Review Article

The differentiation of pleural effusions

F. J. MARITZ

Summary

The causes and pathophysiology of pleural effusions are briefly discussed. A method for staining pleural effusions is described and the importance of side-room microscopy in the evaluation of pleural fluids is emphasized. The value of various investigations in the differentiation of pleural effusions is reviewed.

S Afr Med J 1982; **62**: 553-556.

Pleural effusions are a common problem in South Africa. At Tygerberg Hospital, which is a training hospital of 1 700 beds, an average of 11 new cases, the majority of which have benign or treatable causes, are seen per week. Many different investigations have been used for the differentiation of pleural effusions, but a large proportion of them are of limited clinical relevance. A thorough knowledge of the investigations available as well as their uses and limitations will lead to their rational use, reduce the stay in hospital of these patients and prevent any treatable causes of effusions being overlooked.

Causes and pathophysiology

The causes of pleural effusions are numerous (Table I) and have been the subject of various excellent reviews.[1-3] Many factors can play a part in keeping the pleura free of fluid (Fig. 1) and can be summarized in the following equation: $FM = K (HP_c - HP_{pl}) - (COP_c - COP_{pl})$, where FM is fluid movement, K the filtration coefficient, HP_c the mean capillary hydrostatic pressure, HP_{pl} the pleural hydrostatic pressure, COP_c the mean colloid osmotic pressure of capillary plasma, and COP_{pl} the mean colloid osmotic pressure of pleural fluid. Often insufficient emphasis is placed on the important role of the subpleural lymphatics in the clearance of pleural protein and fluid when the hydrostatic, oncotic pressure or vascular permeability becomes deranged. In many cases, especially when exudates are present, more than one mechanism is operative to account for the effusion.

TABLE I. CAUSES OF PLEURAL EFFUSIONS

- **Transudates**
  - Congestive cardiac failure
  - Hypo-albuminaemic states, e.g. cirrhosis, nephrotic syndrome, malabsorption
  - Myxoedema
  - Peritoneal dialysis
  - Meigs' syndrome
  - Acute glomerulonephritis
- **Exudates**
  - Infective diseases
    - Tuberculosis
    - Bacterial infections, e.g. parapneumonia or septicaemia
    - Viral, fungal or parasitic infections
  - Malignant diseases
    - Metastatic malignant tumours, e.g. lung, breast, or ovary
    - Mesotheliomas
    - Lymphoproliferative disorders, e.g. lymphoma, lymphocytic leukaemia
  - Collagen vascular disorders
    - Systemic lupus erythematosus
    - Rheumatoid arthritis
    - Polyarteritis nodosa
  - Rheumatic fever
  - Pulmonary infarction
  - Abdominal disorders
    - Pancreatitis
    - Oesophageal rupture
    - Subphrenic and hepatic abscess
  - Trauma
    - Haemothorax
  - Chylothorax
    - Traumatic
    - Malignant involvement of lymph vessels
  - Drugs
    - Nitrofurantoin
    - Methysergide
  - Miscellaneous
    - Asbestos exposure
    - Uraemia
    - Dressler's syndrome
    - Sarcoidosis
    - Congenital abnormalities of pleura, e.g. yellow nail syndrome

Differentiation of pleural effusions

Traditionally effusions are divided into exudates and transudates and, with a few exceptions, this distinguishes 'benign' from 'non-benign' causes. If the effusion is a transudate, no further diagnostic procedures on the pleural fluid are indicated and the underlying cause can be treated. However, if the effusion is an exudate, more investigations will be needed to define the cause of the pleural disease.[1]

In most cases the distinction between exudates and transudates can be suspected on clinical grounds and confirmed by the measurement of pleural protein and lactate dehydrogenase (LDH) content (see below).

Therefore, depending on the findings of the initial clinical and side-room microscopic examination of the pleural fluid, one can usually proceed directly to the treatment of the transudate or ask for more specific tests to differentiate between the different

Department of Internal Medicine, University of Stellenbosch and Tygerberg Hospital, Parowvallei, CP
F. J. MARITZ, M.B. CH.B., F.C.P. (S.A.), M.MED. (INT.) (Present address: 326A Loop Street, Pietermaritzburg, Natal)

Date received: 4 January 1982.

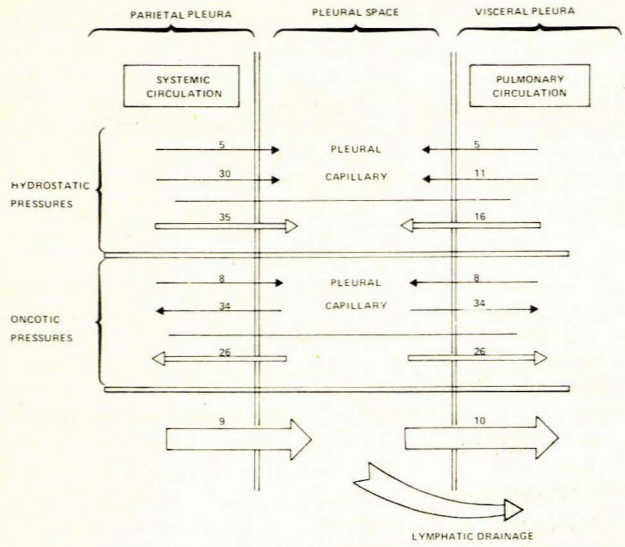

Fig. 1. Schematic representation of the movement of fluid over the pleural space.

causes of exudates instead of procrastinating until the results of the protein and LDH estimations are available. It is unrealistic and unnecessary to ask for a long list of investigations from the outset because most of them are of relevance only in special situations.

Clinical evaluation

With a few exceptions, the history and clinical examination will indicate whether an effusion is a transudate or exudate. The majority of the causes of transudates can be diagnosed clinically and the absence of the characteristic symptoms and signs should indicate that the underlying effusion is an exudate. Nevertheless, a transudate should be confirmed chemically as some patients with cardiac or hypoproteinaemic states may have a simultaneous underlying pleural disease. When an effusion is seen in a patient with cardiac failure, an exudate should be suspected if there are no signs of right-sided failure, because in these patients transudates are seldom seen in the absence of oedema, a raised jugular venous pressure or a congested liver. Similarly, one should be suspicious of left-sided effusions in cardiac disease, as most transudates appearing in this condition are right-sided.

Further clinical examination and a chest radiograph often help to indicate the cause of an exudate. Thus, the clinical examination is invaluable and helps the physician to plan his subsequent diagnostic strategy.

Investigations

After the pleural effusion has been confirmed, diagnostic aspiration should be performed and about 50 ml obtained for side-room microscopy and protein, LDH, adenosine deaminase (ADA) and glucose estimations, including a specimen for microbiological and cytological examination. Care must be taken not to traumatize the patient and cause bleeding into the fluid or introduce air into the pleural cavity, as this can alter the appearance of the fluid in some respects and increase the risk of secondary infection.

Occasionally it may be necessary at this stage to aspirate large volumes of up to 1 litre to relieve a patient's distress. It is advisable not to remove all the fluid at the outset because this can make pleural biopsy difficult or impossible at a later stage. It goes without saying that a chest radiograph is imperative after any procedure on the pleura.

Macroscopic appearance. The presence of blood in effusions, especially on microscopic examination, is common and has many causes. A traumatic tap can usually be recognized by the streaky appearance of the blood-staining and the tendency for the staining to diminish with successive tubes. However, grossly bloodstained fluids with an erythrocyte count of greater than 100 000/μl are invariably due to trauma, pulmonary infarction or a malignant lesion.

The colour of an effusion is of little value except that the darker the colour, the greater the probability that the effusion is an exudate. The presence of a clot indicates a high protein content, whatever the cause. Turbid effusions have a high cellular content and are usually found in emphysemas. A milky fluid suggests a chylothorax or a chyliform effusion. Empyemas can be differentiated from a chylothorax by centrifuging the specimen — the supernatant will be clear in empyemas but not with a chylothorax.

Thick, mucoid fluid suggests an empyema, whereas a thick, bloodstained, mucoid effusion should make one suspect a metastatic adenocarcinoma. A high spinnbarkeit is characteristic of a mesothelioma with a high hyaluronic acid content.

Microscopic appearance. All pleural effusions should initially be examined microscopically as a side-room investigation. The staining method is quick and easy to perform and enables one to plan a logical diagnostic approach. A 10 ml sample of fluid is centrifuged at 2 000 rpm for 15 minutes, the supernatant fluid poured off and the sediment resuspended in the fluid adherent to the sides of the test tube. A smear is made as for blood and then stained with Diff-Quick. The slide is kept for 10 seconds in the fixative, for 10 seconds in solution I and for 15 seconds in solution II, allowing 5 seconds between solutions for the excess fluid to run off. The slide is quickly washed off under running tap water, allowed to dry in air and examined under a thin film of oil for clarity.

For all practical purposes the non-cytologist need only look at two cell types, namely lymphocytes and neutrophils. Lymphocytes predominate in tuberculous and in the majority of malignant and transudative effusions. A lymphocytic exudate is thus an indication for a pleural biopsy, to which one can then proceed. Parapneumonic effusions show a predominance of neutrophils, as do some effusions associated with pulmonary infarcts and a minority of those due to malignant tumours and fulminant early tuberculous effusions. Unless one of the latter two is strongly suspected, pleural biopsy is not necessary or is even contraindicated.

A low mesothelial cell count of less than 1% is a feature of tuberculous effusions,[4,5] and the presence of a large number of these cells makes tuberculosis unlikely. However, the appearance of mesothelial cells can be difficult to interpret and their distinction from malignant cells should be left to an experienced cytologist. The white cell count is of very little clinical value. Cell counts over 10 000/μl suggest a para-infective effusion, but otherwise the count is of little diagnostic value and not worth the effort.

Biochemical investigations. In the first place, chemical tests are used to divide effusions into transudates and exudates. Previously a specific gravity over 1,016 or a protein content over 30 g/l was used to define an exudate. However, exudates can be defined more accurately if one of the following is present:[6] fluid-to-plasma protein ratio over 0,5; fluid-to-plasma LDH ratio over 0,6; and fluid LDH level over 200 U/l.

LDH: Apart from being used to define an exudate, the pleural LDH and protein levels are not very helpful in differentiating exudates from each other. Very high LDH levels with normal protein levels are said to be suggestive of malignancy[1] and are also found in empyemas.[7] Most benign effusions have a predominance of the LDH 4 and LDH 5 iso-enzyme fractions. A predominance of the LDH 2 fraction raises the suspicion of malignancy.[8] Haemolysis of blood in the pleural effusion can raise the total LDH content. In this situation the true LDH

value can be obtained by subtracting the LDH 1 fraction from the total.[1]

Protein: Protein levels are still of value in defining exudates. Levels higher than 60 g/l are said to be suggestive of a tuberculous effusion.[1] Protein electrophoresis and determination of immunoglobulin and mucoprotein levels have no diagnostic use.[1]

ADA: ADA is an enzyme involved in the breakdown of adenosine to inosine in purine catabolism and produced by activated T lymphocytes.[9] Values over 40 U/l are found in 90% of tuberculous and parapneumonic effusions and in only 10% of malignant effusions.[10-12] An ADA level of more than 40 U/l and/or an ADA ratio above 1,1 are found in 100% of tuberculous and in the majority of parapneumonic effusions. Pulmonary embolism, lymphoma, lymphocytic leukaemia and mesothelioma occasionally produce raised values. The importance of an ADA estimation is seen when it is combined with microscopy,[10] and it has its greatest value in differentiating tuberculous from malignant and other effusions. Thus, the following assumptions can be made:[10-12]

1. An ADA level of less than 40 U/l in the fluid and a ratio of less than 1,1 makes a tuberculous effusion highly improbable.
2. Lymphocytic exudates with ADA levels over 40 U/l are highly suggestive of a tuberculous effusion, although a minority of malignant effusions show a similar response. However, a lymphocytic exudate with an ADA content over 60 U/l is very characteristic of a tuberculous pleuritis.
3. With ADA values below 40 U/l in a lymphocytic exudate, a malignant effusion should be strongly considered.
4. A neutrophilic exudate with raised ADA levels and/or a raised ratio makes a para-infective effusion very likely, although a small percentage of early tuberculous effusions and malignant lesions will show a similar response.

Glucose: Levels below 3,3 mmol/l are found in a variety of disorders, such as parapneumonic,[13] rheumatoid,[14] malignant and tuberculous effusions, but are of little discriminating value. However, glucose estimations are helpful in para-infective and suspected rheumatoid effusions. Rheumatoid arthritis as the cause of an effusion is unlikely if the glucose level in the fluid is above 1,6 mmol/l, and this serves as a useful screening test.[1] In para-infective effusions the decline in glucose content parallels the decline in pH;[15] the lower the glucose level, the greater the likelihood that the effusion has become infected and thus requires tube drainage.

pH: Fluid for pH estimations must be air-free and transported on ice. Again, as for glucose, a pH below 7,2 has many causes and may be found in parapneumonic,[7] rheumatoid, and some tuberculous and malignant effusions. A pH estimation is important *in parapneumonic effusions* where a pH below 7,2 or a pH 1,5 lower than the pH of the blood is the earliest indicator that the effusion will require tube drainage.[1] In the presence of para-infective effusions the following criteria indicate the need for tube drainage:[16] (*a*) frank pus; (*b*) organisms seen with Gram staining; (*c*) a glucose level of less than 3,3 mmol/l; (*d*) pH below 7,2; and (*e*) pH 1,5 lower than blood. Without these features daily needle aspiration and serial testing will suffice. The pH need only be estimated when a para-infective effusion is suspected and when microscopic examination shows a neutrophilic response.

Amylase: Acute pancreatitis often causes a left-sided effusion, which is characterized by a high amylase content. The amylase level is also raised in rupture of the oesophagus. Although the level is claimed to be raised in 10% of malignant effusions other than those due to metastasis from the pancreas,[1] its estimation has no role in the diagnosis of malignant effusions.

Lysozyme: Lysozyme content or the pleural fluid-to-plasma lysozyme ratio is raised in a significant proportion of tuberculous and para-infective effusions.[17] However, we have found a considerable amount of overlap[10] with the values found in other effusions and regard ADA estimations as very much more helpful.

Hyaluronic acid: Only effusions caused by mesotheliomas have a raised hyaluronic acid level[18] and its estimation is useful in the diagnosis of these pleural tumours. Unfortunately only about 37% of these patients have elevated levels of over 0,8 g/l.

Rheumatoid factor: Rheumatoid factor is present in most rheumatoid effusions but is also present in a large proportion of parapneumonic, malignant and tuberculous effusions and is therefore too nonspecific to be of any diagnostic value.[1]

Complement: Levels have been shown to be reduced in effusions caused by rheumatoid disease and systemic lupus erythematosus (SLE).[19] Glucose levels are normal in SLE[20] and the finding of LE cells in the pleural fluid is pathognomonic of this disease.

Carcino-embryonic antigen (CEA) and β_2-microglobulin: When a malignant tumour of the pleura is suspected, a CEA estimation may be helpful.[21] Concentrations over 11 ng/ml are found only in malignant effusions.[22,23] The β_2-microglobulin values are increased in lymphomas and immune diseases.[24] Lymphomas sometimes cause a lymphocytic exudate with a high ADA content, a response indistinguishable from that in tuberculosis. The β_2-microglobulin may thus be helpful in differentiating lymphomas from tuberculous effusions.

Attempts have been made to find other markers of disease of the pleura,[24] but most have been found to be either too nonspecific or too insensitive to be of any practical use.

Cytological examination

The examination of pleural fluid by an experienced cytologist is imperative with all exudates. Malignant cells will be found in 60% of effusions due to malignant involvement of the pleura and this percentage will increase if three separate specimens are submitted.[1]

Pleural fluid cytology is difficult and it is important that only those with experience in this field should attempt to distinguish reactive mesothelial cells from malignant cells.[4] Furthermore, it is of great help to the clinician if the dominant cell type and the percentage of mesothelial cells is reported.

Microbiological investigation

Pleural fluid should be cultured for aerobic and anaerobic bacteria, especially in the presence of neutrophilic exudate. Staining for acid-fast bacilli rarely yields positive results and need only be done when a lymphocytic exudate with less than 1% mesothelial cells is seen.[1] *Mycobacterium* is cultured in about 25% of proven tuberculous effusions[2] but should be employed on all exudates, especially in areas with a high incidence of tuberculosis. The bigger the volume submitted for mycobacterial culture, the higher the chances of a positive culture.[1,3]

Pleural biopsy

A pleural biopsy has its greatest value in the diagnosis of granulomatous and malignant disease of the pleura and is indicated in all patients with lymphocytic exudates. Samples of the parietal pleura can easily be obtained with an Abrahams needle. In tuberculosis the diagnostic yield is increased by combining the histological findings with culture of the biopsy specimen and pleural fluid.[22] Repeated pleural biopsies often give an answer when the initial biopsy is negative.[24] Again, it cannot be stressed sufficiently that this procedure must be followed by a chest radiograph if serious complications are to be avoided.

REFERENCES

1. Light RW. Pleural effusions. *Med Clin North Am* 1977; **61:** 1339-1352.
2. Turton CWG. Pleural effusions. *Br J Hosp Med* 1980; **23:** 239-249.
3. Fishman AP. *Pulmonary Diseases and Disorders.* New York: McGraw-Hill, 1980: 1357-1372.
4. Spriggs A, Boddington M. *The Cytology of Effusions.* New York: Grune & Stratton, 1968: 1-39.
5. Hurwitz S, Leiman G, Shapiro C. Mesothelial cells in pleural fluid: TB or not TB? *S Afr Med J* 1980; **57:** 937-939.
6. Light RW, McGregor MI, Luchsinger PC, Ball WC. Pleural effusions: the diagnostic separation of transudates and exudates. *Ann Intern Med* 1972; **77:** 507-513.
7. Chavalittamrong B, Angsusingha K, Tuchinda M, Habanananda S, Pidatcha P, Tuchinda C. Diagnostic significance of pH, lactic acid dehydrogenase, lactate and glucose in pleural fluid. *Respiration* 1979; **38:** 112-120.
8. Light RW, Ball WC. Lactate dehydrogenase isoenzymes in pleural effusion. *Am Rev Respir Dis* 1973; **108:** 660-665.
9. Barton RW, Goldschneider I. Nucleotide metabolizing enzymes and lymphocytic differentiation. *Mol Cell Biochem* 1979; **28:** 135-147.
10. Maritz FJ, Visser HS, Malan C, Wranz P, Le Roux I. 'n Nuwe benadering tot die diagnose van pleurale effusies. *S Afr Med J* 1981; **60:** 217-218.
11. Piras MA, Gikas G, Budroni M, Andreoni G. Adenosine deaminase activity in pleural effusions: an aid to differential diagnosis. *Br Med J* 1978; **2:** 1751-1752.
12. Hankiewicz J, Koterwa A. Adenosine deaminase in effusions. *Mater Med Pol* 1978; **36:** 180-183.
13. Potts DE, Levin DC, Sahn SA. Pleural fluid pH in parapneumonic effusions. *Chest* 1976; **70:** 328-331.
14. Lillington GA, Carr DT, Mayne JG. Rheumatoid pleurisy with effusions. *Arch Intern Med* 1971; **128:** 764-768.
15. Potts DE, Willcox MA, Good JT, Faryl DA, Sahn SA. The acidosis of low-glucose pleural effusions. *Am Rev Respir Dis* 1978; **117:** 665-671.
16. Light RW. Management of parapneumonic effusions (Editorial). *Chest* 1976; **70:** 325-326.
17. Klockars M, Pettersson T, Riska H, Hellström P, Norhagen A. Pleural fluid lysozyme in human disease. *Arch Intern Med* 1979; **139:** 73-77.
18. Rasmussen KN, Faber V. Hyaluronic acid in 247 pleural fluids. *Scand J Respir Dis* 1967; **48:** 366-371.
19. Hunder GG, McDuffie FC, Hepper NGG. Pleural fluid complement in systemic lupus erythematosus and rheumatoid arthritis. *Ann Intern Med* 1972; **76:** 357-363.
20. Halla JJ, Schrohenlober RE, Volanakis JE. Immune complexes and other laboratory features of pleural effusions: a comparison of rheumatoid arthritis, systemic lupus erythematosus, and other diseases. *Ann Intern Med* 1980; **92:** 748-752.
21. Rittgers RA, Loewenstein MS, Teinenmann AE *et al.* Carcinoembryonic antigen in benign and malignant pleural effusions. *Ann Intern Med* 1978; **88:** 631-634.
22. Levine H, Metger W, Lacera D. Diagnosis of tuberculous pleurisy by culture of the pleural biopsy specimen. *Arch Intern Med* 1970; **126:** 269-271.
23. Adrian O, Vladutio MD, Adler RH, Wells Brason F. Diagnostic value of biochemical analysis of pleural effusions. *Am J Clin Pathol* 1979; **71:** 210-214.
24. Scerbo J, Keltz H, Stone DJ. A prospective study of closed pleural biopsies. *JAMA* 1971; **218:** 377-380.

Adenosine deaminase estimations in the differentiation of pleural effusions

F. J. MARITZ, C. MALAN, I. LE ROUX

Summary

Adenosine deaminase (ADA) estimations were performed on the pleural fluid from 368 effusions. The mean (±SD) ADA concentration in tuberculous effusions was 92,11 ± 37,05 U/l, and these values were found to be highly statistically different from the 23,23 ± 13,15 U/l in secondary malignant tumours of the pleura, the 34,86 ± 14,2 U/l in mesotheliomas, and the 23,81 ± 15,07 U/l in pulmonary embolism. The ADA values of 64,3 ± 44,95 U/l in lymphoproliferative disorders were less significantly different. No statistical difference could be found between values in the tuberculous group and the ADA levels of 97,57 ± 82 U/l found in para-infective effusions, but these could be distinguished from each other by microscopic examination of the pleural fluid. The importance of ADA estimations in the diagnosis and differentiation of tuberculous effusions is discussed and the role of microscopy is emphasized.

S Afr Med J 1982; **62:** 556-558.

Departments of Internal Medicine, Chemical Pathology and Cytology, University of Stellenbosch and Tygerberg Hospital, Parowvallei, CP

F. J. MARITZ, M.B. CH.B., F.C.P. (S.A.), M.MED. (INT.) (Present address: 326 Loop Street, Pietermaritzburg, Natal)

C. MALAN, M.B. CH.B., F.C.P. (S.A.)

I. LE ROUX, C.F.I.A.C., *Chief Technologist*

Date received: 6 January 1982.

Pleural effusions are common in South Africa and because of the large number of underlying diseases they often present a diagnostic challenge. Unfortunately tuberculosis is still the most common cause of exudative effusions in the Black population;[1,2] its detection and differentiation from other causes of pleural effusions is therefore an important part of the diagnostic work-up.

Numerous tests are available for determining the cause of pleural effusions, and these have been discussed in detail by Light.[3] Attempts have been made to find markers in the pleural fluid to distinguish malignant from other types of effusion,[4] but they are either not generally available or too nonspecific to be of any clinical value. The suspicion of a tuberculous effusion is usually based on suggestive clinical and radiological findings. The cytological observation of less than 1% mesothelial cells in a lymphocytic exudate greatly increases the probability of a tuberculous effusion,[5] but the protein, lactate dehydrogenase (LDH), glucose and pH estimations are too nonspecific to