Idiopathic Portal Hypertension: A Rare Cause of Recurrent Hematemesis Melena

Griskalia Christine, Irsan Hasan***

*Department of Internal Medicine, Faculty of Medicine, University of Indonesia
Dr. Cipto Mangunkusumo General National Hospital, Jakarta
** Division of Hepatology, Department of Internal Medicine, Faculty of Medicine University of Indonesia/Dr. Cipto Mangunkusumo General National Hospital, Jakarta

ABSTRACT

Idiopathic portal hypertension (IPH) known as non-cirrhotic portal fibrosis (NCPF) is a constellation of liver disorders, in which liver cirrhosis is not present and the main clinical and pathological findings are encountered in the portal venous system. Patients usually come to hospital with esophageal varices and upper gastrointestinal bleeding; however, it is often misdiagnosed as liver cirrhosis. Its etiology is still unknown, but some evidences and epidemiological studies suggest that it is a multifactorial disease with genetic basis. The laboratory evaluation in IPH reveals only mild and subtle abnormalities predominantly related to hypersplenism. The major complications of IPH are esophageal varices and hypersplenism. Endoscopic sclerotherapy or band ligation, shunt surgery, and transjugular intrahepatic portosystemic shunt (TIPS) are modalities to treat the complications of IPH. The case report reported about diagnosis and treatment of a 20-year-old male with idiopathic portal hypertension.

***Keywords**: idiopathic portal hypertension, non-cirrhotic portal fibrosis, diagnosis, treatment*

ABSTRAK

Hipertensi portal idiopatik dikenal juga sebagai fibrosis portal non sirosis merupakan kumpulan kelainan hati tanpa adanya sirosis hati dan temuan klinis-patologi utamanya terletak pada sistem vena porta. Pasien biasanya datang ke rumah sakit dengan varises esofagus dan perdarahan saluran cerna atas, tetapi sering salah didiagnosis sebagai sirosis hati. Etiologi kelainan tersebut belum diketahui, tetapi dari beberapa bukti dan studi epidemiologi mengusulkan bahwa kelainan tersebut merupakan kelainan multifaktor dengan dasar genetik. Evaluasi laboratorium pada pasien hipertensi portal idiopatik hanya menunjukkan kelainan ringan, yang predominan berhubungan dengan hipersplenisme. Komplikasi utama hipertensi portal idiopatik adalah varises esofagus dan hipersplenisme. Endoskoskopi skleroterapi atau ligasi, bedah pembuatan pintas (shunt), dan transjugular intrahepatic portosystemic shunt (TIPS) merupakan modalitas untuk tata laksana komplikasi hipertensi portal idiopatik. Pada laporan kasus ini dilaporkan mengenai diagnosis dan tata laksana pasien laki-laki berusia 20 tahun, dengan hipertensi portal idiopatik.

***Kata kunci**: hipertensi portal idiopatik, fibrosis portal non sirosis, diagnosis, tatalaksana*

INTRODUCTION

Idiopathic portal hypertension (IPH) known as non-cirrhotic portal fibrosis (NCPF) is a constellation of liver disorders, in which liver cirrhosis is not present and the main clinical and pathological findings are encountered in the portal venous system.[1] IPH is characterized by non-pathognomonic pathological changes (with the absence of cirrhosis) of the liver in addition to findings of portal hypertension. It is still one of the most important misdiagnoses of clinical practice. For many physicians, presenting esophageal varices and upper gastrointestinal bleeding usually prompt an unfortunate diagnosis of cirrhosis.

CASE ILLUSTRATION

A 20-year-old male came to emergency unit of Cipto Mangunkusumo Hospital with hematemesis melena since 12 hours before admission. The total volume of hematemesis melena was 400 mL. The patient did not complain any fever, nausea, abdominal pain, abdominal enlargement, dyspnea, edema, or scleral jaundice. The urine was clear yellow and no history of pale color of defecation. Since 1 year ago, the patient had been experiencing hematemesis melena for seven times and had undergone esophageal varices ligations for four times in other hospital. There was no history of chronic viral hepatitis as the risk factor.

On admission, the patient was in hypovolemic shock. The conjunctivas were pale with anicteric scleras. The heart and lung were normal. The abdomen was a little bit bloating, flexible, with non-palpable liver and there was splenomegaly (Schuffner V). Minimal shifting dullness was found. No abdominal pain was found as well as no stigmata of liver cirrhosis, edema of extremity, and flapping tremor.

The laboratory results showed pancytopaenia with morphology of erythrocyte normocytic normochrome. The morphology of leukocyte and thrombocyte was normal with normal prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen, and increased D-dimer. The level of alanine aminotransferase (ALT), aspartate transaminase (AST), bilirubin, alkaline phosphatase, albumin, and globulin were within normal limit. The renal function was normal. There was no evidence of hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) infection. The level of cholinesterase and laboratory result of the autoimmune disease parameter were normal. The level of quantitative hepatitis B virus-deoxyribonucleic acid (HBV-DNA) was examined, and the result revealed unidentified viral load.

A vascular Doppler ultrasound result indicated no thrombus, portal vein diameter 1.5 cm, splenic vein > 1.2 cm, and the umbilical vein was hardly evaluated (Figure 1). An abdominal ultrasound showed that the liver size was not attenuated, with inhomogen echostructure and irregular surface. The hepatic vein was unclear, portal vein and splenic vein were dilatated. A splenomegaly was found. The result of esophagogastroduodenoscopy (EGD) was esophageal varices grade III-IV with gastropathy portal hypertension (Figure 2).

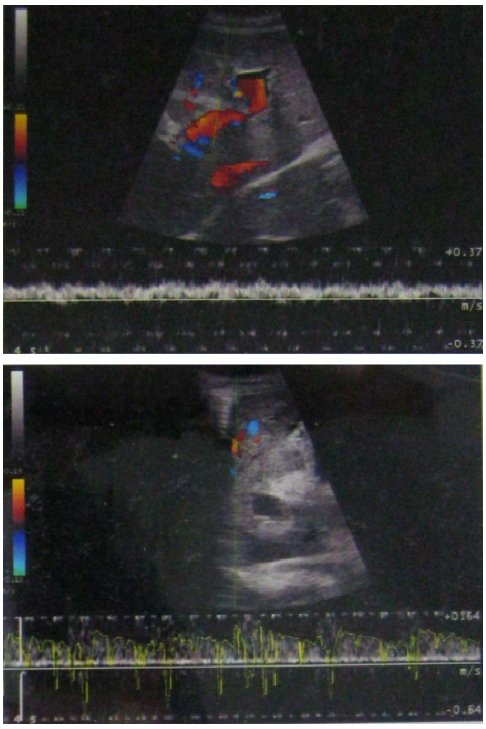

Figure 1. Vascular doppler ultrasound showed dilatation of portal and hepatic vein

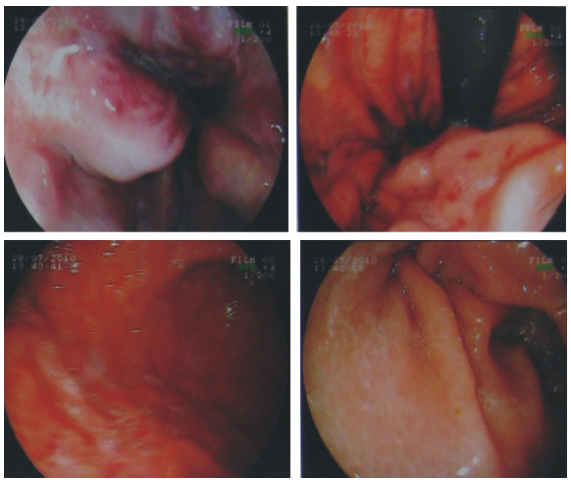

Figure 2. Esophagogastroduodenoscopy (EGD) showed gastropathy, esophageal varices grade III-IV with portal hypertension

An abdominal computed tomography scan (CT-scan) showed liver enlargement, with firm surface, homogenous parenchyma, without dilatation of the intra-hepatic and extra-hepatic biliary tract, space occupying lesion (SOL), or nodule. The portal vein diameter was 1.6 cm without any thrombus. The spleen was large with size of 12.8 x 13.9 x 22.6 cm^3. It pushed the intestinal gas into right lateral aspect and kidney to inferior. Splenic vein was large with diameter of 1.7 cm. There was minimal ascites.

Analysis of ascites fluid revealed yellow color, clear fluid with negative Rivalta test, total cell count 70/µL, polymorphonuclear (PMN) cells (segment) of 67/µl, serum ascites albumin gradient 3.5. Cytology of the ascites fluid showed no malignancy. The first liver biopsy done prior the surgery showed an image of chronic hepatitis with histology activity index (HAI) grading of focal necrosis 0, piece-meal necrosis 1, HAI 1 (mild), stage F3.

The final diagnosis were hematemesis melena caused by rupture of esophageal varices with a history of hypovolemic shock, idiopathic portal hypertension and, pancytopenia caused by hipersplenism. Fluid rescucitation and pack red cell transfusion were given until the patient had been recovered from hypovolemic shock. Hematemesis melena occurred only for one day and emergency endoscopy was performed. Other treatment included 2 x 40 mg intravenous omeprazole, 4 x 15 ml oral sucralfate, oral hepatoprotector 3 x 1 tablet, 3 x 10 mg intravenous vitamin K, 2 x 10 mg oral propranolol, 3 x 1 gram intravenous cefotaxime for 12 days, transfusion of platelets prior to ligation and surgery. There was no financial support for intravenous somatostatin therapy.

A splenectomy and distal splenorenal shunt with end-to-side technique were performed with a prior vaccination of *Meningococcus* and *Pneumococcus*. Before and after the surgery, 3 x 1 gram ceftazidime was reintroduced. Intravenous ketorolac with 3 x 30 mg of dose was given as an analgesic after the surgery.

A second intraoperative liver biopsy was performed. It showed that the hepatocytes were in the lamellar arrangement, very mild lobular necrosis, dilatation of portal system, fibrosis with septa, and mild periportal necrosis. Portal vein and central vein were dilated and groups of hepatocytes containing blue granule in the cytoplasm were seen in VB stain.

After the splenectomy and distal splenorenal shunt, the hemoglobin, leukocyte and platelet count increased. No complication was found in the surgery procedure. After surgery, the patient's condition became better and the patient was discharged with a good condition.

DISCUSSION

Idiopathic portal hypertension (IPH) or non-cirrhotic portal fibrosis (NCPF) is one of the important disease entities comprising non-cirrhotic portal hypertension, a group of diseases that are characterized by an increase in portal pressure, due to intrahepatic or prehepatic lesions, in the absence of cirrhosis of the liver.[1,2] In the Indian subcontinent, it is known as non-cirrhotic portal fibrosis, while in Japan and other Asian countries, it is referred to as idiopathic portal hypertension.[3,4]

Although, the terms NCPF and IPH often have been used interchangeably, there are subtle differences between the two. NCPF is more common among male. The mean age of NCPF patients varies from 25 to 35 years, which is much lower than patients who have IPH. Autoimmune features are common in IPH while rare in NCPF.[5] Irregular parenchymal nodules and bile duct proliferations are more common in NCPF than IPH. Wedged hepatic venous pressure is almost normal in NCPF, while it is moderately raised in IPH. This case presents a male patient aged 20 years old, without any sign and result of an autoantibody disorder. These characteristics were suitable with a NCPF. However, in our institution, a term of IPH is more commonly used. In Japan, the yearly number of new cases ranged from 8 to 20, averaging 11 cases per year up to 1994.[2]

The pathogenesis of IPH is still not understood and there are some controversies about this subject. Although there are some theories on the pathogenesis of IPH, unfortunately none have been proven to be a single factor fully explaining the pathogenesis. These theories include the trace element-chemical theory, autoimmunity theory, infection theory, thrombosis theory, and genetic theory. IPH seems to be a multi-factorial disease, in which two or more etiological factors may play a role.[1]

In this patient, the diagnosis of systemic lupus erythematosus has been ruled out. The ANA (anti-nuclear antibody) profile was negative and autoimmune hepatitis has been ruled out. The patient had never suffered from recurrent infection, especially gastrointestinal infection. But, because the patient lives in the tropical zone, such pathogenesis cannot be ruled out.[2] The patient had undergone a Doppler ultrasound and abdominal multi-sliced computed tomography (MSCT) to rule out thrombosis cause and there was no thrombus found in the patient. Maruyama et al, showed that a contrast-enhanced ultrasound can differentiate IPH from liver cirrhosis. Delayed periportal enhancement on the sonograms based on perflubutane microbubble agent may be a characteristic of IPH.[6]

A high degree of human leukocyte antigen DR3 (HLA-DR3) aggregation was found in family members with IPH.[1] There was a chance for this patient to have a high degree of HLA-DR3. But the laboratory examination was not done because it was not cost effective.[1]

The pathological findings in IPH are very heterogeneous.[7] This heterogeneity is most probably due to changes occurring with the progression of the disease and changes in hepatic blood flow dynamics. Macroscopically, the liver may be atrophic and/or nodular. Liver atrophy is a later finding in the course of the disease due to collapse of the peripheral liver architecture, along with ischemia related to hepatocyte drop-out via apoptosis. In this patient, a liver enlargement was found. In histological examination, the classical findings of IPH can be divided into two aspects. The primary finding directly related to IPH is intimal fibroelastic thickening of medium and small branches of the intrahepatic portal vein.[8] The second aspect, resulting secondarily to obliterated portal branches, is aberrant neo-vascular formations, sinusoidal dilatation and hepatocellular nodular hyperplasia. These vessels play an important role in shunting blood flow from the obliterated portal segment towards unaffected sites. Biopsy material may show only mild and subtle changes from normal.[2]

Nakanuma et al, proposed a staging of IPH with a combination of hepatic parenchymal atrophy and portal venous thrombosis. Stage I is non-atrophic liver without subcapsular parenchymal atrophy, stage II is non-atrophic liver with subcapsular parenchymal atrophy, stage III is atrophic liver with sub-capsular parenchymal atrophy, and stage IV is portal venous occlusive thrombosis. IPH livers can progress from stage I to stage III, while stage IV occurs relatively late.[7] The patient in this case seemed to be on the stage I.

The patient has a relatively normal liver function, i.e. normal albumin level and prothrombin time, but he presents with variceal bleeding, which was detected in investigations of hypersplenism. Ascites is almost always a finding of advanced cases indicating the liver atrophies and residual capacity are limited.[1]

Sarin et al, reported that 13.5% of patients had splenomegaly, 84.5% of patients had upper gastrointestinal bleeding, 92% of patients had esophageal varices, and 22.3% of patients had gastric varices.[9] When they compared these patients with portal vein thrombosis patients, the IPH group was found to have larger spleens, but lower prevalence of ascites, gastric varices, history of upper gastrointestinal bleeding and almost no jaundice. Dhiman et al, reported that 96.7% of patients had splenomegaly and 64.9% of patients had upper gastrointestinal bleeding.[10]

Okuda et al, reported that the main presenting symptom of these patients were anemia related symptoms (26.2%), hematemesis (23.7%), splenomegaly (18.4%), and varices (84%) of all cases.[11] The clear difference in presentation patterns suggests that there are two, non-homogenous IPH groups in those countries. This important clue has a very important and basic message, i.e. the Indian IPH population is formed of more chronic and advanced IPH cases than the Japanese and Western cases and it is one of the main causes of conflict in the IPH literature.[1]

The Asian Pacific Association of the Study of the Liver (APASL) divides the clinical manifestation into two groups, NCPF and IPH. In NCPF, the patient presents with well-tolerated episodes of gastrointestinal hemorrhage, splenomegaly, anemia, and consequences of hypersplenism. Development of ascites, jaundice, and hepatic encephalopathy is uncommon and may be seen only after an episode of gastrointestinal hemorrhage. Left upper quadrant pain due to perisplenitis and splenic infarction is not uncommon.[2] The laboratory evaluation in IPH reveals only mild and subtle abnormalities predominantly related to hypersplenism.[2] The parenchymal damage manifest by increased aminotransferase levels is very minimal in IPH. Results of conventional tests of liver function are normal or near normal.[10]

Pancytopenia caused by hypersplenism is found in the majority of patients with IPH. Whether the leucopenia in IPH increases susceptibility to infections, and whether splenectomy is required in such cases remain debatable. The bone marrow is hypercellular, which was shown in this patient by the increase of the reticulocyte count.[2]

In this patient, the level of D-dimer increased, with normal PT, APTT, and fibrinogen. A state of mild, compensated, and disseminated intravascular coagulation secondary to endotoxemia or portosystemic collaterals has been reported in some cases of IPH, but it does not occur in this case report. A study by Bajaj et al, reported that 78% of IPH patients had a significantly increased international normalized ratio (INR) and a decrease in fibrinogen and platelet aggregation.[12]

The patients had a significant prolongation in partial thromboplastin time with increased levels of fibrinogen degradation products, which is usual in IPH. This suggests a mild-disseminated intravascular coagulation disorder in these diseases. However, previous study reported only low platelet aggregatability. Deficiency of proteins C and S has been proposed along with mutations in factor V Leiden; however, a cause-and-effect hypothesis remains to be confirmed.[2]

The major complications of IPH can be summarized as esophageal varices and hypersplenism as shown in

this case report. The walls of these variceal veins are relatively thicker than the varices observed in cirrhosis. They rarely harbor "red-spots" that herald variceal bleeding. They are simply dilated veins that rarely complicate, and are relatively easy to treat compared to cirrhosis. Esophageal varices are reported to be found in 90% of the IPH patients. The principles and modes of management of esophageal varices remain the same as those for patients with cirrhosis.

Bacterial infections are more common in patients with cirrhosis having variceal bleeding (35–66%) than in non-cirrhotic patients (5–7%).[13] It has been shown that infected cirrhotic patients have a higher rate of variceal rebleeding (43%) than non-infected patients (10%).[12] There is no study on the use of prophylactic antibiotics.[9]

Hirashita et al, conclude that 44% from 18 patients had portal vein thrombosis (PVT) after splenectomy. The mean interval until detection after splenectomy was 22 ± 41 months. But, there were no significant differences in the cumulative gastrointestinal bleeding and survival rates between patients with and those without PVT.[14]

Vasoactive drugs, such as somatostatin, octreotide, or terlipressin, have been used in the treatment of acute variceal bleeding while endoscopic therapy is being arranged. However, there is no data on the efficacy of vasoactive drugs in IPH patient with acute variceal bleeding.

Endoscopic sclerotherapy and band ligation are effective in 80–90% of patients in controlling acute bleeding from esophageal varices and preventing rebleeding. Combination treatment with drugs plus endoscopic therapy is more effective than endoscopic therapy or drug therapy alone in controlling acute bleeding (88% vs. 76%) and preventing rebleeding for 5 days (77% vs. 58%), while there is no difference in mortality.[15]

Failure of endoscopic therapy is defined, as further variceal bleeding after two endoscopic treatments during a single hospital admission for acute bleeding. The current therapies fail to control bleeding or prevent early rebleeding in 8–12% of patients, who should be treated by alternative modes of treatment like surgery or transjugular intrahepatic portosystemic shunt (TIPS).[15]

Endoscopic ligation can be performed as a primary prophylaxis for variceal bleeding. A decrease in the size of esophageal varices, as seen in patients with cirrhosis with an improvement in liver functions is unlikely in IPH, unless interventions like endoscopic sclerotherapy are applied, which after variceal obliteration results in the development of spontaneous splenorenal shunts.[2]

Shunt surgery for primary prophylaxis is likely to be indicated if the patient of IPH has large esophageal varices with a symptomatic large splenomegaly, a very low platelet count (< 20,000), stays far away from a good medical center where an upper GI bleeding can be tackled, or has a rare blood group.[2]

Patients with gastric varices of more than 2 cm could be taken up for surgical shunt or balloon-occluded retrograde transvenous obliteration if a splenorenal shunt is present, although studies are lacking.[2] The selective distal spleno-renal shunt (DSRS) proposed has been considered to be the best procedure available for surgical decompression of patients with portal hypertension.[16] Meta-analysis of the studies compared DSRS and sclerotherapy showed that DSRS significantly reduces the incidence of rebleeding and only slightly increases the occurrence of chronic encephalopathy, but does not improve survival.[17]

TIPS is an interventional radiology technique that has shown a 90% success rate to decompress the portal circulation. As a non-surgical intervention, without requirement for anesthesia and very low procedure-related mortality, TIPS is applicable to patients, who are otherwise untreatable, for example, nonsurgical candidates. Regarding esophago-gastric variceal bleeding, TIPS has excellent hemostatic effect (95%) with low rebleeding rate (< 20%). TIPS is an accepted rescue therapy for first line treatment failures in 2 settings (1) acute variceal bleeding and (2) secondary prophylaxis. In addition, TIPS offers 70 to 90% hemostasis to patients presenting with recurrent active variceal bleeding.[18]

Transjugular intrahepatic portosystemic shunt is more effective than standard therapy for patients with hepatic venous pressure gradient > 20 mmHg. Transjugular intrahepatic portosystemic shunt is particularly useful to treat bleeding from varices inaccessible to endoscopy. But, this procedure should not be applied for primary prophylaxis of variceal bleeding. Portosystemic encephalopathy and stent dysfunction are TIPS major drawbacks.

If the patient were not treated well, the liver would have become atrophy, but it is not necessarily progressive, and the liver functional reserve is well maintained. Although mortality from variceal rupture is generally lower in IPH, because of better liver functions compared with cirrhosis, the major cause of death is variceal bleeding.[1] Good prognostic features

in patients with IPH, a 2- and 5-year survival of nearly 100% after successful eradication of esophagogastric varices, have been described.[10] The incidence of portal vein thrombosis is higher in patients with IPH than in those with cirrhosis, but has a poor prognosis.[1,2]

From this case, we conclude that the patient has an idiopathic portal hypertension, with varying clinical pictures, including splenomegaly and recurrent variceal bleeding. Early diagnosis is needed to avoid delayed treatment. Although the prognosis is excellent, careful follow up and management of patients, with extra attention to treatment esophageal varices, is required. Further studies are essential in order to clarify the etiology and possible genetic background.

REFERENCES

1. Harmanci O, Bayrakar Y. Clinical character of idiopathic portal hypertension. World J Gastroenterol 2007;13:1906-11.
2. Sarin SK, Kumar A, Chawla YK, Baijal SS, Dhiman RK, Jafri W, et al. Non- cirrhotic portal fibrosis/idiopathic portal hypertension: APASL recommendation for diagnosis and treatment. Hepatol Int 2007;1:298-413.
3. Rai T, Ohira H, Fukaya E, Abe K, Yokokawa J, Takiguchi J, et al. A case of merged idiopathic portal hypertension in course of mixed connective tissue disease. Hepatol Res 2004;30:51-5.
4. Takagi K, Nishio S, Akimoto K, Yoshino T, Kawai S. A case of systemic sclerosis complicated by idiopathic portal hypertension: case report and literature review. Mod Rheumatol 2006;16:183-7.
5. Sarin SK, Kumar A. Non-cirrhotic portal hypertension. Clin Liver Dis 2006;10:627-51.
6. Maruyama H, Shimada T, Ishibashi H, Takahashi M, Kamesaki H, Yokosuka O. Delayed periportal enhancement: a characteristic finding on contrast ultrasound in idiopathic portal hypertension. Hepatol Int [cited 2011 Jun 28]. Available from: URL: http://www.ncbi.nlm.nih.gov/pubmed/21710291.
7. Nakamuna Y, Tsuneyama K, Ohbu M, Katayanagi K. Pathology and pathogenesis of idiopathic portal hypertension with an emphasis on the liver. Pathol Res Pract 2001;197:65-76.
8. Nayak NC, Jain D, Saigal S, Soin AS. Non-cirrhotic portal fibrosis: one disease with many names? An analysis from morphological study of native explants livers with end stage chronic liver disease. J Clin Pathol 2011;64:592-8.
9. Sarin SK, Kapoor D. Non-cirrhotic portal fibrosis: current concept and management. J Gastroenterol Hepatol 2002;17:526-36.
10. Dhiman RK, Chawla Y, Vasishta RK, Kakkar N, Dilawari JB, Trehan JB, et al. Non-cirrhotic portal fibrosis (idiopathic portal hypertension): experience with 151 patients and a review of the literature. J Gastroenterol Hepatol 2002;17:6-16.
11. Okuda K. Non-cirrhotic portal hypertension: why it is so common in India? J Gastroenterol Hepatol 2002;17:1-5.
12. Bajaj JS, Bhattacharjee J, Sarin SK. Coagulation profile and platelet function in patients with extrahepatic portal vein obstruction and non-cirrhotic portal fibrosis. J Gastroenterol Hepatol 2001;16:841-6.
13. Goulis J, Patch D, Borrough AK. Bacterial infection in the pathogenesis of variceal hemmorage. Lancet 1999;253:139-42.
14. Hirashita T, Ohta M, Kai S, Masuda T, Eguchi H, Iwashita Y, et al. Implications of portal vein thrombosis after splenectomy for patients with idiopathic portal hypertension. Surg Today 2001;41:1475-80.
15. De Franchis R, Dell'Era A, Lannuzzi F. Diagnosis and treatment of portal hypertension. Dig Liver Dis 2004;36:787-98.
16. Yoshida H, Mamada Y, Taniai N, Mineta S, Kawano Y, Mizuguchi Y, et al. Shunting and non-shunting procedures for the treatment of esophageal varices in patients with idiopathic portal hypertension. Hepatogastroenterology 2010;57:1139-44.
17. Spina GP, Henderson JM, Rikkers LF, Teres J, Burroughs AK, Conn HO, et al. Distal spleno-renal shunt versus endoscopic sclerotherapy in the prevention of variceal rebleeding: a meta-analysis of 4 randomized clinical trials. J Hepatol 1992;16:338-45.
18. Colombato L. Transjugular intrahepatic portosystemic shunt (TIPS). J Clin Gastroenterol 2007;41 (suppl 3):S344-51.

Correspondence:
Irsan Hasan
Division of Hepatology, Department of Internal Medicine
Dr. Cipto Mangunkusumo General National Hospital
Jl. Diponegoro No. 71 Jakarta 10430 Indonesia
Phone: +62-21-31900924 Facsimile: +62-21-3918842
E-mail: irsan_h@yahoo.com