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LETTER TO THE EDITOR

Chronic lymphocytic leukemia presenting with hematuria

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Figure 1. Histology and immunohistochemistry of bladder biopsy. (A) Low-power photomicrograph of bladder biopsy (H&E). Attenuated urothelium with an underlying dense lymphocytic infiltrate in the lamina propria. (B) High-power photomicrograph of lymphocytic infiltrate (H&E). (C) CD20 positive lymphocytes. (D) Scattered reactive T cells with CD3 expression. (E) CD5 expression in essentially all lymphocytes. (F) Strong expression of CD23 in the lymphocyte population.

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To the Editor,

Chronic lymphocytic leukemia (CLL), a primary bone marrow malignancy, accounts for approximately 40% of all leukemias in adults [1]. Skin and the central nervous system (CNS) are the most common sites of non-lymphoid, extramedullary disease [2]. CLL/small lymphocytic leukemia (SLL), involving the urinary bladder is rare, with only five documented cases [3–6]. In this paper, we report a rare case of CLL presenting with hematuria, and review literature on this topic.

An 80-year-old female presented to the emergency department with hematuria. She denied fever, chills, unintentional weight loss or drenching night sweats. Physical exam revealed normal vitals, and her systemic examination was negative for any significant abnormalities. There was no lymphadenopathy or hepatosplenomegaly.

Complete blood count revealed the following: white cell count 10 900/ul with 60% lymphocytes and 35% neutrophils, hemoglobin 14.1 g/dl, and platelet count 211 000/ul. Lactate dehydrogenase was mildly elevated at 196 U/l (normal range: 100–190 U/l). Cystoscopy revealed a superficial mucosal abnormality of the bladder which was biopsied. Pathology examination (Figure 1) of the specimen demonstrated an attenuated urothelium and a dense lymphocytic infiltrate within the lamina propria. The infiltrate consisted of a monotonous population of small lymphocytes with scant cytoplasm and condensed chromatin. Immunohistochemistry identified the cells as predominantly B cells that were positive for CD20, PAX5 and CD23. They were CD10 negative and cyclin D1 negative. There were scattered reactive T cells with CD3 expression. The findings were consistent with CLL/SLL. A positron emission tomography/computed tomography (PET/CT) scan did not reveal any lymphadenopathy. The bladder wall thickness was normal.

CLL/SLL primarily affects individuals over the age of 65 [1]. Even though 70–80% of patients are asymptomatic and are diagnosed incidentally on routine blood count analysis, some patients may present with fever, night sweats, fatigue and weight loss [1]. Involvement of non-lymphoid, extramedullary organs, is rare. In a large systematic review conducted by Ratterman et al., only 192 documented cases of extra medullary CLL/SLL were identified between 1975 and 2012 [2]. Skin involvement accounted for 33% of these cases, followed closely by CNS disease at 27%.

Schniederjan et al. reviewed 40 cases of genitourinary lymphoid neoplasms diagnosed between 1986 and 2008 [7]. Of these patients, 15 had neoplasms localized to the kidney, eight had neoplasms of the prostate and five had urinary bladder involvement. Diffuse large B cell lymphoma accounted for 43% of all cases. However, there were no reports of CLL/SLL in the urinary bladder. Based on our literature search, we were able to identify only five documented cases of CLL/SLL in the bladder (Table 1). In contrast to our patient, these individuals had an established history of CLL/SLL. Notably, majority of the cases (5/6) were reported in females. Our patient did not have a history of CLL/SLL, nor did she present with any common disease manifestations. Her hematuria improved over time, and she has been under surveillance every 4–6 months, without disease progression.

In conclusion, CLL/SLL primarily developing in the bladder is extremely rare. Diagnosis requires cystoscopy and biopsy of bladder.

Disclosure statement
The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

References
Prolymphocytic leukemia (PLL) is a rare, aggressive lymphoid malignancy, characterized by marked lymphocytosis (prolymphocytes >55%) and splenomegaly, accounting for 2% of all mature lymphocytic leukemias. There are two subtypes of PLL, B-cell prolymphocytic leukemia (B-PLL) and T-cell prolymphocytic leukemia (T-PLL). Morphologically, B-PLL is identical to T-PLL, but extramedullary features are less common, with favorable survival (3 years vs. 7 months) [1]. More than half of patients with B-PLL carry abnormalities in TP53 tumor suppressor gene. The most common chromosome abnormality in T-PLL is abnormality of chromosome 14 (80%), and Trisomy 8 (53%) [2]. Treatment of B-PLL is extrapolated from chronic lymphocytic leukemia (CLL), and alemtuzumab-based chemotherapy improved survival of T-PLL patients.

The development of a second malignancy is a serious complication of prolonged survival in cancer patients, which accounts for 16% of incident cancers in the USA [3]. Immunologic defects [4], genetic susceptibility [5] and treatment-related factors [6] increase risk of second cancers in CLL, however no reports addressed this issue in PLL. Therefore, I evaluated the overall risk of second primary malignancies (SPMs) after six months diagnosis of 399 patients with a first primary PLL who were selected from the Surveillance, Epidemiology, and End Results (SEER) 13 registries (1992–2012) of US National Cancer Institute (www.seer.cancer.gov). We excluded cases diagnosed by autopsy or reported by death certificate. The standardized incidence ratio (SIR) with corresponding 95% confidence interval (95% CI) was calculated by SEER*stat software (version 8.2.1).

Of the total 399 PLL patients, the median age at diagnosis was 69 years (range 11–100 years), 60% male (male-female ratio of 1.5:1), and 82.6% white (Table 1). There were 94 cases (27.7%) with T-PLL, 71 cases with B-PLL (20.9%), and 174 cases (51.4%) with PLL-not otherwise specified (PLL-NOS). The median latency time to develop 29 SPMs among 399 PLL patients was 41 months (range 8–174 months). As shown in a Table 1, the overall risk of SPMs was relatively constant between latency period 1–4 years (SIR 1.52) and >5 years (SIR 1.77).

With a median follow-up of 26 months (range 6–244 months) and contributed 1119 person-years (PY), 26 patients (6.5%) developed 29 SPMs during the study period. The most common second cancers was non-Hodgkin lymphoma (NHL) (n = 8), multiple myeloma (MM) (n = 4), digestive system cancers (n = 3), leukemias (n = 2), urinary system cancers (n = 2), and prostate cancers (n = 2) (Figure 1). The solid cancers have been reported in 3.8% (n = 13) of patient cohort, compared to 6% that reported in CLL patients received fludarabine, cyclophosphamide and rituximab [6]. We also observed eight of 339 patients (2.3%) developed NHL, however misclassification of PLL is inevitable [7]. Of note, Richter syndrome occurs in approximately 2–10% of CLL patients [8].

Regarding CLL patients, the risk of second cancers is twice higher than general population in a recent reports [6,9]. We found that the overall risk of all new malignancies in PLL patients was 49% higher than the malignancy in the general populations [Observed (O) 29; SIR 1.49; 95% CI 1–2.14], and an absolute excess risk (AER) of 85.42 per 10 000 PY. It seems that risk of a SPMs is significantly higher in T-PLL (SIR 2.92), compared with B-PLL (SIR 1.93) and PLL-NOS (SIR 1.05).

Compared with the US general population, the overall risk for hematologic malignancies in PLL patients was significantly increased by 7.92-fold. However, the overall risk of a SPMs was non-significantly lower for solid cancers (SIR 0.76; 95% CI 0.4–1.29). This pattern of cancer excesses is in line with a second cancers reported in CLL [9]. The risk of hematological malignancies was remarkably increased for lymphomas (SIR 10.53) and MM (SIR 13.66) (Figure 1). The most frequent lymphomas was NHL (n = 8), with risk of 9.86-fold. In one report [10], the risk of NHL after CLL was 2.73-fold higher than expected. In a SEER database study [11], the risk of MM

LETTER TO THE EDITOR

Risk of second cancers in survivors of prolymphocytic leukemia: a SEER data analysis

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