Paraneoplastic leukemoid reaction – poor prognostic marker in urothelial bladder carcinoma

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Certain cancers have been observed to cause symptoms called paraneoplastic syndromes that are not directly attributed to tumor invasion or compression. This phenomenon is believed to be secondary to a tumor's secretion of functional hormones, peptides, cytokines, or its immune cross-reactivity. One such variant is a paraneoplastic leukemoid reaction (PLR), defined as a leukocytosis level of >50 x 10^3 cells/mm^3, where the white blood cell (WBC) count differential exhibits a neutrophilia or left-shift, in which a predominance of early neutrophil precursors is observed. A PLR is believed to be incited by the tumor cell's production of its own growth factors such as granulocyte-colony stimulating factor (G-CSF) and a number of different cytokines. These reactions may at first be mistaken for infectious processes, and it is only after an infection has been ruled out or when a leukocytosis is disproportionately high in the setting of a treated infection, that a paraneoplastic leukemoid reaction (PLR) is considered and an oncologic work-up pursued.

PLR has been previously described in a variety of malignancies including lung, esophageal, nasopharyngeal and laryngeal, gastric, cholangiocarcinoma, melanoma, multiple myeloma, renal, prostate, and hepatocellular carcinoma, but has rarely been described in urothelial carcinoma.[1] Leukemoid reactions and autocrine growth induced by paraneoplastic production of G-CSF have rarely been associated with urothelial carcinoma of the bladder,[2] as in the case we present here of a 67-year-old white man with invasive high-grade urothelial carcinoma of the bladder. The case highlights PLR as a negative prognostic marker, secondary to urothelial bladder cancer cells' presumed production of G-CSF, rarely reported as in the literature previously.

Case presentation and summary

A 67-year-old white man was diagnosed with clinical stage III (T3N0M0), invasive high-grade urothelial carcinoma of the bladder (Figure 1). He received neoadjuvant chemotherapy with the standard gemcitabine-cisplatin combination (1,000 mg/m^2 of gemcitabine on days 1, 8, and 15 with 70 mg/m^2 of cisplatin on day 1 of a 28-day cycle for 3 cycles), and had less than partial response at the end of a 3-month course. A computed tomography scan of his pelvis obtained at treatment completion revealed persistent disease with noted enhancement of the right distal ureter and a right posterior bladder mass at the ureterovesical junction measuring 1.7 x 2.6 x 2.6 cm (0.6 x 1 x 1 in), for which, a cystoprostatectomy was recommended to remove remaining disease. The patient was seen in routine follow-up 3 weeks after his last chemotherapy treatment, when his WBC count was noted to be within normal limits at a value of 8.4 x 10^3 cells/mm^3 (normal range, 4.5-11 x 10^3 cells/mm^3).

One week later (a month after treatment completion), the patient presented to the emergency department with complaints of dysuria, urinary frequency, and suprapubic pain. He was found to have leukocytosis, with a WBC count of 47 x 10^3 cells/mm^3, (normal range, 4.5-11 x 10^3 cells/mm^3), with an elevated neutrophil count of 82.7% (normal range 40%-60%), without clinical signs of systemic infection (fevers, chills, or rigors). A urinalysis revealed pyuria with 25-50 WBC/high power field, negative nitrite, positive leukocyte esterase, and moderate bacteria, consistent with what was presumed to be a urinary tract infection. The patient was discharged home with a 1-week course of the antibiotic levofloxacin and the alpha-blocker tamsulosin to make

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urination easier. Of note, the final results of the urine culture, which returned 48 hours after discharge, showed no growth.

One week prior to surgery, the patient underwent a cystoscopy for ureteral stent exchange, which revealed a necrotic tumor at the right bladder base surrounding the ureteral orifice and stent. Renal pelvis urine, sampled during stent exchange, revealed >100,000 CFU/ml (colony forming units; normal value, $<10^3$) Candida albicans, for which the patient was started on intravenous fluconazole for fungal infection. We consulted with our colleagues in the infectious disease department and continued to follow the patient throughout his hospital course, which included several antibiotic regimens, a comprehensive hematological work-up and eventual urologic surgery. Work-ups for myeloproliferative disorders, leukemia, JAK-2, and BCR-ABL were all negative. A peripheral blood smear analysis showed mostly neutrophils, no immature cells, and occasional hypersegmented neutrophils, but was overall inconsistent with myeloproliferative disease. Despite the patient's persistent leukocytosis, he remained completely asymptomatic and his neutrophilia was attributed to his malignancy.

The patient subsequently underwent a cystoprostatectomy with ileal conduit. The surgical pathologic analysis showed a high-grade, invasive urothelial (transitional cell) carcinoma measuring 5.2 x 5.0 x 4.5 cm (2 x 1.9 x 1.8 in) with squamous differentiation, extensive tumor necrosis, lymphovascular invasion, invasion into the adjacent seminal vesicle and prostatic stroma, and negative margins (pT4a pN0 pMX; Figure 2). On the day of surgical resection, the patient's leukocytosis was 70 x 10^3 cells/mm^3.

Despite a transient improvement in his leukocytosis to 37.7 x 10^3 cells/mm^3 on postoperative day 1, the patient remained in the medical intensive care unit for uncontrolled pain and management of his leukocytosis. It is worth noting that the patient remained afebrile throughout his entire 45-day hospitalization, with negative culture data, and despite receiving an extensive broad spectrum antibiotic regimen (levofloxacin, piperacillin-tazobactam, cefazolin, metronidazole, ceftriaxone and fluconazole), his leukocytosis continued to progress, peaking at 161.5 x 10^3 cells/mm^3 less than a month after his surgery (Figure 3).

The patient continued to deteriorate rapidly, with a progressive leukocytosis, and developing metastases to the lung, perineum, and penis. He died a month after surgery (2 months after completion of neoadjuvant chemotherapy). The leukocytosis exhibited in this patient and the aggressive tumor cell growth are believed to have been secondary to a paraneoplastic leukemoid reaction incited by the urothelial bladder cancer cells' presumed production of G-CSF, which has been rarely reported in the literature previously.

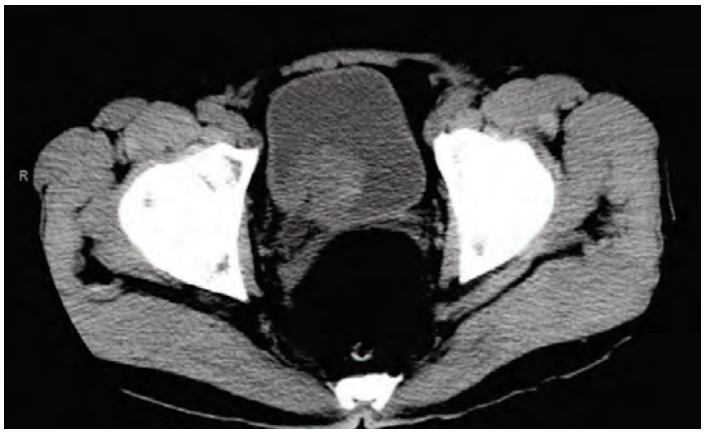

FIGURE 1 Pre-neoadjuvant chemotherapy computed tomography scan of bladder tumor. Moderate-sized focal heterogeneous soft tissue mass density in right posterior bladder about 3 cm in size.

Discussion

We report here on the rare occurrence of PLR in a urothelial bladder cancer. Several mechanisms have been proposed to explain the pathophysiology of PLR. The levels of IL-1[alpha and beta], IL-3, G-CSF, GM-CSF, IL-6, and TNF-[alpha] have all been reported to be elevated in various solid tumors and suggested to contribute to an elevated leukocyte count.[3] With previous reports that receptors for G-CSF have been found on cell surfaces of several non-hematopoietic cell types, Tachibana and Murai have proposed the mechanism of a cancer cell's simultaneous acquisition of the ligand promotion and its receptor expression conferring an autocrine growth advantage.[4] They have also reported on the capability of bladder cancer cells to induce a leukemoid reaction in their host through the stimulation of leukocyte production, which has been associated with aggressive tumor cell growth and a poor clinical outcome. In addition, He and colleagues have also described the cor-

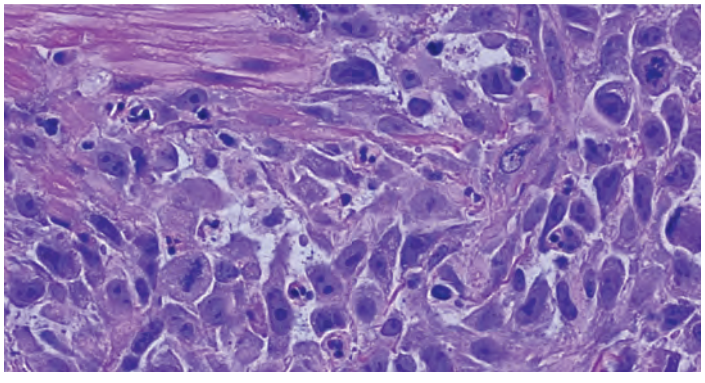

FIGURE 2 Surgical pathology of bladder resection. High-grade urothelial carcinoma, with large and pleomorphic neoplastic cells with variable nuclear size and shape, and irregular nuclear membranes displaying prominent nucleoli. Mitoses are frequent and abnormal. Muscularis propria invasion is present.

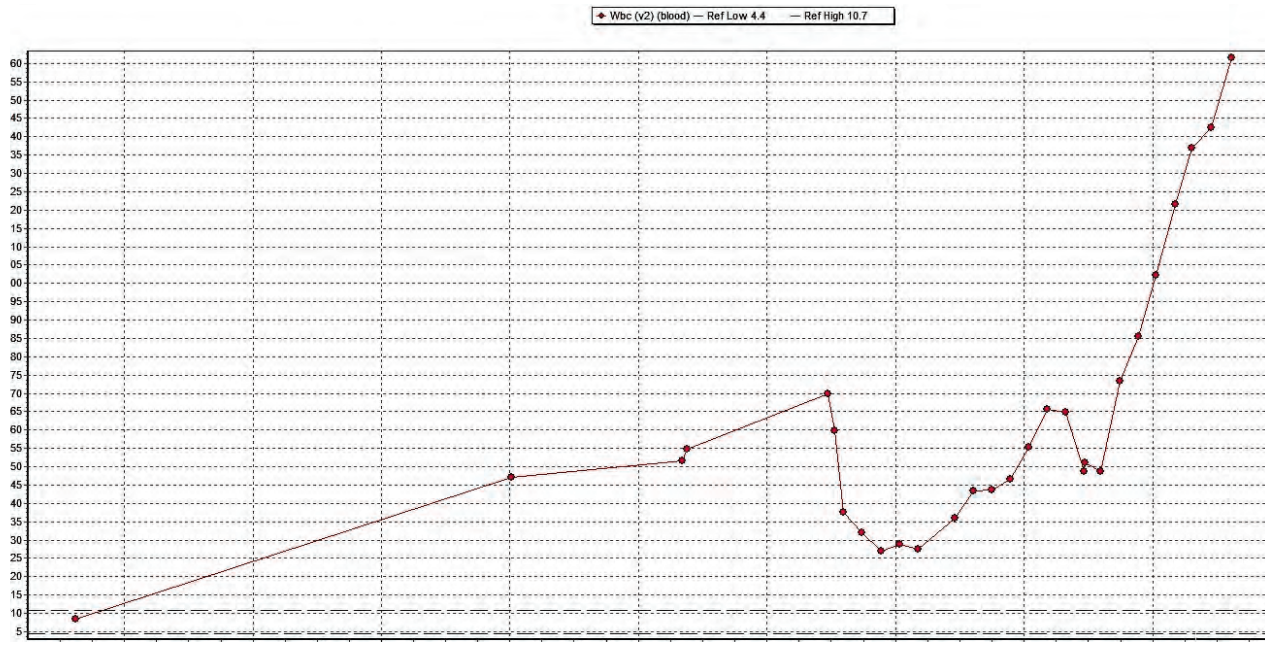

FIGURE 3 White blood cell trend. Three-month trend of leukocytosis with peak of 70 x 10^3 cells/mm^3 on day of resection, with persistent and progressive leukocytosis postoperatively with peak of 161.5 x 10^3 cells/mm^3 1 month after resection

relation between PLR and high degree of malignancy, high probability of metastasis, recurrence, and poor prognosis.[5]

We observed the leukocytosis of 70 x 10^3 cells/mm^3 on the day of resection with a slight drop postoperatively, peaking at 161.5 x 10^3 cells/mm^3 less than a month after resection of the tumor. There is no clear understanding of the cause of the persistent and rapid progression of leukocytosis seen in this patient postoperatively. There is also a dearth of literature describing similar occurrences, with even fewer attempting to explain the pathophysiology of this occurrence.

When faced with similar occurrences in patients, clinicians usually treat for occult infection. Once infections and myeloproliferative diseases have been ruled out, clinicians may consider obtaining a patient's serum G-CSF level or performing an immunohistochemistry analysis of urothelial cells for overexpression of G-CSF, when available.[5] However, despite any efforts to diagnose earlier, there is little clinicians currently have to offer these patients as treatment.

As presented in this report, PLR portends a worse prognosis for patients because of its ability to not only masquerade as an infection leading to a delay in the proper treatment, but also because of its association with a more aggressive tumor cell behavior and growth, making it critically important for clinicians to be able to identify these patients early on. With further investigation into immune regulation and G-CSF receptor signaling, there may be future discoveries of novel methods to diagnose this condition and also advancements in the treatment options made available to these patients.

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