Review Article

Diagnostic approach to pleural effusions

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Abstract: The increasing incidence of pleural effusions from a variety of etiologies is associated with significant socioeconomic burden. Effective treatment for pleural effusions first requires a comprehensive diagnostic work up encompassing analysis of pleural fluid chemistry, microbiology studies and invasive sampling, all of which should be incorporated with relevant clinical data to reach a final diagnosis. This review article addresses current diagnostic approaches to pleural effusions.

Keywords: Pleural effusions; diagnostic approaches; treatment

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Introduction

There are approximately 1.5 million newly diagnosed pleural effusion in the United States each year (1). Physiologically, there is a small amount of fluid within the pleural cavity that is bound by the parietal and visceral pleural membranes. One study estimated the pleural fluid volume of one hemithorax to be about 8.4 mL, or 0.26 mL/kg, in humans (2). Normal pleural fluid enters the pleural space from systemic pleural vessels in both pleurae, and exits in a bulk-flow fashion (rather than by diffusion or active transport) via the lymphatic stomata present on the parietal pleural surface (3). The production rate of pleural fluid is approximately 0.01 mL/kg per hour (4), and the maximal fluid removal rate can be as high as 0.28 mL/kg per hour (5). When there is an excess of fluid formation, compromised fluid reabsorption, or both, a pleural effusion accumulates.

Common things are common

Several common etiologies of pleural effusion [malignancy, heart failure, tuberculosis (TB), pneumonia, hepatic hydrothorax, etc.] explain the majority of cases. Common etiologies are associated with local epidemiology of certain conditions and population characteristics such as age and socioeconomic status. For instance, the estimated TB burden in 2016 in Malaysia and Nigeria is appropriately 92 and 219 cases per 100,000 population, respectively (6); accordingly, tuberculous effusion is the most common etiology of pleural effusion-TB (44%) followed by malignancy (30%) in Malaysia and TB (33%) followed by malignancy (29%) and pneumonia (15%) in Nigeria (7,8). In contrast, the TB burden in Spain in 2016 is only 10 cases per 100,000 population. Accordingly, tuberculous effusions are only the fourth leading cause (9%) of pleural effusions with malignancy (27%), heart failure (21%) and pneumonia (19%) being more common (9). Patients with tuberculous pleural effusions tend to be younger, as compared to those with heart failure associated pleural effusion who tend to be older (32-year-old *vs.* 80-year-old) (9). In the US, heart failure, pneumonia and malignancy are the most common etiologies. Pulmonary embolism (PE)-related effusion and hepatic hydrothorax were estimated to be 60 and 20 times more common than tuberculous effusion (10).

A thorough history, physical examination, and imaging along with pleural fluid analysis are fundamental to the

Table 1 Light's criteria to distinguish pleural fluid transudates and exudates

An exudative effusion meets ≥1 of the following criteria; a transudate meets none of the following criteria:
Pleural fluid protein/serum protein >0.5
Pleural fluid/serum lactate dehydrogenase (LDH) >0.6
Pleural fluid LDH >2/3 the upper normal limit of serum LDH

identification of a specific etiology for pleural effusions. The first step of pleural fluid analysis is to differentiate transudates (as in heart failure and hepatic hydrothorax) from exudates (as in malignancy, pneumonia and TB) utilizing Light's criteria (*Table 1*). This categorization helps guide further investigations as needed (11). The importance of this differentiation lies in the fact that underlying conditions for exudative pleural effusions, such as malignancy and pleural infections, need more urgent diagnostic and therapeutic attention. Light's criteria have 97.5% sensitivity for identifying exudates (12); however, they also misclassify 29% of transudates as exudates in heart failure patients who are taking diuretics, the so-called "false exudates" (13). Therefore, several additional criteria have been proposed in order to improve the diagnostic accuracy of identifying true exudates:

- A serum-to-pleural fluid albumin gradient >1.2 g/dL corrects 83% and 62% of the heart failure and hepatic hydrothorax false exudates (14). This gradient should be chosen in identifying suspected heart failure-related effusions.
- Pleural fluid levels of NT-proBNP >1,500 pg/mL have a positive likelihood ratio of 15.2 and a negative likelihood ratio of 0.06 in identifying heart failure-related effusions (15) and has an area under the receiver operating characteristic curve of 0.931 (16).
- A serum-to-pleural fluid total protein gradient >3.1 g/dL corrects 55% and 61% of the heart failure and hepatic hydrothorax false exudates (14); this criterion is less favored due to its inferior performance to that of albumin gradient (17).
- A pleural fluid-to-serum albumin ratio <0.6 corrects 78% and 77% of mislabeled cardiac and liver-related effusions (14) and can be used to identify both heart failure- and cirrhosis-related transudative effusions.
- A pleural fluid level of cholesterol >45 mg/dL can be used to classified effusions as exudates with an area under curve of 0.933 (18,19).

After the initial differentiation between transudates and exudates, a diagnosis can often be reached when interpreted in the context of the clinical picture. Heart failure associated effusions can be diagnosed relatively easily if patients have signs and symptoms of fluid overload and the pleural fluid is transudative. So is the case for pneumonia related effusions when patients have neutrophilic predominant exudates and appear to be infected clinically. For tuberculous effusions, patients usually have history of or high risk for TB infection; the pleural fluid is lymphocytic predominant and exudative. A pleural fluid adenosine deaminase (ADA) level can support the diagnosis: a level greater than 40 U/L has a sensitivity, specificity and receiver operating curve (ROC) of 92%, 90% and 0.95, respectively (20) for tuberculous effusions. An ADA level less than 40 U/L can virtually rule out TB related effusions. On the other hand, an ADA >250 U/L suggests a diagnosis of empyema or lymphoma and TB is highly unlikely (21).

Fluid cell counts and differential also provide diagnostic data. For instance, pleural fluid eosinophilia usually indicates a response to nonspecific injury to mesothelial cells such as that from air, blood or tumor invasion; the most common causes are found to be malignancy (26%), idiopathic (25%) and parapneumonic effusions (13%) (22), although it is neither sensitive nor specific for these conditions. Fluid hematocrit helps distinguish hemothorax from conditions such as malignancy that produce bloody pleural effusions; while a fluid hematocrit >5% is sufficient to render the fluid indistinguishable from blood, a value of >50% is required for a diagnosis of hemothorax (23).

Infection-related pleural effusions

Pneumonia is the most common condition responsible for infection-related pleural effusions; among the estimated 1.5 million patients being hospitalized for pneumonia annually in the US (24), up to half of them may develop pleural effusion by ultrasonographic criteria (25). There has been a rise in incidence over the past 2 decades, from 3.04 per 100,000 in 1996 to 5.98 per 100,000 in 2008 in the US (26), partially due to increasing awareness and advancements in diagnostic techniques that facilitate fluid detection. Infection-related pleural effusions impact prognosis, as its presence translates into worse clinical outcomes including longer hospital stays and higher mortality (26,27).

Parapneumonic effusions range from simple to complex to frank empyema. Simple and complicated parapneumonic effusion can be distinguished by the gross appearance (clear

in simple effusion and more turbid in complicated one) and fluid analysis (pH >7.20, LDH <1,000 IU/L and glucose >40 mg/dL for a simple effusion whereas pH <7.20, LDH >1,000 IU/L and glucose <40 mg/dL for a complicated one); fluid culture may be positive in complicated ones (28,29). Empyema is usually self-evident with the purulent fluid. Pleural fluid pH has the highest diagnostic accuracy for complex parapneumonic effusion (30), although there is false positivity in certain conditions such as rheumatoid pleuritis and malignant pleural effusions (31). The pH value can also be altered by improper sample handling, such as mixing the fluid with air, lidocaine, heparin and delay in analysis for more than 24 hours. In contrast, fluid glucose is not affected by these factors (32). Lastly, pleural fluid culture is positive in only 60% of cases even in apparently purulent samples (9); the direct inoculation of blood culture bottles may increase the culture yield by 21% (33).

Malignant pleural effusion

The diagnosis of malignant effusion is often confirmed by pleural fluid cytology. Recent data suggests a sensitivity of 60% of fluid cytology for the first specimen and an increase by 15% with a second sample (34); repeating a third procedure for further cytology does not show meaningful improvement in diagnostic yield (35). The types of malignancy can also affect the yield of fluid cytology. The diagnostic yield is higher in adenocarcinoma and much lower in mesothelioma (as low as 26%) with fluid cytology (36-38). Other factors that may affect the cytologic diagnostic yield include the tumor burden in the pleural cavity, coexisting pleural conditions such as infections, specimen preparation and cytopathology expertise.

PE related pleural effusion

The incidence of pleural effusion in patients with PE is about 20–50% (39) depending on the imaging modality (i.e., CT *vs.* X-ray). PE occurred in more than 220,000 patients in 20% of acute hospital beds in the US in 2005 (40) and the projected annual incidence of PE nationwide is 300,000–500,000 cases. This would make it one of the most common causes of pleural effusion (10,41). The reported incidence is, however, only less than 7% overall in patients with PE (34,42). A PE associated effusion is usually small, and even when it is significant in size, the diagnosis of PE is often overlooked (41). Almost all PE related effusions are exudates and its diagnosis requires a high clinical suspicion.

Hepatic hydrothorax

Hepatic hydrothorax occurs in the setting of chronic liver disease such as cirrhosis and hepatitis. In cirrhotic patients, 20% have pleural effusion, and 6% have concurrent pleural effusion and ascites (43). Eighty-five percent of hydrothoraces occur on the right, 13% on the left, with only 2% having bilateral effusions (44). The pathophysiology behind the right predominant laterality is the propensity of the right hemidiaphragm to form developmental defects in the tendinous portion; in the setting of elevated intraabdominal pressures, the peritoneum herniates through these defects towards the pleural cavity, producing pleuroperitoneal blebs which may rupture and create direct communication between the peritoneal and pleural cavities (45). A free flow of ascites to the pleural cavity is facilitated by the negative pleural pressure generated during inspiration. The diagnosis can be established based on the clinical picture combined with fluid analysis and exclusion of other conditions. A total of 10–15% of patients with hydrothorax will develop spontaneous bacterial pleuritis, among whom 40–50% do not have concomitant spontaneous bacterial peritonitis (46).

Uncommon transudates

Etiologies of transudative pleural effusions other than heart failure and hepatic disease are uncommon. It is often a sequela of the imbalance of the pleural fluid-forming forces or abnormal anatomic communication between the pleural cavity and its surrounding structures, although it is impossible to categorize all causes of transudates into these two entities.

Conditions that break the balance of hydrostatic and oncotic pressures between the parietal and visceral pleurae and the pleural space *per se* can often result in transudates. Examples include nephrotic syndrome, hypoalbuminemia, superior vena cava syndrome and constrictive pericarditis, to name a few. Clinical signs and symptoms are often self-evident.

Body fluid from other organs can translocate to the pleural cavity via abnormal or pathologic communication. For example, urinothorax is caused by injury (either due to trauma or procedures) or obstruction (stone, congenital defect or malignancy) of the genitourinary track, permitting

urine to enter the pleural space either via the anatomic defect of the diaphragm (as discussed above in hepatic hydrothorax) or diaphragmatic lymphatics. A systemic review analyzed a total of 88 patients with reported cases of urinothorax (47). In most cases the effusion is transudative with a urine-like odor, unless it is mixed with blood or there is concurrent infection or malignancy (47,48). A pleural fluid-to-serum creatinine ratio greater than 1.0 is consistent with a diagnosis of urinothorax. Other examples include cerebrospinal fluid leak or ventriculopleural shunt, both of which may be confirmed with the presence of β_2-transferrin in the fluid. In patients undergoing peritoneal dialysis intraabdominal fluid translocates to the pleural space through diaphragmatic defects and is transudative on analysis.

Uncommon exudates

There are many uncommon exudative effusions and are difficult to categorize into distinct groups mechanistically (*Table 1*). Generally speaking, the production of exudates is due to increased vascular permeability which is often a consequence of inflammation, as well as a direct violation of pleural integrity due to surgery or trauma. A few of the more frequently seen disease entities will be discussed here.

Post coronary artery bypass grafting (CABG) pleural effusion

Mechanistically post CABG pleural effusions can be arbitrarily categorized into perioperative (within the first week but possibly up to a few weeks postoperatively), early (30 to 90 days postoperatively) and late effusions (after 90 days). By the criteria discussed above, these are exudative effusions (49,50).

Perioperative pleural effusion is mostly bloody; it is usually small and limited to the left hemithorax. Pleural fluid is notable for eosinophilia and the lactase dehydrogenase (LDH) level of the fluid is usually more than three times the upper limit of reference range in serum. It is believed to be related to the trauma and bleeding from surgery (50). Perioperative effusions usually resolve without intervention. The prevalence of perioperative pleural effusions has been reported to be 89%, 77% and 57% on post op days 7, 14 and 30, respectively (51). Approximately 10% of the effusions are large within the first month of the surgery (49), potentially requiring intervention.

As opposed to perioperative effusions, those occurring or persisting after 30 days are non-bloody, mostly lymphocytic predominant, with an LDH level that is not as high. It has been speculated that there is an immunologic component, as seen in postcardiotomy syndrome where there is an autoimmune reaction directed against the epicardium (52). This could trigger a significant inflammatory response in the pleura, reflected in the higher vascular endothelial growth factor (VEGF) level in the pleural fluid one month after the surgery (53), leading to increased permeability of the pleural vasculature. The prevalence of pleural effusion is estimated to be 10–20% within 3 months postoperatively, especially with internal mammary artery grafting (IMA) more than saphenous vein grafting (SVG) (54,55); the use of IMA graft is thought to cause a higher incidence of pleural effusion due to the violation of pleura integrity during harvesting (56).

Pleural effusions that occur 90 days after the surgery are unlikely to be related to the CABG surgery *per se*, but rather to other conditions such as congestive heart failure, pericarditis or PE (50).

Chylothorax

Lymphatic capillaries in the peritoneal cavity coalesce to form cisterna chyli, which are sac like structures located in front of the first and second lumbar vertebrae. These become the thoracic duct which enters the right hemithorax via the aortic hiatus of diaphragm then courses its way upwards medially and posteriorly to the esophagus; it then crosses midline to the left hemithorax typically at the level of the third/fourth thoracic vertebrae and continues to ascend along the left border of the esophagus until it eventually terminates at the junction of left subclavian and internal jugular veins. This anatomic pattern is seen in 65% of the general population (57). Chylothorax occurs when the integrity of the thoracic duct and/or its tributaries is compromised and chyle, the lymphatic content enriched with fat, digestive products and vitamins in the thoracic duct, leaks into the pleural cavity. Broadly speaking, traumatic (such as penetrating injuries and thoracic surgeries) and non-traumatic etiologies (i.e., malignancy, congenital disorders, lymphatic obstruction, etc.) each account for approximately 50% of cases (58).

The classic white, milky gross appearance of the pleural fluid strongly indicates the diagnosis of chylothorax; however, this is an insensitive criterion for diagnosis and <50% of chylous effusions have this appearance (59), possibly due to differences in nutritional status and lipid ingestion. When chylothorax is suspected, a triglyceride

level in the pleural fluid >110 mg/dL is consistent with the diagnosis. A level >110 mg/dL has a positive predictive value of greater than 99% in diagnosing chylothorax, whereas a level <50 mg/dL has a negative predictive value of greater than 95% in ruling out the diagnosis (60). An intermediate level between 50–110 mg/dL requires confirmation by the presence of chylomicrons in the fluid to establish the diagnosis. The presence of chylomicrons is considered the gold standard for diagnosis of chylothorax. Cholesterol levels are usually <200 mg/dL. Subsequently, conventional lymphangiography and lymphoscintigraphy can be used to locate the leak or obstruction of the thoracic duct (58).

Pseudochylothorax

Pseudochylothorax is also known as chyliform or a cholesterol pleural effusion. It is believed to be a chronic process (months to years) during which blood cells (erythrocytes and neutrophils) that are trapped in the pleural cavity undergo disintegration, releasing cholesterol and other lipid components such as lecithin-globulin complexes from degenerating cell and organelle walls. Meanwhile, there is concurrent pleural thickening which limits the absorption of the cholesterol retained in the pleural space (61). In cases of pseudochylothorax without pleural thickening, the cholesterol effusion is believed to originate from serum lipids bound to lipoproteins accumulating in the pleural space during active inflammation (62). A systematic review showed TB and rheumatoid arthritis account for 88% of pseudochylothorax cases, and 20% of the cases are without pleural thickening (63). Other more rare causes include chronic hemothorax, empyema, heart failure, and chronic pneumothorax.

The pleural fluid in pseudochylothorax is exudative with a lymphocytic predominance; it has been described as a "protein-discordant" exudate (high protein with LDH in the transudative range) (64). It can be milky-appearing. In contrast to chylothorax, the pleural fluid from pseudochylothorax usually has cholesterol levels >200 mg/dL and triglyceride levels <110 mg/dL; the ratio of cholesterol/triglyceride >1 is found in 97% of cases (63). The presence of cholesterol crystals confirms the diagnosis of pseudochylothorax. Once a diagnosis is made, further testing may indicate the underlying cause. For example, a low glucose level (<29 mg/dL) and low pH (<7.20) suggest a rheumatoid arthritis related effusion (34); a fluid ADA >40 U/L is suggestive of TB.

Systemic lupus erythematosus (SLE)-related pleural effusions

RA and SLE are the two most common rheumatologic diseases with pleural manifestations (65). The underlying mechanism is thought to be immune complex deposition and the binding of auto-antibodies to the mesothelium, eliciting an inflammatory response which leads to an increase in vascular permeability (66). Associated effusions tend to be small and bilateral. There is no specific fluid testing to differentiate it from other types of exudates. Suggestive findings include low complement levels and elevated titers of antinuclear antibodies (ANA, >1:160). Neither are recommended for routine measurement, although a negative ANA titer essentially rules out the diagnosis of SLE-induced effusion due to its excellent negative predictive value (34,67).

The undiagnosed exudate

Twenty percent of pleural effusions remain undiagnosed after an extensive diagnostic workup described above (34) and a pleural biopsy should be considered. In general, there are three types of pleural biopsy: (I) blind closed percutaneous pleural biopsy; (II) imaging-guided biopsy with ultrasound or CT; (III) invasive pleural biopsy via medical thoracoscopy or video-assisted thoracoscopic surgery (VATS).

Blind percutaneous needle biopsy

Blind percutaneous pleural biopsy, usually with Abrams needles (68), is more commonly used in less developed countries where there is limited availability to more sophisticated methods. The Abrams needle is a reverse beveled punch needle which permits for collecting tissue during withdrawal of the needle. The yield of an Abrams needle biopsy depends on the nature of the disease. For example, the sensitivity of this biopsy modality for malignant disease was only 57% in a large cohort (69). The low diagnostic yield is thought to be because of tumor lesions being scattered and the tendency of tumor deposits to cluster close to midline structures and the diaphragm, which are usually avoided when performing a blind biopsy to minimize complications (34). On the other hand, in diseases that affect the pleura diffusely such as TB, the sensitivity has been shown to be reasonably high (79%) (70). This being said, along with relatively high complication

rates (34), blind percutaneous pleural biopsy with Abrams needles is recommended only in resource-constrained areas with high prevalence of diseases that cause diffuse pleural involvement (especially TB), and up to six specimens should be obtained to maximize sensitivity (71).

Image-guided biopsy

Image-guided biopsy, with either ultrasound or CT, is a relatively new modality of biopsy. Imaging guidance, favorable pleural anatomy (such as pleural thickening >1 cm) and the use of cutting needles rather than the Abrams needles are the factors which increase biopsy sensitivity (34). A representative example in a well-designed prospective randomized trial described the higher sensitivity of a CT-guided cutting needle biopsy when compared to blind Abrams biopsy for malignancy (87% *vs.* 47%, P=0.02) (72). On the other hand, ultrasound guidance for biopsy has similar performance with CT guidance (73), but may be more convenient due to its greater portability.

Thoracoscopy

About 20% of exudative pleural effusions remain undiagnosed despite repeated thoracentesis and needle biopsy (74). Thoracoscopy is the next recommended diagnostic step (34). Thoracoscopic guided biopsy permits direct visualization of the pleural space, helps identify pleural lesions, and has a higher sensitivity than the aforementioned biopsy modalities. Pooled results of more than 1,300 thoracoscopy cases reflect a sensitivity of 92.6% for malignant pleural disease (75). Among these were 337 cases with a previous non-diagnostic blind pleural biopsy. This reflects a sensitivity 90.1% in the setting of a negative blind pleural biopsy (75). Thoracoscopy is especially important if mesothelioma is suspected, as the diagnostic yield of cytology from pleural fluid alone is notoriously low (26–32%) (76), whereas thoracoscopic biopsy has a diagnostic yield of over 98% in a large prospective cohort (36). Procedural complication rates have been reported to be quite low at 0.34% (75) with most complications related to talc usage, rather than the procedure itself.

Regarding more specific technical details, this modality includes medical thoracoscopy (also referred to as pleuroscopy or local anesthesia thoracoscopy) and VATS. Medical thoracoscopy can be performed in endoscopy suites or operating rooms, under local anesthesia with or without conscious sedation, with one or two entry ports, and done by trained interventional pulmonologists. In contrast, VATS is performed in operating rooms, under general anesthesia with single-lung ventilation often with double-lumen endotracheal intubation, typically utilizing three entry ports, and performed by thoracic surgeons (77). So far, there has only been one direct comparison of these two techniques for diagnostic yield, safety and cost (78). The two techniques were reported to have similar diagnostic yields in undiagnosed exudative pleural effusions and similar overall low incidence of complications. However, medical thoracoscopy is almost 3 times less costly than VATS (2,815 *vs.* 7,962 Canadian dollars) (78). This is largely due to the fact that medical thoracoscopy can be performed in an outpatient setting.

Conclusions

The diagnosis of pleural effusion requires a thorough systematic approach. It begins with distinguishing transudates from exudates, testing disease-relevant or disease-specific biomarkers, and may require an invasive pleural biopsy in uncertain cases. The diagnostic approach for pleural effusion is an evolving field in pulmonary medicine. The increasing burden of pleural disease summons ongoing multidisciplinary efforts to maximize diagnostic accuracy in a cost-effective fashion.

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