Interleukin-6-producing Giant Cell Carcinoma of the Lung with Multicentric Castleman’s Disease-like Presentation

Yasutomi Higashikuni¹, Masaya Mori² and Hiroyoshi Kino¹

Abstract

We encountered a 59-year-old man with advanced lung cancer with multiple swollen lymph nodes. At autopsy the lung cancer was revealed as giant cell carcinoma. Microscopic examination showed no cancer cells, but there was polyclonal proliferation of plasma cells in the lymph nodes and in the bone marrow. In the kidneys, proliferation of mesangial matrices and mesangial cells was found. This presentation resembled multicentric Castleman’s disease (MCD), in which interleukin-6 (IL-6) has a great role. Immunohistochemical staining was positive for IL-6 in cancer cells. This is the first reported case of an IL-6-producing giant cell carcinoma of the lung with MCD-like presentation.

Key words: lung cancer, interleukin, pathology

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Introduction

Interleukin-6 (IL-6) is a multifunctional cytokine which regulates immune responses, hematopoiesis and acute phase reactions (1). It has been demonstrated that IL-6 plays an important role in the pathogenesis and progression of various malignancies (2-6). In patients with lung cancer, it has been shown that IL-6 is associated with tumor proliferation and its prognosis (7-10).

Multicentric Castleman’s disease (MCD) is a rare lymphoproliferative disorder characterized by systemic lymphadenopathy and constitutional inflammatory symptoms (11, 12). In this disease, dysregulated overproduction of IL-6 has been revealed to be responsible for the clinical abnormalities (12, 13). The prognosis of MCD has been reported to be poor (11, 12).

Herein, we describe a case of an IL-6-producing giant cell carcinoma of the lung with MCD-like presentation.

Case Report

A 59-year-old man was referred to our hospital for the investigation of leukocytosis, thrombocytosis, anemia, and a large nodular shadow in the right upper lung field in the chest roentgenogram of March 2004. He was a previous smoker (30 cigarettes/day×40 years). On physical examination, his heart rate was 78 beats/min, and blood pressure was 132/74 mmHg. The body temperature was 39.4°C. Cardiac sounds revealed no murmurs, and pulmonary auscultation detected reduced respiratory sounds in the right upper lung field. On palpation, superficial lymph nodes were not swollen. On laboratory tests, white blood cell and platelet cell counts were 21,200/μL with 84.0% of neutrophils, 9.5% of lymphocytes and 6.5% of monocytes, and 60.3×10⁴/µL, respectively. Severe normocytic anemia was found to the extent of 5.8 g/dL of hemoglobin concentration. The total protein and albumin levels were 7.2 g/dL and 2.4 g/dL respectively, which implied the existence of hypergammaglobulinemia. The serum levels of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, γ-glutamyl transpeptidase, and total bilirubin were 10 IU/L, 6 IU/L, 560 IU/L, 39 IU/L and 0.6 mg/dL, respectively, which showed no obvious injury in liver and biliary duct system. The blood urea nitrogen and serum creatinine levels were 7.0 mg/dL and 0.6 mg/dL. A urinalysis revealed the existence of proteinuria. The C-reactive protein level was 21.8 mg/dL. Plasma levels of tumor markers were as follows: squamous cell carcinoma antigen, 45 ng/mL (normal range, 0 to 1.5 ng/mL); cytokeratin fragment, 15 ng/mL (normal range, 0 to

¹Division of Internal Medicine, Center for Respiratory Diseases, Mitsui Memorial Hospital, Tokyo and ²Division of Pathology, Mitsui Memorial Hospital, Tokyo

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Correspondence to Dr. Yasutomi Higashikuni, tommi-h@tc4.so-net.ne.jp
Figure 1. CT scan of the chest demonstrates a large tumor in the right upper lung field with compression of the superior vena cava (A), swelling of multiple mediastinal lymph nodes (B) and pleural effusion (A and B).

Figure 2. Pathological findings of the tumor. The tumor was 13×13×11 cm large (A) (macroscopic specimen). The tumor was microscopically diagnosed as giant cell carcinoma (B) (Hematoxylin-Eosin stain, original ×200).

3.5 ng/mL); carcinoembryonic antigen, 1.0 ng/mL (normal range, 0 to 2.5 ng/mL); sialyl Lewis-Xi, 25 U/mL (normal range, 0 to 38 U/mL); neuron-specific enolase, 7.8 ng/mL (normal range, 0 to 10 ng/mL); and pro-gastrin-releasing peptide, 17.4 pg/mL (normal range, 0 to 46.0 pg/mL). Levels of soluble interleukin-2 receptor and granulocyte-colony stimulating factor were 3,410 U/mL (normal range, 220 to 530 U/mL), and 390 pg/mL (normal range, 0 to 18.1 pg/mL), respectively. Blood, sputum, and urine cultures were examined, but there were no evidence of bacterial or fungal infection. Although culture examinations were negative, antibiotics such as cefazolin, clindamycin and meropenem were used because the existence of severe infectious disease could not be completely ruled out. However, antibiotic therapy turned out to be ineffective.

A chest CT showed a large tumor in the right upper lung field with compression of the superior vena cava (SVC), swelling of multiple mediastinal lymph nodes, and pleural effusion (Fig. 1A, B). Bronchofibroscopy was performed, revealing slightly reddish and edematous mucosa and the obstruction of the apical segmental bronchus (B1) of the right lung. A transbronchial lung biopsy showed only inflamed bronchial mucosa and no malignancy. Subsequently, a CT-guided lung biopsy was performed, and revealed the tumor as a poorly-differentiated adenocarcinoma. Pleural effusion was exudative, but cytological examination was graded as class I. The culture of pleural effusion was negative for bacterial or fungal infection.

At this time, the diagnosis was lung cancer with compression of the SVC and multiple lymph node metastases. Persistent severe inflammation and worsening of general condition prevented him from receiving chemotherapy, and he died of respiratory failure on the 45th admission day.

An autopsy was performed, revealing a large 13×13×11 cm tumor which was microscopically diagnosed as giant cell carcinoma (Fig. 2A, B). The swelling of multiple mediastinal lymph nodes was found, and the maximum diameter was 4 cm (Fig. 3A). The microscopic findings of the swollen lymph nodes showed no cancer cells. However, polyclonal proliferation of plasma cells was found in the interfollicular areas, which was confirmed by κ- and λ-light chain staining (Fig. 3B, 3C, and 3D). Polyclonal plasma cell proliferation was also found in the bone marrow. The microscopic findings of the kidneys revealed proliferation of mesangial matrices and mesangial cells. These findings inferred
multicentric Castleman’s disease, in which IL-6 has been reported to have a significant role. Immunohistochemical staining of the tumor with a goat anti-human IL-6 polyclonal antibody (DakoCytomation) was positive in the cancer cells (Fig. 4A, B). It was also positive in plasma cells of the lymph nodes and the bone marrow, though very few in number.

Discussion

We encountered a case of IL-6-producing lung cancer with MCD-like presentation. In this case, the swelling of lymph nodes demonstrated by radiographic studies was attributed not to metastases, but to polyclonal plasmacytosis, which was determined by pathological examinations. The bone marrow was also involved with polyclonal plasmacytosis, and the kidneys showed evidence of exposure to cytokines.

IL-6 is a pleiotropic cytokine which regulates immune responses, hematopoiesis and acute phase reactions (1). Overexpression of IL-6 has been shown to lead to systemic manifestations such as fever, general malaise, myalgia, muscle weakness and edema, as well as laboratory abnormalities such as leukocytosis including neutrophilia, anemia, thrombocytosis, hypergammaglobulinemia, hypoalbuminemia, proteinuria, and an increase in serum level of creatinine, transaminases, alkaline phophatase and C-reactive protein (13, 14). It has also been demonstrated that IL-6 plays an important role in the pathogenesis and progression of various malignancies (2-6). In animal systems, IL-6 appears to induce cancer cachexia (15).

Castleman’s disease is a lymphoproliferative disorder with benign lymphadenopathy characterized histologically by follicular hyperplasia and capillary proliferation with endothelial hyperplasia (16). Based on histopathological findings, Castleman’s disease is classified into hyaline vascular type and plasma cell type. Plasma cell type or mixed hyaline vascular and plasma cell type of Castleman’s disease frequently have systemic lymph nodes swelling with interfollicular plasmacytosis and constitutional inflammatory manifestations such as fever, anemia, hypergammaglobulinemia, hypoalbuminemia and an increase in acute phase proteins (11, 17). This multicentric form of Castleman’s disease, known as MCD, is often refractory to treatment even with corticosteroids or chemotherapy, and consequently the prognosis is poor (11, 12). The median survival of MCD has been reported to be 29 months (12). Infections, renal failure, and malignancies including malignant lymphoma and Kaposi’s sarcoma, are common causes of death in patients with MCD. Male gender, presence of enlarged mediastinal lymph nodes, and episodic pattern of disease have been revealed to be independent predictors of fatal outcomes (11).

The pathogenesis of Castleman’s disease remains unclear, but has been attributed to dysregulated overproduction of
IL-6 from the germinal centers of hyperplastic lymph nodes (13). In fact, in cases of localized Castleman’s disease, clinical abnormalities may resolve after excision of the affected lymph nodes (11, 13, 17). Leakage of locally produced IL-6 into the systemic circulation has been thought to cause systemic manifestations of this disease.

Recently, some cases of IL-6-producing lung cancer have been reported (18, 19). In these cases, marked leukocytosis and thrombocytosis, hypoalbuminemia and increased serum concentrations of C-reactive protein were found, as in the present case. IL-6 production by cancer cells has been demonstrated to play an important role in tumor proliferation by autocrine stimulation in some cases of lung cancer (9). An elevated serum IL-6 level has been often found in large cell carcinoma frequently with leukocytosis and elevated levels of acute phase proteins (7, 8). In these cases, it has been reported that clinical stages were often advanced, and that the patient’s prognosis was poor (19). However, in most of the previous reports, immunohistochemical assessment of IL-6 production by cancer cells and the pathological examinations of lesions suspected of metastases such as swollen lymph nodes were not fully performed, as they were in the present case.

In this case, systemic manifestations, laboratory findings, and non-malignant multiple lymph node swelling with interfollicular plasmacytosis resembled the presentation of MCD. We demonstrated that cancer cells in the tumor were positive for IL-6 immunohistochemical staining. These findings indicate that IL-6 produced by cancer cells might have a great impact on persistent severe inflammation and worsening of general condition as in MCD, which prevented him from receiving chemotherapy. However, as the serum IL-6 level was not measured, there remains the possibility that cancer cells positive for IL-6 immunohistochemical staining did not secrete IL-6, and that other cytokines other than IL-6 were associated with the clinical presentation.

**Conclusion**

To our knowledge, this is the first reported case of an IL-6-producing giant cell carcinoma of the lung with multiple mediastinal lymph node swelling caused not by metastases, but by polyclonal plasmacytosis, which was proven by pathological examinations. In this case, polyclonal plasmacytosis was thought to be caused by leakage of IL-6 produced by cancer cells into the systemic circulation. Clinical presentation resembled MCD, a disease in which IL-6 also plays an important role. In some cases of lung cancer, cytokines produced by cancer cells may have a great influence on the patient’s general condition.

**References**

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