Case Report

Be(a)ware of Leukocytosis in Papillary Thyroid Cancer

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Leukocytosis can be present at any time during various malignancies. A 42-year-old male was admitted to our department for surgical management of his metastatic papillary thyroid cancer. Persistent white blood cell (WBC) elevation with left shift led to a thorough investigation. Having excluded other causes, leukocytosis was attributed to thyroid cancer itself. Positive immunostaining for IL-6 and CEA, as well as elevated serum levels, established this connection.

1. Introduction

Tumor-related leukocytosis is associated with advanced tumor-stage and poor patient outcomes. However, it has been largely ignored or misinterpreted. If the underlying malignancy is not clinically evident, leukocytosis could be attributed to myeloproliferative neoplasms, misleading the patient’s management. Solid tumors such as lung, genitourinary, gastrointestinal, melanoma, and head and neck may secrete cytokines, mainly granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage CSF (GM-CSF), and/or interleukins. As far as thyroid cancer is concerned, squamous and anaplastic cancer cases associated with leukocytosis have been reported. We report the rare case of a well-differentiated papillary thyroid carcinoma linked to neoplastic leukocytosis and elevated CEA levels.

2. Case Report/Case Presentation

In February 2021, a 42-year-old male was admitted to our surgical department due to metastatic papillary thyroid carcinoma detected on an outpatient investigation. He had previously visited a maxillofacial surgeon due to palpable right neck lymphadenopathy, who suggested a neck ultrasound (US). The US showed a 21 × 12 mm hypoechoic solid lesion in the thyroid isthmus and a 33 × 32 × 25 mm lesion with abnormal parenchymal composition and calcifications occupying the right lobe. Central and right lateral cervical lymph nodes were highly suspicious. Fine needle aspiration of the two tumors and a region III lymph node suggested the presence of a metastatic multifocal papillary thyroid carcinoma (PTC).

Thyroid function examination and anti-thyroglobulin antibodies were within the normal range while serum thyroglobulin was 176.9 ng/ml (normal range: 0–50 ng/ml). It was noteworthy that his laboratory tests showed leukocytosis with neutrophilia (WBC: 21,390 K/µl, NE: 18,300 K/µl), although further investigation was not considered.

The patient underwent thyroidectomy with central and right lateral selective lymph node dissection. Due to the aggressive behavior of the tumor, the right thyroid lobe and specimens from the trachea were sent for intraoperative histologic examination, which confirmed the presence of PTC in the right lobe and neoplastic infiltration of the fibroadipose tissue from the trachea along with a metastatic lymph node. The operation was completed, and the patient had an uneventful recovery.

Gross examination of the thyroid specimen revealed multiple white to tan nodules scattered throughout the gland, both in the lobes, but also in the isthmus, measured...
from 0.2 cm to 5 cm in diameter. Hematoxylin and eosi- 
sin-stained sections showed that the described lesions corre- 
respond to PTC characterized mainly by papillary structures "(shown in Figure 1(a))." The lining epithelium consisted of medium-sized cells with eosinophilic cytoplasm and dis- 
tinctive nuclear features, namely, nuclear overlapping, 
chromatin clearing, irregular nuclear contour, and nuclear 
grooves and pseudo-inclusions "(shown in Figure 1(b))." 
Psmammas bodies were also present in the adjacent area. 
Stroma was fibrous with dense collagenous with sparsely 
inflammatory cells. Despite the multiple sections, areas of 
low differentiation or anaplastic features were not observed. 
Cancer cells invaded the thyroid capsule and expanded in the 
surrounding tissues. In addition, seven cervical lymph 
nodes displayed metastases from the carcinoma. Histologic 
findings were consistent with a multifocal PTC of the classic 
variant pT4aN1b according to the pTNM classification 
scheme.

The patient was reevaluated on the second postop- 
erative month. The US showed left lateral cervical 
lymphadenopathy and a recurrence of 24×19×22 mm 
in the central region despite the meticulous operation. 
Cervical computed tomography (CT) depicted the 
aforementioned pathologic lymph nodes. Chest and ab- 
dominal CT did not reveal further metastatic lesions. TSH 
and TG were elevated (18.1 μU/ml and 131 ng/ml, re- 
spectively) while leukocytosis with neutrophilia (WBC: 
23,720 K/μL, NE: 19,800 K/μL) remained. Blasts and im- 
mature white blood cells were not found, while eryth- 
rinocytic hemolytic anemia (ESA), C-reactive protein 
(CRP), and carcinoembryonic antigen (CEA) levels were 
elevated (22 mm/L, 16 ng/ml, and 18 ng/ml, respectively). 
After a thorough investigation by the internal medicine 
department, infectious diseases, leukemia, and myelo- 
proliferative neoplasms were excluded. Searching for the 
cause of leukocytosis, serum concentrations of gran- 
ulocyte colony-stimulating factor (G-CSF) and IL-6 were 
measured. IL-6 levels were found elevated (71 pg/ml, 
normal range<7), which partially explained the observed 
leukocytosis.

In June, the patient underwent a second operation with 
left lateral neck dissection and excision of the recurrence in 
the central compartment. Histologic examination revealed 
nine metastatic lymph nodes. After being informed of high 
serum IL-6 levels, immunohistochemistry with IL-6 anti- 
body was performed, which revealed positivity in a few 
neoplastic cells "(shown in Figure 2(a))." Few cells were 
immunoreactive to CEA antibody as well "(shown in 
Figure 2(b))."

Postoperatively, he received a dose of 120 mCi iodine 
131. Whole-body scan showed foci of uptake in the 
thyroid bed. Appropriate thyroxine suppressive therapy was 
added and on the second post-iodine month patient 
new examinations were ordered revealing normalized 
levels of TSH and TG (0.8 μU/ML and 0.1 ng/ml re- 
spectively). Surprisingly, WBC and neutrophils, ESR, 
CRP, and CEA were also within the normal range (WBC: 
9800 K/μL, NE: 5,000 K/μL, ESR:12, CRP:0.5, CEA: 1.2). IL- 
6 levels were also measured (2.8 pg/ml). The patient 
remains under close endocrinologic and surgical sur-
veillance without evidence of recurrence.

3. Discussion

This patient may represent the first established classic 
papillary thyroid carcinoma case with associated leukocy-
tosis and elevated CEA levels caused by IL-6 and CEA 
expression by tumor cells. Leukocytosis and malignancy 
have long been linked and known as paraneoplastic leuk- 
emoid reaction [1]. In its formal definition, leukemoid 
reaction refers to persistent leukocytosis (WBC >40 000/μL) 
in the absence of a hematologic malignancy. Various in-
festions, intoxications, malignancies, severe hemorrhage, or 
aacute hemolysis may be the etiology [2]. Paraneoplastic 
leukemoid reaction occurs in the presence of a non-
metastatic thyroid cytokine-secreting tumor and in the ab- 
ence of bone marrow infiltration by that tumor [3]. In many 
malignancies, a less profound leukocytosis may be observed, 
although.

It seems that irregular cytokine production by tumor 
cells, such as granulocyte colony-stimulating factor (G- 
CSF), granulocyte-macrophage colony-stimulating factor 
(GM-CSF), and interleukins (IL-3, IL-6, and TNF-α) 
initiate the pathogenesis [4] leading to granulocytosis. 
This ability may be present along with tumor develop-
ment or secondarily after dedifferentiation and can also 
be seen in metastatic sites even if it is absent in the 
primary tumor [5]. Cytokine-producing tumor foci grow 
farther than the nonproducing ones due to an autocrine 
growth induction phenomenon [6]. In addition to 
stimulating bone marrow granulocytosis, an inhibition of 
myeloid cell differentiation in the tumor microenviron-
ment may be observed, causing the accumulation of 
immature myeloid cells. These myeloid-derived sup-
pressor cells "protect" the tumor, contributing also to 
neoplasia and cancer progression. Such patients 
seem to have a poor prognosis [3].

A variety of tumors may be associated with elevated 
WBC. Tumor-related leukocytosis may be present at any 
time during the disease, simultaneously, late, or even prior to 
the diagnosis. Although lung and kidney malignancies are 
commonly associated with leukocytosis, gastrointestinal, 
hepatobiliary, genitourinary, melanoma, and head and neck 
cancers [2] have also been reported.

Thyroid malignancies have also been associated with 
paraneoplastic leukocytosis. Two cases of squamous 
cell carcinoma [7, 8] and seventeen cases of anaplastic 
tumor have been reported [9–23]. Both cases of 
squamous cell carcinoma were related to marked leu-
kocytosis and hypercalcemia. The authors proposed that 
tumor cells produced G-CSF, IL-1α, and PTH-rP, 
suggesting the existence of a new paraneoplastic syn-
drome. Elevated G-CSF levels were detected in anaplastic 
thyroid cancer cases. Only a few case reports evaluated 
IL-6 levels as either elevated or within the normal range 
[10–12, 23].

A unique case of aggressive papillary thyroid cancer 
associated with neutrophilia has been published.
Vassilatou et al. hypothesized that the presence of CSF-producing tumor was indicated by elevated GM-CSF serum levels. Bone marrow biopsy revealed infiltration by the papillary thyroid carcinoma [24]. Our patient differed from the above since the tumor cells synthesized and secreted IL-6, which seemed to be the cause of leukocytosis. Perhaps, both cases indicate papillary thyroid cancer as a precursor of anaplastic.

Moreover, tumor cells were positive for CEA with elevated CEA serum levels. CEA is produced as an expression of CEA-related cell adhesion molecule 5 gene and is found in 90% of gastrointestinal cancers, 70% of lung cancers, and 50% of breast cancers [25]. Elevated levels may also be seen in ovarian cancer, appendix, mucinous cystadenoma, and medullary thyroid carcinoma. Since only single cases of CEA-positive papillary thyroid cancer have been observed, its significance remains uncertain.

4. Conclusion

Tumor-related leukocytosis is associated with tumor aggressiveness and probably poor prognosis. When dealing with patients with unexplained leukocytosis, a high level of suspicion is required for this entity.

**Data Availability**

The datasets used during the current study are available from the corresponding author on reasonable request.

**Additional Points**

Tumor-related leukocytosis could represent a form of paraneoplastic syndrome caused by cytokine secretion from tumor cells.

**Consent**

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

**Conflicts of Interest**

The authors have no conflicts of interest to declare.

**Authors’ Contributions**

S.L. perceived the idea, collected the samples, processed the data, drafted the manuscript, and designed the figures. K.S. was involved in planning and supervised the work. T.K. and C.T. performed the histopathological analysis and designed
the histopathologic figures. I.K. was the supervising physician. All authors discussed the results and commented on the manuscript.

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