CASE REPORTS
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Lymphoma of the uterine cervix – a rare clinical presentation

Limfom grlića materice – retka klinička prezentacija

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Abstract

Introduction. Lymphomas are malignant diseases of the lymphocyte lineage. There are two basic types of lymphoma: Hodgkin's lymphoma (HL), whose main characteristic is the presence of Reed-Sternberg cells, and non-Hodgkin's lymphoma (NHL), which presents a heterogeneous group of diseases, and depending on the growth rate and the course of the disease, they can be indolent (slow-growing) and aggressive (fast-growing). Follicular lymphoma (FL) is the most common indolent form of NHL, while diffuse large B-cell lymphoma (DLBCL) is the most common aggressive form. **Case report.** The study presents a case of NHL, DLBCL, localized in the cervix, histopathologically diagnosed in a 35-year-old woman who, after a cervical biopsy, was histopathologically diagnosed with mild dysplasia (CIN1/L-SIL) of the cervical epithelium and, after that, an infection with human papillomavirus (HPV) subtypes 16 and 31 was proven. The diagnosis of DLBCL was histopathologically confirmed on a conical section of the vaginal portion of the uterus, after which the disease was treated with eight cycles of chemotherapy according to the RCHOP protocol. **Conclusion.** The coexistence of CIN1/L-SIL and NHL is random. However, this fact may cause the concomitant cervical lymphoma to be overlooked since the lymphoma is usually subepithelial if biopsies are not taken adequately and if HPV serotyping of the biopsy sample is not performed.

Key words:
biopsy; lymphoma, non-hodgkin; papillomaviridae; serotyping; uterine cervical dysplasia.

Apstrakt

Uvod. Limfomi su maligne bolesti limfocitne loze. Postoje dva osnovna tipa limfoma: Hodgkin-ov limfom (HL), čija je osnovna karakteristika prisustvo Reed-Sternberg-ovih ćelija, i non-Hodgkin-ov limfom (NHL), koji predstavlja heterogenu grupu bolesti, a u zavisnosti od brzine rasta i toka bolesti mogu biti indolentni (sporastući tok) i agresivni (brzorastući tok). Folikularni limfom (FL) najčešći je indolentni oblik NHL, dok je difuzni krupnoćelijski B-limfom (*diffuse large b-cell lymphoma*, DLBCL) najčešći agresivni oblik. **Prikaz bolesnika.** U radu je prikazana bolesnica stara 35 godina sa NHL, DLBCL, lokalizovanim u grliću materice, kojoj je nakon biopsije grlića materice, patohistološki dijagnostikovana displazija lakog stepena (CIN1/L-SIL) pokrovnog epitela grlića materice, a zatim dokazana infekcija humanim papiloma virusom (HPV), podtipovima 16 i 31. Dijagnoza DLBCL je patohistološki potvrđena na koničnom isečku vaginalne porcije uterusa, nakon čega je bolesnica lečena sa osam ciklusa hemioterapije po protokolu RCHOP. **Zaključak.** Koegzistencija CIN1/L-SIL i NHL je slučajna. Usled toga, može se prevideti prateći cervikalni limfom, koji je uobičajeno lokalizovan subepitelno, ukoliko se biopsije ne uzimaju na adekvatan način i ukoliko se ne uradi HPV serotipizacija uzorka biopsije.

Ključne reči:
biopsija; limfom, nehodžkinov; papillomaviridae; serotipizacija; grlić materice, displazija.

Introduction

Primary non-Hodgkin's lymphoma (NHL) of the cervix is extremely rare. Only 0.5% of extranodal lymphomas in women originate from the female genital tract. To date, more than 130 cases of primary NHL of the cervix have been reported [1].

The most common histological subtype is diffuse large B-cell lymphoma (DLBCL). The symptomatology is diverse.

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Fever, night sweats, and weight loss are not usually the characteristics of primary cervical lymphoma. Gynecological symptoms may occur, including pelvic pain, postcoital bleeding, postmenopausal bleeding, and dyspareunia. The differential diagnosis of primary cervical lymphomas includes benign inflammatory and malignant diseases such as cervical cancers, sarcomas, and lymphoma-like lesions.

The diagnostic procedure of choice for the final diagnosis is a deep cervical biopsy that detects histopathological characteristics and immunophenotype. Because they are subepithelial, Papanicolaou (PAPA) swabs play a very insignificant role in the diagnosis of cervical lymphoma. Ann Arbor stage, disease extent, number of affected extranodal organs, performance status, and serum lactate dehydrogenase (LDH) values present significant prognostic features [2].

Case report

A 35-year-old female patient was diagnosed with cervical intraepithelial neoplasia (CIN)1 / low grade squamous intraepithelial lesion (L-SIL) during a routine gynecological examination, which included a PAPA test. After that, curettage of the cervical canal and cervical biopsy were performed, and the diagnosis of CIN1/L-SIL was confirmed by pathohistological findings. The presence of the human papillomavirus (HPV) infection was proven after that (subtypes 16 and 31). After adequate preoperative preparation, a large loop excision transformation zone (LLETZ) conization was carried out. The diagnosis of CIN1/L-SIL and DLBCL was set by histopathological processing of the obtained cone-shaped portion of the cervix. The histopathological finding showed that in the obtained tissue samples of the vaginal portion of the uterus, there was a pronounced mixed inflammatory infiltration, composed of lymphocytes, plasma cells, and polymorphonuclear leukocytes, with a larger number of reactively altered follicles. Interfollicular lymphoid tumor tissue of diffuse growth type was present, which consisted of medium- and large-sized cells, rare slightly basophilic cytoplasm, a large oval, easily cut vesicular nucleus with 1-3 nuclei, which morphologically corresponded to immunoblasts and centroblasts. The mitotic and apoptotic indices were high. Necrosis was absent. There were no tumor cells at the edges of the cone resection. Immunohistochemically, tumor cells demonstrated diffuse immunoreactivity to LCA+, CD20+, bcl-6+, Vimentin+, Pax5+, with a high proliferative index of Ki-67 of about 50% (Figure 1). The patient was diagnosed with primary cervical diffuse B-large cell non-Hodgkin's lymphoma, centroblastic, germinal center B-cell-like (GCB) subtype.

After the diagnosis, the patient underwent multidetector computerized tomography (MDCT) (Figure 2) of the chest, abdomen, and small pelvis, as well as a postoperative gynecological examination, during which no secondary deposits were diagnosed. The patient was referred to the Hematology Clinic for further treatment.

A bone marrow biopsy was performed with a normal finding, without elements of the lymphoproliferative disease. The Hematology Council suggested that the patient be treated with eight cycles of chemotherapy (HT) according to the RCHOP protocol [rituximab, cyclophosphamide, hydroxydaunorubicin hydrochloride (doxorubicin hydrochloride), vincristine (older name oncovin), prednisone], with an assessment of the response after the second cycle. The patient was monitored by a hematologist after each cycle of HT, which she tolerated well due to the administration of antiemetics and gastroprotective therapy.

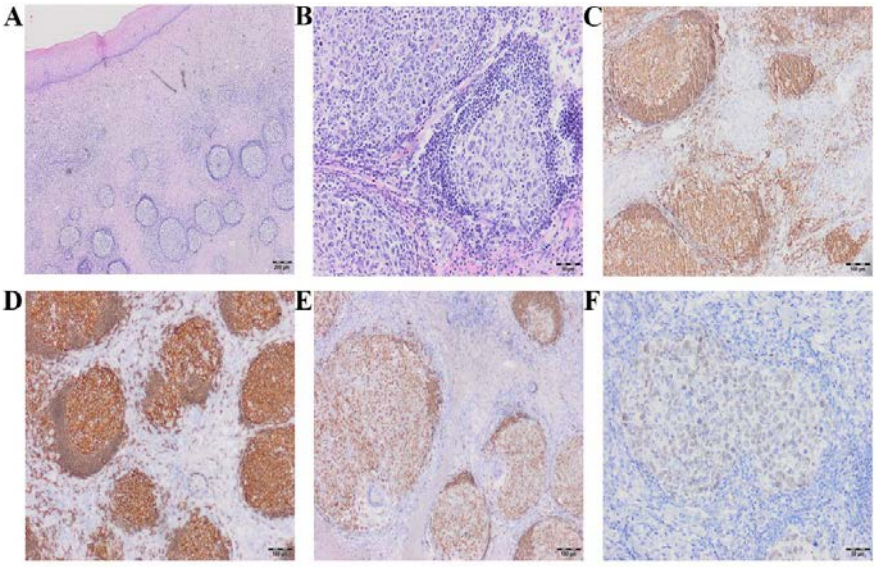


Fig. 1 – Histological and immunohistochemical features of *cervix uteri* lymphoma. Hematoxylin and eosin staining: A) ×400; B) ×200 original magnification; Immunohistochemical staining: C) diffuse positivity of the LCA (×100 original magnification); D) CD20 (×100 original magnification); E) PAX5 (×100 original magnification); F) Bcl 6 (×200 original magnification).

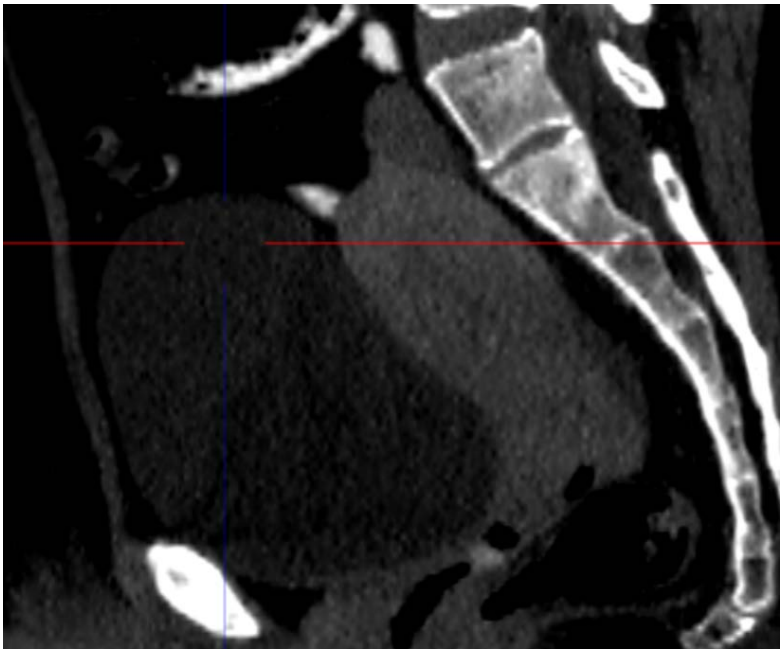


Fig. 2 – Computed tomography (CT) of the pelvis. Sagittal sections, prolapse of soft tissue mass from cervix *uteri* to the proximal third of the vagina. There are no CT signs of the infiltration of surrounding adipose tissue and organs.

After starting the hematological therapy, the patient has been regularly examined by a gynecologist every 4 months. Initially, there have been signs of increased vaginal secretion under the speculum. *Portio vaginalis uteri* (PVU) was voluminous, about 4–5 cm in diameter. At the control gynecological examinations, 4 months after the administration of HT, it was noticed that the volume of the cervix decreased (cervix 3 cm long, up to 4 cm wide). The findings of gynecological examinations, colposcopy, and PAPA tests were in order, as well as the exploratory curettage of the endocervical canal and endometrium – (pathohistological finding: secretory altered endometrium).

Discussion

Malignant lymphomas originate from the cells of the immune system - lymphocytes. There are more than 30 types of lymphoma, and each represents a disease with different biological behavior. This biological heterogeneity leads to significant differences among lymphomas in terms of epidemiology, pathohistological characteristics, and clinical presentation [3]. The NHL is ranked as the 5th to 9th most common malignancy in most countries around the world [4].

Primary lymphomas of the female genital tract are extremely rare, representing 0.2–1.1% of extranodal NHL and less than 0.5% of total gynecological malignancies [5].

Histological classification of all species is based on World Health Organization (WHO) standards. The most common histological type of lymphoma of the female genital tract, DLBCL, has several recognizable histopathological characteristics, with a poor prognosis and a preference for central nervous system dissemination [6].

According to the Globocan database, available on the Internet in 2020, uterine cervix neoplasms are in fourth place in terms of frequency. Precursors of cervical neoplasms originate from any squamous, glandular cell lineage (0.2%) or lymphocytes (0.1%) [7].

Clinical features, cervical biopsy, especially conization, and detailed immunohistochemical analyses are crucial for diagnosing cervical lymphoma [8].

In the United States, the incidence of NHL has increased significantly in recent decades and accounts for approximately 4% of all malignancies today [9]. Lymphomas are extremely rare tumors of the uterine cervix. DLBCL is the most common tumor of all lymphomas that can be localized at that site [10].

Immunodeficiency or autoimmunity is crucial for an increased risk of developing DLBCL. In addition, DLBCL can be caused by a large number of etiological factors such as infectious agents, pesticides, organic solvents, long-term use of hair dye, ultraviolet radiation, some drugs, genetics, and diet. Therefore, persistent antigen stimulation plays an important role in the development of lymphomas, especially extranodal lymphomas.

The WHO defines DLBCL as a neoplasm of large B lymphoid cells of a diffuse mode of growth whose nucleus size is close to or larger than macrophage nuclei or more than twice the size of lymphocytes. This tumor has clear histogenesis and originates from lymphocytes, cells of the immune system. Cells of DLBCL origin are considered to be centroblasts and immunoblasts. Centroblasts are located in the germinal center of the lymph follicle. Immunoblasts are located in the paracortex and are also called activated B cells.

Macroscopically, the cross-sectional area of the affected lymph node or extranodal organ is homogeneous, grayish-white in color, and bacon-like in appearance. Depending on the presence of areas of bleeding or necrosis, the cross-section area may be pink or yellowish, with a softened consistency. The histological picture is not uniform in all DLBCL subtypes.

These tumors have aroused interest due to their unique subepithelial localization and diverse clinical presentation. DLBCL is a disease of all ages but most commonly occurs in middle and old age. In most cases, DLBCL begins in the lymph nodes. Approximately 71% of patients have extranodal involvement during primary nodal disease. The most common sites of the occurrence of extranodal disease are the stomach and ileocecal region, but any part of the body may be the primary site of the disease, for instance, skin, bone, testis, spleen, Waldeyer's ring, salivary glands, thyroid, liver, kidney, adrenal gland, and uterus cervix. The disease can be localized or disseminated.

Initially and during disease monitoring, all patients should have a complete blood count, biochemical analysis including lactate dehydrogenase (LDH), and a bone marrow biopsy. Chest radiography and computed tomography (CT) scans of the chest, abdomen, and pelvis are also required. Functional scans, such as positron emission tomogrpahy (PET) scans, can enhance internships, especially by detecting occult diseases in the abdomen or spleen.

DLBCLs are aggressive but potentially curable with combined chemotherapy. DLBCL is a systemic disease; therefore, the therapy is systemic. Complete remission is nowadays achieved in 75–80% of patients, with long survival in about 50% of patients. The CHOP protocol has been the backbone of the therapy for decades.

Morphological, biological, and clinical studies have classified DLBCL into morphological variants, immunophenotypic, and molecular subtypes. There are also a large number of cases that may be biologically heterogeneous but for which there are no clear or accepted criteria for classification. They are classified as DLBCL, not otherwise specified (NOS), i.e., without a more precise specification, and include all cases that do not belong to specific subtypes.

Based on cytological characteristics, existing morphological subtypes of DLBCL are the following: centroblast, immunoblast, anaplastic, and rare morphological variants. DLBCL has two molecular subgroups: GCB and activated B-cell-like (ABC). Based on the immunophenotype, they are classified into the following: CD5-positive DLBCL, GCB, and non-GCB.

The Ann Arbor classification system is used to determine the stage: stage I – involvement of one region of lymph nodes or one extranodal organ; stage II – involvement of two or more lymph node regions on the same side of the diaphragm or localized involvement of the extranodal organ and one or more lymph node regions on the same side of the diaphragm; stage III – lymph node involvement on both sides of the diaphragm, with or without localized involvement of extranodal tissue or organ, spleen, or both; stage IV- diffuse or disseminated involvement of one or more distant organs, with or without lymph node involvement. Body temperature over 38 °C, night sweats, and/or weight loss over 10% for six months are called systemic symptoms and are denoted by the suffix B; asymptomatic patients are denoted by the suffix A.

Persistent HPV infection can cause carcinogenesis by hyperactivation of the immune system. One national cohort study examined the correlation between HPV infection and Hodgkin's and non-Hodgkin's lymphoma risk. All women who underwent conization between 1978 and 2011 were identified. In 87,435 women who underwent conization, an increased incidence of Hodgkin's and only a slight increase for non-Hodgkin's lymphoma was observed, but a correlation of HPV infections with an increased risk of lymphoma was proven [11].

The American Cancer Society (ACS) recommends that people over 25 should begin screening for cervical cancer and undergo primary testing for HPV every 5 years up to 65 years of age. Persistent high risk HPV (hrHPV) infection, primarily HPV types 16 and 18, are the cause of almost all cervical cancers. Although HPV infections are common in healthy adults, only a small proportion of infections survive and progress to precancerous cells in the cervix. This progression to a precancerous condition lasts for years. Thus, although HPV infections and CIN are common, they rarely lead to cervical cancer. Understanding HPV infection as the main causative factor for cervical neoplasia provided the basis for the introduction of HPV testing, which is a reliable predictor and risk element for precancerous and cervical neoplasia [12].

Conclusion

Lymphomas occur at all ages. Cervical lymphomas are extremely rare. The coexistence of CIN1/L-SIL and NHL may be completely random, and concomitant cervical lymphoma may be overlooked if biopsies are not performed adequately. Determining the presence of HPV infection is a significant predictive factor in the development of cervical lymphoma. Deep cervical biopsy, conization, and detailed immunohistochemical analyses are crucial for diagnosing cervical lymphoma. The differential diagnosis of primary cervical lymphomas includes benign inflammatory and malignant diseases such as cervical cancers, sarcomas, and lymphoma-like lesions. Since lymphomas are subepithelial, in the absence of ulceration, the PAPA swab plays a very insignificant role in the diagnosis of cervical lymphoma, but determining the presence of HPV infection is very significant. The key to diagnosis is histopathological analysis with the determination of immunophenotypic characteristics.

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