The Clinical Role of Endoscopic Ultrasound for Management of Bleeding Esophageal Varices in Liver Cirrhosis

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Abstract
Bleeding esophageal varices (BEV) is a serious clinical condition and can potentially be life-threatening. Esophageal varices are caused by abnormal dilated submucosal and collateral veins in the esophagus wall as a result of portal hypertension due to liver cirrhosis. Consequently, it is important to administer appropriate preventive treatment for the disease in order to decrease morbidity and mortality rates. The current gold standard to identify esophageal varices is the use of esophagogastroduodenoscopy (EGD). However, EGD has limitations due to its inability in observing detailed information of varices morphology and esophagogastric hemodynamics. This report shares the potential role of endoscopic ultrasound (EUS) to overcome the limitation of EGD in clinical practices. Two cases of BEV in hepatitis B liver cirrhosis patients were described in the report. In case 1, large esophageal varices were found through EGD, and large paraesophageal varices were found through EUS. In case 2, small esophageal varices were found through EGD, and submucosal varices with a large periesophageal collateral vein and perforating vein in the distal esophagus were found through EUS. Cyanoacrylate injection guided by EUS was performed in both cases, and no rebleeding occurred after the procedure. In these cases, we showed that EUS is proven to be a potential tool in diagnosis and management of BEV in liver cirrhosis. EUS provides more accurate diagnostic aspects to find varices, assess bleeding risk, and predict bleeding recurrence. EUS also provides more beneficial treatment aspects to guide the treatment procedure and to monitor post treatment response.
Introduction

Gastrointestinal bleeding is a serious clinical condition which is associated with high morbidity and mortality. In general, for every 100,000 people in a year, 102 cases of upper gastrointestinal bleeding are accounted, and 14% of these cases are represented by esophageal varices [1]. Bleeding esophageal varices (BEV) can potentially be life-threatening; hence, it is crucial to administer appropriate preventive treatment to decrease morbidity and mortality rates. Esophagogastroduodenoscopy (EGD) is an endoscopic procedure that is used to visualize the lumen of the esophagus, stomach, and proximal duodenum. The patient is positioned in left lateral decubitus, and the endoscope is inserted while simultaneously examining the mucosa for any inflammations, ulcerations, furrowing, varices, narrowing, or strictures. The use of EGD comes with a limitation, i.e., only the internal lumen can be observed properly while surrounding conditions outside the lumen of the esophagus and gaster cannot be visualized [2, 3].

Recently, there have been reports regarding the use of endoscopic ultrasound (EUS) in BEV management for gastroesophageal vascular hemodynamics evaluation, treatment selection, prediction of recurrence, acute variceal bleeding condition, and follow-up after treatment [4]. We report 2 cases which show the significant role of EUS procedure in BEV management.

Case Report/Case Presentation

Case 1: A 64-year-old male was admitted to the hospital due to acute gastrointestinal bleeding. One year ago, the patient experienced a similar condition and underwent conservative treatment at another hospital. At that time, he was never screened for esophageal varices due to limited facilities. The patient also had type-2 diabetes mellitus.

During the examination, the patient was conscious, had stable hemodynamics with blood pressure of 132/76 mm Hg, pulse rate of 74 beats/minute, body temperature of 36.4°C, and 98% oxygen saturation. Examination of the sclera and skin showed no signs of jaundice. His cardiopulmonary, abdominal, neurological, and genitourinary systems were normal.

Laboratory tests performed on the patient showed the following results: hemoglobin 6.2 g/dL, platelet 166,000/μL, prothrombin time 12.3 s, aspartate aminotransferase 24 U/L, alanine transaminase 25 U/L, albumin 3.46 g/dL, total bilirubin 0.53 mg/dL, urea 92.7 mg/dL, creatinine of 0.80 mg/dL, random blood glucose 266 mg/dL, sodium 138 mEq/L, and HBsAg was positive. The diagnosis of suspected BEV in hepatitis B liver cirrhosis Child-Pugh A class with severe anemia and type-2 diabetes mellitus was made.

Based on the EGD result, large esophageal varices with a red color sign and small gastric varices were found (shown in Fig. 1a). Due to the existence of large esophageal varices as well as small gastric varices, it was decided to perform EUS to get more detailed examination, especially regarding esophagogastric varices vascular anatomy, hemodynamics, and existence of deep collateral varices, prior to standard endoscopic management. EUS was performed by using a linear echoendoscope (EG-3870UTK®; Pentax Europe GmbH, Hamburg, Germany), which is connected to the Hitachi Avius® platform (Hitachi Medical Systems Europe, Zug, Switzerland), and the result showed large paraesophageal collateral vein (para-ECV) (shown in Fig. 1b). It was decided to use EUS-guided cyanoacrylate (CYA) injection due to the existence of large paraesophageal varices in addition to large esophageal varices. EUS-guided CYA injection was chosen over esophageal band ligation (EBL) because, to the extent of our knowledge, EBL was not effective to treat paraesophageal varices. EUS-guided CYA injection was performed at large esophageal and paraesophageal varices on four different
Two millilitres of the mixture (1 mL:1 mL) of the tissue glue N-butyl-2-cyanoacrylate (Histoacryl®, B Braun Surgical, Rubi, Spain) and Lipiodol Ultra Fluide 480 mg iodine/mL (Guerbet, Aulnay-Sous-Bois, France) was injected into the distal esophagus using a 19-G slimline needle (Boston Scientific, Marlborough, MA, USA).

Observation after injection showed varices were subsided. Although there was still residual blood flow in the varices, blood flow has decreased significantly compared to before injection (shown in Fig. 1d). After the injection, there was neither bleeding at the injection site nor evidence of bleeding after the procedure, and the patient’s hemodynamic signs were stable. In addition, the hepatic-venous pressure gradient measurement was performed, and the result was 14 mm Hg. EGD re-examination after 2 months reported no occurrence of gastroesophageal variceal rebleeding.

Case 2: A 51-year-old male, with hepatitis B liver cirrhosis, was admitted to the emergency department due to recurrent melena. The patient also had complaints of decreased appetite and bloating. Patient had an 8-year history of hepatitis B and received oral antiviral therapy, i.e., tenofovir disoproxil fumarate, in the last 6 months prior to the admission. Eight years ago, he was treated with EBL for the same variceal bleeding problem. The patient also had diabetes mellitus and received insulin therapy since 2013.

The patient was alert and had stable vital signs with a blood pressure of 110/60 mm Hg, pulse rate of 61 beats/minute, body temperature of 36.2°C, and 98% oxygen saturation. He had anemic conjunctiva but no sign of jaundice. There was evidence of ascites and splenomegaly. His cardiopulmonary, neurological, and genitourinary systems were normal.

Laboratory tests performed on the patient showed the following results: hemoglobin 4.3 g/dL, platelet 81,000 μL, prothrombin time 14.7 s, aspartate aminotransferase 58 U/L, alanine transaminase 42 U/L, albumin 3.09 g/dL, total bilirubin 2.29 mg/dL, direct bilirubin 1.17 mg/dL, indirect bilirubin 1.12 mg/dL, urea 91.7 mg/dL, creatinine 1 mg/dL, random blood glucose 266 mg/dL, and sodium 131 mEq/L. The diagnosis of suspected BEV in hepatitis B liver cirrhosis Child-Pugh B class with severe anemia and type-2 diabetes mellitus was made.

EGD examination only revealed small varices in the distal esophagus and obliterated varices due to previous EBL sites (shown in Fig. 1e). It was then decided to perform EUS due to the recurrent melena in the patient with no evidence of large gastroesophageal varices.
EUS examination showed submucosal varices with a large periesophageal collateral vein (peri-ECV) and perforating vein (PV) in the distal esophagus (shown in Fig. 1f). EBL was not a treatment option for this patient because we could only see small varices in the esophageal lumen. EUS-guided CYA injection to the peri-ECV was done, and there was no residual blood flow after CYA injection (shown in Fig. 1g). The patient’s condition was stable, and no bleeding occurred after the procedure.

Discussion

As a result of portal hypertension, BEV is one of the most common causes of mortality in patients with cirrhosis. EUS has improved the diagnostic and therapeutic approach in managing gastroesophageal varices, such as bleeding risk stratification, recurrence prediction, treatment selection, and post treatment evaluation. Looking at both of our cases, EUS was proven to be beneficial for BEV management which is showcased through observation of the esophageal collateral vein (ECV), and EUS-guided intra-variceal CYA injection with no rebleeding reported afterward. CYA is known as an agent of hemostatic. When CYA mixes with blood, it will solidify in 20 seconds and change varices into thrombosis, which can stop the bleeding. Previous study aligns with our present cases where EUS greatly contributes to visualizing better images of esophageal varices and is useful for sclerotherapy treatment and decreasing the risk of rebleeding [5].

Through EUS examination, detailed observation of the varices morphology, including all collateral and deep vessels of the esophageal wall, can be seen in detail; therefore, the hemodynamic-related structures surrounding the esophagus can be observed properly. Hemodynamics of localized esophageal varices includes the peri-ECVs, para-ECVs, and PV. The ECVs often communicate with esophageal varices via PV, serve the lateral esophagus, and greatly contribute to variceal bleeding and recurrence. Meanwhile, conventional endoscopy procedure is only able to observe the esophageal lumen and cannot observe deep varices [6, 7]. On the contrary, in our cases with EUS, we can clearly observe peri-ECVs, para-ECVs, and PV, especially in our second case, where conventional EGD can only observe small varices in the esophageal lumen, while EUS was able to identify large peri-ECV and PV.

Furthermore, many studies have reported the benefit of EUS in managing gastroesophageal varices. Study by Liu et al. [8] showed that EUS enables the detection of gastric varices in the fundus and cardia in 11 out of 23 portal hypertensive patients (48%) which were overlooked by endoscopy. EUS can also be beneficial to evaluate the risk of variceal bleeding by identifying the hematocystic spot on the surface of esophageal varices which strongly associates with a high risk of esophageal variceal rupture. Shibukawa et al. [9] noted the importance of developing an appropriate treatment strategy based on EUS findings. Liao et al. [10] stated that EUS can evaluate the recurrence inhibitory effect of propranolol, which reduces portal vein pressure and is a useful tool to measure ECV and predict recurrence of EV.

In addition, EUS can provide useful information regarding treatment. Several studies reported the implementation of EUS in management of portal hypertension. Lahoti et al. [11] conducted sclerotherapy injection directing to perforating vessels until the flow was completely impeded and reported that dynamic EUS-guided sclerotherapy with color flow Doppler may be safely and effectively used for the treatment of esophageal varices. Previous study also proclaimed the potential of EUS-guided sclerotherapy to decrease the risk of recurrence and diameter of the azygos vein compared to endoscopic sclerotherapy [12, 13]. In our case, both patients were treated with EUS-guided CYA injection successfully without any bleeding recurrence. Furthermore, EUS enabled us to evaluate response after treatment by observing residual blood flow in the varices by using color Doppler EUS.
The absence of residual blood flow in the varices indicates that the therapy was sufficient, as presented in our case.

**Conclusion**

EUS has been showed to be a potential and important tool in diagnosis as well as management of BEV in the aspect of getting more precise risk stratification, predicting recurrence, selecting treatment option, and monitoring post treatment response.

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**Statement of Ethics**

This study has been reviewed and approved by the Ethics Committee of Faculty of Medicine Universitas, Indonesia (Approval no. 0887/UN2.F1/ETIK/2018). Written informed consent was obtained from the patients for publication of this case report and any accompanying images.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

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**Author Contributions**

Kemal Fariz Kalista, Saut Horas Nababan, Cosmas Rinaldi Adithya Lesmana, Irsan Hasan, and Rino Gani are the physicians involved in the cases. Kemal Fariz Kalista and Syifa Amalia Hanif wrote the manuscript in consultation with Cosmas Rinaldi Adithya Lesmana, Irsan Hasan, and Rino Gani. Kemal Fariz Kalista and Cosmas Rinaldi Adithya Lesmana supervised the writing process of the manuscript. Kemal Fariz Kalista, Syifa Amalia Hanif, Saut Horas Nababan, Cosmas Rinaldi Adithya Lesmana, Irsan Hasan, and Rino Gani provided feedback and contributed to the final manuscript.

**Data Availability Statement**

All data generated or analyzed during this study are included in this article. Further inquiries may be directed to the corresponding author.
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