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

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INTRODUCTION

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) type, according to the current WHO classification of 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, 4, 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, have been described in literature in English [6]. In our paper, we present the case of a 45-year-old patient with menometrorrhagia caused by the primary endometrial MALT lymphoma.

CASE REPORT

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

Due to the suspicion of the existence of endometrial polyps, endometrial curettage was performed, and a diagnosis was established by the histopathological examination including immunohistochemical staining: extranodal MALT lymphoma of endometrium. In order to confirm the histopathological 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 consisted of small, uniform, ovoid cells without necrosis. The immunohistochemical 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 it was negative. The proliferation marker Ki-67 was expressed in approximately 15% of the tumor cells.

Nuclear magnetic resonance imaging of the abdomen and the lesser pelvis showed no...
presence of any change on the abdominal organs or lymphadenomegaly. Within the preoperative preparation, an X-ray image of the lungs was taken and was normal. Complete blood count 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 was performed. Lymphadenomegaly was not detected by means of careful exploration of the abdominal cavity and the lesser pelvis. The postoperative recovery was uneventful. The patient was discharged from the hospital on the fifth postoperative day. The final histopathological finding showed the presence of reparative changes on endometrium without lymphoproliferative neoplasm with prominent chronic reactive bilateral salpingitis. Clinically, it was a stage of infective endocarditis 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, used to identify patients with 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 level was within the limits of the reference values [8].

After the surgery, the medical review board decided that additional therapy was not necessary. To date, the patient has been in complete remission for 3.5 years, without clinically evident recurrent disease, with normal 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 female genital organs may be found within the disseminated, systemic lymphoma more often [4]. According to a comprehensive study conducted by Nasioudis et al. [9] in 2017, in 697 cases of women with primary genital lymphoma, the ovary was affected in 37% of the cases, the cervix in 21.4%, while in 16.5% of the cases the lymphoma was endometrially localized. 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 the literature in English so far. Most cases include postmenopausal women with a bleeding issue as the dominant symptom whose diagnosis is based on histopathological examination of the material obtained by curettage. In a minority of cases, the disease was severe and diagnosis was established after the histopathological 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 had for 10 months.

In the case of our patient, histopathological examination showed that the tumor consisted of small, uniform ovoid cells (Figure 1). Immunohistochemical examination of the specimen obtained by the exploratory curettage showed that the tumor cells were positive for the immunohistochemical markers CD20 and CD45. Marker 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, which represents a marker for B-lymphocytes, was positive as well. 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 in only 5% of the tumor cells (Figure 2B). CD5 is also the marker of T-lymphocytes (all mature T-cells), but it 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 the CD23 antigen, as an important marker of lymphocytic lymphoma, 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 labeling index indicates 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 testing (e.g. examination of clonality) was not performed given the fact that this quite expensive testing was only performed in specialized centers. In addition, they only represent an additional tool in lymphoma diagnostics and have their limitations in terms of sensitivity and specificity [17].

Etiology 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 [11]. There was no evidence of chronic endomtritis in the case of our patient, nor in the cases of MALT lymphoma of endometrium described in the 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, 20, 21].

For detection of other possible disease localizations 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 localized disease, while chemotherapy is used in cases of 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 menometrorrhagia and the ultrasound image of endometrial polyps.

REFERENCES


