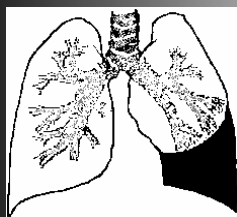


# International Pleural Newsletter



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## Transudative Pleural Effusions

### Effusions from Cardiac Failure

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Heart failure (HF) is the most common cause of pleural effusion in patients above 70 years of age. Overall, more than two-thirds of patients with decompensated HF have pleural effusions as demonstrated by CT or autopsy<sup>1</sup>. The origin of the accumulated pleural fluid in patients with HF is probably the interstitial spaces of the lung.

The diagnosis of cardiac effusion is usually suggested by the clinical picture and should be considered whenever a patient has one or more of the following: orthopnea or paroxysmal nocturnal dyspnea, an elevated jugular venous pressure, a positive abdominojugular test result, a displaced apical impulse, a third heart sound, an abnormal blood pressure response to the Valsalva maneuver, cardiomegaly or any other radiological signs of left ventricular failure. It should be noted that about 20% of patients with decompensated HF has no vascular congestion, interstitial or pulmonary edema on chest radiography<sup>2</sup>. Thus, pleural effusion secondary to HF may often be diagnosed clinically. Thoracentesis is helpful if the clinical picture is unclear or the response to treatment is poor.

Radiographically, these effusions are usually bilateral (70%), but they may be unilateral right- (20%) or left-sided (10%)<sup>3</sup>. More than 80% of cardiac effusions occupy  $\leq 1/3$  of the hemithorax.

Examination of pleural fluid reinforces the diagnosis of HF if Light's criteria for a transudate are met. Light's criteria misclassify approximately 25% of cardiac effusions as exudates. This mislabeling

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most commonly occurs either by the effect of diuretics or by the presence of a fluid containing  $>10,000$  RBC/mm<sup>3</sup> (15%), which may increase protein and/or LDH to the level consistent with an exudate. In this case, if the albumin or protein gradient between the serum and pleural fluid is  $>1.2$  g/dL and  $>3.1$  g/dL respectively, the fluid can be said to be transudative<sup>1</sup>.

The availability of tests for brain natriuretic peptide (BNP) and bedside echocardiography has aided in the diagnostic precision of HF. BNP is a peptide hormone released primarily from the cardiac ventricles in response to myocyte stretch. It is synthesized as an inactive prohormone that is split into the active hormone BNP and the inactive N-terminal fragment (NT-proBNP). Recent data indicate that pleural fluid NT-proBNP levels  $>1500$  pg/mL have  $>90\%$  sensitivity and specificity for discriminating effusions caused by HF from those attributable to other causes<sup>4</sup>. Because of its comparable diagnostic accuracy at the same cutoff value, serum rather than pleural NT-proBNP measurement is preferable for making the diagnosis of HF<sup>5,6</sup>. It is our experience that pleural or serum NT-proBNP, pleural to serum albumin gradient and pleural to serum protein gradient correctly identify  $>80\%$ ,  $75\%$ , and  $55\%$  of cardiac transudates mislabeled by Light's criteria, respectively<sup>4,6</sup>.

The vast majority of cardiac effusions resolve with diuretics in days to weeks, with a few refractory cases requiring therapeutic thoracentesis or pleurodesis for symptomatic relief.

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## Effusions from Hepatic Failure

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Up to 10% of cirrhotic patients will have a hepatic hydrothorax (HH). This can exist in the absence of ascites. HH presents a challenge in management due to its rapid symptomatic re-accumulation and the ongoing risk of spontaneous bacterial empyema (SBEM) which is associated with a higher mortality and poorer prognosis. HH impacts quality of life and often requires medical attention for symptom relief<sup>1-3</sup>.

The mechanisms for HH include hypoalbuminemia and elevated intra-abdominal pressure which drives ascitic fluid across the diaphragmatic defects.

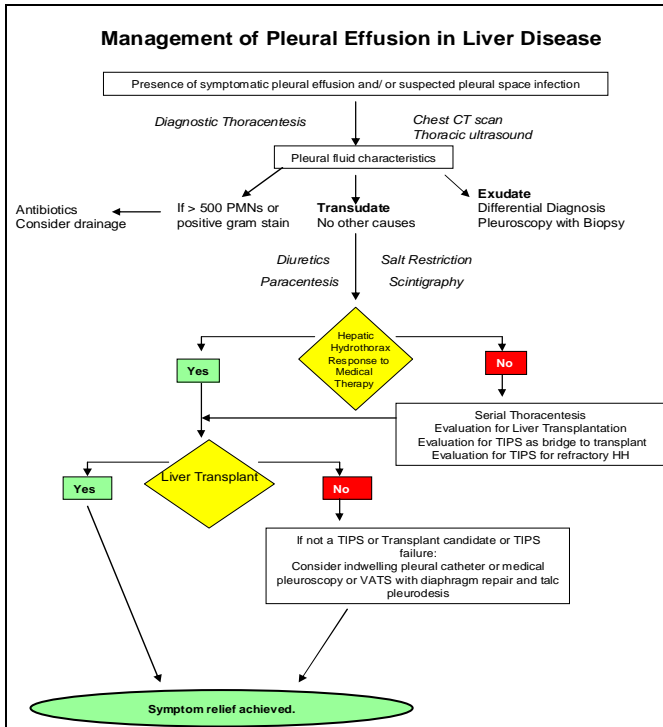
The general characteristics of HH:

- Predominantly right sided
- Transudative
- Serum : Pleural albumin gradient  $> 1.1$
- Cell count  $<250$  PMN cells mm<sup>-3</sup>  
( $>500$  PMN cells or positive gram stain = SBEM)

The presentation can be indolent, in the setting of longstanding ascites, or sudden and massive, *eg* after radiofrequency ablation of hepatic tumors with subsequent iatrogenic defects in the diaphragm. Although patients can tolerate large volumes of ascitic fluid, the presence of a moderate to large pleural effusion often has a great symptomatic impact. Patients with refractory HH who are deemed not candidates for liver transplantation may be prognosticated much like patients with a malignant pleural effusion and a declining functional score.

In addition to diagnostic and therapeutic thoracentesis, imaging with ultrasound and CT or MRI may assist in ruling out other etiologies for pleural fluid as well as assessing for diaphragmatic defects. Nuclear scintigraphy or peritoneal injection of contrast agents can also be used to assess for diaphragmatic communications<sup>1-3</sup>.

Often the patient becomes progressively more refractory to medical management with diuretics and salt restriction. Many require frequent thoracentesis and/or paracentesis. Although these patients have coagulopathies, the risk of bleeding is less than previously ascribed<sup>4</sup>.



[Copyright of the figure belongs to Dr C Lamb.]

No single treatment option is ideal. The MELD (Model for End-Stage Liver Disease) score assessing liver disease severity is important to guide treatment for HH, specifically portosystemic shunts (TIPS) and liver transplantation. Patients <60 in age with a MELD score of <10 are best suited for TIPS<sup>5</sup>. TIPS has a success rate of 79% in selected patients and can serve as a bridge for liver transplantation<sup>1</sup>.

It is worth listing other treatment options that have variable but sufficient efficacy to be considered: sequential thoracentesis, video-assisted thoracoscopy with diaphragm defect repair and pleurodesis, and indwelling pleural catheter drainage<sup>1-3, 5-6</sup>.

Most would not advocate the placement of a chest tube and bedside pleurodesis due to the lack of pleural symphysis to the chest wall from rapid ongoing pleural fluid re-accumulation and the uncontrolled loss of proteins.

It is important to avoid indwelling pleural catheters in those who are transplant candidates as even the slightest risk of infection would be unacceptable. However, we have found that indwelling catheter drainage gives excellent palliation of symptoms in those with rapidly recurring HH and are not transplant candidates. In patients draining 1-2L daily, we found no significant decline of serum albumin and protein in serial measurements.

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## Uncommon Transudative Effusions: Pleural Effusions of Extravascular Origin

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There are a limited number of transudates that result from imbalances in hydrostatic and oncotic pressures including CHF, hepatic hydrothorax, and nephrotic syndrome. Other effusions that qualify as transudates by protein and LDH criteria result from the movement of fluid from an extravascular origin into the pleural space. These transudates include peritoneal dialysis (CAPD), urinothorax, duropleural fistula, extravascular migration of a central venous catheter with saline infusion, a ventriculopleural shunt or ventriculoperitoneal shunt with migration into the pleural space, and glycinothorax. I will briefly comment on the more common transudates of extravascular origin<sup>1</sup>.

Patients undergoing CAPD who develop a pleural effusion may be asymptomatic, complain of dyspnea, or present with acute respiratory failure<sup>2</sup>. Risk factors for effusions include multiparity and peritonitis. Chest radiograph typically shows a small right-sided pleural effusion without other abnormalities. An acute, massive, right-sided pleural effusion occurs predominantly in women from one day to two years after initiation of dialysis. The pleural fluid protein ranges from 0.07-0.50 g/dL with an LDH of 6-55 IU/L. The glucose concentration ranges from 200 to

2000 mg/dL. The diagnosis is presumptive based on a total protein <0.5 g/dL with a high pleural fluid glucose. Most patients require a change to hemodialysis.

Any cause of obstructive uropathy can cause a urinothorax<sup>3</sup>. Perirenal urine moves retroperitoneally into the pleural space, typically ipsilateral to the obstructive kidney. The most common presentation is dyspnea following surgery or trauma. Chest radiograph shows a small-to-moderate pleural effusion ipsilateral to the obstructed kidney. The pleural fluid protein is <1.0 g/dL. The diagnosis is established when the pleural fluid/serum creatinine ratio is >1.0 (range 1.08-15.7). The pleural fluid glucose is similar to blood glucose, and the pH may be <7.30 or alkaline. Urinothorax is the only single cause of a low pH transudative effusion. Relief of the obstructive uropathy results in rapid reversal of the pleural fluid to creatinine difference and resolution of the effusion.

Duropleural fistula represents a communication between the subarachnoid and pleural spaces<sup>4</sup>. The most common cause is trauma followed by spinal surgery. On chest radiograph, effusions range from small to massive. The pleural fluid looks like "water", has a low nucleated cell count and glucose less than but not <0.5 compared to serum. The total protein is <1.0 gm/dL with a low LDH. Finding beta-2 transferrin in the pleural fluid establishes the diagnosis. Management usually requires surgical correction.

Extravascular migration of a central venous catheter, particularly those placed using the left subclavian vein, can result in a pleural effusion<sup>5</sup>. The catheter initially moves into the mediastinum and the infusate enters the pleural space following mediastinal pleural rupture. The most common complaint is dyspnea followed by chest pain. Chest radiograph demonstrates a pleural effusion which may be unilateral or bilateral. The association of the effusion with an abnormal location of the catheter tip suggests perforation. If the patient is receiving saline or dextrose and water, the fluid is a transudate with a protein concentration <1.0 g/dL. The best management strategy is prevention of vascular erosion via catheter insertion from the right side. Clues to the diagnosis include new progressive cardiopulmonary symptoms, mediastinal widening, a new or enlarging pleural effusion, increased central venous pressure combined with systemic

hypotension, and a curving or extravascular location of the distal catheter. The inability to withdraw blood from the catheter supports the diagnosis but free blood return does not exclude it. Upon diagnosis, the catheter should be removed. If the effusion is small observation is warranted; with a large effusion causing respiratory distress, therapeutic thoracentesis or tube thoracostomy should be performed.

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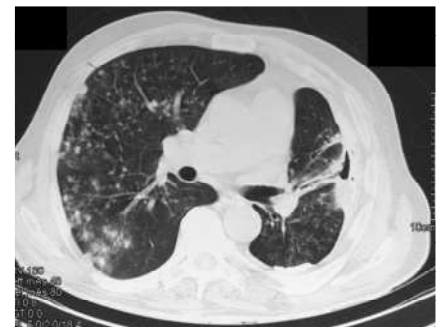
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## IMAGES OF THE PLEURA

### **Bronchopleural Fistula from TB:**

A 73 year old Iraqi man presented with a five month history of a productive cough and breathlessness. In 1949 he had left-sided TB pleuritis, treated with thoracentesis and 2 years of isoniazid monotherapy. He migrated to Australia in 1990 and was observed in a TB clinic for 4 years with no evidence of active TB.

In 2006 his sputum grew *Mycobacterium tuberculosis*, resistant to isoniazid. CT showed a left bronchopleural fistula and possible miliary TB. He is debilitated, so surgical drainage of the empyema was considered risky. He improved on moxifloxacin, pyrazinamide, ethambutol and rifampicin and the empyema is draining endobronchially via the fistula.



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## CASE REPORT

### *Pleural Effusion as Late Complication of Radiotherapy for Hodgkin's Disease*

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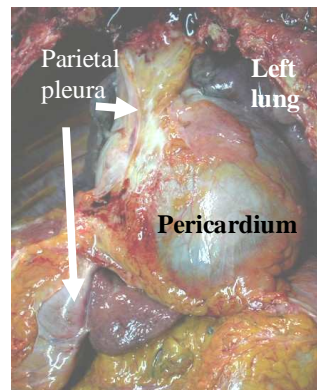
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A 53-year-old man was hospitalized after a 2-week history of increasing dyspnea. He had been diagnosed of Hodgkin's lymphoma (stage IIB, sclerosis nodular type) 16 years earlier and treated with a MOPP regimen and mantle field radiation therapy at 40 Gy. In the ensuing years, he suffered from several radiation-induced toxicities, namely bilateral brachial plexus neuropathy, skin fibrosis, hypothyroidism and chronic pericardial effusion of moderate size without hemodynamic compromise. Eight months before admission the patient presented with dyspnea and a left-sided pleural effusion. The pleural fluid was an exudate. A therapeutic thoracentesis was performed and the patient remained asymptomatic until the present admission.

At this presentation, he was tachycardiac (110/min), hypotensive (110/80 mmHg), tachypneic and hypoxic (oxygen saturation 89% on room air). The jugular veins were distended, and there were neither heart murmurs nor a pericardial rub. Assessment of the paradoxical pulse was inconclusive. Laboratory studies, including complete blood count and thyroid-stimulating hormone, were normal. A chest radiograph showed large bilateral pleural effusions. Pleural aspirate showed an erythrocyte count of 1680/ $\mu$ L, WBC count of 740/ $\mu$ L (95% lymphocytes), glucose 108 mg/dL, protein 4.2 g/dL (serum 7.4), LDH 198 U/L (serum 371), ADA 17.5 U/L, cholesterol 68 mg/dL, triglycerides 21 mg/dL, pH 7.45, and a negative cytological analysis.

The patient died before urgent thoracic CT scan and echocardiography could be performed. The autopsy revealed massive bilateral pleural and pericardial effusions, severe mediastinal fibrosis as well as thickened, fibrotic, and adherent ("pearly" appearance) pericardium and pleura (below) and no evidence of active Hodgkin's disease. It was concluded that these findings were late complications of mediastinal radiation and contributed to the development of cardiac tamponade.



Patients who survive Hodgkin's lymphoma may experience late complications attributable to radiation therapy, including second solid tumors (eg lung or breast cancer), cardiac toxicity (eg fatal myocardial infarction due to the intimal injury of the coronary arteries, constrictive pericarditis) and pleural effusions. The developments of pleural effusion six<sup>1</sup>, eight<sup>2</sup> and 17<sup>3</sup> years after mediastinal radiotherapy for Hodgkin's disease have been reported. Potential mechanisms of pleural fluid accumulation include impaired pleural lymphatic drainage, constrictive pericarditis and superior vena caval syndrome, caused by pleural and/or mediastinal fibrosis. Chemical pleurodesis should be considered in patients with severe respiratory symptoms<sup>4</sup>. It should be stressed that these late effusions are different from the moderate and often asymptomatic pleural effusions that can accompany radiation pneumonitis within 6 months of completing radiation therapy.

Mantle (extended-field) radiotherapy at  $\geq 40$  Gy is no longer recommended for the treatment of Hodgkin's disease. Instead, patients with early-stage disease should receive an ABVD chemotherapy regimen plus involved-field radiation therapy at 20 Gy. Limited fields, lower doses, and improved techniques used in current radiation therapy are likely to ameliorate the toxicity profile.

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