Chronic lymphocytic leukemia/small lymphocytic lymphoma presenting as acute renal failure

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Lymphoma of the urinary bladder is quite rare, accounting for a small percentage of all bladder neoplasms. Here we discuss the case of a 68-year-old male patient who initially presented with acute renal failure and severe bilateral hydronephrosis on ultrasound. Cross-sectional imaging further revealed a diffusely thickened bladder wall with extensive retroperitoneal and mesenteric lymphadenopathy. Bladder biopsies ultimately led to a diagnosis of stage IV chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). This is a rare instance of upper tract dilatation being the first sign of a widely disseminated hematologic malignancy.

Key Words: bladder, cancer, hydronephrosis, lymphoma

Introduction

Lymphoma of the urinary bladder accounts for less than 1% of all bladder neoplasms and has various clinical presentations including gross hematuria, dysuria, urinary frequency, as well as lower abdominal and back pain.[1] There are three clinical categories of urinary bladder lymphoma: primary bladder lymphoma, where the disease process originates in the bladder; secondary bladder lymphoma, where a patient with a known history of systemic lymphoma develops recurrence or metastasis at the bladder; and non-localized bladder lymphoma, where there is synchronous involvement of the bladder and other viscera at the time of first diagnosis.[1] Here we present the case of a 68-year-old male who was ultimately diagnosed with non-localized, stage IV chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) of the bladder after initially presenting with renal failure from bilateral hydronephrosis. This case highlights the importance of setting a broad differential diagnosis for causes of obstructive uropathy.

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Case report

A 68-year-old male with mild obstructive lower urinary tract symptoms (LUTS) presented to the emergency department with hyperkalemia (7.3 mEq/L) and an elevated creatinine (Cr 11.7 mg/dL) on routine outpatient labs. The patient had a history of hyperlipidemia, hypertension, and benign prostatic hyperplasia (BPH) with LUTS including nocturia

and he was prescribed tamsulosin (Flomax) by his primary care provider for years prior to presentation. The patient had a remote history of smoking for 15 years, with 35.9 years since cessation. During work up in the emergency department, the patient complained of drenching night sweats, unintentional weight loss of 20 pounds in the previous 6 months, worsening irritative voiding symptoms, and new onset nocturnal enuresis. A complete blood count (CBC) with differential revealed leukocytosis (15.5 K/uL) with increased absolute lymphocyte count and anemia (hemoglobin 10.3 g/dL). Urinalysis (UA) showed 5-9 red blood cells and too-numerous-to-count white blood cells.

A renal/bladder ultrasound was performed, which identified severe bilateral hydronephrosis, a distended bladder, and an enlarged prostate, Figure 1. A Foley catheter was placed for 1.1 liters of urine. The patient was started on combination therapy for BPH and admitted for acute kidney injury. With foley catheter drainage, his electrolytes and kidney function improved and he was ultimately discharged. He then returned to the emergency room shortly after discharge with recurrent hyperkalemia (6.4 mEq/L) and a rebound increase in Cr (5.2 mg/dL). A CBC with differential showed persistent leukocytosis (19.6 K/uL) with lymphocytosis and anemia (hemoglobin 11.1 g/dL).

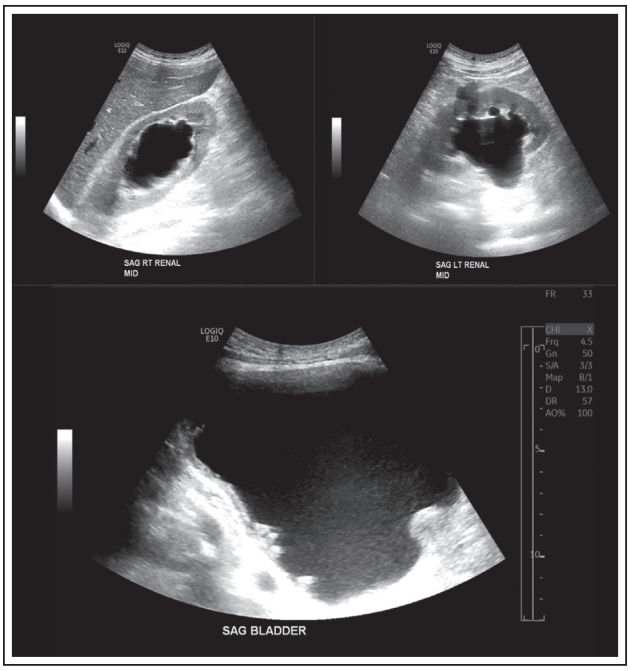

Figure 1. Renal ultrasound – first admission – bilateral hydronephrosis with a large median lobe and full bladder.

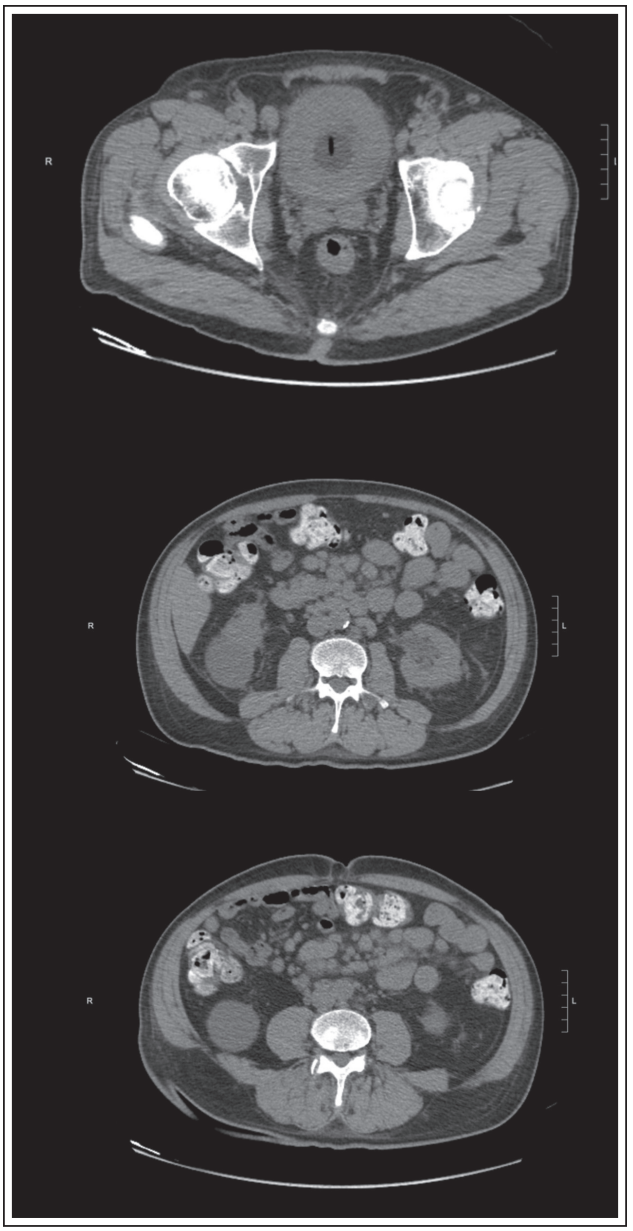

Figure 2. CT of abdomen and chest – second admission – **(A)** Thickened bladder wall; **(B)** Mild left hydronephrosis with diffuse retroperitoneal lymphadenopathy; **(C)** Mesenteric lymphadenopathy.

A non-contrast computed tomography (CT) scan of the abdomen and pelvis was performed revealing mild bilateral hydroureteronephrosis and a diffusely thickened bladder wall as well as extensive retroperitoneal and mesenteric lymphadenopathy, Figure 2. Due these abnormal imaging findings, the decision was ultimately made to perform cystoscopy to evaluate for any anomalies that might be contributing to the patient's clinical condition. In the operating

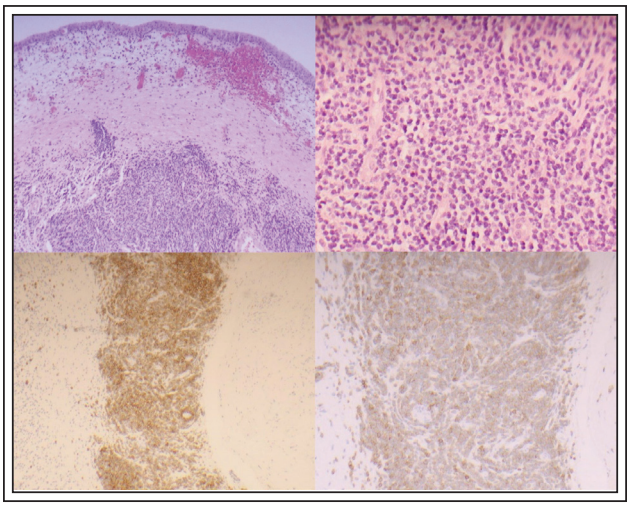

Figure 3. Posterior wall bladder biopsy – **(A)** Atypical small lymphocytic infiltrate; **(B)** High power, small atypical lymphocytic infiltrate; **(C)** Positive CD20 immunohistochemistry; **(D)** Positive CD5 immunohistochemistry.

room, cystourethroscopy revealed a large prostate and a small, trabeculated bladder with normal appearing bladder mucosa. Random biopsies of the posterior bladder wall were obtained and sent for pathology. Microscopically, biopsies showed normal urothelial mucosa with smooth muscle infiltration of small, atypical lymphocytes demonstrating hyperchromic round nuclei, clumped chromatin, and scant cytoplasm. Immunohistochemical staining identified CD20, Bcl-2, and CD23 positive cells with aberrant expression of CD5 and CD43, Figure 3. Flow cytometry demonstrated a monotypic kappa light chain restricted B-cell population with an aberrant expression of CD5 suggestive of a CD5 positive B-cell lymphoproliferative neoplasm. Further imaging included 18F-fluorodeoxyglucose-positron emission tomography (FDG-PET/CT), which found lymphadenopathy in the bilateral axillary, subpectoral, supraclavicular, lower cervical and mediastinal regions. Ultimately, these findings were compatible with stage IV chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) involving the bladder.

After diagnosis, the patient was seen by medical oncology and started on rituximab (Rituxan) infusion therapy and daily prednisone. Following 4 weeks of treatment, an interval CT of the abdomen pelvis revealed a decrease in bladder wall thickness and improvement in the degree of mesenteric lymphadenopathy and hydronephrosis. Based on the CT results, the patient was found to have stable disease with a conservative response to rituximab therapy. Currently, the patient continues with rituximab infusions and palliative pelvic radiation therapy for bladder wall thickening. Despite treatment, however, he remains dependent on intermittent catheterization as he has failed multiple outpatient void trials and has loss of bladder compliance with filling and an inability to empty completely on urodynamic studies.

Discussion

CLL/SLL is a subtype of non-Hodgkin lymphoma (NHL) and is one of the more common subtypes of NHL, constituting approximately 7% of newly diagnosed cases of NHL.[2] In the US population, CLL/SLL accounts for 1.1% of all new cancer cases, with an annual incidence rate of 4.6 per 100,000 men and women.[3] In western countries, the median age at diagnosis is 68 years old with a predominance of cases in non-Hispanic white males.[3] Risk factors for CLL/SLL include: male sex, older age (greater than 50), family history of lymphoma, smoking history, and immunosuppression. Our patient did have multiple risk factors including a remote smoking history, older age, and being a white male. Regarding CLL/SLL involvement of the genitourinary (GU) system and bladder, it is extremely rare and is limited to a small number of case reports. Patients present with a range of symptoms, including chronic irritative voiding symptoms, gross hematuria, anemia, and significant leukocytosis.[4-9] The majority of bladder lymphoma cases are classified as either non-localized or secondary lymphomas and occur more commonly in men than women.[1] In the case of our patient, because his bladder malignancy was identified as the first sign of systemic CLL/SLL, it can be classified as non-localized bladder lymphoma.

Diagnosis requires immunohistochemistry and flow cytometry to identify specific surface markers and cell line anomalies. The standard immunophenotype for CLL/SLL is positive surface expression of CD5, CD19, and CD23 with dim positive surface expression of CD20 as well as negative expression of cyclin D1 and CD10.[2] In the case of our patient, immunohistochemical staining and flow cytometry identified CD20, Bcl-2, and CD23 positive cells with aberrant expression of CD5 and CD43, as well as negative findings for CD10 and cyclin D1 consistent with the standard CLL/SLL immunophenotype.

Because of its rarity, there are no standard guidelines for management of CLL/SLL of the bladder and data regarding overall survival varies greatly. In the

literature, CLL/SLL of the bladder has been managed with transurethral bladder resection and systemic therapies such as chlorambucil with prednisone.[4-9] Given the fact that our patient presented with non-specific bladder wall thickening rather than a definitive bladder mass, transurethral resection was not feasible. More recently, monoclonal antibodies such as rituximab with prednisone have been used, especially in the setting of systemic CLL/SLL.[2,5] Others have employed a "watch and wait" strategy of treating patients exclusively when they are symptomatic.[6-8] There is no documentation of palliative radiation for CLL/SLL of the bladder, but it has been used occasionally to reduce tumor burden in other bladder lymphomas as well as to minimize lymphadenopathy in patients systemic disease.[1,2] The dearth of information regarding CLL/SLL of the bladder necessitates further research and investigation.

Non-localized CLL/SLL of the bladder is extremely uncommon and clinical presentation varies greatly. Overall prognosis is case-dependent, and treatment is poorly defined. However, an increase in clinical suspicion for variant bladder histologies as well as the utilization of multi-modal treatment delivery will help define a pathway for diagnosing and managing this rare condition. □

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