Adenosine deaminase activity in rheumatoid pleural effusion

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SUMMARY The activity of adenosine deaminase was studied in nine cases of rheumatoid pleural effusion, showing an increase in enzyme activity in all. Rheumatoid arthritis seems unique, however, as it cannot be differentiated from pleural tuberculosis on the basis of this test. Selective increase of adenosine deaminase in both conditions is attributed to stimulation of T lymphocytes in the pleural fluid.

Key words: nucleoside deaminases, arthritis (rheumatoid), tuberculosis (pleural).

In previous studies we confirmed a sensitivity of 100% and a specificity of 95% for the assay of adenosine deaminase (EC 3.5.4.4.) enzyme activity in early diagnosis of tuberculous pleuropericardial, peritoneal, and meningeal effusions.¹⁻⁶ The adenosine deaminase increase has been attributed to the maturative stage or degree of stimulation of T lymphocytes as a response of cell mediated immunity to mycobacterial antigens.

In our first study we observed a case of rheumatoid pleural effusion which exceptionally showed adenosine deaminase increase in the pleural fluid.¹ This observation was later confirmed in two other cases.⁶ Rheumatoid pleural effusion seemed to be unique as it could not be differentiated from pleural tuberculosis on the basis of this test.

This prospective report evaluates the adenosine deaminase test in patients with pleural effusion caused by rheumatoid arthritis.

Patients and methods

We studied the activity of adenosine deaminase enzyme in the pleural fluid of 586 patients with pleural effusion who were admitted to the hospital over a period of five years. The pleural effusions were grouped according to the definite diagnosis as

follows: group I, tuberculous (170 cases); group II, neoplastic (126 cases); group III, parapneumonic (76 cases); group IV, miscellaneous (60 cases); group V, non-specific effusions (45 cases); group VI, transudates (100 cases); and group VII, rheumatoid pleural effusions (nine cases).

In this report we have focused our attention exclusively on the nine patients with rheumatoid pleural effusion in group VII. Patients were included in a previously established prospective protocol.^{1,2} This protocol evaluated clinical data (medical history and physical examination), chest roentgenograms, tuberculin test (5 IU of purified protein derivative of tuberculin), and results of series of diagnostic procedures such as (a) chemistry profile of pleural fluid (protein, glucose, lactate dehydrogenase, and adenosine deaminase activity); (b) tests for rheumatoid arthritis (latex agglutination and Waaler-Rose test); (c) qualitative and quantitative cytology of the pleural fluid in regard to the ratio of lymphocytes to polymorphonuclear leucocytes; (d) cultural identification of micro-organisms from pleural fluid (Ziehl-Neelsen stain, cultures in agar and Löwenstein-Jensen medium); and (e) histological examination of pleural biopsy specimens (Abrams' needle).

Determination of adenosine deaminase in the pleural fluid was carried out by the colorimetric method of Galanti and Giusti.⁷ A diagnosis of rheumatoid pleural effusion was made by exclusion of all other causes of pleurisy in patients with

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rheumatoid arthritis diagnosed according to the criteria of the American Rheumatism Association.⁸

The Mann-Whitney test was used to analyse the data for statistical significance.

Results

Eight men and one woman with an average age of 55.4 years (range 33–68) were studied. In all cases pleural effusion had been preceded by characteristic clinical manifestations of rheumatoid arthritis (RA) for a mean period of 5.5 years, though in one case pulmonary involvement occurred at the onset of the disease. In seven cases pleural effusion was accompanied by fever and swollen, painful joints. Tests for rheumatoid factor were positive in eight of nine patients; eight patients had subcutaneous nodules.

Pleural effusion was left sided in four patients and right sided in the other five. In two patients pleural effusion occurred in association with nodular changes in the pulmonary parenchyma. The tuberculin test was positive (diameter of skin thickness >10 mm read 48 hours later) in five cases.

The effusion was invariably an exudate (mean protein content 55.8 g/l) with low glucose concentration (mean 0.56 mmol/l, range 0.02–2.11 mmol/l) and very high lactic dehydrogenase (LDH) levels (mean 2991 IU/l, range 1275–5290 IU/l). In four cases a glucose load test did not produce significant changes from baseline in glucose concentration in the pleural fluid. Rheumatoid factor was positive in all cases.

Cytological examination showed an exudative effusion with predominant polymorphonuclear cells in six cases and predominant lymphocytosis in the remaining three. Pleural biopsy confirmed the presence of non-specific pleuritis in seven cases, pleural fibrosis with carbon dust and silica deposits in one case, and fibrinopurulent pleuritis in the other case.

In all patients the activity of adenosine deaminase enzyme was >43 U/l (the lower value found in the group of tuberculous pleural effusions); mean (SD) enzyme values were 77.55 (15.62) U/l (range 52–97 U/l).

Clinical and laboratory data of the nine patients with rheumatoid pleural effusions are summarised in Table 1.

In patients with tuberculous and rheumatoid pleuritis the enzyme value was significantly higher than in the rest of the groups ($p<0.001$). The differences in adenosine deaminase activity between the groups of patients with tuberculous and rheumatoid conditions, and among the patients of groups II to V were not significant. Table 2 gives the adenosine deaminase activity in the different groups; individual results are shown in Fig. 1.

Table 1 Clinical data and results of diagnostic procedures in nine patients with rheumatoid pleural effusions

Age (years)	Sex	Duration of RA (years)	Exacerbation of RA	RF	Pleural fluid			Pleural biopsy			
					Glucose (mmol/l)	Protein (g/l)	LDH (IU/l)	ADA (U/l)	RF	PMN/L (%)	
50	M	8	Yes	+	0.78	54	4850	68	+	93/7	Non-specific pleuritis
61	M	2	Yes	–	0.11	62	2200	83	+	98/2	Pleural fibrosis
68	M	2 mo	Yes (1st)	+	2.11	41	1480	77	+	80/20	Non-specific pleuritis
54	M	13	No	+	0.02	58	3110	52	+	90/10	Non-specific pleuritis
67	M	4	Yes	+	0.44	56	4200	97	+	30/70	Non-specific pleuritis
33	F	6	No	+	1.11	57	1600	58	+	24/76	Non-specific pleuritis
44	M	3	Yes	+	0.06	55	2920	88	+	62/38	Fibrinopurulent pleuritis
63	M	9	Yes	+	0.11	62	5290	95	+	90/10	Non-specific pleuritis
59	M	4	Yes	+	0.33	58	1275	80	+	1/99	Non-specific pleuritis

RA=rheumatoid arthritis; RF=rheumatoid factor; LDH=lactic dehydrogenase; ADA=adenosine deaminase enzyme; PMN/L: polymorphonuclear cell/lymphocyte ratio.

Table 2 Results of the adenosine deaminase (ADA) test in the pleural fluid (median values)

Group	Aetiology of effusion	Cases (n)	ADA (U/l)	Range (U/l)
I	Tuberculous	170	83*	43-190
II	Neoplastic	126	8	0-54
III	Parapneumonic	76	14	0-83
IV	Miscellaneous	60	5	0-38
V	Non-specific	45	8	0-45
VI	Transudate	100	0	0-17
VII	Rheumatoid	9	80*	52-97

*Adenosine deaminase activity (mean (SD) was significantly higher than in the rest of the groups ($p < 0.001$).

Fig. 1 Individual distribution of adenosine deaminase activity in the different groups of exudate pleural effusion: group I, tuberculous pleuritis; group II, neoplasms; group III, parapneumonic pleuritis; group IV, miscellaneous; group V, non-specific pleuritis; group VII, rheumatoid pleuritis.

Discussion

Pleural effusion occurs in 3-5% of patients with rheumatoid arthritis with or without nodular changes in the pulmonary parenchyma or on the pleural surface.⁹ Patients are most often men,

usually having subcutaneous nodules. Pulmonary involvement in the form of pleural effusion is commonly preceded by several years of characteristic clinical manifestations of active disease, though it may appear before or together with the onset of rheumatoid arthritis.

A distinguishing characteristic of rheumatoid pleural effusions is their low glucose concentrations (< 2.22 mmol/l) due to impaired glucose transport into the pleural fluid or increased utilisation by pleural cells, and high LDH concentrations. Also, the pleural fluid pH and complement level are low, tests for rheumatoid factor are positive, and crystals of cholesterol are often present.

Pleural fluid has a turbid appearance because of increased numbers of polymorphonuclear leucocytes and mononuclear cells.^{9, 10} Cytoplasmic inclusions in polymorphonuclear cells, containing ingested immune complexes (RA cells), are also observed. Empyema may complicate the course of rheumatoid pleural effusion, and is the result of direct infection of the pleural space due to broncho-pleural fistulas from necrotic subpleural rheumatoid nodules.

In rheumatoid pleurisy 'blind pleural biopsies' most often show non-specific inflammatory changes, and in most cases the purpose of the biopsy is to exclude other diseases. Specific rheumatoid lesions in the pleura corresponding to those found in subcutaneous rheumatoid nodules are seldom seen. Recently, Faurschou *et al* described a characteristic thoroscopic picture of a gritty, granular parietal pleural surface in nine patients with rheumatoid pleurisy.¹¹ Characteristic changes were identified histopathologically in material obtained by biopsy (a pseudostratified layer of epithelioid cells and small papillae containing branching capillaries).

Rheumatoid pleurisy is a diagnosis reached by exclusion. Although the assay of adenosine deaminase enzyme activity in pleural fluid offers a supplement to other laboratory data, increased enzyme activity is also found in tuberculous pleural effusion. Rheumatoid arthritis seems to be the unique entity that cannot be differentiated from pleural tuberculosis on the basis of this test. The abundance of polymorphonuclear cells in rheumatoid pleural effusion may account in part for the adenosine deaminase increase.¹ On the other hand, the predominance and degree of stimulation of T helper/inducer lymphocytes as a response of cell-mediated immunity in rheumatoid and tuberculous pleural effusions¹²⁻¹⁵ may explain the selective increase of adenosine deaminase activity in both conditions.

In conclusion, the biochemical changes in the pleural fluid from our patients did not differ from

those described in cases of tuberculous pleurisy. Clinical and immunological features of pleural effusion in rheumatoid arthritis are highly diagnostic, however, and offer an important supplement to other laboratory data. Furthermore, pleural biopsy may confirm the diagnosis, especially when pathognomonic lesions of pleural tuberculosis are found.

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