Granulocyte-colony stimulating factor producing thyroid cancer: report of a case and review of the literature

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【Summary】

We would like to report a case of thyroid cancer (adenosquamous cell) associated with marked leukocytosis and hypercalcemia. To demonstrate the production of granulocyte-colony stimulating factor (G-CSF) secreted from the tumor, the residual tumor tissue was resected under aseptic condition at autopsy and was minced and cultured. High levels of G-CSF in the culture supernate were detected by enzyme linked-immunosorbent assay (ELISA) using monoclonal antibodies against human recombinant G-CSF. Therefore, it was evident that neutrophilia in this patient was induced by G-CSF secreted from the thyroid cancer cells. Parathyroid like-hormone which induced hypercalcemia was also suggested to be secreted from the cancer cells in this patient. The cases of thyroid cancer associated with neutrophilia and hypercalcemia were reviewed and discussed in this report.

Key words: neutrophilia, granulocyte stimulating factor (G-CSF), thyroid cancer, hypercalcemia

順天堂大学脳原内科（1994・2・14 受付）
悪性腫瘍の一部の症例に好中球増多を伴うことが知られている。近年の造血因子の研究に伴い、好中球増多の原因は、腫瘍から産生される粒球・コロニー刺激因子（G-CSF）に起因することが報告されている。また、好中球増多を伴う悪性腫瘍の症例のなかには高カルシウム血症を同時に合併することがあることも報告され、腫瘍からの骨吸収作用を促す物質の分泌によると考えられている。今回、われわれは甲状腺癌のなかではまれなadenosquamous cell carcinomaの症例において、好中球増多および高カルシウム血症を認め、摘出腫瘍切片の培養上清中に、高濃度のG-CSFの分泌を測定した1症例を経験したので、文献的考察を行い報告した。

I. Introduction

It has been reported that marked neutrophilia occurs in some patients with malignant tumors1)。In recent studies on hematopoietic factors revealed that granulocyte-colony stimulating factors (G-CSF) are secreted by some malignant tumors to induce neutrophilia in these patients2)。Furthermore, it has also been reported that some patients with malignant tumors accompanied with neutrophilia concurrently developed hypercalcemia3)。in which the bone-resorbing factors were thought to be secreted from the tumor cells.

We would like to report on a patient with adenosquamous cell carcinoma of thyroid gland, a rare type of thyroid cancer, who developed neutrophilia and hypercalcemia and high level of G-CSF was detected in the supernate of the tumor tissue culture by enzymed linked-immunosorbent assay (ELISA)。

II. Materials and Methods

Measurement of G-CSF in culture supernate

The residual tumor was resected under the aseptic condition during autopsy. The tumor was minced and cultured in RPMI medium supplemented with 10% fetal calf serum or GIT medium (Nissui Co., Ltd., Tokyo, Japan) for 5 days。The concentration of G-CSF in culture supernate was measured by ELISA using anti-recombinant G-CSF monoclonal antibodies4)。

III. Case report

A 49-year-old male visited our hospital in April, 1990 who had been suffering from cough and hoarseness for six months。He had experienced weight loss of 5 kg over a period of 3 months。Large tumor was palpable in the thyroid gland area。From aspiration biopsy, the tumor was diagnosed as adenosquamous cell carcinoma of the thyroid gland。He was addmitted to our hospital in May 9th, 1990。On physical examination, the temperature was 37.4℃。A firm mass (about 8 cm in diameter) was palpable in front of the neck and firm enlarged lymph nodes were palpable in bilateral inguinal area。Blood examination showed an increased number of leukocyte of 35,000/mm³ with 82.5% being mature neutrophils。Bone marrow examination revealed an increase in the proliferation of granulocytes。A high G/E ratio was recognized (8.25)。Myeloblasts were not detected。Neutrophil alkaline phosphatase (NAP) score was 416 (normal range : 169.5〜335.0)。Philadelphia chromosomes were not recognized。Repeated bacterial cultures of the bone marrow, blood and sputum revealed no evidence of infection。The results of biochemical examination were LDH 329 tumor and induced neutrophilia in this patient。

IV. Discussion

There have been many reports concerning patients who have malignant tumors associated with neutrophilia, which was induced by G-CSF secreted from the tumor cells。The G-CSF activity was previously demonstrated by the acceleration of colony formation of the bone marrow cells on an agar plate cultured with the patient's plasma, or by the leukocytosis in nude mice transplanted with tumor tissue5)。More recently, the development of
molecular technology has allowed us to not make recombinant G-CSF but also elucidate the chemical properties and the biological activities of G-CSF.

In this case, the patient had adenosquamous cell carcinoma of the thyroid gland and developed neutrophilia as well as hypercalcemia. Six cases of thyroid cancer associated with neutrophilia have been so far reported only in Japan. Among these 7 cases including our case, 4 cases showed hypercalcemia (Table 3). Histopathological findings of these thyroid carcinoma revealed two squamous cell carcinoma, two undifferentiated cell carcinoma, one large cell carcinoma, one papillofolicular adenocarcinoma and the adenosquamous cell carcinoma of our case. These types of carcinoma except papillofolicular adenocarcinoma are seldom found among thyroid carcinoma. Adenosquamous cell carcinoma in this patient was also rare.

Among the above 7 patients, thyroid cancer cell lines have been established from two patients associated with hypercalcemia. It was found that these tumor cells not only produced G-CSF but also parathyroid hormone-like factor which has bone-resorbing activity. At present, interleukin-1α is presumed as the factor which is responsible for hypercalcemia. A Serum calcium level was ele-
vated at the same time when the neutrophil counts increased in this patient (Figure 1). Therefore with these findings, it is suggested that the hypercalcemia in this patient is most likely to be caused by the bone-resorbing factor secreted from the tumor, not by simple osteolysis due to bone metastasis.

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References


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