Lung Cancer Producing Interleukin-6

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A patient with complaints of high fever and left shoulder pain was found to have a large mass in the left upper lobe on chest roentgenogram. Laboratory evaluation revealed marked thrombocytosis, hypoalbuminemia, and increased serum concentrations of CRP, fibrinogen and interleukin-6 (IL-6). A transcutaneous biopsy specimen revealed large cell carcinoma. Tumor production of IL-6 was confirmed by immunohistochemical staining with an anti-human IL-6 monoclonal antibody (MH60).

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Introduction

Interleukin-6 (IL-6) is a pluripotent cytokine that has been implicated in the induction of acute phase proteins such as C-reactive protein (CRP) and fibrinogen, the stimulation of B-cell growth, and the maturation of megakaryocytes (1). IL-6 is also thought to be involved in a variety of human diseases including malignant tumors via autocrine or paracrine mechanisms (2). Clinically, however, little is known about IL-6 as a cause of paraneoplastic syndromes in patients with lung cancer. Here, we describe a patient with lung cancer and clinical manifestations possibly due to tumor-associated IL-6 production.

Case Report

A 47-year-old Japanese man was admitted to our hospital because of high fever and left shoulder pain associated with a large solitary mass in the left upper lobe on chest roentgenogram (Fig. 1). The hemoglobin concentration was 7.7 g/dl with a white blood cell count of 18,400/mm³ with 79.9% neutrophils; the platelet count, 924,000/mm³; and erythrocyte sedimentation rate (ESR), 160 mm/h. Other concentrations included: C-reactive protein (CRP), 22.6 mg/dl; total protein, 6.7 g/dl; albumin, 2.6 g/dl; fibrinogen, 622 mg/dl; Carcinoembryonic antigen (CEA), 1.3 ng/ml; squamous cell carcinoma related antigen (SCC), 1.7 ng/ml; and neuron-specific enolase (NSE), 18.9 ng/ml. Bone marrow aspiration demonstrated megakaryocytosis (333/mm³) with mature forms. A transcutaneous lung biopsy specimen revealed a large cell carcinoma of the lung. There was no evidence of infection or a collagen

vascular disease. The lack of other causes for the fever suggested the possibility of cytokine production by the tumor cells. The serum level of IL-6 was markedly elevated compared with that in normal controls (93 pg/ml versus <10 pg/ml), according to a two-step sandwich ELISA method. The serum G-CSF concentration was normal (20 pg/ml) and the serum GM-CSF was a trace level (<8 pg/ml). In addition, immunohistochemical staining of the biopsy specimen for IL-6 was performed using Vectastain ABC staining-kits (Vector Laboratories, Burlingame, CA) and the avidin-biotin-peroxidase technique. Briefly, cryostat sections of the biopsy specimen were fixed with chilled acetone and placed in 3% H₂O₂ in methanol to block endogenous peroxidase activity. To minimize background staining, the samples were blocked with normal horse serum followed by incubation with the primary antibody overnight at 4°C in a humid chamber. Anti-human IL-6 (MH60) monoclonal antibody (mouse IgM) was used as the primary antibody. After washing in phosphate-buffered saline (PBS, pH 7.4), the samples were incubated with biotinylated anti-human IL-6 (MH60) monoclonal antibody for 30 minutes at 37°C, and then incubated with ABC reagent for 45 minutes at 37°C in a humid chamber. The samples were then washed in PBS, and combined with the substrate reagent (3,3-diaminobenzidine tetrahydrochloride). Finally, counterstaining was performed with hematoxylin, and the samples were mounted on the slides with xylene. Immunohistochemical staining of the large-cell carcinoma cells was clearly identified (Fig. 2).

The patient's fever was promptly and completely relieved by Naproxen. The final diagnosis was large cell carcinoma of the lung, stage c-T₃N₃M₀. The patient received concurrent chemo-

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Figure 1. Chest roentgenogram at admission showing a large solitary mass in the left upper lung field. Invasion of the chest wall and the first to third ribs is evident.

radiotherapy consisting of cisplatin 80 mg/m², Day 1; vindesine 3 mg/m², Days 1 and 8; and mitomycin C 8 mg/m², Day 1, every 4 weeks for two courses, associated with daily radiation of 2 Gy for 34 days. He had a partial response, with the following improvements in his laboratory data: CRP, 1.2 mg/dl; PLT, 537,000/mm³; IL-6, 10.6 pg/ml; (Fig. 3), and white blood cell count, 7,200/mm³; albumin, 3.0 g/dl; and fibrinogen, 462 mg/dl. The patient was discharged from the hospital in good condition after completing his therapy, however he died one year later from recurrent lung cancer.

Discussion

IL-6 is a multifunctional cytokine produced by various types of normal cells and tumor cells (2). Recently, it has been well documented that locally produced IL-6, when leaked into the systemic circulation, causes biologic effects such as the induction of CRP and thrombocytosis that are often seen as paraneoplastic phenomena (3). The constitutive production of IL-6 has been reported in human tumors such as myeloma, cardiac myxoma, malignant mesothelioma, lymphoma, and renal cell carcinoma. Some large cell lung carcinomas have been reported to produce IL-6 in vitro (4–7). To our knowledge, this is the first case report of a lung cancer patient with a paraneoplastic syndrome related to autonomous IL-6 production by large cell

A

B

Figure 2. Immunohistochemical staining of the tumor using a human monoclonal IL-6 antibody (A), and negative control (B) (×400).

carcinoma proven by an immunohistochemical method. All of the findings observed in this patient can be attributed to biologic activities of IL-6 except for the leucocytosis. However, in lymphoma patients, the serum concentration of IL-6 and total leukocyte count are correlated (8). The serum concentrations of G-CSF and GM-CSF, which are occasionally increased in patients with large cell carcinoma and leucocytosis, were normal. The leucocytosis improved after treatment of the tumor, this fact suggests that the leucocytosis may have been attributed to the biologic activities of IL-6 or that other hematopoietic cytokines were possibly secreted. The chest roentgenogram showed tumor invasion of the chest wall and the first to third ribs. Tumor invasion of the bone marrow may stimulate hematopoiesis. However, tumor invasion of the ribs persisted after therapy, although the thrombocytosis and leucocytosis

Figure 3. Clinical course.

improved. This result suggests that tumor invasion of the bone marrow was unlikely the cause of thrombocytosis and leukocytosis. The patient's platelet count paralleled the serum concentration of IL-6, although megakaryocytosis is regulated by various cytokines (9). Considered together with the immunohistochemical findings and the improvements in his inflammatory syndrome, these data suggest that IL-6 may have played an important role in the paraneoplastic syndrome observed in this patient.

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