Review Article

Diagnostic tests in pleural effusion – an update

Neville Berkman and Mordechai R. Kramer

Institute of Pulmonology, Hadassah University Hospital, Ein Kerem, Jerusalem, Israel

Introduction

Pleural effusion is a common finding amongst hospitalized patients and indicates the presence of disease which may be pulmonary, pleural or extrapulmonary. The differential diagnosis of pleural effusion is wide but a systematic approach allows a definitive aetiology to be identified in at least 75% of patients.¹ The last few years have seen an escalation in the development of new diagnostic tests and in this article we review these advances.

Biochemistry

The initial step in analysing pleural fluid is to ascertain whether the effusion is a transudate or exudate. Transudative pleural effusion is caused by a limited number of diseases, namely cardiac failure, hypoalbuminaemia, secondary to atelectasis and urinothorax. The differential diagnosis of exudative effusions includes infections, tumours, noninfectious inflammatory conditions and other diseases. In 1972, Light's criteria were published² by which an exudate is defined as fulfilling one or more of the following: (1) pleural fluid/serum protein ratio of more than 0.5; (2) pleural fluid lactate dehydrogenase (LDH) of greater than two-thirds the upper normal limit for blood LDH levels; and (3) pleural fluid/serum ratio of lactate dehydrogenase of greater than 0.6.

Roth *et al.*³ found that despite the high sensitivity of Light's criteria (100%), these criteria had a low specificity (72%). This was due to the fact that many patients with effusion due to chronic cardiac failure have protein values in the exudate range, especially if chronic diuretic therapy has been employed.^{4–6} The author found that the serum–effusion albumin gradient (serum albumin minus pleural fluid albumin) was a sensitive (95%) and more specific (100%) marker of exudative effusions.

A gradient of less than 1.2 g/dl indicates the presence of an exudative effusion and greater than 1.2 g/dl, a transudative effusion.

Hamm *et al.*⁷ measured cholesterol levels in pleural fluid in 62 patients with pleural effusion of known aetiology. They found that using a value of 60 mg/dl as a cut-off (>60 mg/dl indicates an exudate, <60 mg/dl a transudate), this test was 100% sensitive and 95% specific (versus 100% and 70% for Light's criteria). All transudative effusions had cholesterol values below 60 mg/dl (mean 30 ± 12 mg/dl) and all malignant effusions had cholesterol values greater than 60 mg/dl (mean 94 ± 25 mg/dl), therefore this test could definitely separate these two categories of effusions. Patients with inflammatory exudates had cholesterol values between these two groups (mean 76 mg/dl). Measurement of pleural fluid/serum cholesterol ratio did not add to the diagnostic value of pleural fluid cholesterol measurement alone. The value of cholesterol in differentiating between exudate and transudate has subsequently been confirmed by an additional study.⁸

The value of pH, glucose and lactate dehydrogenase measurement has long been established.⁹ Low values for pH, glucose and elevated LDH are found in empyema, malignancy, tuberculosis, rheumatoid arthritis and systemic lupus erythematosus and oesophageal rupture.^{10,11} Measurement of pH and glucose is of special importance in cases of parapneumonic effusions where these tests allow differentiation between complicated parapneumonic effusion (pH <7.0, glucose <40 mg/dl) which requires intercostal drainage for resolution and non-complicated effusion which resolves without drainage.¹²

Measurements of pH and glucose have prognostic significance in cases of malignant effusions.^{13–15} Those patients with pleural fluid pH <7.3 or glucose <60 mg/dl have far shorter life expectancy than those with higher values: 2.1 months *vs* 9.8 months¹³. The low pH group have more extensive pleural disease as assessed at thoracoscopy and a higher failure rate for chemical pleurodesis: 36% *vs* 8%.

Correspondence: N. Berkman, Institute of Pulmonology, Hadassah University Hospital, POB 12000, Jerusalem, Israel.

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Elevated pleural fluid amylase in the absence of pancreatitis or oesophageal rupture is highly suggestive of malignancy.¹⁶ The isoenzyme was found to be salivary amylase. Kramer *et al.*¹⁶ suggest that in cases of malignant effusion where cytology cannot clearly differentiate adenocarcinoma from mesothelioma, an elevated amylase level would favour the presence of the former.

A frequent diagnostic problem is that of exudative pleural effusion with negative cytology and fluid lymphocytosis. Possible diagnoses include tuberculosis, collagen-vascular diseases and tumour including lymphoma. Adenosine deaminase, an enzyme involved in purine catabolism and found especially in T-lymphocytes is markedly elevated in tuberculous effusions¹⁷⁻¹⁹ (mean 92 U/l) as compared to malignant effusions (mean 13 U/l). Levels greater than 45 U/l are highly sensitive and specific for tuberculous effusions, although rheumatoid effusions have similarly elevated levels.²⁰ Increased pleural fluid lysozyme (muramidase) levels and pleural fluid/serum lysozyme ratios (>1.2) also differentiate between malignant and tuberculous effusions (sensitivity 100%, specificity 94.9%).²¹ Lysozyme levels are also increased in empyema and rheumatoid arthritis.²² Combined use of elevated adenosine deaminase (>33 U/l) and elevated pleural fluid/serum lysozyme ratio (>1.2) yields a sensitivity and specificity of 100% for tuberculous effusions if empyema is excluded.²³ Gamma interferon, secreted by activated T-lymphocytes is markedly increased in tuberculous effusions in comparison with effusions due to other causes²⁴ (91.2 U/ml vs 2 U/ml). Soluble interleukin 2 receptor levels have also been found to be higher in tuberculous effusions as compared to malignant and transudative effusions.²⁵ In contrast, levels of interleukin 1 do not clearly differentiate malignant from tuberculous effusions.²⁶ The value of measurement of antinuclear antibodies in the diagnosis of pleural effusions in systemic lupus erythematosus²⁷ and of rheumatoid factor in rheumatoid arthritis²⁸ are well established.

Malignant markers

Increased levels of carcinoembryonic antigen (CEA) (>12 ng/ml) are a specific but insensitive (34%) marker of malignant effusions.²⁹ Raised pleural fluid CEA is more specific and sensitive than are blood levels and there is no correlation between these two values. Measurement of pleural fluid CEA in addition to cytological examination increases the sensitivity for diagnosis of malignancy to 54% as compared to 40% for cytological examination alone.²⁹ Measurement of CEA is of particular value in the diagnosis of adenocarcinoma. A pleural fluid CEA level above 20 ng/ml

is 91% sensitive and 92% specific for adenocarcinoma.³⁰ The finding of increased CEA is of particular value when cytology reveals malignant cells but these cannot be differentiated between carcinomatous and mesothelioma cells. Elevated CEA levels in pleural fluid, or positive staining by immunocytology or immunohistology is strongly against a diagnosis of mesothelioma, but does not definitely exclude this diagnosis.³¹ Levels of hyaluronic acid in pleural fluid are elevated (>100 mg/l) in 73% of patients with malignant mesothelioma, but in no patients with other forms of malignancy.³² Neurone-specific enolase, an enzyme found in nerve and neuroendocrine tissues, is elevated (>26 ng/ml) in 75% of cytology positive effusions due to small cell carcinoma.³³

Many other markers have been examined to assess their value in the diagnosis of malignant effusions. Alpha fetoprotein, beta 2 microglobulin,³⁴ ferritin, acid-soluble glycoprotein, tissue polypeptide antigen and immunosuppressive acid protein³⁵ have not been found to be of value in the diagnosis of malignant effusions. Carbohydrate antigen 19-9 has been found to be higher in malignant effusion as compared to tuberculous effusions.³⁶ Recently, monoclonal antibodies have been used to differentiate between malignant mesothelioma and adenocarcinomatous cells. The antibodies B72-3 and LeuM1 react with carcinomas and not mesotheliomas³⁷ while epithelial membrane antigen (EMA), BMA-120, MY4 and BA-2 react with mesothelioma cells and not with other tumours.³⁸ Lectin binding patterns (lectins are glycoproteins that bind specifically to carbohydrate groups) have also been used to differentiate between mesothelioma and adenocarcinoma cells.³⁹

Cytology

Pleural fluid analysis should always include a differential cell count and careful cytological examination to identify malignant cells. Normal fluid contains 1,500 cells/ μ l with predominance of monocyctic cells, some lymphocytes, macrophages and mesothelial cells, with rare polymorphs.¹⁰ Pleural fluid leucocyte counts in themselves are not diagnostic.¹⁰ Counts $>50,000/\mu$ l are seen in parapneumonic effusions. Transudates usually have counts of $<1,000/\mu$ l, tuberculosis and malignancy usually have $<5,000$ cells/ μ l, inflammatory diseases (infectious and noninfectious) have counts $>10,000/\mu$ l.

Pleural fluid eosinophilia ($>10\%$) is usually associated with benign disease, especially post-haemothorax, pneumothorax, previous thoracentesis and asbestos-associated effusion⁴⁰ but eosinophilia may occasionally be found in malignancy.

nant effusions.⁴¹ Pleural fluid lymphocytosis is non-specific and may be found in malignancy,^{42,43} tuberculosis, collagen vascular diseases, sarcoidosis, lymphoma and in up to one third of transudates.¹⁰

The commonest cause of malignant pleural effusion is primary adenocarcinoma of the lung, followed by breast, ovary and pancreas. In young patients, lympho-reticular malignancies are the commonest cause of malignant effusion.⁴⁴ In the presence of malignant effusion, cytology alone is diagnostic in 33–72% of cases.⁴⁵

Automated flow cytometry allows rapid analysis of the DNA content of a large number of cells (up to 30,000 cells). Aneuploidy (abnormal DNA content) is considered as a marker of malignancy and flow cytometry of pleural fluid has been used to increase the yield of cytology alone in diagnosing malignancy in pleural effusions.⁴⁶ The value of immunocytology and immunohistology has been discussed previously.

Immunocytochemistry is frequently used to identify lymphocyte surface markers and thereby differentiate between malignant and reactive lymphocytes, primarily by demonstrating monoclonality.^{47,48}

Computerized interactive morphometry can also differentiate effectively between malignant and reactive lymphocytes.⁴⁹ This technique uses a computer and video recorder and analyses the size and regularity of the nuclei of cells in a centrifuged, papanicolou-stained preparation. The cells are categorized by the computer as benign or malignant according to these parameters. This technique has also been used to differentiate between malignant and benign reactive mesothelial cells.⁵⁰

Imaging

Standard antero-posterior and lateral chest X-ray films can detect the presence of pleural fluid in excess of 175 ml.⁵¹ Lateral decubitus films may detect pleural fluid not seen on routine films.⁵²

The role of sonography, computed tomography (CT) and magnetic resonance imaging of pleural diseases has recently been reviewed.^{53,54} Ultrasound allows identification of loculated pleural fluid. The presence of septae or loculations on sonography usually indicates that the effusion is an exudate (specificity 74%).⁵⁵ Ultrasound allows differentiation between lung abscess and loculated effusion in 90% of cases.⁵⁶ The major role of sonography is as a guide to thoracentesis when previous unguided thoracentesis has been unsuccessful. It has a success rate of 97% with a 2–7% incidence of pneumothorax.⁵⁷ Closed pleural biopsy and placement of intrathoracic chest tube can also be

performed with ultrasound guidance. Sonography can differentiate between pleural fluid and pleural mass or thickening. As compared to computerized tomography, ultrasound has the advantage of being more rapid and, if necessary, can be performed at the patient's bedside.⁵⁴

Computerized tomography is used extensively in chest medicine. It easily allows differentiation between pleural and parenchymal disease.⁵³ Pleural collections usually have a more homogeneous appearance, a convex border with tapering margins and usually form an obtuse angle with the chest wall. In contrast, in parenchymal lesions the angle is more likely to be acute.^{52,53} In equivocal cases this differentiation is enhanced by using CT with bolus contrast injection.⁵⁸ The presence of pleural masses and thickening are easily noted on CT. The parietal pleura is thickened in 86% of patients with empyema and demonstrates enhancement following contrast injection in 96% of cases.⁵⁹ The resolution of empyema over time can also be assessed by CT.⁶⁰

Computerized tomography is of value in differentiating between benign and malignant involvement of the pleura. The presence of one or more of the following criteria was found to indicate malignancy with a sensitivity of 72% and a specificity of 83%: circumferential pleural thickening, nodular pleural thickening, parietal pleural thickening of greater than 1 cm or mediastinal pleural involvement.⁶¹ In the presence of a known pulmonary malignancy, pleural and chest wall involvement can accurately be ascertained using CT scanning.⁵³

Asbestos-related pleural disease can best be assessed using CT. It is superior to the standard chest X-ray in identifying discrete pleural plaques (95% vs 59%)⁶² and is also of value in guiding biopsy, ascertaining the extent of malignant mesothelioma and identifying coexistent pulmonary parenchymal disease.⁶³ High-resolution CT is more sensitive than regular CT in identifying the presence of asbestos-related pleural and pulmonary parenchymal disease.⁶⁴

The CT features of malignant mesothelioma and the value and limitations of this modality in the follow-up of this disease have also been reviewed.^{65,66}

The value of magnetic resonance (MR) imaging in pleural and pulmonary parenchymal disease is limited, primarily due to motion artifact caused by cardiac and respiratory activity. MR is, however, the imaging modality of choice in evaluating superior sulcus carcinomas.⁵³ Using MR imaging, Davis *et al.* were able to distinguish between transudates, simple exudates and complex exudates (malignant or infectious).⁶⁷

Invasive tests

Closed pleural biopsy is indicated in patients with an undiagnosed pleural effusion (following pleural fluid analysis) in whom malignancy or tuberculosis is suspected.⁶⁸ In the presence of an exudative pleural effusion, closed pleural biopsy provides a definitive diagnosis (i.e. malignancy or tuberculosis), in 49% of patients.⁶⁹

Cytological examination of pleural fluid is more sensitive than closed pleural biopsy for the diagnosis of malignancy (71% vs 45%),^{70,71} although a recent study has found comparable sensitivities for these two tests (52% vs 60%).⁶⁹ For tuberculosis, Bueno *et al.*⁶⁹ found that closed biopsy was diagnostic in 84% of patients: 77.6% had diagnostic histological findings, 39% were positive on culture and no case was positive on direct Ziehl-Neelsen staining. In contrast, pleural fluid was diagnostic in only 13% of patients with tuberculosis (all on culture and no patients on direct Ziehl-Neelsen staining).

The combination of thoracentesis and closed biopsy increases the diagnostic yield to 86% for tuberculosis and 79% for malignancy. Repeat thoracentesis and biopsy were positive in 56% of initial false negative tests⁶⁹ and these authors therefore recommend that a negative test should be repeated.

A study comparing the use of the Cope versus the Abrams needle in performing pleural biopsy revealed no significant difference in the diagnostic yield.⁷² Several newer methods of pleural biopsy have been tried and found successful.^{73,74} Closed pleural biopsy has a complication rate of 11%,⁶⁹ the commonest being pneumothorax, although vascular trauma has been reported.

Following a complete diagnostic evaluation including closed pleural biopsy, 20% of effusions remain undiagnosed.⁷⁵ In these patients, diagnostic rigid thoracoscopy is advocated and has repeatedly been shown to be highly sensitive (93–97%)^{76–79} and specific (100%) for the diagnosis of malignant and tuberculous pleural effusion. While thoracoscopy accurately identifies benign pleural effusions as non-malignant, it is seldom helpful in identifying the cause of these effusions.⁷⁸

Rigid thoracoscopy can be performed under local or general anaesthesia. Local anaesthesia with sedation or intercostal nerve block allows this procedure to be performed on patients too ill to undergo general anaesthesia.⁸⁰ Major complications (arrhythmia, circulatory or respiratory collapse) and minor complications are uncommon (1.9% and 5.5%).⁷⁸ Following thoracoscopy under local anaesthesia, the mean duration of intercostal chest tube drainage is 11.9 hours and hospital stay 26.5 hours.⁷⁹

Fibreoptic thoracoscopy is not a sensitive test

and adds little to closed pleural biopsy.⁸¹ Thoracoscopy has recently been used for many other indications including adequate drainage of empyema,⁸² pleurodesis under direct vision and to assess pleural involvement by lung carcinoma prior to surgery.⁸¹

In cases of undiagnosed pleural effusion, bronchoscopy is usually not helpful^{83,84} unless there is other pathology on chest X-ray or the patient also has haemoptysis.⁸⁵

In a small number of pleural effusions, complete diagnostic workup does not identify the cause of the effusion⁸⁶ and the decision to observe or perform thoracotomy and open biopsy needs to be made. Open pleural biopsy is diagnostic in only 60% of these cases,⁸⁷ many of which are mesotheliomas.⁸⁸ In cases of pleural effusion where open biopsy is not diagnostic, the effusion disappears spontaneously in 60.8%. Of the remaining patients in whom the diagnosis manifests at a later stage, 73% are malignant effusions especially lymphomas and mesotheliomas.⁸⁸

The finding of pleural effusions in an asymptomatic patient does not significantly change the differential diagnosis; the commonest causes are the same as for symptomatic effusions, namely tumour, parapneumonia, cardiac failure and post-surgery. Asbestos-related effusions and pleural effusions post-delivery tend to be asymptomatic.⁸⁹

Conclusion

In a patient presenting with pleural effusion, unless the cause of the effusion is readily apparent, the initial diagnostic step is thoracentesis. The pleural fluid should routinely be analysed for protein, albumin, LDH, glucose and cholesterol. A simultaneous blood level for protein, albumin, LDH and glucose should be obtained. If empyema or malignancy is suspected, pH measurement should also be performed. Pleural fluid amylase should be measured if malignancy, pancreatitis or oesophageal rupture are considered. Immune and malignant markers should be sent if autoimmune or malignant disease is suspected. If tuberculosis is suspected, pleural fluid adenosine deaminase or lysozyme (and preferably both) should be measured. Pleural fluid samples should be sent for Gram's stain, KOH and Ziehl-Neelsen staining and for bacterial, fungal and mycobacterial culture if an infective process is considered.

A full cell count and differential count as well as cytological examination should always be performed. Flow cytometry, computerized morphometry and examination of lymphocyte surface markers is carried out if necessary.

If initial thoracentesis is not diagnostic and the fluid is an exudate, repeat thoracentesis with closed

pleural biopsy should be performed. The biopsy specimen is sent for histopathology and culture for tuberculosis. If the diagnosis is still not apparent, closed pleural biopsy can be repeated or rigid thoracoscopy with guided biopsies can be per-

formed. If at this stage a diagnosis is still not apparent, the decision to perform open thoracotomy or to simply follow the patient is made on an individual case by case basis.

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