

# Leukemoid Reaction Associated with Transitional Cell Carcinoma

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Leukemoid reaction is an exaggerated myeloid response to several stimuli including infections, allergies, burns, intoxication, acute hemorrhage, and malignant neoplasms [1,2]. It is defined as a persistent neutrophilia of 30,000–50,000 cells/ $\mu$ l or greater. The term is used to distinguish this degree of neutrophilia from leukemia. In leukemoid reaction, neutrophils are usually mature and not clonally derived.

Carcinomas of colon, lung and kidney have been associated with leukemoid reaction as a paraneoplastic syndrome. This was attributed to the secretion of granulocyte colony-stimulating factor by the tumor, and was associated with aggressive tumor cell growth and a poor clinical outcome [1]. Leukemoid reaction has rarely been reported in patients with primary bladder cancer. We report a case of

leukemoid reaction associated with transitional cell carcinoma of the urinary bladder. To our knowledge, this is the fifth case reported in the literature.

## Patient Description

A 72 year old man was admitted for elective transurethral resection of a bladder tumor. He had a history of heavy smoking and glaucoma. Physical examination revealed

right flank tenderness and a right pelvic firm fullness on rectal examination. Body temperature was normal. Laboratory analysis revealed leukocytosis with left shift ( $24,000/\text{mm}^3$ ; 90% neutrophils) while other hematologic parameters were normal. Urine and blood culture showed no bacterial growth. Preoperative intravenous urography and sonography demonstrated right moderate ureterohydronephrosis and a large mass in the right wall of the urinary bladder.

The patient underwent incomplete transurethral resection of a bladder tumor because of the tumor size. Due to persistent ureterohydronephrosis a percutaneous nephrostomy was inserted. The patient was discharged in good physical condition with no fever, but with high leukocyte count ( $20,000/\text{mm}^3$ ). The pathologic examination revealed high grade muscle-invasive (T2) transitional cell carcinoma. Elective radical cystectomy was scheduled. Two weeks later, the patient was admitted with high fever of  $39^\circ\text{C}$  and right flank pain, and parenteral antibiotic was initiated. Leukocyte count was  $32,400/\text{mm}^3$  (91% neutrophils). Blood smear showed marked leukocytosis with neutrophilia but no immature forms. Three days after admission the fever resolved, but the leukocyte count was still high ( $33,000/\text{mm}^3$ , 92% neutrophils). Repeated blood and urine cultures were sterile. Chest X-ray and abdominal computerized tomography showed no metastasis, abscess or other reasons for leukocytosis.

Radical cystectomy with ileal conduit was performed. Leukocyte count before the operation was high –  $42,900/\text{mm}^3$  (93% neutrophils), but 12 hours after the operation leukocyte count decreased to  $14,500/\text{mm}^3$ . In subsequent blood counts 2 days and 1 week after surgery the leukocyte counts were  $11,900/\text{mm}^3$  and  $10,900/\text{mm}^3$ , respectively. Two weeks after the operation, leukocyte count decreased to  $9,000/\text{mm}^3$ .

## Comment

Paraneoplastic syndrome is defined as hormonal, neurologic, hematologic and other clinical and biochemical disturbances associated with malignant neoplasms not directly related to invasion by the primary tumor or its metastases [2]. As many as 20% of all cancers may be associated with paraneoplastic syndromes caused by tumor secretion of hormone or cytokine-like substances [1].

A few paraneoplastic syndromes have been reported in patients with metastatic transitional cell carcinoma including hypercalcemia, thrombocytosis, eosinophilia, nephrotic syndrome, acanthosis nigricans, dermatomyositis, polymyositis, and leukemoid reaction [2].

Leukemoid reaction has rarely been reported in patients with primary bladder carcinomas. In a literature review we found only five cases of a leukemoid reaction in bladder cancer. All five cases were associated with aggressive tumor cell growth and unfavorable clinical outcome. Two patients had rapid local recurrence 6 weeks after surgery [1]. Distant liver metastases at initial presentation were present in another two patients [2,3]. In one patient the tumor had already invaded the pelvic wall at the time of diagnosis [4]. The leukocyte count ranged from  $34,700$  to  $76,000/\text{mm}^3$ .

Paraneoplastic leukocytosis associated with bladder carcinoma has been shown to result from autonomous production of G-CSF by the tumor [1,3,5]. As a consequence of this autonomous production, the serum levels of this factor increase significantly and lead to marked leukocytosis [1].

Fever is an integral component of leukemoid reaction. In our patient, the source of the fever was unclear. All blood and urine cultures were sterile, and chest X-ray and abdominal CT were normal. In our case, even when the patient had no

G-CSF = granulocyte colony-stimulating factor

fever, marked leukocytosis persisted. A dramatic decrease in leukocyte counts was demonstrated after surgery. G-CSF level was not measured, and the diagnosis of paraneoplastic leukemoid reaction in our patient was reached on a clinical basis.

In our patient leukocytosis was present at the time of diagnosis of the primary tumor and in the absence of metastases, which is in contrast to other reports where leukocytosis appeared with recurrence of the neoplasm and in the presence of metastases [3].

Leukocytosis in a patient with advanced transitional cell carcinoma may represent leukemoid reaction due to paraneoplastic secretion of G-CSF. When no other source for leukocytosis can be found, leukemoid reaction may be suspected and may be resolved with surgery.

## References

1. Tachibana M, Miyakawa A, Tazaki H, et al. Autocrine growth of transitional cell carcinoma of the bladder induced by granulocyte-colony stimulating factor. *Cancer Res* 1995;55(15):3438–43.
2. Block NL, Whitmore WF. Leukemoid reaction, thrombocytosis, and hypercalcemia associated with bladder cancer. *J Urol* 1973; 110:660.
3. Ito N, Matsuda T, Takeuchi Y, Takeuchi E, Takahashi T, Yoshida O. Bladder cancer producing granulocyte colony-stimulating factor. *N Engl J Med* 1990;323:1709.
4. Ito S, Iwai Y, Fujii T, Yoshida N, Hayashi S. Two cases of bladder tumor producing granulocyte colony stimulating factor. *Hinyokika Kyo* 1999;45(1):57–60.
5. Satoh H, Abe Y, Katoh Y, Komine Y, Nakamura M, Tamaoki N. Bladder carcinoma producing granulocyte colony-stimulating factor: a case report. *J Urol* 1993; 149:843.

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*Happiness is salutary for the body, but it is sorrow that develops spiritual strength*

*Marcel Proust (1871-1922), French novelist and critic, in The Past Recaptured*