CLINICAL REVIEW

Hepatic Hydrothorax

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Hepatic hydrothorax (HH) is an uncommon complication of liver cirrhosis and portal hypertension that signifies decompensated disease and portends a poor prognosis. HH most often present as a right-sided pleural effusion with varying symptoms. The pathogenesis of HH is thought to be related to diaphragmatic defects and the unidirectional flow of fluid from the peritoneal to the pleural cavity. Diagnostic thoracentesis is required to confirm the diagnosis and rule out infection or other causes of pleural effusion. HH is managed similarly to ascites, with salt restriction and diuretics being the mainstay of therapy. Treatment is often difficult for refractory HH and liver transplantation is the only definitive treatment. Other therapeutic options are not firmly established and are associated with high morbidity and mortality. These include portal system decompression, therapeutic thoracentesis, indwelling pleural catheters, pleurodesis, and surgical repair of diaphragmatic defects. Due to limited availability of organ transplantation and the large proportion of patients who are not transplant candidates, therapeutic strategies to relieve symptoms and attempt to improve morbidity and survival are necessary. We present a classic case of hepatic hydrothorax in a patient with alcoholic liver cirrhosis.

Case Report

A 47-year-old male with alcoholic liver cirrhosis presented to the hospital with dyspnea. History included decompensated cirrhosis with ascites, encephalopathy, and esophageal varices, status post prophylactic variceal banding. He was admitted one-month ago with encephalopathy and sepsis. During that admission, a chest radiograph (CXR) showed a new right pleural effusion. Notable labs included albumin 2.5 g/dL, lactate dehydrogenase (LD) 287 U/L, and brain natriuretic peptide (BNP) 43 pg/mL. Diagnostic and therapeutic thoracentesis was performed with removal of 1500 cc of pleural fluid. Chemical analysis showed pleural fluid albumin <0.3 g/dL, LD 54 U/L, protein <0.6 g/dL, a polymorphonuclear (PMN) cell count of 50 cells/mm^3, and negative bacterial cultures. Serum-pleural albumin gradient (SPAG) was > 2.2. These findings were consistent with a transudative effusion (values >1,1 indicate a transudative effusion) and uncomplicated HH without evidence of pleural infection. Furosemide 40 mg daily and spironolactone 50 mg daily in addition to a low sodium diet were prescribed. Since discharge, despite compliance with diuretic treatment, the patient developed progressive shortness of breath prompting return to the hospital. He denied fever, chills, chest pain, confusion, abdominal pain, abdominal bloating, and leg swelling. Current home medications included lactulose, furosemide, spironolactone, and pantoprazole. Of note, the patient had stopped all alcohol consumption more than a year ago.

Initial vital signs showed blood pressure of 120/51 mmHg, heart rate of 70 beats/minute, temperature of 37°C, respiratory rate of 23 breaths/minute, and oxygen saturation of 89% on ambient air which increased to 97% with 2-liter nasal cannula oxygen. The patient was speaking in full sentences. Physical examination was otherwise significant for normal mentation without asterixis, minor scleral icterus, and trace pitting edema in the lower extremities. Pulmonary exam revealed mild accessory muscle use for respiration with diminished breath sounds and dullness to percussion throughout the right hemithorax. Laboratory testing in comparison to prior testing showed a stable complete blood count with chronic thrombocytopenia secondary to splenomegaly, stable electrolytes (sodium 136 mEq/L, potassium 4.6 mEq/L) with elevation in creatinine (1.23 mg/dL from 0.9 mg/dL). Total bilirubin was 4.1 mg/dL and albumin 2.6 g/dL. Stable coagulopathy consistent with advanced liver disease was present with INR 1.9. Model for End-stage Liver Disease (MELD) score was calculated to be 22. CXR revealed recurrence of large right-sided pleural effusion with associated mediastinal shift suggesting at least partial collapse of the right lung. The left lung was normal in appearance (Figure 1). Subsequent computed tomography (CT) scan of the chest showed a massive right pleural effusion with collapse of the right lung and mediastinal shift. No significant lung nodules, abnormal lymphadenopathy, or pleural masses were identified. The liver was noted to be cirrhotic with associated sequelae including splenomegaly, paraesophageal, perigastric, and perisplenic varices (Figure 2).

Pulmonology and hepatology consultations were obtained. The patient was diagnosed with decompensated alcoholic liver cirrhosis with acute hypoxic respiratory failure due to rapidly recurrent hepatic hydrothorax. The diuretic regimen was increased, and octreotide was initiated for splachnic vasoconstriction, but he quickly developed worsening renal function. The patient was not a candidate for transjugular portosystemic shunt (TIPS) due to recent history of hepatic encephalopathy and MELD score of >18. Consequently, therapeutic thoracentesis was performed with symptomatic improvement and diuretic doses were reduced. Repeat CXR several days later showed improvement in right pleural effusion (Figure 3), and renal function subsequently stabilized. The patient was dis-

charged with close hepatology follow-up and referred for outpatient liver transplant evaluation.

Discussion

Pathogenesis and Diagnostic Criteria of HH

"Pleural effusion may present itself either as the herald or as the accompaniment of significant disease…".[1] The association of pleural effusion and liver disease was first described in the nineteenth century by Laennec.[2] In 1958, Morrow et al. coined the term 'hepatic hydrothorax' to describe this relationship. In this early report by Morrow et al., a 63-year-old patient with alcoholism presented with ascites and lower extremity edema and was diagnosed with decompensated liver cirrhosis. He subsequently developed dyspnea and a massive right pleural effusion requiring weekly serial thoracentesis for several months. Analysis of the pleural fluid showed a transudate. In a review of the literature available at the time, the authors noted that hepatic hydrothorax seems to only occur with advanced cirrhosis complicated by ascites and hypoalbuminemia. It was hypothesized that local factors could contribute to hepatic hydrothorax including increased pressure in the azygous vein, movement of ascitic fluid through diaphragmatic lymphatics from the peritoneal to the pleural cavity, and holes or defects in the diaphragm allowing direct passage of fluid to the pleural space. The authors concluded that therapy of hepatic hydrothorax should be directed at treating portal hypertension and that the prognosis depends primarily on the underlying cirrhosis.[1]

Currently, hepatic hydrothorax (HH) is defined as the excessive (>500 mL) accumulation of fluid in the pleural space in association with cirrhosis and portal hypertension, without underlying cardiac or pulmonary disease. HH is seen in only 5-10% of patients with cirrhosis and accounts for 2-3% of all pleural effusions.[3-7] HH develops most frequently on the right-side (~80%) but can also be left-sided (~15%) or bilateral (~2-10%).[7,8] HH is more frequent in those with advanced liver disease with ascites, but ascites is not required for diagnosis and may be undetectable in ~15-20% of patients.[3,5,7,8] Symptoms vary from an asymptomatic pleural effusion to dyspnea and hypoxic respiratory failure. Despite the progress in modern medical treatment, HH remains difficult to manage and has a poor prognosis with a high mortality. HH should be viewed as a manifestation of advanced and decompensated cirrhosis, similar to ascites, hepatic encephalopathy, or variceal hemorrhage.[3-9]

While several mechanisms have been proposed for the development of HH, the most widely accepted explanation is direct passage of ascitic fluid from the peritoneal to the pleural space through diaphragmatic defects.[2-9] This theory of HH has been confirmed by imaging techniques where dyes or radiolabeled material were injected into the peritoneal cavity and subsequently detected in the pleural space. These holes are more frequent in the right hemidiaphragm as it is more tendinous than the left side accounting for the right sided predominance of HH. In patients with cirrhosis, ascitic fluid build-up occurs as a result of portal hypertension and concomitant splachnic vasodilation and activation of neurohormonal pathways leading to renal dysfunction and decreased sodium and water excretion. The flow of ascitic fluid is unidirectional into the pleural cavity due to the pressure gradient created by the negative intrathoracic pressure during respiration and positive intra-abdominal pressure exacerbated by ascites. In cases of 'isolated' HH (i.e. ascites is not clinically detectable), it is thought that the pleural reabsorption rate of ascites is essentially equal to the ascites production rate in the abdominal cavity.[2-9]

Clinical Presentation, Diagnosis and Differential Diagnosis of HH

The clinical presentation of HH is variable. Due to severe underlying liver disease, symptoms from cirrhosis and ascites often predominate. Respiratory symptoms vary and some patients have asymptomatic pleural effusion discovered incidentally on CXR while others have progressive respiratory symptoms. Symptom severity depends on effusion volume, how rapidly it accumulates, and the presence of underlying cardiopulmonary disease. Dyspnea at rest (~35%), cough (~20%), pleuritic chest pain, and hypoxic respiratory failure can occur. Isolated HH, without clinical evidence of ascites, has been reported in up to 20% of patients. If fever, pleuritic chest pain, or encephalopathy is present, spontaneous bacterial empyema or pleuritis (SBPE) (described below) should be suspected.[2-5]

If a pleural effusion is found in a patient with cirrhosis, diagnostic thoracentesis with fluid analysis is required. Other causes of pleural effusion such as infection and primary cardiac, pulmonary, or pleural disease must be excluded. CT scan of the chest, brain natriuretic peptide (BNP), and echocardiogram to evaluate cardiac function are often indicated to evaluate these other causes of pleural effusion. In a study of patients with cirrhosis and pleural effusions who underwent thoracentesis, 70% of effusions were due to uncomplicated HH and 30% were from other causes (e.g. SBPE, tuberculosis, malignancy, parapneumonic effusions, etc). When the effusion was left-sided only, 35% were determined to be from HH.[5-7] While caution is needed, the complication rate of diagnostic thoracentesis is minimal even in patients with liver disease and significant coagulopathy.

In uncomplicated HH, analysis of pleural fluid will reveal a transudate according to Light's criteria in the vast majority of patients.[3,5-9] Routine tests include protein, albumin, lactate dehydrogenase, cell count, gram stain and culture. Inoculation of pleural fluid into a blood culture bottle immediately at the bedside can dramatically increase yield of bacterial growth (~33 to 75%). Cell count is needed to exclude SBEP. In patients with ascites, it is important to do paracentesis prior to thoracentesis to decrease rapid inflow of ascitic fluid back into the pleural space. Both the serum-to-ascites albumin gradient (SAAG) and the serum-to-pleural fluid albumin gradient (SPAG) will be > 1.1 g/dL which is consistent with portal hypertension. Rarely,

patients with HH may have elevated pleural fluid protein concentration in the exudative range due to excessive diuretic treatment. These patients will still have a SPAG > 1.1 g/dL.[5-7]

In patients with an isolated left sided effusion and/or the absence of ascites, the diagnosis may be uncertain. In these cases, tests to evaluate for communication between the peritoneal and pleural spaces are available. In practice, these diagnostic methods are usually only performed if surgical repair of diaphragmatic defects is being considered. The test of choice is nuclear scintigraphy, which involves infusing radiolabeled microspheres intraperitoneally. Migration of the radioisotope to the pleural cavity confirms communication between these spaces. Sensitivity of this procedure is excellent if thoracentesis is performed prior to the administration of peritoneal isotope thus reducing the pleural pressure and increasing the pressure gradient between the spaces.

SBEP, also called spontaneous bacterial pleuritis, is a serious complication of HH with a high morbidity and mortality (~20%).[3,7] The incidence of SBEP is ~15% in patients with HH.[6] By definition, SBEP is pleural fluid infection in a patient with HH after pneumonia is excluded. SBEP is not the same as empyema associated with pneumonia and is treated differently. SBEP is comparable to spontaneous bacterial peritonitis (SBP) with similar pathogenesis. It is more common in patients with more severe liver disease and those with associated SBP. It is notable that ~40% of patients with SBEP do not have SBP. Presentation typically includes dyspnea, abdominal pain and/or pleuritic chest pain, fever, encephalopathy, and often worsening of renal function. Similar to SBP, *Escherichia coli, Streptococcus* species, *Enterococcus*, and *Klebsiella* are the most commonly identified bacteria in SBEP. Pleural fluid analysis in SBEP reveals a transudate. Diagnosis relies on a high index of suspicion and cell count and culture. Diagnostic criteria for SBEP are a PMN cell count >250 cells/mm^3 with a positive culture or a PMN count > 500 cells/mm^3 regardless of culture. In addition, the SPAG is > 1.1 g/dL and pneumonia or other contiguous infection must be excluded by CXR.[3,7,10] Treatment of SBEP is similar to that of SBP, with the drug of choice being third generation cephalosporins (e.g. ceftriaxone) for 7-10 days. Chest tubes should be avoided due to a high complication rate. Mortality is high in patients with SBEP and urgent liver transplantation evaluation is warranted if this serious complication occurs.[5]

Treatment of HH

HH is often difficult to manage and transplant organs are in limited supply and many patients either are not candidates or die while awaiting transplantation. In general, other treatment strategies are aimed at reducing formation of ascitic fluid, draining or obliterating the pleural space, or preventing fluid movement across the diaphragm.[2-9] In addition, strict alcohol abstinence along with avoidance of medications that decrease blood pressure and/or impair renal perfusion (e.g. angiotensin converting enzyme inhibitors, angiotensin receptor blockers, non-steroidal anti-inflammatory drugs, and non-selective beta blockers such as propranolol) is also recommended.[8] Approximately 25% of patients are not responsive to initial medical treatment (e.g. salt restriction and diuretics) and are considered to have 'refractory HH'.[3,5-9] Patients with refractory HH often have renal as well as liver dysfunction and are at high risk for complications. There is no standard of care for these patients and treatment must be individualized depending on comorbidities and severity of underlying disease. As outlined below, TIPS is typically the next treatment of choice in patients who are candidates and can be a 'bridge' to transplantation. For those who are not candidates for TIPS, repeated therapeutic thoracentesis, indwelling pulmonary catheters, or surgery including VATS with pleurodesis or direct repair of diaphragmatic defects can be considered (Table 1).[2-7,9]

For all patients, initial treatment includes a low-sodium diet (< 2g/day) with the addition of diuretics in a stepwise fashion to promote negative sodium balance and reduce fluid accumulation. Specifically, spironolactone is usually initiated at 50-100 mg/day and gradually titrated up over several weeks with close monitoring of weight and electrolytes. If monotherapy with spironolactone is insufficient or if hyperkalemia develops, furosemide is added beginning at 40 mg/day and titrated up over several weeks. Doses can be increased every 3-5 days to maximum doses of spironolactone 400 mg/day and furosemide 160 mg/day as tolerated. Urinary sodium can also be monitored to help guide diuretic dosage. Goal weight loss should be at least 2kg/week. For patients with tense ascites, large-volume paracentesis (with albumin infusion) is recommended. Poor compliance, resistance to diuretic treatment, volume depletion, renal dysfunction, or electrolyte disturbances can lead to treatment failure.[3-6]

Refractory HH occurs in ~25% of patients when salt restriction and diuretics are either ineffective in relieving respiratory symptoms or not tolerated due to side effects. Several options are available to attempt to relieve symptoms and minimize pulmonary complications.[9] Repeated therapeutic thoracentesis is typically required to rapidly relieve symptoms. As stated previously, paracentesis to remove ascites should always be performed prior to thoracentesis to minimize rapid recurrence. Frequent therapeutic thoracentesis should not be used as maintenance treatment as its benefits are often short lived and the risk of complications increases.[7] While thoracentesis is generally a safe procedure, complications can include bleeding, pneumothorax, empyema, and re-expansion pulmonary edema if a large volume of fluid is removed. The more significant problem with repeated thoracentesis is fluid, albumin, and electrolyte depletion that can be associated with clinical deterioration (e.g. renal failure, hepatorenal syndrome, infection) and decreased quality of life. If a patient is on maximum medical therapy and still requiring thoracentesis more than once every 2 weeks, another intervention should be considered.[3-6,8]

TIPS is a procedure that creates a shunt between the portal and hepatic vein leading to decreased portal pressure and decreased rate of production of ascites and pleural effusion. Due to its efficacy and lack of better treatment options, TIPS is often the

procedure of choice for qualifying patients with HH.[3-7,9] While some debate remains, the main contraindications to TIPS include advanced age (> 65 years old), MELD score > 18, hepatic encephalopathy, heart failure, and pulmonary hypertension. As patients with refractory HH often have advanced liver disease, many may not be candidates.[9] TIPS is a 'bridge' to transplantation in those who are candidates for a transplant and can be viewed as definitive palliative therapy for those who are not. Several non-controlled studies have evaluated TIPS in patients with refractory HH and showed a ~80% response rate. However, more than 25% of patients will require repeated pleural drainage following TIPS procedure.[6,9,11] Complications of TIPS may include worsening pulmonary hypertension, shunt blockage, infection, and hepatic encephalopathy. It is important to note that TIPS does not improve the overall prognosis of patients with advanced liver disease and 1-year average survival is reported at ~50%.[9]

Chest tubes should not be placed in patients with HH due to extremely high morbidity and mortality.[2-9,12] Pleural fluid can rapidly reaccumulate and output is high making removal of the chest tube difficult. This leads to malnutrition and other complications. In one series of patients with HH treated with chest tubes, >90% had at least one complication (e.g. acute kidney injury, infection, pneumothorax) and the overall 3-month mortality was 35%.[12] In another study, >80% of patients had serious complications. Even in cases of SBEP, chest tubes should not be placed unless there is frank pus.[3,6]

Tunneled indwelling pleural drainage catheters (IPC) (e.g. *PleurX*) have been used extensively to alleviate dyspnea in patients with malignant pleural effusions. Due to the controlled method of evacuating pleural fluid with IPC, there are less complications related to uncontrolled fluid loss. Recently, IPC is more frequently utilized for nonmalignant effusions including HH. Multiple small series in patients with HH have shown promising results for IPC as a 'bridge' to transplant and as a palliative treatment. Proposed benefits of IPC include avoiding recurrent thoracentesis and a reported ~30% spontaneous pleurodesis rate in patients with HH, although it takes a median time of > 4 months to achieve pleurodesis.[9] As with other treatment strategies for HH, complications are still a concern, including a high infection rate. Further study on IPC, including larger randomized trials, is needed to determine efficacy and long-term safety.[4-6,8,9]

Other treatments that can be considered in selected patients include pleurodesis (via tube thoracotomy or VATS) and/or surgical repair of diaphragmatic defects, though these procedures also have a high rate of complications.[8,9] Pleurodesis is an option in cases of failed repeated thoracentesis. Unfortunately, when used for HH, pleurodesis is less effective (only 50-75% success rate) than when it used for malignant effusions (~90% success rate) and the recurrence rate is significant (~ 25%).[3,5,9,13] This results from the constant inflow of ascitic fluid into the pleural space not allowing apposition of the visceral and parietal pleura and disrupting the process. Pleurodesis is typically reserved for patients with minimal ascites who do not have other options. Continuous positive airway pressure (CPAP) has been used in combination with pleurodesis to increase the thoracic pressure therefore decreasing the ascitic fluid shift.[6] VATS can also improve the success rate (~70-90%) of pleurodesis.[13] Unfortunately, a variety of complications including fever, bleeding, sepsis, encephalopathy, liver, and renal failure have been described following attempted pleurodesis.[3]

Surgical closure of diaphragmatic defects, often done in combination with pleurodesis, with fibrin glue, suturing, pleural flap or synthetic mesh material has also been used for refractory HH.[2,3,9,14] Thoracic surgery itself carries a high risk of morbidity and mortality in patients with portal hypertension and should be avoided in patients with a MELD score > 15.[9] Various reports from small series of patients undergoing VATS have shown successful results for these procedures, but complications can be significant. One study of thoracoscopic mesh to repair diaphragmatic defects was initially effective in 80-90% of patients. However, there was a significant 30-day (~10%) and 90-day mortality (~25%) rate. When data from ten case series was combined, the average 30-day mortality was ~22%. Deaths were mainly related to complications of severe end-stage cirrhosis including infection, renal failure, gastrointestinal bleeding, and encephalopathy with liver failure.[3,6] A recent paper suggests a '4-step approach' to the minimally invasive surgical strategy for HH that includes localizing defects in the diaphragm by creating a pneumoperitoneum, thoracoscopic pleurodesis, postoperative CPAP to increase thoracic pressure, and postoperative peritoneal drainage to decrease intraperitoneal pressure. The strategy was successful in a small number of patients but ~70% of patients died during the 11-month follow up period from non-surgical causes.[14] These procedures do not change the natural history of the underlying liver disease and the absence of randomized prospective trials makes evaluation of their efficacy and safety difficult to determine at this time.[3,7]

Pharmacologic treatment of portal hypertension that causes splachnic vasoconstriction (e.g. octreotide, midodrine, and terlipressin) may help selected patients but further study is needed.[3,4,6]

Several authors have proposed algorithms for the management of HH.[3,5-7,9,11] The first step in treatment for all patients is sodium restriction and diuretics. If HH is refractory to initial medical treatment, liver transplant evaluation should begin without delay. Management is otherwise challenging, and treatments should be viewed as a 'bridge' to transplant or as palliative therapy in patients who are not transplant candidates. Due to the shortage of high-quality evidence and significant risks of complications, treatment should be individualized. Repeated thoracentesis is reasonable if the wait time for transplant is short (< 3 months) but if it is needed more than every 2 weeks other options should be considered. TIPS is the next treatment choice in patients who are candidates. In those who do not qualify for TIPS, other options such as pleurodesis,

IPC, or surgical repair of diaphragmatic defects in a center of expertise can be considered.

The outcome of patients with HH, regardless of severity, is encouraging after liver transplantation. Refractory HH does not appear to affect early postoperative outcomes or long-term survival after transplant.[3,15] While pleural effusion can persist in the early postoperative period after liver transplant, it resolves within a short time and patients with refractory HH have similar outcomes as other patients undergoing transplantation. Unfortunately, organs are limited. In 2016, there were over 7,000 liver transplants done with nearly 15,000 patients on the waiting list. The median wait time for patients with a MELD score of 15-29 was nearly 2 years.[11] As a result, is it imperative to develop alternative evidence-based strategies to improve survival in patients with HH.

Conclusion

In conclusion, HH is an uncommon manifestation of decompensated liver cirrhosis that indicates a poor prognosis. HH typically presents as a right-sided pleural effusion and diagnosis is straightforward in most cases, but diagnostic thoracentesis is necessary to rule out infection and other causes of pleural effusion. Treatment is often challenging and is aimed mainly at treating underlying ascites. Liver transplantation remains the only definitive therapy. Due to limited availability of transplant organs, the goal of other therapeutic strategies is to relieve symptoms and prevent pulmonary complications in selected patients. It is imperative for clinicians to be aware that HH is a severe complication of cirrhosis and early referral for transplant evaluation is important for all patients.

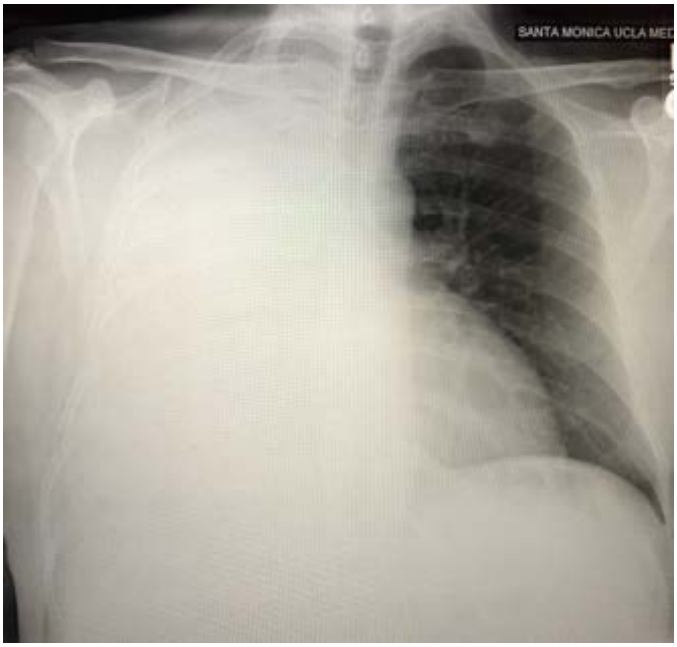

Figure 1. CXR. Large right-sided pleural effusion with associated mediastinal shift suggesting at least partial collapse of the right lung. The left lung is normal in appearance.

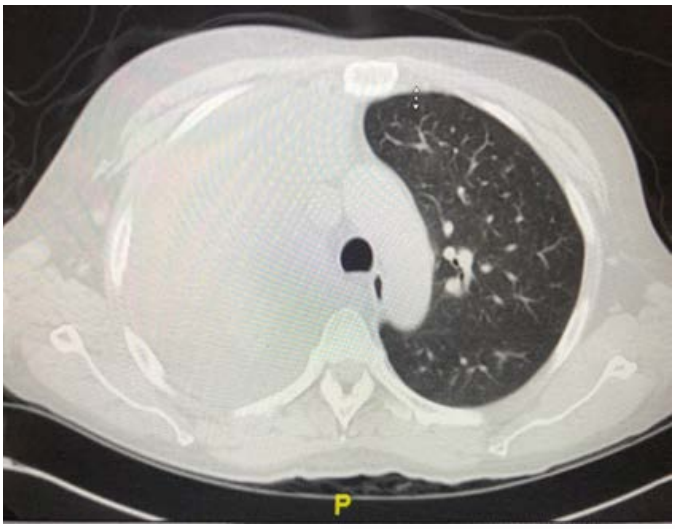

Figure 2. CT Scan Chest. Hyper-expansion of the right hemithorax with large right-sided pleural effusion and associated complete collapse of the right lung. Mild leftward shift of the mediastinum. Left lung is clear. The liver is cirrhotic with associated sequelae including splenomegaly, and numerous para-esophageal, peri-gastric, and peri-splenic varices.

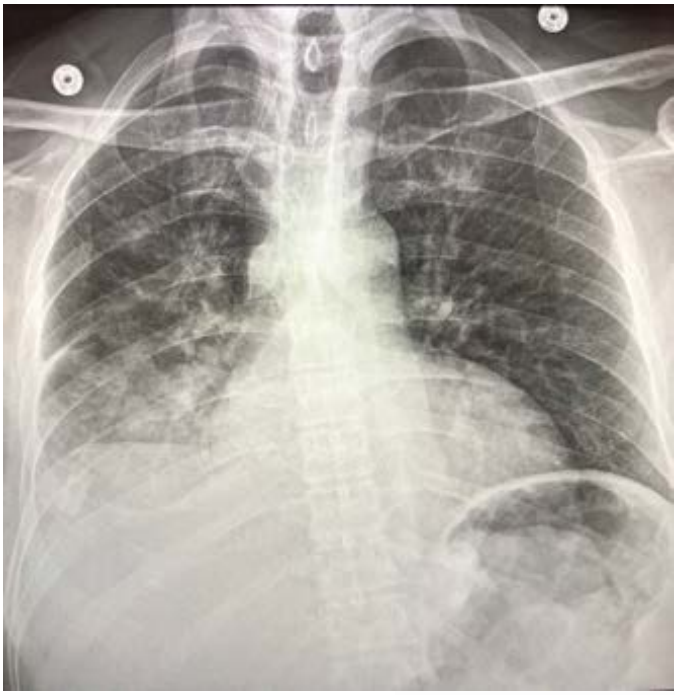

Figure 3. CXR after thoracentesis. Right pleural effusion has decreased with small residual. No pneumothorax. Improved aeration in the right base with residual opacities, likely atelectasis.

Table 1. **Treatment Options for Refractory Hepatic Hydrothorax[5]**

A. Liver transplantation –the only definitive treatment.
B. Repeated thoracentesis
C. Transjugular intrahepatic portosystemic shunts (TIPS)
D. Indwelling pleural catheters (IPC)
E. Pleurodesis
F. Surgery to repair diaphragmatic defects

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