Case Report
Yonsei Med J 2021 Feb;62(2):182-186
https://doi.org/10.3349/ymj.2021.62.2.182
Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

Two Cases of Fungemia after Endoscopic Variceal Obturation for Gastric Variceal Bleeding

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Fever is a common complication of endoscopic variceal obturation (EVO) therapy for gastric variceal bleeding. However, fungemia related to EVO therapy has not yet been reported. Herein, we report two cases of post-EVO fungemia in cirrhotic patients who underwent therapeutic EVO for gastric variceal bleeding. Both patients developed sustained high fever after repeated EVO procedures while on prophylactic antibiotic use. In both patients, blood cultures revealed yeast, and they were finally diagnosed with *Candida* infection. *Candida* is a common member of the intestinal flora; however, it can cause invasive infection with consequent poor prognosis in cirrhotic patients. The route of *Candida* invasion is unclear; however, repeated EVO may predispose patients to *Candida* infection, particularly those who are in the end stage of liver disease and receiving prophylactic antibiotics. Our cases highlight that repeated invasive procedures can increase the risk of fungal infections, and fungemia should be considered in the differential diagnosis of post-EVO fever.

Key Words: Fungemia, endoscopic variceal obturation, fever, liver cirrhosis

INTRODUCTION

Fungal infections in cirrhotic patients have emerged as a life-threatening problem in the era of abundant use of broad spectrum antibiotics.[1,2] The diagnosis of invasive fungal infections is often delayed with poor prognosis.[1,3] Herein, we report two cases of fungemia in patients who were treated with therapeutic endoscopic variceal obturation (EVO) for acute gastric variceal bleeding.

Received: October 12, 2020 **Revised:** November 18, 2020
Accepted: November 24, 2020
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•The authors have no potential conflicts of interest to disclose.

CASE REPORT

Case 1

A 55-year-old man with a history of alcohol-related liver cirrhosis and type 2 diabetes mellitus presented to the emergency room (ER) with hematemesis. He reported a 30-year history of alcohol consumption (>150 g/day) and showed a low-grade fever (38.1°C). Blood culture was done. Viral marker for hepatitis B or C was all negative, and abnormal laboratory data showed white blood cell count of 11.4×10^9/L, hemoglobin (Hb) of 12.4 g/dL, platelets of 34×10^9/L, International Normalized Ratio (INR) of 1.5, albumin of 3.1 g/dL, total bilirubin of 7.3 mg/dL, and glycated hemoglobin (HbA1c) of 10.6%. Abdominal computed tomography (CT) revealed liver cirrhosis without gastrorenal shunt. Child-Pugh Score (CPS) was classified as class C with a score of 10, and the model for end-stage liver disease (MELD) score was 18. Gastrofibroscopy revealed a large gastroesophageal varix with red-color sign on the posterior fundic wall (Fig. 1A). Three injections of a cyanoacrylate (0.5 mL) and lipiodol (0.5 mL) mixture [1 mL, 1 mL, and 0.5 mL (total 2.5 mL)] were done (Fig. 1B). Intravenous (IV) terlipressin, proton pump inhibitor, and prophylactic 3rd generation cephalosporin (ceftriaxone 2 g/day) were administered. Follow-up abdominopelvic CT revealed cyanoacrylate-lipiodol mixture in the varices without distant migration. After 2

days, additional EVO procedure was done for secondary prophylaxis with two injections (1 mL and 0.5 mL). From the following day, the subject developed high fever (38.7°C) that lasted for 5 days (Fig. 3A). Follow-up investigations including urinalysis, sputum cultures, chest radiography, and CT were unremarkable. Antibiotics were stepped up to piperacillin/tazobactam, and blood cultures were repeated every 1–2 days. The blood culture conducted at ER visit was negative; however, yeast was detected on the 6th day of blood culture conducted since the the day of high fever, and yeast was also detected in all subsequent follow-up cultures. Fever was immediately subsided, and the subject showed clinical improvement to IV fluconazole. Yeast was finally reported as *Candida glabrata*. We discontinued piperacillin/tazobactam. Fluconazole was switched to caspofungin for more than 14 days after negative conversion in the blood culture. The subject was discharged with complete improvement of symptoms.

Case 2

A 53-year-old woman with a history of alcoholic liver cirrhosis

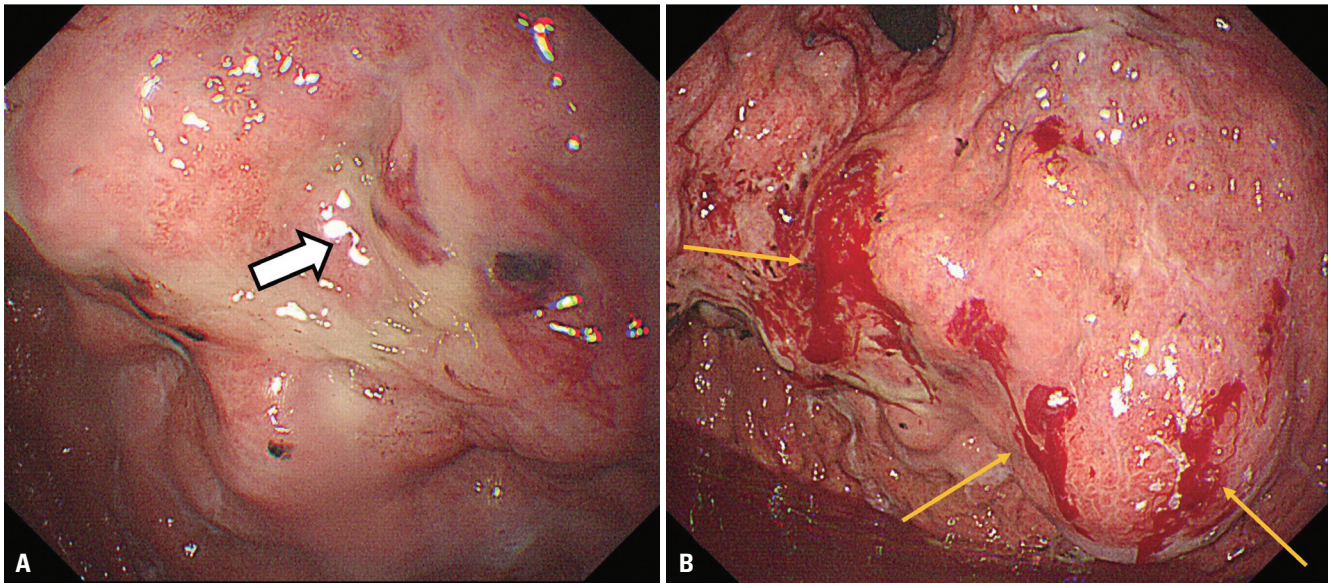

Fig. 1. Endoscopic findings of the patient described in Case 1. A: Initial endoscopic image showing a large GOV with red-color sign at the gastric fundus. B: Endoscopic image after 3 times of injections around the stigma. Wide arrow: suspicious bleeding stigma, Narrow arrow: injection sites. GOV, gastroesophageal varix.

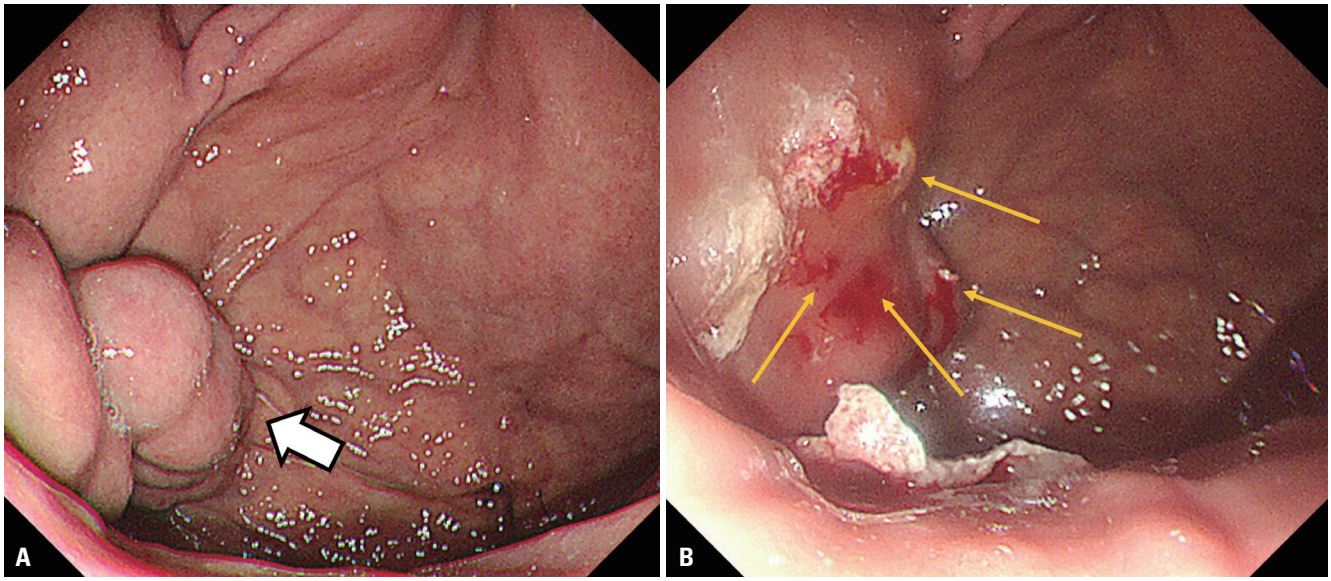

Fig. 2. Endoscopic findings of the patient described in Case 2. A: Initial endoscopic image showing a large IGV at the gastric fundus. B: Endoscopic image after 4 times of injections at the EVO target. Wide arrow: suspicious bleeding stigma, Narrow arrow: injection sites. EVO, endoscopic variceal obturation; IGV, isolated gastric varix.

presented with melena and hematemesis. She reported a 30-year history of alcohol consumption (300 g of alcohol/week). She was alert and showed blood pressure of 81/53 mm Hg with heart rate of 75 bpm and hypothermia (35.4°C). Blood culture was immediately done. Viral marker for hepatitis B or C was all negative, and abnormal laboratory data showed in Hb of 7.6 g/dL, platelets of 86×10^9/L, total bilirubin of 4.1 mg/dL, albumin of 2.8 g/dL, and INR of 1.47. Abdominopelvic CT revealed liver cirrhosis with gastrorenal shunt. CPS was classified as class B with a score of 8, and MELD score was 16. Endoscopy revealed a large isolated gastric varix on the posterior fundic wall (Fig. 2A). Four injections of a cyanoacrylate (0.5 mL) and lipiodol (0.5 mL) mixture were done [1 mL, 1 mL, 0.5 mL, and 1 mL (total 3.5 mL)] (Fig. 2B). IV terlipressin, 2 g/day of ceftriaxone, and PPI were administered to the subject. Post-EVO abdominopelvic CT revealed cyanoacrylate-lipiodol mixture deposition the posterior fundic wall without evidence of embolism. Two additional EVO for secondary prophylaxis were done on day 2 and day 6 (one injection of 0.5 mL during the 1st session, two injections of 1 mL and 0.5 mL during the 2nd session). We attempted a plug-assisted retrograde transvenous obliteration procedure for the complete prophylactic treatment, but it was unsuccessful due to the huge diameter of gastrorenal shunt. On the third day after the 3rd EVO procedure, the subject developed high fever (38.8°C) (Fig. 3B). The blood culture conducted at ER visit had been reported as negative.

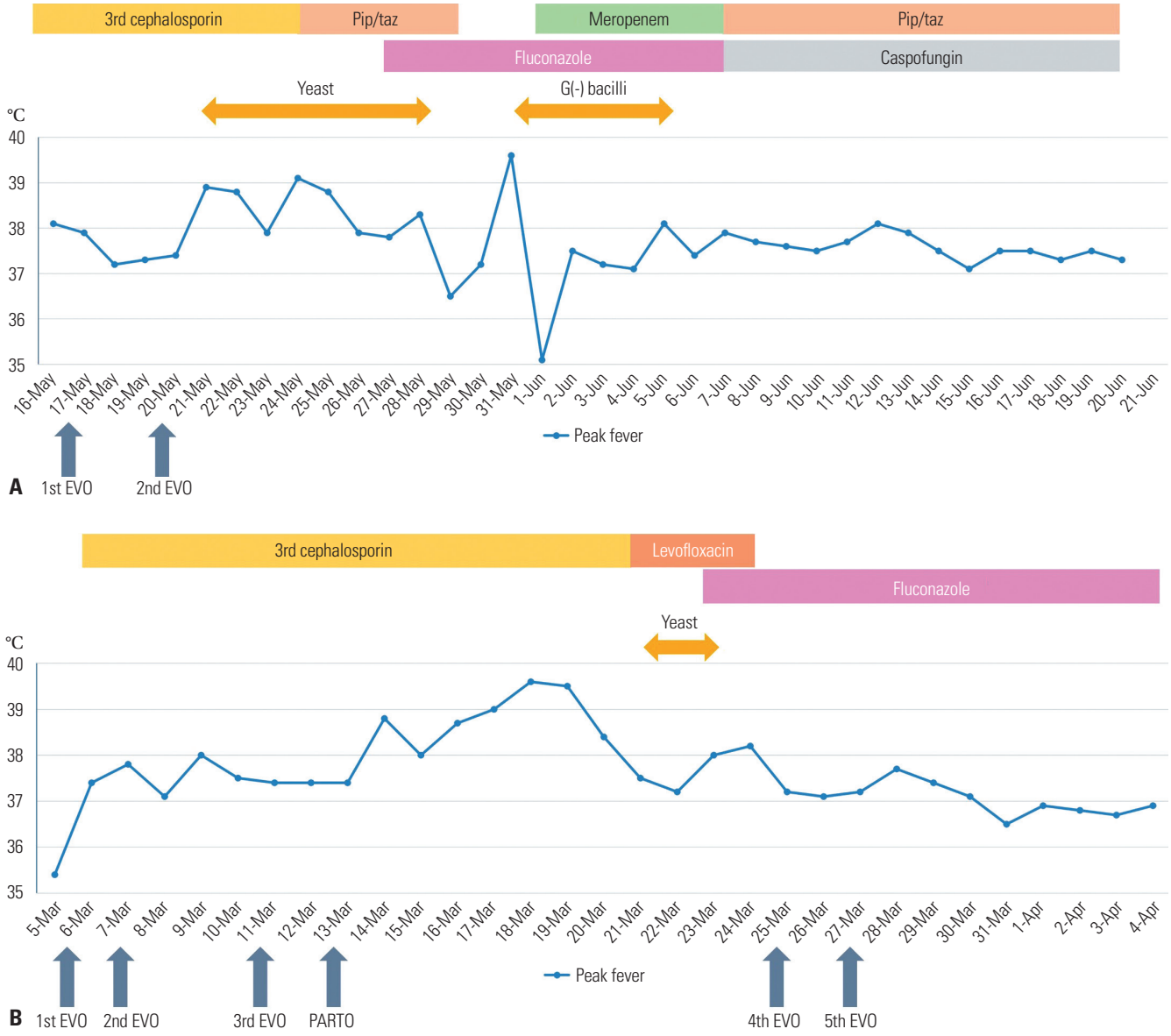

Fig. 3. Clinical course of the patient. A: Horizontal axis indicated the timeline of case 1 including EVO dates, period of antibiotic or antifungal agents use, and identificated culture period. Vertical axis indicated fever pattern of case 1. B: Horizontal axis indicated the timeline of case 2 including EVO dates, period of antibiotic or antifungal agents use, and identificated culture period. Vertical axis indicated fever pattern of case 2. EVO, endoscopic variceal obturation; PARTO, plug-assisted retrograde transvenous obliteration.

https://doi.org/10.3349/ymj.2021.62.2.182

Neutropenia was gradually progressed down to 0.63× 10^9/L during the high fever. We switched antibiotics from ceftriaxone to levofloxacin with the concern of drug fever or cytopenia. One pair of blood cultures revealed yeast on the seventh day of high fever (Fig. 3B). We immediately initiated IV fluconazole. Fever subsided after 3 days of fluconazole administration, and the causative organism was *Candida albicans*. During fluconazole administration, the subject received two additional EVO procedures for recurrent variceal bleeding (two injections of 0.5 mL during both sessions), without fever. Fluconazole was maintained for 15 days, and the subject was discharged without any symptoms.

We obtained informed consent from the patients regarding the reporting and publication of this case report.

DISCUSSION

Transient fever occurs in 90% of patients after EVO.[4,5] Possible causes include abscess, distant embolism,[6] and bacteremia.[4,5,7] Isolated post-EVO bacteremia has been reported in 0–50% of cases,[8] which can be caused by bacterial invasion through contaminated needle tips or by bacterial migration through a cyanoacrylate plug.[5,9] Liberal use of prophylactic antibiotics exposes patients to gut dysbiosis and consequent bacterial or fungal infections.[3,10] In particular, decompensated cirrhotic patients are vulnerable to fungal infection due to liberal use of PPI, and a few cases of fungal infections in end-stage liver disease were reported to be related to prophylactic antibiotics usage in patients with variceal bleeding.[11] The prevalence of fungal infections in patients with cirrhosis were reported to be 4–20%,[1,12] and mortality rates as high as 30–78%.[1,3,12] However, there has been little evidence for prophylactic antifungal treatment, and it is still not recommended.

Our two patients had high risks of opportunistic fungal infection such as excessive alcohol use, pancytopenia, and poorly controlled diabetes mellitus. Both cases had poor liver function with large size varix, and complete eradication of the feeding vessel was thought to be helpful in reducing the rebleeding risk.[13-16] For complete obturation of a large varix, multiple injections of cyanoacrylate are required to restrict the amount of cyanoacrylate to less than 1.0 mL per injection and 3.0 mL for each session, considering the risks of embolism or ulcer formation.[6,17,18] Since cyanoacrylate causes acute endovascular necrosis and increased vascular permeability by foreign body reaction, repeated punctures with short intervals could increase the risk of microbial invasion and subsequent blood stream infection,[19] which may contribute to candidemia. In particular, the risk of fungal infection may increase at the following EVO session due to the greater suppression of normal intestinal flora resulting from longer use of antibiotics and PPIs.

In both patients, there were no other signs indicating candida infection on urine and sputum cultures or chest x- ray. Both subjects did not have an intravascular or foley catheter, and there were no signs of esophageal or oral candidiasis in gastrofibroscopy. Therefore, we considered the possibility of blood stream infection of candida by repeated punctures at the EVO site. Focal invasion of candida through the ulcer occurring at the EVO site may cause candidemia, but it is known that the ulcer formation after EVO usually occurs about 1–3 months after the procedure.[20] Therefore, the possibility of candida invasion through the ulcer of EVO site was considered to be low. Indeed, in both cases, ulcers at the EVO site were not observed in gastrofibroscopy until before candidemia was developed. Additionally, the whole stomach was evaluated again to exclude the possibility of other bleeding focus in every EVO procedure, and there were no findings that could be regarded as gastric candidiasis, such as multiple ulcers or ulcers with dirty margins. Therefore, we could exclude gastric candidiasis as the cause of candidemia.

In conclusion, fungemia should be carefully considered in post-EVO fever, especially in patients with high risks of opportunistic infection. The number of EVO sessions for secondary prophylaxis should be minimized in patients with liver cirrhosis.

ACKNOWLEDGEMENTS

This study was supported by a National Research Foundation of Korea grant from the Korean government (the Ministry of Education, Science and Technology, 2018R1D1A1B07048487).

AUTHOR CONTRIBUTIONS

Conceptualization: Eileen L. Yoon. Data curation: Eileen L. Yoon. Funding acquisition: Eileen L. Yoon. Investigation: Soo In Choi. Resources: Eileen L. Yoon. Supervision: Eileen L. Yoon. Visualization: Soo In Choi. Writing—original draft: Soo In Choi. Writing—review & editing: Soo In Choi and Eileen L. Yoon. Approval of final manuscript: all authors.

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https://doi.org/10.3349/ymj.2021.62.2.182