Multiple Cytokines-Producing Pleomorphic Carcinoma of Lung with Metastasis to the Small Intestine

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A 58-year-old man underwent upper lobectomy for primary pleomorphic carcinoma of the lung. Nine months later, the pleomorphic carcinoma was recurred with marked peripheral leukocytosis and an elevated C-reactive protein. Chest and abdominal computed tomography (CT) revealed enlarged mediastinal lymph nodes and a bulky tumor in the small intestine. An enectectomy was performed and the intestinal tumor was removed. Immunostaining revealed tumor cells positive for G-CSF and TNF-α as well as an increased level of serum G-CSF and TNF-α. We describe a rare case of G-CSF and TNF-α producing pleomorphic carcinoma of the lung with metastasis to the small intestine.

Keywords: cytokine, pleomorphic carcinoma, lung, G-CSF, TNF-α

Introduction

Pleomorphic carcinoma of the lung is defined as a group of poorly differentiated non-small cell carcinoma that contains a component of sarcoma or sarcoma-like elements and shows carcinomatous as well as spindle and/or giant cell components.1) Pleomorphic carcinoma of the lung is rare and accounts for less than 1% of all lung malignancies.2) Although there have been several reports that some types of lung cancers produce various cytokines such as granulocyte colony-stimulating factor (G-CSF), interleukin 6 (IL-6), and IL-8,3) there have been few reports of pleomorphic carcinoma of the lung producing these cytokines. We describe a rare case of G-CSF and tumor necrosis factor (TNF)-α producing pleomorphic carcinoma of the lung.
cells positive for G-CSF (Fig. 2C) and TNF-α (Fig. 2D). The clinical symptoms of the patient improved, and the levels of these plasma cytokines decreased for 2 months after the surgery. Despite intensive systemic chemotherapy, the patient died 4 months after the surgical removal of the intestinal metastasis.

**Discussion**

There have been several reports that some types of lung cancers produce various cytokines such as G-CSF, IL-6, TNF-α, and vascular endothelial growth factor (VEGF) *in vitro*. These cytokines are thought to have various effects on tumor growth and antitumor immune responses.
G-CSF is a member of the CSF family of glycoproteins that control the survival, proliferation, differentiation, and functional activation of hematopoietic progenitor cells. Ectopic production of G-CSF is a cause of leukocytosis in solid tumors, including tumors of the lung, stomach, and urinary bladder.\(^5,6\) G-CSF is associated with tumor cell proliferation; it has been found to stimulate the clonal growth of nonhematopoietic tumor cells.\(^7\) However, there have not been any reports of non-small cell lung cancer cells with G-CSF receptors (G-CSFR), which suggests that tumor proliferation does not occur through a G-CSF-dependent autocrine mechanism. In our patient, the tumor cells were also negative for G-CSFR and may therefore not have been susceptible to a G-CSF autocrine growth loop.

TNF-\(\alpha\) is one of the most potent proinflammatory cytokines produced in the microenvironment of the tumor. TNF-\(\alpha\) induces the activation of inhibitor \(\kappa\)B kinase, which phosphorylates nuclear factor-kappa B (NF\(\kappa\)B) inhibitor and triggers its rapid degradation through proteasome proteolysis, resulting in the liberation of NF\(\kappa\)B. NF\(\kappa\)B can then translocate to the nucleus where it activates the transcription of numerous immune system genes.\(^8\) The contribution of NF\(\kappa\)B signaling to the initiation and progression of cancer has been clearly documented, and several lines of evidence have demonstrated that TNF-\(\alpha\) and NF\(\kappa\)B signaling play key roles in the invasive/metastatic spread of cancer cells.\(^9-11\)

To the best of our knowledge, this is the first case of a G-CSF and TNF-\(\alpha\) producing pleomorphic carcinoma of the lung. Certain cytokines may be used as tumor markers in some cases of pleomorphic carcinoma of the lung. Elucidation of the function of these cytokines may lead to overcome the tolerance towards pleomorphic carcinoma of the lung.

**Disclosure Statement**

The authors declare no conflicts of interest.

**References**