

Neuron-specific enolase in the diagnosis of small-cell lung cancer with pleural effusion: a negative report

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ABSTRACT: We measured the concentration of neuron-specific enolase (NSE) and carcinoembryonic antigen (CEA) in the serum and pleural fluid of 53 patients with pleural effusions, including seven patients with small-cell lung cancer (SCLC). High levels (above $12.5 \mu\text{g}\cdot\text{l}^{-1}$) of NSE in pleural fluid were observed in five patients with SCLC (sensitivity 71%). However, pleural fluid NSE levels were also increased in five patients with other types of cancer and in four patients with non-malignant inflammatory diseases (specificity 80%). We conclude that although SCLC with pleural effusion can be associated with elevated pleural fluid NSE activity, this increase in enzyme levels is not specific for malignancy.

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The $\gamma\gamma$ subunit of 2-phospho-D-glycerate hydrolase, E.C. 4.2.1.11 (enolase), neuron-specific enolase (NSE), is a glycolytic enzyme found in the brain, in peripheral nervous tissue, and in cells of the neuroendocrine system [1]. NSE has been detected in a variety of neuroendocrine tumours, among them small-cell lung cancer (SCLC) [2]. Measurement of NSE in serum has been used to assess the extent of the disease and monitor the response to therapy in patients with SCLC [3, 4]. However, the clinical value of NSE as a tumour marker in serum or effusion fluid ultimately depends on the sensitivity and specificity of the assay.

To test whether determination of NSE aids in the diagnosis of SCLC with pleural effusion, we measured this enzyme in the serum and pleural fluid of patients with pleural effusions due to various causes.

Patients and methods

The series consisted of 53 patients with pleural effusion, including 49 admitted consecutively and four previously diagnosed as having SCLC. The patients were divided into two groups on the basis of the final diagnosis, which rested on clinical, radiological and laboratory findings. Group 1: thirty-one patients had pleural effusion due to a malignant tumour. Twenty-three of these patients had cancer which originated from the lungs or pleura (seven with SCLC, four with squamous-cell carcinoma, five with adenocarcinoma, one with large-cell carcinoma, three with mesothelioma

and three with unclassifiable carcinoma of the lung). Eight patients had extrapulmonary cancer (six with breast carcinoma, one with thyroid carcinoma and one with carcinoid tumour). Group 2: twenty-two patients had pleural effusion caused by non-malignant disease (six with tuberculosis, one with pneumonia, two with rheumatoid arthritis, eleven with non-specific exudative pleural effusion and two with congestive heart failure). NSE was measured in serum and in cell-free pleural fluid (stored at -20°C until assayed) with a radioimmunoassay (Pharmacia AB, Uppsala, Sweden). This double antibody radioimmunoassay has a detection limit of $2.6 \mu\text{g}\cdot\text{l}^{-1}$ and a measuring range of $3.2-260 \mu\text{g}\cdot\text{l}^{-1}$. The suggested upper limit of normal serum is $12.5 \mu\text{g}\cdot\text{l}^{-1}$. As haemolysis is known to affect the concentration of NSE in serum, haemorrhagic pleural effusions and sera with visible haemolysis were not included. Carcinoembryonic antigen (CEA) was determined by radioimmunoassay (Pharmacia AB).

Results

Concentrations of NSE in serum were elevated, *i.e.* above $12.5 \mu\text{g}\cdot\text{l}^{-1}$ in two patients with SCLC, two with unclassifiable carcinoma of the lung and one with breast carcinoma (fig. 1).

The NSE concentrations in the pleural fluid of five of the seven patients with SCLC were higher than the upper normal serum value (fig. 1 and table 1). Increased pleural fluid NSE concentrations were also observed in

Table 1. - Clinical data on seven patients with small-cell lung carcinoma (SCLC)

Patient	Age/sex	Cytology			NSE ($\mu\text{g}\cdot\text{l}^{-1}$)		CEA ($\mu\text{g}\cdot\text{l}^{-1}$)	
		pf	Sputum	Pulmonary histology	pf	s	pf	s
1	70 M	+	+	SCLC	13.4	24.1	3.1	2.9
2	56 M	+	+	ND	25.6	87.4	2.3	2.5
3	69 M	-	-	SCLC	167.6	10.3	6.1	1.6
4	72 M	-	+	no neoplasia	5.5	7.5	4.7	4.9
5	55 M	-	+	no neoplasia	2.5	4.2	9.9	5.4
6	54 F	Susp.	-	no neoplasia. Autopsy: anaplastic SCLC	293.0	93.0	1.5	1.4
7	66 M	+	+	no neoplasia. Autopsy: SCLC with features of "mixed" tumour	42.9	10.4	4.5	3.6

-: negative; +: positive; pf: pleural fluid; s: serum; ND: not diagnosed.

Discussion

The value of biological tumour markers in the diagnosis of cancer has remained limited, because the required sensitivity and specificity have not been achieved. However, an advantage in sensitivity has been gained by assaying the tumour marker, e.g. CEA, in exudates close to the tumour, such as pleural fluid [5].

With accumulating experience the potential value of NSE determinations in serum for the diagnosis of SCLC has become evident. A raised serum NSE has been observed in 77-100% of patients at the start of SCLC [6, 7]. The specificity has usually been high also, although raised serum levels of NSE may be encountered in association with some undifferentiated lung cancers. Our study shows that SCLC with pleural effusion can be associated with high concentrations of NSE in pleural fluid, probably originating in tumour cells in the pleural fluid and the pleural membranes. A correlation between the degree of serum NSE elevation and tumour burden has been reported [7], hence a large local tumour mass would explain the high concentration of NSE in pleural fluid. The increase in NSE levels in pleural fluid of some patients with adenocarcinoma is in agreement with immunohistochemical evidence that about half of adenocarcinomas contain NSE activity [8].

False positive results in the pleural fluid NSE assay were observed in a few patients with tuberculosis and rheumatoid arthritis. These active inflammatory conditions do occasionally show elevated levels of other tumour markers, such as CEA, CA-125 antigen [5, 9], and CK-BB [10]. This may be related to the large amount of tissue destruction and repair which occurs in inflammation.

Although the sensitivity of the pleural fluid NSE test is rather high, the low specificity limits its use in the diagnosis of SCLC with pleural effusion.

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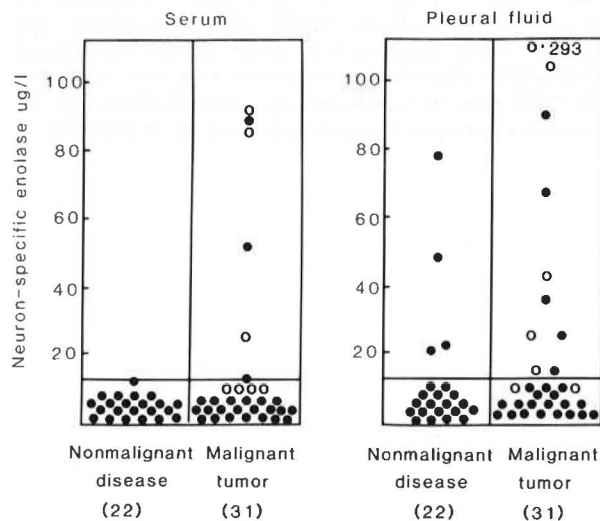


Fig. 1. - Concentration of neuron-specific enolase (NSE) in the serum and pleural fluid of 53 patients with pleural effusions due to malignant tumours and non-malignant diseases. The open circles represent patients with small cell lung cancer.

one patient with adenocarcinoma of the lung ($15.0 \mu\text{g}\cdot\text{l}^{-1}$), two with unclassifiable carcinoma of the lung (25.5 and $35.5 \mu\text{g}\cdot\text{l}^{-1}$), two with breast carcinoma (66.7 and $90.0 \mu\text{g}\cdot\text{l}^{-1}$), one with tuberculosis ($22.1 \mu\text{g}\cdot\text{l}^{-1}$), two with rheumatoid arthritis (48.3 and $79.2 \mu\text{g}\cdot\text{l}^{-1}$), and one with non-specific pleural effusion ($21.1 \mu\text{g}\cdot\text{l}^{-1}$). With a cut-off value of $12.5 \mu\text{g}\cdot\text{l}^{-1}$ the sensitivity of pleural fluid NSE determination in the diagnosis of SCLC was 71% and the specificity 80%.

Results of pleural fluid and sputum cytology, pulmonary histology and determination of NSE and CEA in serum and pleural fluid of the seven patients with SCLC are shown in table 1. None of the patients with SCLC had CEA levels above $10 \mu\text{g}\cdot\text{l}^{-1}$, whereas the concentration of CEA in the pleural effusions due to other types of cancer was elevated in 46% of the patients. No correlation between the presence or absence of tumour cells in pleural fluid and NSE levels was observed.

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RÉSUMÉ: Nous avons mesuré la concentration de neuron specific enolase et de l'antigène carcino-embryonnaire dans le sérum et le liquide pleural chez 53 patients atteints d'épanchements pleuraux, y compris 7 patients avec atteinte d'un cancer pulmonaire à petites cellules. Les niveaux élevés (supérieurs à 12.5 µg/l) de NSE dans le liquide pleural, ont été observés chez 5 patients atteints de cancer pulmonaire à petites cellules (sensibilité: 71%). Toutefois, les niveaux de la neuron specific enolase dans le liquide pleural, étaient également augmentés chez 5 patients avec d'autres types de cancer, et chez 4 patients avec des maladies inflammatoires non maligne (spécificité: 80%). Nous concluons que, quoiqu'un cancer pulmonaire à petites cellules accompagné d'épanchement pleural peut être associé à un taux élevé d'activité NSE dans le liquide pleural, cette augmentation des niveaux enzymatiques n'est pas spécifique de la malignité.