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Adenosine deaminase estimations in the differentiation of pleural effusions

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Summary

Adenosine deaminase (ADA) estimations were performed on the pleural fluid from 368 effusions. The mean ($\pm$SD) ADA concentration in tuberculous effusions was $92,11 \pm 37,05$ U/l, and these values were found to be highly statistically different from the $23,23 \pm 13,15$ U/l in secondary malignant tumours of the pleura, the $34,86 \pm 14,2$ U/l in mesotheliomas, and the $23,81 \pm 15,07$ U/l in pulmonary embolism. The ADA values of $64,3 \pm 44,95$ 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 $97,57 \pm 82$ 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.

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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

distinguish between tuberculosis and other causes of pleural exudates. Tuberculous involvement of the pleura can be confirmed by the histological examination of a pleural biopsy specimen or by culture of *Mycobacterium* from the pleural fluid or biopsy material. Nevertheless, many cases remain unconfirmed and are treated empirically for tuberculosis.[1]

Until recently there was no investigation of pleural fluids available which was specific enough to indicate that a patient might have a tuberculous effusion. Klockars *et al.*[6] reported that a raised pleural lysozyme level or pleural-to-plasma lysozyme ratio was found in tuberculous effusions and empyemas. Our unpublished experience confirms this, but we have found that the low sensitivity and specificity of this test limits its clinical usefulness. In 1973 Piras and Gakis[7] found that the adenosine deaminase (ADA) level was raised in the cerebrospinal fluid of patients with tuberculous meningitis, and later reports indicated that ADA concentrations were increased in tuberculous effusions.[8,9] An abstract published by us supported these findings and pointed out the value of combining the ADA values with the findings on microscopy of the fluid.[10]

The object of this study was to extend the number of patients in our previous report and to determine the role of ADA and microscopy in the diagnosis of tuberculous effusions and their differentiation from other effusions, particularly those of malignant origin.

Patients and methods

A final diagnosis was obtained in 368 cases in which ADA estimations of the pleural fluid had been performed. Simultaneous ADA activity in the plasma was determined in 226 cases (61%). Those with incomplete records or in whom no conclusion could be reached were excluded from the study.

The diagnoses of these 368 patients are shown in Table I. The exudates were separated from the transudates by the criteria suggested by Light *et al.*,[11] namely a pleural/plasma protein ratio over 0,5, a pleural/plasma LDH ratio over 0,6 or a pleural LDH value of more than 200 U/l. Of the 107 tuberculous effusions 73 (68%) were diagnosed by histological or microbiological means and 34 (32%) were diagnosed by clinical and radiological features and on their response to antituberculosis therapy.

TABLE I. DIAGNOSES IN 368 PATIENTS

Transudates		102
Cardiac failure	90	
Hypoproteinaemia	12	
Exudates		266
Tuberculosis	107	
Metastases	59	
Mesotheliomas	15	
Lymphoproliferative disorders	9	
Para-infective effusion	44	
Pulmonary embolism	24	
Other	8	
Total		368

In the group of 59 patients with secondary malignant tumours of the pleura 43 diagnoses (73%) were confirmed histologically or cytologically, while in the remaining 16 (27%) the diagnosis was made on clinical and radiological grounds. In all the mesotheliomas and lymphoproliferative disorders positive histological or cytological findings were obtained. Clinical, radiological and microbiological criteria were used to diagnose all the para-infective effusions, and confirmation by means of a ventilation/perfusion radio-isotope scan was obtained in all cases of effusion due to pulmonary emboli.

The pleural fluids and plasma for ADA estimations were collected in lithium heparin tubes. The assay for ADA was performed according to the method described by Giusti.[12] Microscopy was performed on 195 of the 368 exudates. These smears were stained by Giemsa stain and also by a method previously described by us,[10] which is ideally suited for a side-room investigation.

Results

Fig. 1 shows the pleural ADA levels in the different groups. The mean ($\pm$SD) ADA concentration was as follows: in tuberculous effusions 92,11 $\pm$ 37,05 U/l, in secondary malignant tumours 23,23 $\pm$ 13,15 U/l, in mesotheliomas 34,86 $\pm$ 14,2 U/l, in lymphoproliferative disorders 64,3 $\pm$ 44,95 U/l, in pulmonary embolism 23,81 $\pm$ 15,07 U/l, and in para-infective effusions 97,57 $\pm$ 82 U/l. In a two-sample t-test, the two-tail test showed a highly significant difference between the ADA values in the tuberculous effusions and those associated with metastases ($P <$ 0,0001), mesothelioma ($P < 0,0001$) and pulmonary embolism ($P < 0,0001$). This difference was much less significant in the lymphoproliferative group ($P < 0,03$), and no significant difference was found in the para-infective group ($P = 0,57$). Fig. 2 shows the distribution of the pleural/plasma ADA ratio in the different groups. The statistical analysis of these results gave figures similar to those shown above.
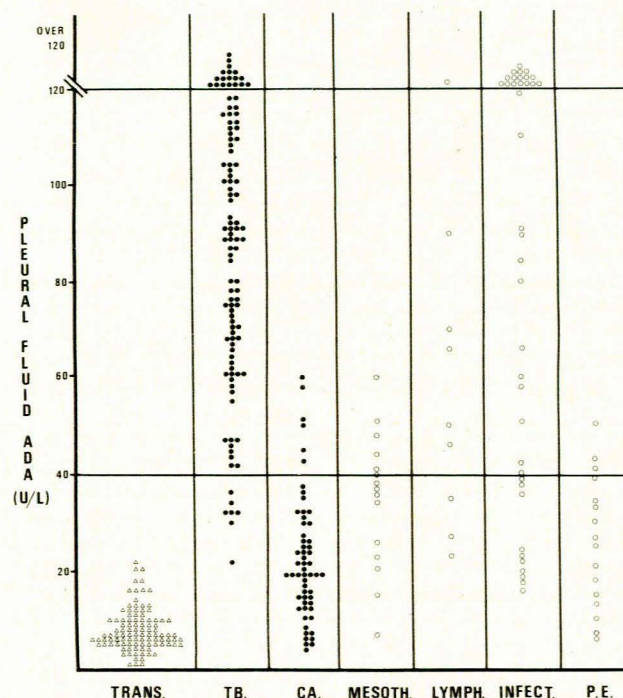

Fig. 1. Pleural ADA concentrations.

A predominant lymphocytic response was found in 94% of the tuberculous effusions, in 85% of those due to secondary malignant tumours, in 90% of those due to mesotheliomas, in 100% of those due to lymphoproliferative disorders, and in 53% of those associated with pulmonary embolism, but in none of the para-infective group. The remainder of the exudates, including all the para-infective effusions, showed a neutrophilic response. The mesothelial cell count was less than 1% in most of the tuberculous effusions and higher than this in exudates due to other causes.
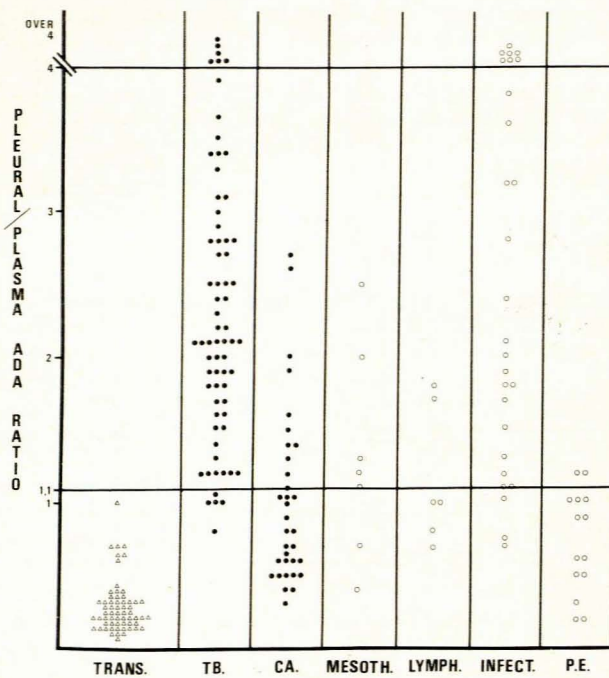
Fig. 2. Pleural/plasma ADA ratio.

Discussion

The most common problem when dealing with pleural exudates is to distinguish those due to tuberculosis from those due to malignant involvement of the pleura. The results of this study show that this can be done by using pleural ADA estimations. High ADA values would indicate that the patient has a tuberculous effusion, whereas low values serve to exclude tuberculosis and suggest the probability of a malignant effusion. We used an arbitrary cut-off value of 40 U/l. Seven per cent of the tuberculous group had a value below this and none of them had a value below 20 U/l. Of the patients with malignant tumours 15% had an ADA concentration above 40 U/l but in no case was a value above 60 U/l obtained. Therefore, ADA values below 40 U/l make tuberculosis unlikely. With ADA values between 40 and 60 U/l the likelihood of tuberculosis is greatly increased, and values above 60 U/l, and especially those above 80 U/l, would seem to be diagnostic of a tuberculous effusion. For the plasma/pleural ADA ratio we used an arbitrary cut-off point of 1,1. As can be seen in Fig. 2, high ratios are found in tuberculosis but there is a greater degree of overlap with effusions due to malignant tumours at the lower end of the scale. We can see no advantage in determining the ADA ratio in all cases. It was found, however, that in all cases of tuberculous effusion either the ADA value was above 40 U/l or the ratio was more than 1,1 and that these criteria can be used to exclude tuberculosis.

Our results show that there is no statistical difference between the ADA values of tubereculous effusions and of para-infective effusions. Microscopic examination of the pleural fluid therefore becomes important in differentiating these two effusions from each other. Except for a 5% minority of acute or fulminant cases, all the tuberculous effusions will show a predominant lymphocytic response whereas all the para-infective effusions will show a neutrophilic response. ADA can therefore not be used as a marker for tuberculosis when neutrophils predominate in the pleural fluid. However, values below 40 U/l tend to exclude tuberculosis in this setting and high values should make one suspect a para-infective effusion.

The above methods cannot be used to differentiate tuberculosis from pleural involvement by a lymphoma or leukaemia in all cases. These conditions also produce a lymphocytic exudate which at times has a very high ADA concentration. Estimation of β_2-microglobulin may be of help in making this distinction as the concentration is said to be high in lymphoproliferative disorders.[4]

ADA is an enzyme involved in the breakdown of purine metabolism and seems to be produced to a greater extent by more differentiated or activated T lymphocytes.[13] This would explain the high values in tuberculous effusions where the immune response is to a large degree T-cell-mediated. Blood ADA levels are also raised in certain T-cell lymphoproliferative disorders and this can be expected to spill over to the pleura in these conditions. A combination of the above mechanisms may account for the high pleural ADA values found in para-infective effusions.

This series shows that tuberculosis is the most common cause of pleural effusions at our hospital and that malignant tumours are the next most common cause of pleural exudates. ADA estimations, especially when combined with microscopic examinations, have much to offer in differentiating these diseases from each other and from other causes of pleural exudates. In summary, the following assumptions can be made:

1. An ADA value below 40 U/l and/or an ADA ratio below 1,1 makes tuberculosis highly unlikely.

2. A lymphocytic exudate with high ADA values indicates a tuberculous effusion.

3. A lymphocytic exudate with low ADA values should make one suspect a malignant tumour.

4. In a neutrophilic exudate with a high ADA concentration, a para-infective effusion should be considered.

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