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Case Report

Paraneoplastic Neutrophilic Leukocytosis in a Rare Variant of Papillary Thyroid Carcinoma: A Diagnostic Dilemma with Fatal Outcome

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Abstract

Background: *Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy, typically associated with a favorable prognosis. However, rare histological variants and unusual clinical presentations can pose significant diagnostic challenges. Paraneoplastic neutrophilic leukocytosis is an uncommon manifestation in thyroid malignancy and may mimic infectious or inflammatory conditions, leading to diagnostic confusion.*

Case Description: *We report a case of an adult male patient with an advanced, rare variant of papillary thyroid carcinoma who presented with persistent and marked neutrophilic leukocytosis. Despite extensive evaluation, no evidence of infection or hematologic disorder was identified. Histopathological examination confirmed a rare aggressive variant of PTC. The paraneoplastic leukocytosis was attributed to tumor-related cytokine production. The disease progressed rapidly, culminating in a fatal outcome despite supportive management.*

Discussion: *Paraneoplastic leukocytosis is a rare but important clinical entity in thyroid malignancies, particularly in aggressive variants. It results from tumor secretion of granulocyte colony-stimulating factors and often indicates advanced disease with poor prognosis. Recognition of this paraneoplastic phenomenon is essential to avoid unnecessary antimicrobial therapy and to anticipate rapid disease progression.*

Conclusion: *This case highlights the diagnostic dilemma posed by paraneoplastic neutrophilic leukocytosis in rare variants of papillary thyroid carcinoma. Awareness of this uncommon presentation is crucial for timely diagnosis, appropriate management, and prognostication.*

Keywords: *Papillary thyroid carcinoma, Anaplastic thyroid carcinoma, Leukocytosis, Paraneoplastic syndrome, leukamoid reaction, GM-CSF, IL-6.*

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Introduction:

Marked elevation of white blood cells (WBC), particularly neutrophils, often points clinicians toward severe acute infections, inflammatory processes, or myeloproliferative neoplasms (MPNs). In patients without hematologic malignancy, however, neutrophilia may instead be attributed to bone marrow involvement, nonspecific inflammation, medication effects, or paraneoplastic syndromes. Various malignant solid tumors can also produce extreme leukocytosis, creating significant diagnostic challenges[1].

Persistent WBC counts exceeding 50,000/ µL in such settings are termed leukemoid reactions. These cases are diagnostic dilemmas because they require exclusion of chronic myeloid leukemia and chronic neutrophilic leukemia, as the conditions can appear similar[2]. Leukemoid paraneoplastic reaction (LPR) is another poorly defined phenomenon, triggered by cytokines produced by tumors—most notably granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage–CSF (GM-CSF), interleukin-1a (IL 1a), and IL 6[3, 4].

Reports describe LPR in patients with various solid tumors, including large cell lung cancer, sarcoma, bladder carcinoma, skin cancer, melanoma, and pancreatic cancer[5, 6]. Anaplastic thyroid carcinoma (ATC), a highly aggressive malignancy, has also been associated with marked leukocytosis linked to tumor-driven production of G CSF, GM CSF, and IL 6[7, 8]. Elevated and progressively rising WBC levels are correlated with worse survival outcomes[9].

Despite this, only a limited number of reports describe leukocytosis as the primary presenting feature leading to an eventual ATC diagnosis. Here, we present a case of metastatic recurrent papillary carcinoma thyroid in which a dramatic increase in WBC count, predominantly granulocytic, initially treated as severe acute infection. But ultimately clinicians procced to the diagnosis of paraneoplastic syndrome due to disseminated Anaplastic Thyroid carcinoma leading to grave outcme in a short interval.

Case Report:

In September 2025, a 59-year-old male patient, suffering from recurrent metastatic papillary carcinoma of the thyroid, presented to CMH Dhaka with a large axillary abscess. At that time, the patient was febrile and complained of mild pain at the abscess site. The abscess was drained, and pus was sent for culture and sensitivity, which showed no growth of microorganisms. During the disease course, the patient's condition deteriorated significantly, and he developed breathing and swallowing difficulties.

The patient had a known history of recurrent papillary thyroid carcinoma since 2019. He underwent total thyroidectomy with repeated bilateral neck dissections approximately six times. He also received radioiodine therapy four times. Despite aggressive treatment, tumor progression continued. Lung metastasis was identified in 2020. He was BRAF-V600E positive, and due to this genetic mutation, the disease was refractory to radioiodine therapy. His last surgical treatment was performed in January 2025. Biopsy of specimens revealed a tumor with significant atypical cells and focal squamoid features. These indicate that he had an Anaplastic transformation of Papillary carcinoma thyroid. Recently, he was started on targeted therapy with oral Cabozantinib. Prior to this, due to tumor progression and repeated surgeries, he developed right-sided vocal cord palsy, resulting in hoarseness of voice and difficulty swallowing liquid food.

Initial laboratory investigations revealed a total WBC count of 25.6 × 10y /L with marked neutrophilia. No blasts or immature white cells were found. Mild anemia was present, with hematocrit 25.9% and hemoglobin 8.7 g/dL. ESR and C-reactive protein levels were elevated. Blood and urine cultures were initially negative. Thyroid function tests were normal. Ultrasound of the neck revealed small nodules on both

sides. CT chest showed massive pleural effusion in the right lung along with multiple lung nodules scattered throughout both lung fields. A drain tube was inserted, and hemorrhagic pleural fluid was aspirated. Pleural fluid cytology was negative for organisms. CT scan of the brain revealed brain metastasis near the brainstem, causing left-sided hemiparesis.

Right vocal cord paralysis and partial airway obstruction led to inspiratory wheezing. The patient's condition rapidly worsened. Repeated blood and urine cultures later became positive for microorganisms. Despite broad-spectrum antibiotics, the infection could not be controlled, and neutrophilic leukocytosis progressed. His WBC count rose continuously, reaching 83.7 × 10y /L.

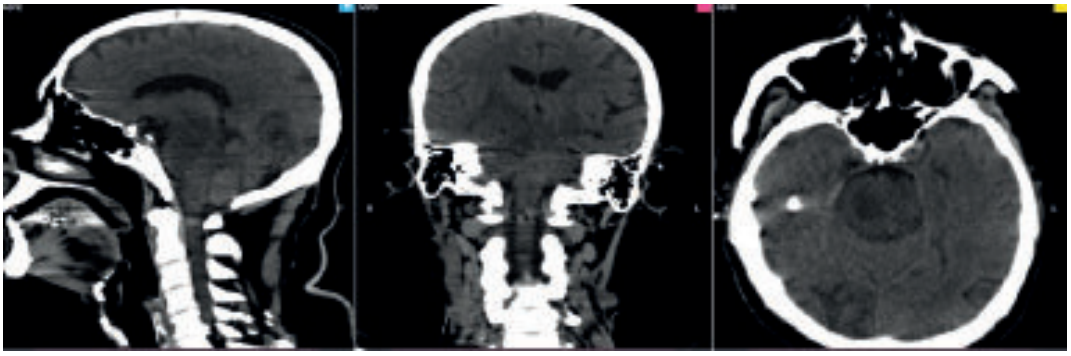

Figure 1: *CT scan of brain showing metastasis of tumor to brain near the brainstem.*

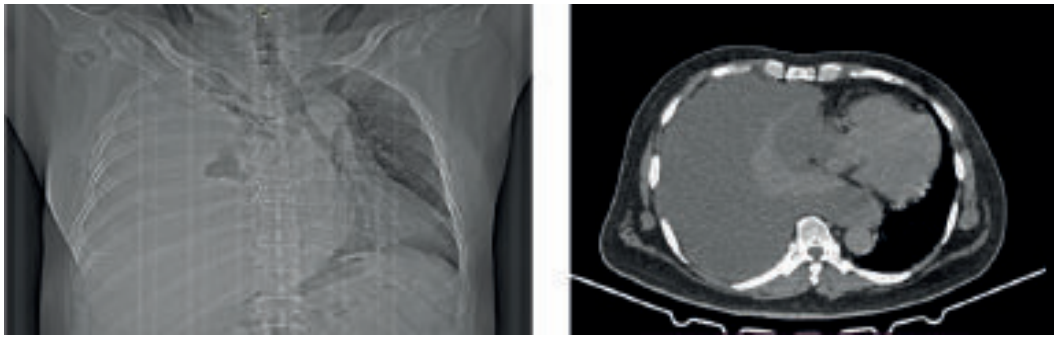

Figure 2: *CT scan of lung showing massive pleural effusion right lung shifting the mediastinum to left.*

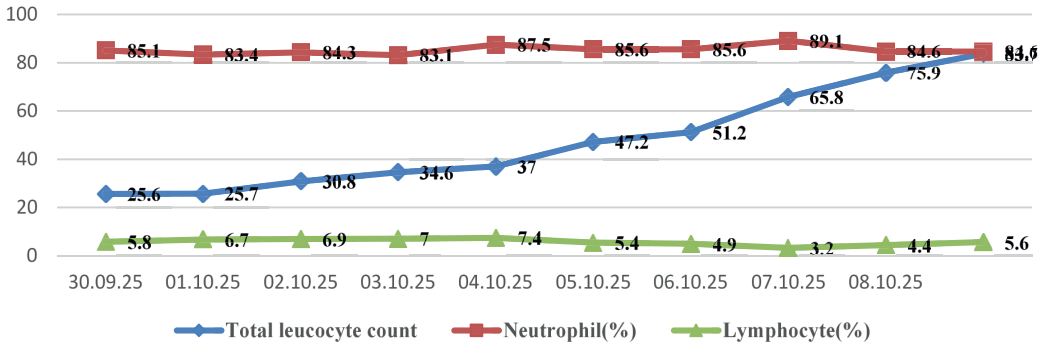

Figure 3: *Flow chart of the number of Total Leucocyte count, Neutrophil and Lymphocyte from diagnosis to the patient's passing (all count in X10^9/L)*

Due to his deteriorating condition, bone marrow study was not performed. His anemia worsened, and he received red blood cell transfusions. Searching for the cause of leukocytosis serum IL-6 was measured. IL 6 levels were markedly elevated, (ranging from 76 pg/ml to 120 pg/ml) in the absence of any hematologic malignancy.

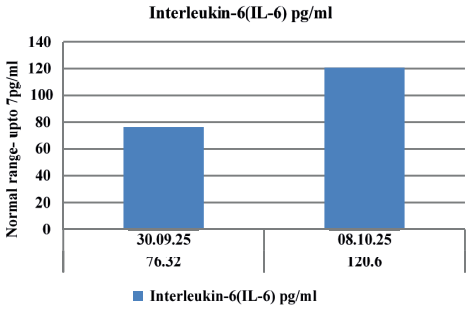

Figure 4: *Demonstrated graphical rise of serum IL-6 level*

Procalcitonin levels were also checked and found to be within normal limits, which excluded the probability of septicemia.

Table I
Showing the level of measured serum Procalcitonin

Serum Procalcitonin	Level
Normal	<0.1 ng/ml to <0.5 ng/ml
Elevated	>2.0 ng/ml
1st measured during hospital admission	0.38 ng/ml
2nd measured for ongoing treatment	0.84 ng/ml

Despite all possible supportive measures, the patient's condition continued to decline. Respiratory insufficiency worsened, requiring oxygen support. He eventually suffered cardiac arrest and was placed on life support. After two days of intubation, he expired due to cardiac arrest, completing 15 days of hospital admission.

Discussions

Our 59 year old euthyroid, recurrent metastatic papillary carcinoma thyroid patient, presented with a large axillary region abscess accompanied by profound leukocytosis, and neutrophilia, which prompted hospital admission. The workup, revealed that the markedly elevated white blood cell count was due to a leukemoid paraneoplastic syndrome. The patient was diagnosed with aggressive anaplastic thyroid carcinoma (ATC) transformed from papillary thyroid carcinoma, which had metastasized to the lungs and brain. He also had elevated C-reactive protein levels, which were attributed to aging, anemia, and malignancy, after excluding infection, inflammation, and myeloproliferative disorders. Although the anemia could have been associated with bone marrow metastasis, further diagnostic procedures such as bone marrow biopsy or positron emission tomography–computed tomography (PET/CT) were considered but ultimately not performed due to his declining health status and reluctance to undergo additional investigations. Despite advancements in antineoplastic therapies, ATC continues to carry a poor prognosis.

Leukocytosis persisted (WBC: 83.7 × 10y / L), while mature and immature white blood cells were not detected. Erythrocyte sedimentation rate (ESR), C reactive protein (CRP), and carcinoembryonic antigen (CEA) were elevated. After extensive evaluation by internal medicine, infectious diseases, and hematology departments, leukemia and other myeloproliferative disorders were excluded. To determine the cause of leukocytosis, serum interleukin 6 (IL 6) was measured. IL 6 was markedly increased (120 pg/ml; normal 7 pg/ml) despite the absence of any hematologic malignancy.

In our patient, serum IL 6 levels were markedly increased than the upper limit of normal, which

may explain the extreme leukocytosis observed. While leukocytosis is often associated with myeloproliferative neoplasms, it can also be seen though rarely in solid tumors and exceptionally in ATC. ATC with squamous differentiation is particularly uncommon. Because the tumor lacked a specific immunophenotype, the distinction from true squamous carcinoma relied largely on clinical, radiological, and histological findings, with the primary mass located in the thyroid gland, as observed in this case.

Various factors such as infection, inflammation, malignancy, severe hemorrhage, or acute hemolysis may contribute to leukemoid reactions. Paraneoplastic leukemoid reaction typically arises when a non hematologic tumor secretes cytokines without bone marrow infiltration. Many malignancies may show mild leukocytosis, but irregular cytokine production, including G CSF, GM CSF, IL 3, IL 6, and TNF á, can trigger significant granulocytosis[7, 8]. Cytokine producing tumors may develop rapidly because their proliferating cells expand faster than non producing cells due to enhanced autocrine growth signaling. Tumor related leukocytosis may also result from bone marrow granulocytosis or impaired myeloid cell differentiation. Tumor derived myeloid suppressor cells can protect tumor survival and promote cancer progression, and patients with high WBC counts generally have a poorer prognosis.

Leukocytosis may appear at any stage of malignancy—before diagnosis, during active disease, or at recurrence. Lung, kidney, gastrointestinal, hepatobiliary, melanoma, and some head and neck cancers can present with paraneoplastic leukocytosis[5, 6]. Thyroid cancers, including papillary and anaplastic variants, have also been associated with this phenomenon. CEA, produced by the CEA related cell adhesion molecule 5 genes, is increased in up to 90% of gastrointestinal cancers, 70% of lung cancers, and 50% of breast cancers[7, 8]. Elevated levels may also be seen in ovarian cancer, appendix tumors, mucinous cystadenoma, and medullary thyroid carcinoma.

Reports describe cases of squamous cell carcinoma and anaplastic thyroid carcinoma presenting with marked leukocytosis and hypercalcemia. Tumor cells in these cases produced G CSF, IL 1á, and PTH rP, indicating a paraneoplastic syndrome. Elevated G CSF has been observed in several anaplastic thyroid carcinoma cases. Only a few reports have assessed IL 6, with most showing normal levels.

In many patients, upper airway infiltration caused by ATC can result in obstruction, making respiratory support essential. Most cases require a multimodal treatment plan often combining radiotherapy and chemotherapy to improve survival and quality of life[9- 12]. Numerous solid tumors, including those of the lung, ovary, gallbladder, kidney, colon, and stomach, are known to release cytokines such as G CSF, GM CSF, IL 1, and IL 6, which contribute to elevated WBC levels, particularly neutrophils. When this rise is significant, it is referred to as LPR. However, the appearance of severe leukocytosis as a primary feature in ATC is exceptionally rare.

Multiple studies indicate that patients with ATC who develop marked leukocytosis, especially when their WBC count exceeds 10,000/ìL, often experience worse survival outcomes. For this reason, WBC levels have been proposed as a potential prognostic marker, along with factors such as distant metastasis, platelet count, and patient age[9, 13]. Although leukocytosis was previously linked to squamous thyroid cancer in Japan in 1979[10], the first documented association between ATC and elevated CSF levels was published in 1984[15]. Subsequent research

has shown that elevated GM CSF and other cytokines including IL 6, IL 1, G CSF, and M CSF are also related to ATC[7, 8]. Only a limited number of reports have connected ATC with cytokine driven leukocytosis, and many such studies have had inconsistent findings[14, 16]. IL 6, for example, has been reported as both elevated and normal in different cases[7, 8]. No related publications have emerged from Greece except for a case involving CSF producing papillary thyroid carcinoma from the same department. That case represented the first instance of aggressive ATC in Greece associated with a markedly elevated WBC count due to LPR[17]. A rare case of aggressive papillary thyroid carcinoma with neutrophilia has been documented. Serum GM CSF elevation suggested cytokine producing tumor activity. Bone marrow biopsy demonstrated infiltration by papillary thyroid carcinoma[18]. Another two articles published with the information regarding leucocytosis in advanced papillary carcinoma thyroid. They stated that leucocytosis in case of advanced papillary carcinoma thyroid is alarming, as outcome is grave.[19, 20]

Conclusion

Paraneoplastic neutrophilic leucocytosis associated with rare variants of papillary thyroid carcinoma represents a diagnostic challenge due to its ability to mimic infectious or inflammatory conditions. Early recognition of this atypical presentation is crucial for prompt evaluation, appropriate clinical decision making, and timely therapeutic intervention. This case highlights the importance of maintaining a high index of suspicion when unexplained leucocytosis accompanies thyroid malignancy, particularly in recurrent or aggressive disease. Improved understanding of such unusual paraneoplastic manifestations can aid clinicians in avoiding misdiagnosis, guiding oncologic management, and ultimately improving patient outcomes.

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