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Case Report / Приказ болесника

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**Primary endometrial extranodal marginal zone lymphoma of  
mucosa-associated lymphoid tissue type**

Ендометријални примарни екстранодусни нехоџкинов лимфом  
маргиналне зоне

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## Primary endometrial extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue type

### Ендометријални примарни екстранодусни нехоџкинов лимфом маргиналне зоне

#### SUMMARY

**Introduction** Primary lymphomas of the female genital system are rare and represent about 2% of extranodal lymphomas and about 0.5% of malignant gynecological diseases which occur in only 0.5% of cases in the cervix and uterine body. Mucosa-associated lymphoid tissue (MALT) lymphoma represents a rare variant of the primary genital lymphoma.

**Case outline** This paper presents the case of a 45-year-old patient who has visited a gynecologist due to abnormal menstrual bleeding within last three years and a bloody excrement between them. The ultrasound examination raised doubts about endometrial polyps, thus the fractional exploratory curettage was performed. Histologically, a dense infiltration of stromal endometrium was demonstrated in the endometrium through fine-tuned lymphocytic cells that were highly positive for immunohistochemical markers CD20, CD79a, CD45, positive for CD5 in up to 5% of tumor cells, negative for Cyclin D1, CD10 and bcl-2. The proliferation marker Ki-67 has been expressed in approximately 15% of the lymphocytic tumor cells. The patient's uterus and adnexa have been surgically removed and she did not receive any additional therapy. After a 3.5-year follow-up, the patient is without a relapse of the disease.

**Conclusion** Although non-Hodgkin's lymphomas of the genital organs, especially the MALT type of non-Hodgkin's lymphoma, are extremely rare, they should also be considered as a differential diagnosis in women with menometrorrhagia and the ultrasound image of the endometrial polyps.

**Keywords:** endometrial lymphoma; non-Hodgkin's lymphoma; MALT-type lymphoma

#### САЖЕТАК

**Увод** Примарни лимфоми женског гениталног система су ретки и представљају око 2% екстранодалних лимфома и око 0,5% злоћудних гинеколошких оболења која се јављају свега у 0,5% случајева у грлићу и телу материце. Лимфом маргиналне зоне (*MALT*) представља јединствени клиничко – патолошки ентитет и ретку варијанту примарног гениталног лимфома.

**Приказ болесника** У раду је приказан случај 45-годишње пацијенткиње која се јавила гинекологу због обилних менструација које су трајале три године, и сукрвавог исцетка између менструација. УЗ прегледом је постављена сумња на ендометријални полип те је урађена фракционирана експлоративна киретажа. Хистолошки се у киретману ендометријума показала густа инфилтрација строми ендометријума, ситним, униформним лимфоцитонидним ћелијама које су на имунохистохемијске маркере CD20, CD79a и CD45 биле високо позитивне, на CD5 само фокално позитивне, у мање од 5% туморских ћелија, на *Cyclin D1* и *CD10* и *bcl-2* негативне. Пролиферациони маркер *Ki-67* експримирао се у око 15% туморских ћелија. Пацијенткињи је хируршким путем одстрањена материца и аднекса и није примила никакву додатну терапију. Након 3,5-годишњег праћења пацијенткиња је без релапса болести.

**Закључак** Иако су нехоџкинови лимфоми гениталних органа, посебно нехоџкинов лимфоми типа *MALT*, изузетно ретки, треба мислити и на њих у диференцијалној дијагнози, код жена са менометрорагијама и ултразвучном сликом ендометријалног полипа.

**Кључне речи:** лимфом; лимфом типа *MALT*; лимфом ендометријума

#### INTRODUCTION

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) type, according to the valid WHO classification 2016, is a subtype of B-cell non-Hodgkin's lymphoma and accounts for 7.5% of all non-Hodgkin's lymphomas [1,2]. They are most commonly found within the gastrointestinal tract (30-40%), skin and CNS, unlike female genital organs where they are scarcely

found, in only about 2% of cases [1, 3–5]. The primary endometrial MALT lymphoma represents an extremely rare variant of the primary genital lymphoma and only 14 cases, as far as we know it, have been described in English literature [6]. In our paper we will show the case of a 45-year-old patient with menometrorrhagias caused by the primary endometrial MALT lymphoma.

## CASE REPORT

A 45-year-old patient (G: 2, Para: 2) has asked for a gynecological examination due to the highly abundant periods every 23-24 days she has had for the last 3 years and a bloody excrement between them occurring over the past 10 months. She did not have any other problems. She did not lose weight, did not have high fever or perspiration. Pap smear was normal (II group, NILM). Transvaginal ultrasound showed a normally large uterus with endometrium which could not be clearly separated from the myometrium in the presence of a 20 mm thickened endometrium. Both ovaries were characterized by a regular size and echostructures. There was no free fluid in the small pelvis.

Due to suspicion of the existence of the endometrial polyps, endometrial curetage was performed, and a diagnosis was established by pathohistological (PH) examination including immunohistochemical staining: extranodal MALT lymphoma of endometrium. In order to confirm the PH diagnosis, another examination was performed at the Institute of Pathology, the City Clinic of Cologne, where the previous diagnosis was confirmed.

The histopathological examination revealed that the tumor tissue consists of small, uniform, ovoid cells without necrosis. The immunohistological response of tumor cells to CD20, CD45 and CD79a was highly positive, to CD5 positive in only a minor percentage of tumor cells (up to 5%), to Cyclin D1 and CD10 and bcl-2 negative. The proliferation marker Ki-67 has been expressed in approximately 15% of the tumor cells.

A NMR imaging of the abdomen and small pelvis has been done without presence of any change on abdominal organs or lymphadenomegaly. Within the preoperative preparation, an X-ray image of lungs was performed that was normal. Complete blood count (CBC) was also normal (the number of leukocytes and lymphocytes was within the limits of the reference values). The level of liver enzymes was within the limits of the reference values. The *Helicobacter pylori* test was negative.

Hysterectomy with bilateral salpingo-oophorectomy has been performed. Lymphadenomegaly has not been detected by means of careful exploration of the abdominal cavity and small pelvis. The postoperative recovery has been successful. The patient was released from the hospital on the fifth postoperative day. A final PH finding has shown the presence of reparative changes on endometrium

without lymphoproliferative neoplasm with prominent chronic reactive bilateral salpingitis. Clinically, it was a stage of IE disease according to the Ann Arbor classification, since only one organ has been involved [7]. The postoperative surgical stage was FIGO stage IA. According to The International Prognostic Index (IPI), used to identify patients with a high risk of a disease relapse, our patient has been categorized as a low-risk patient because she was under 60 years old, in the first stage of the disease, the tumor was only localized to the endometrium and the lactate dehydrogenase (LDH) level was within the limits of the reference values [8].

After the surgery, the medical review board decided that additional therapy was not necessary. Patient has already spent 3.5 years in complete remission without clinically evident recurrent disease, with regular radiographic and laboratory findings.

## DISCUSSION

Primary lymphoma of the female genital organs are extremely rare and make less than 0.5% of all malignant diseases of female genital organs [1]. Lymphomas of the female genital organs may be found within the disseminated, systemic lymphoma more often [4]. According to a comprehensive study conducted by Nasioudis D. and associates in 2017, in 697 cases of women with primary genital lymphoma, the ovary was affected in 37% of cases, the cervix in 21.4%, while in 16.5% of cases the lymphoma was endometrially localized [9]. Most commonly, diffuse large B-cell lymphoma occurs on the genital organs, followed by follicular lymphoma subtype while the primary endometrial MALT lymphoma is quite rare [4].

Thirteen cases of MALT lymphoma of the endometrium have been described in English literature so far. Most cases include postmenopausal women with bleeding issue as a dominant symptom whose diagnosis is based on a pathohistological examination of material obtained by curettage. In a minority of cases, the disease was severe and diagnosis was established after the pathohistological examination of the uterus after surgery for other reasons (uterovaginal prolapse) [1,5,10,11]. Our patient was 45 years old and the only symptom was menometrorrhagia she had since 10 months.

In the case of our patient, a pathohistological examination showed that the tumor consisted of small, uniform ovoid cells (Figure 1). Immunohistochemical examination of the preparation obtained by the exploratory curettage showed that the tumor cells were positive for the immunohistochemical markers CD20 and CD45. CD45 is a common leukocyte antigen, i.e. marker for all leukocytes. It is the most important marker in the delimitation process between lymphoma and non-lymphatic tumors. The CD20 marker was positive as well and represents a marker for B lymphocytes. Additional

immunohistochemical tests were performed in Cologne: the tumor was highly positive for CD79a (broader marker for B lymphocytes, including all B-lymphocyte populations, mature and immature variants) indicating that it consisted exclusively of B lymphocytes (Figure 2A). The tumor was positive for the CD5 marker only in 5% of tumor cells (Figure 2B). CD5 is also the marker of T-lymphocytes (all mature T- cells), but may also be expressed from a subpopulation of B-cells. CD5 is rarely expressed in the extranodal MALT lymphoma. A stronger positive response to CD5 would be expected in the case of lymphocytic lymphoma and mantle cell lymphoma. The immunological phenotype of MALT lymphoma is not specific (no single marker is specific), so it is a diagnosis of exclusion to other small cell lymphomas. Cyclin D1 as the main marker of mantle cell lymphoma was negative, CD10 as the main marker of follicular lymphoma was also negative and expression of CD23 antigen, as an important marker of lymphocytic lymphoma (CLL), was also negative. The immunohistological reaction to bcl-2 protein, as a relevant marker for follicular lymphoma, was also negative. Bcl-2 is mostly positive in the case of MALT lymphoma, but it may be negative as well. Ki-67 labelig index, indicates a moderate cell proliferation of about 15% consistent with low grade malignant lymphoma (Figure 2C). The overall finding indicated an extranodal MALT lymphoma of endometrium with no lymphadenopathy being clinically present [12-16]. Further molecular testings (e.g. examination of clonality) have not been performed given the fact that these quite expensive testings are only performed in specialized centers. Besides this, they only represent an additional tool in lymphoma diagnostics and also have their limitations in terms of sensitivity and specificity [17].

Aetiology and pathogenesis of MALT lymphoma are unknown, although chronic antigen stimulation (chronic infection, autoimmune disease) is thought to have a significant role in the emergence of this disease [1,3]. A case of MALT thyroid gland lymphoma in a patient with Hashimoto thyroiditis as well as a case of gastrointestinal MALT lymphoma in a patient with atrophic gastritis have been published [4]. Two thirds of patients with MALT lymphoma of the stomach have a chronic *Helicobacter pylori* infection [18]. It is also believed that there is a relationship between *Chlamydia psittaci* infection and the occurrence of ocular adnexal MALT lymphoma, *Campylobacter jejuni* and immunoproliferative disease of small intestine as well as *Borrelia burgdorferi* infection and MALT lymphoma of the skin [1]. There was no evidence of chronic endometritis in the case of our patient, nor in the cases of MALT lymphoma of endometrium described in literature [1,3,5]. Other studies have shown the connection between chromosomal translocations and trisomy in cases of MALT lymphoma of the non-genital region which indicates that, apart from chronic infection, other factors can have a significant role in the emergence of this malignant disease as well [19-21].

For detection of other possible disease localisations and determination of exact stage of the disease, performing a CT of abdomen and small pelvis is very important. It is thought that about 25-

45% of all patients with extragastric MALT lymphoma at the time of establishing the diagnosis have a disseminated disease [22,23].

The survival of patients with multifocal changes in MALT lymphoma without bone marrow being affected is identical to those in patients with unifocal localization, which leads to the conclusion that the multifocal localization of MALT lymphoma does not necessarily mean dissemination of the disease [22]. The standard therapy has not been clearly defined yet due to the fact that it is a very rare type of tumor. In general, the extranodal marginal MALT lymphoma has a slow clinical course, remains in the form of a local illness for a long time and its dissemination begins after a long time. About 75% of patients are at the moment of determining the diagnosis of MALT lymphoma in clinical stage I/II and less than 10% have metastases in the bone marrow [24]. As a result, the prognosis is significantly better than in other types of B-cellular extranodal lymphoma [3,25]. In most cases therapy is primarily surgical or radiotherapy in patients with a localized disease, while chemotherapy is used in cases of a disseminated disease.

In our case, since the tumor was localized in the uterus, radiological images did not show lymphadenomegaly and the patient had no intention of giving birth, it was decided to do hysterectomy with bilateral salpingo-oophorectomy as the first therapeutic line. Since lymphoma was limited only to the endometrium, further therapy was not recommended.

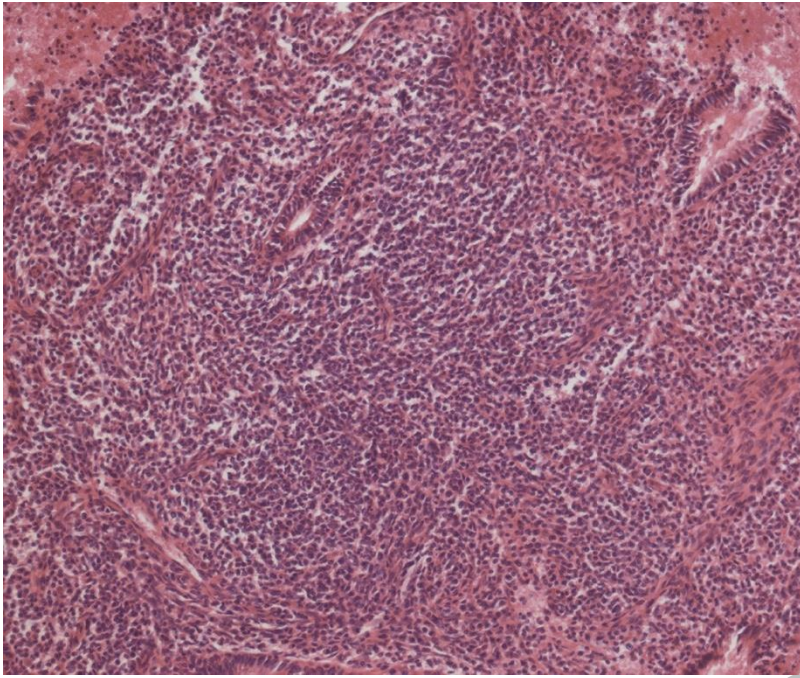
Although non-Hodgkin's lymphomas of the genital organs, especially the MALT type of non-Hodgkin's lymphoma, are extremely rare, they should also be considered in women with menometrorrhagias and the ultrasound image of the endometrial polyps.

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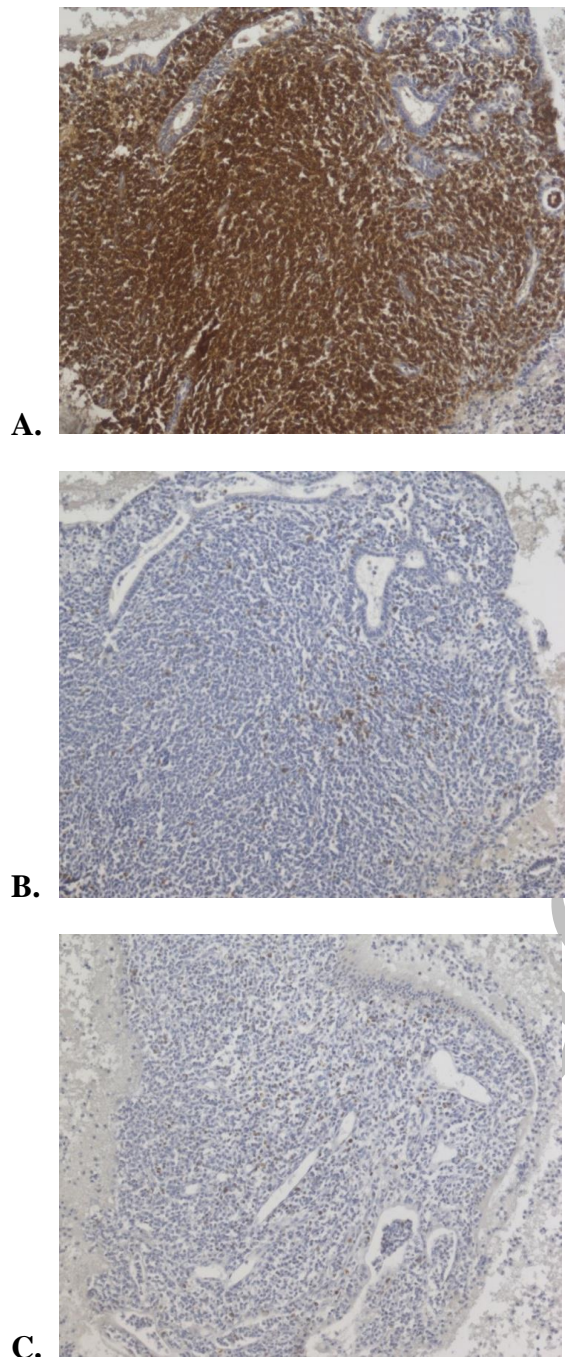
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**Figure 1.** Hypercellular stroma consists of small, uniform, ovoid cells without necrosis. Endometrium glands have regular cytomorphological properties. (Haematoxylin & Eosin, × 10)



**Figure 2.** A) The immunohistological reaction to the B-lymphocyte marker CD 79a shows a monotone lymphocytic infiltrate that predominantly (almost exclusively) consists of B-lymphocytes ( $\times 10$ ); B) The immunohistological reaction to the CD5 marker shows a positive reaction in a small percentage of tumor cells (up to 5% of tumor cells) ( $\times 10$ ); C) The proliferative marker KI67 (B) is expressed in approximately 15% of the neoplastic lymphoid cells ( $\times 10$ )