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• BRIEF REPORTS •

Candida esophagitis: Risk factors in non-HIV population in Pakistan

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Abstract

AIM: *Candida* esophagitis is a frequent infection in immunocompromised patients. This study was designed to determine its characteristics in non- human immune deficiency virus (HIV) infected patients attending a teaching hospital.

METHODS: Clinical records of all patients coded by international classification of diseases 9th revision with clinical modifications' (ICD-9-CM), with *candida* esophagitis diagnosed by esophagogastroduodenoscopy (EGD) and histopathology over a period of 5 years were studied.

RESULTS: Fifty-one patients (27 males, 24 females, range 21-77 years old and mean age 52.9 years) fulfilled the criteria (0.34 % of the EGD). The common predisposing factors were carcinoma (OR 3.87, CI 1.00-14.99) and diabetes mellitus (OR 4.39, CI 1.34-14.42). The frequent clinical symptoms were retrosternal discomfort, dysphagia and epigastric abdominal pain with endoscopic appearance of scattered mucosal plaques. Another endoscopic lesion was associated with *candida* esophagitis in 15 % patients.

CONCLUSION: Carcinomas, diabetes mellitus, corticosteroid and antibiotic therapy are major risk factors for *candida* esophagitis in Pakistan. It is an easily managed complication that responds to treatment with nystatin.

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INTRODUCTION

Infective esophagitis is a rare disease, affecting mostly immunocompromised patients. *Candida* esophagitis is one of the most common opportunistic infections in patients with impaired immunity and the most common cause of esophageal disease in patients with acquired immune deficiency syndrome (AIDS)[1]. It also occurs in debilitated patients who have received broad-spectrum antibiotics, steroids and immunosuppressants. With the advent of transplantation and AIDS, esophageal infection is now a common medical problem[2]. The common infections involving immunocompromised non-human immunodeficiency virus (HIV) infected patients include *candida* and viral diseases such as *cytomegalovirus* (*CMV*) and *herpes simplex virus* (*HSV*)[2]. Immunocompromised patients who develop esophageal symptoms need to undergo endoscopy to rule out *candida* esophagitis. It is well recognized that *candida* esophagitis may coexist with other esophageal disorders in these patients[3]. The occurrence of multiple simultaneous processes makes definitive endoscopic examination important[4]. Several studies have been carried out in the west for *candida* esophagitis but it has not been studied before in Pakistan. Incidence of AIDS and HIV prevalence are still very low in Pakistan[5]. The purpose of our study was to assess the risk factors associated with *candida* esophagitis in our patients who came from an area with a low incidence of AIDS.

MATERIALS AND METHODS

Patients

The study was conducted at Agha Khan University Hospital (AKUH) in Karachi, a private Academic Medical Center that offers state of the art medical facilities and is used as a referral center for patients from all over the country for expert opinion and treatment. Karachi is a southern port and the largest metropolitan city in Pakistan with a population of over 11 million. In August 2002 we carried out a retrospective analysis of medical records of all the patients who attended endoscopy unit of gastrointestinal section at the AKUH from January 1997-December 2001 and were diagnosed as *candida* esophagitis. These patients had undergone endoscopy for symptoms arising from the upper gastrointestinal tract over this period and were diagnosed on the basis of endoscopy and histopathology as *candida* esophagitis. Clinical symptoms at the time of presentation, diagnosis, drug treatment dosage and duration preceding the symptoms such as nystatin suspension or fluconazole, past history of oral candidiasis, candida esophagitis, neutrophil and lymphocyte counts from complete blood picture, random blood glucose, hepatitis B, C and HIV serology were noted. A lymphocyte count was described as low when it was less than 1.5×10^9 per liter[6]. All endoscopic examinations were performed by staff-members of our hospital's gastroenterology section, using an Olympus videoscope GIF x Q 140. *Candida* esophagitis was diagnosed when characteristic *candidal* plaques were endoscopically identified and pathological confirmation of yeast forms typical for *candida* was found in association with an active esophagitis. Case patients were labeled as group A and the control group as group B which consisted of those patients without a diagnosis of *candida* esophagitis and in whom an endoscopic examination was performed immediately before and after every case patient was examined endoscopically (2 controls per case). Therefore, *candida* esophagitis cases and controls were evaluated by the same medical team using the same diagnostic criteria.

Endoscopy

To describe the severity of *candida* esophagitis both in AIDS[7,8] and in non-AIDS populations, a grading scale was described by Kodsi *et al*[9] or a modification thereof has been

used[10]. *Candida* esophagitis was graded as the following: Grade 1 as scattered mucosal plaques involving less than 50 % of the esophageal mucosa, grade 2 as mucosal plaques involving more than 50 % esophageal mucosa, grade 3 as confluent plaque material circumferentially coating at least 50 % of the esophageal mucosa but without luminal impingement, grade 4 as circumferential plaque mat coating at least 50 % of the esophageal mucosa with luminal impingement despite air insufflations. In most cases, an ulcer could be readily distinguished endoscopically by the marked hyperemia and granularity of the ulcer base from the surrounding *candida* esophagitis.

Histopathology

At the time of endoscopy, routine biopsies were performed on all endoscopic abnormalities. At least 2 biopsies were performed on each esophageal lesion with standard biopsy forceps. All tissue specimens were submitted for routine histopathology, and stained with hematoxylin-eosin (H-E) and periodic acid-Schiff stains (PAS). In the presence of ulcer tissue, immuno-histochemical staining for *CMV* and *HSV* was performed using previously described technique to confirm infection[3]. An ulcer was considered secondary to *candida* esophagitis alone when it was found endoscopically and histopathologically. Fungal organisms compatible with *candida* were seen in the superficial epithelium, there was an absence of viral cytopathic effect histopathologically, no clinical or endoscopic evidence of gastroesophageal reflex disease or drug-induced esophagitis existed.

Statistical analysis

Results were expressed as mean ± standard deviation, median range for all continuous variables (e.g., age) and number (percentage) for categorical data (e.g., gender, diabetes mellitus, steroids, etc) were provided. Univariate analysis was performed using the independent sample *t*-test, Pearson Chi-square test and Fisher exact test when ever appropriate. A *P* value <0.05 was considered as statistically significant. All *P* values were two sided. Statistical interpretation of data was performed using the computerized software programme SPSS version 10.0.

RESULTS

Patients

During the study period, 15 000 upper endoscopies were performed in our endoscopy unit. Fifty-one patients were diagnosed with *candida* esophagitis on the basis of endoscopic and histopathologic criteria. The age, sex and percentage of inpatients are given in Table 1.

Risk factors

The common risk factors for candida esophagitis were carcinoma (OR 8.05, 95 % CI 1.91-47.1 and *P*=0.001), uncontrolled diabetes mellitus (OR 7.34, 95 % CI 2.26-27.5 and *P*=0.001), corticosteroid therapy (OR 6.67, 95 % CI 2.20-22.3 and *P*=0.001) and antibiotics (OR 4.56, 95 % CI 1.14-21.5 and *P*=0.02) (Table 2).

Clinical feature

The clinical details are given in Table 1. The clinical symptoms in group A were retrosternal discomfort in 39.2 % (20/51) patients, of these 6/20 were associated with dysphagia and 3/20 with epigastric pain. Dysphagia was present in 25.4 % (13/51) and epigastric symptoms in 35.2 % (18/51) with only 9/18 describing it as an epigastric pain (Table 1). In control group B, retrosternal discomfort was described in 30.3 % (31/102), dysphagia in 19.6 % (20/102) and epigastric symptoms in 50 % (51/102). These patients responded well to treatment with nystatin or fluconazole, 84.3 % (43/51) and 15.7 % (8/51), respectively (Table 1).

Table 1 Details of patients presenting with *candida* esophagitis and controls

	Cases *n*=51	Control *n*=102
Sex		
Male	27 (53)	58 (57)
Female	24 (47)	44 (43)
Age in years (yrs)		
Range:	21-77	19-74
Mean ±SD	52.9±14.6	50.08±12.64
No: % of In-patients	34 (64)	58 (54)
Risk factors for *candida* esophagitis		
Steroid therapy	15 (29.4 %)	6 (5.8 %)
Diabetes mellitus type 1 and 2	14 (27.4 %)	5 (4.9 %)
Carcinoma (e.g. breast, gastric, esophagus)	10 (19.6 %)	3 (2.9 %)
Broad spectrum antibiotics	8 (15.6 %)	4 (3.9 %)
Chronic liver disease	2 (3.9 %)	6 (5.8 %)
Tuberculosis	2 (3.9 %)	1 (0.9 %)
Ischemic heart disease	-	26 (25.4 %)
Peptic ulcer disease	-	26 (25.4 %)
Hypertension	-	20 (19.6 %)
Chronic anemia	-	2 (1.9 %)
Arthritis	-	1 (0.9 %)
Primary Infertility	-	1 (0.9 %)
Osteoporosis	-	1 (0.9 %)
Clinical symptoms		
Retrosternal discomfort	20 (39.3 %)	31 (30.3 %)
Dysphagia	13 (25.4 %)	20 (19.7 %)
Epigastric symptoms	18 (35.3 %)	51 (50 %)
Endoscopic grading		
Grade 1	9	
Grade 2	19	
Grade 3	10	
Grade 4	13	
Treatment		
Nystatin	84.3 % (43/51)	
Fluconazole	15.7 % (8/51)	

Results were expressed as number and percentage, mean ± standard deviation (SD).

Polymorphonuclear leucocyte and lymphocyte counts

All of our patients had polymorphonuclear leucocyte count within the normal range, while 33.3 % (17/51) had lymphocyte count below the normal range. These patients were mostly those who were on steroid or antibiotics therapy (Table 3).

Endoscopy finding

The endoscopic appearance of plaques varied in color from yellow to white. With increasing severity, scattered mucosal plaques coalesced circumferentially coating the mucosal surface and impinged into the esophageal lumen. In group A, 9 patients had localized disease, 5 patients had disease more prominent in the distal esophagus than in proximal esophagus, while it involved middle esophagus and middle to distal esophagus equally in 4 patients (Table 1). Esophageal ulceration was noted endoscopically and histopathologically in 3.9 % (2/51). In these patients, ulcer was believed to be secondary to *candida* esophagitis alone, as other etiologies of esophageal ulceration were excluded by testing for *CMV*, *HSV* and *HIV* by serology and immuno-histochemistry. In 15.6 % (8/51) of group ‘ A’ patients, associated endoscopic findings included 7.8 % (4/51) with antral gastritis, 1.9 % (1/51) with gastric ulcer, 5.8 % (3/51) with duodenitis. In control group B

esophageal disease was found in 35.3 % (36/102) cases, gastric disease in 38.3 % (39/102) cases, and duodenal pathology was seen in 26.4 % (27/102) cases.

Correlation of clinical symptoms and endoscopic feature

There was no correlation between clinical symptoms and endoscopic findings.

Hepatitis B, C and HIV serology

HIV serology was negative for hepatitis B, and 9.8 % (5/51) were positive for hepatitis C virus.

Histopathology

Histopathology revealed varying degrees of hyperplastic squamous mucosa with moderate-severe degree of acute-chronic inflammation in the surface epithelium. Mucosal surface was covered with desquamated epithelium and inflammatory necrotic slough. Superficial colonies of *candida* organism showed non-branching hyphae. In cases of ulcerative esophagitis, intact and focally ulcerated mucosa revealed moderate-severe inflammation, basal cell hyperplasia with non-septate fungal hyphae.

Table 2 Results of univariate analysis of potential risk factors for acquisition of *candida* esophagitis

Variable	No. of cases (%)	No. of control (%)	Odd ratio (95% CI)	*P* value
Carcinoma	10 (19.6 %)	3 (2.9 %)	8.05 (1.91-47.1)	0.001
Diabetes mellitus	14 (27.4 %)	5 (4.9 %)	7.34 (2.26-27.5)	0.001
Prior use of steroid	15 (29.4 %)	6 (5.8 %)	6.67 (2.20-22.3)	0.001
Prior use of antibiotics	8 (15.6 %)	4 (3.9%)	4.55 (1.14-21.5)	0.02

Table 3 Distribution of low lymphocyte counts in patients presenting with *candida* esophagitis

Association	Cases (*n*=17)
Steroids	6
Antibiotics	6
Malignancy	3
Diabetes mellitus	1
Chronic liver disease	1

DISCUSSION

Our study is the first attempt to evaluate the risk factors and endoscopic manifestations of *candida* esophagitis in Pakistan, an area where AIDS is not endemic. All of our patients diagnosed with *candida* esophagitis did not have oral thrush. This was similar to a study by Bonacini *et al* in which 110 HIV positive patients with esophageal symptoms, 38 % of those without oral thrush had *candida* esophagitis[11]. In this study, the patients had oral, intravenous and nebulizer steroid treatment in varying durations and doses of therapy. Steroid levels were not measured on admission. However, steroid therapy was associated with lymphopenia and 33.3 % of our patients presented with a low lymphocyte count[12]. Diabetic patients complicated with *candida* esophagitis had uncontrolled diabetes at the time of presentation, irrespective of its type. Malignancies beside other mechanisms were also associated with esophageal stasis due to mechanical obstruction that predisposes to *candida* esophagitis[13]. However, esophageal obstruction was not a feature in our cases of *candida* esophagitis associated with malignancies. A high frequency of bacterial or mycotic infections has been reported in HCV-associated membranoproliferative glomerulonephritis and diabetes mellitus due to acquired defects of polymorphonuclear leukocyte (PMN) functions[14,15]. In HIV seropositive cases, coexistent *candida* esophagitis and tuberculosis have been frequently described [16], but in non-HIV immunosuppressed patients, there were few reports of active pulmonary or intestinal tuberculosis associated with *candida* esophagitis[17].

Epigastric pain has been known to be associated with *candida* infection[18]. In our study, no correlation was found between the symptoms and the endoscopy grade score similar to another study[19]. At endoscopy, the presence of classic whitish exudates or plaques should predict candidiasis in at least 90 % of cases, although viral infection occasionally might cause a similar appearance[11]. We found that *candida* esophagitis resulted in typical endoscopic appearances and both characteristic and uniform histopathologic findings. These *candida* esophagitis patients were treated with either nystatin 5 ml QDS/fluconazole 100 mg a day by mouth for 5 days. None of these candida esophagitis patients was found to be resistant to this treatment. As treatment with fluconazole was expensive, fewer patients were prescribed this medication. Culture for identifying *candida* species was not carried out, as it would have added cost to the management of disease. The limitation of our study included a small number of patients and a retrospective design. There were few patients with risk factors in the control group B as their stable disease did not predispose them to *candida* esophagitis (Table 1).

The implications of our study are that in Pakistan *candida* esophagitis is associated with chronic diseases and those on treatment with corticosteroids and antibiotics are predisposed to it. Patients on these medications need to be monitored and reviewed frequently. *Candida* esophagitis should be considered early in patients who have been on steroids and antibiotic treatment and presented with upper gastro-intestinal symptoms. Oral candidiasis does not accompany candida esophagitis. Our study showed that *candida* esophagitis by itself was an easily managed complication. In conclusion, *candida* esophagitis in Pakistan is more common due to chronic diseases, corticosteroid and antibiotic therapy which impaires the immune system rather than as an AIDS-defining disease. It occurs in the absence of local obstructive lesions and responds to treatment with nystatin and fluconazole.

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