Primary Bladder MALT Lymphoma in a Patient with Rheumatoid Arthritis

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Abstract

MALT lymphoma of the urinary bladder is an uncommon entity. It typically arises from an inflammatory milieu, within which chronic antigenic stimulation leads to the formation of ectopic germinal centers. Within these immune sites, B-cell clones rapidly proliferate and neoplasia results. In this report, we present a case of bladder MALT lymphoma in a patient with rheumatoid arthritis. We then review the literature and suggest an inflammatory pathway that may link this autoimmune disease with lymphomagenesis.

Introduction

Primary lymphoma of the urinary bladder is a rare clinical finding that accounts for only 0.2% of extranodal lymphomas [1]. Approximately 100 cases of bladder lymphoma have been described [2]. Mucosa-associated lymphoid tissue (MALT) lymphoma is the most common pathologic subtype [3].

Extranodal MALT lymphoma is oftentimes associated with chronic infection; however, it has also been described to arise in association with autoimmune diseases [4]. Rheumatoid arthritis is a systemic autoimmune disease associated with a baseline two-fold higher risk of lymphoproliferative malignancies which increases with autoimmune disease severity [5].

Here, we present the case of a patient with rheumatoid arthritis (RA) who developed primary bladder MALT lymphoma. To the best of our knowledge, the association between bladder MALT lymphoma and RA has not been described in the literature.

Case Presentation

A 71 year-old white woman with a history of rheumatoid arthritis presented to her primary care physician with a complaint of persistent suprapubic discomfort. She had no hematuria or other lower urinary tract symptoms. A series of urine cultures were obtained that were negative. A pelvic ultrasound showed an intravesical mass, which prompted a contrast-enhanced computed tomography (CT) scan of her abdomen and pelvis. This showed a two-centimeter filling defect arising from the bladder floor (Figure 1). Cystoscopy confirmed a smooth nodular lesion at the trigone that was resected in the operating room.

Histologic examination of this lesion revealed a dense lymphoid aggregate showing focal residual germinal centers. This aggregate infiltrated beyond the urothelium into the lamina propria and submucosa. The lymphoid aggregates were composed of small to medium sized lymphocytes showing nuclear membrane irregularity, chromatin dispersion, inconspicuous nucleoli and relatively abundant pale cytoplasm (Figure 2). Lymphoid cells were positive for CD20, CD43 and BCL2 and were negative for CD5, CD23 and CD10 (Figure 3). The proliferation index assessed by KI67 was approximately 10%. Taken together, these findings were consistent with MALT lymphoma. A positron emission tomography CT scan demonstrated no evidence of metastatic disease. The diagnosis of primary MALT lymphoma of the bladder was made. Six weeks of oral ciprofloxacin were given as per the recommendation of her oncologist. No systemic chemotherapy was administered. A repeat transurethral resection was performed two months later and revealed no evidence of malignancy. CT scan of the abdomen and pelvis was performed eight months after diagnosis and showed no evidence of disease. Interval cystoscopies have been performed for one year and show no evidence of recurrence.
Discussion

MALT lymphoma of the bladder is a rare diagnosis. It occurs most commonly in older patients, with a median age of 69 years. Females are three-times more likely to be affected than males. Hematuria is the most common symptom, reported by nearly two-thirds of patients, while one-third of patients will describe dysuria. The pathway to developing bladder MALT lymphoma has yet to be fully defined. However, increasing evidence suggests that extranodal MALT lymphomagenesis is driven by chronic immune stimulation [6]. Specifically, it has been proposed that continuous antigenic stimulation leads to the recruitment of lymphoid tissue to ectopic sites to form germinal centers, which are precursors for extranodal lymphoma development. Within this extra-nodal lymphoid aggregate, the immune stimulus promotes rapid proliferation of antigen-specific B cell clones, resulting in errors in mitosis which cause inactivation of tumor suppressor genes and chromosomal rearrangements, ultimately leading to neoplasia.

Most commonly, the continuous immune reaction is caused by chronic infection. This phenomenon has been observed at several sites of MALT lymphoma. Over 90% of patients with gastric MALT lymphoma are positive for Helicobacter pylori [7], 80% of ocular adnexal lymphomas are associated with Chlamydia psittaci [8] and spirochete infections are commonly implicated in MALT lymphoma of the skin [9]. Indeed, amongst cases of MALT lymphoma of the bladder, 20-33% are associated with chronic bacterial cystitis [1,10].

However, autoimmune disorders have also been linked to the development of extra-nodal MALT lymphoma. An elevated risk of lymphoma has been noted in patients with Hashimoto’s thyroiditis, Sjogren’s syndrome, and relapsing polychondritis [11-13]. RA is associated with a two-fold increased risk of lymphoproliferative malignancy development and mortality, with the greatest risk observed in patients with more severe disease [5]. The mechanism of development of lymphoma in RA is not well understood. Constant stimulation of the immune system leading to clonal selection and predisposition of CD5+ B cells to malignant transformation, decreased T-suppressor lymphocytes, and decreased natural killer cell activity are some proposed mechanisms [14]. There is also uncertainty as to whether disease modifying antirheumatic drugs (DMARDs) contribute to the development of lymphoma, however, studies have failed to find a correlation [5,15-16]. Similar to those with chronic infection, it is likely that a persistent inflammatory milieu at the site of lymphomagenesis perpetuates the development of malignancy.

Our patient was being treated for a significant case of rheumatoid arthritis. Amongst her medications was leflunomide, a pyrimidine synthesis inhibitor reserved for moderate-to-severe rheumatoid disease. Thus, a potential pathway through which this MALT lymphoma developed is through chronic inflammation of the bladder driven by her underlying severe autoimmune disease.

This is the first reported case of bladder MALT lymphoma in a patient with rheumatoid arthritis. Evidence is accumulating for the association between extranodal MALT lymphoma and chronic inflammation, either from an infectious or autoimmune source. While the clinical significance of this finding is still to be determined, it does suggest that in patients with autoimmune disorders, especially those with higher disease activity, hematuria and otherwise unexplained lower urinary tract symptoms should prompt careful consideration for malignancy evaluation. Although MALT lymphoma has been described as a clinically indolent disease, its early detection and treatment are paramount, as 10% of MALT lymphomas are reported...
to convert to high-grade lymphomas, which have a far more aggressive course [17].

**Conclusion**

Bladder MALT lymphoma is a rare finding, however, it is more likely in female patients with chronic infections or autoimmune diseases. In these patients, a full work up should be completed in the setting of hematuria or unexplained lower urinary tract symptoms. MALT lymphoma is very treatable if caught early however a subset can convert to high-grade lymphomas with an aggressive clinical course.

**References**