We report a case of pulmonary infiltration with eosinophilia (PIE), associated with increased serum levels of squamous cell carcinoma-related antigen (SCC) and neuron specific enolase (NSE). The diagnosis of PIE was confirmed by examination of bronchoalveolar lavage fluid and specimens of transbronchial lung biopsy. It was suggested that PIE was probably induced by a course of amoxicillin for a sore throat. Corticosteroid therapy resulted in clinical improvement of symptoms, resolution of pulmonary infiltrates on chest roentgenogram and reduction in serum levels of SCC and NSE.

Key words: tumor marker, bronchoalveolar lavage, corticosteroid therapy, amoxicillin

Introduction

Several serum tumor markers have been evaluated in a variety of malignancies, and are mostly used to determine evolution of tumors. It has, however, been reported recently that tumor-associated carbohydrate antigens are elevated in non-malignant lung diseases (1-3), thus casting doubt on the specificity of serum tumor markers. For example, squamous cell carcinoma-related antigen (SCC), a tumor marker for squamous cell carcinoma, and neuron specific enolase (NSE), a particularly interesting marker for small cell lung cancer (4), have been reported to be elevated in benign dermatoses (5) and non-malignant lung diseases such as chronic obstructive pulmonary disease, pneumonia and asthma (1). We present here the first case, according to our knowledge, of pulmonary infiltration with eosinophilia (PIE) associated with increased serum levels of SCC and NSE, probably caused by amoxicillin.

Case Report

A 67-year-old man was admitted to our hospital because of cough, exertional dyspnea and generalized eruptions. One month prior to admission he suffered from a sore throat, and amoxicillin was administered at a clinic. Thereafter, erythema appeared on his whole body, and cough and exertional dyspnea developed a month later. He was referred to our hospital for further investigation and treatment. His past and family histories were not remarkable. He had smoked 15 cigarettes daily for 50 years. On admission, his height was 159.0 cm, body weight 52.0 kg, body temperature 37.9°C, pulse rate 88/min, and blood pressure 126/78 mmHg. There were generalized ripple-like erythema and edema on the limbs. The axillary and inguinal lymph nodes were palpable. Clinical examination of the chest revealed fine crackles present at the lower back of the chest, a palpable liver about 3 cm below the right costal margin, but no cyanosis, anemia or jaundice.

Results of several laboratory tests on admission are summarized in Table 1. The white blood cell count was 20,000/mm³ with 31% eosinophils. Blood biochemical examination demonstrated hypoalbuminemia, hypergammaglobulinemia and a mild liver dysfunction. Elevation of the erythrocyte sedimentation rate (43 mm/h), positive C-reactive protein (3.3 mg/dl) and a marked elevation of serum IgE level (2,000 U/ml) were also observed. Measurement of arterial blood gases during breathing of room air showed severe hypoxemia (PaO₂: 62.5 Torr). The drug lymphocyte stimulation test (DLST) against amoxicillin was false-positive (stimulation index: 190%). Skin biopsy specimens were compatible with erythema gyratum repens, indicating a possible internal malignancy. Serum levels of SCC and NSE were elevated with 8.1 and 14.0 ng/ml, respectively (Table 1). However, computed tomography (CT) of the abdomen, endoscopic examination of the upper gastro-
intestinal tract, barium enema and pharyngolaryngeal examination, and histological examination of a right axillary lymph node biopsy specimen revealed no malignant lesion.

Chest roentgenogram (Fig. 1) and CT scan (Fig. 2) demonstrated diffuse reticulonodular shadows with infiltration in both lungs on admission with bilateral pleural effusions, but no mass shadows. Bronchoalveolar lavage (BAL) and transbronchial lung biopsy (TBLB) were performed using a flexible fiberoptic bronchoscopy (Olympus, P-20) with the informed consent of the patient. Table 2 summarizes the results of analysis of BAL fluid obtained from the right B5a. A high number of cells were present, consisting of mainly eosinophils (66.8%). TBLB specimens obtained from the right B5a revealed thickening of alveolar septa with eosinophilic infiltration (Fig. 3). Diagnosis of amoxicillin-induced PIE was made. Accordingly, corticosteroid therapy was started at 40 mg/day, seven days after hospitalization. Treatment for 13 days improved clinical symptoms and resulted in a reduction of eosinophils in peripheral blood and a decrease in SCC and NSE to normal levels (Fig. 4). Most of the diffuse shadows also disappeared, and there was a decrease in...
bilateral pleural effusion on the chest roentgenogram (Fig. 5). Corticosteroid was tapered two months later. No relapse of the disease or increase in the level of tumor markers had been observed one year later (Fig. 4).

**Discussion**

SCC is a protein appearing during the proliferating process of the normal squamous epithelium, and is well known as a tumor marker against cervical, esophageal, oral, cutaneous, head, neck and lung squamous cell carcinoma (6, 7). However, it has also been reported that SCC levels are elevated in serum of patients with widespread epidermal inflammatory diseases such as psoriasis and eczema (5), suggesting that the high serum level of SCC in the present patient may have been due to the generalized skin eruption. High serum levels of SCC have been demonstrated in 13% of patients with non-cancerous lung diseases, especially among those with severe infections (8).

NSE is a glycolysis enzyme existing in cells of the neuroendocrine system such as the pituitary gland, thyroid, pancreas, adrenal gland, lung and intestine; it is a tumor marker against highly malignant neuroendocrine tumors and advanced small cell carcinoma of the lung (4, 9). The false-positive indication of this marker, however, is low in non-malignant lung diseases (1). There are no reports of elevated serum SCC and NSE levels in PIE. Here, it was of interest that SCC and NSE decreased to normal range in parallel with improvement in

<table>
<thead>
<tr>
<th>Date</th>
<th>Prednisolone (mg)</th>
<th>Dyspnea</th>
<th>Cough</th>
<th>WBC (/mm³)</th>
<th>Eosinophil (%)</th>
<th>CRP (mg/dl)</th>
<th>ESR (mm/1h)</th>
<th>PaO₂ (Torr)</th>
<th>SCC (ng/ml)</th>
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<tr>
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<td></td>
<td></td>
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<td>43</td>
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<td>28</td>
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<td></td>
<td></td>
<td>8,100</td>
<td>1</td>
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<td>35</td>
<td>N. T.</td>
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<td></td>
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<td>8,500</td>
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<td>13</td>
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<td>1.3</td>
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<td>7,300</td>
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<td>N. T.</td>
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<td></td>
<td>4,800</td>
<td>4</td>
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Fig. 4. Clinical course of the patient. Corticosteroid therapy improved clinical symptoms, reduced blood eosinophil count and decreased serum levels of tumor markers.
the clinical condition and laboratory tests of PIE after corticosteroid therapy. We previously reported that increased levels of tumor-associated carbohydrate antigens, sialyl SSEA-1 and sialyl Lewisα are observed in BAL fluid of patients with diffuse panbronchiolitis (3). It was suggested that these antigens may originate from bronchiolar epithelial cells and are then released into the blood stream through neutrophil-mediated tissue injury (3). Accumulation of eosinophils in the lung of PIE may induce lung tissue damage through the effect of granular contents of eosinophils, particularly by the major basic protein and cationic proteins. Since malignancy was ruled out in the present patient, SCC and NSE most likely originated from eosinophil-mediated inflammatory lung tissues and/or injured epithelial cells. Furthermore, the accumulation of eosinophils in the lung may have altered the blood vessel barrier, ultimately releasing these tumor markers into circulation. These mechanisms may, thus, have contributed to the high level of these markers in the serum of our patient.

The etiology of PIE in the present patient was considered to be amoxicillin-induced since: (a) DLST against amoxicillin was false-positive, (b) skin eruptions and hepatic dysfunction were present, and (c) there was no relapse one year after cessation of corticosteroid therapy. Most cases of drug-induced PIE improve soon after withdrawal of the drug, but fibrosis may occur in prolonged or chronic cases. Thus, adequate corticosteroid therapy is recommended in severe cases of PIE associated with hypoxemia.

The differential diagnosis of the clinical findings in our patient included the hypereosinophilic syndrome (HES). HES consists of prolonged blood eosinophilia and organ system dysfunction caused by invasion of tissue by eosinophils (10). Fauci and his coworkers have established three criteria for the diagnosis of HES: (a) persistent eosinophilia of 1,500/mm³ for at least 6 months, (b) lack of evidence for parasitic, allergic, or other recognized causes of eosinophilia, and (c) signs and symptoms of organ system involvement or dysfunction directly related to eosinophilia (11). The present case, however, was not thought to be HES since eosinophilia was considered to be due to an allergic (drug-induced) reaction. This was confirmed later by cellular and histological examination of BAL and TBLB and the rapid improvement after corticosteroid therapy and lack of recurrence during the one-year period without therapy.

In summary, we presented a case of PIE with elevated serum SCC and NSE levels, probably caused by amoxicillin. Our results indicate that both SCC and NSE, which have been used as tumor markers for malignancy, can also be elevated in non-malignant inflammatory diseases including PIE.

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References