Fever and leukemoid reaction in bladder cancer: A case report

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Abstract. The current study presented and analyzed the clinical data of a patient who had bladder cancer complicated by a leukemoid reaction, aiming to discuss the diagnosis, treatment and underlying mechanism of leukemoid reactions in bladder cancer. The patient had a significant smoking history and underwent six transurethral resections of bladder tumors between August 2016 and October 2023. Pathological diagnosis deteriorated from low-grade papillary urothelial carcinoma (UC) to high-grade papillary urothelial carcinoma. The patient did not adhere to regular cystoscopy or routine follow-up cystoscopy and declined radical cystectomy. The most recent computed tomography scan revealed the following: i) Multiple tumors in the bladder; ii) invasion at the bilateral ureteral orifices; iii) dilation of the bilateral renal pelvis and ureters; and iv) multiple lymphadenopathies in the pelvis and along the right iliac artery. Following cystoscopy examination and urethral catheter placement, the patient's creatinine level gradually decreased; however, there was an increase in body temperature and white blood cell count. The patient was diagnosed with a leukemoid reaction secondary to bladder cancer. The patient refused a bone marrow biopsy and palliative care was administered. The patient passed away in October 2023. Cases of bladder cancer complicated by a leukemoid reaction are rarely reported clinically. Even after surgical resection, the prognosis remains poor. Monitoring granulocyte-colony stimulating factor (G-CSF) levels in blood can aid in predicting the condition of the patient's health. Blocking the G-CSF signaling pathway might serve as a future therapeutic target for bladder cancer complicated by a leukemoid reaction.

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Introduction

Bladder cancer ranks as the 9th most common malignant tumor globally and the 7th among men. Muscular invasive bladder cancer is a particularly lethal form, ranking 13th in mortality among malignant tumors (1). Smoking is a well-evidenced risk factor for bladder cancer, elevating the risk by two to three times. The risk of bladder cancer escalates with both the duration and quantity of smoking (2-4). Common treatments for bladder cancer include c(TURBT), bladder irrigation and radical cystectomy.

Paraneoplastic syndromes refer to a number of symptoms that occur in patients with malignant tumors that cannot be readily explained by local invasion or distant metastasis of the tumor. Instead, these symptoms might be related to primary tumor autocrine hormones or cytokines. A white blood cell (WBC) count >$50x10^9$/l, in the absence of leukemia or infection, is defined as a leukemoid reaction (5). The leukemoid reaction has been reported in nearly all solid tumor types as a paraneoplastic syndrome, with an incidence ranging from 1 to 4% (6). Furthermore, a leukemoid reaction is frequently observed clinically in advanced stages of highly invasive and metastatic cancer (7-9). Bladder cancer, especially urothelial carcinoma, is rarely associated with a leukemoid reaction. Globally, <40 cases have been reported in the literature in the past 40 years, with most patients experiencing poor prognosis within months; in the present study seven of these cases were summarized in Table I.

In the present report, a rare case of bladder cancer complicated by fever and a leukemoid reaction was presented. The clinical and histological features were described, and the relevant literature on these rare cases was reviewed.

Case report

The current patient had undergone several TURBT procedures and experienced hematuria and decreased urine output for 2 months prior his admission in the Shanghai Municipal Hospital of Traditional Chinese Medicine (Shanghai, China). The patient had been treated in other hospitals before and the early examination report was incomplete. A 62-year-old male native of Shanghai with a 40-year history of smoking, the patient presented with hematuria in August 2016. A cystoscopy examination revealed a cauliflower-like growth on the right wall of the bladder. Subsequently, a TURBT was

performed. Postoperative pathological diagnosis confirmed papillary urothelial carcinoma (UC), staged as pTa (low grade) according to the American Joint Committee on Cancer TNM classification system (10).

Following the procedure, the patient began a standard regimen of intravesical epirubicin instillation (50 mg weekly for 8 weeks, then monthly for 10 months), with surveillance cystoscopy scheduled at 3-month intervals. During the year, the patient also underwent routine cystoscopy examinations, which revealed no evidence of recurrent bladder cancer. However, in October 2017, during a routine cystoscopy examination, tumors were found on the right and top wall of the bladder. Subsequently, the patient underwent another TURBT. Postoperative pathological diagnosis confirmed papillary urothelial carcinoma, UC, pTa, low grade. The same adjuvant intravesical epirubicin regimen was administered (50 mg weekly for 8 weeks, then monthly for 10 months), alongside surveillance cystoscopy every 3 months.

In March 2019, the patient presented with visible hematuria. Cystoscopy examination revealed tumors on the right and top walls of the bladder. Another TURBT was performed. Pathological diagnosis following this surgery confirmed papillary urothelial carcinoma, high grade, non-muscle invasive. In June 2019, during a routine cystoscopy examination, tumors were found on both walls of the bladder and another TURBT was performed. Postoperative pathological diagnosis confirmed papillary urothelial carcinoma, high grade. In August 2020, during his regular cystoscopy examination, tumors were found once again on the left, right and top walls of the patient's bladder. The patient refused further treatment, such as radical cystectomy, and no subsequent follow-up visits were conducted.

In May 17 2022, the patient was admitted to Shanghai Municipal Hospital of Traditional Chinese Medicine due to hematuria. Cystoscopy examination revealed multiple tumors in the urethra, trigone and both walls of the bladder. A TURBT was performed in May 2022. Postoperative pathological diagnosis confirmed papillary urothelial carcinoma, high grade (Fig. 1). Post-surgery treatment consisted of intravesical instillation of epirubicin at a dose of 50 mg per session, administered once weekly for 8 weeks. In July 2022, the patient was admitted for follow-up and underwent a cystoscopy examination, which again revealed multiple tumors in the urethra, trigone and both walls of the bladder. A radical cystectomy was recommended; however, the patient refused. Instead, another TURBT was performed the next day, with the pathological diagnosis once more indicating high grade papillary urothelial carcinoma (Fig. 2). After the surgery, the patient did not adhere to regular bladder irrigation or follow-up cystoscopy examinations.

In August 2023, the patient started experiencing painless visible hematuria and decreased urine output. The patient was then admitted to Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine (Shanghai, China) in October 2023. Upon admission, the patient's body temperature was recorded at 38˚C. Urinalysis revealed 500 leukocytes/μl and 3+ leukocyte esterase. Blood analysis revealed a WBC count of 67.83x10^9/l with neutrophils at 64.5x10^9/l, C-reactive protein (CRP) at 150.43 mg/l, and creatinine at 1,006 μmol/l.

Urology computed tomography (CT) scan results revealed: i) Multiple tumors in the bladder (Fig. 3A); ii) multiple lymphadenopathies in the pelvis and along the right iliac artery (Fig. 3B); iii) bilateral ureter bladder entrance invasion (Fig. 3C) resulting in bilateral renal pelvis and ureter dilatation (Fig. 3D). Meropenem was administered as anti-infective therapy at a dosage of 0.5 g via intravenous infusion every 8 h. Cystoscopy performed under local anesthesia identified: Multiple tumors in the posterior urethra, bladder neck and bladder walls, with no tumors observed in the bilateral ureters. A biopsy sample was obtained, and a urinary catheter was placed. Pathological diagnosis confirmed high grade papillary urothelial carcinoma with massive necrosis (Fig. 4).

The day after admittance (October 2023), the patient's body temperature increased to 39.2˚C. Blood analysis revealed marked leukocytosis with neutrophilia, significantly elevated inflammatory markers, and acute kidney injury. Admission laboratory results are presented in Table II. The patient refused a bone marrow biopsy chest CT, bone scan and PET-CT. Considering the patient's deteriorating health and the high risk associated with surgery and anesthesia, palliative care was administered. The patient's body temperature dropped to 38.6˚C following an intramuscular injection of 2 ml of compound aminophenazone and barbital injection (containing 200 mg aminophenazone, 40 mg antipyrine and 18 mg barbital) during nighttime. At 2 days post-admittance (October 2023), the patient's body temperature increased again to 40˚C. Blood analysis revealed a WBC count of 53.89x10^9/l with neutrophils at 50.87x10^9/l, CRP at 60.65 mg/l and creatinine at 480 μmol/l. The patient's white blood cells were too high, so urosepsis was ruled out. A urine culture was not performed following the shift to palliative care. The patient passed away that afternoon. Because the Shanghai Municipal Hospital of Traditional Chinese Medicine hospital has not yet acquired the relevant technology, granulocyte-colony stimulating factor (G-CSF) levels in specific patients cannot be measured and tracked for a long time. The timeline of the disease progression is summarized in Table III, and changes in temperature, WBC count, CRP and creatinine are illustrated in Fig. 5 [prepared using GraphPad Prism (version 9.5; Dotmatics)].

Discussion

In urological malignancies, renal tumors are most frequently associated with a leukemoid reaction. By contrast, bladder tumors, particularly urothelial carcinoma, are rarely linked to such reactions (11). The incidence of a leukemoid reaction tends to be higher in cancer patients who are older or have higher-grade tumors. A leukemoid reaction, according to the type of leukocytes involved, can be classified into: Neutrophilic, lymphocytic, monocytic or eosinophilic, with neutrophilic leukemoid reaction being the most prevalent (12). The leukocyte alkaline phosphatase score is often helpful in diagnosing a leukemoid reaction; however, its utility may vary, especially in identifying chronic neutrophil leukemia (13). Iyengar *et al* (14) proposed and established a supervised machine learning model (based on a support vector machine algorithm) that effectively distinguishes between leukemic reactions and myeloid malignancies using routine clinical data with a sensitivity of 96% and a specificity of 95.9%.

Table I. Cases in the literature.

Author, year	Age/sex	Tumor type	White blood cell count	Prognosis	(Refs.)
Turalic *et al*, 2006	51/woman	Poorly differentiated bladder carcinoma with G-CSF production	14,000/ml then increased to 34,000/ml	Deceased before additional treatment could be instituted	(36)
Kato *et al*, 2016	38/woman	Urothelial cell carcinoma with G-CSF and PTHrP production	107,000/mm^3	Deceased within 3 months of initial symptoms	(37)
Harsha *et al*, 2020	59/man	High-grade urinary bladder cancer	Significantly elevated, mainly eosinophils	Deteriorated rapidly, deemed inoperable, referred for palliative management	(12)
Perez *et al*, 2009	63/man	High-grade urothelial carcinoma invasive into muscularis propria	42,000/μl with 37,000/μl neutrophils	Died nearly 4 weeks after surgery, 4 months after initiation of neoadjuvant chemotherapy	(19)
Shapiro *et al*, 2014	43/man	Muscle-invasive squamous cell carcinoma	76,000/μl with predominant polymorphonuclear cells	Died within 1 month after hospital readmission with similar symptoms	(11)
He *et al*, 2014	64/man	Transitional cell carcinoma, Grade 3	58,400/mm^3 with neutrophil granulocyte count of 54,900/mm^3	Died of systemic metastasis within 6 months after cystectomy	(38)
Kumar *et al*, 2014	39/woman	Invasive high-grade urothelial carcinoma	57800/μl	Death within 10 months from first diagnosis	(7)

G-CSF, granulocyte-colony stimulating factor; PTHrP, parathyroid hormone-related protein.

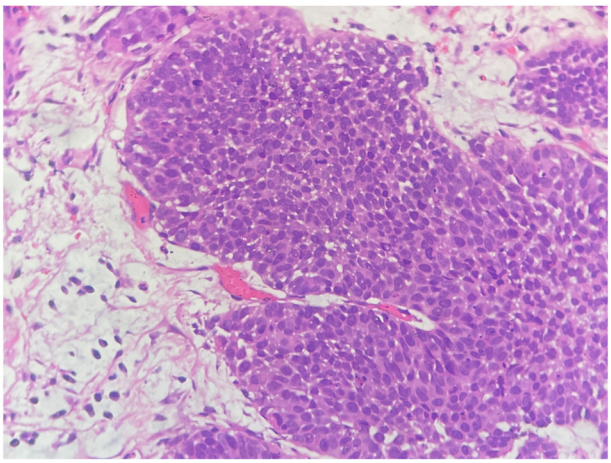

Figure 1. Transurethral resection of bladder tumors (May 2022). Pathological diagnosis confirmed high grade papillary urothelial carcinoma (magnification, 10x40).

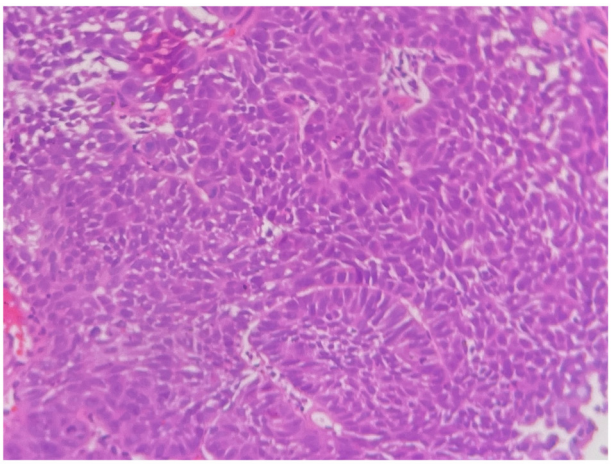

Figure 2. Transurethral resection of bladder tumors (July 2022). Pathological diagnosis confirmed high grade papillary urothelial carcinoma (magnification, 10x40).

The patient in the present case had a significant smoking history and lacked regular cystoscopy follow-ups and bladder irrigation. Presenting with hematuria, decreased urine output and fever, along with urinalysis indicative of urinary tract infection, the patient was initially treated with antibiotics followed by a cystoscopy examination. Some cases report urinary tract

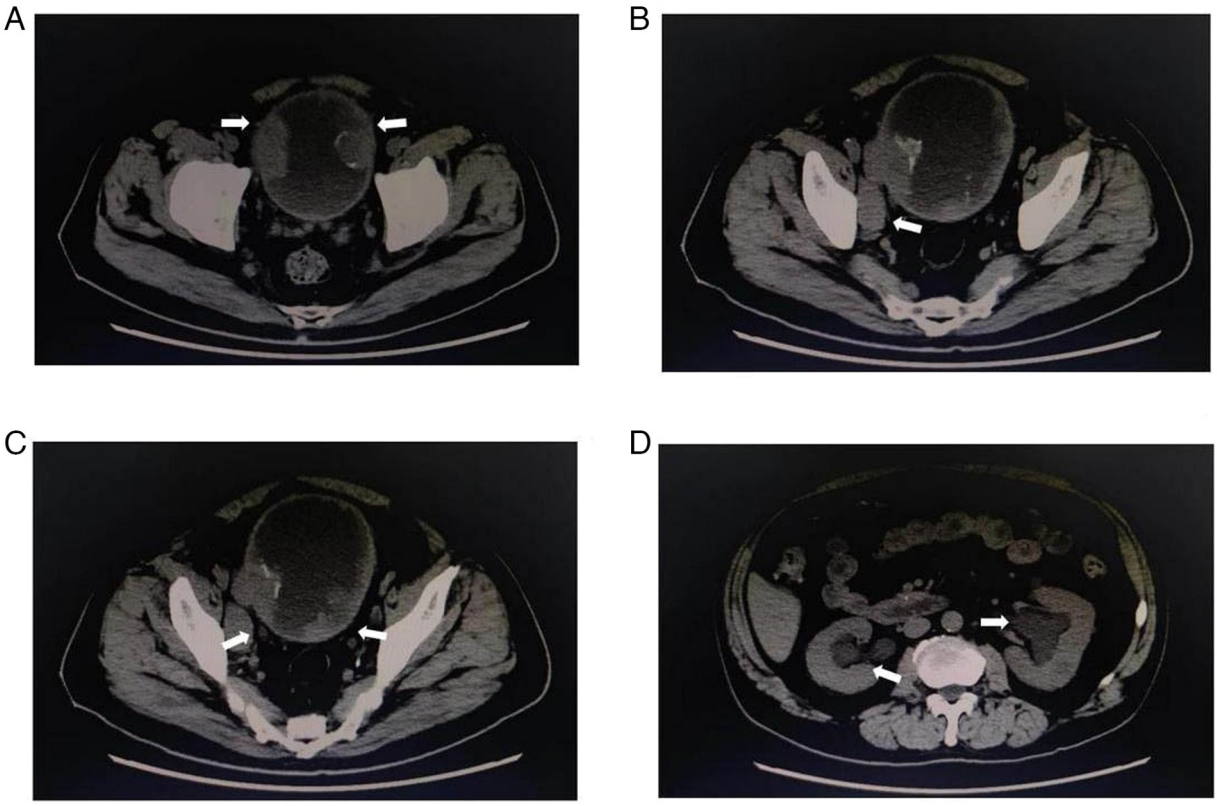

Figure 3. Urology computed tomography scan revealed (A) multiple tumors in the bladder (indicated by arrowheads), (B) multiple lymphadenopathies in the pelvis and along the right iliac artery (indicated by arrowheads), and (C) bilateral ureter bladder entrance invasion (indicated by arrowheads), (D) resulting in bilateral renal pelvis and ureter dilatation (indicated by arrowheads).

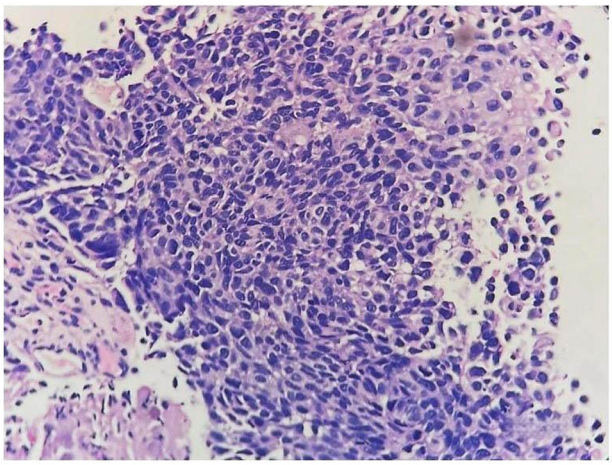

Figure 4. Cystoscopy and bladder biopsy (October 2023). Pathological diagnosis confirmed high grade papillary urothelial carcinoma with massive necrosis (magnification, 10x40).

infection rates of 5-10% after transurethral surgery, despite proper prophylactic antibiotics (15). However, in the present case, antibiotic treatment failed to resolve the patient's fever and the WBC count continued to rise, indicating that antibiotic therapy was ineffective. The patient has no history of leukemia and no previous history of other hematological conditions. Therefore, it was deduced that the patient did not have severe infections; instead, the patient exhibited a leukemoid reaction secondary to bladder cancer, predominantly neutrophilic in nature.

The patient's August 2023 CT scan indicated the presence of multiple tumors in the bladder and multiple lymphadenopathies near the right iliac artery and in the pelvis. The pathophysiological mechanism underlying fever and a leukemoid reaction caused by urothelial carcinoma of the bladder may be elucidated as follows: Urothelial cancer cells stimulate and infiltrate lymph nodes, leading to the activation of macrophages, which subsequently produce a substantial quantity of cytokines, such as IL-6, TNF-α (16). Additionally, necrotic malignant tumor cells release a significant amounts of endotoxins pyrogens known as damage-associated molecular patterns, which stimulate the production of pro-inflammatory cytokines, contributing to the manifestation of fever in the patient (17). Meanwhile, these cytokines facilitate the activation and proliferation of T cells or induce autocrine production of G-CSF, thereby promoting the differentiation and proliferation of granulocytes and significantly increasing peripheral leukocytes and neutrophils (18). Furthermore, urothelial carcinoma may also lead to bone marrow microinvasion, which can stimulate myelofibrosis and lead to extramedullary hematopoiesis, further elevating peripheral leukocyte counts (7,19).

Chemotherapy may be considered for patients who refuse surgical intervention or for whom surgery is not feasible. However, in the present case, given the patient's impaired renal function (creatinine level of 1,006 μmol/l as of October 2022) and the rapid rise in body temperature, the patient was considered unsuitable for gemcitabine and cisplatin chemotherapy.

Table II. Laboratory test results.

Parameter	Patient's value	Normal reference range
White blood cell count, x10^9/l	72.17	4.0-10.0
Neutrophil count, x10^9/l	70.27	2.0-7.5
C-reactive protein, mg/l	95.65	0.0-5.0
Creatinine, μmol/l	577.00	53-106

Table III. Timeline of the disease.

Date	Treatment	Findings
2016.8	TURBT1 + bladder irrigation	UC, pTa, low grade
2017.10	TURBT2 + bladder irrigation	UC, pTa, low grade
2019.3	TURBT3 + bladder irrigation	UC, pTa, low grade
2019.6	TURBT4 + bladder irrigation	UC, pTa, high grade
2020.8	Cystoscopy	Bladder tumor and patient refused further treatment
2022.5	TURBT5 + bladder irrigation	UC, pTa, high grade
2022.7	TURBT6 + bladder irrigation	UC, pTa, high grade and patient rejected total cystectomy
2023.10	Computed tomography and cystoscopy	Multiple tumors in the bladder, multiple lymphadenopathy, bilateral ureter bladder entrance invasion, bilateral renal pelvis and ureter dilatation
2023.10	Palliative treatment	The patient passed away

TURBT, transurethral resection of bladder tumors; UC, urothelial carcinoma.

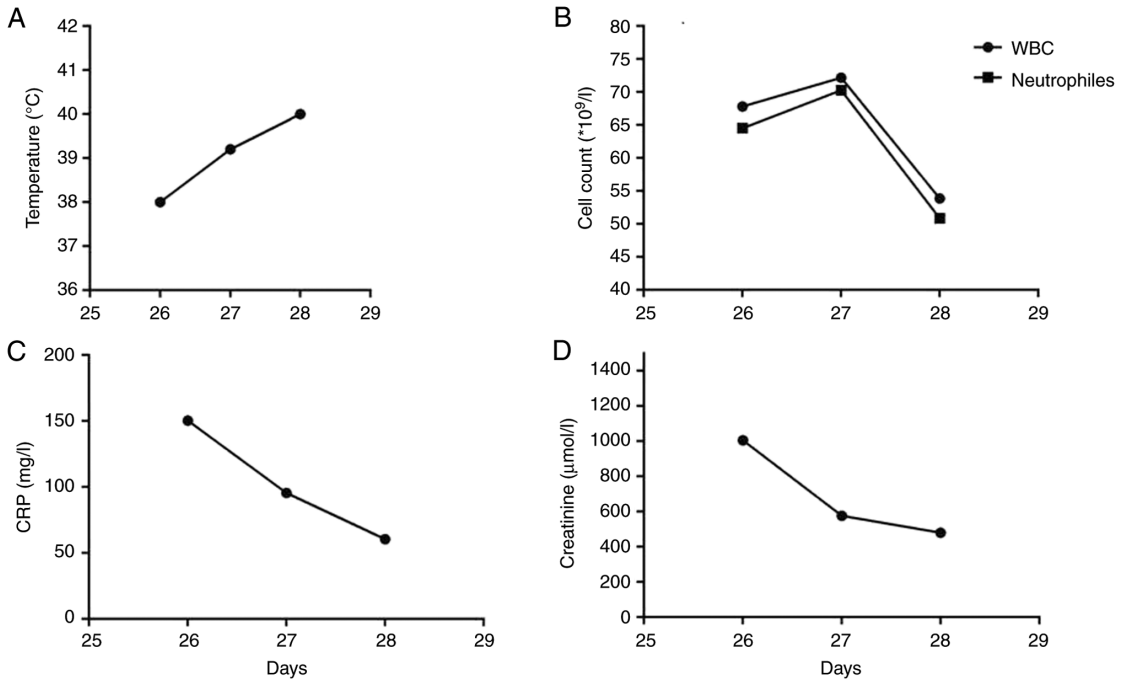

Figure 5. The graphs demonstrate (A) changes in temperature, (B) WBC count, (C) CRP levels and (D) creatinine levels. CRP, C-reactive protein; WBC, white blood cell.

Surgical resection is generally regarded as the most effective treatment for bladder cancer complicated by a leukemoid reaction (20,21), as the aforementioned atypical clinical features often resolve following tumor removal (22,23). Nevertheless, surgical resection does not consistently ensure prolonged remission. Following the onset of a leukemoid reaction,

patients frequently succumb within a few months despite surgical intervention (19,24-28).

In urological malignancies, a leukemoid reaction might be associated with increased G-CSF expression in patients with bladder cancer, a phenomenon less commonly observed in other malignancies (11). Under normal physiological conditions, G-CSF stimulates the proliferation and differentiation of neutrophil colony-forming cells and alters several functions of mature neutrophils. During a leukemoid reaction, increased G-CSF expression is associated with heightened leukocytosis and promotes a growth advantage to bladder cancer cells, infiltration into the muscular layer and metastasis to surrounding lymph nodes (29). A total of ~9% of patients with bladder cancer exhibit increased G-CSF levels, and these patients demonstrate a lower overall 5-year survival rate compared with those without increased G-CSF levels (30). Tachibana *et al* (31) reported elevated G-CSF levels and expression in the cancer cells of a 76-year-old patient with urothelial carcinoma complicated by a leukemoid reaction. Furthermore, this study confirmed that exogenous administration of G-CSF can stimulate bladder cancer cell proliferation, an effect that can be inhibited by the administration of anti-G-CSF antibodies (31).

The autocrine and paracrine mechanisms of CSF in bladder cancer may be associated with the re-arrangement of the G-CSF gene occurring within one of the alleles (32) and intrinsic activation of nuclear factors that work on the promoter region of the G-CSF gene (33). The G-CSF/G-CSFR biological axis promotes the expression of STAT3 protein, thereby promoting the growth of bladder cancer cells. In addition, G-CSF can induce the expression of β-1 integrin in bladder cancer cells, with β-1 integrin further acting on fibronectin and laminin, thereby promoting the invasion and metastasis of bladder cancer cells (34,35). In conclusion, cases of bladder cancer complicated by a leukemoid reaction are rarely reported clinically. The literature suggests that even with radical cystectomy, the prognosis remains poor. Monitoring of G-CSF levels in blood can help to make predictions of the patient's health condition. Blocking the G-CSF signaling pathway might serve as a future therapeutic target for bladder cancer complicated by a leukemoid reaction.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

JLi conceptualized and designed the present study. TH, JX, CChu, YS, JLu, PA and CChe acquired the data. TH and YH analyzed and interpreted the data. TH and JX drafted and critically revised the manuscript. All authors read and approved the final version of the manuscript. JLi and TH confirm the authenticity of all the raw data.

Ethics approval and consent to participate

All procedures were approved (approval no. 20230015) by the Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine (Shanghai, China).

Patient consent for publication

Written informed consent has been obtained from the relative of the patient for the publication of images and data.

Competing interests

The authors declare that they have no competing interests.

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