

Consolidation radiotherapy for a rare case of extranodal mucosa-associated lymphoid tissue non-Hodgkin's lymphoma synchronous with prostate adenocarcinoma

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ABSTRACT

Nongastric primary extranodal mucosa-associated lymphoid tissue (MALT) lymphomas are uncommon, with around 0.1% occurring in the prostate. Even less frequent is the presence of MALT lymphoma synchronous with another type of neoplasm in the same organ, especially the prostate. Only a single case of concurrent adenocarcinoma and MALT lymphoma of the prostate has been reported in the literature. We report a rare case of primary extranodal marginal zone MALT lymphoma incidentally diagnosed during radical prostatectomy for an adenocarcinoma of the prostate in a 53-year-old patient. Fourteen months later a recurrence of the MALT lymphoma involving both sides of the diaphragm was found and was treated with chemoimmunotherapy. High-dose radiotherapy was delivered to residual bulky disease in the pelvic region. At 18 months from the end of radiation treatment the patient was without signs of relapse of MALT lymphoma. This preliminary result confirms that rare cases of MALT lymphoma of the prostate should be discussed and treated under the collaborative supervision of hematologists and medical and radiation oncologists. In fact, at an advanced stage of the disease, a chemotherapy regimen with additional consolidation radiotherapy could be an effective strategy, as in all other lymphomas. Free full text available at www.tumori-online.it

Introduction

Extranodal lymphoid tissue is found in association with specialized epithelia, in particular in Waldeyer's ring, in the gastrointestinal tract of the distal ileum, in the colon and rectum, and in the bronchus. These mucosal lymphoid aggregates are named mucosa-associated lymphoid tissue (MALT). MALT lymphomas can be found in other organs or anatomical districts that usually do not contain lymphoid tissue¹. They frequently appear after chronic infection or inflammation². Primary malignant MALT lymphomas (also called MALTomas) of the prostate are very rare; in fact, less than 0.1% of MALT lymphomas are found in the prostate. Even less frequent is the presence of synchronous MALT lymphoma and adenocarcinoma in the same organ, especially the prostate³. Only a single case of concurrent adenocarcinoma and MALT lymphoma of the prostate has been reported in the literature so far⁴. Here we present a case of MALT lymphoma incidentally discovered in a patient submitted to surgery for prostate adenocarcinoma. Persistent pelvic bulky disease was treated with consolidation radiation therapy after chemoimmunotherapy.

Key words: extranodal MALT lymphoma, adenocarcinoma, prostate, radiotherapy.

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Received July 17, 2009; accepted November 17, 2009.

Clinical case

A 53-year-old patient was referred to our department of radiotherapy. His history began 24 months previously with a PSA of 6.1 ng/mL. He was submitted to a prostate biopsy resulting in a histological diagnosis of adenocarcinoma, Gleason score 3 + 3. One month after the biopsy a radical nerve-sparing prostatectomy with pelvic lymph node dissection was performed in our institute. The definitive histological report showed an adenocarcinoma in both prostate lobes, Gleason score 3 + 4. In the left lobe the tumor involved the apex without margin infiltration. Twenty-two lymph nodes were resected in the pelvic region without signs of adenocarcinoma metastasis. A type B non-Hodgkin marginal zone lymphoma was incidentally found in the same prostatic tissue in both lobes with infiltration of all resected margins and focal bladder involvement. A left obturator lymph node showed focal localization of lymphoma. According to the American Joint Committee on Cancer (AJCC) TNM classification, the stage of adenocarcinoma of the prostate was pT2c pN0 Mx. The lymphatic proliferative disease was defined by the pathologist as primary extranodal marginal zone MALT lymphoma of the prostate. According to the Ann Arbor classification for non-Hodgkin lymphoma, the stage was IIE. The patient was not submitted to postoperative hematological examination because he disappeared after discharge from the hospital.

The only subsequent information about the patient that we received was that 2 months later upper gastrointestinal endoscopy with concomitant biopsy showed chronic inflammation of the stomach with lymphoid infiltration, CD20+, with the presence of *Helicobacter pylori*. Pharmacological therapy with omeprazole, clarithromycin and amoxicillin was prescribed.

At 14 months from the prostatectomy the patient was again referred to our institute reporting night sweats. One month later he was submitted to ultrasound evaluation of the pelvic region that revealed bilateral urinary tract dilatation, with grade II ureter nephrosis. An inhomogeneous mass of 7 cm was found in the bladder. Several days later the patient was submitted to total body CT, which revealed a hilar mass in the right lung and a pelvic mass of 9 × 8 cm involving surgical clips from a previous surgical intervention that surrounded and raised the bladder floor, causing ureter obstruction. Posteriorly the mass was directly in contact with the anterior wall of the rectum and with the anorectal junction. Suspicious enlargement (slightly more than 1 cm) was observed in some lymph nodes in the pelvic region near the mass and in the common iliac region. Two days later a biopsy of a pelvic lesion showed fibroid-muscular tissue with significant lymphoid infiltration, compatible with recurrence of lymphoma. The tissue was CD20+, CD3-, CD5-, and CD10-. In the same month a bone marrow biopsy documented the absence of lym-

phatic disease. After restaging according to the Ann Arbor classification for non-Hodgkin lymphoma, the stage changed from stage II to III.

The patient was prescribed chemoimmunotherapy with R-CHOP: the rituximab dose was 375 mg/m², the cyclophosphamide dose was 750 mg/m², the doxorubicin dose was 50 mg/m², and the vincristine dose was 1.4 mg/m² on the first day of the cycle; oral prednisone at a dose of 100 mg was given on the first to fifth days of each cycle. This scheme was repeated for 6 cycles and was well tolerated. The first total body CT scan during chemotherapy showed a reduction in size of the right hilar lesion and a minimal reduction of the pelvic mass (8.5 × 7.4 cm). The lymph node enlargement in the pelvic region also diminished. The second total body CT after 2 months showed further reduction of the hilar lesion and pelvic mass (7.9 × 5.2 cm). A reduction of 10% was observed in the enlarged pelvic lymph nodes.

After 2 months, PET/CT performed for radiation treatment simulation and morphofunctional restaging revealed pathological accumulation of tracer (18FDG) only in the pelvic region, in correspondence to the pelvic mass (Figure 1). CT with contrast medium during the PET/CT procedure showed reduction of the mass (6.5 × 3.0 cm) without changes in the regional lymph nodes.

Considering the partial response to chemotherapy with a single remaining biologically active site, the patient was submitted to radiation treatment to the pelvic region. The prescription dose to the planning target volume (PTV) was 45 Gy in 25 daily fractions, 5 fractions per week. The first part of the treatment fields was extended to a volume encompassing the pelvic lymph nodes that were found to be involved on CT, using a dose of 36 Gy; the second part reduced the treatment fields to only a target volume involving the persistent mass defined by CT with contrast medium (gross tumor volume or GTV) corresponding to the 18FDG accumulation (biological target volume or BTV). The second part of the reduced treatment volume received a boost of 9 Gy. We adopted a conformal radiation technique with 4 shaped fields fitted to the PTV (0, 180, 90, and 270 degrees) in the first part and 3 reduced fields (0, 90, and 270 degrees) in the boost phase. 18 MV energy was used to irradiate the pelvic region with a Varian Clinac (Varian Medical Systems, Palo Alto, CA, USA); a multileaf collimator was used to shape treatment fields fitted to the PTV. During radiation treatment, weekly clinical assessment by physicians revealed no signs or symptoms of disease. An increased frequency of bladder activity with urinary urgency was recorded as grade 1 RTOG acute toxicity without the need for pharmacological or medical treatment. The patient has been followed up for more than 18 months to date.

18FDG PET/CT 3 months after the end of radiation treatment showed a partial metabolic response to the treatment in the form of a >50% reduction of radiotracer uptake in the pelvic region without any other patho-

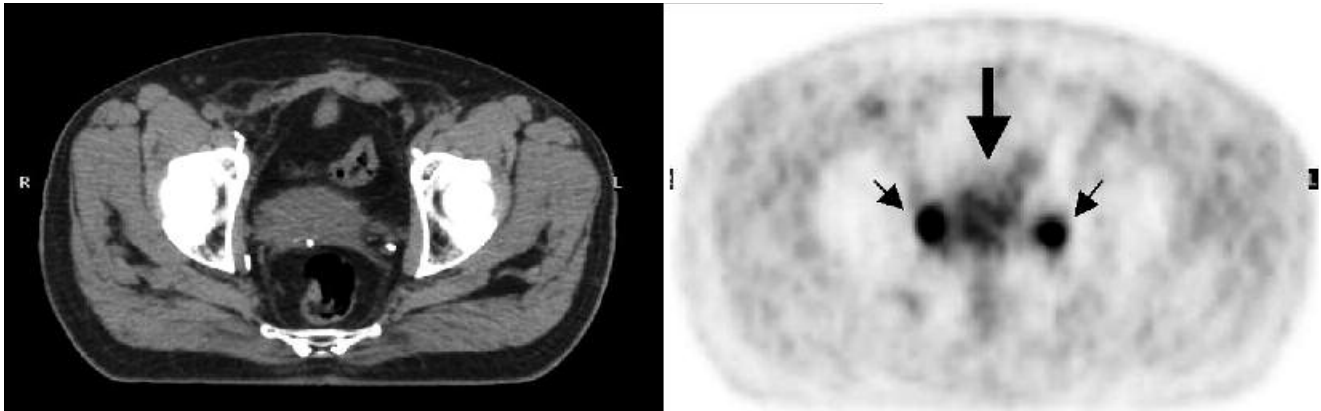


Figure 1 - 18FDG PET/CT before radiation treatment: pathological accumulation in the pelvic region in correspondence to the pelvic mass (large arrows), and bilateral dilatation of the urinary tract (small arrows).

logical tracer uptake. Eight months from the end of radiotherapy, 18FDG PET/CT showed a complete metabolic response with no evidence of disease (Figure 2). The metabolic result was confirmed by 18FDG PET/CT 12 and 18 months from the end of radiation treatment. PSA was 0.04 ng/mL in each blood test during follow-up for prostate adenocarcinoma. No late side effects or signs of clinically superficial lymph node recurrence were recorded by radiation oncologists during clinical control visits at 3, 8, 12 and 18 months.

Discussion

Primary lymphoma of the prostate is rare, representing around 0.1% of newly diagnosed lymphomas³. Fewer than 100 cases of prostate lymphoma have been reported, mostly as case reports⁵. Even more rare in the prostate are MALTomas: indolent extranodal MALT lymphomas most frequently involving the gastrointestinal

district, salivary glands, breast, thyroid, orbit, conjunctiva, skin, lung, but rarely other organs^{6,7}. MALT lymphomas are generally diagnosed after chronic infection or inflammation in mucosa-associated lymphoid tissues, most frequently in the stomach. Treatment with antibiotics to eradicate possible copathogenic *Helicobacter pylori* has been discussed as an innovative therapeutic approach and we adopted this strategy in the current case after a diagnosis of chronic inflammation of the stomach with *Helicobacter pylori* infection⁸.

Around 50% of patients with nongastric MALT lymphomas show disseminated disease during staging^{9,10}. It has been established that, if the disease is not yet disseminated, it tends to remain localized for an extended period. Consequently, local treatment approaches such as surgery or radiotherapy are suggested to be effective in the nondisseminated phase. In the current case, extranodal marginal zone MALT lymphoma was incidentally diagnosed during radical prostatectomy for adenocarcinoma of the prostate gland. It is rare to find a syn-

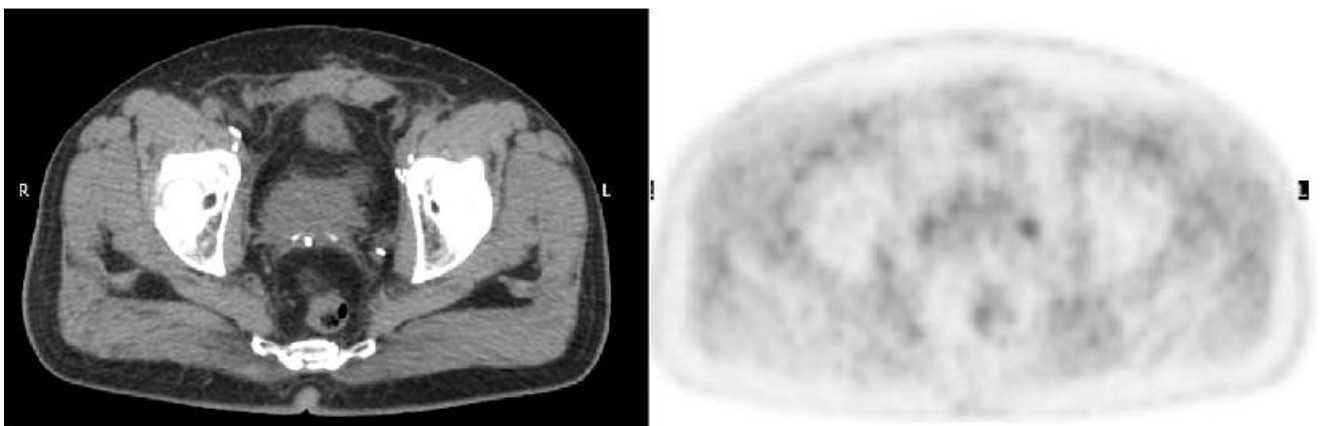


Figure 2 - 18FDG PET/CT after 8 months showing complete metabolic response without evidence of disease, confirmed at 12 and 18 months.

chronous primary MALT lymphoma with another type of neoplasm in the same organ. Only one case of such a concurrent diagnosis has been reported for the prostate⁴.

In the current case the prostate carcinoma was treated only with surgery because of the disappearance of the patient after discharge from the hospital; in the case of infiltrated margins and/or adjacent organ and lymph node involvement, MALTomas require assessment by a hematologist to complete restaging and to evaluate adjuvant treatment options.

The most common site of spread in MALTomas are the lymph nodes, but other extranodal sites may also be involved. In the case described, the initial stage of the disease after surgery was stage II because the non-Hodgkin lymphoma was limited to one extranodal organ and had spread to one or more lymph node groups on the same side of the diaphragm; staging was refined to stage IIE because there was involvement of a single extranodal site (prostate) directly adjoining or next to the nodal group (obturator).

The treatment strategy for disseminated MALT lymphomas is similar to that for follicular lymphomas, where chemotherapy followed by radiotherapy to the involved field is the most common approach. In follicular lymphomas a clinical benefit has been demonstrated in patients treated with a monoclonal antibody in combination with the CHOP chemotherapy regimen¹¹⁻¹³.

The present case was ultimately staged as disseminated disease because of residual tumor in the prostatic fossa and involvement of the pelvic lymph nodes and the hilum of the right lung. We adopted the R-CHOP scheme and obtained a partial response in all involved sites. "Active" persistence of disease at a single site observed in restaging 18FDG PET suggested radiotherapy for treatment consolidation.

Malignant lymphomas are generally radiosensitive^{14,15}. Data on radiation therapy in extranodal marginal zone MALT lymphomas are related to disease localization in the stomach, for which high local control rates have been achieved with doses of approximately 30 Gy¹⁶. In some series of patients, the response and local control rates were 95% and 100%, respectively, with doses of around 30 Gy^{16,17}. Similar data, although in smaller numbers, are available for sites other than the stomach.

In the present case it was decided to irradiate the involved pelvic field, where a mass was evident during restaging after chemotherapy; this was the only site of active disease documented by 18FDG PET. The biologically active disease was encompassed in the clinical target volume. It involved areas at risk for microscopic infiltration such as the pelvic lymph nodes (not active on PET but enlarged before chemotherapy). A cumulative dose higher than 30 Gy in relation to the residual bulky mass was prescribed in spite of the previous chemotherapy. In fact, for all types of low-grade non-Hodgkin lymphoma bulky disease radiation doses be-

tween 36 and 40 Gy are recommended. In a published case a similar dose to the one we used was reported: Jhavar *et al.* prescribed 44 Gy in 22 fractions, obtaining a complete response at 36 months' follow-up⁷. However, their case was an extranodal MALT lymphoma with primary localization in the prostate and no disease spread, treated with radiotherapy only.

Fewer than 10 primary MALTomas have been reported in the prostate¹⁸, and this is the second case where it occurred synchronously with prostatic adenocarcinoma. Considering the nature of extranodal MALT lymphoma, longer follow-up is necessary to firmly establish the long-term efficacy of the treatment. In any case, our objective was to highlight the extreme rarity of synchronous adenocarcinoma and incidentally detected MALT lymphoma in the prostate, and to stress the importance of managing such rare cases with a multidisciplinary approach. In fact, patients with disseminated marginal zone MALT lymphoma of the prostate could be effectively treated with additional radiotherapy after chemotherapy, as in all other lymphomas, under the collaborative supervision of hematologists, medical oncologists and radiation oncologists.

References

- Gospodarowicz M, Tsang R: Mucosa-associated lymphoid tissue lymphomas. *Curr Oncol Rep*, 2: 192-198, 2000.
- Parsonnet J, Hansen S, Rodriguez L, Gelb AB, Warnke RA, Jellum E, Orentreich N, Vogelman JH, Friedman GD: Helicobacter pylori infection and gastric lymphoma. *N Engl J Med*, 330: 1267-1271, 1994.
- Sarris A, Dimopoulos M, Pugh W, Cabanillas F: Primary lymphoma of the prostate: good outcome with doxorubicin-based combination chemotherapy. *J Urol*, 153: 1852-1854, 1995.
- Uthoff D, Schmidt S, Matthies C, Tiemann M, Wagner W: Coincidence of adenocarcinoma and MALT lymphoma of the prostate - first report. *Aktuelle Urol*, 40: 113-115, 2009.
- Bostwick DG, Mann RB: Malignant lymphomas involving the prostate. A study of 13 cases. *Cancer*, 56: 2932-2938, 1998.
- Tomikawa S, Okumura H, Yoshida T, Mochizuki H, Miwa A, Takayanagi K, Yoshino T, Ohtake S, Fujimura M, Nakamura S, Matsuda T: Primary prostatic lymphoma of mucosa-associated lymphoid tissue. *Intern Med*, 37: 628-630, 1998.
- Jhavar S, Agarwal JP, Naresh KN, Shrivastava SK, Borges AM, Dinshaw KA: Primary extranodal mucosa associated lymphoid tissue (MALT) lymphoma of the prostate. *Leuk Lymphoma*, 4: 445-449, 2001.
- Wotherspoon AC, Dogliani C, Diss TC, Pan L, Moschini A, de Boni M, Isaacson PG: Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication of Helicobacter pylori. *Lancet*, 342: 575-577, 1993.
- Berger F, Felman P, Thieblemont C, Pradier T, Baseggio L, Bryon PA, Salles G, Callet-Bauchu E, Coiffier B: Non-MALT marginal zone B-cell lymphomas: a description of clinical presentation and outcome in 124 patients. *Blood*, 95: 1950-1956, 2000.
- Zinzani PL, Magagnoli M, Galienucci P, Martelli M, Poletti V, Zaja F, Molica S, Zaccaria A, Cantonetti AM, Gentilini P, Guardigni L, Gherlinzoni F, Ribersani M, Bendandi M, Al-

- bertini P, Tura S: Nongastrointestinal low-grade mucosa-associated lymphoid tissue lymphoma: analysis of 75 patients. *J Clin Oncol*, 17: 1254, 1999.
11. Kahl B: Chemotherapy combinations with monoclonal antibodies in non-Hodgkin's lymphoma. *Semin Hematol*, 45: 90-94, 2008.
 12. Ghielmini M, Schmitz SF, Cogliatti SB, Pichert G, Hummerjohann J, Waltzer U, Fey MF, Betticher DC, Martinelli G, Peccatori F, Hess U, Zucca E, Stupp R, Kovacsovic T, Helg C, Lohri A, Bargetzi M, Vorobiof D, Cerny T: Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly x 4 schedule. *Blood*, 103: 4416-4423, 2004.
 13. Conconi A, Martinelli G, Thiéblemont C, Ferreri AJ, Devizzi L, Peccatori F, Ponzoni M, Pedrinis E, Dell'Oro S, Pruneri G, Filipazzi V, Dietrich PY, Gianni AM, Coiffier B, Cavalli F, Zucca E: Clinical activity of rituximab in extranodal marginal zone B-cell lymphoma of MALT type. *Blood*, 102: 2741-2745, 2003.
 14. Tsai HK, Li S, Ng AK, Silver B, Stevenson MA, Mauch PM: Role of radiation therapy in the treatment of stage I/II mucosa-associated lymphoid tissue lymphoma. *Ann Oncol*, 18: 672-678, 2007.
 15. Tsang RW, Gospodarowicz MK, Pintilie M, Wells W, Hodgson DC, Sun A, Crump M, Patterson BJ: Localized mucosa-associated lymphoid tissue lymphoma treated with radiation therapy has excellent clinical outcome. *J Clin Oncol*, 21: 4157-4164, 2003.
 16. Tsang RW, Gospodarowicz MK, Pintilie M, Bezjak A, Wells W, Hodgson DC, Crump M: Stage I and II MALT lymphoma: results of treatment with radiotherapy. *Int J Radiat Oncol Biol Phys*, 50: 1258-1264, 2001.
 17. Schechter NR, Portlock CS, Yahalom J: Treatment of mucosa-associated lymphoid tissue lymphoma of the stomach with radiation alone. *J Clin Oncol*, 16: 1916-1921, 1998.
 18. Rajnics P, Demeter J, Csomor J, Krenács L, Pajor L, Kollár B, Kertész Z, Egyed M: Rare primary extranodal lymphomas: diffuse large B-cell lymphomas of the genital tract. *Ann Hematol*, 88: 1223-1228, 2009.