Nutritional and Prognostic Significance of Sick Euthyroid Syndrome in Non-small Cell Lung Cancer Patients

Seyhan Ekrem Cengiz¹, Erdogan Cetinkaya¹, Sedat Altin¹, Zeki Gunluoglu¹, Adalet Demir², Gulsah Gunluoglu¹ and Kursat Epozturk¹

Abstract

Objectives Our study aimed to determine the frequency of sick euthyroid syndrome (SES) among patients diagnosed as non-small cell lung cancer (NSCLC) and its association with the stage of the disease, Karnofsky index (KI), and nutritional parameters.

Methods We enrolled 80 consecutive patients with newly diagnosed NSCLC. Cases with NSCLC were staged by using the TNM system. The cases were examined for thyroid function tests, KI and nutritional evaluation before treatment. Moreover, cases were investigated for their overall survival ratio.

Results Out of 80 patients, SES was identified in 28 (35%). SES was more frequent among stage III (26%) and stage IV (62%) cases. The body mass index (BMI), KI and serum albumin level were found to be significantly low in cases with SES when compared to cases without SES. SES was found to be negatively correlated with BMI, KI and serum albumin level, and it was positively correlated with disease stage and weight loss. Additionally, the presence of SES was found as a prognostic factor at survival analysis (p=0.0002).

Conclusion SES was frequently seen in cases with NSCLC. SES can be used as a predictor of poor prognosis in NSCLC patients.

Key words: sick euthyroid syndrome, NSCLC, nutritional parameters

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Introduction

Sick euthyroid syndrome (SES) is characterized by alterations in the levels of thyroid hormones due to non-thyroidal diseases, in the absence of any disorder related to hypothalamic-hypophysial axis or thyroid gland (1). The most common hormone pattern in this syndrome is a decrease in serum free triiodothyronine (fT3) level accompanied by normal thyroxine (T4) and thyrotropin (TSH) levels (2). Although it is suggested that SES results from a decrease in the deiodinase enzyme responsible for conversion of T4 to T3 in peripheral tissues, the real underlying pathogenesis is not fully understood (2). SES has been observed in almost all serious medical conditions including malnutrition, sepsis, liver disease, renal failure, trauma, uncontrolled diabetes, and malignancy. It is also reported that the presence of SES is associated with the gravity of the underlying disease and the nutritional state of the patients, and that is increases mortality (3-5).

The prognosis for the patients with non-small cell lung cancer (NSCLC) is related to the stage of the disease. Moreover, cell type, proliferate fraction and DNA content of the tumor, gender, nutritional and psychological state of the patient are other factors affecting the prognosis. A few studies showing that SES is observed in cancer sufferers and that prognosis is poorer for these patients have been published (6-9).

In the present study, we aimed to determine the frequency of SES, to identify its relation with the Karnofsky index (KI), and nutritional parameters such as body mass index (BMI), lymphocyte count, serum albumin and transferrin levels, to investigate its association with the stage of the disease and to clarify whether it can be used as an indicator of prognosis or not in non-small cell lung cancer (NSCLC) patients.

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Material and Methods

Eighty consecutive patients (63 men, 17 women; mean age: 63.6±8.9, range: 54-78) with histologically diagnosed NSCLC, Between March 2004 and March 2006 were enrolled in this study. Exclusion criteria were presence of a known thyroid disease, and presence of any drug use (such as propylthiouracil, levothyroxine, amiodarone, beta-blockers, steroids, sulfacluate, furosemide, phenobarbital, carbamazepine, phenytoin, salicylates, and rifampin) and any disease (such as secondary malignancy, diabetes mellitus, protein-losing enteropathy, nephrotic syndrome, AIDS, chronic hepatic or renal disease) associated with thyroid function anomalies. Four cases of NSCLC with liver metastasis had albumin levels within normal limits (4.1, 3.6, 3.7 and 3.7 g/dL); therefore, these cases were not excluded. Before treatment, all subjects were evaluated with Karnofsky performance scale (10). Moreover, the subjects underwent thyroid function tests and nutritional evaluation, and staging of the disease. Duration between onset of symptoms and admittance to hospital was recorded.

Subjects were followed up in regular intervals from the time of diagnosis until the 18th month. Patients who missed their appointment were reached via telephone. The patients were checked at the sixth, twelfth and eighteenth months to inspect their survival. General survival period was described as the time period between the time of diagnosis and time of death. The research was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association, and this study was approved by the Ethics Committee of our hospital. Written informed consent was obtained from each patient.

Thyroid function tests: For the measurement of thyroid hormone levels, 5 mL of venous blood was sampled; the blood samples were evaluated in our hospital biochemistry laboratory using chemoluminescence immunoassay method in a Coulter-Access analyser. Normal ranges were 0.34-5.6 mIU/mL (Beckman kit, Catalog no: 33820, Beckman Coulter Inc., Fullerton, CA) for TSH, 2.39-6.79 pg/mL (Beckman kit, Catalog no: 33850) for fT3, and 0.58-1.64 ng/dL (Beckman kit, Catalog no: 33830) for fT4.

Diagnosis of SES was established when fT3 and/or fT4 levels were below the normal lower limit and TSH levels were within the normal limits mentioned. Patients with SES were divided into two subgroups: SES type 1, cases with exclusive decrease in fT3, and SES type 2, those with a combined decrease in fT3 and fT4.

Nutritional-biochemical evaluation: Anthropometric and biochemical measurements have been done to assess the nutritional and biochemical state of the cases. Weight loss ratios of the patients were categorized in three groups: patients with no weight loss as group 1, patients with weight loss up to 10% of their original weight as group 2 and patients with weight loss higher than 10% of their original weight as group 3. For anthropometric measurement, BMI [weight (kg)/height (m$^2$)] was calculated. Subjects were categorized according to World Health Organization classification (BMI: < 18 kg/m$^2$ thin, 18-25 kg/m$^2$ of acceptable weight, 25-30 kg/m$^2$ of excessive weight and >30 kg/m$^2$ obese) (11). For biochemical measurements albumin level (N: 3.5-5.5 g/dL), transferrin level (N: 200-400 mg/dL), and leukocyte (3,600-10,800/mm$^3$), thrombocyte (130,000-450,000/mm$^3$) and lymphocyte count (N: 1,200-3,400/mm$^3$) were quantified. Serum albumin levels were measured using Abbot-labeled kits (catalog no: 30-3050/R2) in Beckman Coulter-Synchron LX-20 chemistry autoanalysator and lymphocyte counts were performed with Beckman Coulter-Gen-S device in the biochemistry laboratory of our hospital. Serum transferrin levels were measured by using nefelometric method with Dade Behring-labeled kits (catalog: osax 15) and BCT (Dade Behring, Deerfield, IL) device in Istanbul University Cerrahpasa Medical Faculty Central Laboratory (12, 13).

Tumor staging: Cases with NSCLC were staged by using the TNM system proposed by “American Joint Committee on Cancer” (14). Positron emission scintigraphy and cranial magnetic resonance imaging was used for staging in most of the patients. Transbronchial fine needle biopsy or mediastinoscopy was done for staging tumors of patients without any distant metastasis.

Statistical evaluation: Statistical analyses were performed with SPSS 10.0 program. Data were presented as mean value and standard deviation. In order to compare numeric values, the Shapiro-Wilks test was utilized for SES patients and the Kolmogrov-Smirnov test was used for patients without SES; the final results were analyzed with Mann-Whitney U test. Chi-square test was performed to compare ordinal values. Stages were compared with each other at the aspect of SES incidence, using Fisher chi-square test. For correlation analysis, Spearman correlation test was executed. For survival analysis, Kaplan-Meier method as a univariate and Cox proportional hazard model as a multivariate analysis method was used. p<0.05 was considered as statistically significant.

Results

Histological tumor types were squamous cell carcinoma in 37, adenocarcinoma in 26, large cell carcinoma in 3 and unclassified non-small cell carcinoma in 14 patients. Stages of the tumor were stage I in 7, stage II in 8, stage III in 38 and stage IV in 27 patients. Out of 80 patients, SES has been identified in 28 (35%). As the stage of the disease increased, SES was more frequent (p<0.05) (Table 1). SES incidence was significantly higher in Stage IV (62%) compared to Stage III (26%) (p<0.05). Among these cases, 22 (79%) showed decreased fT3 levels exclusively and 6 (21%) showed decrease in both fT3 and fT4 levels.

Considering the gender, age, and hospital admission time of the patients, there was no statistically significant difference between the subjects with or without SES. BMI (p<0.001), K.I (p<0.001), and serum albumin levels (p<0.001)
were detected significantly lower in cases with SES in comparison to cases without SES (Table 2). When NSCLC cases were grouped according to BMI, it was observed that SES was present in 54% (12/22) of subjects with low body weight, in 30% (15/49) of subjects with normal body weight and in 10% (1/9) of subjects with excessive body weight. Although SES frequency was significantly higher in subjects with low body weight compared to those with normal body weight (p<0.05), no difference regarding SES frequency was found between subjects with normal and excessive body weight.

The presence of SES had negative correlations with BMI (r=-0.70, p<0.001), K.I (r=-0.89, p<0.001) and albumin level (r=-0.33, p=0.025); and positive correlation with weight loss (r=0.26, p=0.019) and disease stage (r=0.38, p<0.01). No patient in this series had massive leucocytosis or thrombocytosis. However, a positive and significant correlation was found between the presence of SES and thrombocyte count (r=0.3, p=0.006).

Mean follow-up time was 13.3±7 months. Mean survival times were 9.2 and 15.2 months in cases with and without SES, respectively. This survival difference was found highly significant at univariate analysis (p=0.0002) (Fig. 1). Then a multivariate analysis was done including histological type and stage of the tumor, BMI and ratio of weight loss with presence of SES as factors affecting the survival. The presence of SES was found as a significant prognostic factor at multivariate analysis (p=0.04). NSCLC cases with SES type 1 and those with SES type 2 showed no difference in general survival rate (p=0.8).

**Table 1.** SES Incidence According to Stages

<table>
<thead>
<tr>
<th></th>
<th>Stage I (n=7)</th>
<th>Stage II (n=8)</th>
<th>Stage III (n=38)</th>
<th>Stage IV (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SES(+)</td>
<td>0</td>
<td>1</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>SES(-)</td>
<td>7</td>
<td>7</td>
<td>28</td>
<td>10</td>
</tr>
<tr>
<td>SES frequency</td>
<td>0</td>
<td>12%</td>
<td>26%</td>
<td>62%</td>
</tr>
</tbody>
</table>

**Discussion**

It is known that some systemic diseases may alter thyroid hormone levels. Non-thyroidal disorders may lead to the development of SES by affecting hormone secretion, transport and metabolism (2). In healthy subjects, 20% of total T3 in circulation is secreted by thyroid gland and 80% is obtained through the conversion (deiodination) of T4 to T3 in the peripheral tissues. In SES, this later process is weakened although T3 production in the thyroid gland is normal. It is estimated that low plasma T3 concentration is mainly the result of a decrease in peripheral deiodination of T4 (1). It is still debated whether it is a physiologic response to underlying disease or an impaired adaptation mechanism. Nevertheless, the pathogenesis of SES is not fully understood.

This ignorance about the pathophysiology of SES led to a number of studies in this field (9, 15). These studies focused on the role of cytokines in the development of SES. In particular, interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-α and interferon-β are thought to participate in this process. It was demonstrated that these cytokines inhibit the enzyme 5-deiodinase responsible for the conversion of T4 into T3 in peripheral tissues (15). Feelders et al detected onco-logy patients with SES had higher TNF-α and IL-6 levels compared to those without SES (9). We could not measure any cytokine level. But we count the number of leucocytes and thrombocytes which possibly associated with inflammatory cytokines. Although there was no any patient with massive leucocytosis or thrombocytosis, a slight correlation was found between the presence of SES and count of thrombo-cytes.

Several studies described the presence of SES in pulmonary diseases and malignancies (16, 17). Stage of malignant

**Table 2.** Comparison of Different Parameters According to the Presence of SES

<table>
<thead>
<tr>
<th></th>
<th>Cases with SES (n=28) mean±SD</th>
<th>Cases without SES (n=52) mean±SD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (g/dL)</td>
<td>2.8±0.8</td>
<td>3.6±0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>65.4±8.8</td>
<td>62.9±8.4</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>19±3</td>
<td>23±4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Transferrin (mg/dL)</td>
<td>244±75</td>
<td>276±99</td>
<td>NS</td>
</tr>
<tr>
<td>Time until diagnosis (days)</td>
<td>58±32</td>
<td>68±36</td>
<td>NS</td>
</tr>
<tr>
<td>K.I.</td>
<td>42±12</td>
<td>70±14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lymphocyte (/mm³)</td>
<td>2.08±0.519</td>
<td>2.26±0.824</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS: statistically not significant, SD: standard deviation
diseases and severity affects thyroid function tests. Chow et al reported a 63% incidence of SES in 40 pulmonary TB patients (16). Wawrzynska et al found out in their survey that SES is frequent in patients with severe respiratory failure requiring intensive care (17). Tellini et al investigated thyroid hormone levels in 220 cases with malignancy in different organs and found out SES in 58% of the patients (6). Vexiau et al reported the incidence of SES in 220 cases with hematological malignancies as 37% (7). Wehmann et al found SES incidence as 54% in a similar group of patients (8). As a result of our study, we determined SES in 35% of cases with NSCLC. This result is less than what was found by Tellini et al (58%) but comparable to that of Vexiau et al (37%) (6, 7). However, these studies did not include lung cancer patients and we could not find any other studies using with lung cancer patients in the medical literature (Medline, 1996-2006).

The essential characteristics of SES are a decrease in fT3 alone or in fT3 and fT4 together, with a TSH level within or below normal limits (18). Among our 28 SES cases, 22 (79%) had only decreased fT3 (type 1), 6 (21%) had decreased fT3 and fT4 levels (type 2). SES type 1 which is characterized by exclusively decreased fT3 levels is the most common type according to literature, as justified by our data. It was reported that TSH levels were normal or just below normal in 80% of SES patients but significantly decreased in 10%, and that prognosis was poorer in the later (19, 20). TSH levels were within normal limits in all of the present patients.

SES type 2 can be difficult to differentiate from central hypothyroidism (hypothalamic-hypophyseal axis) and interpretation of thyroid function tests may be problematic because fT3 and fT4 levels may be decreased and TSH level may be decreased, normal or slightly increased in central hypothyroidism as well (21). Furthermore, it was demonstrated that cortisole, IL-6 and TNF-α which increase in SES resulted in a transient central hypothyroidism through suppression of TSH and that this situation was resolved when the underlying disease causing SES improved (9). Central hypothyroidism can be excluded by the facts that, unlike genuine central hypothyroidism, plasma cortisole levels are increased while prolactin and gonadotropin levels are normal and that TSH levels become normal when disease is overcome in SES patients with transient central hypothyroidism but with no hypophyseal or hypothalamic disease, and by the use of TRH test (21). Moreover it was reported that central hypothyroidism is an infrequent cause (1%) among all hypothyroidism causes and that isolated cases (without panhypopituitarism) are extremely rare (21, 22). In our study, TRH test was not performed to exclude central hypothyroidism in our 6 patients with SES type 2 since this test is not used in our hospital and it is difficult to carry out. However, we believe that, though not certainly, we could practically exclude central hypothyroidism in 6 SES type 2 cases based on the facts that the statistical probability of this situation is very low and that indirect findings of panhypopituitarism such as electrolyte imbalance and disorder of secondary sex characteristics were absent.

Previous studies demonstrated that SES is correlated with the gravity of underlying disease and that low hormone lev-

Figure 1. Survival curves of NSCLC patients with and without SES. NSCLC: non-small cell lung cancer, SES: sick euthyroid syndrome.
els (especially combined decreased levels of fT3 and fT4) predict a poor prognosis in most diseases (8, 23-28). Caregaro et al found that the frequency of SES in cirrhotic patients was about 30% and that it was correlated with Child classification defining severity of cirrhosis (23). Moreover, they pointed out that survival rates were lower in SES cases. Karon et al investigated thyroid hormone levels within 12 hours before death in 53 SES patients lost during hospitalization period and in 50 other patients discharged alive. In conclusion, T3 and T4 levels were found to be significantly lower in the former group (24). In a study including subjects with chronic heart failure, SES cases were found to have a higher mortality rate during follow-up period (28). In the consensus reports on prognostic factors of NSCLC, stage of the disease and performance status were indicated as the main prognostic factors determining survival; it was also emphasized that cell type, tumour proliferative fraction, gender of the patient, weight loss, serum albumin level, nutritional and psychological states were significant prognostic factors that can affect survival (29). Several studies demonstrating the presence of SES in malignant diseases and its association with poor prognosis have been published (6, 7, 25). Schulte et al examined patients with hematological malignancy who underwent bone marrow transplantation and reported that cases with SES have a higher mortality rate compared to those without SES (25). Vexiau et al (7) pointed out that the presence of SES in a similar group of patients was related to increased mortality (51% vs. 17%). The fact that SES was more frequent in higher stages (stage III: 26%, stage IV: 62%) in our study population and it was correlated with disease stage demonstrates that SES is associated with disease severity.

Moreover, we found that the general survival rates of NSCLC patients having SES were significantly lower than the patients without SES. Among other major prognostic factors we assessed in our study (stage, age, gender, performance and nutritional states), the presence of SES continued to be as a prognostic factor in multivariate analysis. So, we indecisively conclude that SES reduces the general survival time. All of the studies in the medical literature emphasized that the initial performance state and serum albumin levels are important prognostic factors in NSCLC cases (29). The facts that stage III and stage IV cases with low KI had decreased general survival rates and that SES was found to be related to decreased albumin levels and poor performance state (KI) in our study suggest that negative influence of SES on general survival rates can be associated with poor performance state and decreased albumin levels.

Nutritional insufficiencies, prolonged hunger and calorie limitation have been reported to play a role in SES development (25, 30). It is known that loss of appetite and increased catabolism in NSCLC cases lead to feeding disorders and create nutritional insufficiency. Grivent et al examined elderly patients undergoing emergency operations for their preoperative thyroid functions and nutritional states. They reported that patients with SES had lower albumin levels and triceps skin fold thickness than patients without SES; they also identified a strong association between serum albumin levels lower than 3.5 g/dL and SES (30). Schulte et al, in their study on SES incidence among blood marrow transplant patients, found that SES cases had lower BMI and serum albumin levels (25). Tellini et al described the correlation between SES, and albumin level and degree of weight loss in oncolgy patients (6). Bossoni et al (31) evaluated thyroid hormone levels, serum albumin levels and body mass indices of 282 elderly women. They identified SES in 22 (8%) cases and found a strong correlation of BMI with decreased fT3 levels but not with albumin levels. The present study, similar to the previous ones, showed significant correlations between SES and nutritional parameters including BMI, and serum albumin levels.

It is known that, through the aging process, functional and structural alterations occur in the hypothalamus, hypophyseal and thyroid glands (31). Bossoni et al detected a high incidence of SES in elderly subjects (31). Although the subjects in the present study were aged in general, no relation was recognized between SES and age.

In conclusion, we determined that SES may be frequently seen in cases with NSCLC. Furthermore, the presence of SES can be used as an indicator defining the severity of the illness and predicting the prognosis of NSCLC patients.

References


