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Therapeutic Algorithm for Duodenal Varices: A Case Series

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ABSTRACT

Background: Duodenal varices cause fatal bleeding and are potentially life-threatening. Treatment guidelines for duodenal varices have not yet been established due to their low incidence. We report a case series of patients with duodenal varices admitted to our hospital between April 2012 and June 2017 and share our therapeutic algorithm for duodenal varices.

Case Report: This is a retrospective case series of six patients with duodenal varices. Three of the cases were emergent, two were elective, and one was prophylactic. Therapeutic options for duodenal varices can be classified into endoscopic and endovascular therapies. Using our algorithm, endoscopic injection sclerotherapy with n-butyl-2-cyanoacrylate, endoscopic band ligation, or balloon-occluded retrograde transvenous obliteration or both, were performed to eradicate the duodenal varices. In two of the emergent cases, rebleeding occurred after successful primary hemostasis by endoscopic band ligation. In these patients, secondary hemostasis was achieved with a combination of endoscopic and endovascular therapies. No recurrences of duodenal varices were reported in any patient.

Conclusion: Duodenal variceal hemorrhage is fatal, and therefore, needs to be treated with an effective therapy as soon as possible. The appropriate treatment method should be chosen on a case-by-case basis considering the hemodynamics and patients' condition.

KEYWORDS: Duodenal varices; Ectopic varices; Endoscopic injection sclerotherapy; Endoscopic band ligation; Balloon-occluded retrograde transvenous obliteration

BACKGROUND

Duodenal varices are a type of ectopic varices associated with portal hypertension and cause fatal bleeding that can be life-threatening.

ing. Therefore, these varices should be treated prophylactically if necessary, and hemostasis must be achieved as soon as possible when bleeding occurs. However, the treatment guidelines for duodenal varices have not been established due to the various unusual factors that may influence decision-making, including the location of the hemorrhage, clinical presentation, and underlying medical disorders. It has been reported that ectopic varices account for between 1% and 5% of all variceal bleeding, and 17% of hemorrhagic ectopic varices are ruptured duodenal varices [1]. The endoscopic diagnosis of duodenal varices can be difficult and is often delayed due to a lack of awareness. Various procedures for the treatment of duodenal varices have recently been reported, includ-

ing Endoscopic Injection Sclerotherapy (EIS) [2-4], Endoscopic Band Ligation (EBL) [4,5], endoscopic clipping [6], Transjugular Intrahepatic Portosystemic Shunt (TIPS) [7], endovascular obliteration (including Balloon-Occluded Retrograde Transvenous Obliteration (BRTO)) [8,9], Percutaneous Transhepatic Obliteration (PTO) [10], and surgery [11]. We report a case series of patients with duodenal varices admitted to our hospital between April 2012 and June 2017 (Table 1) and share our therapeutic algorithm. We have categorized the cases into three types, based on the general rules for the study of portal hypertension, edited by The Japan Society for Portal Hypertension [12]: emergent, elective, and prophylactic (Figure 1).

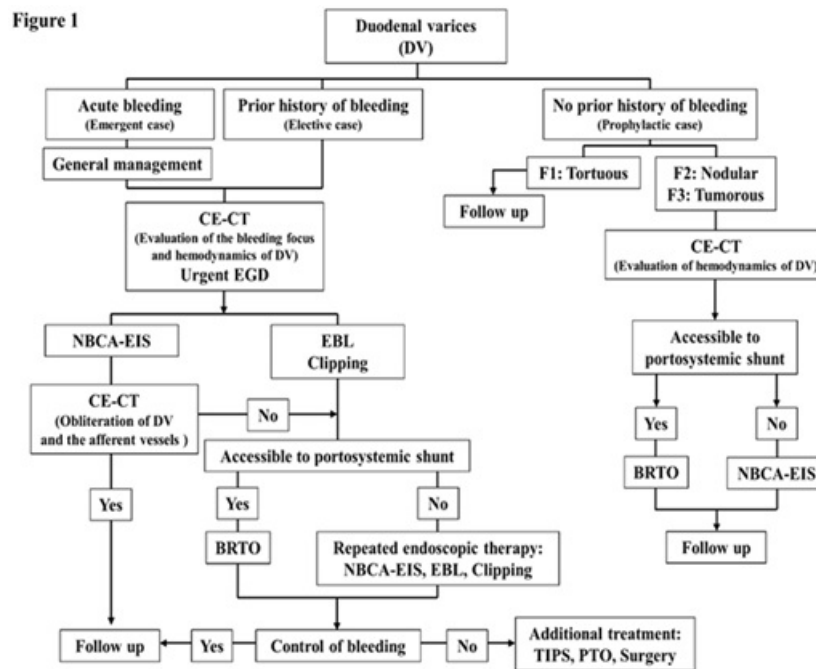


Figure 1: Therapeutic algorithm for duodenal varices

In cases of acute duodenal variceal bleeding (emergent cases) or duodenal varices with a prior history of bleeding (elective cases), urgentEGD and CE-CT should be performed to evaluate the bleeding focus and to assess the variceal hemodynamics. NBCA-EIS should be performed if an experienced endoscopist can access the bleeding point and the varices are tense enough for the successful intravariceal injection of NBCA-Lip. If the conditions do not meet these requirements, band ligation or clipping can be performed to temporize the bleeding. When CE-CT after endoscopic therapy shows residual blood flow in the varices or the afferent vessel, additional treatment is needed. If the varices have portosystemic shunts accessible from efferent vessels, BRTO should be actively considered unless the patient's condition is severe (Child-Pugh class C, uncontrolled ascites, portal vein thrombosis, or renal failure). If there is no accessible portosystemic shunt by BRTO, repeated endoscopic therapies should be attempted, depending on the situation (NBCA-EIS, EBL, and clipping). If bleeding from the varices is not controlled by repeated endoscopic therapies or BRTO, the patient can undergo other therapies such as TIPS, PTO, or surgery. In prophylactic cases, if the varices are nodular or tumorous, and if they have an accessible portosystemic shunt, BRTO should be performed. When the duodenal varices do not have an accessible portosystemic shunt, NBCA-EIS should be performed as a prophylactic treatment.

Abbreviations: DV: Duodenal Varices; CE-CT: Contrast-Enhanced Computed Tomography; EGD: Esophagogastroduodenoscopy; NBCA-EIS: N-Butyl-2-Cyanoacrylate Endoscopic Injection Sclerotherapy; EBL: Endoscopic Band Ligation; BRTO: Balloon-Occluded Retrograde Transvenous Obliteration; TIPS: Transjugular Intrahepatic Portosystemic Shunt; PTO: Percutaneous Transhepatic Obliteration

Table 1: Patient characteristics, and diagnostic and therapeutic information

Case (Category)	Age	Sex	Etiology	Location of DV	Afferent vessels/Efferent vessels	Treatment
1 (Emergent)	46	F	LC (PBC)	Transverse part	Pancreaticoduodenal vein/Right gonadal vein	NBCA-EIS
2 (Emergent)	73	M	LC (Alcohol)	Descending part	Pancreaticoduodenal vein/Right adrenal vein	EBL NBCA-EIS
3 (Emergent)	56	M	LC (HBV)	Descending part	Pancreaticoduodenal vein/Right testicular vein	EBL BRTO
4 (Elective)	66	F	IPH	Descending part	Pancreaticoduodenal vein/Veins of Retzius	NBCA-EIS
5 (Elective)	87	M	LC (HCV)	Afferent loop	Branch of SMV/Veins of Retzius	NBCA-EIS
6 (Prophylactic)	64	M	LC (Alcohol)	Transverse part	Branch of IMV/ Left gonadal vein	BRTO

Abbreviations: DV: duodenal varices; M: male; F: female; LC: liver cirrhosis; HBV: hepatitis B virus; HCV: hepatitis C virus; PBC: primary biliary cholangitis; IPH: idiopathic portal hypertension; SMV: superior mesenteric vein; IMV: inferior mesenteric vein; NBCA-EIS: N-butyl-2-cyanoacrylate- late endoscopic injection sclerotherapy; EBL: endoscopic band ligation; BRTO: balloon-occluded retrograde transvenous obliteration

CASE REPORT

All patients described in this case series provided written informed consent.

EMERGENT CASES

Case 1

A 46-year-old woman with decompensated, Child-Pugh class C cirrhosis secondary to primary biliary cholangitis presented with melena and anemia. An urgent Esophagogastroduodenoscopy (EGD) revealed nodular varices with spurting bleeding in

the transverse part of the duodenum (Figure 2A). EIS using n-butyl-2-cyanoacrylate (NBCA) (NBCA-EIS) was performed with 1.5 mL of 67% NBCA with lipiodol (NBCA-Lip). The accumulation of NBCA-Lip in the varices was confirmed by post-treatment contrast-enhanced computed tomography (CE-CT) (Figure 2B). As the patient's condition was classified as severe (Child-Pugh class C), she was not a candidate for any additional endovascular therapies. The patient was discharged on postoperative day 15, and an EGD performed six months postoperatively revealed shrunken varices (Figure 2C), and an EGD performed one year postoperatively revealed that the varices had disappeared (Figure 2D).

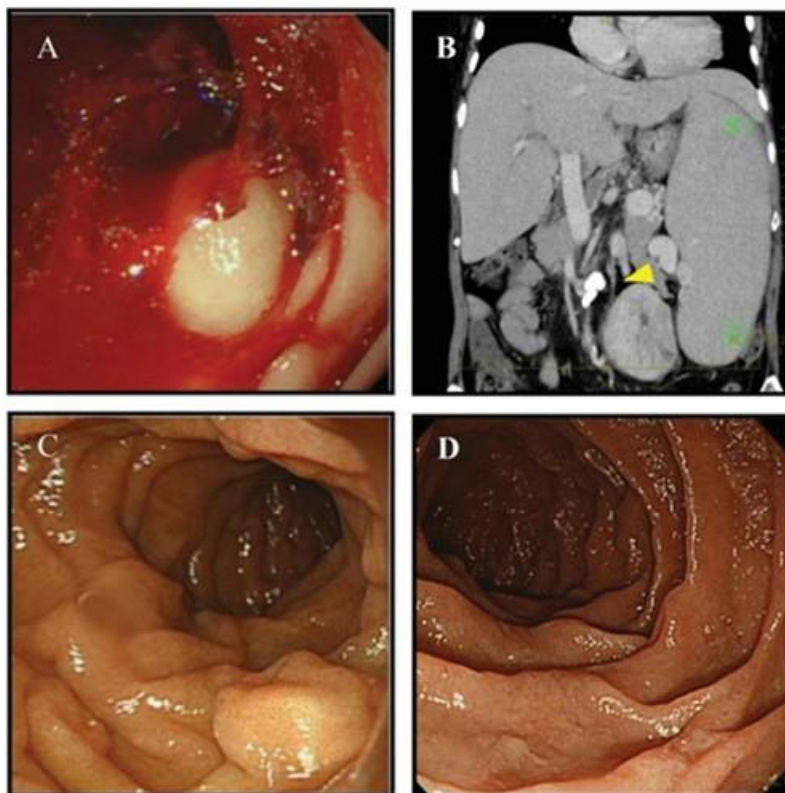


Figure 2: Case 1: NBCA-EIS for emergent duodenal varices bleeding

- A. An EGD reveals nodular varices with spurting bleeding in the transverse part of the duodenum.
- B. A post-NBCA-EIS CE-CT reveals accumulation of NBCA with lipiodol (arrowhead) in the varices.
- C. An EGD obtained six months postoperatively reveals shrunken varices.
- D. An EGD obtained one year postoperatively reveals that the varices have disappeared.

Abbreviations: NBCA-EIS: N-Butyl-2-Cyanoacrylate Endoscopic Injection Sclerotherapy; CE-CT: Contrast-Enhanced Computed Tomography; EGD: Esophagogastroduodenoscopy

Case 2

A 73-year-old man with a history of melena and hematemesis is referred to our hospital from an outside hospital for advanced therapy of duodenal varices secondary to alcoholic cirrhosis with portal hypertension. He had undergone EBL for primary hemostasis of ruptured duodenal varices (Figure 3A) at the outside hospital one day prior to being transferred to our hospital. A CE-CT revealed extravasation of contrast media in the duodenum (Figure 3B) and the development of collateral vessels. The afferent vessel was the pancreaticoduodenal vein and the efferent vessel was the right

adrenal vein. An urgent EGD showed that the ligated band had fallen off. Nodular varices with red plugs in the descending part of the duodenum were observed (Figure 3C). The patient underwent NBCA-EIS with 2.5 mL of 67% NBCA-Lip to achieve secondary hemostasis (Figure 3D). A postoperative CE-CT revealed complete obstruction of the varices (Figure 3E) and complete thrombosis of the afferent vessel with NBCA-Lip. An EGD obtained one year after the NBCA-EIS revealed that the varices had disappeared (Figure 3F) and no recurrences of duodenal varices have occurred for three years post-operatively.

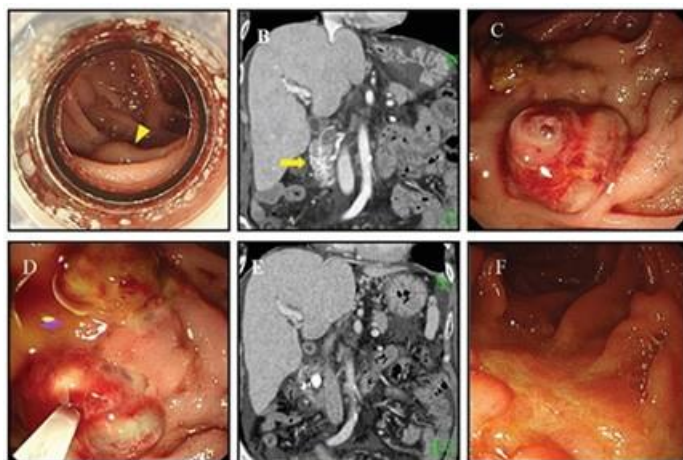


Figure 3: Case 2: EBL followed by NBCA-EIS for emergent duodenal varices bleeding

- A. An EGD obtained at an outside hospital shows tortuous duodenal varices with erosion (arrowhead).
 B. At our hospital, a post-EBL CE-CT reveals extravasation of contrast media in the duodenum (arrow) and the development of collateral vessels.
 C. An EGD reveals that the ligated band has fallen off. Nodular varices with red plugs are also seen.
 D. Hemostasis is achieved via the injection of 2.5 mL of 67% NBCA-Lip into the varices.
 E. A postoperative CE-CT reveals complete obstruction of the varices and complete thrombosis of the afferent vessel with NBCA-Lip.
 F. An EGD obtained one year post-NBCA-EIS reveals that the varices have disappeared.

Abbreviations: EBL: Endoscopic Band Ligation; NBCA-EIS: N-Butyl-2-Cyanoacrylate Endoscopic Injection Sclerotherapy; CE-CT: Contrast-Enhanced Computed Tomography; EGD: Esophagogastroduodenoscopy; NBCA-Lip: N-Butyl-2-Cyanoacrylate with Lipiodol

Case 3

A 56-year-old man with hepatitis B virus-related liver cirrhosis presented with melena and was admitted to our hospital for treatment of obscure gastrointestinal bleeding. Although EGD, colonoscopy, and dynamic CT had been performed at an outside hospital, no bleeding lesions were identified. A CT angiography performed at our hospital demonstrated bleeding duodenal varices with collateral vessels (Figure 4A). An urgent EGD revealed varices with gushing bleeding in the descending part of the duodenum (Figure 4B). We performed EBL to temporarily stop the acute variceal bleeding, as the varices were flattened (Figure 4C). BRTO was scheduled for post-EBL day 2 as an additional treatment; however, the patient presented with hemorrhagic shock on the morning of post-EBL day

2. An urgent EGD revealed that the ligated band had fallen off, and EBL was repeated to stop the variceal bleeding. Immediately after hemostasis, the patient underwent BRTO with the aim of eradicating the varices. A balloon catheter was advanced into the right testicular vein, and retrograde venography was performed. After placing an embolic coil in the outflow of the shunt, 4 mL of 5% ethanolamine oleate with iopamidol (EOI) was infused to fill the varices under fluoroscopic guidance (Figure 4D). An EGD obtained on post-BRTO day 4 revealed tense varices with no signs of bleeding (Figure 4E), and an EGD obtained six months post-BRTO revealed shrunken varices (Figure 4F). A post-treatment CE-CT revealed complete thrombosis in the varices and the afferent vein, and no recurrences of duodenal varices have occurred for five years post-treatment.

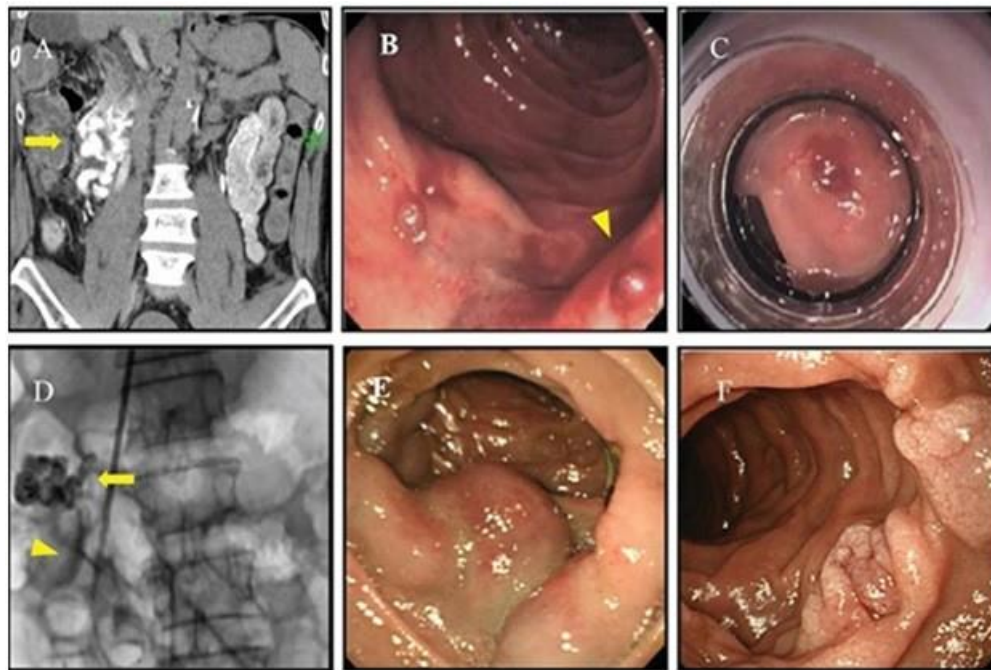


Figure 4: Case 3: EBL followed by BRTO for emergent duodenal varices bleeding

A. A CT angiography demonstrates extravasation of contrast media from the duodenal varices (arrow).

B. An urgent EGD reveals flattened varices with gushing bleeding (arrowhead) in the descending part of the duodenum.

C. An EBL is performed to temporize the acute variceal bleeding.

D. A balloon catheter is advanced into the right testicular vein (arrowhead), and retrograde venography is performed. After placing an embolic coil in the outflow of the shunt, the varices are filled with 4 mL of 5% EOI injected under fluoroscopic guidance.

E. An EGD obtained four days post-BRTO shows that the varices are tense with no signs of bleeding.

F. An EGD obtained six months post-BRTO reveals shrunken varices.

Abbreviations: EBL: Endoscopic Band Ligation; BRTO: Balloon-Occluded Retrograde Transvenous Obliteration; CT: Computed Tomography;

ELECTIVE CASES

Case 4

A 66-year-old woman with idiopathic portal hypertension was referred to our hospital for the management of pancytopenia and splenomegaly. On admission, she had episodes of melena and anemia. A CE-CT revealed duodenal varices with collateral vessels. The afferent vessel was the superior pancreaticoduodenal vein and the efferent vessels were the veins of Retzius that led into the inferior vena cava (Figure 5A). An EGD revealed tumorous varices with erosion in the descending part of the duodenum (Figure 5B). EIS was performed using 1.5 mL of 67% NBCA-Lip. ACE-CT at one-week post-NBCA-EIS showed complete thrombosis in the afferent vein and obliteration of the varices with NBCA-Lip (Figure 5C). An EGD obtained one year postoperatively revealed no signs of recurrence (Figure 5D).

Case 5

An 87-year-old man with hepatitis C virus-related liver cirrhosis

and a history of partial gastrectomy with Billroth-II reconstruction was transferred to our hospital for the management of melena. Although an EGD and a colonoscopy had been performed at the outside hospital, no evidence of bleeding was found. A CE-CT performed at our hospital revealed varices in the afferent loop and collateral vessels around the duodenum. We performed single-balloon endoscopy, as the location of the varices would be difficult to reach using a standard endoscope. The single-balloon endoscopy revealed nodular varices with minor erosion in the afferent loop of the duodenum (Figure 6A). These varices were considered the bleeding focus. We injected 1.5 mL of 67% NBCA-Lip into the varices (Figure 6B, 6C). An abdominal CT obtained one week postoperatively demonstrated NBCA-Lip in the varices and the afferent vessel (Figure 6D); thus additional treatment was unnecessary. The patient was discharged in stable condition on post-operative day 9.

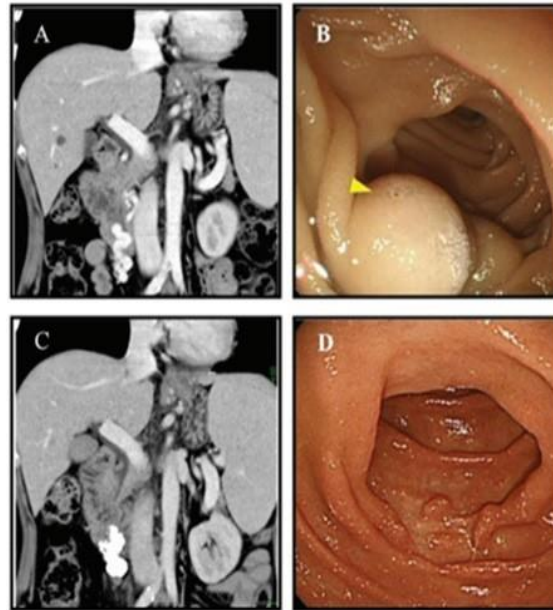


Figure 5: Case 4: NBCA-EIS for the elective treatment of duodenal varices

A. A CE-CT reveals duodenal varices and collateral vessels.

B. An EGD reveals tumorous varices with erosion (arrowhead) in the descending part of duodenum.

C. A CE-CT obtained one week postoperatively shows complete thrombosis of the afferent vein and obliteration of the varices with NBCA-Lip.

D. An EGD obtained one year postoperatively reveals that the varices have disappeared.

Abbreviations: NBCA-EIS: N-Butyl-2-Cyanoacrylate Endoscopic Injection Sclerotherapy; CE-CT: Contrast-Enhanced Computed Tomography; EGD: Esophagogastroduodenoscopy; NBCA-Lip: N-Butyl-2-Cyanoacrylate with Lipiodol

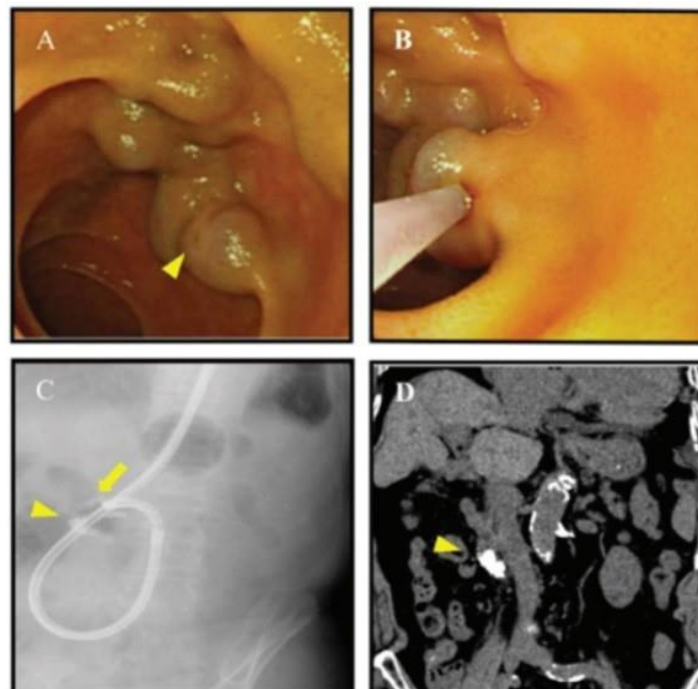


Figure 6: Case 5: NBCA-EIS using a single-balloon endoscope for the elective treatment of duodenal varices

A. A single-balloon endoscopy shows nodular varices with red plugs (arrowhead).

B. The varices are filled with 1.5 mL of 67% NBCA-Lip.

C. A plain radiograph of the abdomen during the NBCA-EIS procedure shows the NBCA-Lip in the duodenal varices (arrowhead) and in part of the afferent vessel (arrow).

D. An abdominal CT obtained one week post-NBCA-EIS shows NBCA-Lip in the varices (arrowhead) and the afferent vessel.

Abbreviations: NBCA-EIS: N-Butyl-2-Cyanoacrylate Endoscopic Injection Sclerotherapy; NBCA-Lip: N-Butyl-2-Cyanoacrylate with Lipiodol; CT: Computed Tomography

PROPHYLACTIC CASE

Case 6

A 64-year-old man with alcoholic cirrhosis was referred to our hospital for an anemia workup. An EGD revealed nodular varices in the horizontal part of the duodenum with no signs of bleeding (Figure 7A). A CE-CT revealed duodenal varices arising from the branches of the inferior mesenteric vein and the efferent vessel drained through the left gonadal vein (Figure 7B). We performed

BRTO as prophylactic therapy for the duodenal varices. Retrograde venography was performed while the outflow tract was occluded with the balloon, and the varices and the afferent vessel were visualized (Figure 7C). We injected 18 mL of 5% EOI to fill the varices under fluoroscopic guidance. A CE-CT obtained one month postoperatively revealed a complete thrombus in the varices and afferent vessel (Figure 7D). A CE-CT and an EGD at six months post-BRTO revealed that the varices had disappeared (Figure 7E, 7F).

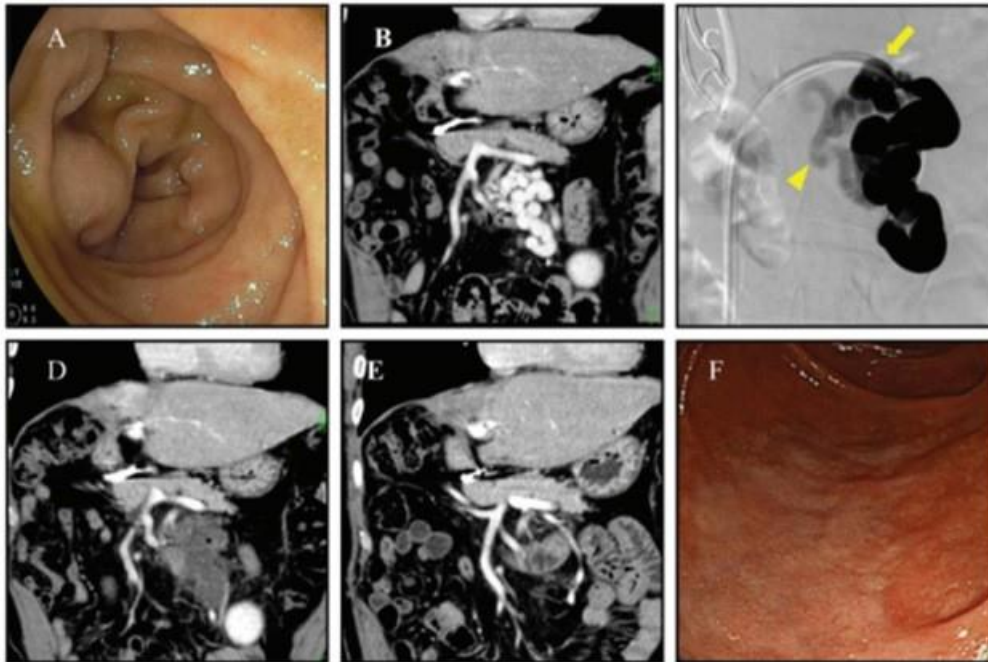


Figure 7: Case 6: Prophylactic BRTO for duodenal varices

A. An EGD reveals nodular varices in the horizontal part of the duodenum with no signs of bleeding.

B. A CE-CT reveals that the duodenal varices arise from the branches of the IMV and the efferent vessel drains through the left gonadal vein.

C. A retrograde venography obtained while the outflow tract was occluded with the balloon shows the varices (arrow) and the afferent vessel (arrow-head).

D. A CE-CT obtained one month postoperatively reveals complete thrombosis of the varices and the afferent vessel. At six months post-BRTO

E A CE-CT

F. An EGD reveal the disappearance of the varices.

Abbreviations: BRTO: Balloon-Occluded Retrograde Transvenous Obliteration; EGD: Esophagogastroduodenoscopy; CE-CT: Contrast-Enhanced Computed Tomography; IMV: Inferior Mesenteric Vein.

DISCUSSION

We proposed an algorithm for the treatment of duodenal varices based on cases that we had experienced. Prior to treatment, it is important to evaluate the variceal hemodynamics and hepatic function of the patient, and to estimate the patient's prognosis in order to make the appropriate decision regarding which therapeutic strategy to perform. From an anatomical perspective, duodenal varices typically consist of a single vessel with associated afferent and efferent vessels that form a portosystemic shunt [13]. The afferent vessel often arises from the superior or inferior pancreaticoduodenal vein, cystic branch of the superior mesenteric vein,

pyloric vein, or gastro duodenal vein. The efferent vessels often arise from the gonadal vein, capsular renal vein, or the vein of Retzius and ultimately drain into the inferior vena cava [14].

In our algorithm, the therapeutic options are classified as endoscopic endovascular (Figure 1). Important factors in the therapeutic strategies for duodenal varices include reliable hemostasis as soon as possible and the prevention of rebleeding in cases with active bleeding or a bleeding history. In addition, the obliteration not only of varices themselves, but also of the afferent vessels is undertaken in order to prevent variceal recurrence.

In cases of acute duodenal variceal bleeding (emergent cases) or

duodenal varices with a prior history of bleeding (elective cases), an urgent EGD and CE-CT should be performed under the management of general conditions to evaluate the bleeding focus and assess variceal hemodynamics. An NBCA-EIS should be performed if an experienced endoscopist can access the bleeding point and the varices are tense enough for the successful intravariceal injection of NBCA-Lip. If the conditions do not meet these requirements, band ligation or clipping can be performed to temporize the bleeding. When a CE-CT after endoscopic therapy shows residual blood flow in the varices or the afferent vessels, additional treatment is required to prevent rebleeding or the recurrence of duodenal varices or both. If varices have portosystemic shunts that are accessible from efferent vessels, BRTO should be considered unless the patient's condition is severe (Child-Pugh class C, uncontrolled ascites, portal vein thrombosis, or renal failure). If there is no accessible portosystemic shunt by BRTO, repeated endoscopic therapies should be performed, depending on the situation (NBCA-EIS, EBL, and clipping). If bleeding from varices is not controlled by repeated endoscopic therapies or BRTO, patients can undergo other therapies such as TIPS, PTO, or surgery.

Unlike esophageal varices, it is difficult to predict acute bleeding from duodenal varices. Therefore, when duodenal varices are found on EGD or CE-CT, the patient should be counseled regarding the risk of bleeding, and if the varices are nodular or tumorous, we recommend a prophylactic treatment even though predicting rupture of duodenal varices is difficult. If they have an accessible portosystemic shunt, BRTO should be performed. When the duodenal varices do not have an accessible portosystemic shunt, NBCA-EIS should be performed as a prophylactic treatment.

Several studies have reported that EBL and NBCA-EIS are useful first-line therapies for bleeding duodenal varices, as they can be performed faster than other methods [2,3]. EBL is an easier technique than NBCA-EIS; however, EBL is only effective in the short term and for small varices [15]. Peristalsis and segmental contractions frequently occur in the duodenum and may result in the ligated band falling off [16], as occurred in cases 2 and 3 in this series. In both of these patients, the ligated bands fell off within two days of the EBL procedure and the varices started rebleeding. Therefore, additional treatment should be scheduled as soon as possible. The NBCA-EIS procedure can eradicate duodenal varices and collateral vessels. However, a risk of post-procedural perforation has been reported [17], and NBCA can lead to complications such as pulmonary embolism [18]. We performed NBCA-EIS in four cases presented in this series (cases 1, 2, 4, and 5) with no complications. The absence of complications after NBCA-EIS in this series may be attributed to the fact that we performed NBCA-EIS only for nodular or tumorous varices in order to avoid paravariceal injections of sclerosants, and we used a balloon endoscope to maintain a view of the varices in the distal duodenum during treatment.

When the varices were flattened after bleeding, we performed EBL to safely obtain primary hemostasis before performing an additional treatment, following the algorithm. Moreover, we used 67% NBCA-Lip based on a previous report suggesting that a concentration of at least 62.5% should be used in treating gastric fundal varices [19].

As mentioned above, BRTO can be performed as an additional treatment following endoscopic therapies or as a first-line treatment for prophylaxis of ruptured duodenal varices. BRTO is a less invasive and more effective procedure for treating isolated gastric varices with portosystemic shunts [20,21]. However, when BRTO is performed on acute, hemorrhagic duodenal varices without any primary treatment, it may promote variceal bleeding due to an increase in portal venous and intravariceal pressure resulting from the balloon occlusion. Therefore, we do not suggest BRTO for emergent cases without any prior endoscopic hemostasis, as in case 3 of this series.

Duodenal variceal bleeding may achieve hemostasis without treatment due to a temporary decrease in blood pressure. However, the varices eventually rebleed, which can be fatal. Duodenal varices with recent bleeding signs, such as tiny erosions or white or red plugs should be treated as soon as possible, as in cases 4 and 5 of this series, as well as ongoing variceal bleeding.

Following BRTO or endoscopic therapies, careful monitoring for the presence of postprocedural complications reflecting aggravated portal hypertension is necessary. The aggravation of non-duodenal varices appears to be a major long-term adverse effect. TIPS has been widely performed in patients with portal hypertension, especially in Western countries. However, TIPS has not been approved by the Ministry of Health Labor and Welfare in Japan, and is not commonly performed compared to endoscopic therapies or other endovascular therapies. Thus, to control post-treatment portal pressure elevation, the administration of nonselective beta-blockers or partial splenic embolization or both [22], should be considered to reduce the risk of postprocedural complications. This study has several limitations, such as being a single-center study and a small number of patients. Due to the wide variety of duodenal variceal anatomy and variable institutional expertise, establishing a treatment guideline for duodenal varices is challenging. More research is necessary in large cohorts from multiple institutions to develop a more generalizable therapeutic strategy for duodenal varices.

CONCLUSION

Duodenal variceal hemorrhage is fatal and should be treated with an appropriate strategy as soon as possible. The best treatment for each patient with duodenal varices should be determined on a case-by-case basis considering hemodynamics and patients' condition. We have reported a case series of duodenal varices, and proposed a useful therapeutic algorithm.

Author Contributions

Matsuda T and Ihsikawa T contributed to manuscript drafting; Sasaki R, Nishimura T and Iwamoto T were in charge of the patients; Takami T and Sakaida I were responsible for the revision of the manuscript for important intellectual context; all authors issued final approval for the version to be submitted.

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