

MUCOSA-ASSOCIATED LYMPHOMA OF THE BLADDER WITH RELAPSE IN THE STOMACH AFTER SUCCESSFUL LOCAL TREATMENT

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A 64-year-old woman was referred to our hospital for management of an ovarian tumor. Abdominal computed tomography and magnetic resonance imaging revealed a dermoid cyst of the ovary and a bladder tumor. Transurethral resection of the bladder tumor was performed. Histopathological examination of the tumor revealed non-Hodgkin's lymphoma of the mucosa-associated lymphoid tissue MALT type. The patient received radiotherapy for the bladder and had a complete response. Nineteen months later, gastrointestinal endoscopy revealed the presence of a mass lesion in the stomach. Histopathological examination of biopsy specimens from this tumor indicated the same tumor as that in the bladder as they showed identical IgH gene rearrangement. Because of the detection of evidence of *Helicobacter pylori* (HP) infection in the gastric mucosal biopsy specimens, the patient was administered HP eradication therapy, but, the tumor persisted. After radiotherapy, the stomach tumor disappeared. Since then she remains without evidence of local recurrence or relapse.

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Key words : Bladder tumor, Lymphoma, Mucosa-associated lymphoid tissue, Relapse, Stomach

INTRODUCTION

Primary lymphoma of the urinary bladder is a rare tumor. In most cases, the tumors have been reported to be mucosa-associated lymphoid tissue (MALT) lymphomas¹⁾, classified as extranodal marginal zone B cell lymphomas in the revised "World Organization Classification"²⁾. The prognosis is good and few cases of recurrence or death due to MALT lymphoma have been reported. We report here a very rare case of MALT lymphoma of the bladder with relapse in the stomach.

CASE REPORT

A 64-year-old woman was referred to our hospital for management of a right ovarian tumor. The patient had a history of well-controlled diabetes mellitus. Abdominal computed tomography (CT) and magnetic resonance imaging (MRI) (Fig. 1) revealed a dermoid cyst of the right ovary and a bladder tumor. The patient had no history of hematuria or cystitis. The urine cytology was negative. Urine cultures showed no significant bacterial growth. The patient was investigated by cystoscopy. A solitary tumor measuring 3 cm in diameter, with the clinical appearance of a submucosal tumor was detected in the neck and trigone of the bladder. Therefore, we removed part of the tumor for diagnosis by transurethral resection and histopathological examination of the specimens revealed proliferation of small- to medium-sized lymphocytes having slightly irregular nuclei in the bladder submucosa (Fig. 2). The tumor cells colonized the germinal centers of the reactive follicles. The composite immunohistochemical phenotype of the tumor was CD5–, CD10–, CD20+, bcl-2+, cyclin D1–. No genetic abnormalities were noted,



Fig. 1. MRI (T2-weighted image) revealed a bladder tumor.

except for rearrangement of the immunoglobulin heavy chain gene. The findings were consistent with the diagnosis of primary low-grade extranodal B-cell lymphoma of the MALT type. No evidence of lymphoma was found on CT scans of the head, chest, abdomen and pelvis, chest X-ray, gastrointestinal endoscopy, gallium scintigraphy or bone marrow biopsy. In addition autoimmune diseases such as Hashimoto's disease, Sjogren syndrome suggesting that lymphoma arises from acquired MALT were not found. The patient received radiotherapy for the whole bladder (40 Gy). We performed biopsy of the bladder and confirmed a complete response.

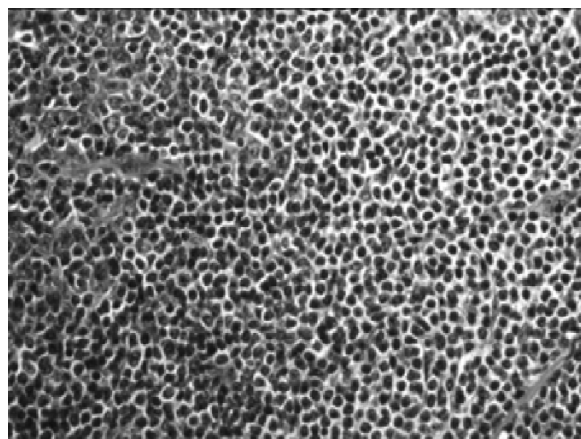


Fig. 2. Histopathological findings of the bladder tumor: diffuse proliferation of small- to medium-sized lymphoid cells (H & E $\times$ 40).

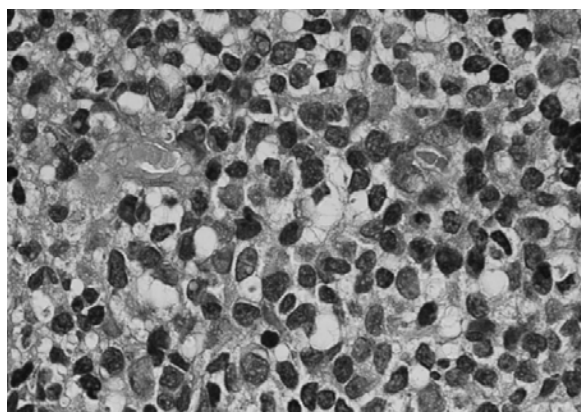


Fig. 3. Histopathological findings of the stomach (H & E $\times$ 100).

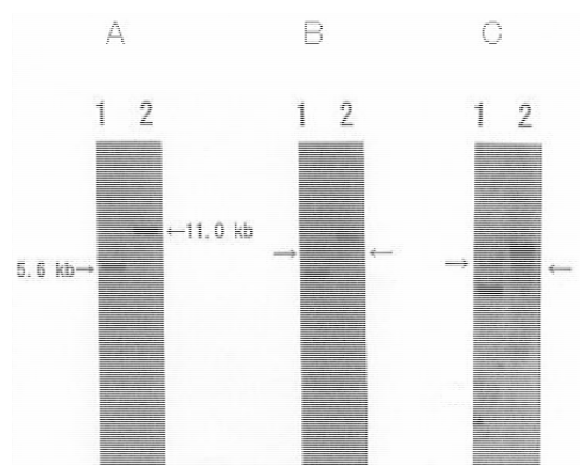


Fig. 4. Molecular analysis of immunoglobulin heavy chain gene rearrangement by polymerase chain reaction using Bam H I + Hind III (Lane 1), Hind III (Lane 2). Lane A, negative control. Lane B, bladder tumor sample. Lane C, gastric tumor sample. The same monoclonal IgH gene rearrangement was found in both the samples (arrows).

Nineteen months later, gastrointestinal endoscopic examination of periodic health screening revealed the presence of a mass lesion in the stomach. Although there was no lymphoepithelial lesion (LEL) characteristic of MALT lymphoma, other histopathological and immunochemical examinations of biopsy specimens of which revealed the diagnosis of MALT lymphoma (Fig. 3). The bladder and stomach lesions were concluded to be manifestations of the same tumor, as they showed identical IgH gene rearrangement (Fig. 4). Whole-body positron emission tomography (PET) revealed a mass lesion only in the stomach. Because of detection of evidence of *Helicobacter pylori* (HP) infection in the specimens of the gastric mucosa, the patient was administered HP eradication therapy. Subsequently, even though serologic examination for HP was negative after this treatment, the mass lesion persisted, with no evidence of HP in the lesion. The patient refused systemic chemotherapy, but successfully underwent radiotherapy for the stomach (45 Gy). She has been followed up with 6-monthly cystoscopy and gastrointestinal endoscopy. However, at present, 30 months after the radiotherapy for the stomach tumor, she remains without evidence of local recurrence or relapse.

DISCUSSION

Malignant lymphoma of the bladder has been divided clinically into three groups: primary, nonlocalized and secondary. The primary type is localized to the bladder, without any evidence of involvement of any other organs, such as the liver, spleen, lymph nodes, peripheral blood, or bone marrow within 6 months of the diagnosis of the bladder involvement. When the lymphoma manifests in the bladder as the first sign of disseminated disease, it is categorized as nonlocalized, and in cases where the lymphoma recurs in the bladder in patients with a history malignant lymphoma, it is classified as being the secondary type¹⁾.

Primary lymphoma of the bladder is a rare non-epithelial tumor. It accounts for less than 1% of primary neoplasms of the bladder, and 0.15–0.2% of all cases of extranodal lymphomas³⁾. Low-grade lymphoma of the MALT type has been shown to be the most frequent type of primary bladder lymphoma. However, the reported histologic types have been categorized according to various lymphoma classification schemes over the years¹⁾. In Japan, malignant lymphoma of the bladder were categorized according to the LSG (lymphoma-Leukemia Study Group of Japan) classification in 1979 and Working Formulation in 1982, but MALT lymphoma which is considered to be one of the most important types of extranodal lymphomas according to the WHO classification published in 2005⁴⁾ was not specifically listed in either classification. Most of malignant lymphomas of the bladder previously reported might have been MALT lymphoma.

MALT lymphoma of the bladder is usually

encountered in middle-aged women, and the mean age at presentation is 58 years. Clinically painless hematuria, urgency and frequency are the principal symptoms¹⁾.

The most common macroscopic appearance at cystoscopy is a solitary submucosal mass with edematous overlying mucosa. Any site in the bladder could be affected although the trigone and the lateral walls are probably the most commonly involved³⁾.

The histologic features include diffuse proliferation of small- to medium-sized tumor cells with slightly irregular nuclei in the bladder submucosa and muscularis. The lymphoma cells sometimes specifically colonize the germinal centers of the reactive follicles. Lymphoepithelial lesion is a typical but not invariable feature of primary lymphoma of the bladder⁵⁾.

There are no specific markers of MALT lymphoma at present. However, immunophenotypically the tumor cells are CD20+, CD79a+, CD5-, CD10-, CD23-, cyclin D1-. Immunoglobulin heavy and light chain genes are rearranged and show somatic mutations of variable regions⁴⁾.

Although evidence of HP infection was found in the gastric mucosal biopsy specimens, we did not consider HP as a very likely cause in our case, as an identical immunoglobulin heavy chain rearrangement was detected in both the bladder and gastric lesions. We concluded that our case represented a relapse of the MALT lymphoma of the bladder. To the best of our knowledge, there has been no previously reported case of relapse of MALT lymphoma of the bladder.

The etiology of MALT lymphoma of the bladder is still unknown. Although some authors have suggested that an underlying inflammatory process in the bladder may be necessary, indeed few cases have a history of recurrent UTIs. t (11; 18) (q21; q21) is a specific chromosomal translocation associated with MALT lymphomas of the stomach and lung⁶⁾, while with those of salivary gland, thyroid gland abnormal autoimmune response may be implicated⁷⁾. Further study of the etiology of the MALT lymphoma of the bladder is needed.

Treatment of primary lymphoma of the bladder is not uniform, perhaps because of the rarity of the disease¹⁾. Currently, radiotherapy and chemotherapy are usually selected after histological diagnosis is established following transurethral resection of the bladder tumor. Tsang et al⁷⁾ reported a local control rate of 95.3% following radiotherapy in patients with MALT lymphomas of various sites, including 2 cases with the tumor arising from the bladder. They treated patients presenting with localized recurrence by radiotherapy and reported almost 100% response rate. Kempton et al.¹⁾ described performing resection/partial cystectomy followed by radiotherapy, with a mean survival of 18 years and no case of death related to the disease. Zucca studied 180 patients with stage I to IV disease and did not find a difference in clinical outcome between initial

localized treatment approaches and systemic chemotherapy⁸⁾. However Wazait et al.³⁾ reported good results with chemotherapy, and suggested that chemotherapy has the advantages of treating occult disease with few complications. Furthermore recurrences may involve the contralateral organ in the case of paired organs or other mucosa-associated lymph nodes^{4,7)}, retrospectively, we should probably have chosen chemotherapy at least after radiotherapy to the bladder. On the other hand there are another interesting cases. Suzuki et al.⁹⁾ reported one case with complete disappearance of the tumor following antibiotic therapy. Bosch et al.¹⁰⁾ reported the disappearance of MALT lymphoma of the bladder following HP eradication therapy.

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和文抄録

胃に再発した膀胱 MALT リンパ腫の 1 例

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厚生連篠ノ井総合病院泌尿器科

患者は64歳, 女性. ドックで卵巣腫瘍を指摘された. 画像検査で膀胱腫瘍を確認したため経尿道的膀胱腫瘍切除術を行った. 病理組織学的検査は MALT リンパ腫であった. 全身検索したが, 膀胱以外に腫瘍はなく, 膀胱に放射線療法を行った. 19ヵ月後, 上部消化管検査で胃の粘膜に腫瘍が認められた. 生検の結果

MALT リンパ腫であり, 遺伝子再構築が認められ, 膀胱 MALT リンパ腫と遺伝子学的に同一と考えられた. *Helicobacter pylori* の感染があり, 除菌が行われたが腫瘍は縮小せず, 胃に放射線療法を行った. その後, 膀胱, 胃に再発は認められていない.

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