Leukemoid Reaction in Lung Cancer Patients

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Worldwide, lung cancer is the most common and the deadliest form of cancer. The presenting symptoms of patients with lung cancer are determined by the sites involved, either primary lung, or metastases in bone, brain, liver, and adrenal glands. In addition, patients may exhibit various paraneoplastic manifestations, often preceding other clinical signs and symptoms. Prognostic factors for patients with lung cancer can be divided with regard to patient, tumor, and treatment-specific parameters. The three most important prognostic factors are classically considered stage, performance status, and weight loss. In addition, a range of prognostic biomarkers, including mutations involving genes that regulate cell cycle progression and apoptosis, as well as invasion and metastasis have been described in these patients. An increased level of white blood cells is often found either at the time of diagnosis or during the course of their disease [1]. It may be caused by one or more factors, such as concomitant infections, bone marrow metastasis, or administration of corticosteroids. However, patients with lung cancer may show leukocytosis without these conditions. Such patients are considered to have tumor-related leukocytosis, which may be caused by the unregulated production of hematopoietic cytokines.

We report two cases of metastatic lung cancer presenting with severe systemic symptoms including fatigue, weight loss, fever and night sweats associated with leukocytosis. In both cases, extensive studies to find causes other than lung cancer were negative, and leukemoid reaction with WBC levels above 100,000 cells/μl was observed during the course of their disease. Their prognosis was ominous, with tumors refractory to all treatments.

PATIENT DESCRIPTIONS

PATIENT 1

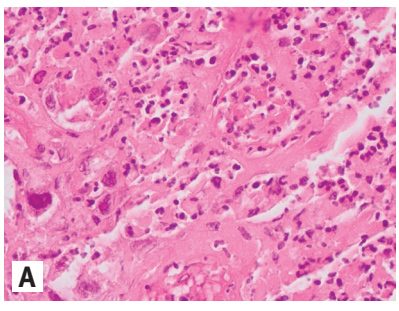
A 61 year old woman, a smoker, presented with complaints of cough, fatigue, weight loss, night sweats, and fever up to 39°C of 6 weeks duration. Superficial transitional cell carcinoma was diagnosed 9 years before her presentation. At that time, she was successfully treated with intravesical installation of Bacillus Calmette-Guérin. Her WBC level was 15,000 cells/μl, most of them mature neutrophils. Imaging studies showed a 6 cm mass in the right upper lobe with central necrosis [Figure A], lymph node enlargement in the right hilum and mediastinum, and a metastasis in the left adrenal. Cultures for infectious etiology were sterile and serology was negative. Computed tomography-guided lung biopsy showed atypical, poorly differentiated large cells suggesting a diagnosis of poorly differentiated large cell carcinoma with areas of necrosis [Figure B]. The patient was treated with chemotherapy consisting of cisplatin and vinorelbine but did not respond to the treatment. Neither did she respond to other subsequent treatments, including erlotinib and palliative radiotherapy to the chest. Fever persisted and her WBC continued to rise reaching a level of 122,000 cells/μl, with neutrophils comprising 96% of the cells. The patient expired 7 months after the initial diagnosis.

PATIENT 2

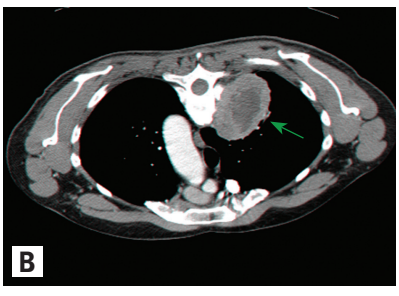
A 43 year old man, also a smoker, presented with complaints of fatigue, rapid

WBC = white blood cells

[A] Biopsy proven poorly differentiated large cell carcinoma of the lung in a 61 year old woman. CT image of the chest with intravenous contrast medium at the level of the aortic arch shows right lung tumor (arrow), 6 cm, with central necrosis.



[B] Photomicrograph of the lung showing atypical large cells with abundant eosinophilic cytoplasm and enlarged nuclei consistent with large cell type, undifferentiated carcinoma. (Hematoxylin-eosin x 400).



weight loss, fever and night sweats during the 3 preceding months. Physical examination revealed cervical lymphadenopathy and left flank tenderness. The WBC count was 28,000 cells/μl with neutrophils comprising 84% of the cells. Imaging studies showed a right lung mass of 6 cm, massive mediastinal lymphadenopathy, a 7 cm mass in the left adrenal, and multiple brain metastases. Lung CT-guided biopsy showed poorly differentiated squamous cell carcinoma with extensive areas of necrosis. The patient received cranial irradiation combined with steroids and his WBC rose to 151,000 cells/μl, which dropped to 127,000 cells/μl after steroids were discontinued. Tests for infectious etiology, including cultures and serologic studies, were all negative as was a polymerase chain reaction study for the abl/bcr sequence. The patient did not respond to chemotherapy consisting of cisplatin and vinorelbine. Systemic manifestations worsened and he expired 4 months after the initial diagnosis.

COMMENT

A combination of several clinicopathologic features makes these two cases unusual. Systemic symptoms such as fatigue, weight loss, night sweats and fever preceded the diagnosis of lung cancer. These symptoms also dominated the clinical course of their disease. Imaging studies showed a metastatic disease, with tumors marked by central necrosis. Their lung cancer histology revealed poorly differentiated neoplasms with areas of tissue necrosis. These clinicopathologic features were accompanied by progressive leukocytosis with WBC levels exceeding 100,000 cells/μl; most cells constituted neutrophils. The tumors in both patients were refractory to all treatments, showing rapid growth, and the prognosis was ominous.

Asano and co-authors [2] first described colony-stimulating factor-producing lung cancer in a patient presenting with neutrophilia. Transplanting malignant cells onto nude mice was followed by the development of neutrophilia in mice. Subsequently, a few other studies reported elevated levels of serum hematopoietic factors including granulocyte-CSF, granulocyte-monocyte CSF or interleukin 6 in patients with lung cancer and neutrophilia [3]. Most cases of lung cancer and leukocytosis were associated with the histology of large cell carcinoma. Kasuga et al. [4] reported a series of 33 patients with tumor-related leukocytosis from among 227 patients with lung cancer. Except for one patient with small cell lung cancer, all the others had non-small cell lung cancer, with the highest incidence noted in patients with the large cell type. Most patients had a WBC level < 50,000 cells/μl, and only one patient showed a WBC exceeding that level. In this study, G-CSF, GM-CSF, and interleukin-6 serum levels of one or more cytokines were high in most patients, along with positive tissue immunoassays. The majority of tumors stained positively for the anti-G-CSF antibody. Patients whose tumors stained positively generally showed a worse prognosis.

A few CSF-producing cell lines were studied for the mechanism causing cytokine production. Aggressiveness was linked to metalloproteinase secretion by tumors, stimulated by GM-CSF, or to tumor expression of CSF receptors. Proliferation of lung cancer cells could be enhanced by G-CSF and GM-CSF. CSF-stimulated signal transduction could be blocked by cyclooxygenase-2 inhibitors. It is therefore plausible that leukocytosis in lung cancer patients not only indicates poor prognosis, but may itself contribute to the aggressive biology of these tumors. A similar observation has also been made in other tumor types [5].

In summary, we described two cases of lung cancer manifested by severe systemic symptoms and leukemoid reaction. Lung cancer in both patients was refractory to all treatments and their course was rapidly fatal. We suggest that the aggressive behavior of the disease in these two cases was closely linked to the development of a leukemoid reaction.

CSF = colony-stimulating factor
G-CSF = granulocyte-CSF
GM-CSF = granulocyte-monocyte CSF

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"God may be in the details, but the goddess is in the questions. Once we begin to ask them, there's no turning back"

Gloria Steinem (born 1934), American feminist, journalist, and social and political activist. A prominent writer and political figure, Steinem is considered one of American history's most important women and one of the most transformative figures of the twentieth century.