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ORIGINAL ARTICLE

Liver cirrhosis as a predisposing factor for esophageal candidiasis

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Summary *Background:* Esophageal candidiasis (EC) often occurs in human immunodeficiency virus (HIV)-infected patients, but is uncommon in non-HIV-infected patients. It is known that malignancy, diabetes mellitus, previous gastric surgery, and medications (antibiotics, proton pump inhibitors, and steroids) are risk factors for esophageal candidiasis in non-HIV-infected patients. However, the relationship between liver cirrhosis and esophageal candidiasis was unclear. This study aimed to elucidate the role of liver cirrhosis in esophageal candidiasis.
Methods: A retrospective chart review study was conducted on non-HIV-infected patients with esophageal candidiasis who presented to Tri-Service General Hospital from January 2009 to December 2012. The diagnosis of EC was primarily based on endoscopic findings. The incidence of EC in cirrhotic and noncirrhotic patients was compared. Furthermore, differences in baseline characteristics, clinical variables, and mortality after antifungal treatment between the two groups were analyzed.
Results: In this study, 43,217 non-HIV-infected patients were enrolled, 3017 of whom had liver cirrhosis. The incidence of EC in cirrhotic patients was higher than that in noncirrhotic patients (0.8% vs. 0.36%; relative risk $= 2.2$; $p < 0.001$). Multivariate logistic regression analysis identified liver cirrhosis as an independent risk factor for EC (odds ratio, 1.74; 95% confidence interval, 1.06—2.87; $p = 0.029$). Moreover, cirrhotic patients tended to be asymptomatic compared with noncirrhotic patients (45.8% vs. 9%; $p < 0.01$). The most common coexisting endoscopic finding was reflux esophagitis (83.9%). However, antifungal treatment did not decrease the mortality of patients with EC during hospitalization.

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Conclusion: Liver cirrhosis is an independent risk factor for EC. EC may be asymptomatic in cirrhotic patients. Although antifungal treatment did not improve the outcome in this study, a prospective study is still required to investigate this issue.

Introduction

Esophageal candidiasis (EC) is a common opportunistic infection that occurs most often in immunocompromised patients who have either AIDS caused by human immunodeficiency virus (HIV) infection, or iatrogenic immunosuppression caused by cancer treatment and prevention of transplanted-organ rejection [1—6]. In non-HIV-infected patients, the prevalence of EC is approximately 0.3% [7—9]. However, prior to the introduction of highly active antiretroviral therapy, 42% of HIV-infected patients had been diagnosed with EC [10]. Under current highly active antiretroviral therapy regimens, 17% of HIV-infected patients experience EC [10], suggesting that the incidence of EC has substantially increased in HIV-infected patients. Similarly, renal allograft recipients who received three immunosuppressive drugs had a higher incidence of EC compared with recipients who took two immunosuppressive drugs (28.6% vs. 10.4%) [6]. These examples demonstrate that the incidence of EC is related to immune status.

Candida albicans is the most common pathogen causing EC. It has been isolated from 90% of EC patients [11,12]. The common presenting symptoms are odynophagia, dysphagia, and retrosternal pain [2], but some patients are asymptomatic [13—16]. Esophagogastroduodenoscopy (EGD) plays an important role in the diagnosis of EC. EGD reveals the gross appearance of esophageal mucosa and provides an opportunity to perform biopsy [1,16—18]. The typical endoscopic appearance is multiple raised small or thick white plaques on the esophageal mucosa [1,10,16]. Histological examination of the biopsy specimens using a potassium hydroxide smear reveals yeast cells and pseudohyphae [19,20]. Sensitivity and specificity of EGD for the diagnosis of EC are 100% and 83.3%, respectively; positive and negative predictive values are 88.5% and 100%, respectively [17]. Therefore, EGD is a reliable method for the diagnosis of EC.

Among HIV-negative patients, those with cancer have a higher incidence of EC compared with those without cancer [4,7,8,21]. A double-blind study showed that oropharyngeal candidiasis was detected in 54% of cancer patients who received placebo and in 3% of cancer patients who received antifungal prophylaxis during hospitalization [22]. Another double-blind study also revealed that 78.6% of patients with acute leukemia undergoing chemotherapy developed oropharyngeal candidiasis, but only 7.1% of acute leukemia patients undergoing both chemotherapy and antifungal prophylaxis had oropharyngeal candidiasis [5]. Furthermore, oropharyngeal candidiasis is a marker for EC in cancer patients [4], suggesting that the risk for EC is increased in cancer patients. Similarly, other risk factors have been proven to increase the incidence of EC, such as diabetes mellitus (DM), previous gastric surgery, reflux esophagitis, and use of antibiotics, steroids, and proton pump inhibitors (PPIs) [6—9,16,23—25]. In addition, the number of $CD4^+$ T cells is crucial for determining the immune status, and it was decreased in cirrhotic patients [26]. The decrease in $CD4^+$ T-cell count plays an important role in the disease progression of HIV-infected patients [27,28]. Therefore, liver cirrhosis, similar to HIV infection, may also increase the incidence of EC. However, the relationship between cirrhosis and EC remains unclear.

In this study, our aim was to elucidate the role of liver cirrhosis in non-HIV-infected patients with EC. The clinical characteristics and symptoms of our patients with EC were first examined, and subsequently coexisting endoscopic findings were investigated. Finally, we analyzed the putative predisposing factors, and determined whether liver cirrhosis was an independent risk factor for EC.

Materials and methods

Patients

In this retrospective study, medical records of patients who underwent EGD at Tri-Service General Hospital, Taipei, Taiwan from January 2009 to December 2012 were analyzed. Age, sex, symptoms, medical history (such as liver cirrhosis, DM, malignancy, or end-stage renal disease), medications (such as PPIs, antibiotics, corticosteroids, immunosuppressive drugs, or chemotherapy), and endoscopic findings were investigated. HIV-infected patients were excluded from the study. The diagnosis of EC was based on the findings of endoscopy (Fig. 1) or biopsy. To verify the diagnosis of EC, endoscopic images were reviewed by two endoscopists.

Patients with EC were divided into two groups. The first group (Group 1) was associated with liver cirrhosis and the second group (Group 2) was without cirrhosis. The diagnosis of cirrhosis was based on the findings of coarsening parenchymal echo pattern, irregular surface, enlargement of caudate lobe, vascular irregularities, accompanied with splenomegaly, or ascites in abdominal sonography. The incidence rate of EC in the two groups was calculated. To confirm whether liver cirrhosis is an independent risk factor of EC, different putative risk factors were compared between these two groups. The mortality after antifungal treatment between the two groups was also analyzed. The study was approved by the Institutional Review Board of Tri-Service General Hospital.