Hematuria—A Rare Presentation of Hodgkin Lymphoma

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Introduction

Hodgkin lymphoma (HL) is an uncommon malignancy of the lymphoid system characterized by the presence of Reed-Sternberg cells, which are multinucleated giant cells of B-cell origin. The average age at diagnosis is 30 years, and there is a second, but smaller, peak at 50 years or older. Patients often present with an asymptomatic mass or may have associated B symptoms like fever, drenching night sweats, and unexplained weight loss. Other symptoms include fatigue, weakness, anorexia, and pruritus.

We present a rare case of HL, where the initial manifestation was hematuria, and have also included a brief review of the literature.

Case Presentation

A 42-year-old man with no significant medical history presented with hematuria in August 2007. He was a non-smoker and drank alcohol socially. Review of systems was positive for hematuria and negative for renal stones, weight loss, night sweats, fever, chills, abdominal pain or mass, low back pain, melena, hemoptysis, and bleeding tendencies. At the time of physical examination, the patient was obese, weighing 336 pounds, with a body mass index of 45; his blood pressure was 130/72 mmHg. The rest of the examination was unremarkable, and there was no palpable lymphadenopathy in the supraclavicular, cervical, axillary, or inguinal areas.

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Laboratory analysis was unremarkable except for mildly elevated levels of creatinine of 1.6 mg/dL and calcium at 11.0 mg/dL. His baseline creatinine levels in the last year have been 1.5–1.6 mg/dL.

The patient underwent cystoscopy, and a nodular urinary bladder mass was found. A hematology consultation was obtained after a urinary bladder biopsy revealed lymphocyte-predominant HL. Computed tomography (CT) scans (Figure 1) revealed retroperitoneal and bilateral inguinal lymph nodes measuring 11 mm, which were also avid on positive emission tomography (PET) scan. The PET and CT scans also revealed increased uptake in the spleen and suspected mesenteric lymphadenopathy (Figure 2). Biopsy of the pelvic lymph node showed Reed-Sternberg cells consistent with lymphocyte-predominant HL. Slides were sent to Mayo clinic for review, and clinicians there concurred with the diagnosis of HL, which was negative for CD15 and CD30 and positive for CD45 and CD20. Bone marrow biopsy showed 60% cellularity without lymphomatous involvement. Flow cytometry, gated heart scan, and pulmonary function tests were normal. The patient's stage IVA HL was treated with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). Initially, the patient was given 3 chemotherapy cycles with resolution of bulky lymphadenopathy and clearing of bladder mass per repeat cystoscopy. This was followed by 2 more chemotherapy cycles after best response, for a total of 5 cycles and subsequent complete response.

The patient had recurrence of hematuria in June 2008, and a repeat cystoscopy showed a suspicious lesion in the bladder. Biopsies of the bladder and prostate were done, confirming recurrent lymphocyte-predominant HL in both the bladder and prostate. There were features sug-

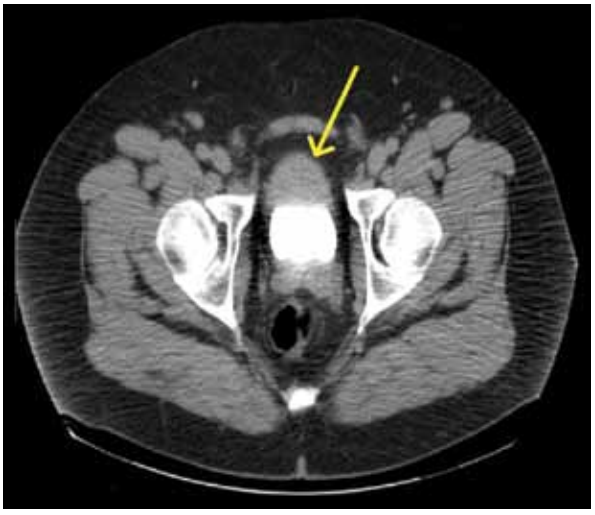

Figure 1. Computed tomography scan axial cut with diffuse urinary bladder wall thickening.

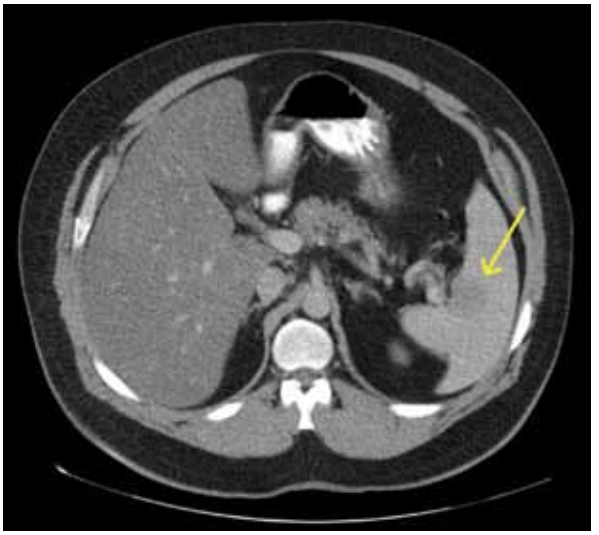

Figure 2. Computed tomography scan axial cut showing a hypodense lesion in the spleen.

gestive of large B-cell transformation, positive for CD20, and negative for CD15 and CD30. Repeat imaging showed lymphadenopathy in the pelvic and bilateral iliac chains. The patient underwent excisional biopsy of the left inguinal lymph node, which was benign.

The patient underwent salvage chemotherapy, followed by autologous stem cell transplant.

Discussion

A literature search revealed that urogenital involvement in lymphomas is very rare. Few case reports that have been published show that secondary involvement of the urinary bladder is relatively more common in non-Hodgkin lymphoma (NHL) than in HL. Although primary lymphoma of the urinary bladder has also been reported, most of the literature is limited to sporadic case reports.

HL is generally considered a widespread lymphatic disease and usually presents with supra-diaphragmatic lymph node involvement and only later with generalized and extranodal lymphatic spread. This is a very rare case, with initial sites of involvement from HL in the urinary bladder and prostate.

In one case report from Bocian and colleagues,[1] a 91-year-old patient relapsed 10 years after a known diagnosis of HL with urinary bladder involvement. Reed-Sternberg cells seen on urine cytology helped in diagnosing the relapse. The authors presumed that relapse occurred in the pelvic lymph nodes, which were outside the radiation field, with subsequent tumor extension into pelvic structures and direct invasion of the urinary bladder. Vascular invasion was not observed in biopsies of the bladder, and a peripheral blood smear did not reveal abnormal lymphocytes or Reed-Sternberg cells.

In 1981, Weimar and associates[2] performed a retrospective analysis over a 10-year period of 1,068 patients with malignant lymphomas, and reported that there was no urinary bladder involvement radiographically, at the time of surgery, or at the time of autopsy among patients with HL. Overall, there was a reported 5.8% incidence of urogenital involvement (kidney and ureter only) by HL at some point in the course of disease. The reported incidence of urogenital involvement with NHL was higher, at 7.3%. They also concluded that almost all patients who had urogenital involvement were in the advanced stage of disease, that the kidney is the urogenital organ most frequently involved by solid lymphatic tumors, and that NHL results in more serious urologic consequences (obstruction, renal infiltration).

A case reported by Sosna and coworkers[3] in 2000 reported a fourth relapse of HL, which manifested as painless hematuria. Their patient had a stem cell transplant after his third relapse, and he was treated with local radiation to the bladder and 3 courses of chemotherapy with mechlorethamine, vincristine, procarbazine, and prednisone (MOPP). He had a positive outcome, with a disease-free interval of more than 3 years.

Sufrin and coauthors[4] performed an autopsy case series of 599 patients who died from malignant lymphoma, and compared primary versus secondary vesical

involvement by lymphoma. They reported the following noteworthy facts: HL caused only 4% of vesical involvement, and secondary vesical involvement tends to occur in patients younger than 50 years as compared to primary vesical involvement, which occurs more often in patients older than 50 years. Men were noted to have more frequent secondary involvement than women, clinical symptoms were uncommon, and prognosis was usually poor.

Prostate involvement by lymphoma is far more rare than previously believed. In 1983, Sridhar and colleagues[5] evaluated 12 cases with prostate involvement from leukemia or lymphoma. HL was seen in only 1 case. They concluded that there is no clinical feature to suggest prostatic involvement in leukemia or lymphoma, and that the prognosis is related to the primary generalized disease rather than to the prostate infiltration.

The urinary bladder lacks lymphatics and so primary lymphoma of the bladder is a rare entity; in our patient, the initial working diagnosis was bladder carcinoma. Less than 100 cases of primary lymphoma of the bladder have been reported to date. These tumors cannot be distinguished from other bladder tumors on the basis of their radiologic or endoscopic appearance; only histology provides the diagnosis.

This case may also represent a composite lymphoma with features of both HL and NHL.

Conclusion

Secondary involvement of the urinary bladder by HL is rare but has been reported. The kidney is the most common urogenital organ involved in lymphoma. Many patients noted to have urogenital involvement are already in the advanced stage of disease. Extranodal disease, as in this case, can confuse the working diagnosis and should be kept in the differential diagnosis of a patient with hematuria. The majority of cases of urinary bladder involvement by lymphoma—either clinically or at the time of autopsy—are of the NHL variety. Cystoscopy and cystography are valuable in diagnosing gross lesions. The treatment of secondary vesical lymphoma is symptomatic, and local radiation can be given for palliation. The treatment of primary disease has yet to be established, but would logically include systemic chemotherapy and/or radiation therapy.

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Review
A Rare Presentation of Hodgkin Lymphoma

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Dembla and colleagues[1] describe an interesting case of a 42-year-old man with hematuria as the presenting form of Hodgkin lymphoma (HL). He was treated with chemotherapy without radiation. New hematuria, representing recurrence of HL, developed almost 1 year later. Diagnosis and management of cases like this remain somewhat unclear.

Lymphomas of the urinary bladder are very rare tumors. They represent less than 1% of all malignant bladder lesions. Typically, there is secondary involvement in patients with a previously diagnosed lymphoma (secondary bladder lymphoma), and rarely, it may occur as a disease localized to the bladder (primary bladder lymphoma). The latter is not exactly "primary" bladder lymphoma, as it represents the site of first evidence of a disseminated lymphoma.[2]

In the bladder, most lymphomas are B-cell non-Hodgkin lymphoma (NHL) type, but there are some differences in the first localization of the tumor. In the case of primary bladder lymphomas, the most frequent histologic type is the low-grade mucosa-associated lymphoid tissue (MALT) type, and in cases of secondary dissemination to the bladder, diffuse large B-cell lymphoma is the most common histologic type.[3]

Bladder involvement by HL is extremely rare, and only occasional reports of both primary and secondary bladder involvement in patients with HL have been published.[4,5] This could be explained by the lack of lymphoid tissue in the urinary bladder. Continuity and hematogenous dissemination have been postulated to explain the development of these tumors in the bladder. The case of prostate involvement is somewhat different. Lymphomas involving the prostate account for less than 0.1% of all lymphomas. Occasional rudimentary lymphoid nodules and some cases of primary lymphomas limited to the prostate have been described as NHL, predominantly B-cell type. HL affecting the prostate is even more rare.[6]

Extranodal presentation of HL is extremely infrequent, representing less than 1% of all HL in non-AIDS patients. It has been recommended that stringent morphologic and immunophenotypic criteria be used before establishing this diagnosis. In the case of bladder lymphomas, chronic antigenic stimulation by repeat urinary tract infections or the effect of viruses like HIV or Epstein-Barr is believed to be an important risk factor in the development of these tumors.[7]

The most frequent symptom of bladder lymphomas is gross hematuria, as in the patient reported by Dembla and colleagues.[1] However, dysuria, concomitant urinary tract infection, or increased urinary frequency have also been reported.[8] Cystoscopy is a key procedure in the management of gross hematuria, and it leads to diagnosis in most patients with bladder masses. After making the diagnosis of HL, a staging study must be performed, including computed tomography (CT) and positron emission tomography (PET) scans, as well as bone marrow biopsy. A PET scan is especially useful in determining whether or not a bladder lymphoma is truly "primary," and it is superior to CT scans for staging and assessing disease extension in both HL and NHL.[9]

Morphologic study of the lymph nodes and bone marrow specimens should look for Reed-Sternberg cells, and immunohistochemical studies must also be performed. The positivity for CD30 and CD15, together with the negativity for CD45 and CD20, and the lack of expression of transcription factors OCT-2 and BOB-1 strongly suggest the diagnosis of classic HL (the latter is useful to rule out lymphocyte-predominant HL). Flow cytometry and molecular characterization are also very

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useful in the diagnosis, especially in order to differentiate classic and non-classic forms of HL.[10,11]

Treatment of HL depends on the histologic type, the extension of the lymph node field, and bone marrow involvement. If the extension is large, radiation should be avoided, as in the present case. Nevertheless, in this case, the lack of radiation could play an important role in the relapse of the HL. Therapeutic modalities have evolved over the last few years, and some of them are clearly related to the immunophenotypic classification, such as the use of rituximab (Rituxan, Genentech) for CD20-positive lymphomas.[12] The best therapeutic approach for bladder HL and NHL remains controversial. Management options include chemotherapy, radiation, and surgery, but chemotherapy (currently with cyclophosphamide, mitoxantrone, vincristine, doxorubicin, or bleomycin in different combinations) is favored because it treats detectable and undetectable early systemic disease.[13]

Bladder and prostate involvement by HL, whether primary or secondary, is very rare. Careful diagnosis with special attention to immunohistochemical studies and disease extension using CT and PET scanning is needed. The therapeutic approach has not yet been defined. This diagnosis must be kept in mind in patients with bladder masses, even though the most common diagnosis at present is bladder carcinoma.

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