Pleural Fluid Analysis for Diagnostic of Pleural Effusion: A Literature Review

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Abstract

A condition known as pleural effusion occurs when fluid builds up in the pleural cavity that exceeds normal limits and can be caused by infectious or non-infectious diseases. Pleural fluid analysis plays an important role in establishing the diagnosis, along with the clinical picture and radiological examination. A literature study was carried out with the aim of describing pleural fluid analysis examinations that can be carried out to help confirm the diagnosis.

Keywords: pleural effusion, pleural fluid analysis, diagnostic

1. Introduction

Pleural effusion is a condition where fluid accumulates in the pleural cavity in abnormal amounts, either as a result of pleural membrane transudation or excessive exudation as a difficulty arising from multiple medical conditions (Khairani, Syahruddin, and Partakusuma, 2012). Infectious diseases such as tuberculosis, pneumonia, and abscesses, as well as non-infectious diseases such as carcinoma, kidney failure, and pulmonary embolism, can cause pleural effusion (Dewi and Fairuz, 2020).

Cases of pleural effusion in the United States are reported to reach 1–1.5 million new cases each year. Meanwhile, in England, 200,000–250,000 new cases are reported each year (Panjwani and Zaid, 2017). Based on research conducted in India, the main cause of pleural effusion in that country is tuberculosis (68.8%). The second most common cause is malignancy (14%), followed by emphyema (6%), and transudative effusion (2.8%) (Maikap, Dhua, and Maitra, 2018). Meanwhile, at Dr. Moewardi Hospital, Soerakarta, of 107 pleural effusion patients, it was found that 86 patients had exudative pleural effusion, which is usually found in malignancies and tuberculosis. Meanwhile, 21 others experienced transudative pleural effusion, which is usually found in congestive heart failure and chronic kidney failure (Surjanto et al., 2014).

Pleural fluid analysis is an important assessment that can be carried out in pleural effusion patients. Clinical, radiological, and laboratory examinations are needed to diagnose the cause of pleural effusion (Mercer, 2019). Light's criteria are 98% sensitive for distinguishing exudates from transudates. Apart from that, supporting examinations such as, glucose, pH, total and differential leukocyte count,and adenosine deaminase (ADA) can also be carried out (Porcel, 2019).

2. Discussion

2.1. Definition of pleural effusion

Pleural effusion is a the state in which the pleural cavity fills with fluid in abnormal amounts, either due to transudation or excessive exudation from the pleural surface (Khairani, Syahruddin, and Partakusuma, 2012). Pleural fluid accumulates when there is an increase in capillary plasma filtration, that is, the amount of fluid entering exceeds the amount of fluid coming out, or there is a blockage in lymphatic drainage so that the rate of fluid excretion is disrupted (Hunter and Regunath, 2021). Pleural effusions can develop on their own or be brought on by a number of illnesses, including inflammation, malignancy, and infections (Krishna et al., 2021). According to Halim (2007), pleural effusion is rarely found as a primary disease and is often found as a secondary form of other diseases. Pleural effusion often accompanies various other diseases, such as diseases of the lungs, pleura, and systemic diseases (Karkhanis and Joshi, 2012).

2.2. Definition of pleural fluid analysis

Apart from clinical and radiological information, interpretation of pleural fluid examination plays a significant part in establishing a diagnosis because many etiologies of pleural effusion are still unclear (Mercer, 2019). This examination is carried out on pleural fluid obtained by thoracentesis with the help of thoracic ultrasound (Porcel, 2019). A pleural fluid inspection can be done by looking at the color and consistency of the fluid..

Table 1. Pleural Fluid Inspection (Porcel, 2019)

Pleural Fluid Appearance	Causes
Watery (transparent)	Transudate
Serous (yellowish)	Exudate
With blood (redness)	Malignancy (50%), trauma, postcardiac injury syndrome, pulmonary embolism
Purulent with a foul odor	Anaerobic empyema
Thick	Empyema, mucin, hyaluronate-producing tumors
Like milk (white)	Kilothorax, pseudochylothorax
Black	Fungal infections (Aspergillus niger, Rhizopus oryzae), pancreaticopleural infections
Green	Bilothorax or cholethorax

Routine pleural fluid examination includes, glucose, protein, pH, lactate dehydrogenase (LDH), cytology, and microbiology (Mercer, 2019). Adenosine deaminase (ADA), cytology, and bacterial and mycobacterial culture. An ADA examination is carried out if there is a possibility of tuberculosis and such an examination is available. Cytology was not performed if the effusion occurred as a clinical outcome of pneumonia or heart failure. Bacterial culture is performed if there is a possibility of infection (Porcel and Light, 2013).

Several non-routine pleural fluid analysis tests can also be carried out to confirm the diagnosis, such as checking triglyceride levels, amylase, and tumor markers. A triglyceride concentration of more than 110 mg/dL confirms chylothorax. Very high amylase levels of around 1000 U/L are seen in pancreatico-pleural fistulas. Meanwhile, amylase levels of 100–130 U/L are often caused by malignancy (Porcel, 2019).

Pleural fluid examination results are an important part of the clinical evaluation. Generally, this test has high sensitivity and specificity, but a small percentage of false positive and false negative findings are always present. Therefore, all examination results must be interpreted according to the patient's condition to enable an accurate diagnosis and treatment. (Mercer, 2019).

Table 2 Diagnosis Based on Pleural Fluid Characteristics (Porcel, 2019)

Diagnosis	Characteristics of Pleural Fluid
Heart failure	Light transudative criteria, albumin gradient > 1.2 g/dL, NT-proBNP > 1500 pg/mL
Hepatic hydrothorax	Light transudative criteria, pleural fluid to serum albumin ratio <0.6
Empyema	Pus, culture positive
Complications of parapneumonic effusion	pH <7.15, glucose <40 mg/dL, LDH >2000 U/L, CRP >100 mg/L, positive culture
Malignant effusion	Cytology positive, predominantly lymphocytic, CEA >45 ng/mL, CA15-3>77U/mL
Tuberculosis	Predominantly lymphocytic, protein >5 g/dL, ADA > 35 U/L, positive Ziehl-Neelsen stain, positive solid/liquid culture, positive M. Tuberculosis PCR
Hemothorax	Pleural fluid to serum hematocrit >0.5
Pulmonary embolism	Exudates are predominantly neutrophilic or lymphocytic
Pancreatitis	Predominantly neutrophilic, amylase >100U/L
Kilothorax	Criteria Light exudative, predominantly lymphocytic, milky appearance, triglycerides >110 mg/dL, chylomicrons present
Rheumatoid pleurisy	Glucose <60 mg/dL, pH <7.20. positive rheumatoid factor
Lupus pleurisy	Antinuclear antibodies (anti-ENA, anti-dsDNA) positive

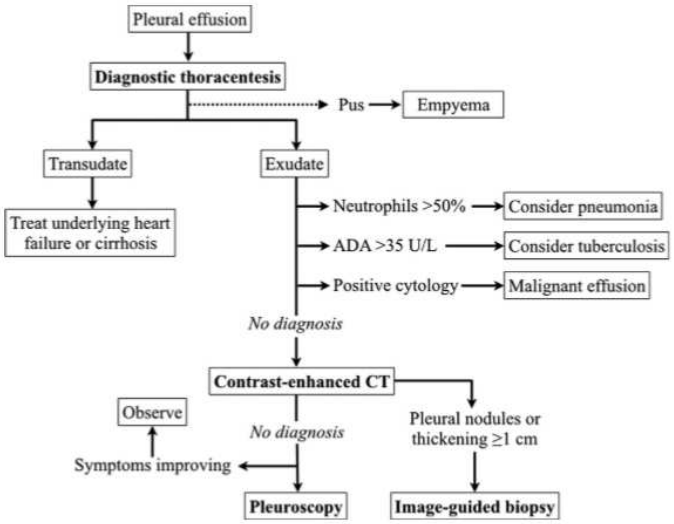

Figure 1. Algorithm of pleural fluid analysis (Porcel, 2019)

2.3. Exudative and transudative

Considering on Light's criteria, pleural effusion can be divided into exudate and transudate. Pleural effusion can be considered an exudate if any one of the following conditions is met:

- The effusion protein concentration compared to the serum protein concentration is >0.5.
- Concentration of lactate dehydrogenase (LDH) in the effusion >200 IU
- Concentration of LDH in the effusion compared to the LDH concentration in serum is >0.6.

Light's criteria are 98% sensitive for differentiating exudate from transudate, with a probability of misclassification of transudate effusion into exudate of approximately 30%. To overcome this, it is necessary to examine the serum (Porcel, 2019).

Table 3. Differences in Transudate and Exudate Fluid Analysis (Yu, H., 2011)

Difference	Transudative	Exudative
Appearance	Serous	Mucous
Leukocyte Count	<10.000/mm3	>50.000/mm3
pH	>7.2	<7.2
Proteins	<3.0 g/dL	>3.0 g/dL
The ratio of pleural fluid to serum proteins	<0.5	>0.5
Lactate dehydrogenase (LDH)	<200 IU/L	>200 IU/L
Ratio of pleural fluid LDH to serum	<0.6	>0.6
Glucose	⩾ 60 mg/dL	<60 mg/dL

Transudates are nearly invariably linked, not to a particular pleural illness, to an imbalance in either fluid or protein throughout the body. There are two ways in which it might occur: first, as in CCF, it can result from fluid overload, in which hydrostatic pressure pushes fluid from the capillaries into the extravascular space. Second, fluid may leave blood vessels and re-accumulate in the extravascular space if the oncotic pressure in the capillaries decreases. This is present in low-albumin situations including nephrotic syndrome and liver failure. Exudative effusion, on the other hand, is typically brought on by a pleural illness. Increased capillary permeability brought on by an illness like an infection or malignancy is what causes fluid leakage (Mercer, 2019).

2.4. Leukocyte Count

Types of leukocytes are divided into polymorphonuclear (PMN) and mononuclear (MN) which consist of cells. This division of leukocyte counts plays a role in differentiating types of inflammation. PMN dominant leukocytes with neutrophil segment shape indicate an acute inflammatory process. Meanwhile, MN dominant leukocytes with lymphocytes indicate chronic inflammation. In pleural effusion, a predominance of PMN

often suggests a diagnosis of parapneumonic effusion, viral infection and pulmonary embolism. Meanwhile, the possible diagnoses for MN dominance are malignancy, tuberculosis and pleurisy (Yovi, et al., 2017)

Based on research that has been conducted, the median value of the percentage of lymphocyte count is greater in patients with TB pleural effusions than in those with malignant pleural effusions, namely 86% and 61%. In patients with pleural effusion with predominant TB, more lymphocytes are found, making it the main cause of pleural lymphocytosis. Meanwhile, in pleural effusions with malignancy, a predominance of neutrophils can be found with a low incidence rate of around 8% (Verma, 2016). Mercer, et al. (2019) also stated that the results of pleural fluid analysis with a predominance of lymphocytes are often caused by tuberculosis, kidney failure, heart failure. Neutrophil predominance is more common in parapneumonia and early stage tuberculosis. Meanwhile, eosinophil predominance is more often found in malignancies, idiopathy and parapneumonia.

2.5. Glucose

Glucose levels need to be checked because they can help determine the management of pleural cavity drainage in patients with suspected parapneumonic effusion (Rahman et al., 2008). Normal glucose levels in the pleural fluid of patients with TB are around 3.3 to 5.6 mmol. Glucose levels <2.8 mmol/L are seen in patients with effusion (Voster, 2015). Glucose levels in patients with TB pleurisy may decrease but are similar to serum levels. (Cohen and Light, 2015).

2.6. LDH

LDH is a sensitive but not specific pathological marker for inflammation or cell injury (Mercer et al., 2019). LDH levels more than three times normal often indicate a pleural infection. A significant increase can be characteristic of parapneumonic effusion, pleuritic tuberculosis, or malignancy (Chubb and Williams, 2018).

2.7. Protein

High protein levels in pleural fluid analysis are often caused by exudative effusion and various etiologies, with the most common cause being tuberculosis. Meanwhile, low protein levels (<15 g/dL) are often caused by dural leaks, urinothorax, and trapped lungs. By calculation of serum albumin levels against pleural fluid or total protein gradient, effusions that seem exudative but are more likely to have a transudative etiology based on clinical findinga can be reclassified (Mercer, 2019).

In research conducted at a hospital in Myanmar with patients with pleural effusion and malignancy studied, the mean value of protein concentration was 41.02 g/L, serum protein ratio 0.61, LDH 599.56 U/L, LDH ratio pleural fluid, and serum 1.18 (Soe, 2012).

2.8. pH

Although LDH and glucose are also utilized, pleural fluid pH levels play a role being the most helpful indicator of infection (Chubb and Williams, 2018). Acidosis of pleural fluid is found in complications of pleural infection, rheumatoid arthritis, tuberculosis, and malignant effusion. Pelural drains should be performed without delay in patients with a pleural fluid pH of less than 7.2, even if the effusion is caused by

parapneumonia (Jany and Welte, 2019). In patients with pleural effusion and malignancy, pH levels of less than 7.3 are often found, which is associated with low glucose levels as well as high leukocyte and LDH levels. Meanwhile, the pH level of pleural effusion fluid in pleural effusion patients with TB is below 7.4 (Houston, 1987).

2.9. ADA

ADA is checked to see if the patient has possible tuberculosis and if testing is available (Porcel, 2019). In one study, it was stated that of 254 patients with tuberculosis infection, it was found that 99.6% had ADA levels of more than 47 U/L. In another study conducted in populations with a low prevalence of tuberculosis and non-tuberculosis, 97% and 98% had ADA levels of less than 40 U/L (Vorster, 2015). In India, the ADA examination has a good level of accuracy in diagnosing tuberculous pleural effusion, with a threshold value of 40 IU/L in 18 studies (Aggarwal et al., 2016).

3. Conclusion

The diagnosis of pleural effusion is made based on clinical features, radiology, and pleural fluid analysis. Routine pleural fluid analysis examinations include checking glucose, protein, LDH, pH, leukocyte count, and ADA levels, which play a role in helping to determine the type of fluid and possible causes of pleural effusion.

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