will help increase awareness about EC and its possible risk factors in HIV uninfected individuals who are healthy or have other comorbidities.

Materials and Methods

The study is a retrospective study of all patients diagnosed with EC admitted to King Abdullah University Hospital, in Irbid, Jordan between June 2005 and December 2016. All patients diagnosed with EC using esophagoscopy were included while those with no endoscopic findings were excluded. Additionally, patients were screened for other forms of esophagitis, including viral (cytomegalovirus and herpes simplex virus), medication-induced, and eosinophilic esophagitis, using patient history, histopathology, and tissue cultures. If any of these conditions were diagnosed, then the case was excluded. The study protocol was approved by The Jordan University of Science and Technology Research Committee and the committee on Human Experimentation at King Abdullah University Hospital. Patients' confidentiality was protected and the study was carried out maintaining the ethical standards of the University.

Esophageal candidiasis was diagnosed via the identification of *Candida* species in esophageal brush cytologies or biopsies obtained by esophagoscopy, during which white plaques covering esophageal mucosa were noticed. Endoscopic procedures were performed by three experienced endoscopists at the same center, using an Olympus (EVIS EXTRA II CV-180) scope. Cytology brush samples were submitted to the hospital pathology laboratory.

A comprehensive review of patient medical records was conducted in order to ascertain clinical and demographic characteristics of those diagnosed with EC. After asserting the diagnosis, the cases were analyzed if they have HIV as documented by enzyme-linked

immunosorbent assay (ELIZA). Also, cases were analyzed if patients had diabetes, renal failure, liver problems, and connective tissue diseases. The indicators tested to determine the presence of these comorbidities were fasting blood sugar, creatinine and albumin levels, transaminases, bilirubin, total protein, erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, anti-nuclear antibody, and the complement components C3, C4, and CH50.

Patients were considered immunocompromised, if they have impaired cell mediated immunity, or were known to have diabetes, active malignancy, connective tissue disease, or were treated with cytotoxic medicines or corticosteroids within 2 weeks of EC diagnosis.

In all cases, treatment consisted of an orally administered antifungal agent (Fluconazole 100-200 mg/day) continued for 14-21 days after clinical improvement. This is in accordance with the guidelines issued by the Infectious Disease Society of America, published in 2004[19].

Results

Between June 2005 and December 2016, 20826 patients underwent upper endoscopy at King Abdullah University Hospital. Only 16 (0.0007%) of these cases were diagnosed with EC. None of these patients had other forms of esophagitis and thus all of them were included in the study.

Table 1 summarizes patients' demographic and clinical data.

Table 1. Clinical and demographic characteristics for patients diagnosed with esophageal candidiasis in King Abdullah University Hospital, in Jordan between June 2005 and December 2016 (n=16)

Age	**N=16 (%)**
Median (years)	54
Interquartile Range	19-73
Gender	
Male	13 (81%)
Female	3 (19%)
Clinical symptoms	
Dysphagia	1 (6%)
Odynophagia	1 (6%)
Epigastric pain	7 (43%)
Chest discomfort	9 (56%)
Endoscopic Kodsi's grade	
Grade 1	5 (31%)
Grade 2	3 (18%)
Grade 3	4 (25%)
Grade 4	2 (13%)
Unknown	2 (13%)

Table 2. Risk factors for esophageal candidiasis among 16 patients diagnosed in King Abdullah University Hospital in Jordan, between June 2005 and December 2016

Risk factors	No. of patients (% of total)
Advanced age ≥ 60	6 (38%)
Diabetes	6 (38%)
Cancers	3 (19%)
Smoking	11 (69%)
Steroid therapy (systemic/inhaled)	3 (19%)
Antibiotic use	1 (6%)
PPIs/Anti acids	14 (88%)
HIV infection	0 (0%)
Esophageal motility disorders± Sphincter	1 (6%)
Foregut surgery	1 (6%)
Connective tissue diseases	2 (13%)

All patients were adults, age range (20-70 years), with a median of 54 years. Three patients were females (19%), 13 were males (81%). In all patients, *Candida albicans* was the causative organism; no other species were detected upon cytology.

Many patients presented with more than one indication for endoscopy. The main indication was chest discomfort (56%), while other presenting symptoms included epigastric pain (44%), dysphagia defined as difficulty in swallowing (6%), and odynophagia defined as pain during swallowing (6%). Eight (50%) patients had mild EC while 6 (38%) had severe EC; disease severity was unknown for 2 (13%) patients (Table 1).

Ten (62%) of the EC patients were immunocompromised and most patients reported at least one possible risk factor for EC (Table 2). The main risk factors identified were the consumption of antacids (n=14, 88%) followed by smoking (n=11, 69%). All of the patients in this study were HIV uninfected. However, 62% met the definition of immunodeficiency due to the following conditions: connective tissue diseases (n=2, 13%), active malignancy (n=3, 19%), diabetes (n=6, 38%), use of cytotoxic drugs (n=2, 13%), and corticosteroid therapy (n=3, 19%).

EC was graded according to Kodsi's classification[20]. Grade 1 (5 patients, 31%) was defined as the presence of a few raised white plaques up to 2 mm in size without edema or ulceration, Three patients were considered grade 2 where plaques were greater than 2 mm in size. In grade 3 (4 patients), plaques were confluent, linear, nodular and elevated, and in grade 4 (2 patients), plaques were associated with increased friability of the mucous membranes and occasional narrowing of the lumen. Grades 1 and 2 EC are classified as mild disease, while grades 3 and 4 are considered severe disease. There was no apparent

association between type and duration of exposure to the predisposing factor and the grade of esophagitis in our patients.

Discussion

Esophageal candidiasis is the most common esophageal infection[8]. To the best of our knowledge, this is the first case series from the Middle East, which is not an HIV endemic area[21].

The proper diagnosis of EC is essential, particularly in severe cases, as these may be associated with esophageal bleeding, or may be complicated by stricture or fistula formation[10,22]. In addition, possible associated symptoms of EC, such as reduced appetite, chest pain, and/or dysphagia, can significantly affect quality of life, thus proper management is imperative.

Various studies have targeted non-HIV endemic areas in order to elicit EC prevalence in HIV uninfected patients. A review of approximately 9000 upper endoscopies in Korea revealed EC prevalence of 0.3%[11]. Another study from Virginia, USA, found that 0.8% of HIV uninfected patients who had an upper endoscopy were diagnosed with EC[23]. In a large cohort of patients from Japan, Takahashi *et al.* reported an EC prevalence of 1.6% HIV uninfected patients compared to 9.8% in HIV infected patients[10].

Candida overgrowth in the esophagus may complicate impaired cell mediated immunity due to AIDS, chronic mucocutaneous candidiasis, malignancies, or cytotoxic drugs and/or steroid therapy[18, 24, 25]. Other non-immunologic risk factors include acid suppressing therapy, antibiotics, smoking, and stasis (secondary to abnormal esophageal motility). The frequencies of the risk factors identified in our study population are comparable to those found in other studies[11, 17, 18]; However, the prevalence of EC in our study was markedly lower. Other factors such as dietary habits and herbal medicine usage, which are popular in this region, were not investigated. These factors might have contributed to the variability between studies. Since biopsies were submitted every time esophageal pathology was suspected, it is unlikely that EC was under-diagnosed in our study population.

Corticosteroids, which are common predisposing agents for EC, are known to primarily affect human monocyte defense against *Candida albicans*. Heidenreich *et al.* suggested that glucocorticoids affect the ability of monocytes to indirectly control the growth of *Candida* via suppression of TNF-alpha formation. TNF-alpha is required as an autocrine cofactor for full monocyte activation[25].

Patients with diabetes are more susceptible to esophageal changes including altered motility, secondary to increased mucosal and submucosal thickness, in addition to autonomic neuropathy, thus increasing the risk of EC neuropathy[26].

Antibiotics may predispose individuals to fungal infection by allowing overgrowth and colonization of the *Candida* species[9]. Similarly, excessive growth of fungus may result in functional or mechanical obstruction of the esophagus, due to stasis and decreased clearance[13].

Self-prescription of antacids as a first-line treatment for mild esophageal symptoms is increasingly observed worldwide.

Approximately, 88% of our patients were on chronic antacid therapy for at least one month before EC diagnosis. These data suggest that antacids might play a significant role in EC development among immunocompetent patients. The acid barrier of the stomach inhibits growth of most ingested or upwardly mobile microorganisms; therefore, the incidence of gastro-enteric infections is reduced. Depletion of this barrier by acid suppressing agents possibly explains the association between EC and the use of these agents[8].

Although proton pump inhibitors (PPI) decrease the acidity of esophageal refluxuate, they do not decrease the relative reflux frequency of non-acid fluids likely to include viable *Candida* organisms[27]. A study from Japan revealed that the active derivatives of a PPI known as lansoprazole, suppressed the anti-Candida activity of macrophages for 14 hours by binding to SH-molecules to inhibit the proton pump[28]. Given the aforementioned observations on the contribution of acid suppressing agents to the development of EC, it is likely that the incidence and severity of this pathology will potentially be reduced by discontinuation of PPIs and H2-blockers.

Tobacco smoking was considered a predisposing factor to oral candidiasis[29]. In addition, it has been demonstrated that the isolation frequency of *C. albicans* was higher in smokers than in non-smokers[29]. In a mouse model, Ortega *et al.* proved that a smoke filled atmosphere leads to decreased phagocytic function of alveolar macrophages, thereby facilitating candida colonization and host infection[30]. With the high prevalence of smoking among EC patients (66%), the potential causative association between smoking and EC needs further investigation.

Our study has some limitations. Firstly, it is a retrospective, nonrandomized study. Secondly, the sample size of patients with EC was too small to evaluate statistically significant differences in the risk factors. Despite these limitations, to the best of our knowledge, this is the first study addressing the prevalence of EC in Jordan, a non-HIV endemic area. Findings may reflect rarity of this pathology in this region and should encourage investigation of the likely factors contributing to this low prevalence.

Conclusion:

Prevalence of EC in our study population seems to be markedly lower than in other countries. Future studies to elucidate mechanisms of EC in immunocompetent individuals and investigate protective factors in low prevalence population are recommended.

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دراسة مرجعية لبيضيات المريء في الأردن؛ منطقة عدم شيوع لفيروس نقص المناعة المكتسبة

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الملخص

الخلفية: المبيضات البيض، التي تسكن المريء في حوالي 20٪ من الأفراد الأصحاء، هي الكائن المسبب الأكثر شيوعا التهاب المريء الفطري. على الرغم من أن التهاب المبيضات المريئي يعد من معرفات متلازمة نقص المناعة المكتسبة (الإيدز) في المرضى المصابين بفيروس نقص المناعة البشرية، يتم الإبلاغ عن هذا المرض على نحو متزايد في الأشخاص الأصحاء. نحن نهدف إلى التحقيق في عوامل انتشار وعوامل خطر داء المبيضات المريئي بين الأردنيين وزيادة الوعي بهذا المرض لدى غير المصابين بفيروس نقص المناعة البشرية.

الأسلوب والأدوات: أجريت هذه الدراسة بأثر رجعي لجميع حالات مبيضات المريء التي أدخلت إلى مستشفى الملك عبد الله المؤسس الجامعي، بين يونيو 2005 وديسمبر 2016. شملت جميع المرضى الذين تم تشخيصهم بمبيضات المريء على أساس التقييم الخلوي لخزعات المريء. عُدَّ المرضى مصابين بنقص مناعة، إذا كان لديهم ضعف المناعة بوساطة الخلايا، والسكري، والخباثة النشطة، وأمراض النسيج الضام، أو إذا كان المريض تعامل مع الأدوية السامة للخلايا أو الستيروئيدات القشرية في غضون أسبوعين من تشخيص مبيضات المريء.

النتائج: بين يونيو/ حزيران 2005 وديسمبر/ كانون الأول 2016، خضع 20826 مريضا للتنظير العلوي في مستشفى الملك عبد الله المؤسس الجامعي، تم تشخيص 16 منهم (0.0007) ٪ بمرض داء المبيضات المريئي. وكان جميع المرضى من البالغين، من الفئة العمرية 20-70 عاما . وكان ثلاثة مرضى من الإناث (19٪). في جميع المرضى، كانت المبيضات البيض هي الكائن المسبب .وعُدَّت ستة (38٪) من المرضى سليمين مناعيا.

الخلاصة: كان انتشار التهاب المبيضات المريئي في فئة السكان المدروسة أقل بكثير مما كان عليه في بلدان أخرى .وهناك حاجة إلى دراسات مستقبلية لتوضيح آليات الاصابة بالمبيضات المريئية في الأفراد الأصحاء والتحقيق في العوامل الوقائية في المناطق منخفضة الانتشار.

الكلمات الدالة: مبيضات المريء، تنظير المريء، ايدز، الأردن.