Mucosa-associated lymphoid tissue lymphoma and concurrent adenocarcinoma of the prostate

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Abstract

Primary mucosa-associated lymphoid tissue (MALT) lymphoma of the prostate is a rare disease that characteristically follows an indolent course. It is believed that infection or chronic inflammation may be triggers for malignant transformation in the prostate, but it is of unknown etiology. Reports of MALT lymphomas of the prostate with other concurrent primary prostate cancers are even more limited. We present the unique case of a 67-year-old male with concurrent adenocarcinoma of the prostate and primary MALT lymphoma of the prostate. The patient was treated with standard therapy for prostate adenocarcinoma, which would also treat a primary MALT lymphoma. He has been disease-free for over one year for both his primary malignancies. This case confirms that MALT lymphoma can arise concurrently with adenocarcinoma of the prostate.

Introduction

In 1983, Issacson and Wright identified a variant of B-cell lymphoma in the gastrointestinal tract that they defined as malignant lymphoma of mucosa-associated lymphoid tissue (MALT).[1] Marginal cell lymphomas of MALT, nodal, and splenic origins were subsequently included in the 1994 REAL and 1998 WHO classifications.[2,3] MALT lymphoma is usually indolent, but may transform into aggressive large cell lymphomas. It constitutes 8-10% of non-Hodgkin's lymphomas, with most cases being localized at presentation and remaining so for long periods of time. They are usually highly responsive to local radiation therapy, with 30 Gy to involved nodal or extranodal sites yielding a control rate close to 100% and the chance of long-term cure in approximately 75% of patients.[4-8] Relapses tend to occur at other extranodal sites where MALT lymphomas usually occur, or in a nonirradiated contralateral paired organ.

The literature on MALT lymphomas of the prostate is very limited. MALT of the prostate may be the result of disseminated or primary disease.[9] One case report describes a patient with an indolent course of salivary gland disease that later disseminated to the renal sinuses and prostate.[10] Accordingly, MALT lymphoma in the prostate should be considered in the differential diagnoses for lymphoma patients with systemic disease who present with obstructive urinary symptoms.[11] There are only seven case reports of primary prostatic MALT lymphoma.[10,12-17] Typically, the patient presents with symptoms of urinary obstruction, and workup for what is presumed to be another prostatic process returns a diagnosis of MALT lymphoma in the resection specimen.[10,14-16,18] Treatment can range from radiation therapy, with external beam to 44 Gy over 22 fractions,[13] to chemotherapy,[16] to transurethral resection alone.[14,15] Regardless of the presentation or treatment used, the disease course is typically indolent.[10,13,15-17] In one case of recurrence, a man who had been treated for benign prostatic hyperplasia with atypical lymphoid infiltration presented seven years later with a diagnosis of relapsed MALT lymphoma after a newer, more detailed analysis had been conducted on the initial and relapsed lesions.[19] The disease had not been aggressive, as the patient presented with stage IA disease at the time of relapse and remained disease-free for two years after the second transurethral resection.

Concurrent prostatic adenocarcinoma and lymphoma of the prostate is rare, but usually tends to be with B-cell lymphomas.[11] There is one case report of a prostatic adenocarcinoma and concurrent chronic lymphocytic lymphoma.[18] The patient presented with urinary obstruction, hematuria, and a PSA of 46 ng/mL, and prostatectomy showed disease in both lobes as well as nodes.

Case Report

We report on an unusual case of a patient who had concurrent primary MALT lymphoma of the prostate and adenocarcinoma of the prostate. A 67-year-old Hispanic man presented with urinary frequency and nocturia. He had no history of acute prostatitis, chronic prostatitis, or *Helicobacter pylori (H. pylori)* infection, and the urine culture was negative. The physical examination was unremarkable. He had no palpable nodules on the digital rectal examination. Laboratory values revealed a PSA level of 7.0 ng/mL, which had increased from 2.8 ng/mL over a one-year time frame. The biopsy revealed adenocarcinoma of the prostate, with a Gleason Score of 3+3. The patient then underwent definitive therapy for his prostate cancer with a radical prostatectomy. Pathological results from his surgery returned a diagnosis of adenocarcinoma of the prostate with a pathological stage of pT2cN0. However, his Gleason score was upstaged to 3+5 with margin status unassessable secondary to surgical specimen fragmentation.

Microscopically, the sections of the prostate showed an extensive lymphoid infiltrate (Figure 1) besides a carcinoma, which was present in a different area, mostly at the prostate apex. Figure 2 shows the adenocarcinoma of the prostate, Gleason score 3+5. The lymphoid infiltrate showed monomorphic, small lymphoid cells with small follicles in multifocal areas. The interfollicular areas were expanded and showed a diffuse infiltrate by small lymphoid cells, which had round to irregular nuclear membranes and scanty cytoplasm. Rare lymphoepithelial lesions were seen in the specimen (Figure 3). This may be characteristic for MALT of the prostate as this was also noted by Li *et al.*[19] The pattern of this

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Key words: MALT, prostate cancer, prostate lymphoma.

Contributions: JK and ME contributed equally to, authored, and revised this manuscript; ME was the treating resident physician for this case; JK did the primary literature review; YM was the attending pathologist and completed all the slide preparations, immunohistochemical stains, and pathological diagnosis; OS was the treating attending physician for this case; OS and PK offered criticism and advice for this manuscript.

Conflict of interest: the authors report no conflicts of interest.

Received for publication: 25 May 2010.
Revision received: 6 August 2010.
Accepted for publication: 9 August 2010.

Rare Tumors 2010; 2:e54
doi:10.4081/rt.2010.e54

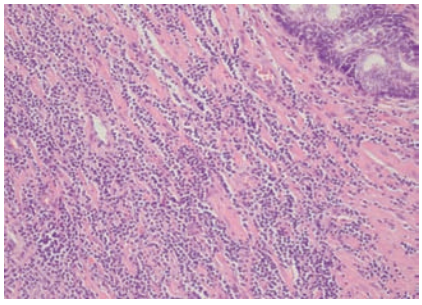

Figure 1. MALT lymphoma of the prostate. A monomorphic lymphoid population infiltrates the prostate tissue. The lesional lymphocytes are uniform and small in size, some with clear cytoplasm. There are some benign prostate glands in the upper right corner of the section. (Hematoxylin-and-eosin stain; low-power magnification.)

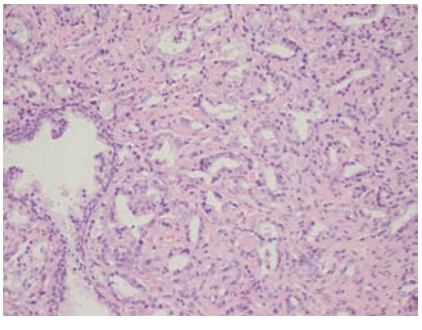

Figure 2. Adenocarcinoma of the prostate (Gleason 3+5). Most of the neoplastic cells form variable sized glands in an infiltrative growth pattern (Gleason score 3); some single tumor cells are also present (Gleason score 5). (Hematoxylin-and-eosin stain; high-power magnification.)

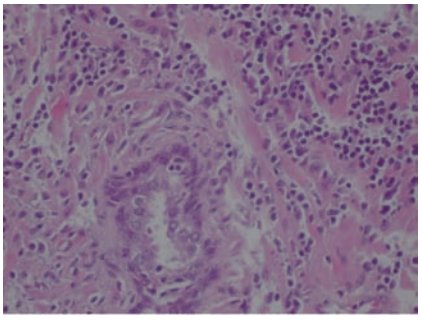

Figure 3. Lympho-epithelial lesion characteristic of MALT. (Hematoxylin-and-eosin stain; high-power magnification.)

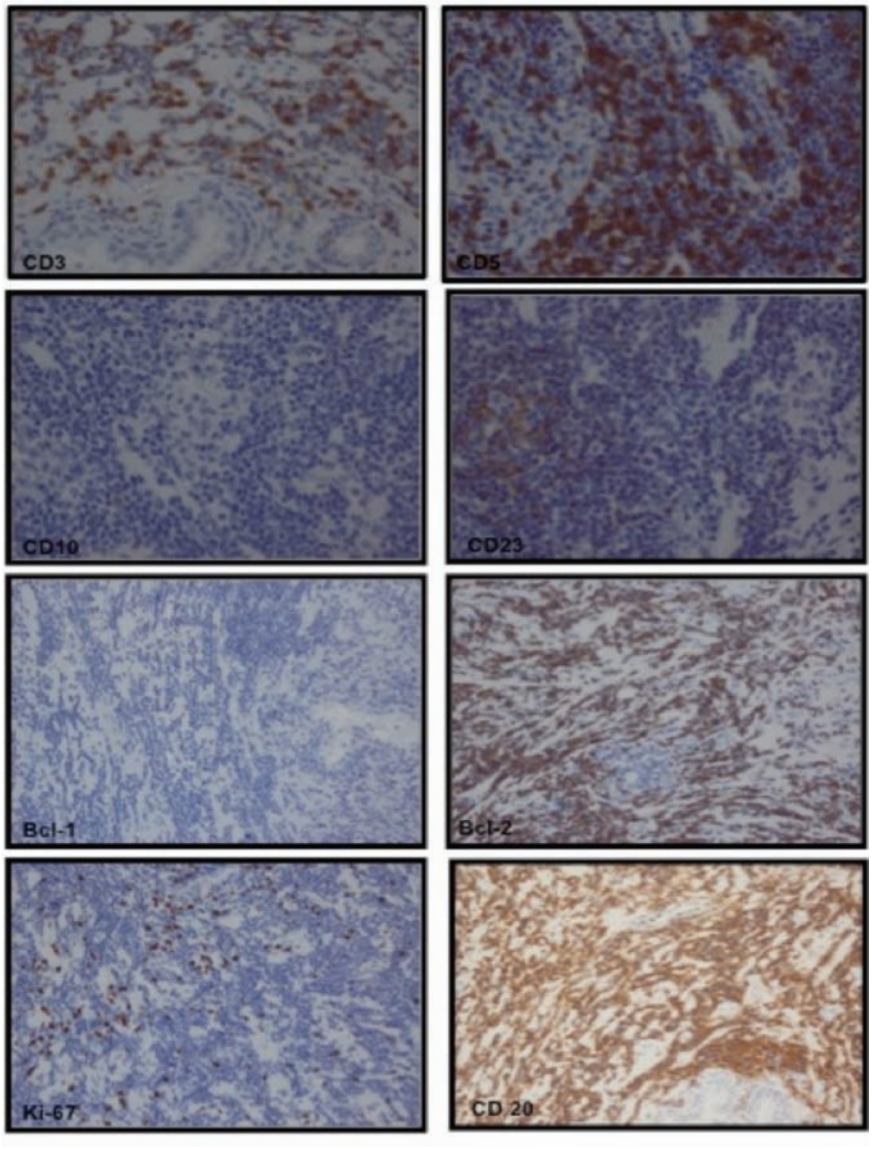

Figure 4. Immunostaining of the prostatic tissue.

lymphoid infiltrate was highly suggestive of a malignant lymphoma. The differential diagnosis for further classification included follicular lymphoma, mantle cell lymphoma, small lymphocytic lymphoma (SLL), and extranodal marginal zone lymphoma of a MALT type. The latter was favored based on morphology. Immunostains were performed for a definitive classification of this lesion. Immunostains showed that the follicular center cells were CD10, bcl-6 (marker for follicular center cells) positive but bcl-2 (marker for follicular lymphoma) negative (which ruled out follicular lymphoma). The interfollicular small lymphocytes were positive for CD20 (a B-cell marker) and negative for CD3 (a T-cell marker), CD5 (marker for both mantle cell and small lymphocytic lymphoma), CD23 (marker for small lymphocytic lymphoma), and bcl-1 (marker for mantle cell lymphoma), which ruled out mantle cell lymphoma and small lymphocytic lymphoma. The Ki67 immunostain showed that less than 10% of the lymphoma cells were positive (low proliferation rate). Therefore, this lymphoid lesion was classified as extranodal marginal zone B-cell lymphoma of a MALT type. Figure 4 shows the immunostaining of the sections. Imaging was positive for residual disease in the prostatic fossa only. The patient was recommended adjuvant radiation treatment to the prostatic fossa for both his MALT lymphoma and potentially positive margin of his Gleason 8 prostate cancer. His prostatatic fossa was treated to 6600 cGy, which was a sufficient dose to treat both his MALT lymphoma and adjuvant therapy for a positive prostate cancer margin after radical prostatectomy. The patient has remained disease-free for over one year with an undetectable PSA.

Discussion

There is only one other case report in the literature of a prostate MALT lymphoma with concurrent adenocarcinoma, in which the adenocarcinoma was treated according to the

stage while the MALT lymphoma was managed according to individual treatment strategies.[17] Because MALT lymphomas are characteristically indolent and prostatic adenocarcinomas are more aggressive in nature, therapy is targeted toward treating the adenocarcinoma. Unfortunately, the chronology in which the cancers appeared is unknown, but perhaps the difference in their prognoses may give insight into the etiology.

The long, indolent course of MALT lymphomas might suggest that the disease is the result of a chronic process. Typically, they arise in extranodal sites that lack native lymphoid tissue but acquire MALT in close association with chronic inflammation or autoimmune processes, like Sjogren's syndrome and chronic sclerosing sialadenitis.[20] They arise most commonly in the stomach, orbit, thyroid, salivary glands, breast, lung, skin, and bladder. However, they have also been reported to occur in the gallbladder, nasopharynx, and thymus.[21] MALT is known to develop in regions associated with infection or inflammation. Gastric MALT lymphoma is associated with *H. pylori* infection,[22] cutaneous MALT is associated with *Borrelia burgdorferi* infection in Europe but not in the United States, orbital adnexal MALT lymphoma is associated with *Chlamydophila psittaci*, and intraocular MALT is associated with *Toxoplasma gondii*.[23] Even though there have been specific infectious agents associated with MALT, not all MALT can be linked to a specific microbe. The genitourinary tract is part of the mucosal immune system, and includes prostate-associated lymphoid tissue (PALT). PALT consists of intra-epithelial leukocytes (mostly T-cells) and lymphoid aggregates below the epithelia, which constitute sufficient machinery for cellular and humoral immune responses.[24] The PALT contains some native B-cells, and thus houses an entirely local prostatic source of progenitor cells for the development of MALT lymphoma.

There has been discussion in the literature that prostate MALT lymphoma may be associated with *H. pylori* infection, but eradication of *H. pylori* is not yet a standard treatment for MALT lymphoma of the prostate because the role of infection has not been validated.[22] Previous case reports of urine cultures have been negative and often there is no history of acute prostatitis in patients with the disease.[15,16] However, given the long history of urinary obstruction in four out of six case reports and another with noted prostatism, chronic inflammation would seem likely to play a significant role in the etiology of MALT lymphoma of the prostate. The unique composition of the prostate provides a suitable environment for MALT to arise from normal prostate-associated lymphoid tissue. It is noted that prostate cancer and benign prostatic hyperplasia (BPH) can be associated with prostatitis. There are some investigators who hypothesize that inflammation may be linked to the development of prostate cancer. Pathological specimens from transurethral resection of the prostate (TURP) and radical prostectomy have been shown frequently to be associated with inflammation.[25] Areas of inflammation show up the regulation of bcl-2.[26] It is still unknown if BPH and prostate cancer promote or develop in response to inflammation. Thus it is difficult to assess if the two primary cancers occurred in a synchronous or metachronous fashion. Did chronic inflammation increase the risk of developing both prostate adenocarcinoma and MALT or did the prostate cancer create a local inflammatory environment more likely to induce MALT transformation from normal prostate-associated lymphoid tissue? MALT of the prostate is a rare entity and concurrent disease is even rarer. With such few cases reported in the literature, while there are millions of men diagnosed with BPH and prostate cancer annually, determining the sequence of events is likely impossible.

It has been difficult to establish the precise roles of infection (with one pathogen or multiple) versus inflammation in instigating MALT lymphoma of the prostate. MALT lymphomas may also arise from more than one clonegen adding even more complexity to the question of synchronous versus metachronous occurrence.[27,28] The prostate is a site with the potential for such transformation but this is rare. Nevertheless, this case shows that MALT lymphoma of the prostate can arise concurrently with adenocarcinoma of the prostate.

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