Case Report

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A case of thyroid anaplastic carcinoma presenting marked neutrophilia and eosinophilia due to co-production of gm-CSF, m-CSF and il-6

Abstract

Thyroid anaplastic carcinoma is an extremely aggressive neoplasm. Even in the recent reports, the prognosis of anaplastic thyroid carcinoma has been unhopeful, and the median survival is limited to months. We experienced a case of thyroid anaplastic carcinoma which exhibited a marked increase in the number of white blood cells (neutrophils, eosinophils and monocytes) and the elevation of serum levels of GM-CSF, M-CSF and IL-6.

Keywords: thyroid anaplastic carcinoma, tumor-related leukocytosis, colony-stimulating factors

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Abbreviations: CSF, colony-stimulating factor; G-CSF, granulocyte-macrophage-colony stimulating factor; GM-CSF, granulocyte--macrophage-colony stimulating factor; M-CSF, macrophage-colony stimulating factor; IL-6, interleukin-6; WBC, white blood cell

Introduction

Increased levels of white blood cells in cancer patients are sometimes noticed. These are caused by coexisting infectious disease for the most part. Tumor-related leukocytosis without infection is seen in some cases. Recently, it has been known that the tumor cells themselves occasionally produce colony-stimulating factors (CSF) such as granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage-colony stimulating factor (GM-CSF), macrophage-colony stimulating factor (M-CSF) and bring on marked leukocytosis, but the incidence and mechanism of leukocytosis caused by malignant neoplasms are still unclear. Asano et al. reported G-CSF producing lung carcinoma in 1977,[1] and CSF-producing carcinomas have been reported arised from various site, such as lung, pancreas, bladder, kidney, uterus, stomach, gall bladder, esophagus, soft tissue, oral cavity, brain, and so on. Relatively high incidence of tumor-related leukocytosis is seen in lung cancer patients. Kasuga et al.[2] reported 33 cases revealed tumor-related leukocytosis in 227 lung cancer patients (14.5%) and 29 of 33 cases showed high serum levels of either G-CSF, GM-CSF, or interleukin-6 (IL-6).[2] However, in thyroid cancer patients, there are a few reports about tumor-related leukocytosis which were accompanied by the production of CSF. And there are extremely rare case those represented the co-elevation of the serum levels of GM-CSF and M-CSF.

We report a case of thyroid anaplastic carcinoma which exhibited a marked increase in the number of white blood cells (neutrophils, eosinophils and monocytes) and the elevation of serum levels of GM-CSF, M-CSF and IL-6.

Case presentation

A 73year old male was admitted to our hospital because of hoarseness and a right neck nodule. From a month prior to admission, he suffered from cough and sputum, and consulted to another doctor first. He was pointed out the tumor in the right lobe of thyroid gland and the deviation of trachea on chest X-ray and CT scan of the neck and upper mediastinum (Figure 1), and he referred to our hospital for further investigation and treatment.

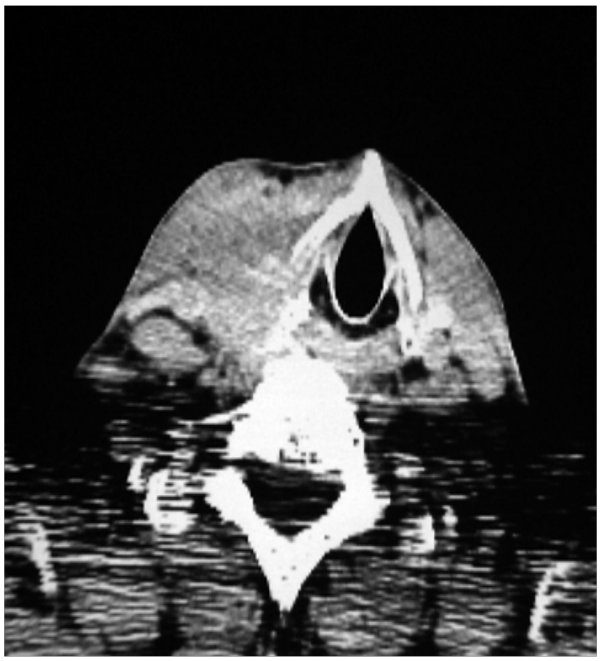

Figure 1 CT image of thyroid tumor before treatment.

In his family history, his father died of esophageal carcinoma when he was 77years old. In the past history, he came up with pleuritis when he was a student, and he got pneumonia 21years ago. On admission, an elastic hard tumor of about 40mm in diameter was noted in the right supraclavicular region, and right cervical and supraclavicular lymph nodes were palpable. Redness of skin was not observed. General condition was relatively good. On physical examination, no rales could be heard in the bilateral lung fields. Ultrasound imaging showed high echogenic solid nodules in the right lobe of the thyroid gland. The next day after admission, CT scan was performed again for re-evaluation. The cervical CT revealed a heterogeneous low density mass lesion in the right lobe of the thyroid gland and the tracheal shift to the left. The chest CT showed multiple nodules in bilateral lung fields, which were not recognized in the first CT scan three weeks ago. Aspiration biopsy of the thyroid tumor was performed, and the diagnosis of class V, anaplastic carcinoma was made cytologically (Figure 2). Laboratory investigations on admission was summarized in Table 1A. Total white blood cell (WBC) count was 9800/μl, and the counts of neutrophils, eosinophils, monocytes were 6760/μl (69%), 1130/μl (12%), 680 (7%), respectively. C-reactive protein was 0.2mg/dl. Serum thyrogloblin was markedly elevated, the numeric value of which was 12555ng/ml.

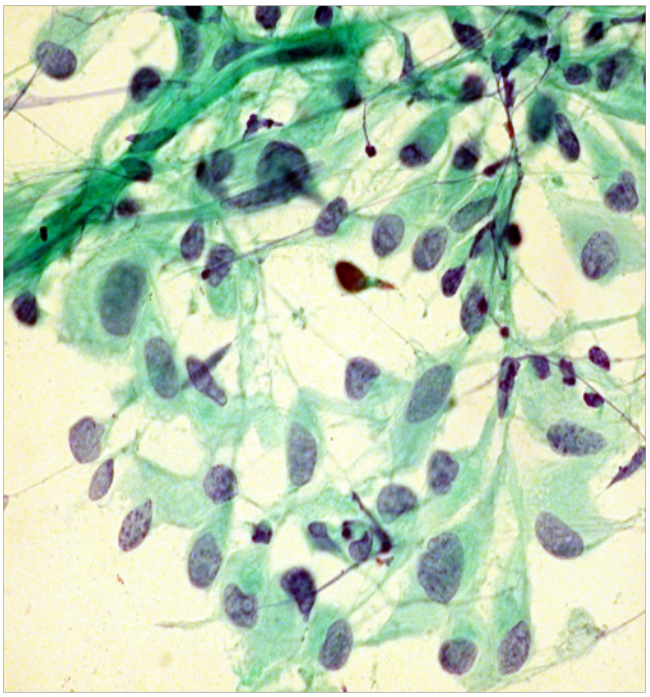

Figure 2 A cytologic specimen of aspiration biopsy from thyroid tumor.

As to the treatment, there was no indication of radical surgical treatment, because of local tumor invasion, metastatic lung nodules and histological finding. Radiation therapy was performed using 10MV X-ray, anteroposterior opposed fields for prevention of airway narrowing. The treatment was performed with accerelated hyperfractionation schedule (1.6Gy per fraction, twice daily). At first, the tumor increased in volume in spite of the treatment, but it decreased gradually. However, multiple lung metastases developed extremely rapid. Because a marked elevation of thyroglobulin was observed on laboratory finding, we anticipated that the tumor cells had the characteristic of well differentiated thyroid carcinoma. So the treatment by internal use of ^{131}I (1.85GBq) was performed for the control of metastatic tumors. However, whole body scintigraphy showed accumulation of ^{131}I only in the thyroid gland and accumulations in the metastatic lesions were not distinct. A month after the start of treatment, gradual increase in total WBC count was observed without inflammatory reaction. WBC count exceeded 30000/μl, and the growing fractions were neutrophils, eosinophils and monocytes (Figure 3). Antibiotic therapy was performed, but number of peripheral white blood cells increased moreover according to tumor progression. Considering the possibility of tumor-related leukocytosis, the serum CSF levels was examined. Serum G-CSF level was within normal limit. On the other hand, serum GM-CSF was elevated, the value of which was 89pg/ml (normal value<2pg/ml). In a month later, we additionally examined serum levels of other cytokines and CSF. The results of examination were shown in Table 1B. Second measurement of serum GM-CSF value showed 749pg/ml. Serum levels of M-CSF and IL-6 also elevated, the values were 1950pg/ml(normal value<515pg/ml), 68.8pg/ml(normal value<4.0pg/ml), respectively. Two months after the start of treatment, multiple huge nodules with interstitial shadows could be seen in his chest radiographs, and the patient died of respiratory failure.

Autopsy was performed. Yellow multinodular mass was seen in the right lobe of the thyroid gland. Uncounted numbers of metastatic nodules were seen in bilateral lungs. One of the largest nodules had the necrotic cavity. Metastases were also found in liver, kidney, stomach, small intestine, colon, mesenterium, and left adrenal gland. In the microscopic findings, tumor cells were large and spindle-shaped. Multinucleated giant cells were observed in the tumor. Partially, component of well differentiated papillary carcinoma could be seen in thyroid tumor. Infiltration of neutrophils were also found in thyroid mass.

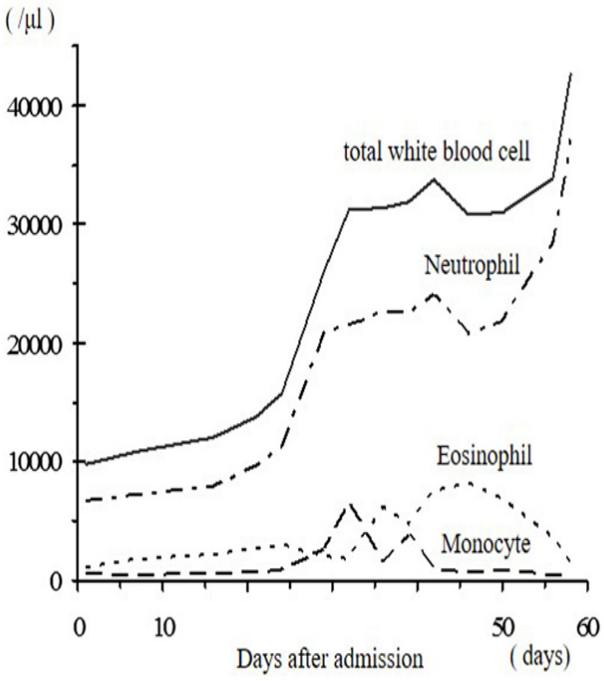

Figure 3 A transition of counts of white blood cells.

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Table 1 Laboratory test values

Table 1A		**Table 1B**
Peripheral blood	**BUN(12mg/dl)**	**Colony stimulating factors**
White blood cells(9800/μl)	Creatinine(0.8mg/dl)	G-CSF(24.2pg/ml)
Neutrophil(69%)	Uric acid(4.2mg/dl)	GM-CSF(749pg/ml)
Eosinophil(12%)	Sodium(141mEq/l)	M-CSF(1950pg/ml)
Basophil(0%)	Potassium(4.3mEq/l)	Cytokines
Monocyte(7%)	Chloride(108mEq/l)	IL-3(<8pg/ml)
Lymphocyte(12%)	Calcium(8.4mg/dl)	IL-5(<15pg/ml)
Red blood cells(441×10^4/μl)	Inorganic phosphate(3.5mg/dl)	IL-6(68.8pg/ml)
Hemoglobin(12.9g/dl)	Serology	
Hematocrit(38.9%)	CRP(0.2mg/dl)	40 days after admission
Platelets(22.1×10^4/μl)	Blood sugar(87mg/dl)	White blood cells(31900/μl)
Blood chemistry	Thyroid function	Neutrophil(71%)
Total protein(6.5g/dl)	Triiodothyronin(1.73ng/ml)	Eosinophil(15%)
Albumin(3.5g/dl)	Thyroxine(8.1μg/dl)	Monocyte(12%)
Total bilirubin(0.7mg/dl)	Thyroid stimulating hormone	
AST 11(IU/l)	0.97μIU/ml	
ALT 8(IU/l)	Tumor marker	
LDH 390(IU/l)	Thyroglobulin(12555ng/ml)	
ALP 140(IU/l)	Calcitonin(18pg/ml)	
γ-GTP 4(IU/l)	CEA(<1.0ng/ml)	

Discussion

Thyroid anaplastic carcinoma is an extremely aggressive neoplasm. The prognosis of anaplastic thyroid carcinoma has been unhopeful, and the median survival is limited to months.[3] If surgical complete resection is possible, favorable outcome might be promising.[3] But many patients who could be completely resected the anaplastic thyroid carcinoma were found their tumors incidentally. In 40-60% of all cases, distant metastases were found on admission, and curative surgical resection was impossible in greater part of thyroid anaplastic cancer patients. In this patient, primary endpoint of treatment was to prevent the upper airway obstruction. Radiation therapy was performed with acceralated hyperfractionation schedule, and upper airway management was possible until his death. Metastatic lesions in the lung grew extremely rapid, compatible with the aggressive course of thyroid anaplastic carcinoma. Because manifest rise in serum thyroglobulin was seen in this patient, we expected that metastatic tumors in this patient have a character of well differentiated thyroid carcinoma. The internal use of ^{131}I which is generally effective for the treatment of metastatic well differentiated thyroid carcinoma, but therapeutic gain was not at all observed. At autopsy, component of well differentiated papillary carcinoma could be seen partially in thyroid tumor. It is known that about half of the patients with anaplastic thyroid carcinoma have a previous or co-existing differentiated thyroid carcinoma. The malignant transformation of a differentiated thyroid carcinoma towards an anaplastic carcinoma is thought due to a mutation of a family of proteins, like p53.

CSF-producing neoplasms are relatively rare, and there are a few reports about CSF-producing thyroid carcinoma. In 1979, Saito et al. reported the case of thyroid carcinoma presenting marked neutrophilia and provided evidence that neutrophilia could also be caused in nude mouse which was transplanted a part of that tumor.[4] Case reports of CSF-producing thyroid carcinoma with leukocytosis have been listed in Table 2. Within these reports, histological type was anaplastic carcinoma in 11 of 14 cases.[4–16] Anaplastic carcinoma might sometimes have a possibility of production of CSF. However, the case exhibiting co-production of GM-CSF, M-CSF, IL-6 was thought to be very rare, so here we reported this case.

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Table 2 Reports of colony-stimulating factor producing thyroid carcinoma

	Age	Sex	Histology	WBC count	Ne%	E%	M%	G-CSF	GM-CSF	M-CSF	Detection of CSF	Year	Ref
1	71	F	Squamous	26000	84	<1	7	?	?	?	Nude mouse	1979	4
2	72	M	Anaplastic	20000	86	4	4	?	?	?	Progenitor cell	1984	5
3	67	F	Squamous	32800	90	0	<5	?	?	?	Progenitor cell	1986	6
4	55	M	Anaplastic	17700	75	0	2	?	?	?	Progenitor cell	1986	7
5	59	F	Anaplastic	41000	97.5	1	2	?	?	?	Progenitor cell	1989	8
6	61	M	Medullary	100000	2	96	0	?	?	?	Progenitor cell	1989	9
7	71	F	Anaplastic	38000	86	2	4	?	?	?	Progenitor cell	1991	10
8	61	M	Anaplastic	35300	88	0	3	?	↑	?	Serum	1992	11
9	65	F	Anaplastic	85300	93	0	2	↑	→	?	Serum, IHC	1995	12
10	72	F	Anaplastic	36200	65	26	3	↑	↑	?	Serum	1996	13
11	80	F	Anaplastic	30100	93	<7	<7	↑	→	↑	Serum	2000	14
12	88	F	Anaplastic	51000	95	<5	<5	→	→	↑	Serum	2000	15
13	60	F	Anaplastic	43200	85	?	?	↑	?	?	Serum, IHC	1995	16
14	73	M	Anaplastic	31900	71	15	12	→	↑	↑	Serum	This case	

WBC, white blood cell; Neu%, fraction of neutrophils: Eo%, fraction of eosinophils; Mo%, fraction of monocyte; G-CSF, granulocyte-macrophage-colony stimulating factor; GM-CSF, granulocyte-macrophage-colony stimulating factor; M-CSF, macrophage-colony stimulating factor; CSF, colony-stimulating factor; IHC, immunohistochemical method; Ref, number of cited reference

Acknowledgements

None.

Conflict of interest

Author declares that there is no conflict of interest.

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