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Persistence of Primary MALT Lymphoma of the Urinary Bladder after Rituximab with CHOP Chemotherapy and Radiotherapy

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Abstract. *We present a case of a patient with primary extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue of the urinary bladder that persisted after chemotherapy, immunotherapy and radiotherapy. Case Report: A 48-year-old male underwent a routine ultrasound examination. A tumour mass in the urinary bladder was found and a transurethral biopsy was performed. Pathohistological examination revealed MALT lymphoma. Results of computed tomographic scan, positron emission tomography scan and bone marrow biopsy defined the tumour as primary malignant lymphoma of the urinary bladder. The patient received eight cycles of chemo-immunotherapy (CHOP) and radiotherapy. Five months after therapy, there is a partial radiological remission, but with metabolic progression of the tumour. To our knowledge, this is the first case of MALT lymphoma of the urinary bladder with chemo-immunotherapy and radiotherapy resistance.*

Primary lymphoma of the urinary bladder is rare, comprising 0.2% of extranodal lymphomas, with extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) being the most common type (1). Such tumors have a low rate of recurrence and are usually successfully treated with various therapies (2, 3). We present a case of primary MALT lymphoma of the urinary bladder which persisted after therapy with rituximab in combination with chemotherapy (R-CHOP) and radiotherapy.

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Case Report

An asymptomatic 48-year-old male with good performance status underwent a routine ultrasound examination of the abdomen and urinary tract in August 2011. A mass in the urinary bladder was found suggesting neoplasm. Cystoscopy revealed a tumour mass in the right posterolateral part of the urinary bladder wall. Transurethral biopsy of the bladder was carried out.

Microscopic examination revealed a diffuse subepithelial infiltrate composed of monomorphic small to medium-sized lymphoid cells including centrocyte-like cells and plasmacytoid cells in lamina propria with few reactive germinal centres (Figures 1 and 2).

Immunohistochemically, tumour cells were positive for membrane-spanning 4-domains, subfamily A, member 1 (CD20) and B cell lymphoma-2 antibody (BCL2) (Figure 3) and negative for BCL1, CD5, CD23 and CD43. Staining for Ki-67 was positive in approximately 5% of the tumour cells (Figure 4). The diagnosis was MALT lymphoma.

After histopathological findings, a computed tomographic (CT) scan was performed and showed an expansive lesion of the bladder wall measuring 85 mm in the greatest diameter along with bilateral enlargement of iliac lymph nodes measuring up to 2.1 cm in diameter. Positron emission tomography-CT scan showed pathological metabolism of fluorodeoxyglucose (FDG) with maximum standardized uptake values (SUV) of 5.1 within the lesion and maximum SUV of 4.2 within the bilateral iliac lymph nodes. Fine-needle aspiration cytology of the bone marrow was performed and no evidence of disseminated disease was found.

Based on the clinical data, pathohistological findings and immunohistochemical profile, the diagnosis of primary MALT lymphoma of the urinary bladder was established. According to the urologist there was no indication for operative treatment.

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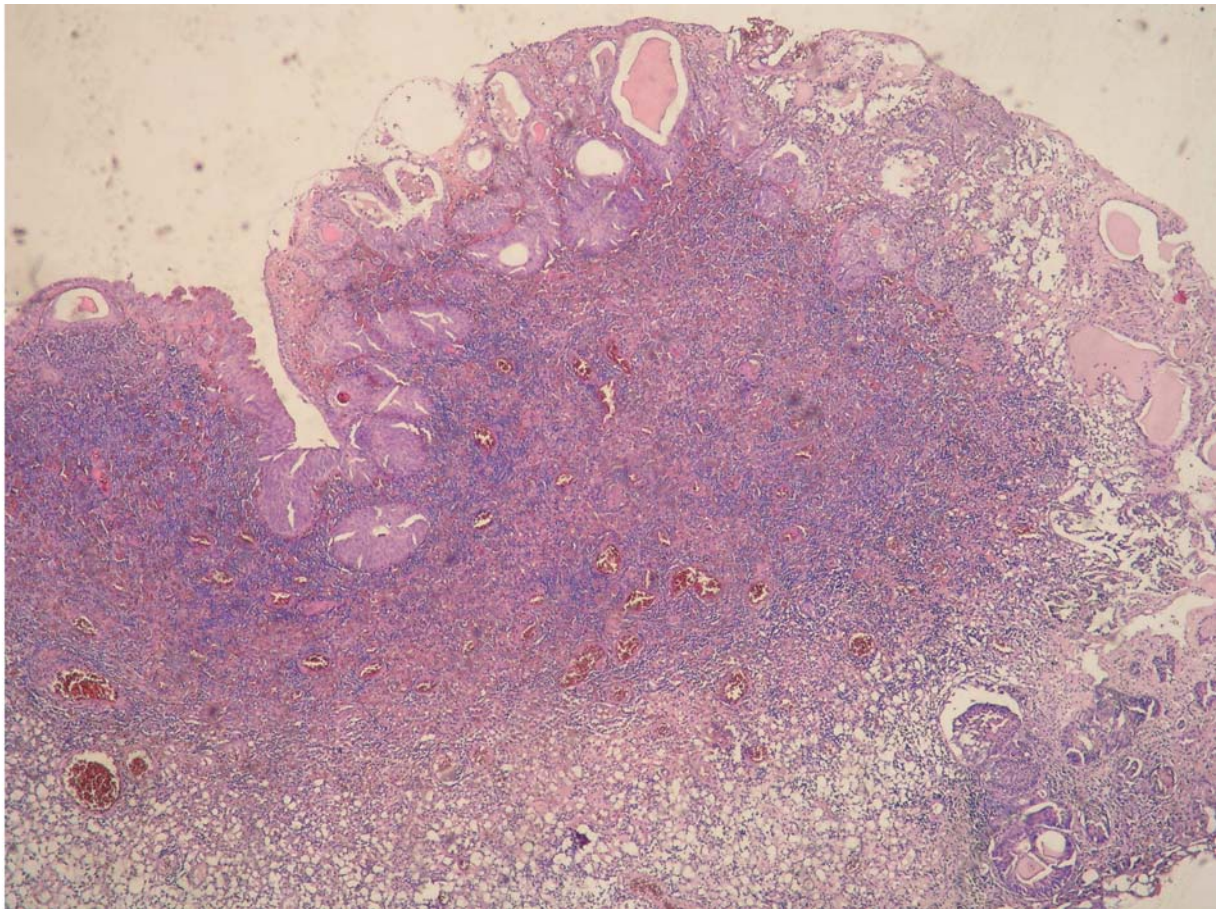

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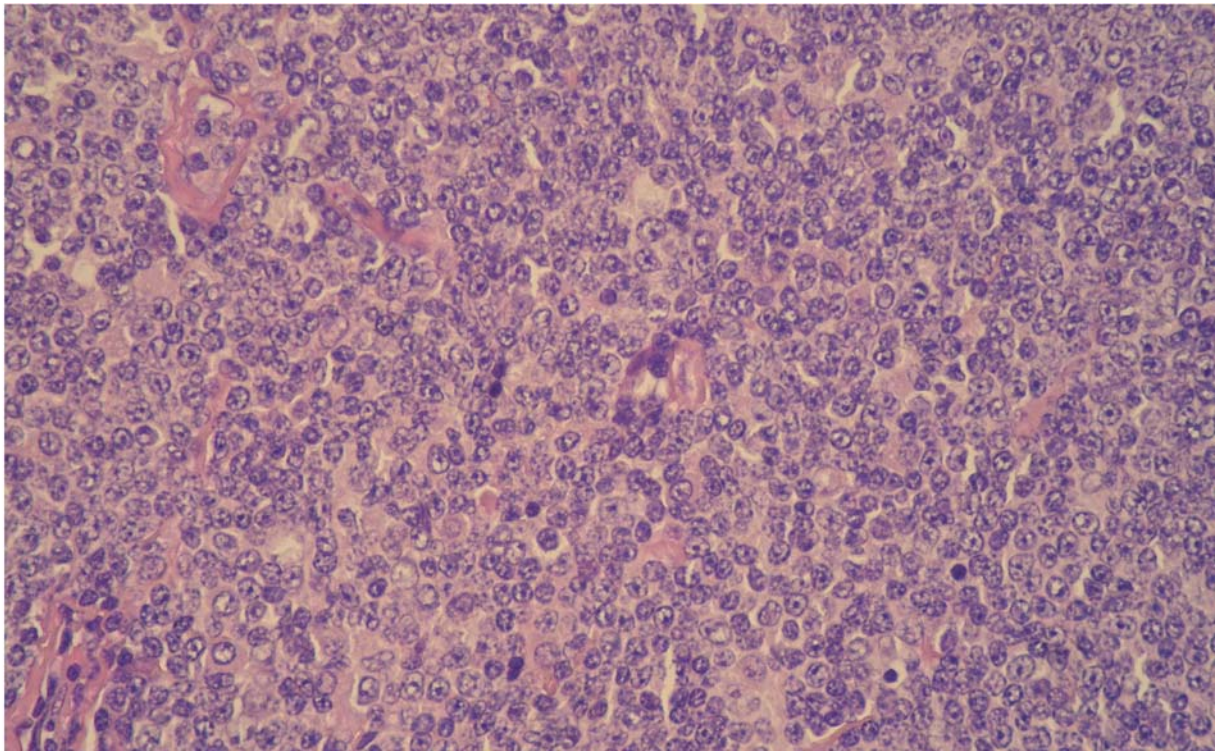

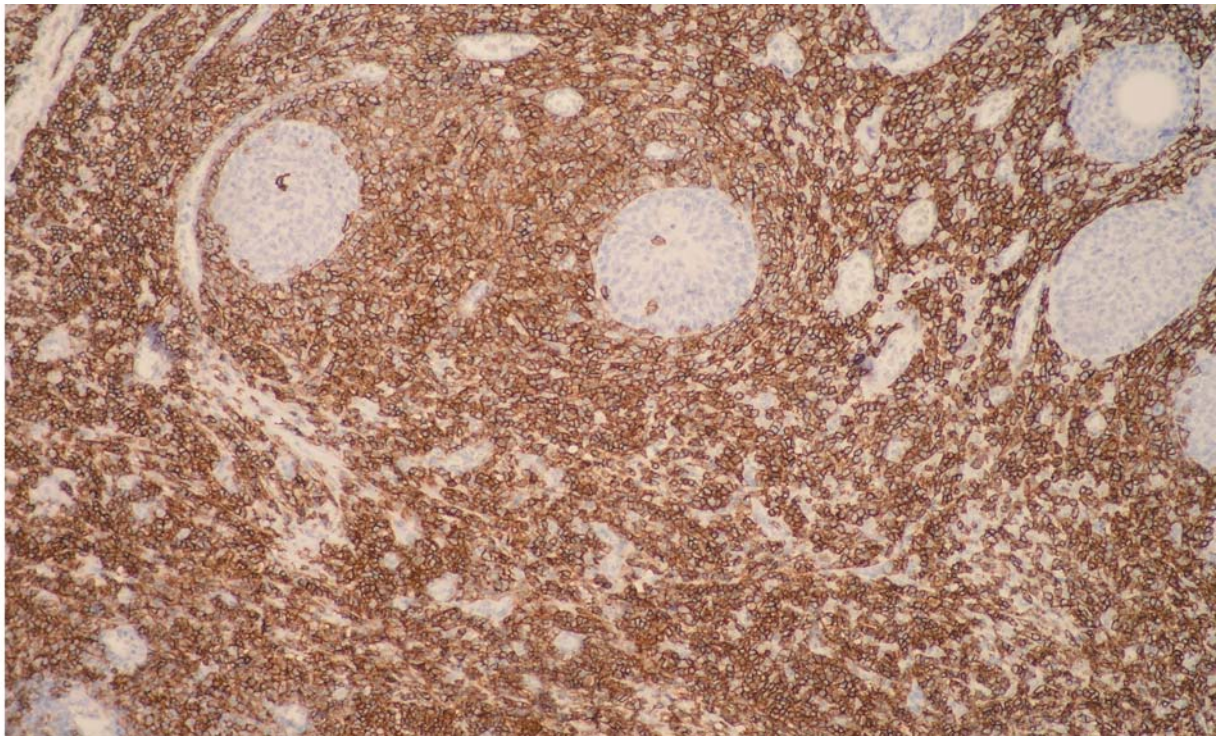

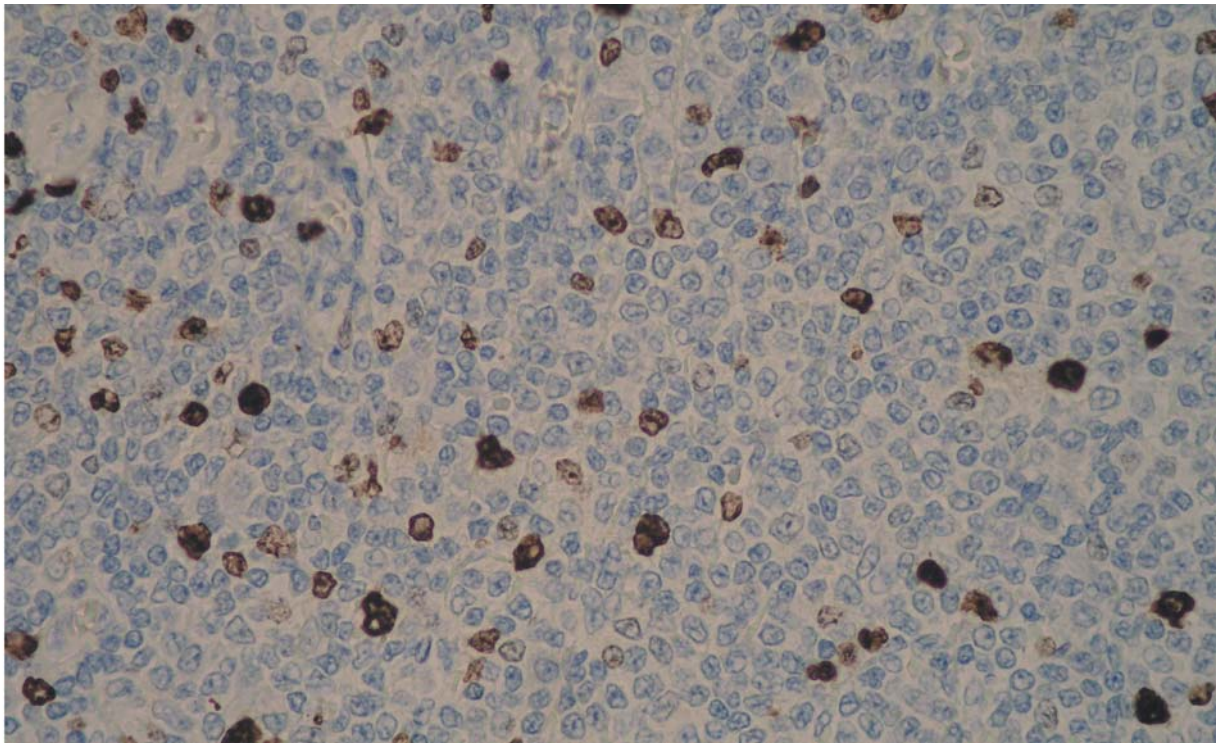

Figure 1. *Bladder biopsy showing diffuse dense subepithelial infiltrate of lymphoid cells in the lamina propria (hematoxylin-eosin staining, magnification ×40).*

Figure 2. *Infiltrate of the tumour cells was composed of monomorphic small- to medium-sized lymphoid cells, including centrocyte-like cells and plasmacytoid cells (hematoxylin-eosin, original magnification ×400).*

Figure 3. *Tumour cells in lamina propria positively stained for CD20 (original magnification ×100).*

Figure 4. *Positive immunohistochemical staining for Ki-67 in around 5% of the tumour cells (original magnification ×400).*

The patient received eight cycles of R-CHOP chemoimmunotherapy (375 mg/m^2 of rituximab with 45 mg/m^2 of doxorubicin, 750 mg/m^2 of cylophosphamide, 2 mg of vincristine and 100 mg of metilprednisolone, applied intravenously, every three weeks) from October 2011 to April 2012. During the treatment he developed mild fatigue and vomiting, consistent with grade one toxicity according to the Common Terminology Criteria for Adverse Events version 3.0 (4). He did not develop any major toxicities and for this reason chemotherapy was not delayed.

One month after chemoimmunotherapy completion, a PET-CT scan showed partial morphological remission, with expansion of the lesion of the urinary bladder wall, measuring 56 mm in greatest diameter, and partial metabolic remission with discrete accumulation of FDG (maximum SUV of 2.3). There was a complete morphological and metabolic remission of pelvic lymph nodes.

From July to August 2012 external irradiation therapy was applied using a linear accelerator with a 3D conformal technique. The patient received a planned tumour dose of 30 Gy in 15 fractions to the pelvic lymph nodes and urinary bladder followed by a boost of 6 Gy in three fractions to the urinary bladder. The patient experienced grade one radiation cystitis, with mild urinary discomfort. After irradiation therapy, in October 2012, pelvic magnetic resonance imaging (MRI) showed a reduction of the tumour size (45 mm in greatest diameter).

In February 2013, a PET-CT scan showed partial morphological remission with tumour lesion of the bladder wall, now measuring 20 mm in the greatest diameter with intensive accumulation of FDG, with maximum SUV of 14, indicating metabolic progression of the disease.

Histopathological examination of the bone marrow showed no dissemination of the disease.

Transurethral biopsy of the bladder was performed. Histopathological examination revealed infiltration of the bladder wall with lymphocytes and plasmacytoid tumour cells, with immunohistochemical expression of kappa-light chains. The finding was consistent with persistence of the primary tumour.

Escherichia coli was isolated from the patient's urine culture and therefore the patient was treated with antibiotic therapy according to antibiogram with 1,000 mg of amoxycillin, twice a day for a seven days period. Three days after the treatment another urine culture was performed and *Klebsiella pneumoniae* was isolated. The patient was treated according to the antibiogram with 400 mg of norfloxacin, twice a day for 10 days. After this last treatment, the patient's urine culture was negative.

After antibiotic therapy, abdominal CT scan showed stable disease according to RECIST criteria (5).

Discussion

MALT lymphomas comprise 7-8% of all non-Hodgkin's B-cell lymphomas (6). Although most MALT lymphomas arise in the gastrointestinal tract, predominately in the stomach, they can arise in almost any organ (7, 8). They have also been reported in thyroid gland, salivary glands, conjunctiva, thymus, breast, lung, kidney, and urinary bladder. MALT lymphomas frequently arise in the context of autoimmune disease or chronic bacterial infection (8).

Primary lymphoma of the urinary bladder is very rare, with MALT lymphoma being the most common type and other types being diffuse large B-cell lymphoma, anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma, follicular lymphoma and unspecified low-grade lymphomas (9, 10). Secondary lymphoma involvement of the urinary bladder is 13% and it is more commonly affected in non-Hodgkin's lymphoma (11).

The first case report of MALT lymphoma of the urinary bladder was described by Kuhara *et al*. in 1990 (12). Review of the English medical literature (*via* Pub Med) revealed approximately 40 primary MALT lymphomas of the urinary bladder described in total.

Primary MALT lymphoma of the urinary bladder follows an indolent clinical course, although cases of transformation from low-grade MALT lymphoma to diffuse large B-cell lymphoma were described (7, 11).

The aetiology of MALT lymphoma arising in the urinary bladder remains unknown. A history of chronic cystitis was reported in 20% of cases and it usually affects female patients (4). There is no naturally occurring lymphoid tissue in the bladder, so one explanation for MALT pathogenesis at this site is that repetitive recurrent infection results in the accumulation of extranodal lymphoid tissue that can eventually undergo malignant alteration (2). MALT lymphoma of the urinary bladder rarely extends to other organs or tissues and in most cases carries an excellent outcome (6, 13-16).

The most effective therapeutic procedure for primary MALT lymphoma of the urinary bladder is still debated. Increasing evidence indicates that eradication of *Helicobacter pylori* with antibiotics can be effectively used as the sole initial treatment for gastric MALT (17). Localized gastric MALT lymphoma was previously treated mainly by surgery, but radiotherapy is now the recommended therapy for *H. pylori*-negative lymphomas and for *H. pylori*-positive cases resistant to *H. pylori* eradication (18, 19). Unfortunately, no specific treatment has been identified for non-gastric location of MALT lymphoma. The treatment of non-gastric MALT consists of radiotherapy if the disease is localized, or chemotherapy if disseminated. There are also posibilities of using new therapeutic approaches, including immunotherapy, proteasome inhibitors, antibiotics and oxaliplatin (20).

Oscier *et al*. reported two cases of primary MALT lymphoma superimposed on chronic cystitis that were successfully treated with antibiotic therapy alone. In these cases, there was no tumour recurrence 19 and 25 months after treatment respectively. The authors suggest that antibiotic therapy can only be a therapeutic option in a patient with localized MALT lymphoma of the bladder that is associated with microscopic or microbiological evidence of urinary tract infection (2).

Van den Bosch *et al*. presented a case of primary MALT lymphoma of the urinary bladder that was successfully treated with *H. pylori* eradication therapy. Three years after therapy, the patient was in persistent complete remission. This is the first known case of the disappearance of a MALT lymphoma of the urinary bladder after treatment with such eradication therapy (21).

In our case, the patient was an asymptomatic male who had no evidence of urinary tract infection. Consequeatly, the antibiotic therapy was not considered as an initial treatment of choice for our patient. Due to the locoregional status of the disease at presentation (PET-positive regional lymph nodes), the decision was made to start with R-CHOP chemoimmunotherapy. The treatment lead to partial morphological and metabolic remission of the disease. In our effort to eradicate the tumour, consolidation radiotherapy was applied but only partial morphological and metabolic remission of the disease was achieved. Afterwards, antibiotic therapy according to an antibiogram was given to the patient, with stable disease as the best response.

To our knowledge, this is the first case of MALT lymphoma of the urinary bladder with chemoimmunotherapy and radiotherapy resistance. It seems that additional treatment options should be considered in such cases.

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