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Antifungal Treatment is Not Required for Immunocompetent Individuals With Asymptomatic Esophageal Candidiasis

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Abstract: Although esophageal candidiasis (EC) is an opportunistic infection, asymptomatic EC (AEC) is occasionally encountered in otherwise healthy individuals. This study evaluates the impact of antifungal treatment in immunocompetent individuals with AEC and investigates risk factors for persistent or recurrent EC. The authors identified patients with biopsy-proven AEC from the database of individuals receiving screening endoscopy (n = 99,255). After excluding patients receiving immunosuppressive therapy, being positive for human immunodeficiency virus, receiving no follow-up endoscopy, or having no antifungal treatment data, a total of 142 patients were divided into remission and nonremission groups. Remission was defined when EC was not detectable on follow-up endoscopy. On baseline comparison, nonremission group was older (57.5 ± 10.3 versus 52.5 ± 10.5 years, $P = 0.017$) and more likely to have cardiovascular disease (12.9% versus 1.8%, $P = 0.021$) and history of pulmonary tuberculosis (PTB) (22.6% versus 4.5%, $P = 0.004$) and exhibited a lower triglyceride level (101.4 ± 37.4 versus 122.6 ± 79.6 mg/dL, $P = 0.039$) than remission group, whereas grade of EC and concomitant endoscopic findings did not differ between 2 groups. Antifungal treatment was also similarly performed between 2 groups. Multivariate analysis revealed that history of PTB is independently associated with nonremission (odds ratio 4.495, 95% confidence interval 1.023–19.762, $P = 0.047$). No patients demonstrated EC-related complications during a mean follow-up of 28.0 ± 12.0 months. In conclusion, our results suggested that antifungal treatment is not required for immunocompetent individuals with AEC and past history of PTB is an independent predictor for persistent or recurrent EC.

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Abbreviations: AEC = asymptomatic esophageal candidiasis, AIDS = acquired immune deficiency syndrome, BMI = body mass index, CI = confidence interval, MTB = *Mycobacterium tuberculosis*, OR = odds ratio, PTB = pulmonary tuberculosis.

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INTRODUCTION

Candida species are yeast-like fungi that reproduce by budding and can form true hyphae as well as pseudohyphae. They can be found as normal commensals in the gastrointestinal and genitourinary tracts and on the skin. Candidiasis caused by yeasts of the genus Candida encompasses a wide spectrum of diseases ranging from localized mucous membrane infection to life-threatening disseminated disease. The major determinant in the severity of infection is the host's immune response to the pathogen.[1,2]

Esophageal candidiasis (EC) is the most common opportunistic infection in immunocompromised patients, such as individuals diagnosed with acquired immune deficiency syndrome, lymphoma or leukemia, or having received organ transplants followed by immunosuppressive therapy.[3,4] The development of EC is almost always related to immune dysfunction and not simply to local factors.[2] An impaired cellular immunity has been suggested to predispose the host to EC.[1,5,6] The practice guidelines state that systemic antifungal therapy is always required for EC.[7]

During upper endoscopic examination, asymptomatic EC (AEC) is occasionally found in immunocompetent individuals. In these cases, diabetes mellitus, inhalation of steroid agent, and use of broad-spectrum antibiotics have been known to be the predisposing factors.[8,9] Although there have been some studies regarding EC in immunocompetent individuals, they have mainly addressed the risk factors for having acquired EC and in addition, are limited by having relatively small datasets and representing a heterogeneous study population.[8–10] As such, the clinical course of AEC in immunocompetent individuals remains poorly understood, and the necessity of antifungal treatment for individuals with AEC is unclear. For antifungal treatment in individuals with AEC, there needs to be an established management strategy.

Given the high incidence of gastric cancer,[11] screening upper endoscopy is routinely performed in Korea.[12] Accordingly, many cases of AEC were identified at our Health Promotion Center. We aimed to evaluate the clinical impact of antifungal treatment in healthy individuals with AEC and to investigate the risk factors for recurrent or persistent EC using our database.

METHODS

Study Population

We reviewed the database of screening upper endoscopy (n = 99,255) performed at Health Promotion Center in Samsung Medical Center (Seoul, South Korea) between January 2009 and June 2011. According to the histologic results,[13] we identified a total of 246 patients with biopsy-proven AEC. The diagnosis of EC was made by visualization of pseudohyphae or hyphae in tissue samples taken by endoscopic biopsy. Patients who met any of the following criteria were excluded: esophageal

symptoms such as dysphagia and odynophagia, human immunodeficiency virus (HIV) infection, receiving immunosuppressive therapy, no data whether received antifungal treatment or not, and obtained no follow-up endoscopy (Figure 1). The study was approved by the Institutional Review Board at Samsung Medical Center, Seoul, South Korea (No. 2015–07–044).

Data Collection and Definitions

At baseline, the following information was collected from each patient: age, sex, body mass index, comorbidity (hypertension, diabetes, dyslipidemia, chronic liver disease, bronchial asthma, thyroid disease, chronic pulmonary disease, chronic kidney disease, and cardiovascular disease, such as heart failure, valvular heart disease, and arrhythmia), list of medications within 6 months before endoscopy, past medical history, such as cancer and pulmonary tuberculosis (PTB), current smoking, alcohol consumption, and laboratory findings (creatinine, fasting glucose, glycosylated hemoglobin, triglyceride, high- and low-density lipoprotein cholesterol, rheumatoid factor, and thyroid-stimulating hormone).

Endoscopic data were obtained from the report. All endoscopic images were reviewed for grading EC by 2 experienced endoscopists (EK and YWM). The severity of EC was graded on a scale of I to IV according to the method of Kodsi et al[14] Grade I is a few raised white plaques up to 2 mm in size; grade II is multiple raised white plaques greater than 2 mm in size; grade III is confluent, linear, and nodular elevated plaques; and Grade IV is increased friability of the mucous membranes and occasional narrowing of the lumen.

Information regarding antifungal treatment was obtained from the medical chart review and complemented by conducting a telephonic interview with the patients. Remission was defined when EC disappeared on follow-up endoscopy (remission group). If not, patients were classified into the nonremission group (Figure 1).

Statistical Analysis

Statistical results are presented as the mean ± SD or number of patients (%). Continuous variables were compared parametrically using Student *t* test. Categorical variables were compared using the χ^2 test or Fisher exact test as appropriate.

Subgroup analysis was performed on a group of patients who received fluconazole. Between the remission and nonremission groups, the duration and dose of fluconazole treatment were compared.

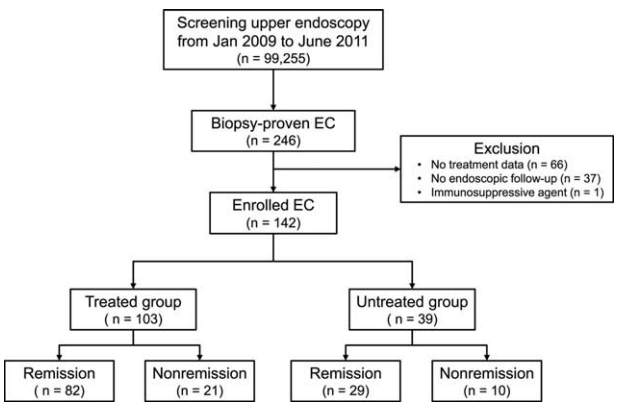

FIGURE 1. Flow sheet. Esophageal candidiasis.

Univariate and multivariate analyses included variables, such as age, sex, antifungal treatment, and those were associated with nonremission on the comparison of demographics and clinical characteristics ($P < 0.200$). Odds ratios were presented together with the 95% confidence interval. Two-sided *P* values <0.05 were taken as statistically significant. Statistical analyses were conducted using the SPSS Statistics 21 software (IBM, Armonk, NY).

RESULTS

Study Population

Among a total of 246 patients with biopsy-proven AEC, 104 were excluded from the study: 66 in whom data regarding antifungal treatment could not be acquired, 37 who did not undergo follow-up endoscopy, and 1 receiving immunosuppressive therapy. Finally, a total of 142 patients were enrolled into this study. Of them, 103 patients received antifungal treatment and 39 did not (Figure 1). Remission was similarly observed among the treated and untreated groups (79.6% versus 74.4%, respectively, $P = 0.499$).

Comparison of Demographics and Clinical Characteristics Between the Remission and Nonremission Groups

There was no standard guideline regarding follow-up for AEC. Follow-up endoscopy was performed mean 15.4 ± 7.7 months after diagnosis of AEC by the attending physician's decision. Time to follow-up, however, did not differ between the remission and nonremission groups (15.7 ± 7.4 versus 14.2 ± 8.8 months, respectively, $P = 0.349$). Although 41 patients (28.9%) underwent follow-up endoscopy within 12 months, no patients demonstrated EC-related symptoms during follow-up.

As shown in Table 1, the nonremission group was older (57.5 ± 10.3 versus 52.5 ± 10.5 years, $P = 0.017$) and more likely to have cardiovascular disease (12.9% versus 1.8%, $P = 0.021$) and experience PTB (22.6% versus 4.5%, $P = 0.004$) and exhibited lower triglyceride level (101.4 ± 37.4 versus 122.6 ± 79.6 mg/dL, $P = 0.039$) than the remission group. All patients with past medical history of PTB had been cured and did not have active tuberculosis (TB). There, however, were no significant differences between the 2 groups with regard to sex, body mass index, other comorbidities including hypertension, diabetes, dyslipidemia, chronic liver disease, bronchial asthma, thyroid disease, chronic pulmonary disease, chronic kidney disease, and current medication usage, including aspirin, lipid-lowering agent, ginseng, nonsteroidal anti-inflammatory drug, estrogen, steroid (oral or inhaler), antibiotics, and proton pump inhibitor. Between the 2 groups, there were also no significant variations in history of malignancy, current smoking, alcohol consumption, and other laboratory findings, including creatinine, fasting glucose, glycosylated hemoglobin, high- and low-density lipoprotein cholesterol, rheumatoid factor, and thyroid-stimulating hormone.

Comparison of Endoscopic Findings Between the Remission and Nonremission Groups

As shown in Table 2, the grade of EC and concomitant endoscopic findings at the initial endoscopy, including reflux esophagitis, hiatal hernia, chronic atrophic gastritis, gastric ulcer, duodenal ulcer, and gastric cancer did not differ between the remission and nonremission groups. Grade I, II, and III EC was observed in 64.9%, 34.2%, and 0.9% of the remission group

TABLE 1. Comparison of Characteristics Between Remission and Nonremission Groups

Variables	Remission (n = 111)	Nonremission (n = 31)	*P* Value
Age (years)	52.5 ± 10.5	57.7 ± 10.3	0.017
Sex, male	81 (73.0)	22 (71.0)	0.825
BMI (kg/m^2)	23.8 ± 2.6	23.5 ± 3.6	0.718
Comorbidity	56 (50.5)	15 (48.4)	0.839
Hypertension	23 (20.7)	8 (25.8)	0.544
Diabetes	18 (16.2)	1 (3.2)	0.074
Dyslipidemia	26 (23.4)	4 (12.9)	0.205
Chronic liver disease	5 (4.5)	1 (3.2)	1.000
Cardiovascular disease	2 (1.8)	4 (12.9)	0.021
Bronchial asthma	2 (1.8)	1 (3.2)	0.525
Thyroid disease	4 (3.6)	1 (3.2)	1.000
Others	4 (3.6)	1 (3.2)	1.000
Medication			
Aspirin	14 (12.6)	7 (22.6)	0.250
Lipid-lowering agent	9 (8.1)	2 (6.5)	1.000
Ginseng	8 (7.2)	0 (0)	0.200
NSAID	6 (5.4)	0 (0)	0.339
Estrogen	5 (4.5)	1 (3.2)	1.000
Steroid	3 (2.7)	3 (9.7)	0.118
Antibiotics	3 (2.7)	2 (6.5)	0.300
Proton pump inhibitor	2 (1.8)	1 (3.2)	0.525
Past Medical History			
Pulmonary tuberculosis	5 (4.5)	7 (22.6)	0.004
Malignancy	0 (0)	1 (3.2)	0.218
Current smoking	18 (19.6)	5 (20.0)	1.000
Alcohol	71 (78.9)	17 (68.0)	0.256
Laboratory			
Creatinine (mg/dL)	0.88 ± 0.17	0.87 ± 0.14	0.893
Fasting glucose (mg/dL)	99.7 ± 23.9	94.8 ± 14.7	0.289
HbA1c (%)	5.7 ± 0.8	5.7 ± 0.4	0.570
Triglyceride (mg/dL)	122.6 ± 79.6	101.4 ± 37.4	0.039
LDL-C (mg/dL)	117.6 ± 29.7	122.6 ± 33.5	0.422
HDL-C (mg/dL)	54.3 ± 15.2	52.5 ± 11.6	0.540
Rheumatoid factor (IU/mL)	7.3 ± 3.7	11.7 ± 18.2	0.194
TSH (μIU/mL)	2.6 ± 1.8	2.6 ± 1.4	0.975

Data are shown as the mean ± SD or number (%) of patients. BMI = body mass index, HbA1c = hemoglobin A1c, HDL = high-density lipoprotein, LDL-C = low-density lipoprotein cholesterol, NSAID = nonsteroidal anti-inflammatory drug, TSH = thyroid-stimulating hormone.

TABLE 2. Comparison of Endoscopic Findings Between Remission and Nonremission Groups

Variables	Remission (n = 111)	Nonremission (n = 31)	*P* Value
Esophageal candidiasis grade			0.145
I	72 (64.9)	16 (51.6)	
II	38 (34.2)	13 (41.9)	
III	1 (0.9)	2 (6.5)	
IV	0 (0)	0 (0)	
Concomitant Findings			
Reflux esophagitis	12 (10.8)	3 (9.7)	1.000
Hiatal hernia	6 (5.4%)	0 (0)	0.339
Chronic atrophic gastritis	12 (10.8)	3 (9.7)	1.000
Gastric ulcer	6 (5.4)	1 (3.2)	1.000
Duodenal ulcer	6 (5.4)	1 (3.2)	1.000
Gastric cancer	1 (0.9)	0 (0.0)	1.000

Data are shown as the number (%) of patients.

versus 51.6%, 41.9%, and 6.5% of the nonremission group, respectively. The most common concomitant endoscopic findings were reflux esophagitis and chronic atrophic gastritis both which were observed in 10.8% and 9.7% of the remission and nonremission groups, respectively.

Details of Antifungal Treatment in the Treated Group

As shown in Table 3, antifungal treatment was similarly performed between the remission and nonremission groups (73.9% versus 67.6%, $P = 0.499$). Similar antifungal agents were used among the 2 groups ($P = 0.467$). Overall, fluconazole (86.4%) was the most common antifungal agent used, followed by nystatin suspension (3.9%) and intraconazole (2.9%). In 7 patients (6.8%), details of antifungal agent were not identified.

In the patients who received fluconazole, subgroup analysis was performed regarding antifungal treatment. The mean treatment duration did not differ between the remission and nonremission groups (9.0 ± 2.8 versus 10.2 ± 3.1 days, $P = 0.099$). According to the duration categories (≤ 7, >7 and <14, and ≥ 14 days), there were no significant differences between the remission and nonremission groups. In addition, the daily and total dose used did not differ between the 2 groups (106.5 ± 35.3 versus 107.5 ± 33.5 mg, $P = 0.912$ for daily usage and 973.9 ± 443.1 versus 1075.0 ± 408.3, $P = 0.363$ for total usage, respectively). According to the total dose categories (≤ 700, >700 and <1400, and ≥ 1400 mg), there were no significant differences between the remission and nonremission groups.

Prognostic Factors Associated With Remission

In the univariate analysis, old age, current cardiovascular disease, and past history of PTB were associated with the nonremission ($P < 0.05$; Table 4). In addition to these variables, sex, diabetes, steroid use, triglyceride, rheumatoid factor, grade of EC, and antifungal treatment were included in the multivariate analysis. The results of logistic regression analysis revealed that past history of PTB is independently associated with nonremission (odds ratio 4.495, 95% confidence interval 1.023–19.762, $P = 0.047$).

Long-Term Clinical Course of Asymptomatic Esophageal Candidiasis

The patients with AEC ($n = 142$) received subsequent upper endoscopy 2.0 ± 0.9 times further after enrollment during a mean follow-up of 28.0 ± 12.0 months. Among the nonremission group, the severity of EC was increased in 19.4%, constant in 58.1%, and decreased in 22.6% at the follow-up endoscopy. All patients, however, showed grade I or II EC during follow-up. In addition, no patients demonstrated EC-related symptoms or complications including systemic dissemination.

DISCUSSION

Although AEC in immunocompetent individuals is increasingly encountered, its clinical course remains unclear. Previous studies have mainly addressed risk factors for development of EC in patients without a human immunodeficiency virus infection and were limited by relatively small series and a heterogeneous study population.[8–10] Recently, Lee et al[15] reported the risk factors for AEC and a good prognosis of AEC without antifungal treatment. In contrast, this current study evaluated the clinical impact of antifungal treatment in immunocompetent individuals with AEC and investigated the prognostic factors associated with recurrent or persistent EC. In addition, our study used a prospectively collected large database and minimized missing follow-up data by telephonic interviews with the patients.

The main finding of the current study is that antifungal treatment is not associated with remission on a follow-up endoscopic examination. Neither univariate nor multivariate analysis showed a relationship between antifungal treatment and remission on follow-up endoscopy. Even though once daily antifungal medication of fluconazole 100 mg was mostly frequently used, its duration and total dose usage were rather

TABLE 3. Comparison of Antifungal Treatment Between Remission and Nonremission Group

Variables	Remission (n = 111)	Nonremission (n = 31)	*P* Value
Antifungal treatment	82 (73.9)	21 (67.7)	0.499
Antifungal agent			0.467
Fluconazole	69 (84.1)	20 (95.2)	
Itraconazole	3 (3.7)	0 (0)	
Nystatin	3 (3.7)	1 (4.8)	
Unknown	7 (8.5)	0 (0)	
Treatment duration (days)*	9.0 ± 2.8	10.2 ± 3.1	0.099
Treatment duration categories*			0.090
≤ 7 days	32 (46.4)	8 (40.0)	
>7 and <14 days	28 (40.6)	5 (25.0)	
≥ 14 days	9 (13.0)	7 (35.0)	
Daily dose (mg)*	106.5 ± 35.3	107.5 ± 33.5	0.912
Total dose (mg)*	973.9 ± 443.1	1075.0 ± 408.3	0.363
Total dose categories*			0.438
≤ 700 mg	28 (40.6)	5 (25.0)	
>700 and <1400 mg	18 (26.1)	7 (35.0)	
≥ 1400 mg	23 (33.3)	8 (40.0)	

Data are shown as the mean ± SD or number (%) of patients.
* Subgroup analysis was performed in a group of patients who received fluconazole.

TABLE 4. Univariate and Multivariate Analyses of Predisposing Factors for Nonremission of Esophageal Candidiasis

Variables	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age (years)	1.052 (1.009–1.098)	0.019	1.031 (0.978–1.087)	0.258
Sex				
Female	1		1	
Male	0.905 (0.375–2.186)	0.825	0.752 (0.250–2.259)	0.612
Diabetes	0.172 (0.022–1.345)	0.093	0.247 (0.029–2.117)	0.202
Cardiovascular disease	8.074 (1.405–46.412)	0.019	5.661 (0.785–40.831)	0.085
Steroid use	3.857 (0.738–20.152)	0.110	2.649 (0.313–22.443)	0.372
History of pulmonary tuberculosis	6.183 (1.807–21.159)	0.004	4.495 (1.023–19.762)	0.047
Triglyceride (mg/dL)	0.995 (0.988–1.002)	0.157	0.994 (0.985–1.003)	0.165
Rheumatoid factor (IU/mL)	1.071 (0.981–1.169)	0.127	1.031 (0.945–1.124)	0.490
Esophageal Candidiasis Grade				
I	1		1	
II	1.539 (0.671–3.533)	0.309	1.164 (0.423–3.200)	0.768
III	9.000 (0.768–105.430)	0.080	6.932 (0.469–102.427)	0.159
Antifungal treatment	0.743 (0.313–1.762)	0.500	0.682 (0.238–1.950)	0.475

CI = confidence interval, OR = odds ratio.

variable. Thus, we could demonstrate that no dose-response relationship between antifungal treatment and remission by comparing patients with different durations and total doses (7 versus 14 days and 700 versus $\geq$1400 mg) in a subgroup consisted of patients who received fluconazole. Although dose and duration of fluconazole used in the current study were less than those recommended for EC in the practice guidelines,[7] the evidence of guidelines did not come from immunocompetent individuals with AEC. Indeed, EC-related symptoms or complications were not observed during follow-up regardless of antifungal treatment in the current study. Furthermore, no patients showed endoscopically severe EC (grade III or IV) during follow-up. These observations indicated that antifungal treatment would not change the clinical course of AEC in immunocompetent individuals.

Isn't an antifungal treatment necessary for immunocompetent individuals with AEC? Probably not. In the current study, no patients with AEC including the untreated group (n = 39) demonstrated EC-related complications including systemic dissemination during a mean follow-up of 28.0 ± 12.0 months. This observation is consistent with a previous study, where no severe complications of EC had been found among 20 patients with persistent EC on follow-up endoscopy.[10] We should note that in the current study, few patients with endoscopically severe EC (3 grade III's and no grade IV's) were included and all of them received antifungal treatment. Thus, our results need to be interpreted in the context of this limitation.

Candida albicans is the most common species that causes EC.[1,2,16] Actually, *C. albicans* commensalism is not the result of its benign behavior, but rather the result of host's potent innate and adaptive immune responses.[16–19] Unlike oropharyngeal candidiasis, the development of EC is almost always related to immune dysfunction and not simply to local factors, such as the use of broad-spectrum antibiotics or inhaled corticosteroids, xerostomia, or radiation treatment.[2] Especially, selectively depleted Th17 cell functional subset within the $CD4^+$ T cell lineage is associated with the development of opportunistic infections including EC, with the progression of HIV infection.[19,20] Although the magnitude of the contribution of the T cell immunity to the development of EC is unclear in immunocompetent individuals, $CD4^+$ T cell functional deficit might play a role in the pathogenesis of AEC.

Of interest, a history of PTB was independently associated with recurrent or persistent EC in our study. Tuberculosis is a chronic granulomatous disease usually caused by the *Mycobacterium tuberculosis* (MTB) with the lung as the most common site of disease.[1] Initial primary infection, however, is self-limiting in most individuals and among the latent individuals, only 5% to 10% develop active TB in their lifetime.[21] Like EC, the risk of active PTB is increased in HIV-infected individuals.[22] This may result from high risk of reactivation of latent MTB infection and progression of MTB infection to primary active TB.[1] Although the immune response to MTB is multifaceted, $CD4^+$ T cell function is central to the orchestration of cell-mediated responses to MTB for the formation of competent granulomas, which restrict growth of the organism.[1,23,24] Thus, $CD4^+$ T cell functional deficit might exist in the individuals with a history of active PTB. This observation supports that the T cell dysfunction might play a role in the development of AEC in immunocompetent individuals. This, however, needs to be confirmed in future studies.

Our study had a few limitations. Because this was a single-center study, there could have been selection bias. In addition, the study population could not include enough young patients. This study, however, included relatively large number of patients with biopsy-proven AEC. Moreover, this was the first study to investigate the impact of antifungal treatment in immunocompetent individuals with AEC. We also tried to complete the follow-up data by additional telephonic interviews with the patients. In conclusion, our results suggest that antifungal treatment is not necessary for immunocompetent individuals with AEC and past history of PTB is an independent predictive factor for persistent or recurrent EC.

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