Primary low-grade B-cell lymphoma of the urinary bladder: case report and literature review

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The first recorded case of lymphoma of the bladder was reported by Eve and Chaffey in 1885.[1] Malignant lymphoma of the bladder can be classified into one of three different clinical groups: 1) Primary lymphoma localized to the bladder; 2) Lymphoma presenting in the bladder as the first sign of disseminated disease (non-localized lymphoma); 3) Recurrent bladder involvement by lymphoma in patients with a history of malignant lymphoma (secondary lymphoma). Primary extranodal marginal zone lymphoma of mucosa associated lymphoid tissue (MALT type) of the urinary bladder, first described by Kempton et al in 1990, is the most common primary bladder lymphoma and associated with an excellent prognosis.[2] We present a patient with gross hematuria who was found to have a primary bladder lymphoma and review the relevant literature.

Key Words: bladder lymphoma, MALT

Case report

A 61-year old female presented complaining of gross hematuria with blood clots on two separate occasions during first-morning micturition. Her past medical history includes polyarthritis rheumatica, a benign thyroid nodule, and a benign prolactinoma treated medically 8 years prior. Her past surgical history includes elbow surgery, choleycystectomy, and a pyloroplasty for peptic ulcer disease. Her medications include plaquenil, celebrex, methotrexate, folic acid, iron, and calcium. She denied smoking or excessive alcohol intake. She is allergic to demerol and codeine. She denied any family history of cancer or genitourinary ailments. Upon further questioning, she denied any urgency, frequency, dysuria, nocturia, recent or recurrent urinary tract infections, weight loss, change in energy, lower abdominal or back pain. Physical exam revealed a healthy appearing woman. Vital signs were normal and she was afebrile. Chest and abdominal exam were normal. There was no sign of peripheral adenopathy. Her gynecological exam revealed normal adnexa and uterus, but a 0.7 cm cervical polyp. Rectal exam was normal. Urinalysis was positive for leukocytes, negative for blood,

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nitrites, and bacteria, and had a pH of 6.5. Urine culture and cytology were negative. Lab tests, including a complete blood count, electrolytes, renal function, and liver function tests were all normal.

She was referred to gynecology for evaluation of the cervical polyp, and underwent an endometrial and cervical biopsy. This revealed simple glandular hyperplasia of the endometrium without atypia and a benign inflammed endocervical polyp.

She was sent for intravenous pyelography, which revealed normal renal excretion and no signs of obstruction. At the level of the bladder, there were multiple lobulated filling defects consistent with intravesical or perivesical lesions Figure 1. Abdominal sonography revealed normal kidneys, liver, spleen, pancreas, and aorta. Computed tomography of the abdomen and pelvis was normal except for a lobulated bladder mass Figure 2. Cystoscopy revealed a solid, smooth non-ulcerated erythematous lesion on the left lateral wall and anterior bladder neck region, suspicious for a tumor Figure 3. She underwent uneventful trans-urethral resection of this mass. The pathology reported a lympho-proliferative low grade B-cell process consistent with the diagnosis of extranodal marginal zone lymphoma of mucosa associated lymphoid tissue (MALT) type Figure 4. Chest roentography and bone marrow biopsy was normal. A gallium scan revealed intense activity in

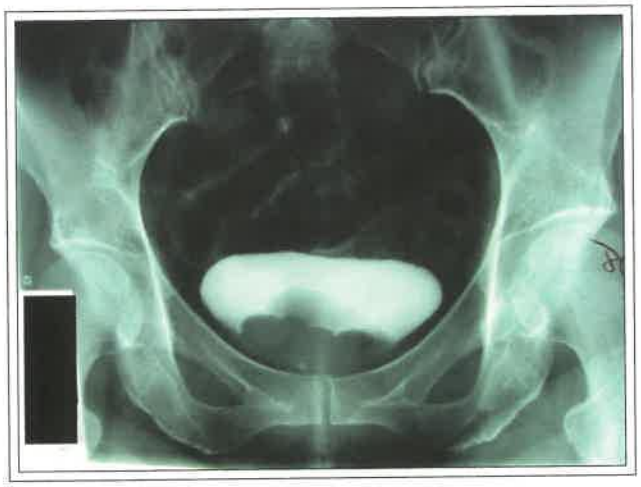

Figure 1. Intravenous pyelography demonstrates multiple lobulated intravesical filling defects which represent the lymphomatous tumor.

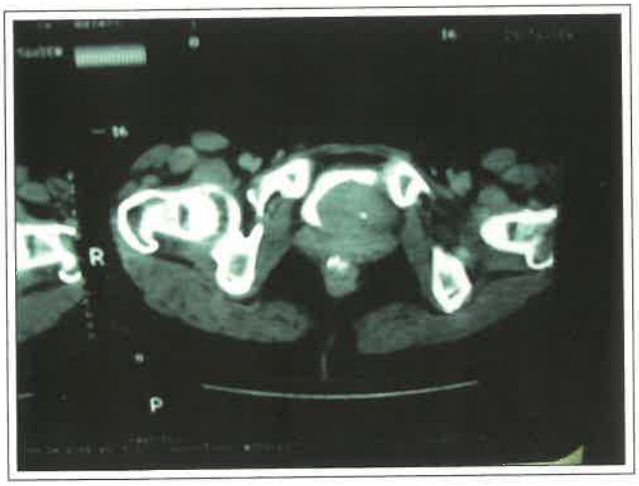

Figure 2. CT scan of the abdomen and pelvis revealed a lobulated mass in the bladder, but no associated retroperitoneal or pelvic lymphadenopathy.

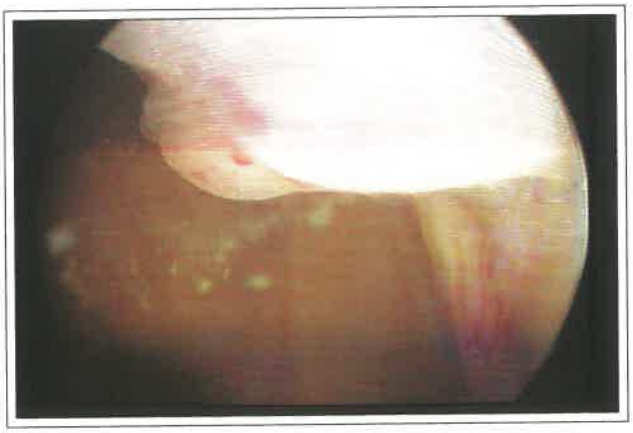

Figure 3. Cystoscopy revealed a solid, smooth non-ulcerated erythematous lesion on the left lateral wall of the bladder, consistent with a bladder tumor.

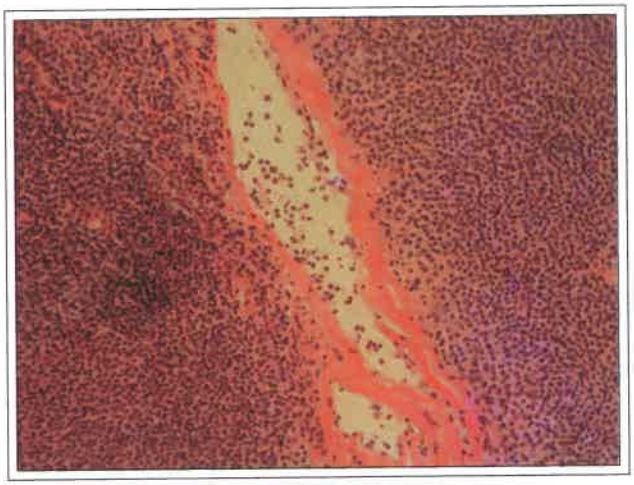

Figure 4. This histological representation of the tumor specimen shows marked infiltration by numerous small lymphocytes with areas of vascular invasion, consistent with the diagnosis of a low-grade lymphoproliferative syndrome.

the bladder region compatible with a lymphomatous infiltration at this level.

The patient was referred to radiation oncology and received whole bladder radiation therapy consisting of 36 Gy given in 20 separate treatments over a 4 week period. She underwent follow-up cystoscopy at 3 months post completion of radiation therapy, which revealed the presence of a residual lesion in the area of the prior tumor, but reduced in size. She remained asymptomatic, without any recurrent urinary symptoms. The radiation oncologists maintain that the presence of a residual lesion does not preclude the possibility of a complete response, and that it may take longer than 3 months for the tumor to resolve completely post successful radiation therapy. At 6 months, she remains asymptomatic, and the tumor on subsequent cystoscopy continues to shrink slowly.

Discussion

Malignant metastatic lymphoma is a common disorder seen in North America. The incidence of secondary involvement of the urinary bladder in these disseminated lymphomas is about 13% overall; including 4.5% of Hodgkin's lymphoma and 12% of NHL.[3] In contrast, primary localized malignant lymphoma of the urinary bladder is a rare entity and the topic of these discussions.[4]

Mucosa-associated lymphoid tissue (MALT) lymphomas were first described in 1983 by Isaacson and Wright in the gastrointestinal tract, but have recently been discussed in other sites, including lung, trachea, thymus, skin, meninges, gallbladder, salivary glands, and bladder.[4,5] Most MALT lymphomas arising in extranodal sites, arise in a region that previously did not have any lymphoid tissue present. It is postulated that the MALT was induced by inflammation secondary to infection or autoimmune disorders. Koss stated that primary malignant lymphoma of the bladder most likely originates from submucosal lymph follicles such as observed in follicular cystitis.[6] Examples include Helicobacter Pylori infection in the stomach, Sjogren syndrome in the salivary glands, and Hashimoto disease in the thyroid gland. The MALT concept provides a mechanism by which malignant lymphomas could develop in the bladder, as they do in other sites that normally possess no lymphoid tissue, after chronic inflammation. Large aggregates of lymphoid tissue are not normally found in the bladder, but it is possible that the neoplasm begins in the lymphocytes that collect in the submucosa of the bladder as a result of some inflammatory reaction or immune response.[7] Two separate studies reported 20%-22% of cases of primary lymphoma of the bladder were preceded by documented cases of chronic cystitis.[4,8,9] Arguments against cystitis as a precursor state that the lymphoid aggregation seen in chronic cystitis is usually on the luminal aspect of the lamina propria (cystitis follicularis), whereas most of the florid lymphomatous involvement in lymphoma is in the deeper layers of the lamina propria and muscle.[10] This controversial issue remains ill-defined.

Extranodal marginal zone lymphoma of the MALT type arising in and localized to the bladder was first described in 1990.[2] It is a rare entity, with fewer than 100 cases reported in the current literature. It is difficult to distinguish this lesion from other vesical or extravesical neoplasms, thus requiring specialized and extensive diagnostic tests. It represents 0.2% of all extranodal lymphomas diagnosed in North America.[11] It usually occurs between the fifth and seventh decade of life, with a female preponderance (male:female ratio 1:6.5). The most common presenting symptom is gross hematuria. Other symptoms include urgency, frequency, dysuria, nocturia, lower abdominal/back pain, weight loss, and a palpable pelvic mass. Hydronephrosis is found in about 50% of patients. The combination of gross hematuria and dysuria or frequency was found in 77% of patients diagnosed with primary lymphoma of the bladder, in contrast to only 12% of patients who experience these symptoms and are found to have other bladder neoplasms.[7] The best diagnostic imaging study to make the diagnosis is computed tomography scanning of the abdomen and pelvis, although there is no defined image specific to this entity. The diagnosis depends on cystoscopic biopsy and careful immunoperoxidase staining for common epithelial and lymphoid markers.[12] The cystoscopic appearance of a lymphoma of the bladder is variable. It can present as a solitary mass or multiple lesions, either discrete or diffuse with nodule formation. The lateral walls are most frequently involved, although any part of the bladder can be affected. The tumor can be necrotic (resembling transitional cell carcinoma), submucosal, smooth, non-ulcerative, edematous, friable, or hemorrhagic.[11,12] Although the tumor may appear to be confined to a small area in the bladder wall, submucosal extension is often not visible but can be extensive.[7] Patients with prostatic involvement of the lymphoma generally have a poor prognosis despite aggressive therapy; their survival is often limited by dissemination to distant nodes and viscera.[10]

If a lymphoma of the bladder is found, it is

imperative to complete an investigation to exclude systemic lymphoma, which would otherwise suggest involvement of the bladder as a secondary tumor. Various methods used to confirm this include: CT scan, bone marrow biopsy, lymphangiography, gallium scan, and operative exploration. Malignant lymphoma of the bladder is considered primary only if other organ systems, including lymph nodes, are free of lymphomatous disease.[9] The diagnosis of a lymphoma that is localized to the bladder is more favorable, and associated with a better prognosis because, by definition, it is at the time of diagnosis confined to a single organ.[8]

The two most common forms of primary lymphoma of the bladder include extranodal marginal zone lymphoma of the MALT type and diffuse large B-cell lymphoma. There can be spontaneous transformation from one to the other. The histologic features suggestive of a MALT-type lymphoma include dense, monomorphic atypical lymphoid (centrocyte-like) infiltrates with reactive lymph follicles in the subepithelial tissue and monocytoid and/or plasmacytoid features. Only 20% of these tumors present as high grade.[4,13]

A variety of treatment options for primary bladder lymphomas are reported in the literature, all associated with a favorable prognosis. A review of the literature highlights the benefit of multimodality therapy and emphasizes the value of aggressive treatment of the tumor.[14] Therapeutic modalities used for these tumors include local radiation therapy alone,[4] whole-bladder irradiation, doxorubicin-containing chemotherapy,[15] partial or radical cystectomy,[9] and intravesical mitozantrone gel.[16,17] Transurethral resection alone is not recommended as primary treatment because the neoplasm often involves the deeper submucosa which is not entirely visible or amenable to transurethral resection. For the same reason, radiotherapy should not be localized to the tumor site alone, but should be applied to the entire bladder, and preferably the entire pelvis. Persistent irritative bladder symptoms can be palliated adequately at times with external beam radiation.[18] Chemotherapy holds promise for the young female patient in whom preservation of fertility is important, since radiotherapy may result in destruction of reproductive and gonadal function. The literature seems to favor cystoscopic biopsy followed by local megavoltage radiation (at least 30 Gy) with or without chemotherapy. Surgical resection followed by radiation or chemotherapy reported a 73% 1-year and 64% 5-year survival.[7] Prognostic factors that influence survival most strongly are the stage and bulk of disease at presentation as well as the histological classification of the tumor.[19,20] □

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