Excessive Leukocytosis Leading to a Diagnosis of Aggressive Thyroid Anaplastic Carcinoma: A Case Report and Relevant Review

Antonis Polymeris^a Christina Kogia^a Dimitrios Ioannidis^a Dimitrios Lilis^a
Maria Drakou^a Nicoletta Maounis^b Loukas Kaklamanis^c
Sofia Tseleni-Balafouta^d

^aDepartment of Endocrinology, Metabolism and Diabetes Mellitus/Sismanogleio-Amalia Fleming Hospital, Athens, Greece; ^bDepartment of Cytology/Sismanogleio-Amalia Fleming Hospital, Athens, Greece; ^cDepartment of Pathology/Mediterraneo Hospital, Glyfada, Greece; ^dFirst Department of Pathology/University of Athens, Medical School, Athens, Greece

Keywords

Anaplastic thyroid carcinoma · Leukocytosis · Paraneoplastic syndrome

Abstract

Introduction: Leukocytosis and particularly neutrophilia are usually caused by acute infection, inflammation, and myeloproliferative neoplasms. However, leukocytosis can also occur in patients with malignancy either due to bone marrow metastases or in the context of a paraneoplastic syndrome.

Case Presentation: An 86-year-old female was admitted to our hospital due to marked leukocytosis (white blood cells [WBC] >40,000/μL), neutrophilia, and monocytosis. She was afebrile and reported hoarseness and mild difficulty swallowing. Upon physical examination, lung auscultation revealed inspiratory wheezing and a non-tender mass was observed in the anterior midline of the neck. Blasts and immature WBC were not found, and polymerase chain reaction for the detection of BCR/ABL gene was negative. A mass (5.4 cm in diameter) of abnormal parenchymal composition with

calcifications occupying the right lobe, was seen on thyroid ultrasound. Cytology, after fine-needle aspiration, showed an anaplastic thyroid carcinoma (ATC). The cervical and chest computed tomography scan revealed a low-density lesion with calcifications that shifts and presses the trachea and multiple lung nodular lesions bilaterally. Since the case was inoperable and the airway was severely obstructed, a DUMON stent was placed. Biopsy of specimens from the trachea lesion revealed a tumor with significant atypical cells and focal squamoid features. The patient's WBC increased to 72,470/μL. Additionally, interleukin-6 (IL-6) was markedly elevated (20.2 pg/mL). The patient passed away due to respiratory arrest 55 days after her initial admission. **Discussion:** Excessive leukocytosis in a patient, having excluded infectious disease and myelodysplastic syndrome, could represent a manifestation of a paraneoplastic syndrome due to various cytokines secretion from the tumor. In our case, ATC synthesized and secreted IL-6, which seems to be the cause of severe leukocytosis.

© 2020 European Thyroid Association
Published by S. Karger AG, Basel

Introduction

Excessively increased levels of white blood cells (WBC), especially neutrophils, typically guide the diagnosis towards severe acute infection, inflammation, or myeloproliferative neoplasms (MPNs). However, in patients with nonhematologic malignancies, neutrophilia could be due to bone marrow metastases, nonspecific inflammation, use of drugs, and/or paraneoplastic syndromes. All types of malignant solid tumors could potentially result in extreme leukocytosis causing diagnostic dilemma [1]. Specifically, persistent WBC count $>50,000/\mu\text{L}$ cells in such cases is characterized as leukemoid reaction, a fairly difficult diagnosis based on the exclusion of chronic myeloid leukemia and chronic neutrophilic leukemia as they share similar characteristics [2]. Leukemoid paraneoplastic reaction (LPR) is also an insufficiently characterized condition caused by tumor-secreted cytokines, mainly granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-CSF (GM-CSF), interleukin-1a (IL-1a), and IL-6, produced by solid tumors [3, 4]. In the literature, there have been sparse studies and case reports of LPR in solid-tumor patients such as in large cell lung cancer [5], sarcoma [6], bladder carcinoma [7], skin cancer and melanoma [8], as well as pancreatic cancer [4].

Specifically, for anaplastic thyroid carcinoma (ATC), one of the most aggressive neoplasms, there have been several reports of leukocytosis due to LPR resulting from G-CSF, MG-CSF, and IL-6 production [9–12]. This excessive and especially gradual elevation of WBC is linked to poorer prognostic survival outcomes [13]. However, there are very few reports where leukocytosis is the primary presenting finding leading to an ATC diagnosis.

In this paper, we report a case of marked increase in the number of WBC primarily of granulocytes that was initially worked up as a MPN but later resulted in an ATC diagnosis.

Case Presentation

An 86-year old female was admitted to our hospital due to marked leukocytosis (WBC $45,000/\mu\text{L}$) found on an outpatient laboratory investigation. She had previously consulted an internist who suggested treatment with hydroxyurea and referred her to our hospital. On admission, the patient was afebrile and in a good general condition. She reported hoarseness and mild difficulty swallowing.

Upon physical examination, lung auscultation revealed inspiratory wheezing and a hard, non-tender mass was observed on the anterior midline of the neck extending to the right supraclavicular region.

On the initial laboratory investigation, her total WBC count was $40,380/\mu\text{L}$, presenting excessive neutrophilia and monocytosis (Neut $32,220/\mu\text{L}$, Mono $3,860/\mu\text{L}$, respectively). Blasts and immature WBC were not found. In addition, mild anemia (hematocrit [Ht] 30.7% and hemoglobin [Hb] 9.8 g/dL) was present.

Erythrocyte sedimentation rate and C-reactive protein were high (80 mm/L and 24.1 mg/L, respectively). Her blood and urine cultures were both negative. Her blood glucose was elevated, serum transaminases were normal besides γGT that was elevated (78 U/L). Urinalysis revealed mild glycosuria. Up to that point, the patient was at the internal medicine clinic of our hospital and the differential diagnosis included chronic myeloid leukemia. Therefore, polymerase chain reaction was performed for the possible detection of the BCR/ABL gene that was also negative. After that, treatment with hydroxyurea was stopped.

The thyroid ultrasound imaging showed a $4.5 \times 5.4 \times 3.5$ -cm mass of abnormal parenchymal composition with calcifications occupying the right lobe. Thyroid function tests revealed low T3 (apparently within the context of low T3 syndrome) and positive anti-thyroglobulin antibodies. We performed fine-needle aspiration of the thyroid lesion that revealed multiple malignant cells with severe nuclear atypia and large nuclei as well as multiple malignant cells with double or numerous nuclei, suggesting either a thyroid anaplastic carcinoma or an aggressive medullary thyroid carcinoma (Fig. 1). However, her normal calcitonin levels led us to exclude the latter.

The cervical computed tomography (CT) scan revealed a heterogeneous enlargement, especially of the right thyroid lobe with low density lesions and calcifications that shifts and presses the trachea. The chest CT showed multiple lung nodular lesions bilaterally. Additionally, in the abdominal CT, a hypodense lesion of a few millimeters in diameter was observed in the liver.

At first, a surgical debulking procedure was considered, and the patient was evaluated by our hospital's surgery, pulmonology, otorhinolaryngology, and anesthesiology teams. Right vocal cord paralysis was observed as well as partial airway obstruction, leading to inspiratory wheezing as mentioned above. The surgery team concluded that the case was inoperable, and the patient was referred to an oncology hospital for further evaluation and airway patency management. The patient's condition was deteriorating rapidly. Bronchoscopy was conducted in order to place a silicone tracheobronchial stent, but due to severe left shifting of the larynx and tracheal stenosis, DUMON stent was suggested to overcome the extreme deviation of the trachea.

During the procedure, specimens from the trachea lesion were taken for biopsy. The histopathological examination revealed an epithelial tumor with significant atypical cells and focal squamoid features or even squamous differentiation (Fig. 1).

At that point, the patient's WBC count had increased to $72,470/\mu\text{L}$ (Fig. 2), her anemia deteriorated (Ht 25.4% and Hb 8.4 g/dL), and she received transfusion with red blood cells concentrate. To clarify the cause of leukocytosis and anemia, blood samples were collected to measure IL-6 and erythropoietin, respectively. IL-6 was markedly elevated (20.2 pg/mL, normal range <7) and erythropoietin was low (3 mU/mL, normal range 4.3–29).

The patient received additional palliative care to deal with the pain, as well as oxygen support at home but passed away due to respiratory arrest 55 days after her initial admission.

Fig. 1. A Microscopically, numerous malignant cells were observed, individually and in groups, with severe nuclear atypia and large nuclei. Additionally, several binuclear and polynuclear malignant cells were observed. No evidence of colloid or necrosis was observed. Diff Quick stain: **a** $\times 100$, **b, c** $\times 400$, **d** $\times 600$. **B** Squamoid highly atypical neoplastic cells with atypical mitotic figures and dense infiltration by leukocytes as well. There is evidence of necrosis with dense leukocytic infiltration. HE stain $400\times$.

Discussion

Our 86-year-old euthyroid patient had a large nodular goiter with profound leukocytosis, monocytosis, and neutrophilia which was the main reason for hospital re-

ferral. The workup showed that the marked WBC elevation was due to leukemoid paraneoplastic syndrome. The patient suffered from an aggressive ATC which resulted in metastatic lesions to the lung and the liver. In addition, she had elevated erythrocyte sedimentation rate and C-

Fig. 2. Flow chart of the number of WBC and neutrophil from diagnosis to the patient's passing (all counts are in μL).

reactive protein levels that were attributed to aging, anemia, and malignancy, having excluded infection, inflammation, and myeloproliferative syndrome. Even though anemia could be attributed to bone marrow metastases, additional measures such as bone marrow biopsy or positron emission tomography-computed tomography (PET/CT) were taken under consideration, but due to her deteriorating health status and her reluctance for further investigation, they were not performed.

The prognosis of ATC, despite the development of new antineoplastic therapeutic strategies and drugs, remains extremely poor, with a median survival of 3–9 months [14]. ATC is characterized by rapid tumor growth, infiltration of the adjacent tissues, and rapid distant metastases mostly pulmonary. Due to its aggressive nature, very few patients benefit from complete surgical excision of the tumor, which carries the best survival outcome [13, 15]. In many cases, infiltration of the upper airway tract due to ATC leads to airway obstruction, and special measures should be taken to prevent respiratory failure. Most cases require a multimodal approach, including radiotherapy and/or chemotherapy, to achieve better results in terms of quality of life and survival [13, 15, 16].

Many solid tumors, such as lung, ovary, gallbladder, kidney, colon, and stomach carcinomas, produce various cytokines, especially G-CSF, GM-CSF, IL-1, and IL-6, leading to WBC elevation especially of neutrophils. This excessive leukocytosis is also referred to as LPR. However,

severe leukocytosis as a primary finding in a patient with ATC is extremely rare. In addition, various studies support the fact that patients with ATC and WBC count $>10,000/\mu\text{L}$, especially when this elevation is gradual, correlate with poorer survival outcomes. Therefore, WBC count could be used as a prognostic factor next to distal metastases, platelet count, and older age [13, 17].

Even though leukocytosis has already been associated with squamous thyroid cancer in 1979 in Japan [18], the first correlation between ATC and elevated CSF was reported in 1984 by Japanese authors as well [19]. Marked elevation of GM-CSF levels in patients with ATC was first reported in 1992 [20]. In the following years, increased levels of other cytokines, such as IL-6, IL-1, G-CSF, and macrophage-CSF (M-CSF), were also associated with ATC. In the literature, few cases have been published over the years that associate leukocytosis and cytokine production with ATC (Table 1) [9–12, 20–29], even though, as previously noted, some other studies relate leukocytosis with poor prognosis in patients with ATC. Most of these reports evaluated CSFs, and in very few cases, IL-6 was measured and was found either elevated or within the normal range [10–12]. No such publications were originated from Greece except for a case report of a CSF producing papillary thyroid carcinoma associated with neutrophilia also from our department [30].

In conclusion, this is the first case of aggressive ATC in Greece associated with initially marked elevation of WBC

Table 1. Review of the literature

Year	Author	Origin	Age, G years	Histology	Primary finding	Lesion	Metastases	WBC	Elevated cytokine		
1	1992	Murabe	Japan	61	M	Anaplastic	Fever	Thyroid	Heart, lung, liver, bladder, lymph nodes	35,300	GM-CSF
2	1995	Yazawa	Japan	65	F	Anaplastic	Thyroid mass	Thyroid	Lung, liver, lymph nodes	85,000	G-CSF
3	1995	Iwasa	Japan	60	F	Anaplastic	Neck mass, respiratory difficulty	Thyroid	N/S	24,200	G-CSF
4	1996	Nakada	Japan	72	F	Anaplastic	Neck mass, hoarseness	Thyroid	Lung, lymph nodes	36,200	G-CSF, GM-CSF
5	2000	Sato	Japan	80	F	Anaplastic	Lumbago, appetite loss	Thyroid	Lung, bone, adrenal	30,100	G-CSF, M-CSF
6	2000	Sato	Japan	88	F	Anaplastic	Dysphagia, fever	Thyroid	Kidney, lung, general	51,000	IL-6, M-CSF
7	2000	Hoshi	Japan	68	F	Anaplastic	Hoarseness, dysphagia, neck mass	Thyroid	Lung, general	15,400	G-CSF, GM-CSF
8	2000	Kitanishi	Japan	86	F	Anaplastic	Neck mass	Thyroid	N/S	Neutrophilia	G-CSF
9	2000	Kitanishi	Japan	77	F	Anaplastic	Neck tumor, bleeding	Thyroid	N/S	Neutrophilia	G-CSF
10	2006	Fujita	Japan	75	F	Anaplastic trans of papillary ca-meta	Axillary mass	Axillary lymph node	Axilla, skin	20,000	G-CSF
11	2010	Zweifel	Switzerland	57	M	Anaplastic	Jugular mass	Thyroid	N/S	50,000	G-CSF
12	2012	Nakayama	Japan	55	F	Anaplastic trans of follicular ca-meta	Hip joint pain	Pelvic bone	Lung, bone	29,800	G-CSF
13	2013	Kang	Korea	75	F	Anaplastic	Fever, appetite loss, pyelonephritis	Thyroid	Lymph nodes, lung	34,900	G-CSF
14	2014	Lee	Korea	69	M	Anaplastic trans of papillary ca-meta	Chest wall pain	Pleura	Liver, bone	32,880	G-CSF
15	2015	Shiraishi	Japan	71	M	Anaplastic	Thyroid mass	Thyroid	Lymph nodes, myocardium, aorta, mesentery, greater omentum, liver, pancreas, skin	29,570 (initially normal)	GM-CSF
16	2017	Saitoh	Japan	73	M	Anaplastic	Hoarseness, neck mass	Thyroid	Lung, liver, kidney, stomach, small intestine, colon, mesentery, and left adrenal gland	Gradual increase	GM-CSG, M-CSF, IL-6
17	2018	This case	Greece	86	F	Anaplastic, squamoid differentiation	Leukocytosis	Thyroid	Lung, liver	40,380	IL-6

G, gender; WBC, white blood cells; ca, carcinoma; trans, transformation; GM-CSF, granulocyte macrophage-colony stimulating factor; G-CSF, granulocyte-colony stimulating factor; M-CSF, macrophage-colony stimulating factor; IL-6, interleukin-6; N/S, not specified.

G, gender; WBC, white blood cells; ca, carcinoma; trans, transformation; GM-CSF, granulocyte macrophage-colony stimulating factor; G-CSF, granulocyte-colony stimulating factor; M-CSF, macrophage-colony stimulating factor; IL-6, interleukin-6; N/S, not specified.

as a result of LPR. The patient's serum IL-6 was found elevated almost three times over the upper limit of the normal, which partially explains the observed extreme leukocytosis. Frequently, leukocytosis is associated with MPNs. However, solid tumors and very rarely ATC, as in our case, may be presented with severe leukocytosis. Additionally, ATC with squamous differentiation is an extremely rare event. Given the absence of a specific immunophenotype, in such cases, the differential diagnosis from other squamous carcinomas is based mainly on the locoregional clinical and radiological findings, with the bulk of the tumor being situated in the thyroid, as in our patient.

Statement of Ethics

The patient's family has given written informed consent to publish this case including the publication of images.

References

- Granger JM, Kontoyiannis DP. Etiology and outcome of extreme leukocytosis in 758 non-hematologic cancer patients: a retrospective, single-institution study. *Cancer*. 2009 Sep; 115(17):3919–23.
- Sakka V, Tsiodras S, Giamarellos-Bourboulis EJ, Giamarellou H. An update on the etiology and diagnostic evaluation of a leukemoid reaction. *Eur J Intern Med*. 2006 Oct;17(6):394–8.
- Wetzler M, Estrov Z, Talpaz M, Markowitz A, Gutterman JU, Kurzrock R. Granulocyte-macrophage colony-stimulating factor as a cause of paraneoplastic leukaemoid reaction in advanced transitional cell carcinoma. *J Intern Med*. 1993 Oct;234(4):417–20.
- Qureshi KM, Raman AK, Tan D, Fakih MG. Leukemoid reaction in pancreatic cancer: a case report and review of the literature. *JOP*. 2006 Nov;7(6):631–4.
- Kasuga I, Makino S, Kiyokawa H, Katoh H, Ebihara Y, Ohyashiki K. Tumor-related leukocytosis is linked with poor prognosis in patients with lung carcinoma. *Cancer*. 2001 Nov;92(9):2399–405.
- Dorn C, Bugl S, Malenke E, Müller MR, Weisel KC, Vogel U, et al. Paraneoplastic granulocyte colony-stimulating factor secretion in soft tissue sarcoma mimicking myeloproliferative neoplasia: a case report. *BMC Res Notes*. 2014 May;7(1):313.
- Ito N, Matsuda T, Kakehi Y, Takeuchi E, Takahashi T, Yoshida O. Bladder cancer producing granulocyte colony-stimulating factor. *N Engl J Med*. 1990 Dec;323(24):1709–10.
- Schniewind B, Christgen M, Hauschild A, Kurdow R, Kalthoff H, Klomp HJ. Paraneoplastic leukemoid reaction and rapid progression in a patient with malignant melanoma: establishment of KT293, a novel G-CSF-secreting melanoma cell line. *Cancer Biol Ther*. 2005 Jan;4(1):23–7.
- Fujita T, Ogasawara Y, Naito M, Doihara H, Shimizu N. Anaplastic thyroid carcinoma associated with granulocyte colony-stimulating factor: report of a case. *Surg Today*. 2006; 36(1):63–7.
- Saitoh JS, Musha A, Mizukami T, Abe T, Nakano T. A case of thyroid anaplastic carcinoma presenting marked neutrophilia and eosinophilia due to co-production of GM-CSF, M-CSF and IL-6. *Int J Radiol Radiat Ther*. 2017;3(2):203–6.
- Sato T, Omura M, Saito J, Hirasawa A, Kakuta Y, Wakabayashi Y, et al. Neutrophilia associated with anaplastic carcinoma of the thyroid: production of macrophage colony-stimulating factor (M-CSF) and interleukin-6. *Thyroid*. 2000 Dec;10(12):1113–8.
- Yazawa S, Toshimori H, Nakatsuru K, Katakami H, Takemura J, Matsukura S. Thyroid anaplastic carcinoma producing granulocyte-colony-stimulating factor and parathyroid hormone-related protein. *Intern Med*. 1995 Jun;34(6):584–8.
- Sun C, Li Q, Hu Z, He J, Li C, Li G, et al. Treatment and prognosis of anaplastic thyroid carcinoma: experience from a single institution in China. *PLoS One*. 2013 Nov;8(11):e80011.
- Kebebew E, Greenspan FS, Clark OH, Woelber KA, McMillan A. Anaplastic thyroid carcinoma. Treatment outcome and prognostic factors. *Cancer*. 2005 Apr;103(7):1330–5.
- Ito K, Hanamura T, Murayama K, Okada T, Watanabe T, Harada M, et al. Multimodality therapeutic outcomes in anaplastic thyroid carcinoma: improved survival in subgroups of patients with localized primary tumors. *Head Neck*. 2012 Feb;34(2):230–7.
- Derbel O, Limem S, Segura-Ferlay C, Lifante JC, Carrie C, Peix JL, et al. Results of combined treatment of anaplastic thyroid carcinoma (ATC). *BMC Cancer*. 2011 Nov;11:469.
- Sugitani I, Miyauchi A, Sugino K, Okamoto T, Yoshida A, Suzuki S. Prognostic factors and treatment outcomes for anaplastic thyroid carcinoma: ATC Research Consortium of Japan cohort study of 677 patients. *World J Surg*. 2012 Jun;36(6):1247–54.
- Saito K, Tomotsune Y, Yamamoto K, Saito T, Kuzuya T, Yoshida S. [A case of primary squamous cell carcinoma of the thyroid associated with marked neutrophilia and hypercalcemia (author's transl)]. *Nippon Naika Gakkai Zasshi*. 1979 Nov;68(11):1466–72.
- Hirayu HI, Sato K, Tomita I, Tomonaga M, et al. A case of thyroid carcinoma with marked activity of colony-stimulating factor. *Horumon To Rinsho* (Clin Endocrinol). 1984;(32):143–5.
- Murabe H, Akamizu T, Kubota A, Kusaka S. Anaplastic thyroid carcinoma with prominent cardiac metastasis, accompanied by a marked leukocytosis with a neutrophilia and high GM-CSF level in serum. *Intern Med*. 1992 Sep;31(9):1107–11.
- Iwasa K, Noguchi M, Mori K, Ohta N, Miyazaki I, Nonomura A, et al. Anaplastic thyroid carcinoma producing the granulocyte colony stimulating factor (G-CSF): report of a case. *Surg Today*. 1995;25(2):158–60.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors did not receive any funding for the present work.

Author Contributions

A.P. was the supervising physician, was involved in planning, and supervised the work, C.K. collected the samples, processed the data, drafted the manuscript, and designed the figures. N.M. performed the cytological analysis, S.T.-B. and L.K. performed the histopathological analysis, D.I., D.L., and M.D. were attending physicians and aided in interpreting the results. All authors discussed the results and commented on the manuscript.

- 22 Nakada T, Sato H, Inoue F, Mizorogi F, Nagayama K, Tanaka T. The production of colony-stimulating factors by thyroid carcinoma is associated with marked neutrophilia and eosinophilia. *Intern Med.* 1996 Oct; 35(10):815–20.
- 23 Hoshi S, Yoshizawa A, Arioka H, Kobayashi N, Kudo K, Niino H. [Anaplastic thyroid carcinoma with lung metastasis producing CA 19-9 and GM-CSF]. *Nihon Kokyuki Gakkai Zasshi.* 2000 May;38(5):391–7. Japanese.
- 24 Kitanishi T, Suzuki M, Fukui J, Taniguchi K, Kitano H, Yazawa Y, et al. Two cases of thyroid carcinoma producing granulocyte colony-stimulating factor. *J Otolaryngol.* 2000 Jun;29(3):174–8.
- 25 Zweifel M, Stenner-Liewen F, Weber A, Samaras P, Zaugg K, Knuth A, et al. Increased bone marrow activity on F-18-FDG PET/CT in granulocyte colony stimulating factor producing anaplastic thyroid carcinoma. *Clin Nucl Med.* 2010 Feb;35(2):103–4.
- 26 Nakayama R, Horiuchi K, Susa M, Hosaka S, Hayashi Y, Kameyama K, et al. Anaplastic transformation of follicular thyroid carcinoma in a metastatic skeletal lesion presenting with paraneoplastic leukocytosis. *Thyroid.* 2012 Feb;22(2):200–4.
- 27 Kang K, Park JH, Ryu JY, Lee SY, Ko GJ, Kwon YJ. Acute pyelonephritis with anaplastic thyroid carcinoma producing granulocyte colony-stimulating factor. *Blood Res.* 2013 Mar;48(1):63–6.
- 28 Lee HR, Baek JS, Lee SH, Cho AR, Lee JY, Jang JM. Paraneoplastic Neutrophilia Originating from an Anaplastic Transformation of Papillary Thyroid Carcinoma in a Metastatic Pleural Lesion. *Med J Chosun Univ.* 2014;39(1): 39–42.
- 29 Shiraishi J, Koyama H, Seki M, Hatayama M, Naka M, Kurajoh M, et al. Anaplastic thyroid carcinoma accompanied by uncontrollable eosinophilia. *Intern Med.* 2015;54(6):611–6.
- 30 Vassilatou E, Fisfis M, Morphopoulos G, Savva S, Voucouti E, Stefanoudaki K, et al. Papillary thyroid carcinoma producing granulocyte-macrophage colony-stimulating factor is associated with neutrophilia and eosinophilia. *Hormones (Athens).* 2006 Oct-Dec;5(4): 303–9.