Induced negative pressure proposed as a new method for diagnosing hepatic hydrothorax involving minor leaks

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Funding information
No funding information provided.

Received: 3 April 2014; Revised: 20 May 2014; Accepted: 20 May 2014

Clinical Case Reports 2014; 2(6): 296–302
doi: 10.1002/ccr3.115

Key Clinical Message
Hepatic hydrothorax is known as pleural effusion of hepatic origin, and is difficult to diagnose. We herein report the novel strategy combining radioisotope scintigraphy with chest drainage to definitively diagnose hepatic hydrothorax of an 85-year-old patient which would have been missed with conventional diagnostic methods.

Keywords
Diaphragmatic defects, hepatic hydrothorax, peritoneo-pleural communication, ⁹⁹mTc-scintigraphy.

Introduction
Pleural effusion in patients with liver cirrhosis in the absence of any primary cardiopulmonary disease is known as hepatic hydrothorax. It occurs in ~5–10% of cirrhotic patients [1–4].

It is believed that the pleural effusion results from migration of ascitic fluid from the peritoneal to the pleural cavity, either via lymphatic channels or through congenital or acquired diaphragmatic defects [5–7]. The negative intrathoracic pressure generated during inspiration favors the passage of fluid from the intraabdominal space to the pleural space [8]. Many diagnostic tests exist to identify transdiaphragmatic communication, including intraperitoneal injection of indocyanine green (ICG) or air, color Doppler ultrasonography (US), contrast-enhanced US, ⁹⁹mTc-scintigraphy, and magnetic resonance imaging [9–12]. The most common procedures utilized in clinical settings are intraperitoneal injection of ICG, contrast-enhanced US and ⁹⁹mTc-scintigraphy [13, 14].

Intraperitoneal injection of ICG is a simple method that can be performed in any hospital [14], but neither have the pharmacokinetics and metabolism of injected ICG in peritoneal space been studied sufficiently. It could be unreliable in case of the minor leaks, where the amount of dye drained from thoracic cavity would be too small to make a diagnosis. An alternative method that uses US to detect transdiaphragmatic communication is less invasive. It reveals presence of diaphragmatic defects as a jet-like flow in the thoracic cavity, and the sensitivity can be enhanced by injecting US contrast such as Sonazoid or Revovist into the peritoneal space, which makes the jet-like flows more apparent [15]. However, methods that involve ultrasound require presence of a certain amount of ascites and have a subjective component [15]. Compared to these methods, ⁹⁹mTc-scintigraphy is considered to be the gold standard for diagnosing hepatic hydrothorax, but it can take anywhere from 2 to 10 h and cannot detect small leakages [16, 17]. Therefore, the diagnosis of hepatic hydrothorax is typically made by exclusion, and definitive diagnosis is particularly difficult in patients who have little or no ascites [18]. Indeed, hepatic hydrothorax is defined as a transudative pleural effusion, usually >500 mL, in patients with portal...
hypertension without any other underlying primary cardiopulmonary cause rather than demonstrating peritoneo-pleural communications in clinical settings [3, 4, 6]. With these diagnostic criteria, there would arise certain number of patients remaining undiagnosed.

We report herein a novel strategy that uses suction drainage combined with conventional 99mTc-scintigraphy which we call the induced negative pressure (INP) method, to diagnose hepatic hydrothorax in patients presenting without ascites. We present the method in the format of a case report.

Case Report

An 85-year-old male presented with a chief complaint of shortness of breath, which exacerbated gradually over several weeks. His medical history was unremarkable except for type 2 diabetes mellitus and hepatitis C virus infection which was diagnosed when the patient was 68 years old. Physical exam revealed no significant findings except for bilateral lower leg edema. Blood test showed no significant abnormalities, and urinalysis revealed neither proteinuria nor any significant findings (Table 1). The clearance of creatinine was within normal limit. The chest X-ray showed a moderate amount of right-sided pleural effusion (Fig. 1A). Abdominal US revealed no demonstrable ascites, but a low-grade shrunken liver. Based on these results, the cause of the patient’s pleural effusion was suspected to be cardiopulmonary. If the patient had been diagnosed as having hepatic cirrhosis at this point, his cirrhotic status would have been class A in the Child-Pugh classification. The patient was admitted to the pulmonology department to determine the cause of the effusion. While computed tomography (CT) of the chest showed a moderate amount of pleural fluid accumulation, abdominal CT revealed no demonstrable ascites but a shrunken liver consistent with chronic liver disease, splenomegaly, and splenorenal shunt, suggesting the presence of portal hypertension. Echocardiography revealed no cardiac abnormality and was determined to be an unlikely cause of the patient’s pleural effusion and lower leg edema. The patient’s pleural fluid obtained by thoracocentesis was found to be a clear, yellow, and aseptic transudate. Cytology examination revealed no malignant cells. Gastroduodenoscopy showed no varices but mosaic patterning of the stomach consistent with portal hypertensive gastropathy. These findings indicated relatively severe portal hypertension, and although his hepatic enzymes were within normal limits, hepatic hydrothorax was reconsidered as the cause of the pleural effusion, and intraperitoneal injection of ICG and color-Doppler US were performed.

We performed the former examination as follows. A 14 Fr single-lumen chest tube was placed into the right thoracic cavity, and connected to a wet control, closed drainage system. The level of suction was adjusted to −15 cm of water. ICG was injected into the peritoneal cavity using a Veress needle under US guidance at a dose of 25 mg dissolved in 5 mL of water, followed by a flush with 10 mL normal saline solution. The patient was hydrated with 500 mL/h of normal saline starting 1 h before the injection of the dye, and which was continued for 4 h. The ICG concentration of the drained pleural effusion and blood was measured every half hour for the first 4 h, then once at 10 h after the injection. The results showed a dissociation in the ICG concentration curves between the pleural fluid and blood, especially in the sample obtained at 10 h after injection, as shown in Figure 2. This finding seemed to provide possible evidence of diaphragmatic defects, but the amount of migrating dye was too small to make a diagnosis of hepatic hydrothorax. In addition, it was also possible that the ICG was systemically absorbed and the same was secreted in pleural fluid rather than the transmigration of ICG from peritoneal cavity to pleural cavity.

We next performed color Doppler US, but no diagnostic finding such as a jet stream was observed. US was performed without use of contrast, because lack of ascites would have prevented diffusion of the contrast in the peritoneal space to allow it to migrate in a significant amount to be visible on the pleural side. Based on the ICG injection and US results, we knew it would be difficult to prove the presence of transdiaphragmatic

| Table 1. Laboratory findings on admission. |
|------------------------------------------|
| **Complete blood count**                  |
| WBC 3600/µL                               |
| Hb 10.6/µL                                |
| Plt 11600/µL                              |
| **Biochemistry**                          |
| TP 6.4 g/dL                               |
| ALB 3.2 g/dL                              |
| T-Bil 0.74 mg/dL                          |
| AST 54 IU/L                               |
| ALT 31 IU/L                               |
| ALP 303 IU/L                              |
| LDH 199 IU/L                              |
| γ-GTP 16 IU/L                             |
| BUN 17.6 mg/dL                            |
| Cre 0.62 mg/dL                            |
| **Coagulation**                           |
| PT% 76%                                   |
| APTT 30.9 sec                             |
| Fbg 201 mg/dL                             |
| D-dimer 2.7 µg/mL                         |
| **Urinalysis**                            |
| Protein –                                 |
| Sugar –                                   |
| Occult blood –                            |
communication using conventional 99mTc-scintigraphy as well. This led us to invent a new strategy: INP method.

We performed the INP method as follows. A 14 Fr chest tube was placed touching the diaphragm. Three hundred seventy MBq of 99mTc-MAA (macroaggregated albumin) was injected with 250 mL of normal saline solution into the peritoneal cavity with a Veress needle under US guidance. The fact that 99mTc-MAA (macroaggregated albumin) whose molecules are relatively large and cannot pass easily through lymphatic vessels manage to migrate to the thoracic cavity is thought to indicate that the lymphatic channel route is less likely to occur.

Figure 1. Images of chest X-ray, 99mTc-scintigraphy, and drainage bag. (A) The chest X-ray on admission showed a moderate amount of pleural effusion. (B–D) The 99mTc-scintigraphy was imaged at 0, 90, and 180 min after the injection of 99mTc-colloids, respectively. In particular, (B) shows anatomical landmarks; small arrows represent the costal margin and the open arrow indicates the xiphisternum. The total radioactivity was $1.6 \times 10^4$, $1.2 \times 10^4$ and $0.96 \times 10^4$ counts/sec, respectively. No images show the radiotracer moving from peritoneal to pleural space. (E and F) The scintigram and the actual image of the drainage bag, respectively. The total radioactivity of image (E) was 45 counts/sec on a highly sensitive gamma camera, which definitively demonstrated the presence of the peritoneo-pleural communication.
93 h. Thereafter, the drainage bag was placed 9 cm from the abdomen and chest were imaged at 30 min intervals for the presence of tracer in the peritoneal cavity. The upper part of the drainage bag radioactivity averaged over 10 min in the negative pressure phase was 275 counts/min, a 1:5 ratio. According to the scintigram, the radioactivity ratio between the thorax and abdomen was 1:1000. In result, the radioactivity ratio was 1:5:5000 for background, pleural effusion, and peritoneal fluid, respectively. This high ratio (absent the Geiger counter data) would have made it impossible to conclude whether the thoracic radioactivity was mere background, or actual signal.

After definitive diagnosis of hepatic hydrothorax was made with the new technique, we started the patient on oral furosemide and spironolactone. The patient’s dyspnea resolved, the amount of pleural fluid decreased to a level undetectable by chest X-ray in a few weeks, and the patient was discharged. We confirmed that his pleural fluid was still under control at 6-month follow-up.

**Discussion**

In the case we reported here we introduced a novel strategy, the INP method, to enhance the sensitivity of conventional scintigraphy, and it successfully led us to a definitive diagnosis of hepatic hydrothorax of a patient whose amount of pleural effusion had not been enough for two conventional tests to detect his diaphragmatic defects. Moreover, we demonstrated the importance of applying negative pressure by conducting the examination.
in two phases, the control water-seal phase and the negative pressure phase.

We believe there are two merits to our method. One is that negative pressure of the pleural space facilitates the movement of fluid from the abdomen to thoracic cavity, which was demonstrated by an acute increase in the amount of pleural fluid right after the beginning of suction drainage as shown in Figure 3A. The other is that radiotracer detection devices with higher sensitivity can be applied to drained pleural fluid than to a patient. Usually with 99mTc-scintigraphy, a relatively large amount of radiotracer is required to flow into the thoracic cavity for diagnosis, because strong signals from peritoneal radiotracers tend to overwhelm the relatively weak signals of the pleural ones on the image. This is partly because the equipment automatically adjusts the density of the entire image so that the highest radioactive area is not completely black, which unfortunately leads to dilution of signals from areas with weak radioactivity to the point of absence. Indeed, in our case, the total radioactivity detected by gamma camera from the drainage bag was about 8 × 10^3 count/min on the Geiger counter 90 min after the suction started, which could not be detected with a normal sensitivity gamma camera.

Figure 3. The trace of pleural fluid and radiotracer activity in the induced negative pressure method. (A) For the first 90 min; the water-seal phase, where the suction level was 0 cm of water, there was little pleural effusion (0–5 mL) drained from the chest tube and radioactivity was not detected in the fluid collected. In contrast, switching to the negative pressure phase immediately increased the amount of the fluid drained to 30 mL/10 min and the radiotracer started to be detected with the Geiger counter. There is an abrupt fall in the quantity of pleural fluid drained post 140 min. This finding would be a mere observation because there was recollection of pleural fluid soon after the examination as the patient moved his body. (B) Total amount of radioactivity of pleural fluid, in other words, the total amount of radiotracers which otherwise would have accumulated in the pleural space. It reached 8 × 10^3 count/min on the Geiger counter 90 min after the suction started, which could not be detected with a normal sensitivity gamma camera.
image to Figure 1B image was ~1000, calculated according to the following numeric formula, taking into account the difference in photographing distance: $0.96 \times 10^4 \text{ (count/sec)} / 45 \text{ (count/sec)} \times 20 \text{ (cm)}^2/9 \text{ (cm)}^2 = 1053$. This large gradient in radioactivity between chest and abdomen would have made it impossible to demonstrate radiotracer migration with scintigraphy. In contrast, the pleural fluid drained outside the body can be examined on its own with a sensitive camera.

Our INP method may be useful as one of the screening test to diagnose pleural effusion of unknown origin, because it is sufficiently time-efficient and sensitive, and can be performed easily and safely with the tools available in any hospital. Two punctures for chest and abdomen constitute the invasive part of the technique, the puncture kit can be connected to a drainage system, and detecting radiotracers in the drainage tube with a sensitive gamma counter would result in demonstration of peritoneo-pleural communication. The adverse clinical outcomes would be the erroneous puncture and radiation exposure, but the extent of it could be reduced with our method because of its high sensitiveness. Pleural effusion can have a cardiac, pulmonary, or hepatic origin. Our new technique offers a way to definitively diagnose pleural effusion of the last type, in what has previously been made by exclusion of the first two. In particular, the patients who need to have invasive intervention including pleurodesis, transjugular intrahepatic portosystemic shunt and closure of diaphragmatic defects to control the pleural fluid would be benefited because it is crucial to demonstrate diaphragmatic defects before the operations.

There is a limitation in our method that the continuous negative pressure introduced to thoracic cavity might overestimate the peritoneal leaks by drawing the injected fluid. It is reported that the pleural pressure of respiratory cycle is from $-8$ cm water to $-3$ cm water and it reaches about $-15$ to $-20$ cm water at maximum inspiration [19]. The value of $-20$ cm water seems to be reasonable to prevent backward flow even in maximum inspiration, but it would be necessary to examine whether it is suitable for our method with a case series study or a case–control study.

This report is case presentation of one patient and it is necessary to apply our method to much more hydrothorax patients with pleural effusion and conduct a case–control study to make a concrete evidence of our method.

Conflict of Interest

None of the authors had any conflicts of interests with regard to the study design, collection, analysis, in the interpretation of data, in writing the report and in the decision to submit the manuscript for publication.

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