Solitary Extramedullary Plasmacytoma of the Bladder

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Plasmacytoma is a rare B-lymphocyte neoplastic disorder that usually presents as the generalized disease multiple myeloma. Less than 5% of the cases present as a solitary mass of monoclonal plasma cells in the bone or soft tissue. Although solitary extramedullary plasmacytoma (SEP) may arise in any organ, it rarely involves the urinary bladder. A 67-year-old male without a history of multiple myeloma presented with urinary frequency and nocturia; he was later diagnosed with SEP of the bladder. The patient was initially treated with a course of radiation therapy without symptomatic improvement; therefore a chemotherapy regimen consisting of lenalidomide and dexamethasone was subsequently given for six cycles. SEP usually carries a better prognosis and higher cure rate than solitary plasmacytoma of bone, as SEP is radiation sensitive. The role of adjuvant chemotherapy in the treatment of SEP that is resistant to radiation therapy is not clear, since most of the recommendations have been derived from the experience of head and neck SEP. The literature also lacks recommendations for choice of a chemotherapy regimen and surveillance of isolated bladder plasmacytoma. Here we present the first case of a radiation-resistant solitary plasmacytoma of the bladder that was successfully treated with lenalidomide and dexamethasone with successful clinical remission.

Case Report

A 67-year-old male with a past medical history significant for hypothyroidism, benign prostatic hypertrophy, hypercholesterolemia, gastroesophageal reflux disease, and osteoarthritis presented with a four-week history of urinary frequency and nocturia. Family history was remarkable for prostate cancer in his father, and rectal examination showed a mildly enlarged nontender prostate.

Evaluation

Urine microscopy showed 8 RBCs and 31 WBCs; culture was negative, and cytology revealed eosinophils, RBCs, and lymphocytes. A one-week course of ciprofloxacin for suspected cystitis resulted in only partial improvement of symptoms. Cystoscopy revealed diffuse erythema in the right
posterior and lateral walls of the bladder. Biopsy showed urothelial mucosa with cystitis glandularis, marked plasma cell infiltrate, and reactive urothelial atypia (Figure 1a). CD138, a plasma cell marker, was diffusely positive, and kappa and lambda immunostains showed predominantly lambda expression (Figure 1b). Genetic analysis of the biopsy sample was positive for clonal immunoglobulin gene rearrangement. All of these findings supported the diagnosis of lambda clonal plasmacytoma of the bladder.

Results of subsequent evaluation, including CT of the abdomen and pelvis, serum and urine protein electrophoresis with immunofixation, bone marrow biopsy with lymphoma markers panel and plasma cell labeling index profile, skeletal survey, and karyotyping, were unremarkable. A repeat cystoscopy three months later showed normal urothelium without erythema. However, random biopsies were again consistent with plasmacytoma.

**Treatment**

The patient was treated with external beam radiation therapy with a total dose of 4,600 cGy. An MRI of the pelvis, repeat plasma-free light chain, and serum protein electrophoresis with immunofixation at completion of radiation therapy were all again negative for metastatic disease. The patient’s symptoms of urinary frequency and nocturia persisted even after the radiation therapy. Follow-up cystoscopy three months post radiation therapy showed a healthy looking urothelium without erythema. However, biopsy showed a reduced but prominent plasma cell population and lambda light chain restriction in the plasma cells. Immunoperoxidase stain showed scattered subepithelial plasma cells with positive CD138 and negative CD20. The patient was referred to another center for a second opinion; there, a repeat evaluation for multiple myeloma was negative. Because the last bladder biopsy showed reduced clonal plasma cells, continued observation was suggested, with this consisting of serial protein electrophoresis and immunoglobulin-free light chains, MRI or PET scan, and surveillance cystoscopy in four to six months.

**Cystoscopy images.** At 4 months post–radiation therapy (A,B), 3 months after initiation of chemotherapy with lenalidomide/dexamethasone (C,D), and 1 month post-chemotherapy (six cycles) (E,F).

**Follow-up**

Four months later, the patient presented with progressive urinary frequency and nocturia, and a repeat cystoscopy showed pronounced erythematous patches in the right posterior wall and a new area of involvement in the left posterior wall (Figure 2 a,b). Biopsies taken during cystoscopy showed plasmacytoma with immunohistochemical staining positive for lambda-restricted plasma cells (Figure 1 c, d). Follow-up bone scan, serum protein electrophoresis with immunofixation, and immunoglobulin-free light chain studies were again negative. Since the biopsy was consistent with persistent plasmacytoma, a course of lenalidomide (25 mg daily, for three weeks on and one week off) with dexamethasone (20 mg daily for the first four days of each cycle) was begun. The patient’s symptoms had improved at follow-up after one month. A three-month follow-up cystoscopy showed reduction in urothelial erythema (Figure 2 c, d); biopsies still revealed a small plasma cell infiltrate. Chemotherapy was discontinued after six cycles. A repeat
cystoscopy one month after stopping chemotherapy showed normal urothelium around the prior biopsy sites (Figure 2 e, f), and repeat biopsies showed very mild and focal lymphoplasmacytic infiltrate with a preponderance of lambda light chain stain (Figure 1 e, f). Patient is currently asymptomatic and has been in clinical remission for almost two and a half years. Ongoing surveillance cytoscopies continue at four-month intervals.

**Discussion**

Plasmacytoma is a rare neoplastic disorder arising from B-lymphocytes. It usually presents as the generalized disease multiple myeloma; however, a few patients (fewer than 5%) with plasma cell malignancies present with either a single bone lesion that is solitary plasmacytoma of bone (SBP), or less commonly, a soft tissue mass of monoclonal plasma cells also known as a solitary extramedullary plasmacytoma (SEP).[1] Median age at diagnosis of SEP is 55 years, with a male predominance of 3:1.[2]

SEP may arise in any organ, either as a primary tumor or as part of a systemic myeloma. SEP is usually localized in the head and neck, especially the upper respiratory tract (in more than 80% of cases).[3] The second-most frequent site is the gastrointestinal tract.[2] Rarely, SEP may involve the central nervous system, urinary bladder, thyroid, breast, testes, parotid glands, or lymph nodes.[3]

SEP is less common than SBP but carries a better prognosis and higher cure rate, as most cases are treated with local radiotherapy.[3] Progression of primary lesions to multiple myeloma occurs in up to 30% of patients. Microvessel density is thought to be associated with an increased risk of progression to multiple myeloma.[4] Progressive disease may present as multiple myeloma, SBP, or soft tissue involvement of lymph nodes, skin, or subcutaneous tissues.

Bladder plasmacytomas are extremely rare, with only 21 reported cases. Most arise as a part of systemic multiple myeloma, but occasionally a urinary bladder primary without evidence of systemic disease is reported.[5] The symptoms at presentation are highly variable and include hematuria, dysuria, urinary frequency, and systemic symptoms of multiple myeloma. A few case reports have emphasized the importance of accurate immunohistochemical analysis to distinguish between plasmacytoma and transitional cell carcinoma, particularly in patients without a prior history of myeloma.[6, 7]

Diagnostic criteria for a solitary plasmacytoma includes a biopsy-proven solitary lesion of soft tissue or bone with evidence of clonal plasma cells, normal bone marrow without evidence of clonal plasma cells, normal skeletal survey and MRI of spine and pelvis, and absence of end-organ damage, such as anemia, hypercalcemia, renal failure or additional lytic bone lesions that can be attributed to a plasma cell proliferative disorder.[8] The role of MRI in the staging of SEP has not been evaluated because of a low risk of progression to multiple myeloma. However, an MRI of the spine and pelvis is recommended in addition to a skeletal survey, since approximately one-third of patients may have additional occult lesions.[1]

Out of 21 cases of bladder plasmacytoma that have been reported, eight had a history of multiple myeloma while five had lymphadenopathy at presentation. Thus, there is little information on the appropriate treatment of isolated bladder plasmacytoma. Most of the recommendations for treatment of SEP have been derived from the experience of head and neck SEP. In general, these tumors are radiosensitive, but there is some evidence suggesting that radiation therapy combined with surgery provides better results.[9] Local control rates of 80%-100% are consistently reported with moderate doses of radiation therapy.[2] There is no firmly established dose-response relationship because of small patient series and low local failure rates. Treatment consists of radiation in the range of 40 to 50 Gy to the involved site.[10] After radiotherapy, the local recurrence rate is less than 5%.[2] The risk of distant relapse seems to be less than 30%, which is significantly less than with SBP.[2] When distant relapse occurs, it tends to be within two to three years of the initial diagnosis. At least two-thirds of patients survive for more than ten years.[2] The risk of progression to myeloma is low in patients with SEP as compared to SBP, with ten-year disease-free survival rates of approximately 70% to 80%.[3]

No evidence has been published to clarify the role of adjuvant chemotherapy in the treatment of SEP.[2] It may have a role in selected high-risk patients, such as those with tumors greater than 5 cm, radiation resistant tumors, and high-grade tumors. As with multiple myeloma, chemotherapy is indicated in patients with refractory disease, relapsed disease, or both. Thalidomide has been used to treat extramedullary plasmacytoma in the context of relapsed multiple myeloma with variable results, but there are no published data on its use in SEP.[2] In patients previously treated with chemotherapy, high-dose melphalan results in an overall survival of no longer than four years.[6]
Controversy surrounding standard treatment for SEP when the bladder is the only involved organ is mainly due to the rarity of the disease and a lack of controlled trial studies. Surgery, radiation therapy, and chemotherapy (either a single modality or in combinations) have been used, but there is no consensus on the optimal chemotherapy regimen and duration. Moreover, treatment recommendations lack guidelines for surveillance and follow-up.

We presented a case of SEP of the bladder that was initially treated with radiation based on the available literature. However, after radiation therapy failed, a chemotherapy regimen consisting of lenalidomide and dexamethasone resulted in complete clinical remission. This case represents the first known case of radioresistant plasmacytoma of the bladder that was successfully treated with six cycles of lenalidomide and dexamethasone. Due to the rarity of solitary bladder plasmacytoma, the case showcases not only a diagnostic challenge but also a therapeutic dilemma. It is important to have a high index of suspicion in order to make the diagnosis of bladder plasmacytoma by utilizing immuohistochemical analysis, especially in patients who lack a history of multiple myeloma.

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