

Poor prognosis of urothelial carcinoma in patients presented with persistent paraneoplastic leukocytosis with anemia

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Abstract

Introduction: Paraneoplastic leukocytosis is a rare manifestation of urological cancer. This condition is well associated with the poor prognosis in other solid tumors. Anemia is the most common hematological manifestation of cancer, affecting 40%–64% of patients with cancer. This condition is also well associated with a poor prognosis. The goal of this research is to determine the clinical presentation and fate of individuals with urothelial carcinoma who have persistent paraneoplastic leukocytosis and anemia.

Methods: From January 2014 to December 2020, a retrospective cohort of patients with a histological result of urothelial carcinoma was collected. Data were extracted from a single National Cancer Center Hospital in Indonesia. Persistent leukocytosis is defined as a leukocyte count $\geq 20,000/\text{mL}$ on at least two occasions with a minimum interval of 30 days. Anemia is defined using the WHO definition of anemia. Urinalysis, chest X-ray, and other blood tests were performed to exclude other probable causes of leukocytosis.

Results: Thirteen of 123 patients screened presented with persistent paraneoplastic leukocytosis and anemia. All patients presented with bladder cancer, with two patients (15.4%) presented with a mixed histological urothelial carcinoma. During the trial, all of the patients died, with a median survival of 20 days after the beginning of paraneoplastic leukocytosis with anemia.

Conclusions: Persistent paraneoplastic leukocytosis and anemia in a patient with urothelial carcinoma are a rare condition that is associated to a poor prognosis and a lower median overall survival time.

Keywords: Anemia, bladder cancer, overall survival, paraneoplastic leukocytosis, urothelial carcinoma

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Received: 07.12.2021, **Accepted:** 10.05.2022, **Published:** 07.09.2022

INTRODUCTION

Paraneoplastic syndrome is a condition that may occur in all types of urological malignancies but rarely occurs in bladder cancer.^[1] These syndromes can manifest as hematological abnormalities such as leukocytosis, thrombocytosis, and anemia.^[1-3]

Paraneoplastic leukocytosis is a rare urological cancer symptom, appearing in 3% of patients with renal cell carcinoma and 1% of urothelial carcinoma.^[4,5] This is more common in solid cancers, including lung cancer,^[6,7] sarcoma,^[7] and skin cancer.^[7,8] The most prevalent hematological symptom of cancer is anemia, affecting

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How to cite this article: Warli SM, Andy A, Prapiska FF, Siregar GP, Sihombing B. Poor prognosis of urothelial carcinoma in patients presented with persistent paraneoplastic leukocytosis with anemia. *Urol Ann* 2022;14:328-31.

Access this article online	
Quick Response Code:	Website: www.urologyannals.com
	DOI: 10.4103/ua.ua_187_21

40–64% of cancer patients.^[9] These symptoms have been associated with a poor prognosis in terms of outcomes and overall survival.^[5-7,10]

METHODS

From January 2014 to December 2020, a retrospective cohort of patients with a histological result of urothelial carcinoma from urological cancer in the renal, pelvic, ureter, and bladder was collected. Data were extracted from a single National Cancer Center Hospital in Indonesia. The ethics committee granted ethical permission before the start of the study.

Persistent leukocytosis in this study is defined as a leukocyte count $\geq 20,000/\text{mL}$ on at least two occasions with a minimum interval of 30 days. The WHO definition of anemia is used to describe anemia.^[11] Hemoglobin levels of less than 13.0 g/dL in a male and less than 12.0 g/dL in a female are considered anemia. Urinalysis, chest X-ray, and other blood tests were performed to exclude other probable causes of leukocytosis.

RESULTS

A total of 123 patients with urothelial carcinoma on histology were screened. Thirteen patients presented with persistent paraneoplastic leukocytosis and anemia. Patient characteristics are shown in Table 1. Two individuals had mixed histology with squamous involvement of the tumor, whereas the other had pure urothelial cell carcinoma histology.

Leukocytosis patients are dominantly neutrophil, with all patients having neutrophilia. All patients have anemia, one patient suffering mild anemia, six suffering moderate anemia, and six suffering severe anemia. Seven out of 13 patients also presented with thrombocytosis.

Table 2 depicts the disease course of the patients who took part in the research. During the trial, all of the patients died, with a median survival of 20 days after the beginning of paraneoplastic leukocytosis with anemia. All seven patients receiving chemoradiation were given gemcitabine-cisplatin regimen with radiotherapy for 35–36 times.

DISCUSSION

Patients with persistent paraneoplastic leukocytosis and anemia have a terrible prognosis, with a median survival of only 20 days, according to this study. Izard *et al.* found a similar finding in a study with persistent leukocytosis in urothelial carcinoma, with a median survival of 71 days

Table 1: Study patient characteristics

	Total (n=13)
Age (years), mean (SD)	54.92 (9.58)
Sex, n (%)	
Male	8 (61.5)
Female	5 (38.5)
Primary tumor site, n (%)	
Bladder	13 (100)
Pelvic ureter	0
Histological, n (%)	
Urothelial	11 (84.6)
Mixed	2 (15.4)
Leukocyte ($\times 10^3/\mu\text{L}$), median (minimum-maximum)	
First visit	27.8 (20.8-51.3)
Second visit	30.1 (20.0-66.8)
Neutrophil ($\times 10^3/\mu\text{L}$), median (minimum-maximum)	
First visit	26.61 (16.6-84.6)
Second visit	27.4 (17.1-61.9)
Lymphocyte ($\times 10^3/\mu\text{L}$), median (minimum-maximum)	
First visit	1.2 (0.3-7.5)
Second visit	1.34 (0.42-5.4)
NLR	
First visit	23.125 (5.24-65.87)
Second visit	21.375 (7.83-130.81)
Hemoglobin (g/dL), mean (SD)	7.61 (1.73)

SD: Standard deviation, NLR: Neutrophil-to-lymphocyte ratio

after leukocytosis. All nine patients also presented with anemia and bladder as the majority of primary cancer sites in the study.^[5]

Increased production of granulocyte colony-stimulating factor (G-CSF) is related to persistent paraneoplastic leukocytosis. Myelopoiesis and the expansion of myeloid-derived suppressor cells and neutrophils are induced by G-CSF secretion. A high neutrophil level will restrict T-cell proliferation, causing a lower lymphocyte, subsequently causing a higher neutrophil-to-lymphocyte ratio (NLR) level.^[12] This condition is rare, although only several case reports have shown leukocytosis in a patient with bladder cancer due to a G-CSF-producing tumor.^[13-15] G-CSF has also been associated to tumor cell proliferation which is aggressive and has a poor clinical outcome.^[15] This condition can explain the cause of poor prognosis and short survival in this study.

As G-CSF promotes tumor progression and metastasis, tumors that produce it have a poor prognosis.^[16] A study by Kowanetz *et al.*^[17] shows that exposure to a high level of G-CSF for an extended time, simulating a G-CSF-producing tumor, enhances metastasis by mobilizing myeloid-derived suppressor cells from the bone marrow into distant organs, resulting in a protumorigenic milieu for metastasis. Anti-G-CSF also shows a significantly reduced risk of metastasis in mice.^[17]

Table 2: Disease course of patient with persistent leukocytosis and anemia

Patients	Age (years)	Sex	Clinical stage	Histology	Survival after leukocytosis and anemia (days)	Treatment
1	67	Female	T2bNOM0	Urothelial	67	Cystectomy
2	39	Female	T4aNOM0	Urothelial	12	Chemoradiation
3	59	Male	T2NOM0	Urothelial	138	TURBT
4	57	Male	T4N2M1	Urothelial	14	Chemoradiation
5	60	Male	T4aNOM0	Urothelial	57	TURBT + chemoradiation
6	63	Male	T4aN3M0	Urothelial	17	TURBT + chemoradiation
7	43	Male	T4aN1M0	Urothelial	278	TURBT
8	53	Male	T4aNOM0	Urothelial	12	TURBT
9	61	Female	T2NOM0	Urothelial	214	TURBT + chemoradiation
10	54	Female	T4bN1M0	Urothelial	20	Chemoradiation
11	37	Female	T4bN1M1	Mixed	12	Chemoradiation
12	57	Male	T4aNOM1	Urothelial	14	Cystectomy
13	64	Male	T2N1M0	Mixed	74	Cystectomy

TURBT: Transurethral resection of bladder

High NLR levels on the study patients may also cause a poor prognosis. In a study by Viers *et al.*, high NLR (≥ 2.7) in patients with urothelial cancer has an increased risk of mortality (Hazard Ratio = 1.03; $P = 0.01$).^[18] A high NLR is associated with a lower lymphocyte-associated immunological response and a higher neutrophil-dependent inflammatory reaction. A high level of neutrophils is related to a larger number of cytokines including interleukin-1, interleukin-6, and tumor necrosis factor, which promote vascular angiogenesis. A low lymphocyte level reflects a lower T-cell level, indicating a weak lymphocyte-mediated immune response to malignancy.^[19] All patients in this study have an NLR of higher than 15, which may cause a dysregulated immune response to cancer, causing rapid progression and poor prognosis.

Leukocyte level may be affected by the treatment given to the patient. Case reports also have shown that cystectomy will reduce leukocytosis level but will gradually increase after due to the natural progression of G-CSF-producing tumor.^[20,21] Chemoradiation received by the patient may cause neutropenia and lymphocytosis, subsequently reducing the NLR level.^[22,23] This condition did not occur in the patients as all patients had a high NLR level. The leukocytosis presenting is likely caused by urothelial cancer activity.

Anemia is also attributed to lower overall survival and cancer-specific survival. A meta-analysis by Luo *et al.* shows that anemia significantly lowers cancer-specific survival (HR = 2.21; 95% confidence interval [CI]: 1.83–2.65), recurrence-free survival (HR = 1.87; 95% CI: 1.59–2.20), and overall survival (HR = 2.04; 95% CI: 1.76–2.37).^[10] Hypoxia in the tumor microenvironment caused by anemia will induce genes such as p53, Vascular endothelial growth factor (VEGF), and Hypoxia-inducible factor 1 (HIF-1). A high VEGF level has been associated with bladder cancer progression and has been associated with a lower incidence of recurrence-free survival.^[24] HIF-1 from hypoxia can trigger angiogenesis that predicts

poor prognosis in patients with urothelial carcinoma.^[25] Mutation in TP53, the gene encoding p53 tumor suppressor protein will cause dysfunction in the apoptotic potential and is significantly associated with relapse-free survival of urothelial carcinoma.^[26]

G-CSF affects erythropoiesis by inhibiting bone marrow erythropoiesis and enhancing splenic erythropoiesis.^[27] In a study by Papaldo *et al.*,^[28] patients who received G-CSF had lower hemoglobin levels than others who did not. Patients who got more G-CSF injections had lower hemoglobin levels according to the study.^[28] Anemia on this study patients may be caused by G-CSF effect on erythropoiesis

Cancer-induced anemia can be caused by multiple etiologies and is usually multifactorial.^[29] Anemia can arise from the treatment received by the patient. Postcystectomy and transurethral resection of bladder (TURBT) may cause blood loss and anemia. This condition, although is usually only short-term after the operation.^[30,31] Chemotherapy using gemcitabine-cisplatin and radiotherapy causes grade 3 or 4 anemia in 27%–40% of patients.^[23,32-34]

CONCLUSIONS

Persistent paraneoplastic leukocytosis and anemia in a patient with urothelial carcinoma are rare, and it is associated to a poor prognosis and a 20-day median overall survival.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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