Recurrent Variceal Bleeding Due to Non-Cirrhotic Portal Hypertension in a Patient with Primary Myelofibrosis: Case Report

Debora Sitorus, Bariani Anwar, Anastasia Asylia Dinakrisma

Department of Internal Medicine, Faculty of Medicine,
Universitas Indonesia/RSUPN Dr. Cipto Mangunkusumo Jakarta

Corresponding author:
Debora Sitorus, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia/RSUPN Dr. Cipto Mangunkusumo Jakarta, deboraeydia26@gmail.com

ABSTRACT

Acute upper gastrointestinal bleeding may arise from variceal or non-variceal sources. Primary myelofibrosis, classified as a subtype of myeloproliferative neoplasms, represents an uncommon clinically significant etiology of non-cirrhotic portal hypertension. The authors reported a case of a 39-year-old woman with recurrent variceal bleeding for six years. She presented with progressive weight loss, splenomegaly, and severe anemia. One year before her first episode of hematemesis, a bone marrow biopsy revealed myelofibrosis grade 2, and JAK2 V617F mutation was positive, confirming primary myelofibrosis. The treatment was discontinued due to high expense. Abdominal ultrasonography showed portal hypertension and changes suggestive of cirrhosis. She underwent successful endoscopic variceal ligation to control active bleeding, and initiation of a JAK inhibitor (ruxolitinib) was recommended for outpatient management to address the underlying disease. This case highlights that in patients presenting with variceal bleeding and portal hypertension in the absence of cirrhosis, myeloproliferative neoplasms, such as primary myelofibrosis should be considered as a differential diagnosis. This study aimed to raise awareness of primary myelofibrosis as a rare cause of non-cirrhotic portal hypertension and emphasize the importance of early recognition and targeted therapy to prevent recurrent bleeding and disease progression.

Keywords: *JAK2 V61F Mutation, Myelofibrosis, Portal Hypertension, Variceal Bleeding*

ABSTRAK

Pendarahan saluran cerna bagian atas akut dapat timbul dari sumber variseal maupun non-variseal. Mielofibrosis primer, salah satu subtipe neoplasma mieloproliferatif, merupakan penyebab hipertensi portal non-sirosis yang jarang tetapi penting. Kami melaporkan kasus seorang wanita berusia 39 tahun dengan riwayat pendarahan variseal berulang selama enam tahun. Pasien datang dengan keluhan penurunan berat badan progresif, splenomegali, dan anemia berat. Satu tahun sebelum episode hematemesis pertama, biopsi sumsum tulang menunjukkan mielofibrosis grade 2 dan mutasi JAK2 V617F terdeteksi positif, sehingga menegakkan diagnosis mielofibrosis primer. Terapi sebelumnya dihentikan karena keterbatasan biaya. Pemeriksaan ultrasonografi abdomen menunjukkan adanya hipertensi portal dan gambaran hati yang menyerupai sirosis. Pasien menjalani ligasi varises endoskopik dengan keberhasilan menghentikan perdarahan aktif, dan inisiasi terapi inhibitor JAK (ruxolitinib) direkomendasikan untuk pengobatan rawat jalan guna menangani penyakit dasarnya. Kasus ini menekankan bahwa pada pasien dengan pendarahan variseal dan hipertensi portal tanpa bukti sirosis, neoplasma mieloproliferatif seperti mielofibrosis primer harus dipertimbangkan sebagai diagnosis banding. Studi ini bertujuan meningkatkan kesadaran klinisi terhadap mielofibrosis primer sebagai penyebab hipertensi portal non-sirosis yang jarang, serta menekankan pentingnya deteksi dini dan terapi terarah untuk mencegah kekambuhan perdarahan dan progresi penyakit.

Kata Kunci: *Mutasi JAK2 V61F, Mielofibrosis, Hipertensi Portal, Perdarahan Varises Esofagus*

INTRODUCTION

The acute hemorrhage in upper gastrointestinal is a prevalent critical emergency associated with a 10% in-hospital mortality rate.[1,2] Based on its etiology, this condition can be classified into bleeding from variceal and non-variceal sources. Hemorrhage from esophageal varices is a life-threatening sequela of portal hypertension (PH), which is a pathological condition characterized by elevated portal venous pressure, typically exceeding 10 mmHg.[1,2] The liver cirrhosis was the most factor causing PH, while portal vein thrombosis not related to cirrhosis represents the second one in the Western populations.[2]

The primary myeloproliferative disorders are the most common etiology of portal venous thrombosis. These conditions are characterized by the clonal growth of hematopoietic stem cells and an elevated production of pro-inflammatory cytokines, which results in reticulin deposition and collagenous fibrosis.[3–6] The incidence is estimated to be 1–2 cases per 100.000 individuals per year in the United Kingdom and gender distribution is equal.[7] The Janus kinase 2 gene (JAK2 V617F) mutation is detected in about 90% of cases of polycythemia vera (PV), 50% of cases of essential thrombocythemia (ET), and 50% of cases of primary myelofibrosis (PMF).[2] PMF presents with a wide spectrum of clinical manifestation and becomes a rare cause of non-cirrhotic PH.[5–7] This study aimed to raise awareness of primary myelofibrosis as an uncommon cause of non-cirrhotic portal hypertension and emphasize the importance of early recognition and targeted therapy to prevent recurrent bleeding and disease progression.

CASE ILLUSTRATION

A 39-year-old woman attempted to the Emergency Department manifested hematemesis for the past three hours prior to admission. She vomited three times, with bright red blood, approximately 50 ml per episode. The patient also reported melena for the past 24 hours, three times before admission, each involving about 100-200 ml of blackish stool. She described feeling weak after vomiting. She denied any fever, jaundice, cough, or dyspnea. The history of abdominal distension, dysuria, or any herbal medicine or painkiller usage was declined. Weight loss was not objectively measured, but she felt a bit loose on daily wear.

The first episode of hematemesis occurred in 2018 (6 years prior to hospital admission). The esophagogastroduodenoscopy (EGD) revealed esophageal varices, for which she underwent two sessions of endoscopic varices ligation (in January and March 2018). The patient felt improvement and did not continue the treatment. No abdominal ultrasound was performed at that time. Recurrent hematemesis happened on 2021 (3 years before admission), yet no endoscopic varices ligation was performed due to no approval from the patient. The patient continued to have recurrent epigastric pain, nausea and early satiety, but these symptoms improved spontaneously without medication.

The patient was diagnosed with primary myelofibrosis in 2017 after presenting with recurrent weakness at a hospital in Palembang. Bone marrow biopsy (BMP) was performed to PMF and JAK2 V617F mutation was detected. Recommended treatments included bone marrow transplantation or pharmacotherapy, but the patient did not continue treatment due to the high cost. She has a history of four pregnancies, with three spontaneous abortions.

Table 1. Laboratory data

Examination Item	Result (Interpretation: E/D)
Hematology	
Hemoglobin/Hb (g/dL)	6.3 (D)
Hematocrit (%)	20.1 (D)
White blood cell (10^3/µL)	23.07(E)
Platelet (10^3/µL)	587 (E)
Neutrophil (%)	81(E)
Serological Test	
HBsAg	Non-reactive
Anti-HCV	Non-reactive
Anti-HIV	Non-reactive
Coagulation	
PT (patient/control)	15.0/11.3
APTT (patient/control)	33/28.8
Liver Biochemistry	
SGOT (U/L)	23
SGPT (U/L)	11
Bilirubin total/direct/indirect (mg/dL)	0.75/0.32/0.43
Protein/albumin/globulin (mg/dL)	6.8/3.3/3.5
Kidney Biochemistry	
Urea (mg/dL)	44.9
Creatinine (mg/dL)	0.4
eGFR (mL/min/1.73m^2)	129
Random Blood Glucose (mg/dL)	106
Sodium/Potassium/Chloride (mEq/L)	137/4.5/112.3

Abbreviations: E/D elevation, decline;

The patient has no history of hepatitis or other significant medical conditions, and no family history of similar symptoms was reported. The patient is the eldest of four siblings, married, and works as a private employee. Alcohol consumption is occasional, limited to approximately one small shot per month, typically in social occasions.

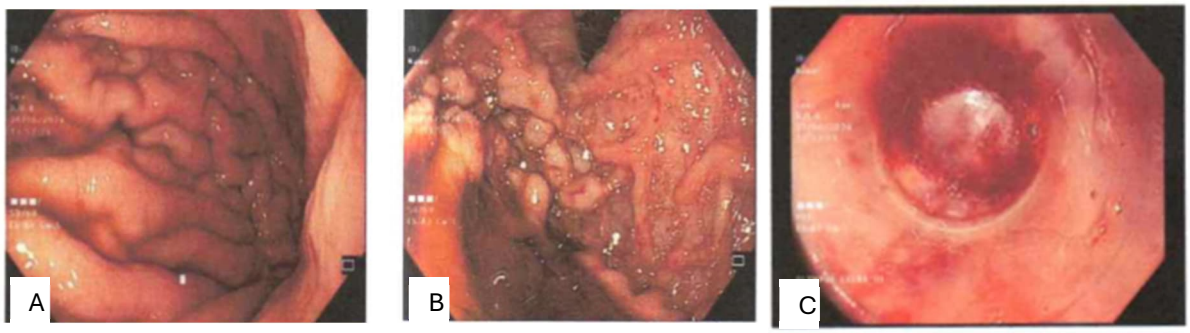

Figure 1. A: Esophageal varices, B:cherry spot, C: Variceal ligation

From physical examination, the hemodynamic was stable and without oxygen supplementation. The body mass index was 18.6 kg/m^2 (normal weight). From head examination, the eyes' conjunctiva was pale, and sclera was non-icteric. Splenomegaly (Schuffner 4) was identified, but no hepatomegaly from abdominal examination. No abnormalities on neck, chest, heart, or extremities examination were found.

In the laboratory findings, as seen in **Table 1**, she had severe anemia with peripheral blood smear showing microcytic hypochromic anemia. Other lab tests showed no abnormalities. Chest X-ray and electrocardiogram (ECG) were unremarkable. Abdominal ultrasound showed splenomegaly and portal vein dilation (diameter = 1.7 cm), suggesting portal hypertension. The echokinetic of liver parenchyma was homogenic and detected no lesion. No dilation was found hepatic vein and biliary system. Neither ascites nor pleural effusion was present. She had undertaken bone marrow biopsy. It showed megakaryocyte escalation leading to tight cluster and cloudy center. The fibrosis was grade 2-3 (according to WHO). The JAK2 mutation was positive detected in V617F point using blood specimen.

During hospitalization, the patient underwent variceal ligation at four sites and received blood pack transfusions. The EGD, as seen in **Figure 1,** viewed esophageal varices with cherry spot, GOV type 2, and portal hypertension gastropathy. She was discharged with cessation of bleeding (Hb 8.5 g/dL), prescribed a clear liquid diet (including milk), and medications including omeprazole (20 mg twice), sucralfate (15 ml three times,) and propranolol (10 mg twice) daily. She was scheduled with outpatient follow-up with ruxolitinib 5 mg twice a day and repeat variceal ligation in one month.

DISCUSSION

Primary Myelofibrosis (PMF) represents the least common of myeloproliferative neoplasms (MPN).[5,6] Its diagnosis is particularly challenging, as PMF lacks disease-specific signs and symptoms, and both myelofibrosis and splenomegaly may also be present in PV (polycythemia) and CML (chronic myeloid leukemia).[5–8] Many patients show no symptoms when diagnosed, and the condition is frequently discovered by chance through the detection of splenomegaly and/or abnormal hematologic findings during routine screening.[8] However, MPNs, including PMF, presents with clinical manifestation, such as night sweats, fever, and unintentional weight loss, which are more commonly observed in PMF.[5,6] Other frequent symptoms include abdominal discomfort, difficulty sleeping, dyspnea, pruritus, easy bruising, cognitive impairment, and dizziness.[5,6] Splenomegaly is present in approximately 90% of patients, resulting from extramedullary haematopoiesis, this can become sufficiently pronounced to cause portal hypertension and lead to the development of varices.[5,6] Mild hepatomegaly could be accompanied but is unusual in its absence. In this patient, due to PMF, patient opposed recurrent weakness. Due to splenomegaly, she felt early satiety and nausea. There was weight loss as a constitutional symptom. Recurrent hematemesis was suspected due to portal hypertension. There was splenomegaly with Schuffner 4 but without palpable liver.

The diagnosis of myeloproliferative neoplasms (MPNs) should follow WHO diagnostic criteria (2017), which involve clinical evaluation, laboratory tests, cytogenetic analysis, and molecular testing.[5,6] The work up recommendation for testing include complete blood cell count, blood smear, and comprehensive metabolic panel, such as uric acid, lactate dehydrogenase, and liver function tests.[5–8] Molecular testing of blood for the JAK2 V617F mutation is also required. If the result is

negative, testing for CALR and MPL mutations should be done, or a multigene next-generation sequencing (NGS) panel that includes JAK2, CALR, and MPL can be applied. [5–8] BMP helps to distinguish PMF from the others myeloid neoplasms including ET, PV, chronic myeloid leukemia, chronic myelomonocytic leukemia, MDS, and "acute myelofibrosis". Multiplex real time polymerase chain reaction (RT-PCR) (preferred) or fluorescence in situ hybridization for BCR-ABL1 is recommended to rule out the CML. [5–8] Bone marrow biopsy aspirate is helpful for cytogenetics examinations and confirmed PMF as suggested by WHO.

In this report, the patient came with severe anemia. The liver and kidney biochemistry was on normal range. The work up tool has been accomplished to confirm PMF with confirmed BMP and JAK2 mutation. The USG show no conviction of liver cirrhosis. However, no treatment was executed to the patient due to steep charge at first period diagnosis. Later, variceal bleeding came after almost a year and endoscopic variceal ligations was performed. No routine visits or follow up for the treatment as the somehow symptom improve continuously. According to the WHO criteria, the positive major criteria were fibrosis grade 2-3 and presence of JAK2 mutation, while the minor criteria were anemia, leucocytosis ($\geq 11 \times 10^9$/L), and palpable splenomegaly.

PMF may be detected on radiological finding incidentally or through laboratory testing, such as anaemia, thrombocytosis, and or thrombocytopaenia. Around 10% of patients with primary myelofibrosis experience a venous thromboembolism.[3,8] Splenomegaly is a common and progressive finding in these patients. This could generate splenic infarction, haemorrhage, splanchnic vein thrombosis, PH, or symptoms related to mass effect as the complications.[3,9] The modalities with MRI and CT angiography are important detecting thrombosis.[3]

Management of PMF is recommended to stratify the risk of each patient before determine the treatment. There are some prognostic scorings to differentiate the risk, such as the International Prognostic Scoring System (IPSS), Dynamic International Prognostic Scoring System (DIPSS), Mutation-enhanced International Prognostic Scoring System (MIPSS70), and Genetics-inspired International Prognostic Scoring System (GIPSS).[8] Due to no karyotype data, based on DIPSS score, the patient was classified in intermediate risk (score 3:Hb <10 g/dl (2 point) and constitutional symptom (1 point).

All patients with PMF should be assessed for eligibility for allogeneic hematopoietic stem cell transplantation.[5,6] Participation in clinical trials is also advised for all patients with such condition. Based on NCCN guideline,[6] monitoring for clinical disease progression every 3-6 month is required for asymptomatic patient in lower risk group. Other following treatments include JAK inhibitor (ruxolitinib), interferon, and hydroxyurea if cytoreductions would be beneficial. The high-intermediate risk group, received either ruxolitinib or momelotinib will show volume reduction ≥35% of spleen and transfusion independence at week 24.[8,10] Meanwhile, for the higher risk, both NCCN and ESMO recommend for allogeneic HCT and for those who are not candidates, the choices are ruxolitinib, fedratinib, and enrolment in clinical trials.[5,6] Indications of splenectomy are abdominal pain and discomfort due to splenomegaly, symptoms of portal hypertension, severe low platelet count, and need for frequent red blood cell transfusion.[5,6,8] In this report, the goal of hospitalization was resolve the acute bleeding and the treatment for PMF was planned at outpatient clinic with ruxolitinib 5 mg twice daily. The patient's compliance was poor, clear explanation about next step, and treatment was required.

The patient admitted to ED due to hematemesis was an emergency situation and a serious complication of PH. [1,2] Portal hypertension in myelofibrosis is thought to result from the formation of microvascular or macrovascular clots, along with injury and damage to both large and small portal veins.[11] Endoscopy plays an important role to diagnose and asses the risk of variceal bleeding.[11,12] The treatment approaches for PH secondary to PMF are still a subject of ongoing research and development. Several interventions have been proposed included endosonographic coiling, cyanoacrylate targeted injection, endoscopic variceal ligation, and endoscopic injection sclerotherapy.[11,13–15]

CONCLUSION

In case of acute esophageal variceal bleeding, the possibility of non-cirrhotic portal hypertension should be carefully considered as an underlying etiology. The presence of constitutional symptom, anemia, and splenomegaly should be suspected as primary proliferative disorder. Performing the endoscopic varices ligation is crucial to terminate the bleeding source, while definitive management must also address the underlying condition to reduce the risk of recurrence.

Conflict of Interest

The authors declare they have no conflict interests.

Funding

The article did not receive any specific grant from funding agencies in the public, commercial or any other sectors.

Author Contribution

All authors contributed equally to this manuscript.

Acknowledgement

We sincerely thank the patient of this report

Data Availability

The datasets are available in the manuscript

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