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Evalutation of Tumor M2 Pyruvatekinase Values in Patients with Lung Diseases

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Summary

Introduction: Tumor M2-PK is an isoform of the glycolytic enzyme pyruvate kinase. This isoform exists in an active tetrameric and less active dimeric form. The less active form is expressed by various tumor cells and can be measured in blood. It is used in the diagnostic procedure of lung tumors besides the already established tumor markers Cyfra 21-1, SCC and NSE. The aim of this study was to evaluate the diagnostic relevance of this new tumour marker in patients with lung affections.

Methods: The sera of 140 patients with lung carcinoma of different histological cell types were collected and tumour markers as Cyfra 21-1, NSE, SCC and Tumor M2-PK were determined. Tumor M2-PK was measured by an ELISA test of ScheBoTech. The test is a two step sandwich immunoassay using one monoclonal antibody. Sera of 195 healthy volunteers served as control group.

Results: At a specificity of 95% the cut-off value was found to be at 17 kU/l. In patients with squamous cell carcinoma Tumor M2-PK was elevated in 78%, in patients with adenocarcinoma in 73% and in patients with non-small-cell-lung-carcinoma in 81% of the cases. In patients with benign lung diseases such as bronchitis or tuberculosis we have not seen a significant elevation of Tumor M2-PK as the serum concentrations were within the normal range.

Conclusion: We conclude that Tumor M2-PK might be helpful in the diagnostic procedure in patients supposed to suffer from a lung carcinoma. Moreover Tumor M2-PK seems to exceed the diagnostic relevance of SCC and NSE in patients with lung carcinoma.
Introduction

At present, the treatment of lung cancer is one of the greatest challenges in medical oncology, because of its high incidence in both men and women and its poor prognosis [1].

Early detection is often the result of an incidental finding, because all diagnostic methods have their limits at small tumour sizes [2-8].

Up to now over 20 tumour markers have been described, with varying tumour and organ specificity and sensitivity. NSE is a sensitive and specific marker for SCLC. Other established markers are CYFRA 21-1 and SCC [8-18]. However, clinical application of tumour markers is far from ideal, owing to the lack of sensitivity/specificity from the diagnostic point of view. For this reason, their use is recommended mainly for monitoring of therapy and postoperative surveillance.

The pyruvate kinase is a key enzyme in glycolysis in healthy cells and catalyses the dephosphorylation from phosphoenolpyruvate to pyruvate. The number of subunits pyruvate kinase consists of is substantial for the degree of activity, which decreases from the tetrameric form to the monomeric which has no function at all [10]. The pyruvate kinase type tumor M2 (Tu M2-Pk) corresponds with the monomeric isoenzyme form [19].

Otto Warburg showed in 1926 that tumor cells produce encreased concentrations of lactat in spite of sufficient oxygen supply which can be attributed to a change in the isoenzyme pattern of glycolysis and glutaminolysis enzymes.

The aim of this prospective study was to examine the clinical value of Tumor M2-PK in the differentiation of malignant and benign lesions in patients with solitary pulmonary lesions.

Methods and Material

Peripheral EDTA blood samples were obtained from 130 consecutive and previously untreated patients suffering from non malignant lung diseases (20 patients with brochitis, 50 patients with sarcoidosis, 20 patients with extrinsic-allergic alveolitis, 20 patients suffering from lung fibrosis and 20 patients with tuberculosis). A total number of 140 probands with malignant lung diseases was examined. 36 had small-cell lung cancer, 104 had non-small-cell lung cancer. Among them 34 had a adenocarcinoma and 34 had a squamous cell carcinoma. Data was also obtained from 195 healthy individuals.

Messuring the concentration of tumor M2-Pk in patients’ blood required EDTA-plasma because of its stability. After centrifugation of the samples the EDTA-plasma was carefully pipetted and investigated by a specific ELISA developed by ScheBo®-Tech (Wettenberg, Germany), which has been proved not to crossreact with other isoforms of pyruvate kinase.
Results

The incidence of TU M2-PK expression in our different study groups is summarized in table 1. At a specificity of 95% a cut-off value of 17 U/ml could be shown for our healthy control group (figure 1). The mean value of TU M2-PK concentration is 12.9 U/ml. 99% of our probands had values below the upper limit of 25 U/ml.

<table>
<thead>
<tr>
<th>Control Group</th>
<th>N</th>
<th>Mean</th>
<th>Std dev.</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non malignant lung diseases (total)</td>
<td>195</td>
<td>12.9</td>
<td>10.2</td>
<td>2.3 - 28.9</td>
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<tr>
<td>bronchitis</td>
<td>130</td>
<td>14.9</td>
<td>10.8</td>
<td>6.9 - 30.2</td>
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<td>allergic alveolitis</td>
<td>20</td>
<td>16.2</td>
<td>5.4</td>
<td>9.2 - 21.4</td>
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<tr>
<td>fibrosis</td>
<td>20</td>
<td>14.7</td>
<td>7.2</td>
<td>6.9 - 18.2</td>
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<tr>
<td>tuberculosis</td>
<td>20</td>
<td>12</td>
<td>4.8</td>
<td>9.4 - 15.6</td>
</tr>
<tr>
<td>sarcoidosis</td>
<td>50</td>
<td>13.8</td>
<td>9.7</td>
<td>11.5 - 32.4</td>
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<tr>
<td>SCLC</td>
<td>36</td>
<td>28.5</td>
<td>10.8</td>
<td>18.5 - 38</td>
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<tr>
<td>NSCLC (total)</td>
<td>104</td>
<td>45.8</td>
<td>21.5</td>
<td>14.8 - 80</td>
</tr>
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<td>adenocarcinoma</td>
<td>34</td>
<td>48</td>
<td>22.5</td>
<td>24.0 - 75</td>
</tr>
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<td>squamous cell carcinoma</td>
<td>34</td>
<td>31.8</td>
<td>19</td>
<td>19 - 82.5</td>
</tr>
</tbody>
</table>

Figure 1: Distribution of the TuM2-PK concentrations in 195 negative controls. The frequency of Tumor M2-PK measurements is indicated on the left.
A significant increase was observed in the mean values of plasma levels of TU M2-PK (Kruskal; p <0.005) at patients with benign pulmonary diseases. Although the increase is within the normal range of TU M2-PK.

The plasma levels of TU M2-PK in cancer patients were significantly higher (p=0.001) than those in the patients with benign pulmonary diseases. The highest values could be shown at patients with non-small-cell lung cancer and squamous cell carcinoma.

The distribution of TU M2-PK levels in our control group is shown in figure 1.

The levels of this marker are very low in benign pulmonary tumours but extremely high in malignant pulmonary lesions.

Figure 2 shows the respective values of TU M2-PK in different malignant diseases. The box/whisker-plots show the concentration of TU M2-PK (indicated on the left as multiple of cut-off value). The whiskers indicate the 95% and 5%, and the box the 75% and 25% percentiles, with the mean shown as a black line.

**Figure 2**

**Discussion**

The distribution of Tu M2-PK values shows that 97.5% of healthy probands have Tu M2-PK concentrations below 12.9 U/ml. This value served as a cut-off for our following investigations. 99% of the healthy individuals had TU M2-PK concentrations below the upper limit of our diagnostic scale which was assumed to be at 25 U/ml.

The poor increase within the normal scale showed that patients with...
benign pulmonary lesions have no diagnostically relevant Tu M2-PK levels.

All patients with lung cancer showed measurable increases of TU M2-PK levels.

Using 12.9 U/ml as cut-off level, only moderate Tumor M2-PK elevations (less than 25 U/ml) were found in 27% of patients with adenocarcinoma, in 19% of the patients with non-small-cell lung cancer and in 22% of the patients with squamous cell lung carcinoma. Accordingly an elevated plasma level above 25 U/ml was found at 73%, 81% and 78%.

Tu M2-PK deserves to be considered for diagnosis of Squamous cell carcinoma. In our study serum Tu M2-PK levels were higher in squamous cell carcinoma patients than in other lung cancer patients.

We suggest that this marker might be regarded for the differentiation between benign and malignant pulmonary lesions.

References


