Incidentally discovered diffuse large B-cell lymphoma limited to the endocervical mucosa in a young female patient

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running title: Diffuse large B-cell lymphoma of the endocervix

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Established Facts:

- *Already known:* Primary high grade non-Hodgkin lymphoma of the female genital tract is extremely rare.
- *Already known:* Vaginal bleeding, abdominal pain, urinary complaints and vaginal or cervicovaginal or pelvic mass are the frequent primary symptom of genital lymphomas.

Novel Insights:

- *New information:* The case is unusual because the patient had no symptoms, specific colposcopic signs or a visible mass.
- *New information:* Cervical cytology has only a limited role in establishing the proper diagnosis, which can be best made on the basis of LLETZ. Although the introduced patient's management was deviated from standard gynecological cancer screening protocols, this led to reveal the hidden disease at an early stage.
- *New information:* It is still unknown whether chemotherapy alone or in combination with radiotherapy or surgical interventions would be the optimal therapeutic approach. In this case R-CHOP 21 immunochemotherapy was introduced and resulted in complete remission without hysterectomy.

ABSTRACT

Backround: Primary high grade non-Hodgkin lymphoma of the female genital tract is extremely rare. Vaginal bleeding, abdominal pain or urinary complaints might be its most frequent symptoms.

Case: We report a 27-year-old multipara who underwent large loop excision of the transformation zone because of the repeated finding of low grade squamous intraepithelial lesion identified during routine cancer screening. Incidentally, CD20 positive, primary, diffuse large B-cell lymphoma infiltrating the mucosa of the endocervix was also diagnosed from this specimen. The case is unusual because the patient had no symptoms, specific colposcopic signs or a visible mass. R-CHOP 21 immunochemotherapy was introduced and resulted in complete remission without hysterectomy. The patient is without evidence of disease after 36 months of follow-up .

Conclusion: Primary cervical lymphomas are mainly subepithelial initially, therefore they may be underrecognized due to the inefficiency of smears to diagnose such lesions. Early diagnosis and available targeted treatment allowed a cure in the reported example.

INTRODUCTION:

Primary non-Hodgkin lymphoma (NHL) involving the uterine cervix is extremely rare with an incidence of 0.008% of all cervical tumors. Secondary involvement of the female genital tract as part of a systemic lymphoma is somewhat more common. Diffuse large-B-cell lymphoma (DLBCL), represents a classical ”high grade” NHL. Although this is one the most frequent lymphoid neoplasm of the cervix, its manifestation as a primary cervical tumor is considered a real rarity [1-4].

The standard treatment for systemic DLBCL patients was the administration of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Since 1997, rituximab immunotherapy has been added to the CHOP regiment (R-CHOP), and has resulted in a significant improvement in the survival rate of these patients [5,6]. Because of the low incidence of primary NHLs in the female genital tract (reflected by only scarce case reports) there is no wide enough multicenter experience regarding their best complex treatment. It is unknown whether chemotherapy alone or in combination with radiotherapy or surgical interventions such as hysterectomy, pelvic node dissection or salpingo-oophorectomy would be the optimal therapeutic approach to this group of diseases. Although R-CHOP could be considered the first-line regimen with promising results, a larger number of reported cases are needed to reach better founded conclusions [1,4,7-9].

The aim of the present case report is to document a rare clinical entity: a 27-year-old multipara incidentally diagnosed with DLBCL (WHO, CD20 positive) infiltrating the mucosa of the endocervix who was given R-CHOP therapy, responded well, and is without evidence of disease after 36 months of follow-up.

CASE REPORT:

The patient’s actual history started with a routine cancer screening, 48 months after her second delivery at the Department of Obstetrics and Gynecology, Bács–Kiskun County Teaching Hospital, Kecskemét, Hungary.

The cervical cytology (Pap smear) was interpreted as representing low-grade squamous intraepithelial lesion (L-SIL, Cervical Intraepithelial Neoplasia grade 1, CIN

1) according to the Bethesda system. Colposcopic examination showed no specific signs and cytologic features raised the possibility of chronic endocervicitis with Human Papillomavirus (HPV) infection. According to the recommendation of the cytopathologist in this case, repeated cervical cytology taken at 3 months interval resulted in LSIL / CIN 1 again, with HPV negativity on the basis of HPV typing performed at an outside laboratory, and LLETZ (large loop excision of the transformation zone) was performed. The cone was 6 mm deep, i.e. somewhat less than the 10 mm suggested for obtaining clear margins most of the time [10]. Histological results from the cone biopsy confirmed the presence of cervical intraepithelial neoplasia grade I (CIN I) with koilocytic atypia and p16 immunohistological staining of the dysplastic cells suggestive of HPV infection and also established the diagnosis of DLBCL infiltrating the mucosa of the endocervix (Figure 1). The CIN I lesion was present in 4 out of 9 histology blocks (the margins were either clear or not assessable), whereas the lymphoma involved 5 blocks and was almost exclusively present in the endocervical part of the biopsy, under the superficial glandular epithelium, around the galnds (the margins being involved). The lymphoma cells were negative for cytokeratin, CD5, and stained positive for CD20 and MUM1, consistent with the activated B-like subtype of DLBCL. The Ki-67 labeling index of the tumor cells was estimated and reported 70%.

On physical examination, no spleno- or hepatomegaly was detected. Only some minimally enlarged lymph nodes, all smaller than 1 cm, were found inguinally on both sides. Although no detectable mass was found during initial colposcopy and physical examination, the pelvic MRI described an abnormal soft tissue mass measuring 6.5 x 2.3 x 1.5 cm between the uterine corpus and the bladder at the time of the diagnosis. B signs were absent. Staging FDG-PET CT and pelvic MRI were performed, and did not indicate any myometrial, nodal or other organ involvement, thus, the patient's DLBCL was categorized as stage IE according to the Ann Arbor staging system. The international prognostic index (IPI) was 0, and the Eastern Cooperative Oncology Group (ECOG) performance status was 0 too.

After the proper diagnosis had been set up, six cycles of rituximab combined with standard CHOP chemotherapy (R-CHOP 21) were administered. In details, the dose of rituximab was 375 mg/m^2, that of cyclophosphamide was 750 mg/m^2, and that of doxorubicin was 50 mg/m^2; vincristine was given in a dose of 1.4 mg/m^2 on the first day

of the cycles, and 100 mg of prednisone was also taken orally from the first to the fifth day of each cycle. The administered therapeutic regimen was planned according to the risk based on the age-adjusted IPI. During the period of the treatment, there were no serious complications. The patient had reached partial remission four months after the introduction of the first cycle of R-CHOP 21 chemotherapy. The dimensions of the pelvic mass have significantly decreased. As a consequence, the corpus of the uterus had become anteflected. Three months after the completion of R-CHOP 21 therapy, no circumscribed abnormality could be identified between the corpus and the bladder on the pelvic MRI scan.

After the completion of the immuno-chemotherapy, repeated cervical cytology was done. FDG-PET CT and pelvic MRI were also performed, and confirmed the patient's complete remission (by the Cheson criteria) [11].

14 months after the completion of chemotherapy, the patient became pregnant spontaneously, but the pregnancy was miscarried due to unknown reasons on the 8th week. After 36 months of follow-up, the patient is without any evidence of disease.

DISCUSSION:

R-CHOP therapy of some subsets of non-Hodgkin lymphoma (NHL) patients significantly improved their event-free and overall survivals [5]. However, there are only limited data available on the R-CHOP immune-chemotherapy of primary NHL of the female genital tract [7,12,13]. Vaginal bleeding is the most frequent primary symptom of genital lymphomas, but other symptoms such as abdominal pain or urinary complaints can also appear. The most common clinical finding is the presence of a vaginal, cervicovaginal or pelvic mass [8,9,14,15]. The identification of the tumor is easier if colposcopy reveals a mass in the uterine cervix. For example, Binesh et al have reported a cervical mass identified by colposcopy, but no other lesions were detected in the case they described [13]. When primary DLBCL appears without a bulky disease, the identification and the diagnosis of the tumor is more difficult. The present case was unusual in several respects, as no detectable mass or any other colposcopic lesions were identified. The patient had no vaginal bleeding or other symptoms which could have referred to the underlying lymphoma, which was a chance finding following further

investigation of a cervical smear disclosing a low grade squamous intraepithelial lesion. Al-Talib et al. have also reported a case of high grade B cell lymphoma of the uterine cervix. They discuss the cytology features and the differential diagnosis with emphasis not just on the importance of the cervical biopsy but on also the potential role of the cervical smear in the initial diagnosis of this tumour [16]. Grace et al. highlight the difficulty of diagnosing cervical lymphoma in the two cases they present, and suggest that cervical biopsy is needed to establish the diagnosis [3].

In line with previous reports, it can be concluded that vaginal bleeding and a mass in the uterine cervix can be the first signs of the disease in most cases, but as our case report shows there may be exceptions too [8,17]. Cervical lymphomas are initially subepithelial, therefore, there is a danger of underdiagnosis with cervical cytology, especially in the early stages. Cytology is unlikely to detect NHL, unless the disease has progressed to the epithelium, and biopsy is generally required to establish the proper diagnosis, as in the present case, where a coexisting low grade squamous intraepithelial lesion initiated the biopsy. Based on previously reported cases, primary DLBCL of the female genital tract can occur at any age. With the introduction of immuno-chemotherapy, we could hope for a promising result regarding the disease free survival, but this introduces another important challenge: how to preserve the childbearing potential [1,18-19]. There are only limited data on the recommended time of contraception, on the risk of miscarriages, or on the pregnancy outcome of women with and after R-CHOP immune-chemotherapy in primary NHL of the female genital tract [1,18,19].

There are some data indicating that CHOP chemotherapy may be given safely to NHL patients in the third trimester of pregnancy [18]. Lorusso et al. have reported a 29-year-old woman who was treated with neoadjuvant chemotherapy and conservative surgery for a primary stage IE non-Hodgkin lymphoma of the uterine cervix in whom pregnancy was possible three years after the primary treatment, and the patient successfully delivered a full-term healthy infant [1]. In contrast, our patient had become spontaneously pregnant 14 months after chemotherapy, but experienced missed abortion. It can be speculated that previous chemotherapy had an influence on the termination of pregnancy, but the opposite may also hold true.

Conclusion:

Primary cervical lymphomas are initially localized and subepithelial; therefore cervical cytology has only a limited role in establishing the proper diagnosis, which can be best made on the basis of LLETZ. Although in this case, the patient's management deviated from standard gynecological cancer screening protocols, this led to reveal the hidden disease at an early stage, and this chance finding led to further treatments which can contribute to the widening experience in the treatment of organ specific, localized NHLs in the female genital tract. In terms of therapy, our case report supports the notion that R-CHOP can be considered as first-line regimen with promising results in these rare manifestations of DLBCL as well. The interest in the case lies not only in its rarity, but also in the fact that our patient recovered from the disease without hysterectomy.

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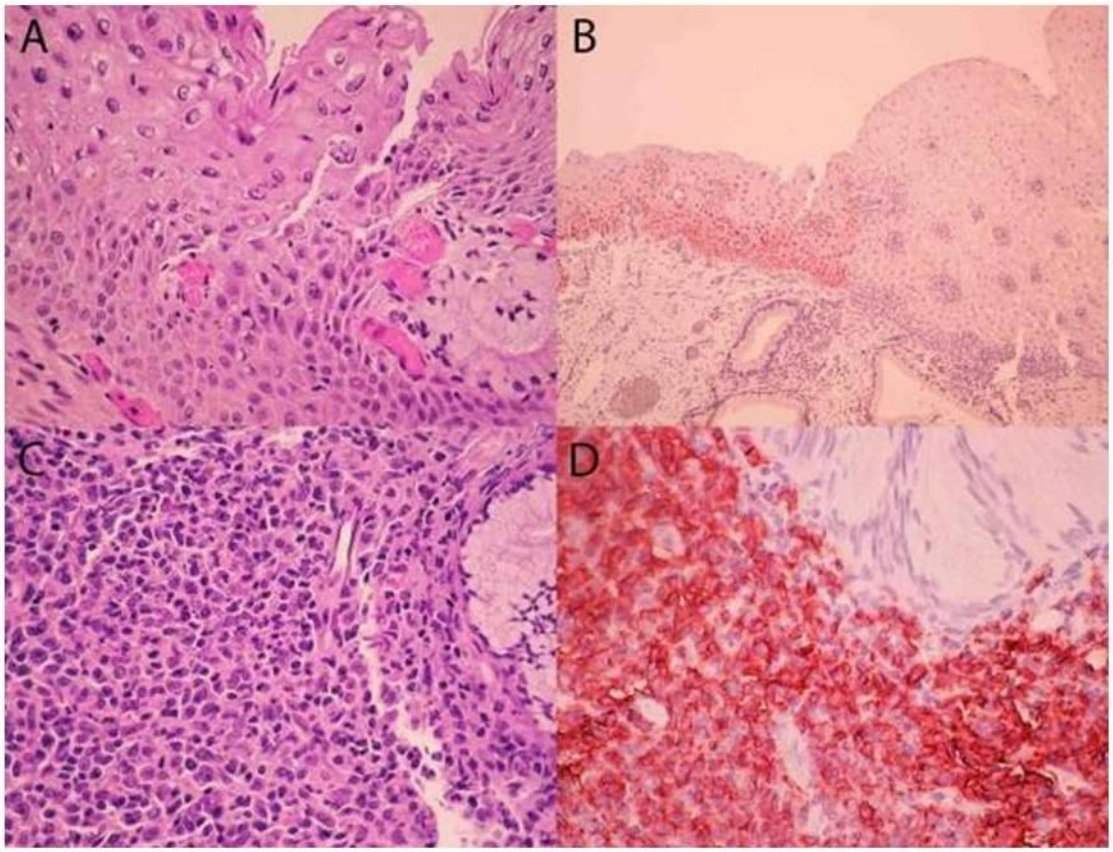

Figure 1: Histological appearance of the squamous intraepithelial lesion and the high grade lymphoma involving the cervix.

A: Low grade squamous intraepithelial lesion with koilocytic atypia in the upper third of the epithelium (HE, x400);

B: Low grade squamous intraepithelial lesion with p16 positive cell (seen as light brown) restricted to the dysplastic cells (p16, x100);

C and D: DLBCL around a cervical gland (HE and CD20, respectively; x400)