CASE REPORT

Anaplastic Thyroid Carcinoma Accompanied by Uncontrollable Eosinophilia

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Abstract

Anaplastic thyroid carcinoma is a rare disease, and cases associated with eosinophilia are even rarer. We herein report a case of anaplastic thyroid carcinoma accompanied by remarkable and uncontrollable eosinophilia. A 71-year-old man was diagnosed with end-stage anaplastic thyroid carcinoma. Throughout the aggressive clinical course of the cancer, eosinophilia dramatically progressed and became extremely refractory to steroid treatment. We measured the serum levels of hematopoietic cytokines potentially involved in eosinophilia, including granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin (IL)-3 and IL-5. Although the GM-CSF level was moderately elevated, both the IL-3 and IL-5 levels were within the normal ranges. In this case, the patient’s eosinophilia may have been related to his severe dyspnea and was likely responsible for the allergic reaction to the anticancer drug. Therefore, it is essential to elucidate the etiology of eosinophilia in patients with thyroid cancer in order to improve the treatment for patients with anaplastic thyroid carcinoma.

Key words: anaplastic thyroid carcinoma, eosinophilia, granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin (IL)-3, IL-5

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Introduction

Although anaplastic thyroid carcinoma accounts for only 1% to 2% of all thyroid carcinomas, it is one of the most lethal neoplasms in humans (1). In addition, while there are some case reports of anaplastic thyroid carcinomas accompanied by neutrophilia as a form of paraneoplastic syndrome (2, 3), cases associated with eosinophilia are extremely rare. We herein describe the case of a patient with anaplastic thyroid carcinoma who presented with remarkable eosinophilia that was extremely refractory to treatment and markedly affected the response to chemotherapy of the carcinoma.

Case Report

A 71-year-old man was admitted to our hospital for an examination and treatment of a rapidly growing thyroid mass in mid-October 2013. Two weeks prior to admission, he had first noticed the mass on the right side of his neck with discomfort while swallowing. The mass had rapidly increased in size in association with slight pain in the neck, which prompted him to visit his doctor 10 days before admission. However, no abnormalities were observed in the laryngopharynx, and he was referred to the Department of Diabetes, Endocrinology and Metabolism, Hyogo Medical College Hospital for a further examination of the thyroid

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The patient had previously been healthy, except for hypertension, fatty liver and urolithiasis. He was a daily drinker and had smoked 20 cigarettes a day before quitting three years prior to the current admission. He had likely been exposed to radiation at approximately 3 years of age after he and his family returned to Hiroshima following an evacuation for three months after the atomic bombing in 1945. His younger sister had died of pancreatic cancer.

Upon a physical examination, the patient appeared to be stout and afebrile and did not complain of general fatigue, loss of appetite or dyspnea. His vital signs were normal. However, a hen’s egg-sized, hard and non-tender mass was palpable on the right thyroid lobe (Fig. 1A), and the right cervical lymph node was swollen. He also displayed hoarseness and right vocal cord paralysis on an examination with a direct laryngoscope. Although there was also slight pitting edema in the lower extremities, the physical examination was otherwise unremarkable.

The findings of the blood examination performed on admission are shown in Table 1. The total white blood cell (WBC) count was 14,000/μL, of which the absolute eosinophil count (AEC) was markedly elevated at 3,346/μL (23.9%). In contrast, the absolute neutrophil (segmented and bands) count (ANC) was only slightly elevated at 8,036/μL (57.4%). No blasts or immature cells were found in the peripheral blood, and both the hemoglobin and platelet counts were normal. In addition, the levels of lactic dehydrogenase (LDH), alkaline phosphatase (ALP), γ-glutamyltranspeptidase (γ-GTP) and uric acid were mildly elevated, although the results of renal function tests were normal, as were the blood levels of electrolytes, including calcium and phosphorus. Meanwhile, the serum iron level was mildly decreased; however, the ferritin level was within the normal range, and the serum C-reactive protein (CRP) was normal. The thyroid-stimulating hormone (TSH) value was suppressed to an undetectable level, whereas the free T3 and free T4 values were normal. Furthermore, the TSH receptor antibody (TRAb) titer was negative, while that of anti-thyroglobulin antibodies was positive. On a tumor marker analysis, the soluble IL-2 receptor (sIL2R) level was found to be elevated, with slightly elevated carcinoembryonic antigen (CEA) and thyroglobulin levels. Finally, the serum calcitonin level was normal, although the total IgE level was elevated.

Thyroid ultrasonography revealed a 44.1×55.5×54.3-mm mass with a heterogeneous echo in the right thyroid lobe (Fig. 1B). The right cervical lymph nodes were also markedly enlarged, and a chest X-ray showed marked deviation of the trachea. Moreover, a CT scan of the neck (Fig. 1C, D) disclosed a thyroid tumor with a diameter of 5 cm, shifting the trachea to the left. The thyroid tumor was heterogeneously enhanced and contained a low-density area consistent with necrosis. The right cervical lymph nodes were enlarged, with a maximum diameter of 25 mm. The tumor appeared to be partly invading the trachea, sternocleidomastoid muscle and strap muscles and compressed the jugular vein. On F-18 fluorodeoxyglucose positron emission tomography (PET), a remarkable uptake was observed in the thyroid tumor and right cervical lymph node (Fig. 1E, F). In addition,
there were several areas of faint uptake of FDG colocalized with tiny nodules dispersed throughout the lung fields on CT.

A fine-needle aspiration biopsy of the thyroid tumor (performed on the day of admission) showed marked nuclear pleomorphism with large nucleoli and giant cells against a background of inflammatory cell infiltration and necrotic substances, compatible with the features of anaplastic thyroid carcinoma (Fig. 2A). However, no eosinophilic infiltration was obvious within the tumor.

On admission day 1, the patient presented with a pruritic maculopapular eruption on the trunk and extremities. The
Dermatological features were suggestive of a drug allergy. Loxoprofen, treatment with which had been started the previous day, or iodinated contrast material, which had been administered five days earlier, were suspected as causative agents. The eruption disappeared within one week following the discontinuation of loxoprofen and administration of an oral histamine antagonist and topical corticosteroid.

The patient’s eosinophilia had been deteriorating since admission. On admission day 18, the WBC count and AEC level had risen as high as 29,570/μL and 15,229/μL (51.5%), respectively. The neutrophil count also increased gradually, ultimately exceeding 10,000/μL (ANC: 10,113/μL on day 14 and 11,089/μL on day 18).

During his clinical course, the patient began to complain of worsening symptoms, including neck pain, dysphagia and dyspnea. Treatment with morphine eased the neck pain; however, the dyspnea was hardly controlled, despite the lack of wheezing or other abnormal respiratory sounds.

Due to known lung metastasis, the patient was in stage IVC, and curative surgery was not indicated. Palliative therapy aimed at achieving local disease control to prevent dysphagia, suffocation and other mechanical complications was deemed optimal. A chemoradiotherapy regimen adopting low-dose weekly docetaxel (DOC) has been reported to be effective for obtaining locoregional control of anaplastic thyroid carcinomas in some cases (4). The current patient was scheduled to receive irradiation for the primary lesion with the administration of 2-Gy single daily fractions, for a total dose of 60 Gy, and weekly treatment with DOC (10 mg/m²) (4). The first few drops of DOC, however, caused an allergic reaction, with a whole-body skin eruption and dyspnea, which prompted us to immediately stop the DOC infusion. We reasoned that the allergic reaction was associated with marked eosinophilia and therefore initiated steroid pulse therapy (intravenous methylprednisolone, 1 g) for three days in order to control the reaction, followed by intravenous betamethasone at a dose of 80 mg/day. After making sure that the eosinophilia had been sufficiently suppressed (AEC: 437/μL), we successfully administered intravenous paclitaxel (PTX), another taxane anticancer drug, at a dose of 30 mg/m². It should be emphasized that the patient’s dyspnea was also dramatically ameliorated a few days after the initiation of steroid pulse therapy.

Although the eosinophilia had initially normalized following treatment with steroid pulse therapy, it soon became uncontrollable, even with the continuation of a high dose of steroids (Fig. 3). On admission day 22, the WBC count and AEC and ANC levels reached 36,770/μL, 11,950/μL (32.5%) and 22,246/μL (60.5%), respectively.

Despite the administration of chemoradiotherapy, the thyroid lesion continued to grow, ultimately enlarging to the size of a man’s fist. The patient consequently suffered from both dyspnea and dysphagia, which worsened daily. In the end, he and his family sought relief from his condition, such that the continuous intravenous administration of sedative agents was started in order to allow him to sleep on day 24. Thereafter, he developed hypoxemia, a high fever and circulatory failure and died on day 28.

In order to elucidate the mechanisms underlying the remarkable eosinophilia observed in this case, we measured the levels of hematopoietic cytokines potentially involved in eosinophilia. The serum levels of granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin (IL)-3 and IL-5 were determined according to an enzyme-linked im-

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**Figure 3.** Clinical course of the patient. WBC: white blood cell, eosino: eosinophils, neutro: neutrophils, mono: monocytes, RT: radiotherapy.
munosorbent assay (ELISA), which showed the GM-CSF level to be moderately elevated, while the IL-3 and IL-5 levels were normal (Table 1).

**Autopsy findings**

The tissue of the thyroid tumor and site of right cervical lymphadenopathy consisted of anaplastic cancer nests, including pleomorphic and giant carcinoma cells (Fig. 2B, C). On cut sections, extensive hemorrhage and necrosis were observed, and a number of carcinoma cells were found to have invaded the lymphatic and blood vessels. Infiltration of inflammatory cells, primarily neutrophils, was also noted in the tumor tissues. In addition, eosinophilic infiltration was almost absent, although no steroid agents had been administered for the last four days prior to the patient’s death. The thyroid carcinoma had invaded the anterior cervical muscles and right sternocleidomastoid muscle, while the trachea, carotid arteries and recurrent laryngeal nerves remained intact. Furthermore, metastases were found in the lungs, myocardium, ascending aorta, mesenterium, greater omentum, liver, pancreas, skin and multiple lymph nodes (bilateral cervical, mediastinal, para-aortic and right iliac nodes), and pleural dissemination was identified. The metastatic lesions were hemorrhagic, although no signs of eosinophilic infiltration were noted. The bone marrow presented with unspecific hyperplasia, without signs of metastasis. Moreover, cancer of the transverse colon (stage 2) was detected; however, it was considered to be irrelevant to the thyroid carcinoma. Fatty liver and liver cirrhosis were also diagnosed histologically, and localized pneumonitis was seen in the inferior lobes of both lungs. A brain autopsy was not conducted due to the family’s refusal.

**Discussion**

We herein reported a rare case of anaplastic thyroid carcinoma with remarkable eosinophilia. Anaplastic thyroid carcinoma sometimes presents with neutrophilia as a paraneoplastic syndrome, a process attributable to the actions of cytokines produced by tumor cells, such as G-CSF and GM-CSF (5). However, eosinophilia is an extremely rare complication of anaplastic thyroid carcinoma; only three cases have been previously reported in English (Cases 1, 3 and 5 in Table 2).

In Cases 1 and 3, the degree of eosinophilia was comparable to that observed in the present case (6, 7), and all three patients showed similar clinical characteristics. First, the size of the thyroid tumors was 4-5 cm in diameter on the initial examination. Second, lung metastases were detected at diagnosis. Third, the clinical courses were fulminating, with only two to three months of survival after diagnosis. Finally, the hypereosinophilia rapidly intensified during each patient’s clinical course. In Case 3 (7), treatment with 60Co irradiation (2 Gy/day) and doxorubicin (10 mg/day) partly suppressed the eosinophilia with slight softening of the thyroid tumor. However, these effects were transient, and the hypereosinophilia subsequently recurred, despite the continuation of chemoradiotherapy. In the present case, irradiation failed to suppress the tumor progression or onset of eosinophilia, and the initial chemotheraphy regimen (DOC) caused an allergic reaction, possibly due to hypereosinophilia. Moreover, the eosinophilia observed in our case was very refractory to steroid therapy; three days of treatment with 1,000 mg of methylprednisolone was only transiently effective, and the hypereosinophilia rapidly recurred even under therapy with the injection of 80 mg/day of betamethasone. Similarly, in Case 1 (6), the administration of 300 mg/day of hydrocortisone failed to suppress the progression of hypereosinophilia. These case reports together suggest that the onset of hypereosinophilia may be a marker for a poor prognosis in patients with anaplastic thyroid carcinoma. The patient in Case 3 underwent an autopsy, which did not show eosinophilic infiltration into the primary or metastatic lesions. In addition, as in the present case, eosinophilic infiltration to the carcinoma tissue was not histologically evident. Therefore, the current and previous cases do not clar-
ify the mechanisms underlying the development of marked hypereosinophilia.

GM-CSF is known to function broadly as a potent activator of the proliferation and differentiation of myeloid stem cells to neutrophils, eosinophils and monocytes/macrophages (8). In contrast, IL-5 functions selectively to produce and activate eosinophils (8). It has also been demonstrated in vitro that neither IL-5, IL-3, GM-CSF nor eotaxin alone induce eosinophils efficiently (9), and it has been shown that the concomitant disruption of GM-CSF/IL-3/IL-5 does not result in the complete loss of eosinophils (10). In the current case and Case 3 (7), elevation of the GM-CSF level was not accompanied by that of the IL-3/IL-5 level. Hence, GM-CSF appears to not be the sole factor responsible for eosinophilia in patients with anaplastic thyroid carcinoma, and other potential factors have yet to be explored.

In summary, we experienced a patient with anaplastic thyroid carcinoma accompanied by remarkable eosinophilia. Anaplastic thyroid carcinoma is a rare disease, and cases associated with hypereosinophilia are even rarer. In addition to its rarity, the rapid progression and extremely aggressive character of this neoplasm makes conducting a comprehensive investigation difficult. In the present case, the patient’s eosinophilia appears to have markedly affected his clinical course in two aspects. First, the eosinophilia may have been related to the patient’s severe dyspnea, since steroid pulse therapy alleviated this condition, although transiently. Second, the eosinophilia was likely responsible for the patient’s allergic reaction to the anticancer drug. Therefore, it is essential to elucidate the etiology of eosinophilia in cases of thyroid cancer in order to provide better treatment for patients with anaplastic thyroid carcinoma.

The authors state that they have no Conflict of Interest (COI).

References