—Case Reports—

Esophagogastric Varix Caused by Extrahepatic Portal Vein Obstruction with Essential Thrombocythemia: A Case Report

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Extrahepatic portal vein obstruction (EHPVO) is a rare disease-causing form of portal hypertension. Myeloproliferative neoplasm (MPN) including essential thrombocythemia (ET) is a reported risk factor for EHPVO due to underlying persistent thrombophilia. A Japanese woman in her 40s was referred to our hospital with a 1-month history of gastric variceal bleeding due to EHPVO. Laboratory investigation showed thrombocytosis despite portal hypertension. She had a mutation in clonal marker JAK2V 617F with EHPVO, which prompted us to consult a hematologist. A bone marrow biopsy revealed megakaryocyte lineage proliferation, which confirmed a diagnosis of ET. Esophagogastroduodenoscopy revealed esophagogastric varices (LsF2CbRC2, Lg-cF1RC1), and abdominal computed tomography and angiography revealed splenomegaly and portal vein thrombosis with cavernous transformation, which suggested EHPVO. The patient had a history of ruptured esophagogastric varices and required prophylaxis against further variceal bleeding before antithrombotic therapy for EHPVO with ET. We performed laparoscopic Hassab's operation followed by endoscopic variceal ligation (EVL) and hematological cytoreduction therapy. Laparoscopic Hassab's operation and three bi-monthly EVL procedures improved the esophagogastric varix (LmF0RC0, Lg-f F0RC0) at 6 months after surgery. Cytoreduction therapy reduced platelet count to 60.1 × 10^4/uL, and the patient was very healthy at 7 months after surgery. Patients with EHPVO are traditionally referred to a gastroenterologist for abdominal pain, intestinal bleeding, or refractory ascites; however, hypercoagulative disease may be occult in such patients and require the attention of a hematologist. When treating patients with EHPVO, gastroenterologists should screen for hematological disease, including MPN. (J Nippon Med Sch 2024; 91: 541–547)

Key words: extrahepatic portal vein obstruction, esophagogastric varices, essential thrombocythemia, JAK2V617F mutation, laparoscopic Hassab's operation

Introduction

Extrahepatic portal vein obstruction (EHPVO) is a rare disease and an important cause of portal hypertension. Injury or congenital anomalies of the portal vein, systemic inflammation, dehydration, and hypercoagulability are factors that increase the risk of EHPVO[1]. Myeloproliferative neoplasm (MPN) including essential thrombocythemia (ET) is a reported risk factor for EHPVO because of underlying persistent thrombophilia[2]. Herein, we report a rare case of EHPVO with ET.

Case Presentation

A Japanese woman in her 40s with a 1-month history of gastric variceal bleeding due to EHPVO was referred to our hospital. The referring hospital used endoscopic variceal ligation (EVL) to control bleeding from the gastric varices. The patient's past medical history was unremarkable. On physical examination, the spleen was palpable 12 cm along its long axis in the left hypochondriac region. No pretibial edema or conjunctival icterus was observed.

Laboratory tests (**Table 1**) showed thrombocytosis (457

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Table 1 Laboratory findings

Variable	unit		reference range
White-cell count	$\times 10^3$/uL	8.6	3.3-8.6
Red-cell count	$\times 10^6$/uL	**3.56**	3.86-4.92
Hemoglobin	g/dL	**9.3**	11.6-14.8
Platelet count	$\times 10^4$/uL	**45.7**	15.8-34.8
Prothrombin-time international normalized ratio		1.21	
APTT	second	37.3	24.0-39.0
D-dimer	ug/mL	0.6	<0.5
Antithrombin III	%	93	80-120
Protein S	%	**53.4**	64-146
Protein C	%	88	64-149
Aspartate aminotransferase	U/L	20	13-30
Alanine aminotransferase	U/L	23	7-23
Alkaline phosphatase	U/L	108	38-113
Total protein	g/dL	7.2	6.6-8.1
Albumin	g/dL	3.9	4.1-5.1
Total Bilirubin	mg/dL	0.8	0.4-1.5
Blood urea nitrogen	mg/dL	11.6	8.0-20.0
Creatinine	mg/dL	0.58	0.46-0.79
Hepatitis B surface antigen		negative	negative
Hepatitis B core antibody		negative	negative
Hepatitis C antibody		negative	negative
hyaluronic acid	ng/mL	23.8	<50.0
M2BPGi	C.O.I.	1.76	<1.00
anti-nuclear antibody		40	<40
anti-mitochondrial M2 antibody		1.5	<6.9
JAK2V617F mutation		**positive**	negative

APTT: activated partial thromboplastin time
M2BPGi: Mac-2 binding protein glycosylated isomers
C.O.I.: cut off index

$\times 10^3$/uL), despite the existence of portal hypertension, and anemia with a hemoglobin level of 9.3 g/dL, a red cell count of 3.56 $\times 10^6$/uL, and a normal leukocyte count. Hepatic and renal parameters were normal. The findings of coagulation testing were normal, except for a slight decrease in Protein S (53.4%). However, she had a mutation of clonal marker JAK2V617F with EHPVO, which prompted a consultation with a hematologist. A bone marrow biopsy revealed megakaryocyte lineage proliferation. There was no significant proliferation of granulocytes or the red cell line in bone marrow. These hematological findings were consistent with a diagnosis of ET.

Esophagogastroduodenoscopy (**Fig. 1**) indicated esophageal varices (LsF2CbRC2 RWM) and gastric varices (Lg-c F1RC1)[3]. Abdominal computed tomography (CT) revealed splenomegaly and portal vein thrombosis extending to the superior mesenteric vein and splenic vein (**Fig. 2a**). CT also demonstrated cavernous transformation indicating numerous vascular structures around the region of the portal vein, which were enhanced during the portal venous phase (**Fig. 2b**). CT showed no evidence of liver cirrhosis (**Fig. 2c**). Angiographic evaluation (**Fig. 3**) indicated extrahepatic portal vein thrombosis contiguous to the superior mesenteric vein and splenic vein with cavernous transformation. These radiologic findings confirmed EHPVO. Angiography also showed that superior mesenteric vein blood flow supplied the esophagogastric varices via collateral veins. The patient had a history of bleeding from gastric varices and re-

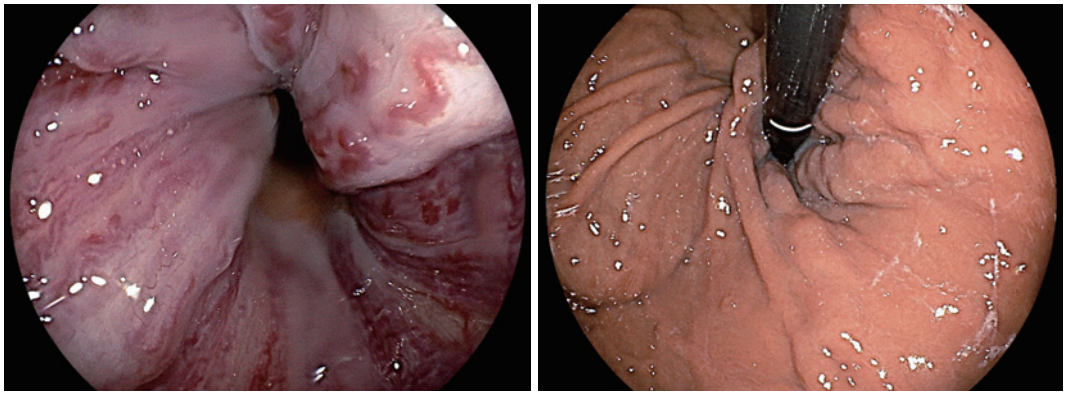


Fig. 1 Esophagogastroduodenoscopy showed esophageal varices (a) and gastric varices (b). Esophageal varices and gastric varices were classified as LsF2CbRC2 RWM and Lg-c F1RC1, respectively.

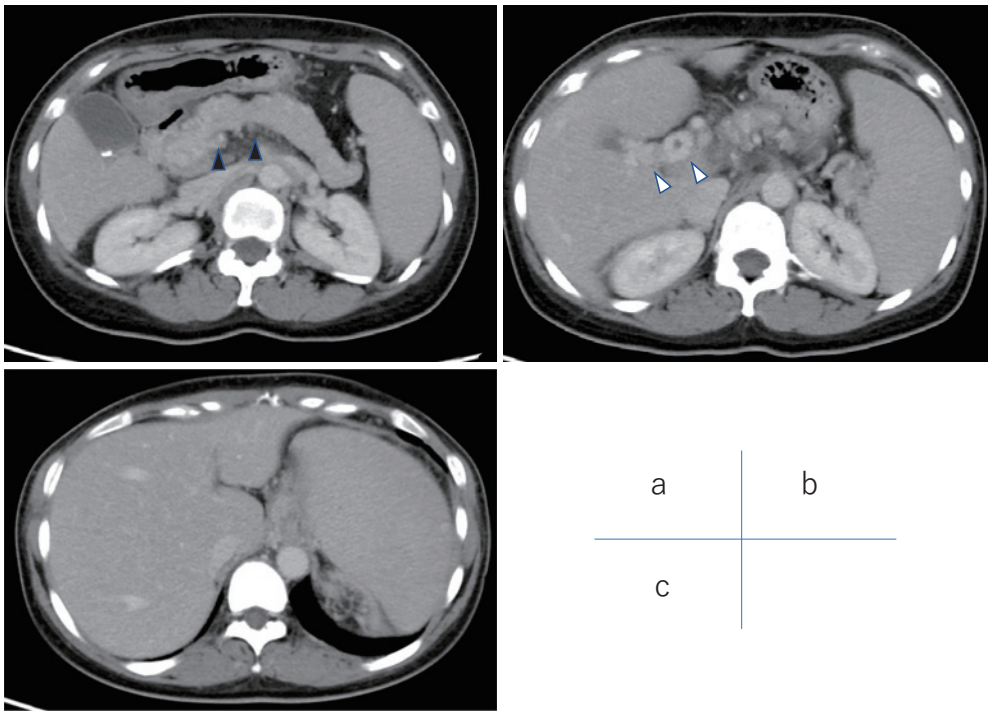


Fig. 2 CT revealed portal vein thrombosis extending to the superior mesenteric vein and splenic vein (a black arrow) and cavernous transformation suggesting numerous vascular structures around the portal vein (b white arrow) and no liver cirrhosis (c).

quired prophylaxis against further esophagogastric varices before antithrombotic therapy for EHPVO with ET.

We selected laparoscopic Hassab's operation, which involves splenectomy and devascularization with perigastroesophageal vessels. In this case, splenic artery clipping in the region of the pancreas body for splenic blood supply control and devascularization for greater curvature of stomach was performed before splenectomy. Division by clipping of the splenic artery and vein in the splenic hilum completed the splenectomy. After removing the spleen, devascularization of the gastric lesser curvature and lower esophagus was followed by clipping division of the left gastric artery and vein and complete laparoscopic Hassab's operation. The absence of liver cirrhosis was confirmed during laparoscopy. Total operation time was 357 minutes and intraoperative body fluid loss was 750 mL.

On postoperative day 1, continuous intravenous infusion of heparin was started to prevent portal thrombosis enlargement and was changed to oral aspirin on day 4 after consultation with a hematologist. On postoperative

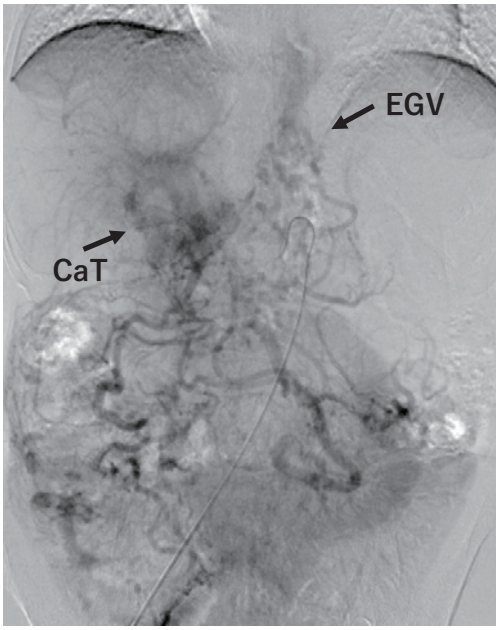


Fig. 3 Angiographic evaluation indicated portal vein thrombosis occupying the superior mesenteric vein and splenic vein with cavernous transformation. Superior mesenteric vein blood flow supplied the esophagogastric varices.
CaT: cavernous transformation, EGV: esophagogastric varices

day 4, the patient was started on enteral nutrition, with no delay in gastric emptying. The patient developed postoperative thrombocytosis due to ET and reached a platelet count of 222 × 10^4/uL on day 10. Thrombocytosis due to ET was treated by cytoreduction therapy (hydroxyurea and anagrelide) administered by a hematologist.

The first EVL was performed on postoperative day 16, in accordance with the bimonthly EVL method[4]. The patient was discharged from hospital on the 22nd postoperative day after the first EVL for esophageal varices and cytoreduction therapy for ET.

Completion of laparoscopic Hassab's operation and three bimonthly EVL improved the esophagogastric varix indicating LmF0RC0 and Lg-f F0RC0 (**Fig. 4**) 6 months after surgery. Platelet count decreased to 60.9 × 10^4/uL by hematological cytoreduction therapy. She was very healthy at 7 months after surgery.

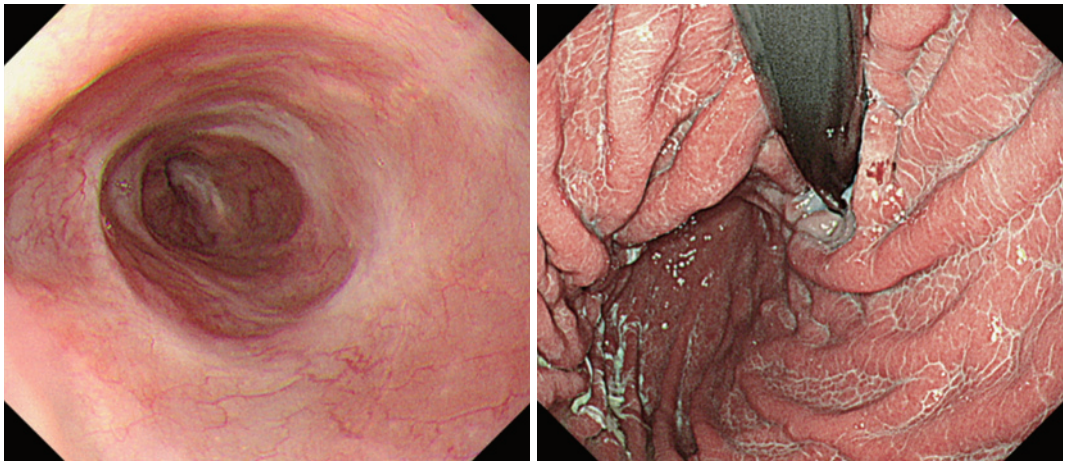
Discussion

EHPVO is the obstruction of the extrahepatic portal vein, with or without involvement of the intrahepatic portal veins or other segments of the splanchnic venous axis. It does not include isolated thrombosis of the splenic or superior mesenteric vein. EHPVO is characterized by features of recent thrombosis or portal hypertension with portal cavernous transformation as a sequela of portal vein obstruction. Cirrhosis, other underlying liver diseases, and malignancy should be excluded, as portal thrombosis in those contexts should be regarded as a different entity[5]. EHPVO is a rare disorder, with an estimated incidence in Europe of 3.78 per 100,000 adults[6].

The diagnosis and treatment of EHPVO was reviewed in the Baveno VI workshop held in 2015, where a consensus statement was issued[5]. All EHPVO patients in which thrombosis has not been recanalized should be screened for gastrointestinal varices[5]. To control acute variceal bleeding, endoscopic therapy is effective[5]. Endoscopic management includes endoscopic variceal ligation (EVL) and endoscopic injection sclerotherapy (EIS), which are equally efficacious for variceal eradication. However, EVL is preferred because it is simple and results in fewer complication[4,7,8]. Yoshida et al.[4] reported that EVL performed bimonthly for treatment of esophageal varices yielded better results than the same treatment performed biweekly.

Baveno VI[5] suggests that beta blockers are as effective as endoscopic ligation therapy for secondary prophylaxis; therefore, beta blockers should also be considered for EHPVO patients in a portal hypertensive state. In cases of EHPVO with marked hypersplenism and repeated esophagogastric variceal bleeding, Hassab's operation and selective shunt surgery are recommended. Hassab's operation involves splenectomy and devascularization with perigastroesophageal vessels. Procedures for Hassab's operation are usually easier than those for shunt surgery. Thus, it tends to be the preferred surgical option. Hassab's operation is very effective for gastric varices and hypersplenism; however, esophageal varices often remain because of the existence of submucosal blood supply from the stomach to lower esophagus. Therefore, endoscopic treatment including EIS and EVL should be performed in addition to Hassab's operation to eradicate esophageal varices[9]. Laparoscopic Hassab's operation is less invasive than open surgery and has gradually become the preferred option with the improvement of laparoscopic procedures and instrumentation[10]. The Meso-Rex shunt should be considered for all children with chronic EHPVO, as it produces a mesenteric-left portal vein bypass via an autologous graft and decompresses portal pressure[11].

Antithrombotic therapy for EHPVO should be administered after adequate portal hypertensive bleeding prophylaxis has been initiated[5,12]. Anticoagulant therapy is



a b

Fig. 4 Esophagogastroduodenoscopy at 6 months postoperatively showed marked improvement of esophageal varices (a) and gastric varices (b). Esophageal varices and gastric varices were classified as LmF0RC0 and Lg-cF0RC0, respectively.

recommended for at least 6 months, and long-term anticoagulation administration is indicated for EHPVO patients with underlying persistent thrombophilia state. In adults, EHPVO is frequently associated with risk factors for other thrombosis, which may be occult at presentation and should be included in screening[5,13]. The Guideline of the Japanese Society of Hematology[14] recommends low-dose aspirin and cytoreduction therapy, including hydroxyurea and anagrelide, in ET patients at high risk of thrombosis. A recent report[15] recommended systemic anticoagulation for ET patients with venous thrombosis, and the addition of aspirin is reasonable when cardiovascular risk is a concern. Antithrombotic therapy in ET differs in relation to the site of thrombosis and hematological condition. Gastroenterologists are often concerned by the thrombohemorrhagic complications of EHPVO in hematological disorders and should consult with hematologists regarding administration of antithrombotic therapy. In the present case, portal hypertensive bleeding prophylaxis treatment by Hassab's operation and EVL before aspirin was important for subsequent indispensable antithrombotic treatment for EHPVO with ET.

The cause of EHPVO can be detected in most patients and includes abnormal angiogenesis, antiphospholipid syndrome, paroxysmal nocturnal hemoglobinuria, and MPN. In a third of patients with EHPVO, no risk factor can be identified[16]. Among these disorders, MPN is reported to be the most common cause of EHPVO[2,17]. MPN includes chronic idiopathic myelofibrosis, polycythemia vera, and ET.

JAK2 tyrosine kinase causes cytokine-independent activation of the JAK-STAT pathway, resulting in proliferation of mature myeloid cells[18]. It was reported that 16-35% of EHPVO patients had a clonal mutation in JAK2V 617F, which increases the risk of thrombosis[17,19]. Previous studies reported that the JAK2V617F mutation is present in up to 95% of patients with polycythemia vera and in about 50% of patients with ET[20,21]. The JAK2V617F mutation was also shown to be an independent risk factor for splanchnic vein thrombosis[2,19,22]. Patients with splanchnic vein thrombosis, including EHPVO and Budd-Chiari syndrome in adults, should be screened for the JAK2V617F mutation[23].

Protein C, Protein S, and antithrombin III (AT III) deficiencies are also reported to be associated with EHPVO pathogenesis[8,16]. Protein C, Protein S, and AT III deficiencies were detected in 3.9%, 2%, and 4.1% of EHPVO cases, respectively[19]. Because these underlying prothrombotic conditions may be present in patients with EHPVO, the risk of hypercoagulability should always be considered in EHPVO patients. Despite the presence of severe hypersplenism due to EHPVO, platelet counts greater than 20×10^4/uL are characterized by MPN. Gastroenterologists examining EHPVO should always suspect hematological disorders as comorbidities[13].

Most patients with EHPVO and Budd-Chiari syndrome are referred to a gastroenterologist for abdominal pain, intestinal bleeding, or refractory ascites; however, hypercoagulative diseases may be occult in these patients and require treatment by a hematologist[24,25]. When encountering patients with splanchnic thrombosis caused by EHPVO and Budd-Chiari syndrome, the gastroenterologist

or surgeon should screen for hematological disease, including MPN, and share the patient's information with hematologists, if necessary.

We experienced a surgical case of esophagogastric varices due to EHPVO with ET. Patients with an elevated platelet count despite portal hypertension due to EHPVO should be screened for MPN, including ET.

Conflict of Interest: None declared.

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