Regression of a Mucosa–Associated Lymphoid Tissue Lymphoma of the Urinary Bladder After *Helicobacter pylori* Eradication Therapy in an Elderly Patient

Jun Hyung Park, MD, Nae Yu Kim, MD, Jung-Ae Lee, MD, Chang Bum Rim, MD, Young-Woong Song, MD, Younghun Kim, MD, Sori Kim, MD, Sang-Ho Shin, MD, Soojung Gong, MD

1Department of Internal Medicine, Eulji University Hospital, Eulji University College of Medicine, Daejeon, Korea
2Department of Internal Medicine, Eulji General Hospital, Eulji University College of Medicine, Seoul, Korea

Primary low-grade lymphoma of the mucosa-associated lymphoid tissue (MALT) type lymphoma of the bladder is rare. A relationship between MALT lymphoma of the urinary bladder and chronic cystitis has been proposed by some reports. Additionally, a relationship between MALT lymphoma of the urinary bladder and *Helicobacter pylori* has been reported. Here we present a case of regression of urinary bladder MALT lymphoma after antibiotic therapy, using *H. pylori* eradication protocol in an elderly patient, who had a high risk of treatment related mortality in curative systemic chemotherapy. The patient is a 74-year-old woman who had a history of chronic cystitis. She was diagnosed with stage IIA primary MALT lymphoma of the urinary bladder and was treated with *H. pylori* eradication triple therapy for 2 weeks. After 2 months, there was a marked regression of the bladder MALT lymphoma lesion in a computed tomography scan of the abdomen.

**Key Words:** MALT lymphoma, Urinary bladder, Helicobacter pylori, Chronic cystitis

**INTRODUCTION**

Isaacson and Wright\(^1\) introduced the concept of mucosa-associated lymphoid tissue (MALT) lymphoma in 1983 from cases of low-grade B-cell gastrointestinal lymphoma. After more than 20 years of clinical research, MALT lymphomas are now recognized as a distinct subtype of non-Hodgkin’s lymphoma (NHL). MALT lymphoma of the urinary bladder was first described in 1990\(^5\). Management has been guided by retrospective clinical studies because primary lymphoma of the urinary bladder is rare. However, the prognosis is excellent with local treatments such as surgery, chemotherapy, or radiotherapy\(^5\), although transformation into a high-grade large B-cell lymphoma has been described.

Since a history of chronic cystitis is common among patients with MALT lymphoma of the urinary bladder\(^6\), a relationship between chronic antigenic stimulation with infectious agents and the occurrence of malignancy has been postulated. It is similar to the relationship between *Helicobacter pylori* and gastric MALT lymphoma. Some data have implicated *H. pylori* in the pathogenesis of bladder MALT lymphoma, and regression of MALT lymphoma after eradication of *H. pylori* was first reported in 2002\(^5\). Therefore, *H. pylori* eradication using antibiotic therapy can be considered as a therapeutic option for MALT lymphoma of the urinary bladder in some situations.
ment reporting low abdominal pain and hematuria on January 10, 2011. She has a history of intracranial hemorrhage (ICH) and chronic cystitis dating to July 2009. She had blood pressure of 140/80 mmHg, pulse rate of 100 beats/min, respiratory rate of 20 beats/min, body temperature of 37.1℃. Most of the laboratory findings were normal except the urine analysis, pyuria and microscopic hematuria, *Escherichia coli* was cultured from urine. An antimicrobial susceptibility test showed sensitivity to amoxicillin/clavulanic acid, aztreonam, cefazolin, cefepime, and imipenem, Ciprofloxacin showed resistance.

An abdominal computed tomography (CT) scan showed diffuse urinary bladder wall thickening with enhancement and perivesical infiltration. There were multiple external and internal iliac lymphadenopathies with enhancing soft tissue mass (Fig. 1A). Liquid-based cytology of urine showed no evidence of malignancy and only a few metaplastic urothelial cells. It seemed like it could be urinary bladder cancer, so she was referred to the Department of Urology.

Cystoscopy showed multiple bulbous lesions at the trigone, and tiny papillary lesions with multiple cysts on both lateral bladder walls. Diffuse erythematous change was observed at the posterior and anterior bladder wall, but there was no sign of bleeding (Fig. 2).

The transurethral resection of bladder was done. Pathologic findings showed diffuse infiltration of the bladder mucosa by centrocyte-like cells characterized by irregular nuclear contours, clumped chromatin, and abundant pale-staining cytoplasm (Fig. 3A). Lymphoepithelial lesions involving cystitis glandularis were also present (Fig. 3B). The immunohistochemical stain revealed: CD20 (+), CD5 (−), CD10 (−), bcl2 (focal+), ki-67 (−); indicating a low grade B-cell lymphoma of MALT.

The patient was referred to the Department of Hemato-Oncology. On physical examination there were no abnormalities. The serum lactate dehydrogenase level was 313 IU/L, and other laboratory results were normal. A chest CT scan showed no mediastinal lymphadenopathy. A diagnosis of NHL, MALT type of the urinary bladder, stage IIA-E was determined.

The patient was old and showed poor performance status, Eastern Cooperative Oncology Group performance status grade 3, because of ICH sequelae. Curative radiotherapy was advised, but refused by the patient. Due to the known relationship of a MALT lymphoma and *H. pylori* infection, the patient was treated with *H. pylori* eradication triple therapy (amoxicillin 1,000 mg twice a day, pantoprazole 40 mg twice a day, clarithromycin 500 mg twice a day) for 2 weeks. Gastroduodenoscopy and gastric mucosa biopsies were negative for both the presence of pathologic lymphoid infiltration and *H. pylori*. The biopsy of the urinary bladder was negative for *H. pylori* like...
Two months later, after the treatment protocol of *Helicobacter pylori* eradication, an abdomen CT scan was done as a follow-up. There was marked improvement of the bladder wall which showed thickening, compared with the previous abdomen CT scan (Fig. 1B). In addition the lymphadenopathy disappeared, and the follow-up cystoscopy revealed marked improvement of bladder lesions.

Fifteen months later, after completion of antibiotics therapy by use of *H. pylori* eradication protocol, a follow-up abdomen CT scan was showed increased size of infiltrative conglomerated metastatic lymphadenopathies (Fig. 4A) and right internal iliac enlarged lymphadenopathy with central necrotic change (Fig. 4B). But the urinary bladder lesion did not show significant interval change since the previous study. We started radiation therapy on the urinary bladder and enlarged intra-abdominal lymphadenopathies, with a total dose of 3,000 cGy.

After completion of radiation therapy, she did not visit the Department of Hemato-Oncology again, and 12 months later she died of a myocardial infarction.

**DISCUSSION**

Isaacson and Wright\(^1\) first proposed the concept of MALT lymphoma in 1983, which was a case of gastrointestinal lymphoma. The following year they proposed that MALT lymphomas accounted for the majority of low-grade B-cell lymphomas of the gastrointestinal tract, lung, salivary glands and thyroid gland\(^6\). MALT lymphomas constitute a group of low-grade extranodal B-cell neoplasms that share similar clinical, pathologic, immunologic, and molecular features and arise in the context of pre-existing, prolonged lymphoid proliferation in mucosal sites. In the past, it was often misinterpreted as "pseudolymphoma", but in recent years, it has been classified as a specific subtype of NHL. The clinical course is indolent and has a long progression-free survival.

Malignant lymphoma primarily involving the urinary bladder is rare. The incidence of secondary involvement of the urinary bladder in lymphoma is about 13%\(^7\). However, primary involvement presents 0.2% of all urinary bladder lymphomas\(^2\). Because of its rarity, limited clinicopathologic data are available and result from single-case observations or small series. It has female predominance, especially in elderly women (average age 58.7 years; male, 45%; female, 55%). Most of the patients were described as Caucasian. The most common presenting symptoms were hematuria, followed by dysuria or nocturia\(^8\).

The best therapeutic approach for bladder MALT lymphomas remains somewhat controversial. Although management options include chemotherapy, radiation, and surgery, chemotherapy is currently favored because it also treats undetectable early systemic diseases\(^9\).

Since there is no naturally occurring lymphoid tissue in the bladder, it is possible that pre-existing chronic inflammation can induce acquired MALT lymphoma\(^4\). Oh-sawa et al.\(^8\) found cystitis in only 20% of primary lymphomas, although in many cases cystitis might have gone undiagnosed. Lucioni et al.\(^10\) reported a 72-year-old white woman who was diagnosed *E. coli* positive recurrent cystitis, and MALT lymphoma of urinary bladder. She achieved complete remission by using antibiotics therapy only (ciprofloxacin for 6 weeks). Oscier et al.\(^11\) reported a 78-year-old female patient with urinary bladder MALT lymphoma who had a history of chronic urinary tract infection, gained a durable complete remission following antibiotic therapy alone. Similar to previously reported data, our patient had a history of chronic cystitis and grossly mimicked an urothelial carcinoma at cystoscopy. She suffered from *E. coli* positive chronic cystitis since 2007, the first visit in Eulji University Hospital and had been treated with ciprofloxacin many times, Antimicrobial susceptibility test showed sensitive in amoxicillin/clavulanic acid, aztreonam, ciprofloxacin, and ceftriaxone. When she was diagnosed with MALT lymphoma of the urinary bladder, her urine culture was positive for *E. coli*. An anti-
micrbiol susceptibility test showed sensitive in amoxicillin/clavulanic acid, aztreonam, cefazolin, cefepime and imipenem, Ciprofloxacin showed resistance.

Antibiotic therapy as a frontline therapy remains experimental. Some reports suggest that antibiotic therapy can be considered one option of treatment in patients with MALT lymphoma of bladder. In our case, the patient was old and showed poor performance status because of ICH sequelae. She had a high risk of treatment related mortality in curative systemic chemotherapy. So focusing on her geriatric status, we selected *H. pylori* eradication antibiotics therapy.

The role of *H. pylori* infection in nongastrointestinal MALT lymphoma was specifically proposed by some reports, but why eradication was successful is still not completely understood. There are some hypotheses about *H. pylori* eradication and regression of nongastrointestinal MALT lymphoma. It is known that urine can contain *H. pylori*, and therefore it is possible to guess, *H. pylori* in the urine might be a cause of urinary bladder MALT lymphoma. Kiesewetter and Raderer proposed another hypothesis about *H. pylori* eradication therapy and regression of nongastrointestinal MALT lymphoma: *H. pylori* eradication including a macrolide antibiotics, and one therefore might speculate that the direct antineoplastic effect of clarithromycin may have played a role in the anti-lymphoma activity.

The relationship between chronic cystitis, *H. pylori* and MALT lymphoma of urinary bladder must be proven through more investigations; these findings will provide important clinical tools in the treatment of MALT lymphoma of urinary bladder.

Our case report presents a possible treatment option for the elderly or poor performance status bladder MALT lymphoma patients who cannot be treated with curative intent systemic chemotherapy or radiation therapy. The other bladder MALT lymphoma cases only had shown immediate treatment results for *H. pylori* eradication treatment or other antibiotics therapy, and did not report long-term follow-up results. In the case of lymphoma treatment, recurrence is a very important problem, Thus we expect that our report will be more interesting and meaningful.

In conclusion, we report the regression of MALT lymphoma of the urinary bladder after the antibiotics therapy, by using *H. pylori* eradication protocol, in an elderly, female patient.

Conflict of Interest Disclosures: The researchers claim no conflicts of interest.

REFERENCES