

Case report

A difficult pleural effusion in a cirrhotic patient

A 61-year-old male presented to medical ambulatory care (MAC) with 2-week history of progressive exertional dyspnoea and dry cough. He denied haemoptysis, constitutional symptoms or diurnal variation. He was a nonsmoker.

His past medical history included alcoholic liver cirrhosis, oesophageal varices, alcohol-induced peripheral neuropathy, previous hepatic encephalopathy, secondary hypertension and a hiatus hernia. He had been abstinent for 5 months.

His medication list was cetirizine 10 mg daily, lactulose 20 mL four times a day, multivitamin capsules, omeprazole 20 mg twice daily, Peptac 10–20 mL as and when required, rifaximin 550 mg twice daily, senna 15 mg daily and thiamine 100 mg daily.

On examination, he was comfortable at rest and his vital signs were normal, with saturations of 98% on air and a respiratory rate of 16 breaths per min.

He had no clubbing or palpable lymphadenopathy. He had dullness to percussion at the right base extending to half way up his hemithorax, with reduced air entry over that same area. Cardiovascular examination was normal and there was no ankle oedema. There was no clinically detectable ascites.

Initial investigations revealed haemoglobin of $129 \text{ g}\cdot\text{L}^{-1}$ (normal range $130\text{--}180 \text{ g}\cdot\text{L}^{-1}$), white cell count of 7.3×10^9 per L (normal range $4\text{--}11\times 10^9$ per L), platelet count 71×10^9 per L (normal range $140\text{--}400\times 10^9$ per L). He had normal renal function. His prothrombin time was 20.4 s (normal range 12.0–15.0 s), activated partial thromboplastin time

120.2 s (normal range 24.0–35.0 s) and fibrinogen count $4.1 \text{ g}\cdot\text{L}^{-1}$ (normal range $1.8\text{--}4.5 \text{ g}\cdot\text{L}^{-1}$). Plasma lactate dehydrogenase (LDH) levels were $200 \text{ U}\cdot\text{L}^{-1}$. His liver functions test results were bilirubin $35 \mu\text{mol}\cdot\text{L}^{-1}$ (normal $<21 \mu\text{mol}\cdot\text{L}^{-1}$), alkaline phosphatase $92 \text{ U}\cdot\text{L}^{-1}$ (normal range $30\text{--}130 \text{ U}\cdot\text{L}^{-1}$), alanine transferase $30 \text{ U}\cdot\text{L}^{-1}$ (normal $<40 \text{ U}\cdot\text{L}^{-1}$), total protein $49 \text{ g}\cdot\text{L}^{-1}$ (normal range $60\text{--}80 \text{ g}\cdot\text{L}^{-1}$) and albumin $26 \text{ g}\cdot\text{L}^{-1}$ (normal range $25\text{--}50 \text{ g}\cdot\text{L}^{-1}$).

His chest radiograph revealed a large right pleural effusion (figure 1). An ultrasound showed a large anechoic pleural effusion. Under asepsis, 1 L straw-coloured pleural fluid was removed *via*

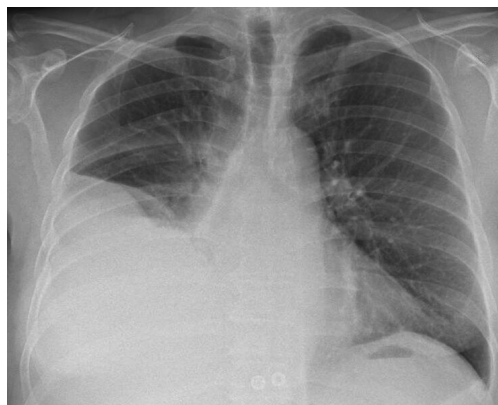


Figure 1 Chest radiograph showing large, right-sided pleural effusion.

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Failure of medical management of hepatic hydrothoraces will require pleural interventions. Indwelling pleural catheters and medical thoracoscopy can help. Careful liaison with liver transplantation teams is required. <https://bit.ly/2XO1naG>



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thoracocentesis with excellent symptom resolution. The pleural fluid was sent for microbiological, cytological and biochemical analysis. An urgent referral to the pleural clinic was made and the patient discharged.

5 days later, the patient re-presented with dyspnoea and was seen again on MAC. A repeat chest radiograph showed re-accumulation of his effusion.

Pleural fluid analysis was then available: fluid LDH $250 \text{ U}\cdot\text{L}^{-1}$, fluid protein $10 \text{ g}\cdot\text{L}^{-1}$, fluid pH 7.59 and fluid glucose $7.4 \text{ mmol}\cdot\text{L}^{-1}$. Microbiology and cytology were negative. Corresponding plasma and glucose levels were not available. Repeated blood tests showed no deterioration in his liver function tests and there was still no ascites on clinical examination.

Respiratory and gastroenterological opinions were sought.

Given his symptoms and good resolution previously with thoracocentesis, a repeat thoracocentesis was performed and 2 L were removed from the pleural space with no complications.

An abdominal ultrasound showed no evidence of ascites and a diffuse irregular outline of his liver, consistent with cirrhosis. There was associated splenomegaly.

This man was well known to the liver service. He had presented previously with hepatic encephalopathy due to decompensated liver disease. Furosemide 40 mg once daily and spironolactone 50 mg twice daily were started, alongside salt and water restriction at $1.5 \text{ L}\cdot\text{day}^{-1}$. Follow up was arranged to check his renal function.

Over the next 5 weeks, the patient presented almost weekly to MAC for review and with recurring breathlessness. His pleural effusion re-accumulated, even to cause a complete white out of his left hemithorax on several occasions. Furosemide was increased to 120 mg twice a day orally and spironolactone to 400 mg once a day but the effusion kept recurring.

Kidney and liver function tests remained stable.

A cardiac echocardiogram was performed. It showed preserved right and left systolic function with no valvular abnormality. His B-type natriuretic peptide levels were normal. His urinary albumin/creatinine ratio was normal. A computed tomography (CT) showed a simple right pleural effusion with no pleural enhancement, thickening or nodularity (figure 2). A small left effusion was also noted.

The patient was reviewed by the pleural disease lead in the hospital.

Task 1

What is the definition of a hepatic hydrothorax?

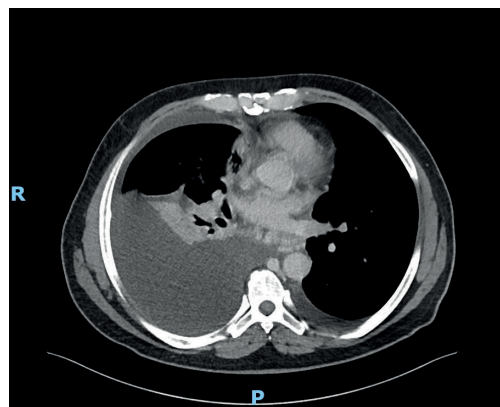


Figure 2 CT image showing large right (R) pleural effusion with no pleural enhancement or nodularity. A small left pleural effusion is also noted. P: posterior.

Answer 1

Light's criteria define a pleural effusion as an exudate if at least one of the following exists: the ratio of pleural fluid protein to serum protein is >0.5 ; the ratio of pleural fluid LDH to serum LDH is >0.6 ; and the pleural fluid LDH is more than two-thirds of serum LDH upper limit of normal. Hence, this patient has a transudate. Differential diagnoses include liver failure, renal failure or cardiac dysfunction. Negative cytology is reassuring but up to 10% of malignant effusions can be transudative. As such, the most likely diagnosis was a transudative pleural effusion due to known cirrhosis.

A hepatic hydrothorax is a transudative pleural effusion that occurs in patients with liver cirrhosis and portal hypertension in the absence of cardiac or pleural disease [1, 2]. Hepatic hydrothoraces are mostly right sided, as diaphragmatic defects through which ascites track up are predominantly right sided. However, up to 17.5% of effusions are on the left and 3% are bilateral. Mechanisms implicated in the tracking of ascites and formation of a hepatic hydrothorax are generation of negative intrathoracic pressure during respiration and a piston-like effect of the diaphragm causing unidirectional movement of fluid into the pleural cavity [1, 2].

Hepatic hydrothoraces have been described in the absence of ascites [3]. Unidirectional flow of radiolabelled colloid (matching the rate of ascites formation) through the diaphragm has been demonstrated [4].

Task 2

What is the initial management of a hepatic hydrothorax?

Answer 2

The first step in the management is sodium restriction and medication such as loop diuretics and direct aldosterone antagonists [2]. Approximately 21–26% of patients develop refractory hepatic hydrothorax and thoracentesis are required for symptom control. This can be needed every few days to every 2–3 weeks.

Refractory hepatic hydrothorax is an indication for referral for consideration of liver transplantation and, potentially, a transjugular intrahepatic portosystemic shunt (TIPSS) procedure [1].

The patient was thus optimised by aspirating his pleural space to dryness and was referred for an urgent assessment by the liver team at the local tertiary centre.

A week after this assessment, 10 weeks after the initial presentation, and after eight aspirations of pleural fluid, the patient was reviewed on MAC and reported increasing dyspnoea again.

Task 3

What are the options for further management?

Answer 3

Options are limited. There were some concerns about the patient not sticking to a strict fluid restriction and of concordance with his prescribed medications. As such, he was admitted under the pleural team and a strict 1-L fluid and salt restriction regime was started.

Intravenous furosemide was administered and the dose was slowly increased to 120 mg twice a day. The spironolactone dose remained unchanged at 400 mg once daily. After 12 days of inpatient medical therapy, the chest radiograph had not changed and still showed a large left effusion. However, the increased medications caused postural hypotension and mild hyponatraemia.

It was felt that ongoing instrumentation of the pleural cavity was inevitable. However, the patient was reluctant to have more aspirations, as the pleural punctures and drainages were increasingly painful. There had also been some fluid leaking from previous puncture sites, requiring deep suturing.

Discussion

Thoracentesis has a very low complication rate, with a pneumothorax rate of 0.6–6% and haemothorax rate of 0–2% [5]. SHOJAE *et al.* [6] described a case-control study of 82 patients with hepatic hydrothorax (274 thoracenteses) and 100 control patients (188 thoracenteses). There was a higher overall complication rate with repeat thoracentesis in the hepatic hydrothorax group (8% *versus* 0%, $p=0.016$; 95% CI 1.5–14.6%) and that the cumulative risk of complications increased with sequential procedures. The Model for End-Stage Liver Disease (MELD) score was an independent predictor of haemothorax (OR 1.19, 95% CI 1.03–1.36; $p=0.012$). Complications were defined as pneumothorax (including pneumothorax *ex vacuo* requiring hospitalisation or observation), haemothorax, re-expansion pulmonary oedema and continued leak from procedure site.

We would argue that pain was a complication. The first aspiration was painless but subsequent ones became increasingly painful despite increasing doses of topical 1% lidocaine (up to 200 mg used for a 69 kg man) and pre-medication with liquid oral morphine. It was also hypothesised that the increasing pain with each procedure was due to the presence of a pneumothorax *ex vacuo*, otherwise known as trapped lung, although this was never demonstrated on a chest radiograph.

BOITEAU *et al.* [7] described successful pleurodesis by using tetracycline and continuous positive airway pressure in six patients with hepatic hydrothorax, although one of the patients died from an infection of the pleural space. However, this has not been reported again in the literature. A chest

drain and medical pleurodesis were not thought to be an acceptable course of action due to the rate of fluid production and high chance of pleurodesis failure.

We are a large pleural centre, providing medical thoracoscopy and indwelling pleural catheters (IPCs) [8].

There is a growing body of evidence for the use of IPCs in nonmalignant pleural effusions including hepatic hydrothoraces [9–11]. We have previously published a case of a 74-year-old patient who had an IPC placed and underwent successful autopleurodesis after 6 months [9]. A large multicentre study over 6 years identified 79 patients from eight hospitals [10]. IPCs were placed for palliation in 58 patients and as a bridge to transplant in 21 patients. Eight patients (10%) developed a pleural space infection; five of those resulted from a catheter-site cellulitis. Two patients (2.5%) died secondary to catheter-related sepsis. The median time from catheter insertion to pleurodesis was 55 days and the rate of pleurodesis was 28%.

Management

A Rocket IPC (Rocket Medical plc, Washington, UK) was placed under asepsis, local anaesthetic, and with the use pre-operative antibiotics and oral liquid morphine, all according to established local guidelines [8]. Despite preemptive analgesia, there was significant pain associated with the procedure, namely with passing the trocar through the pleural membrane. Drainage of 1 L fluid post-procedure provided symptomatic relief, and a chest radiograph showed good positioning of the catheter and no trapped lung. The patient was discharged the next day. The diuretics were reduced to pre-admission doses.

The patient was reviewed a week later. The district nurses had been draining ~1 L fluid a day. There had been significant seeping of fluid from the proximal end of the IPC insertion site. The dressing was continuously soaked, and the patient complained that his quality of life was very poor as all his clothes and bedding were constantly wet. Hence, the IPC was placed in a large stoma bag to collect any leaks and was being regularly emptied. The risks of infection from this were considerable.

Fluid leaking around the sites of procedures for ascitic fluid and hepatic hydrothorax is extremely common due poor wound healing and low albumin levels [6, 11]. Fluid and protein loss is a major concern with drainage of ascites, and intravenous human albumin is routinely administered. There is no clear guidance for hepatic hydrothoraces

but this practice is suggested for patients with hepatic hydrothorax. However, our patient never developed hypotension when fluid was drained and administration of human albumin would have required daily presentation to the secondary services.

His MELD score was 11 and his UK Model for End-Stage Liver Disease score was 50. His Childs Pugh score was 9(B). He had been referred to the liver transplantation team and a pre-transplant assessment was planned.

Case continuation

3 weeks after the IPC was placed, the patient presented with a 24-h history of gradual-onset, severe pleuritic chest pain and dyspnoea. There were no other associated symptoms. His temperature, blood pressure and pulse were normal but he was in pain and tachypnoeic, with a respiratory rate of 22 per min.

The catheter site looked clean and uninfected. He had dullness to percussion and reduced air entry in the right hemithorax but no other abnormal examination findings. The IPC was connected to an underwater bottle and 2 L straw-coloured fluid came out with immediate symptomatic relief from pain and dyspnoea.

Urgent blood tests showed a haemoglobin concentration of $124 \text{ g}\cdot\text{L}^{-1}$ (normal range $130\text{--}180 \text{ g}\cdot\text{L}^{-1}$), white cell count of 9.9×10^9 per L (normal range $4\text{--}11\times 10^9$ per L) and platelet count 68×10^9 per L (normal range $140\text{--}400\times 10^9$ per L). He had normal renal function. C-reactive protein level was $24 \text{ mg}\cdot\text{L}^{-1}$ (normal $<5 \text{ mg}\cdot\text{L}^{-1}$). His prothrombin time was 19.1 s (normal range 12.0–15.0 s), activated partial thromboplastin time 37.5 s (normal range 24.0–35.0 s) and fibrinogen count $3.7 \text{ g}\cdot\text{L}^{-1}$ (normal range $1.8\text{--}4.5 \text{ g}\cdot\text{L}^{-1}$). Plasma LDH levels were $300 \text{ U}\cdot\text{L}^{-1}$. His liver function test results were bilirubin $83 \mu\text{mol}\cdot\text{L}^{-1}$ (normal $<21 \mu\text{mol}\cdot\text{L}^{-1}$), alkaline phosphatase $95 \text{ U}\cdot\text{L}^{-1}$ (normal range $30\text{--}130 \text{ U}\cdot\text{L}^{-1}$), alanine transferase $36 \text{ U}\cdot\text{L}^{-1}$ (normal $<40 \text{ U}\cdot\text{L}^{-1}$), total protein $53 \text{ g}\cdot\text{L}^{-1}$ (normal range $60\text{--}80 \text{ g}\cdot\text{L}^{-1}$) and albumin $22 \text{ g}\cdot\text{L}^{-1}$ (normal range $25\text{--}50 \text{ g}\cdot\text{L}^{-1}$).

Urgent pleural fluid analysis showed a protein count of $8 \text{ g}\cdot\text{L}^{-1}$, LDH $232 \text{ U}\cdot\text{L}^{-1}$, pH 7.18 and glucose $4.2 \text{ mmol}\cdot\text{L}^{-1}$. No corresponding blood glucose levels were available.

Task 4

What are the differential diagnoses and management options?

Answer 4

The very low fluid protein count relative to the serum protein count suggested that this was still a transudate. However, the pH was low, which is suggestive of a high metabolic and anaerobic process. This is usually associated with infection and malignancy. Reduced pH (typically <7.20) is a clear marker for intercostal tube drainage in patients with suspected pleural infection. In malignant pleural effusion, low pleural fluid pH correlates with a poor prognosis and predicts pleurodesis failure [12].

An urgent Gram stain showed Gram-negative bacilli and microbiological analysis revealed a growth of *Acinetobacter ursingii*, *Enterobacter cloacae* complex and *Serratia marcescens*. All organisms were fully susceptible to ciprofloxacin and co-trimoxazole.

Further case development and discussion

This patient had now developed a spontaneous bacterial empyema (SBEM). This term is used interchangeably with spontaneous bacterial pleuritis.

The pathogenesis of SBEM is multifactorial. The entry of pathogens into the pleural cavity can be associated with a generalised bacteraemia, transfer of infected ascitic fluid or intra-abdominally through the diaphragm. In ~40% of patients, no bacterial peritonitis exists. Aetiological factors are immunological dysfunction associated with cirrhosis: defective reticuloendothelial system, low complement 3 and 4 levels, and reduced opsonic activity (opsonins are any molecules that enhance phagocytosis by marking an antigen for an immune response or marking dead cells for recycling) [13].

SBEM and empyemas from parapneumonic effusions differ [13–15]. The latter predominantly

occur with an underlying pneumonia. Furthermore, there are normally three phases for the development of empyemas: the exudative phase, the fibrinopurulent phase and then the organising phase, all of which are absent in a SBEM and thus the fluid in SBEM normally remains transparent to pale yellow. Fluid in SBEM is also overwhelmingly transudative despite positive cultures, whereas the empyemas from parapneumonic effusions are always exudative [12]. SBEM has been described in patients with no ascites, and this is similar to our patient [14].

Escherichia coli is the most common causative agent of community-acquired SBEM. Cases of SBEM with *Klebsiella pneumoniae* and Gram-positive aerobic organisms, such as *Streptococcus*, have also been documented [13–15].

The patient was started on ciprofloxacin 500 mg twice a day and after 10 days, the pleuritic pain had subsided and he was mobilising independently around the ward. The IPC had been connected to an underwater bottle and has been draining ~600 mL straw-coloured fluid a day. There was no associated hypotension or electrolyte imbalance.

On the 11th day, on inspection of the IPC site, it was noted that the cuff had appeared subcutaneously, which suggested displacement. The site remained clean and did not look infected. There was a mild ongoing leak of fluid from the site.

We hypothesised that due to the constant leak of fluid, the cuff of the IPC had never really had a chance to embed itself and almost daily manipulation of the IPC has probably caused it to be pulled out. On the 12th day, the cuff completely migrated outside and thus, the IPC was simply removed on the ward.

The patient was observed for 72 h. Serial radiography showed a re-accumulation of pleural fluid associated with increasing dyspnoea.

Task 5

What are the potential management options now?

Answer 5

Various opinions were sought. The liver transplant team were asked about an inpatient transfer to their service for urgent further transplant assessment. However, the patient would need to again undergo a series of tests, including cardiopulmonary exercise testing, which would be impossible considering his level of dyspnoea. A TIPSS procedure was still contraindicated due to his previous significant encephalopathy. The transplant team were also concerned that in the context of an infection in his pleural space, he could not receive significant immunosuppression that would be required in the post-operative phase.

The cardiothoracic team were consulted. It was felt that options were very limited. There are some case reports that suggest complete drainage of the pleural space and talc poudrage under direct vision followed by the application of negative pressure suction for adherence of the visceral and parietal pleura to maximise the possibility of successful pleurodesis. Inspection of the diaphragm could also potentially identify any defects. There are also case reports of pleurovenous shunts, where the central venous circulation (normally the subclavian vein) is cannulated, but such shunts have high complication rates and have been superseded by the advent of IPCs [16]. A video-assisted thoracoscopic surgical procedure would have required him to be transferred to a tertiary centre and have the appropriate assessment for a general anaesthetic. There were concerns about his fitness and the risks associated with such an anaesthetic. There would also be a considerable delay to this and the evidence for this is summarised in the recent *ERS Monograph* on pleural disease [16].

Given that a local medical thoracoscopy service [8] is provided, we proceeded to that on the 15th day of admission.

Local anaesthetic medical thoracoscopy was thus performed under target-controlled analgesia using remifentanyl and propofol administered and monitored in theatre by anaesthetists, as per local protocols. The patient was given five packs of fresh frozen plasma to reduce any risk of bleeding.

A large right anechoic pleural effusion was seen on thoracic ultrasound and fluid was easily aspirated. A 10-mm incision was made at the site of aspiration. An artificial pneumothorax was induced using a Boutin needle and a 7-mm trocar. A 0° rigid Storz thoracoscope was initially used for inspection of the pleural space after 3 L fluid was aspirated. The pleura looked normal, with no adhesions, fibrins strands or nodularity. There were no visible diaphragmatic defects. However, the right upper lobe was adherent to the upper costal margin. Biopsies were then taken at random from the upper and lower parietal pleura with a 50° scope with no



Figure 3 Chest radiograph showing right-sided IPC in situ and a pneumothorax, presumably due to air from induction at thoracoscopy.

complications. Talc pleurodesis was performed under direct vision and another Rocket IPC was inserted. Deep sutures were applied at the incision sites to prevent any leaks. The IPC was connected to an underwater bottle, which never bubbled except for the first minute after connection (due to outwards migration of air that was introduced to create the pneumothorax), indicating no air leak. The post-operative radiograph was satisfactory and probably showed a pneumothorax, which was presumed to be the introduction of air at the induction of medical thoracoscopy (figure 3). Suction was applied but discontinued within a few minutes due to pain. There were no post-operative problems and with the patient mobilising independently around the ward on day 17, he was discharged on oral antibiotics for 6 weeks and with district nurse support to drain the IPC. He was reviewed weekly and the amount of fluid drained through the IPC steadily declined. He did not drain any fluid for 4 weeks after 3 months and hence, the IPC was removed. Parietal biopsies showed an inflammatory fibrinous pleuritis, which was probably an effect rather than a cause.

He completed the antibiotic course and was reviewed regularly by the transplant team. As his fluid and infection regressed, his liver function tests improved, as did his performance status: at his last review, it was felt that his chronic liver disease was stable and that he did not meet any criteria for liver transplantation anymore. He continues under local gastroenterological and respiratory follow up.

Conclusion

Hepatic hydrothoraces can occur without ascites. Medical management is the mainstay of treatment but pleural interventions may be regularly required. IPCs and medical thoracoscopy can have a role to play. Pleural space infection in effusions due to liver disease can follow a very different course. Every step in management requires careful liaison with local gastroenterology and liver transplantation teams if required.

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Conflict of interest

A. Aujayeb has nothing to disclose. K. Jackson has nothing to disclose. R. Johnston has nothing to disclose. L. Mackay has nothing to disclose.

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