CASE REPORT


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# What can hide an enlarged lymph node of a patient with prostatic adenocarcinoma?

## Šta može da sakrije uvećan limfni čvor kod bolesnika sa adenokarcinomom prostate?

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**Abstract**

**Introduction.** Adenocarcinoma is the most common prostatic malignancy, where clinical management, the Gleason score, and recent updates in prostate cancer staging play critical roles. Mantle cell lymphoma (MCL) originates from the malignant transformation of B lymphocyte in the outer edge of the lymph node follicle, with pathognomonic overexpression of cyclin D1. We present a rare case of two simultaneous neoplasms occurring in the same patient. **Case report.** During the hospital preoperative examinations in a 68-year-old patient planned for radical prostatectomy, using multislice computed tomography, a tumor mass confined to the prostate, but also excessive lymph node enlargement, was revealed. Tissue specimens were analyzed after the hematoxylin and eosin staining was performed, as well as an immunohistochemical (IH) biomarker panel. Having performed a thorough histological examination, a diagnosis of prostatic adenocarcinoma was made, with a Gleason score 3 + 4 = 7 and Grade Group 2 of the International Society of Urological Pathology (ISUP). Microscopic analysis of lymph node involvement showed unexpected, diffuse proliferation of small lymphoid cells with irregular nuclei, wide mantle zone, and hyalinized blood vessels. After using IH staining for specific markers, another diagnosis was set, and it was non-Hodgkin MCL. **Conclusion.** A prostatic adenocarcinoma can rarely coexist with an undiagnosed lymphoproliferative disease, such as non-Hodgkin MCL in our case.

**Key words:**
**adenocarcinoma; comorbidity; diagnosis; immunohistochemistry; lymphoma, mantle-cell; prostatic neoplasms.**

**Apstrakt**

**Uvod.** Adenokarcinom je najučestaliji malignitet prostate, kod koga kritičnu ulogu igraju klinički pristup, *Gleason* skor i obnovljeni i unapređeni načini određivanja stadijuma karcinoma prostate. Limfom *mantle* ćelija (LMĆ) potiče od maligno transformisanih B limfocita spoljašnje zone folikula limfnog čvora, sa patognomoničnom ekspresijom ciklina D1. Prikazan je bolesnik sa retkom istovremenom pojavom dve neoplazme. **Prikaz bolesnika.** Tokom bolničkih preoperativnih pregleda kod bolesnika starog 68 godina, planiranog za radikalnu prostatektomiju, korišćenjem multislajsne kompjuterske tomografije, otkrivena je tumorska masa ograničena na prostatu, ali i značajno uvećanje limfnih čvorova. Uzori tkiva analizirani su posle hematoksilin eozin bojenja i imunohistohemijskog (IH) obeležavanja odgovarajućeg panela markera. Posle histološke procene, postavljena je dijagnoza adenokarcinoma prostate, sa *Gleason* skorom 3 + 4 = 7 i gradusom grupe dva prema *International Society of Urological Pathology* (ISUP). Mikroskopskom analizom regionalnih limfnih čvorova utvrđena je neočekivana difuzna proliferacija malih limfoidnih ćelija sa nepravilnim jedrima, širokom *mantle* zonom i hijalinizovanim krvnim sudovima. Primenom IH bojenja u cilju detekcije specifičnih makera postavljena je i dijagnoza *non-Hodgkin*-ovog LMĆ. **Zaključak.** Adenokarcinom prostate veoma retko može koegzistirati sa prethodno nedijagnostikovanim limfoproliferativnim oboljenjem, kao što je u ovom slučaju *non-Hodgkin*-ov LMĆ.

**Ključne reči:**
**adenokarcinom; komorbiditet; dijagnoza; imunohistohemija; limfom, mantle-ćelijski; prostata, neoplazme.**

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## Introduction

Adenocarcinoma is the most common malignancy of the prostate. Clinical management, the Gleason score, and the World Health Organization/International Society of Urological Pathology (WHO/ISUP) grading system play a critical role in predicting biological behavior and prognosis of adenocarcinoma. Radical prostatectomy with dissection of pelvic lymph nodes (LNs) is a routine procedure in patients with high serum prostate-specific antigen (PSA) level or high combined Gleason score (≥ 8) performed in order to prevent metastatic disease [1]. Due to the high sensitivity of the PSA serum test, surgical procedures are performed in the early stage of the disease. The coexistence of primary prostatic malignancy with another neoplasm is rare and usually referred to as a collision of urinary bladder carcinoma and prostatic adenocarcinoma (PA) [2, 3]. PA synchronously occurring with non-Hodgkin lymphoma is extremely rare. To our knowledge, this is one of the newer reports describing PA with incidental finding of mantle cell lymphoma (MCL) in pelvic LNs.

## Case report

A 68-year-old male was presented to our tertiary care institution due to an elective radical prostatectomy. The procedure was planned after the patient's core needle biopsy. Anamnestic data showed only a history of urination difficulties and occasional urinary hesitancy. The patient did not state any previous disease or medicine consumption. An initial physical exam showed prostate enlargement with palpable irregularities in shape. Laboratory investigation revealed elevated PSA levels (14 ng/mL; reference range up to 4.5 ng/mL in the age group 60–69 years). Based on the previous examination, a core needle biopsy was performed, and the pathohistological diagnosis of PA was confirmed, with the Gleason score 3 + 4 = 7 and ISUP Grade Group 2.

Due to the anamnestic data, physical exam, PSA level, and pathohistological diagnosis, the patient was planned for radical prostatectomy. During his stay at the hospital, preoperative examinations showed that his heart and pulmonary conditions were within normal limits. Multislice computed tomography (CT) scan of the abdomen and pelvis was performed to visualize disease extension. This imaging method showed a tumor mass confined to the prostate but also revealed excessive LN enlargement.

Intraoperatively, the enlargement of both right and left parailiac LNs, right and left obturator LNs, presacral LNs, and those around common iliac veins was noted. The enlarged LNs were removed, along with the prostate, urethral and urinary bladder margin, as well as the small amount of adjacent adipose and connective tissue.

The excised specimens were sent for histopathological examination and definite diagnosis. On gross examination, surgically marked LNs from different pelvic lodges were described as fragments of fibroadipose tissue. Serial sectioning showed a homogenous appearance of many nodes that were white to greyish, with a soft consistency and in different diameters. The prostate was 6 cm in greatest diameter and grossly described as having a partly homogenous appearance and spongy consistency on serial sectioning. Posterior parts of both lobes were described as ill-defined from the rest of the prostatic tissue, white to yellowish, and with elastic to a firm consistency.

Histopathological (Figure 1) and immunohistochemical (IH) (Figure 2) examinations of LNs and prostatic tissue were performed in order to establish a more precise diagnosis. Histologic material was reviewed by two

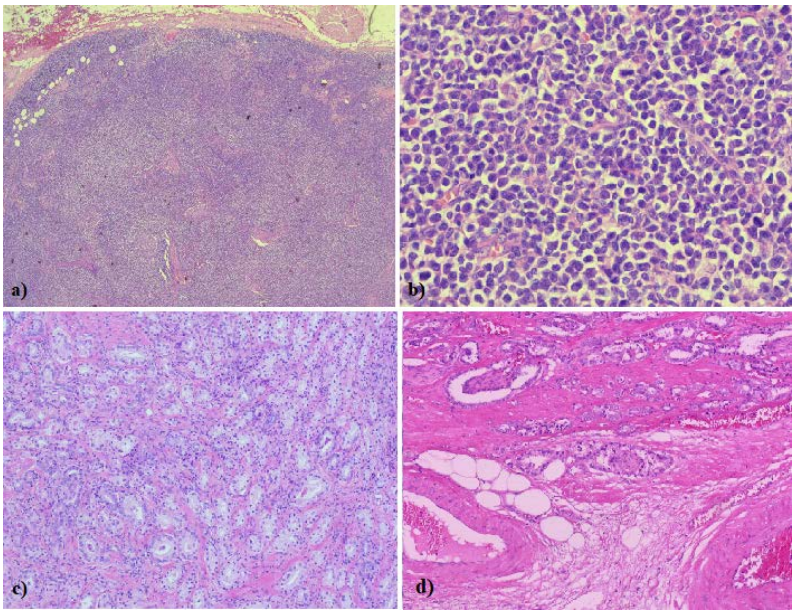


**Fig. 1 – a) Mantle cell lymphoma (MCL) in the pelvic lymph node, hematoxylin and eosin (HE) staining, x25; b) Diffuse proliferation of small and irregularly shaped lymphoid cells in MCL, HE, x40; c) Prostatic adenocarcinoma, Gleason score 3 + 4 = 7, HE, x10; d) Extraprostatic extension of adenocarcinoma, HE, x40.**

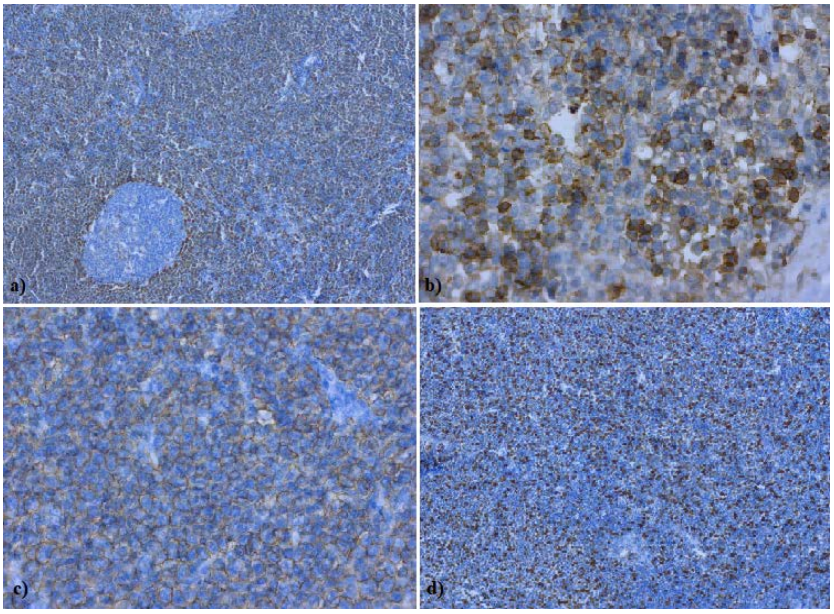


**Fig. 2 – Immunohistochemical analysis of selected lymph node specimens showed: a) Cyclin D1 positivity, x10; b) CD5 positivity, x40; c) CD20 positivity, x40; d) Ki-67 proliferative index, x10.**

pathologists. Microscopic examination of 25 tissue specimens in 50 histological sections, primarily stained with hematoxylin and eosin (HE), showed 32 LNs with no metastatic deposits originating from PA. However, the LNs showed no recognizable architecture due to the neoplastic tissue with a nodular growth pattern (Figure 1a). The tumor tissue showed diffuse proliferation of small and irregularly shaped lymphoid cells with irregular nuclear borders, clumped chromatin, and inconspicuous nuclei (Figure 1b). The mantle zone was extended. Rare epitheloid histiocytes were present. Stromal vessels were hyalinized. IH evaluation was performed in order to confirm the diagnosis. The tissue specimen selected for IH staining was CD20 positive, BCL2 positive, CD5 positive, CD43 positive, cyclin D1 positive, CD3 negative, CD10 negative, and BCL6 negative. Ki67 proliferative index was up to 20% (Figure 2a–d). Based on the clear morphologic appearance and IH staining, the diagnosis of MCL – the classic variant, was given.

Microscopic examination of prostatic tissue specimens showed multiple focuses on tumor tissue. The tumor tissue consisted of small, uniform, and well-formed glands, as well as focuses with distinct infiltrative growth patterns and glands that were ill-defined or fused, with little or no intervening stroma, and in cribriform or glomeruloid appearance. Tumor cells were atypical, mostly cuboidal, with hyperchromatic nuclei and prominent nucleoli. Based on the microscopic appearance and its correlation with gross description, a diagnosis of acinar adenocarcinoma was made. Histologic grade was defined as Grade Group 2 (Gleason score 3 + 4 = 7). Tumor quantitation was defined by percentage, with 21–30% of the prostate being involved by tumor and with Grade 4 present in 31–40% of the tumor tissue (Figure 1c). Tumor tissue was found in specimens from the right and left lobe, left base, and right apex. In a few focuses of the right lobe sections, small tumor glands were noted beyond the confines of the prostate gland, so extraprostatic extension was defined as focal (Figure 1d). Urinary bladder neck and seminal vesicle invasion were not identified, nor was the lymphovascular invasion. Perineural invasion was identified in specimens from the right lobe and right apex. The surgical margin involved by invasive carcinoma was right apical, Gleason pattern 3. As all regional LN s were negative for acinar adenocarcinoma, the pathologic stage was defined as pT3aN0 [4].

During his 7-day stay at the hospital, the patient was asymptomatic, and there were no abnormalities in clinical examination or basic laboratory parameters.

After a short period of time, the patient had multiple control examinations where he presented in stable cardiopulmonary condition, with no signs of the anemic or hemorrhagic syndrome but with palpable neck, axillar and inguinal LNs, and splenomegaly during his last examination at the Clinic for Hematology. In order to evaluate extranodal involvement with the disease, a bone marrow biopsy was scheduled. Microscopic analysis of the biopsy confirmed bone marrow infiltration with MCL and confirmed the diagnosis given after LN dissection during radical prostatectomy. Stage IV of lymphoproliferative disease was given. The chest, abdominal and pelvic CT showed generalized lymphadenomegaly with the predominance of retroperitoneal LNs swelling and splenomegaly. With these results, the patient was presented to the council for therapeutic management of lymphoproliferative diseases, where it was decided that the patient would be treated by following the Knospe treatment protocol, with an adequate dosage of chlorambucil (tablet 2 mg, 6 + 5 + 5, 1$^{st}$ and 15$^{th}$ day of the cycle) and prednisone (tablet 20 mg, 1 + 1+ 1/2). Since the patient was not motivated by the available treatment options, he did not come to the next scheduled follow-up examination, so further clinical data are unavailable, unfortunately.

## Discussion

In the present study, we describe an unusual case of two neoplasms simultaneously occurring in a 68-year-old patient. HE and IH staining of tissue sections, with a demonstration of markers for the targeted lymphoproliferative disorder, supports the diagnosis. In our case, there were no previous signs of an underlying lymphoproliferative disease. Using an imaging method (CT) as a part of preoperative preparation, the patient was diagnosed with a pelvic lymphadenomegaly, not otherwise specified.

MCL is a B cell neoplasm arising from pregerminal center cells of primary follicles or from the mantle zone of secondary follicles. The median age of MCL presentation is 60 years, with a range from 35 to 85 years, as it is approximately in PA [5–7]. The most common involvement site is a LN, with no tendency to infiltrate a particular group of LNs [7]. Morphologically, MCL is present through the expansion of the mantle zone, which surrounds the germinal center. The monomorphic lymphocytes are small to medium-sized, with scanty cytoplasm, irregular nuclear contours, dispersed chromatin, and often inconspicuous nucleolus [8]. They express a variety of B cell antigens, such as CD5, CD19, CD20, CD22, and CD45. The immunopositivity of cyclin D1 is pathognomonic if present [6–8].

The cytogenetic abnormality marking MCL is (11; 14) (q13; q32) translocation between the immunoglobulin heavy-chain locus (IGH) gene on chromosome 14 and the BCL1 locus on chromosome 11. This gene rearrangement results in CCND1 overexpression and potentially increased half-life of cyclin D1. These changes lead to a loss of cell cycle regulating elements, i.e., Rb1 and p27, resulting in the development of MCL [5, 7, 9].

In the case of PA, most patients are asymptomatic. They rarely exhibit symptoms and signs related to the metastatic disease, most commonly in regional LNs and bones [1]. The disease can be managed in a number of ways, such as active surveillance, radical prostatectomy, hormonal therapy, radiation therapy, and cryotherapy. The performance status of a patient should be evaluated, and the morbidity related to surgery and/or chemoradiotherapy should be estimated [1, 7]. The prognosis is expected to be favorable for prostate cancer that is well to moderately differentiated and confined to the prostate gland, and a 5-year outcome is considered excellent [1].

The clinical impact of hematolymphoid malignancies discovered after radical prostatectomy and regional LN dissection has not been completely clarified due to rare cases presented in the literature. Along with individual case reports, there are larger surgical series describing the frequency of the simultaneous presence of PA and lymphoma or leukemia and the possibility of further treatment. In the study by Terris et al. [10], 1,092 patients underwent radical prostatectomy and LN dissection, but only 13 (1.2%) of them had hematolymphoid malignancies, including Hodgkin's lymphoma, hairy cell leukemia, and chronic lymphocytic leukemia. Nine out of thirteen patients had prostatic and LN involvement with lymphoma/leukemia, and LNs were involved in only four patients. An interesting fact is that patients with prostatic involvement with hematolymphoid malignancy had no ultrasound-detected abnormalities other than those corresponding to PA. Similar results were presented in the study by Chu et al. [11], where authors evaluated 4,381 prostatic tissue specimens obtained by biopsy, transurethral resection, or prostatectomy. Only 29 (0.6%) lymphoma cases involving prostate and pelvic LNs were identified, but 11 patients had concurrent known lymphoma. Petković et al. [12] presented a case report where MCL was first discovered as bone marrow infiltration and with the IVB stage of the disease. The coincidental finding of these malignancies led to the patient being double-treated by two separate methods – the CHOP (cyclophosphamide, hydroxydaunorubicin, Oncovin, prednisone) chemotherapeutic protocol and hormonal therapy.

The coexistence of adenocarcinoma and MCL in other anatomical sites, such as the lung, has been reported in the literature. Braham et al. [13] presented the first case of primary lung adenocarcinoma associated with LN MCL. This lymphoma is usually synchronously present with plasma cell dyscrasia or granulomatous diseases such as sarcoidosis [14, 15]. It can also occur with metastasis from a different anatomical site but in the same LN [9]. In addition, there were reports describing the presence of two different variants of MCL in the same LN, usually classic type and blastoid variant [8, 9]. MCL has a wide differential diagnosis, mostly including other lymphoproliferative disorders that can mimic the presence of MCL, especially reactive follicular hyperplasia. Differential diagnosis also includes chronic lymphocytic leukemia/small lymphocytic lymphoma, follicular lymphoma, nodal marginal zone B cell lymphoma, splenic marginal zone lymphoma, as well as Castleman disease [16, 17]. There were several studies describing concomitant PA and chronic lymphocytic leukemia, follicular lymphoma, and B cell lymphoma. The results of these studies point to different therapeutic management due to the various age range, patient's general status, and prognostic parameters, with the stage being the most important one. Furthermore, the results from follow-ups showed different prognoses for these patients. Most frequently, patients presented with recurrent prostatic carcinoma [12, 18–21].

## Conclusion

Synchronous development of these tumors can be a challenging problem in diagnosis and treatment. The therapeutic management required separate consideration due to their different biological behavior. In the case of the presented patient, pelvic LN enlargement discovered on a CT scan was assessed in order to determine if the pelvic lymphadenopathy corresponded to metastasis or a separate process in the LN. In the absence of metastatic adenocarcinoma, the prostatic tumor was treated first due to its stage, and then MCL was treated. Even though there is no metastatic disease, careful examination of the regional LNs is imperative for a proper diagnosis and staging.

## Conflict of interest

The authors declare no conflict of interest.

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