Diagnosis and treatment of malignant pleural effusion

Frederick H. Hausheer 1 & John W. Yarbro 2

1 American Cancer Society Fellow and senior clinical fellow, Division of Medical Oncology, the Johns Hopkins Oncology Center, 600 North Wolfe Street, Baltimore, MD 21205; 2 Professor of Medicine and Director, Division of Hematology and Medical Oncology, University of Missouri School of Medicine Columbia, MO 65212, USA (1 address for offprints)

Keywords: pleural effusion, transudate, exudate, mesothelioma, cytogenetics, pleuroscopy

Summary

Pleural effusion is a common and important complication of malignancy which may at times be difficult to diagnose or treat. Its well recognized association with numerous diseases plus the limitations of our usual diagnostic tests may occasionally cause difficulty. In the oncology patient there are a number of common medical problems associated with the development of pleural effusion which frequently coexist with the malignancy. Pleural effusion may be a presenting or late sign of cancer, and when recurrent can be a vexing symptomatic problem. Fortunately, an increasing number of effective diagnostic and therapeutic modalities are available which, when judiciously applied, facilitate our approach.

Pathogenesis

It is useful to recall the fundamental physiologic processes involved in formation and reabsorption of pleural fluid in order to formulate a more comprehensive diagnostic and therapeutic strategy. Pleural fluid moves from the parietal pleural capillaries into the pleural space and is absorbed by the visceral pleural lymphatics (80% to 90%) and capillaries (10% to 20%). Fluid movement follows dynamics based on the principles initially proposed by Starling, and later modified by other investigators in accordance with the concept of driving pressure (1–6).

Normally the relatively protein-free fluid in the pleural space has a rapid rate of turnover (35% to 75% per hour) which facilitates the movement of 5 to 10 liters of fluid per day [1, 2, 6]. These fluid dynamics are the net result of the variables represented by the Starling equation and the presence of driving pressure (Pd) as shown below:

\[ F = K[(P_{\text{cap}} - P_{\text{if}}) - (O_{\text{cap}} - O_{\text{if}})] \] (1)

where

- \( F \) = flow in ml/sec
- \( K \) = permeability constant in ml/sec/cm water/cm²
- \( P \) = hydrostatic pressure in cm water/cm²
- \( O \) = oncotic pressure in cm water/cm²
- cap = capillary
- if = interstitial fluid

\[ P_d = (P_{\text{cap}} - P_{\text{if}}) - (O_{\text{cap}} - O_{\text{if}}) \] (2)

Disruption of one or more of the physiologic variables represented in the above equations (in association with various disease states) results in fluid accumulation in the pleural space. Under normal conditions fluid movement to and from the pleural space is in a state of equilibrium which may be
Table 1. Classification of pleural effusion by mechanism(s)

1. Increased capillary permeability/decreased lymphatic flow: exudative.
   a) Malignancy
   b) Tuberculosis
2. Increased capillary permeability: exudative.
   a) Pneumonia: bacterial, viral, fungal, parasitic, or Rickettsial.
   b) Parapneumonic effusion/empyema.
   c) Pulmonary embolus or infarct.
   d) Connective tissue diseases: Rheumatoid arthritis, lupus, and mixed connective tissue disease.
   e) Uremia
   f) Pancreatitis
   g) Subphrenic abscess
   h) Hepatic abscess
   i) Whipple's Disease
   j) Dressler's Syndrome
   k) Post radiation exposure
   l) Vasculitides: Wegener's granulomatosis, polyarteritis nodosa
   m) Chronic hemothorax
3. Increased hydrostatic/decreased oncotic pressure: transudative.
   a) Congestive heart failure (plus relatively decreased lymphatic flow).
   b) Cirrhosis
   c) Nephrotic syndrome
   d) Myxedema (occasionally exudative due to increased capillary permeability).
   e) Peritoneal dialysis
   f) Hypoproteinemia
   g) Meig's syndrome: benign ovarian fibroma with ascites and pleural effusion (sometimes exudative).
   a) Chylothorax
   b) Sarcoidosis
   c) Yellow Nail Syndrome
   d) Milroy's Disease
5. Increased negative intrapleural pressure: transudative.
   a) Early atelectasis
6. Other
   a) Intrapleural fluid extravasation from a central venous catheter.
   b) Postpartum pleural effusion
   c) Ibuprofen therapy associated with fatty liver.
7. Drug hypersensitivity: exudative
   a) Nitrofurantoin
   b) Methysergide
   c) Nitrogen mustard and Quinacrine instillation.
   d) Following endoscopic sclerotherapy for esophageal varices.

Incidence

The most common cause of symptomatic pleural effusion is malignancy, which accounts for nearly half of de novo cases as shown in Table 2 [1, 8–14]. Congestive heart failure is probably the most common cause but is under-reported in most series of patients undergoing diagnostic thoracentesis. As illustrated in Table 3 more than 75% of malignant pleural effusions are due to cancers of the lung, breast, lymphoma, leukemia, and adenocarcinoma of unknown primary [1, 8–10, 14–17]. The remaining malignancies associated with pleural effusion are mostly adenocarcinomas. Pleural effusion can be the presenting sign of malignancy. It has been reported to be the initial manifestation of the cancer in from 46% to 64% of patients [15, 18]. It has been frequently stated that 50% of patients with cancer of the breast or lung will develop pleural effusion during the course of the disease [7, 9, 19, 20]. This estimate is probably excessive at present due to alteration in the natural history of these cancers by newer methods of treatment [1]. Pleural effusion presents predominantly as a late manifestation in breast cancer [21].