

Current Management of Refractory Ascites in Hepatoma: A Case Report

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Abstract: Refractory ascites is a complication of chronic liver disease and hepatic malignancy. It occurs in 5-10% cases and indicates a poor prognosis with a survival rate below 50% if no liver transplant is performed. Refractory ascites is difficult to treat and significantly reduce patient's quality of life. A 54 years old male hospitalized with chief complaint of abdominal pain and enlarged abdomen since 2 months ago. The patient has been diagnosed with hepatoma since seven months ago and routinely consumed oral furosemide and spironolactone. Paracentesis has been performed on patients four times in the last four months. Ultrasonography shows enlargement of the liver. During hospitalization, paracentesis of ascites fluid were carried out two times with a total of 12,000 liters fluid evacuated. Large volume paracentesis (LVP) is the most feasible option for rapid management of ascites, and providing symptomatic relief in patients with tense ascites in limited resources setting. Other options such as Transjugular Intrahepatic Portosystemic Shunt (TIPS), Peritoneovascular Shunt (PVS), and Liver transplant should be considered for patients needing frequent LVP, if available and not contraindicated.

Keywords: refractory ascites, chronic liver disease, hepatoma, paracentesis

1. Introduction

Ascites is a condition of fluid accumulation in the abdominal space (peritoneal cavity). Ascites can be caused by portal hypertension, malignancy, or infection. The most common cause of ascites is portal hypertension and 80% found in patient with chronic liver disease. In chronic liver disease, fibrous tissue formation that occurs in liver cells will results in an increase in portal venous pressure, an increase in portal venous pressure followed by fluid retention by the kidneys will eventually cause ascites. Patients with chronic liver disease, have a higher risk of developing hepatoma. Hepatocellular carcinoma itself is the most commonly encountered primary tumor on the liver, represents 90% cases of primary liver cancers. Ascites in hepatocellular carcinoma are often found and is associated with tumoral and cirrhosis factors. It is said that ascites in hepatocellular carcinoma reduce the long term survival rate of the patients. In some cases of liver disease, ascites can occur over and over in a short time despite the evacuation of large amounts of ascitic fluid, this is called refractory ascites.^{1,2}

Refractory ascites is defined as recurrent of ascites that do not respond to the treatment of high doses of diuresis or the recurrence of fluid accumulation immediately after paracentesis. Refractory ascites is rare and only occurs in 5-10% of patients with liver disease. Refractory ascites can significantly reduce a patient's quality of life and indicate a poor prognosis. It is said that 50% of refractory ascites patients will die within 2 years if no liver transplant is performed. Appropriate diagnosis and management is needed to prevent recurrence and improve patient's quality of life.³

2. Case Report

A 54 years old male came to the Emergency Room with right upper quadrant and epigastric abdominal pain since 5 days prior. The pain was described as discomfort, feeling of bloating, and he also feel shortness of breath. His stomach had been enlarging in the last two months. He was diagnosed with chronic liver disease seven months ago and had already undergone paracentesis procedure four times. The patient had history of daily alcohol consumption for more than 20 years before he was diagnosed with chronic liver disease. There was no history of disease such as hepatitis B and C.

From physical examination, the patient looked distressed, having slight shortness of breath, with blood pressure of 140/80 mmHg, pulse of 90 x/minutes, respiratory rates of 22x/minutes, and axillary temperature of 36.7°C. Patient didn't look jaundiced. Abdominal examination revealed distended and tense abdomen with positive undulation and shifting dullness which consistent with massive ascites. After the LVP procedure was done, abdominal examination reveals hepatomegaly, the liver enlarged to four centimeters from arcus costae, and 3 centimeters from xiphoid process, with few nodules palpable. Splenomegaly also observed in schuffner IV.

Laboratory result showed elevated white blood cells of 13.82×10^3 u/L, low hemoglobin value of 9.8 gr/dL, low hematocrit 31.6%, high platelet count of 600×10^3 u/L, low albumin serum 2.9 gr/dL, total bilirubin 0.32 mg/dL, direct bilirubin 0.2 mg/dL, indirect bilirubin 0.12 mg/dL, elevated Alanine Transaminase (ALT) 12 U/L, elevated Aspartate Transaminase (AST) 25 U/L, elevated Blood Urea Nitrogen (BUN) 156 mg/dl, elevated creatinine 2.3 mg/dl, sodium serum 134 mmol/L, potassium serum 4.3 mmol/L, chloride serum 96 mmol/L, HBsAg negative and Anti-HCV negative.

Ultrasonography (USG) revealed enlargement of liver (17.04 cm), roughly-increased echoparenchym, blunt ends, multiple nodule, no dilatation of intrahepatic. This finding is suggestive of hepatoma.



Figure 1: Abdominal USG

Therapy including infusion of aminoleban : D10% in ratio of 1:1 with the speed of infusion of 8 drip per minutes, ceftriaxone 2x1 grams IV, furosemide 3x20mg IV, spironolactone 2x100 mg PO, and morphine tablet 1x10 mg PO was given.

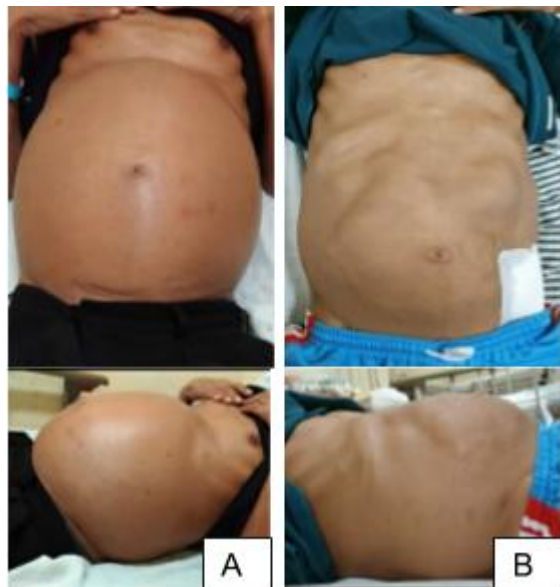


Figure 2: (a) Patient's abdomen before paracentesis procedure, (b) Patient's abdomen after paracentesis procedure

Paracentesis was done twice in this patient, in the first and fifth day of hospitalization. On the first paracentesis, about 6,000 mL of tea-like reddish ascitic fluid was evacuated. After first paracentesis, patient's abdomen kept enlarging and second paracentesis was scheduled. In second paracentesis, 6000 mL of tea-like reddish ascitic fluid was again evacuated. The ascites fluid was examined with the

result of WBC-BF 0.616×10^3 ul, RBC-BF 0.012×10^3 ul, MN 0.567×10^3 ul, PMN 0.049×10^3 ul, MN% 92.1 %, PMN% 7.9%, TC-BF 0.25×10^3 ul, positive rivalta test, glucose 83 mg/dl, protein 4.0 gr/dl, albumin 1.60 gr/dL, Lactate Dehydrogenase (LDH) 1247 U/L, Serum Ascites Albumin Gradient (SAAG) 1.3 g/dL.



Figure 3: Tea-like reddish ascitic fluid

Citology examination of ascitic fluid shows erythrocytes with no malignant cell. After second paracentesis, patient was stable and was planned to be referred for further evaluation and management.

3. Discussion

Fortune et al. defined refractory as ascites that is unresponsive to the appropriated sodium-restricted diet and high-dose diuretics (160 mg of daily furosemide and 400 mg of daily spironolactone) or rapid re-accumulation of ascites after therapeutic paracentesis.¹ Zhao et al. and European Association for the study of the Liver (EASL) divided refractory ascites as diuretic-resistant ascites and diuretic intractable ascites.^{4,5}

Ninety-percent of ascites cases are related to portal hypertension, but with high mortality rate, refractory ascites only occurs in 10% of the patient. Refractory ascites occurs when severe sodium and fluid retention have lost their compensatory pathways.^{3,6} American Association for the Study of Liver Diseases (AASLD) and EASL recommends diagnostic paracentesis for ascites patient to determine the etiology.¹ Serum ascites albumin gradient (SAAG) is also beneficial in determining the cause of ascites. SAAG <1.1 is considered low level of SAAG and indicates the absence of portal hypertension. High SAAG level of ≥ 1.1 shows the presence of portal hypertension.^{7,8}

Chronic alcohol consumption, viral infection (hepatitis B and C), and Non-alcoholic steatohepatitis (NASH) are some of the etiologic factors causing inflammation in the liver cells and eventually leading to cell damage, then cell death (necrosis). As a mechanism of inflammation, regeneration of the cell and collagen deposition happened in the liver, replacing the damaged hepatocytes cells. Fibrosis happened as the end result of the process. Liver's architecture changed from a low resistance structure to become high resistance (fibrotic) system. This leads to increased portal veins pressure, causing portal hypertension, hypoalbuminemia and nitric oxide accumulation. These processes then resulting to the leak of intravascular fluid across the liver surface, to

mesentery and accumulate in the abdominal space. The clinical spectrum of Alcoholic Liver Disease is fatty liver, alcoholic hepatitis, and cirrhosis. From cirrhosis, alcoholic liver disease can advance to hepatoma, or develops other complications such as spontaneous or sudden bacterial peritonitis (SBP), hepatic encephalopathy, and hepatorenal syndrome (HRS).⁹⁻¹²

Beside portal hypertension, other causes of ascites are neoplastic cause (lymphoma, peritoneal carcinomatosis, hepatocellular carcinoma, ovarian cancer and mesothelioma), inflammatory cause (infectious case, chemical cause, immunologic disorder and allergic causes) and miscellaneous cause (nephrotic syndrome, dialysis-associated ascites and thoracic duct obstruction). Portal hypertension can be divided into presinusoidal causes (portal vein thrombosis), sinusoidal causes (cirrhosis) and postsinusoidal causes (congestive heart failure).¹³

3.1 Diagnosis

Diagnostic criteria for refractory ascites are (1) ascites with intensive diuretic therapy (160 mg of daily furosemide and 400 mg of daily spironolactone) for at least 1 week with salt-restricted diet (< 5.2 g/day); (2) lack of response: mean weight loss of < 0.8 kg for 4 days and a urinary sodium output less than the sodium intake; (3) early recurrence of ascites: reappearance of grade 2 or 3 ascites with 4 weeks of initial mobilization; (4) diuretic-induced complications: diuretic-induced hepatic encephalopathy (defined as development of encephalopathy without any other precipitating factor).^{4,5,14}

Because of the history of daily alcohol consumption for the past 20 years, with the exclusion of hepatitis B and C, the presence of ascites that rapidly accumulate after paracentesis, medical history of multiple paracentesis in the last four months, and ultrasound findings; we can assume that the diagnosis of the patient is refractory ascites caused by hepatoma. The etiology is chronic alcohol consumption. From the ascitic fluid analysis it is revealed bloody ascites, which usually appear in hepatoma. Cytology test of ascitic fluid is not recommended as a base to exclude diagnosis of hepatoma because it usually revealed there is no malignant cell, which also seen in this patient. Lactate dehydrogenase (LDH) value in ascitic fluid for diagnosing malignancy is still debatable. A study found that high LDH value is sensitive in diagnosing malignancy but have low specificity. While other studies found that LDH will be lower in ascites with hepatic etiology.¹⁵⁻¹⁷

Due to limitation in our setting, patient was planned to be referred for further evaluation (laboratory and radiology) and management.

3.2 Management

3.2.1 Diuretics

Patient was given furosemide 60 mg daily with spironolactone 200 mg daily. Maximum dose of diuretics can be given to patients with ascites is spironolactone 400 mg/day by combination with furosemide 160 mg/day. Therapy with diuretics can be given for 1 week and then

evaluated. Beside diuretics, patient should also restrict their sodium intake to 2,000 mg per day. For patients showing no response to this therapy is considered as refractory ascites and then given other treatment options, usually LVP is the first choice if there is no contraindication.^{18,19}

With rapid reaccumulation of ascites fluid and no improvement with diuretics given, LVP was done in this patient. Decision to not use diuretics in maximum dose allowed was because the diagnosis of refractory ascites was made and rapid reaccumulation of the ascitic fluid, hence LVP was chosen as the treatment.

3.2.2 Large-Volume Paracentesis (LVP)

Large Volume Paracentesis is the standard and first line treatment for patients with refractory ascites. This procedure followed by administration of 6-8 grams of albumin (per liter of ascitic fluid) if more than 5 liters of ascites fluid evacuated. LVP immediately control massive ascites, providing pain relief and respiratory disturbance caused by intraabdominal pressure, but not improving patients prognosis. Indications for LVP are patient with tense ascites, respiratory disturbance, and abdominal pain because of tense ascites pressure, and refractory ascites that shows no response to medicine. Contraindication to LVP are acute abdomen requiring surgery, thrombocytopenia <20,000, coagulopathy (INR > 2.0), multiple abdominal scars, intraabdominal infection or adhesion, hepatic encephalopathy.²⁰⁻²² Ascites in the patients with chronic liver disease tend to recur with various speed for each individual. If it occurs very quickly, the patients might need frequent LVP. The complication of frequent LVP is circulatory dysfunction including hypovolemia, hypotension, hypoproteinemia, sepsis and intestinal perforation might happen. Indwelling Peritoneal Catheter is a modification of LVP. Using this type of catheter, the drain patency can be maintained for mean duration of 117.5 day. The ascites can be drained thrice a week ranging from 1-2 L for each drainage. Microorganism related to SBP is found in > 30% of the patients, but eradicated successfully with antibiotics. Albumin infusion is given for maximum of 72 hours for patients with tense ascites and large volume ascites.^{18,19,22}

Large Volume Paracentesis was done twice in this patient, with each paracentesis made 6,000 mL of ascitic fluid. We can see that massive ascites cause discomfort and respiratory disturbances in this patient, hence LVP was done as the first line of treatment.

3.3 Other management options and consideration

3.3.1 Vasoconstrictive medication

Midodrine, an α -adrenergic receptor agonist can be used to increase arterial blood volume and improves renal perfusion. This medication can restore the diuretic's sensitivity and usually given as adjunctive to diuretics in cirrhotic patients. Whether given as a single regimen, or combined with octreotide and albumin, midodrine is proved to be beneficial for ascites control. Thus, lowering the frequency of paracentesis. Midodrine is taken orally with the dose of 7.5 or 10 mg, three times a day. It is recommended to be medical treatment before LVP or TIPS.^{18,23-26}

Another α -adrenergic receptor agonist, clonidine, which in the same group of midodrine, shows its sympatho-inhibitory properties and suppresses RAAS in cirrhotic patients. Clonidine with the dose of 0.1 mg and given twice a day. Combination of clonidine and diuretics (spironolactone and/or furosemide) is proven to be beneficial in enhancing the effects of diuretics. Both midodrine and clonidine exhibit superior effects when combined with diuretics, compared to diuretic therapy alone. Although researches had reported the benefit of midodrine and clonidine, EASL did not recommend both medication addition on top of diuretics in their guidelines. While AASLD considered the use of midodrine in patients with hepatorenal syndrome.^{18,25,27}

Terlipressin, a vasopressin V1 receptor agonist in some studies were reported to be beneficial to improve renal function and inducing natriuresis in patients with refractory ascites. Combination of terlipressin and diuretic therapy with albumin shows synergistic effect.^{14,25}

We consider the use of vasoconstrictive medication is debatable for this patient. The reason is because midodrine is not available yet in Indonesia, and further research must be done for clonidine and terlipressin.

3.3.2 Transjugular Intrahepatic Portosystemic Shunt (TIPS)

Transjugular Intrahepatic Portosystemic Shunt is indicated for patient needing very frequent LVP. Several studies have reported TIPS superiority to LVP, but with more risk developing hepatic encephalopathy. Other meta-analysis study found that both TIPS and LVP didn't show difference between patient's survival.^{20,21} TIPS works by reducing portal hypertension, improves renal perfusion and renal excretion of sodium, and depletion in the ascites fluid production. The complication that may happened because of this procedure are stenosis or complete thrombosis of the stent and exacerbates hepatic encephalopathy. Contraindication of TIPS procedure are patient with established hepatic encephalopathy, old age cardio-respiratory disease Child-Pugh score > 11, infected ascites.^{22,28}

Transjugular Intrahepatic Portosystemic Shunt procedure can only be done if the patient referred to another island (Java). Therefore, we choose the available treatment options for this patient that can be done to control the ascites and stabilize the patient for further management planning or referral. LVP is the best choice in our setting, which has been reported with the same survival rate as TIPS.

3.3.3 Peritoneovenous Shunt (PVS)

The candidates for PVS are divided into two main groups; the first group is patients with intractable malignant or cirrhotic ascites not responding to adequate treatment and repeated LVP. Second group is patients with chylous ascites.²⁴ In these cases, other options available is peritoneovenous shunt (PVS). LeVeen Shunt was first introduced back in 1974. It works by placing a fenestrated catheter in the abdominal cavity, connected to another catheter that inserted from the subcutaneous layer of neck skin and enters the subclavian or jugular vein. When the abdominal pressure increased, ascites fluid will pass the

catheter to the vascular system. A variant of this procedure is Denver shunt. There is a manual pump to control the transfer of ascites fluid to the vascular system placed in the subcutaneous layer of the skin. This decreases the possibility of device's occlusion.²³ Contraindication for PVS are patients with hepatorenal syndrome, total bilirubin serum >7 mg/dl, coagulopathy (INR >2.0 or platelet count < 50.000), liver cirrhosis with HCC and prolonged PT, end stage renal disease, severe heart disease, sepsis, spontaneous bacterial peritonitis, nonsterile ascites from bile or urine leak, varicose vein bleeding, hepatic encephalopathy. Three main complications are occlusion, disseminated intravascular coagulation, and volume overload. A case from japan reported sepsis after 486 days after procedure, but the patient's ascites was in a good control. Researches and modifications to this procedure have been made to prevent these complications.^{18,22,28,29}

We should send the patient for further laboratory and radiology assessment to determine whether the patient might need this procedure. Because of the severity of the refractory ascites, PVS is not made a choice either, while being unavailable.

3.3.4 Automated Low-Flow Ascites Pump (Peritoneal Urinary Drainage/ Alfapump)

Also known as alfa pump, this innovative procedure introduced as a part of research in 2010 and available for use in 2011. The automated low-flow ascites pump is a device that pumps ascites from abdominal cavity to vesica urinary (bladder). This procedure can be chosen as one option in patient contraindicated to TIPS and waiting for liver transplantation. The criteria for this procedure are patients with good condition, should be in good nutritional status, normal kidney function, no infection for the last month and relatively good liver function. Contraindications are active infection, especially spontaneous bacterial peritonitis, urinary tract infection, and patients with life expectancy < 3 months, total immobilization, obstruction of the urinary tract, and loculated ascites. Most reported complication is the peritoneal catheter blockage and infection. It is reported that this treatment may be beneficial for the patients with refractory ascites and contraindicated for TIPS with good efficacy. Further modification and research for better optimization of the treatment is currently on progress. Few studies reported alfapump is correlated to better quality of life in patients with refractory ascites and less albumin replacement are required in 33% patients with alfapump.³⁰⁻³²

This treatment option can be considered as an option for our patient, after LVP and while waiting for donor, but not yet available in our setting, and the patient should be referred to other advanced medical facility.

3.3.5 Cell-free and concentrated Ascites Reinfusion Therapy (CART)

CART is modified version of LVP and indicated to patients with refractory ascites unresponsive to medical therapy. Contraindications for CART are infected ascites, bloody ascites, serum total bilirubin >5mg/dL, uncontrollable variceal bleeding, and hepatic encephalopathy. The benefit from this procedure is safety and efficacy, similar to LVP and albumin replacement. CART can prevents prerenal

disfunction and hypoalbuminemia caused by frequent LVP, thus lower the need for albumin transfusion in patients. The problem of CART is the high cost for the procedure.^{18,19,33} Aside from the high cost, this procedure is not suitable for our patient because he had ascites with erythrocytes (bloody ascites) which were contraindicated.

3.3.6 Liver Transplantation

Ascites is a marker of poor prognosis in patient with chronic liver disease. The best therapy for patient with refractory ascites and HRS is Liver Transplantation (LT). However, the shortage of organ donor, made it difficult to be done. In AASLD guidelines, liver transplantation are both in first line and second line treatment group, meaning it should always be considered in patients with cirrhosis and ascites. The goal of the treatment is to achieve the best quality of life for the patients.^{18,21,25,27}

Some indication for liver transplantation are Hepatitis B and C, Alcohol-related liver disease. Contraindication for this procedure is anatomic abnormality, malignancy outside liver, untreated sepsis, advanced state of cardiopulmonary disease, active alcohol or drug abuse, AIDS. Acute or early complications of liver transplantation are graft rejection, infection, stenosis and thrombosis of hepatic artery or veins. Long term complications including chronic kidney disease, hypertension, diabetes mellitus, dyslipidemia, obesity, bone or neurological disorder and tumor development and recurrence of disease such as Hepatitis B, C, Hepatocellular Carcinoma, or autoimmune related disease.^{18,19,22,34}

The best treatment for patient is liver transplant. But, because of lack of resources, facilities and organ donor, this definitive treatment is still considered a difficult option to be realized. Therefore, we should aim for other treatment options which more feasible and available, to improve patients quality of life while waiting for the liver donor.

4. Conclusion

Refractory ascites is a complication of liver diseases that is difficult to treat. The presence of refractory ascites indicates a poor prognosis with a high mortality rate. Liver transplant is the definitive therapy for refractory ascites caused by chronic liver disease and hepatoma. Some other procedures such as LVP, PVS, and TIPS can be done to reduce symptoms before liver transplant procedure is performed. More researches should be done to evaluate the currently available treatment and also as a quest to find the best treatment options for refractory ascites.

5. Author Contribution

All authors contributed equally.

6. Conflict of Interest

There is no conflict of interest in this case report.

7. Acknowledgement

The authors acknowledge and thankful for the patient & family, doctors, nurses, and our hospital superintendent.

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