CASE REPORT

Leukemoid Reaction as a Rare Paraneoplastic Manifestation in Urothelial Cell Carcinoma: A Case Report

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Leukemoid reaction refers to reactive and excessive leukocytosis with a white blood cell count of more than 50,000 cells/mm3 in the absence of myeloproliferative neoplasm and has usually been described in response to inflammation, severe infection, malignancies, hemorrhage, acute hemolysis, or bone marrow stimulants. In contrast, urothelial cell carcinoma is rarely associated with leukemoid reaction, with few cases reported over the past few years. Here, we report a case of an invasive Urothelial carcinoma of a 63 year old patient presenting with terminal dysuria and excessively elevated and persisting leukocytosis accompanied by rapid tumor progression and deteriorating clinical status. For urothelial cell carcinoma patients exhibiting a leukemoid reaction, removal of the inciting tumor is the definitive treatment. Though placing of urethral catheter and resection of the bladder tumor alleviated the worsening renal status and terminal dysuria on the index patient, the patient still had multiple persistent febrile episodes throughout the course, accompanied by leukocytosis with predominant mature looking neutrophils, and a left shift. Extremely persistent leukocytosis appears to be associated with poor prognosis even after surgical resection and extensive medical management.

Key words: Leukocytosis, terminal dysuria, cancer

Introduction

Bladder cancer, commonly referred to as urinary bladder cancer, is the ninth most prevalent cancer worldwide, and its prevalence is gradually increasing globally, particularly in industrialized nationsl'l. It is the most prevalent tumor of the urinary system, with urothelial carcinoma being the most prevalent histologic subtype. Painless hematuria is the most common presenting sign of bladder cancer. Approximately 1.3% of patients with asymptomatic microscopic hematuria (three or more red blood cells per high- power field in a properly collected specimen in the absence of an obvious benign cause will have bladder cancer, with estimates ranging from 0.4% to 6.5% 1[2]1. Gross hematuria is associated with a higher rate of malignancy (estimated at 20%). Irritative voiding symptoms are often present (e.g., urinary frequency, urgency, nocturia, dysuria). Obstructive symptoms, such as reduced or intermittent urine stream, straining, or feeling of incomplete voiding, may be present if the tumor is near the bladder neck or urethra. Patients with advanced disease may present with symptoms related to metastatic involvement.

Physical examination findings are often unremarkable in patients with bladder cancer, unless there is advanced or metastatic disease. In cases of local invasion or distant metastasis, a few subsets of patients present with leukemoid reaction.

The Case

This was a case of a 63 year old male, who presented with a 2 month history of terminal dysuria associated with new onset moderate grade fever, chills, hematuria and hypogastric pain. The hypogastric pain was described as unremitting, nonradiating colicky pain, with moderate intensity (6/10 on pain scale score), aggravated by urination and partially relieved by taking pain relievers as previously prescribed by his attending physician. There were no other associated symptoms such as nausea, vomiting, nor easy fatigability.

This patient's medical history was on a background of sudden unintentional weight loss and generalized body malaise. Patient denies previous hospitalizations and other diseases that require medications. Patient has poor memory of his parents but claims to have

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no heredofamilial diseases such as Hypertension, Diabetes, Bronchial Asthma nor Psychiatric illnesses. He is a nonsmoker, an occasional alcoholic beverage drinker, denies illicit drug use and claims to have no diet preferences.

Upon examination, the patient was described with hyposthenic habitus and was observed to be weak looking. In-hospital monitoring showed stable vital signs with a normotensive blood pressure of 120/70, heart rate of 96 beats per minute, low grade fever at 37.6 C, and no desaturations. Abdominal examinations revealed a slight direct tenderness on the region of hypogastric area upon deep palpation. No mass was noted and the patient did not demonstrate lymphadenopathy nor hepatosplenomegaly at the time. Few days at the ward, the patient started to have painless visible hematuria and decreased urine output. He underwent cystoscopy and transurethral resection of the bladder revealing invasive urothelial carcinoma. On day 8 of hospitalization and day 3 of empiric antibiotic therapy, patient still had febrile episodes with seemingly steady state leukocytosis with blood analysis showing WBC count range of 41-67 x1QA9, a consistent neutrophilic predominance and a very low lymphocytes ranging from 2-4%.

Investigations

A series of diagnostics was done which include repeat Complete Blood Count (CBC), Urinalysis with culture and sensitivity, Serum electrolytes and creatinine, chest X-ray, blood uric acid, 12L ECG, and CT stonogram. CT stonogram revealed irregularly nodular, calcified, predominantly intravesical mass lesion on the floor of the urinary bladder with associated bilateral grade 2 hydroureteronephrosis. Lymph nodes in the perivesical, infrarenal, aortocaval, para-aortic as well as right internal and external iliac areas were noted to be enlarged. An overwhelming leukocytosis with neutrophilic predominance in a series of complete blood counts despite antibiotic treatment was observed throughout the hospitalization. The patient was subsequently referred to a urologist to which he was advised to undergo eystoscopy with transurethral resection of the bladder tumor with histopathologic analysis revealing invasive urothelial carcinoma with squamous metaplasia.

Treatment

Upon admission and acquisition of blood and urine culture and sensitivity results, and with the overwhelming leukocytosis, the patient was immediately started on Piperacillin- tazobactam 4.5 gm intravenously as loading then given 2.25 gm every 6 hours, medications for lysis of fever was also given every 4 hours. An indwelling urinary catheter was warranted at the time since patient began urinary hesitancy and measurement of urinary output has been of utmost importance. Transurethral resection of the bladder tumor was done for histoanalysis as well as therapeutic alleviation of the lower urinary tract symptoms of the patient. A series of complete blood count and with persistence of fever and leukocytosis opted the antibiotic treatment to be shifted to Meropemen then subsequently to vancomycin. A low hemoglobin count was addressed by transfusion of packed RBC to the patient.

Outcome and Follow Up

After a comprehensive and holistic approach to educating the index patient and family through counselling, the family decided not to pursue the more advanced therapy and to halt other pending diagnostic procedures. Financial constraints coupled with bleak uncertainties took toll on their hopefulness. Despite the patient's trust and doctor's deep understanding of his case, the team made it clear that "no cure" doesn't mean "no care". A strategy made for the family is based on the principle of continuity of care.

To optimize his nutrition, high-protein and high-calorie foods were incorporated along with a variety of food groups to prevent further weight loss and nutritional deficiencies.

Managing symptoms for pain was also addressed through prescription medications. Lastly, self care for carers and family members, and proper coping strategies and management were also emphasized during the process of family education to prevent burnout and improve quality of life.

He was discharged from the hospital with home medications and arrangement of follow up once with Biopsy results. One week after hospital discharge, official biopsy results came out revealing Urothelial Carcinoma. The family was advised to follow up for another family meeting.

Two weeks after discharge, the patient's son informed the attending physician that the patient could not walk. Teleconsultation was done instead. Though restoration of the maximal functional capacity of the patient seemed unlikely, focus was on the patient's functional abilities daily living and adaptation to declining functionality to improve his quality of life. Another two weeks later, a social media post was seen with the interment details of the patient.

Discussion

Carcinoma of the urinary bladder is the most common malignancy involving the urinary tract system[3]. It roughly accounts for 95% of bladder cancer. It arises from transitional epithelium that lines the inner surface of the bladder. It can occur due to cigarette smoking, aniline dye used in the paint industry, and agrochemicals. Transitional Cell Carcinoma (TCC) can be papillary, sessile, or carcinoma in situ[4]. Urothelial carcinoma (UC) can also occur in the renal pelvis, ureter, or urethra but their occurrence is far less common than in the urinary bladder and the most common site of metastasis outside pelvis is bone of which most common site is spine.[5]

UCs may show diverse histological differentiation into a wide spectrum of components, including squamous, glandular, small cell, micropapillary, sarcomatoid, and plasmacytoid subtypes. Bladder carcinoma usually presents with hematuria or dysuria, but in some cases, it can present with features of obstruction, and irritative voiding symptoms.

In the present case, the urinary bladder UC showed histological differentiation into squamous arising from the left side of the urinary bladder floor with invasion of the supporting lamina propria. The patient however presented with terminal dysuria, which comprises the lesser known common presentation of bladder carcinoma and the

patient's personal history did not demonstrate a clear correlation with any significant risk factor that may suggest the emergence of bladder cancer aside from possible agrochemical exposure from farming.

The patient is 63 year old Filipino, nonsmoker, no family history of cancers, with questionable exposure to agrochemical exposure used in farming illustrating that there may be idiopathic as well as undiscovered risk factors for the development of the disease.

Many tumor-related diseases particularly some cancers often don't present with symptoms until they have reached an advanced stage. Tumor cells may be detectable in a urine cytology examination. The absence of such cells does not exclude a bladder tumor. Urine cytology has a specificity of 90-100% and sensitivity of 20-50% for detecting low-grade and high-grade bladder carcinoma. Therefore, the method is not suitable for screening. Molecular tumor markers have not been established for clinical practice as yet. In the case of a well-founded suspicion, (fluorescence-assisted, if needed) white light cystoscopy is required as a standard method in the primary diagnostic work-up and always includes an evaluation of the complete bladder due to the possibility of multilocular occurrence.[6] If the urothelium is abnormal, subsequent transurethral bladder resection of tumor (TURBT) is both diagnostic and therapeutic in nature, which was done to the patient.

The diagnosis of muscle invasive urothelial carcinoma aside from TURBT and histological confirmation includes imaging in the form of computed tomography abdomen or pelvis including urographic phase. In the case of BS, a CT Urogram was done revealing hyperdensities of both lower calyx of the kidneys and calyx of the right kidney with attenuation value of 233 HU. There is also an ill defined mixed density structure seen in the right psoas muscle at the level of LS-81 which slightly compresses the adjacent ureter measuring 4.3cm x 6.1cm x 8.7cm (AxPxWxH) as well as the lateral wall of the urinary bladder. Lytic lesion is seen in the left sacral wing which leads to the suspicion of metastatic activities of the neoplasm.

Treatment of urothelial cancer include radical cystectomy with peri- and post operative chemotherapy as part of multimodal concept in a multidisciplinary manner taking into account the individual situation and risk of the index patient. Treatment for metastatic carcinoma of the bladder includes immunotherapy as first line and primary systemic treatment should be performed if the patient's general condition permits since the median overall survival without systemic treatment is 3 months at the metastatic stage[7]. However, the criteria for Cisplatin based immunotherapy excluded the patient for the treatment for having an eGFR of 22, financial constraints also played a major role for the shared decision of the index family for refusing the possible treatment plans.

An associated persistent leukemoid reaction with neutropenia was also seen throughout the clinical course of the patient. This may occur under various conditions including infections, hemolysis, or malignant tumors, however with a series of laboratory tests and with resistance to antibiotic therapy, the closest explanation to this phenomenon is the malignant related paraneoplastic leukemoid reaction. In our case, the patient had bladder cancer with a fever and leukocytosis; thus, the complication of a urinary tract infection was suspected and represented a diagnostic dilemma.

Leukemoid reactions in urothelial cell carcinoma are a especially rare occurrence and has been widely observed clinically to appear at an advanced stage of cancer in association with its highly invasive and metastatic nature, signifying a very poor prognosis and an impending mortality within a few months.[8]

The mechanism driving the paraneoplastic leukemoid reaction is through the production of cytokines, particularly G-CSF, inducing a leukocytosis with a left shift. Mizutani et al. looked at 141 patients with urothelial tumors and 13 had G-CSF-related leukemoid reactions.[9] Serum G-CSF levels also correlated with a higher grade and faster progression of the cancers and it has been hypothesized that G-CSF production by tumor cells may induce autocrine signaling that accelerates growth and progression of the cancer.

Conclusion

Although paraneoplastic leukemoid reaction in urothelial cancer appears to be extremely rare, and with only a handful of literature documenting the phenomenon, extremely persistent leukocytosis appears to be associated with poor prognosis even after surgical resection and extensive medical management . Monitoring of white blood cell count in urothelial cancer showing paraneoplastic leukemoid reactions can be useful in prognostication and possible response to chemo/radiotherapeutic intervention.

Ethical Considerations

Our patient verbally consented and cooperated in writing this paper but the author failed to secure a written informed consent due to the patient's demise. Full anonymity of the patient was done in writing this paper and no personal details were published.

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References

1. Halaseh SA, Halaseh S, Alali Y, Ashour ME & Alharayzah MJ. A review of the etiology and epidemiology of bladder cancer: All you need to know. Cureus 2022; 14(7): e27330. https://doi.org/10.7759/cureus. 27330

2. Tetteh-Quarcoo PB, Akuetteh BK, Owusu IA, et al. Cytological and wet mount microscopic observations made in urine of Schistosoma haematobium-infected children: Hint of the implication in bladder cancer. Canadian J Infect Dis Med Microbiol 2019; 7912186. https://doi.org/10.1155/201917912186
3. Kaseb H, Aeddula NR. Bladder cancer. [Updated 2022 Oct 24). In: StatPearls [Internet). Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK536923/
4. Gandhi J, Chen JF, Al-Ahmadie H. Urothelial carcinoma: Divergent differentiation and morphologic subtypes. Surg Pathol Clin 2022 Dec;15(4):641-59. doi: 10.1016/j.path.2022.07.003. Epub 2022 Oct 13.
5. Venyo A K. Nested variant of urothelial carcinoma. Adv Urol 2014; 192720. https://doi.org/10. 1155/2014/192720
6. Makise N, Morikawa T, Takeshima Y, Homma Y & Fukayama M. A case of urinary bladder urothelial carcinoma with squamous, glandular, and plasmacytoid differentiation. Case Rep Oncol 2014; 7(2): 362-8. https://doi.org/1 O .1159/000363648
7. Rathert I. The importance of urine cytology. Deutsches Arzteblatt Int 2021; 118(31-32): 544-5. https://doi.org/10.3238/arztebl.m2021.0229
8. Wit M, Retz MM, Radel C & Gschwend JE. The diagnosis and treatment of patients with bladder carcinoma. Deutsches Arzteblatt Int 2020; 118(Forthcomi ng): 169-76. Advance online publication. https://doi.orgl 10.3238/arztebl.m2021.0013
9. Mizutani Y, Okada Y, Terachi T, Kakehi Y and Yoshida 0. Serum granulocyte colony-stimulating factor levels in patients with urinary bladder tumour and various urological malignancies. Br J Urol 1995; 76, 580-6. http://dx.doi.org/10. 1111/j.1464-410X.1995.tb07782.x