Paraneoplastic Syndromes of Hypercalcemia and Leukocytosis Associated with Colonic Metastases from Squamous Cell Carcinoma of the Lung: a Case Report

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Lung cancer is the most common cancer-related death in both men and women in the world. Approximately 25% of all cancer deaths are attributable to lung carcinoma. Moreover, about one-half of patients with lung cancer have metastases at the time of initial diagnosis, most frequently of lymph nodes, adrenals, liver, bone and brain. However metastasis to the colon is very rare. Over the past 25 years about 13 cases of symptomatic colonic metastases from lung malignancies of all types have been reported in the literature. Hypercalcemia and leukocytosis are two of the most common paraneoplastic syndromes associated with various malignancies. However, concomitant manifestation of hypercalcemia and leukocytosis are occasionally observed in the same cancer patients. Here, we present a rare case of colonic metastasis from a squamous cell carcinoma of the lung associated with paraneoplastic syndromes of hypercalcemia and leukocytosis.

Case Report

A 72-year-old man was referred to the hospital with a 10-day history of abdominal pain. He complained of passing 6 stools per day with mucus but no obvious blood loss, and also a loss of almost 5 kg in weight. He had a right lower pneumonectomy 5 weeks ago because of squamous cell carcinoma of the lung. On physical examination the patient was thin, and a tender right lower epigastric mass was found that measured 7 x 5 cm. Other clinical evaluation, including rectal examination, was unremarkable. Routine hematological profiles revealed that his white blood cell count was elevated. Laboratory data were as follows: 16.1 x 10⁹/L, NE 0.671, HGB 141 g/L, TP 52.3 g/L, ALB 26 g/L, serum calcium 3.12 mmol/L (2.25 mmol/L - 2.75 mmol/L), CEA 1.85 ng/ml (0 - 3.4 ng/ml), CA19-9 12.4 u/ml (0 - 39 u/ml). A routine chest X-ray was reported as normal. Computed tomography (CT) confirmed a 7 cm mass in the right lower quadrant. He received 2 weeks of conservative treatment for a potential appendiceal abscess, but there was no change in the mass. In view of possible malignant colonic disease, the patient underwent an exploratory laparotomy, which showed the tumor at the cecum to be adherent to the abdominal wall. Regional lymph nodes were also involved. A curative resection...
was not possible so a biopsy of the lesion was made. The pathological examination demonstrated that the colonic lesion was compatible with metastases from squamous cell carcinoma of the lung. He eventually died 4 weeks later due to respiratory failure, from a combination of disease progression and infection.

Discussion

Lung cancer is the most common cancer-related death in both men and women in the world. Around 50% of cases have demonstrable metastases at the time of presentation. The most common metastatic sites are lymph nodes, adrenals, liver, bone and brain, but gastrointestinal metastases are not an unknown finding at post-mortem. Oschner et al. noted gastrointestinal involvement in 4.3% of a series of 3047 autopsies, and Antler et al. reported that solitary metastases occurred in only 3 of 423 cases. Colonic metastasis usually occurs late in the disease and is typically present after diagnosis of the primary tumor. Symptomatic colonic metastases have been reported previously but are rare. In the past 25 years about 13 cases of symptomatic colonic metastases from lung malignancies of all types have been reported in the literature. Occasionally the lung primary and colonic lesions present simultaneously. They are usually associated with widespread metastases. However, our case represents either a rare case of colonic metastasis from a squamous cell carcinoma of the lung or is associated with paraneoplastic syndromes of hypercalcemia and leukocytosis.

The term "paraneoplastic syndromes" refers to symptoms or signs resulting from damage to organs or tissues that are remote from the site of a malignant neoplasm or its metastases. Paraneoplastic syndromes can affect most organs and tissues. Widely known examples include cancer cachexia, hypercalcemia, Cushing's syndrome, and Trousseau's syndrome. Most of these paraneoplastic syndromes occur because the tumor secretes substances that mimic normal hormones or that interfere with circulating proteins. The cancers causing paraneoplastic syndromes are often asymptomatic and sometimes occult.

Among these paraneoplastic syndromes, hypercalcemia is relatively common in patients with lung cancer. The frequency of hypercalcemia has been reported to range between 10–25%. Leukocytosis is another common paraneoplastic syndrome, ranging between 16–30%, in patients with lung cancer. There have been reports that hypercalcemia and leukocytosis occurred simultaneously in patients with lung cancer and other carcinomas. However, concomitant manifestations of hypercalcemia and leukocytosis are occasionally observed in the same cancer patients. Hiraki et al. retrospectively examined 1149 patients with lung cancer for manifestation of hypercalcemia and/or leukocytosis at their first visit. Their results showed that 65 (5.7%) patients manifested hypercalcemia alone, 16 patients (1.4%) had leukocytosis alone and 6 patients (0.5%) displayed both hypercalcemia and leukocytosis.

Hypercalcemia associated with cancer can be classified into 4 types. In patients with local osteolytic hypercalcemia, it results from the marked increase in osteoclastic bone resorption in areas surrounding the malignant cells within the marrow space. The condition known as humoral hypercalcemia of malignancy (HHM) is caused by systemic secretion of parathyroid hormone (PTH)-related protein (PTH-rP) by malignant tumors. PTH-rP causes increased bone resorption and enhances renal retention of calcium. Some lymphomas secrete the active form of vitamin D, 1,25-dihydroxyvitamin D, causing hypercalcemia as a result of the combination of enhanced osteoclastic bone resorption and enhanced intestinal absorption of calcium.

Hypercalcemia and leukocytosis can be caused through a common mechanism. Recent studies have reported that long-term exposure to granulocyte-colony stimulating factor (G-CSF) results in a stimulation of osteoclastic bone resorption in patients with congenital neutropenia and also in normal rodents. Purton et al. described an increase of osteoclast progenitors in G-CSF-mobilized peripheral blood mononuclear cells from normal human donors. Increased osteoclastic bone resorption is one of the major causes of hypercalcemia. Therefore, G-CSF secreted from cancer cells may cause not only leukocytosis but also hypercalcemia by promoting proliferation and differentiation of the common hematopoietic progenitors of granulocytes and osteoclasts. This might be one of the mechanisms by which leukocytosis and hypercalcemia develop concomitantly in some patients with lung cancer. Asahi et al. have recently reported that a lung cancer cell line established from a squamous cell lung cancer of a patient with hypercalcemia and leukocytosis produces both G-CSF and parathyroid hormone-related protein (PTH-rP). It has been widely recognized that PTH-rP and G-CSF produced by cancer cells play a critical role in the pathophysiology of hypercalcemia and leukocytosis. Thus, it seems likely that production of a factor in cancer cells which bipotently promotes the formation of granulocytes and...