Value of Tumour and Inflammatory Markers in Lung Cancer

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Abstract. The aim of this study was to evaluate the individual diagnostic utility of tumour and inflammatory markers in patients with different pulmonary diseases. The usefulness of neuron-specific enolase (NSE), carcino-embryonic antigen (CEA), serum pro-gastrin releasing peptide (ProGRP) and CYFRA 21-1, as tumour markers, and C-reactive protein (CRP) and tumour necrosis factor-alpha (TNFα) as inflammatory markers for diagnosis, treatment and monitoring of patients with different pulmonary afflictions was investigated. Eighty healthy individuals were also included. Serum samples were also obtained from 20 patients suffering from bronchitis, 20 with lung fibrosis and 30 with sarcoidosis. Moreover, serum marker levels were analyzed in 139 patients with different pulmonary malignancies: 29 patients with adenocarcinoma, 30 patients with squamous cell carcinoma, 80 patients with small cell lung cancer (SCLC). All tumour markers showed significantly elevated values in malignant diseases. The levels of ProGRP in patients with benign diseases were significantly higher than those in the healthy group (35.4±6.6 compared with 21.3±9.2 pg/ml respectively). The serum ProGRP levels were elevated in SCLC patients (1673.9±706 pg/ml). The elevation was significantly higher than that of the benign reference group. The acute phase response had a wide range in patients with malignant tumours. Serum CRP levels were significantly higher in patients with SCLC (38.5±7.6 mg/dl) than in the benign reference group. In conclusion, when serum tumour markers are abnormally elevated in patients with lung cancer, CEA, CYFRA 21-1, NSE and ProGRP are useful clinical markers, good indicators of disease extent and may have important prognostic value. In particular, NSE and ProGRP have a very high sensitivity for SCLC detection.

Many different tumour-associated antigens have been described and investigated for lung cancer. The aim of this study was to examine the clinical value of the well-established tumour markers CEA, CYFRA 21-1, ProGRP and NSE in the differentiation of malignant and benign lesions in patients with pulmonary lesions.

Carcinoembryonic antigen (CEA) is a monomeric, 200 kDa, oncofetal glycoprotein with a variable carbohydrate component of approximately 45-60%. Cancer tissues of various cell types may secrete large amounts of CEA into the circulation. However, in certain normal tissues, as well as benign diseases, and in heavy smokers, CEA may still be secreted in small amounts during adult life. Several studies documented the utility of this antigen in the early diagnosis of tumour recurrence in patients with colorectal and lung carcinoma (1, 2).

Neuron-specific enolase (NSE) is one of the enolase isoenzymes. The serum NSE level is used as a marker for diagnosis, disease extent, and treatment response of solid tumours such as neuroblastoma, retinoblastoma, small-cell lung cancer, medullary thyroid cancer, and pheochromocytoma (3-5).

Cytokeratin 19 fragments are released in the blood because of cell lysis and tumour necrosis. CYFRA 21-1 is a cytoskeleton marker with a low molecular weight (40 kDa). Although it is a relatively novel CK-marker evidence regarding this marker, is already abundant. Histopathological studies demonstrate that cytokeratin 19 is increased in several epithelial tumours, including lung cancer. CYFRA 21-1 is especially suitable for NSCLC as it is the most sensitive tumour marker in these histologies, including squamous tumours (6, 7).

Gastrin-releasing peptide (GRP), a hormone originally isolated from porcine stomach, is a 27 amino acid peptide, which has structural and functional similarities to bombesin (8, 9). The bombesin-like immunoreactive substances proved to be GRP and not bombesin (10). These bombesin-like peptides are known to be involved in lung development. Recent scientific studies have shown that gastrin-releasing peptide and pro-gastrin-releasing peptide are produced in high concentrations by cells of small cell lung carcinoma (SCLC) (11, 12), one of the subtypes of lung cancer. For this
The utility of each tumour marker was determined by means of sensitivity and specificity. C-reactive protein was measured using a Hitachi 917 analyzer (Roche Co., Mannheim, Germany). For the measurement of TNFα (ELISA) a biokine TNFα test kit (T-Cell Sciences Inc., Cambridge, MA, USA) was used.

Results

The incidence of ProGRP expression in our different study groups is summarized in Table I.

Patients suffering from benign diseases, such as chronic inflammatory respiratory affections, sarcoidosis and fibrosis served as a reference group. Of patients with benign diseases, 95% had ProGRP levels under 87 pg/ml. This value served as our cut-off.

The positive results of ProGRP levels in all patients were 70.1%. According to the histological type of lung cancer, the positive rate for ProGRP was 100% in the small cell carcinomas and 10.3% in the non-small cell carcinomas. The mean levels of ProGRP in the SCLC and NSCLC patients were 1673.9 and 59.44 pg/ml, respectively. The serum levels of ProGRP in the SCLC patients were significantly higher ($p=1.57 \times 10^{-12}$) than those in the patients with non-small cell lung cancer (NSCLC) (Figure 1). The levels of ProGRP in the patients with benign diseases were significantly higher than those in the healthy control group ($p<0.005$), whereas there was no significant difference in the levels of ProGRP between patients with benign lung diseases (e.g. fibrosis, sarcoidosis) and patients suffering from NSCLC ($p=0.476$). The positive rate for ProGRP was already high at an early stage and tended to increase even more with disease progression in patients with SCLC. After surgical treatment, ProGRP concentrations showed a significant decrease. In the patients with SCLC who could be followed, the serum ProGRP levels were elevated before treatment. After treatment and at the time of relapse, ProGRP levels were significantly decreased ($p<0.01$) compared to those before treatment. At a specificity of 95%, sensitivity of ProGRP was at 84%.

ROC curves for CEA, NSE and CYFRA 21-1 (Table II), discriminating malignancies from benign pulmonary diseases, showed that the area under the curve of ProGRP was significantly greater than that of NSE and CYFRA 21-1,
indicating that ProGRP was apparently superior to NSE for diagnosis of SCLC. Preoperative serum levels of CEA, NSE and CYFRA 21-1 showed sensitivities of 74%, 73% and 69% respectively at a specificity of 95%. In malignant diseases there was a significant difference between NSCLC and SCLC in the mean serum levels of CEA (5.01±0.69 and 3.09±0.23 ng/ml, respectively; \( p<0.05 \)) and NSE (10.37±0.7 and 127.92±17.46 ng/ml, respectively; \( p<0.05 \)). Between squamous cell carcinoma and SCLC, the mean values of CEA (6.88±0.89 and 3.09±0.23 ng/ml, respectively; \( p<0.05 \)) and
Discussion

In recent years, different biochemical parameters and tumour markers have been studied in the differential diagnosis of lung diseases. However, there is no tumour marker that alone has sufficient diagnostic accuracy. There are five possible applications for tumour markers: screening, diagnosis, prognosis, monitoring disease progress and detecting relapse. Most tumour markers seem to be more tumour-associated than tumour-specific. So far, no tumour marker for lung carcinoma has been found to be sufficiently sensitive to justify its use as a screening test in asymptomatic patients. In non-small cell lung carcinomas CYFRA 21-1 showed the best sensitivity-specificity profile and emerged again as a kind of "pan-marker" for the various histological types; the best power of discrimination was reached for squamous cell carcinomas of the lung. We so performed the measurement of CYFRA 21-1 as a leading marker in non-small cell lung carcinomas, and also of CEA as an additional relevant marker in adenocarcinomas of the lung. ProGRP has the highest diagnostic sensitivity in small cell lung cancer, followed by NSE. Based on the high levels reached, especially ProGRP but also NSE have the ability to establish diagnosis of small cell lung carcinoma in patients with lung tumours of unknown origin. Due to a significant additive sensitivity, ProGRP is not able to replace NSE, but, at least at the time of primary diagnosis, combined determination of these markers seems to be useful. During follow-up care and monitoring of therapy, the single determination of the "leading" marker should be sufficient.

Conclusion

The accurate differentiation of malignant pulmonary lesions from benign pulmonary lesions is an important task. We investigated the usefulness of NSE, CEA, ProGRP and CYFRA 21-1 as tumour markers for the diagnosis, treatment and monitoring of patients with different pulmonary afflictions.

The levels of ProGRP in the patients with benign diseases were significantly higher than those in the healthy group. The serum ProGRP levels were elevated in SCLC patients. The elevation was significantly higher than that of the benign reference group. The present study demonstrated that serum levels of ProGRP reflect malignancy more accurately in comparison with CEA, NSE and CYFRA 21-1. Furthermore, combined application of CEA, CYFRA 21-1, NSE and ProGRP improves the diagnostic potential.

References


| Table III. Inflammatory markers in lung diseases. |
|---------------------|---------|---------|
|                      | CRP mg/dl | TNFα pg/ml |
|                      | mean     | range   | mean     | range   |
| Chronic bronchitis   | 2.1      | 1.3-4.3 | 7.8      | 4.9-9.4 |
| Sarcoidosis          | 3.8      | 0.9-5.2 | 4.4      | 1.2-6.8 |
| Fibrosis             | 1.0      | 0.03-1.2| 7.8      | 4.9-9.4 |
| Squamous cell lung cancer | 10-80  | 8-64   | 12.8    | 5.1-15.5 |
| NSCLC                | 5.9      | 6.0-9.8 |          |         |
| NSE                  | 29.32±2.07 pg/ml (smoker), 13.33±1.32 pg/ml (non-smoker)| 19.67±2.98 ng/ml (smoker), 9.47±0.24 ng/ml (non-smoker) and 35.48±1.53 ng/ml (benign) | 13.33±1.32 pg/ml (non-smoker; ProGRP) 13.33±1.32 pg/ml (non-smoker; ProGRP), 8.5±0.39 ng/ml (smoker; NSE), 4.47±0.24 ng/ml (non-smoker; NSE) and 35.48±1.53 ng/ml (benign; ProGRP) and 9.95±0.45 ng/ml (benign; NSE), respectively. No samples from healthy subjects were higher than the cut-off values. All serum tumour markers were higher in the malignant group than in the benign group. The serum tumour marker with the highest sensitivity for malignancy was ProGRP (84%) followed by CEA (74%). The levels of the former marker are very low in benign pulmonary tumours, but extremely high in small cell lung carcinoma. By shifting the cut-off level it is also possible to distinguish between small cell and non-small cell lung carcinoma. At very high cut-off levels, only patients with small cell lung carcinoma are identified. In comparison to the benign lung diseases, the inflammatory markers CRP and TNFα show a significantly higher level in patients with malignant lung diseases p<0.05 (Table III).

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