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Anaplastic Thyroid Carcinoma Producing the Granulocyte Colony Stimulating Factor (G-CSF): Report of a Case

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Abstract: We report herein the unusual case of a 60-year-old woman with an anaplastic thyroid carcinoma which produced granulocyte colony stimulating factor (G-CSF). She presented with large neck masses, respiratory difficulty, and a high fever. Laboratory examinations revealed marked leukocytosis of 43,200/mm^3 with 85% granulocytes and an elevated G-CSF level of 67 pg/dl. Total thyroidectomy with bilateral node dissection and tracheostomy was performed, and a histological diagnosis of large-cell anaplastic thyroid carcinoma was confirmed. Immunohistochemical examination with a polyclonal antibody against G-CSF stained the tumor cells. Although the respiratory difficulty, fever, and marked granulocytosis subsequently improved, she died 1 month after undergoing surgery due to metastatic mediastinal disease.

Key Words: anaplastic thyroid carcinoma, G-CSF

Introduction

Although marked granulocytosis and fever of unknown origin have been observed in patients with non-hematologic malignancies for some time, the mechanism of this effect was not elucidated until an examination of hematopoietic precursor cells led to the discovery of granulocyte colony stimulating factor (G-CSF).[1] In 1974, Robinson[2] reported that cancer patients had elevated G-CSF levels in serum and urine, 3 years after which, in 1977, Ohsawa et al.[3] and Asano et al.[4] demonstrated that patients with lung cancer had elevated levels of G-CSF, and confirmed it by transplanting the tumors into nude mice and measuring G-CSF. Although G-CSF-producing tumors have been found predominantly in association with lung cancers, they have also been found in malignancies of the gallbladder, liver, stomach, pancreas, and thyroid.[5–12] Anaplastic thyroid carcinoma is a rare form of thyroid cancer which grows rapidly and is associated with a poor prognosis,[13] whereas well-differentiated thyroid carcinoma is the most common thyroid malignancy. We report herein the case of a patient with anaplastic thyroid carcinoma producing G-CSF. Only three other cases of a G-CSF-producing anaplastic thyroid carcinoma have been reported in the English and Japanese literature.

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Case Report

A 60-year-old woman was admitted to the hospital in October 1989 with bilateral neck masses, respiratory difficulty, and a fever of 39°C. She had had an anterior neck mass for over 30 years which had not changed in size until just prior to her admission. Physical examination revealed a large ulcerated mass in the anterior neck and enlarged bilateral lymph nodes. There was no hepatosplenomegaly. Cervical plain X-rays revealed a calcified tumor deviating the stenotic trachea, and extending into the upper mediastinum, and computed tomography (CT) revealed a huge mass deviating the trachea and esophagus (Fig. 1). ^{67}Ga-Scintigraphy showed increased uptake in the mass, but ^{99m}Tc-scintigraphy revealed no accumulation in the mass. Cytologic examination of an aspiration needle biopsy of the tumor demonstrated anaplastic carcinoma of the thyroid. Laboratory examinations revealed leukocytosis of 24,200/mm^3 with 79% granulocytes. The serum thyroid hormone and calcium levels were normal, but the serum G-CSF and NCC-ST 439 levels were elevated at 67 pg/ml and 8.5 U/ml, respectively. Serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) levels were normal. A bone marrow biopsy was performed, which showed marked myeloid and megakaryocyte hyperplasia, with

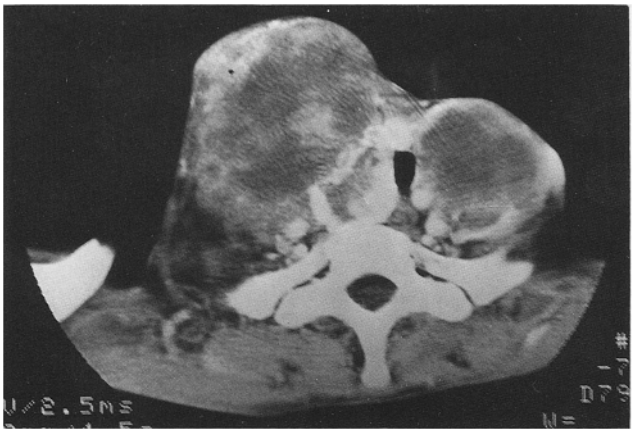

Fig. 1. Computed tomography showed a calcified mass extending to the neck

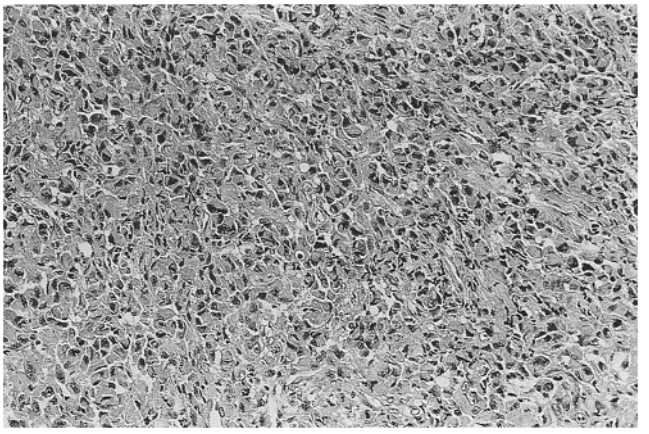

Fig. 2. Microscopic examination of the tumor revealed large cell anaplastic thyroid carcinoma (H&E staining, ×169)

a nuclear cell count of $67.5 \times 10^4/mm^3$ and a myeloid/erythroid ratio (M/E) of 99. There was no evidence of maturation arrest or tumor-cell infiltration. Adriamycin 50 mg and carboplatin 500 mg were administered intravenously, despite which the tumor continued to grow and the leukocyte count reached $43,200/mm^3$, with 85% granulocytes. Because of the progressive respiratory difficulty, the patient underwent total thyroidectomy and bilateral neck dissection with a tracheostomy. The resected specimen contained a calcified thyroid tumor with enlarged metastatic lymph nodes exhibiting central necrosis. The tumor was histologically confirmed as a large-cell anaplastic thyroid carcinoma. The tumor cells were bizarre giant cells with eosinophilic cytoplasm, and large and mitotic nucleoli (Fig. 2). Immunohistochemical staining for G-CSF was performed on paraffin-embedded tissue sections using the avidin-biotin-peroxidase complex (ABC) method.[14] Polyclonal rabbit antibody against G-CSF (Chugai Pharmaceutical, Tokyo, Japan) was utilized. The tumor cells were stained for G-CSF in the cytoplasm (Fig. 3). Postoperatively, the respiratory difficulty, fever, leukocytosis, and G-CSF levels improved, but nevertheless, the patient died 1 month after undergoing surgery due to metastatic mediastinal disease.

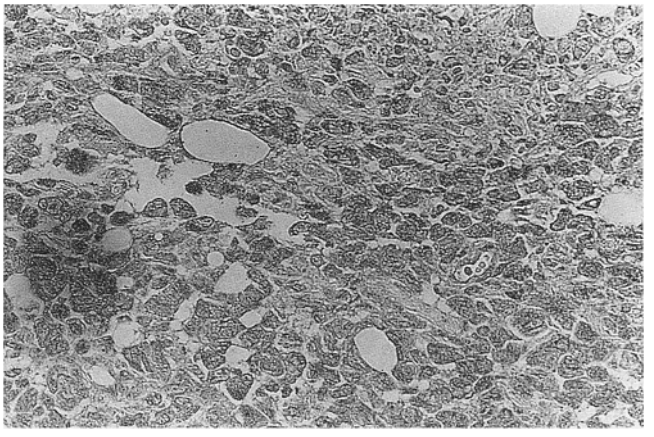

Fig. 3. Immunohistochemical staining with a polyclonal antibody to G-CSF showed staining of the tumor cells (×28)

Discussion

G-CSF-producing tumors have been reported in lung cancers,[3,4] as well as in cancers of the liver, stomach, pancreas, gallbladder, nasopharyx, oral cavity, and thyroid gland.[5,12,15] In fact, a total of 68 patients with non-hematologic G-CSF-producing malignancies have been reported in the Japanese literature.[5–12,15] However, thyroid cancers that produce G-CSF are rare. In 1981, Saito et al.[6] reported the first G-CSF-producing thyroid cancer, and since then six other cases have been reported.[6–11] Three of these seven cases were of squamous cell carcinomas, and the other three were of anaplastic carcinomas. Moreover, there was one patient who had bone metastases from a papillary thyroid carcinoma which produced G-CSF after irradiation.[12] However, none of these reports documented the serum G-CSF levels. G-CSF-producing tumors are associated with mild to moderate leukocytosis ranging from $15,000/mm^3$ to $132,400/mm^3$, with 80%–90% granulocytes. Hypercalcemia has also been reported,[7,16,17] suggesting that co-production of the bone-resorbing factor is the osteoclast-activating factor. Moreover, Sato et al.[16] reported that the osteoclast-activating factor was physicochemically and immunologically similar to interleukin (IL)-1α, and suggested that the excessive production of G-CSF

and the IL-1-α-like factor was responsible for the leukocytosis and hypercalcemia, respectively.

Although surgical resection of the tumor is the most effective treatment, the prognosis of patients with a G-CSF-producing tumor is extremely poor. It has been reported that patients with G-CSF-producing lung cancers have a life expectancy of 4.7 ± 1.3 months after surgery.[5] Moreover, anaplastic thyroid cancer is the most aggressive thyroid malignancy with a dismal prognosis, and little progress has been made in the therapy of this disease.[13] Surgery with a combination of radiotherapy and/or chemotherapy has been employed in the hope of improving survival; however, for our patient, surgery and chemotherapy proved ineffective. It has been hypothesized that anaplastic thyroid carcinoma arises from de-differentiated thyroid tumors[18–21] or long-standing goiters.[19,20] If this proves true, early identification and resection of well-differentiated thyroid tumors could prevent the development of anaplastic tumors.[13]

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