ANTICANCER RESEARCH *36*: 4931-4940 (2016)
doi:10.21873/anticanres.11059

Lymphoma of the Cervix: Case Report and Review of the Literature

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Abstract. *Background: Lymphoma of the uterine cervix (LUCX) is rare and may occur as a primary or secondary manifestation of this disease. Clinical and cytological presentations of LUCX vary and establishing diagnosis is often difficult. Surgery followed by radiation or chemotherapy is the mainstay of treatment. Case Report: We present the case of a 73-year-old woman with recurrent pathological PAP smears of the cervix and a history of chronic lymphatic leukemia 15 years ago. Colposcopy of the cervix showed no acetowhite lesion and a conization was performed. Histology revealed endocervical lymphoid cells, specified as low-malignant B-Non-Hodgkin lymphoma of the cervix based on the expression of CD5, CD20, and CD23, whilst CD10 and cyclin D1 were negative. The diagnosis was confirmed by flow cytometry of peripheral blood. Staging revealed enlarged iliacal, para-aortic, mediastinal, cervical, subclavicular, and inguinal lymph nodes and hepato-splenomegaly. Bone marrow analysis confirmed lymphoid infiltration consistent with B-cell lymphoma. The patient was scheduled for a combined immuno-chemotherapy with obinutuzumab and chlorambucil. In a MEDLINE literature search, 246 cases of LUCX were identified. One hundred and eighty-five cases were primary and 61 cases were secondary manifestations of LUCX. With a mean follow-up time of 38 months, overall survival was 81%. Data in the literature including clinical and histological characteristics of LUCX as well as the clinical management and prognosis are discussed herein. Conclusion: LUCX is rare and has distinct clinical and histological features. LUCX is usually treated with local surgical excision followed by radiotherapy or chemotherapy.*

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Key Words: Lymphoma, cervix, CLL, B-Non-Hodgkin lymphoma, immunohistochemistry.

Lymphoma is a common hematologic malignancy subcategorized into Hodgkin lymphomas and the more common Non-Hodgkin lymphomas (NHL) (1). Typically, lymphoma-associated tumors occur within the lymphatic organs and may have widespread systemic symptoms at the time of diagnosis. Extranodal lymphomas of the female genital tract, however, are rare and account for only 0.5% to 1% of cases (2-4). The most common histological subtype of female genital lymphomas is diffuse large B-cell lymphoma (4). Lymphomas of the female genital tract can be the primary manifestation of this disease or may occur as genital recurrences of lymphomas initially diagnosed elsewhere. Primary or secondary female genital tract lymphomas may occur in all internal and external female genital organs, but the ovary is the organ most often affected. For example, in a series of 147 isolated genital tract lymphomas, 59% were found in the ovary, 16% in the uterine corpus, 12% in the cervix, 7% were vulvar and 6% were vaginal (5). Primary lymphomas of the uterine cervix (LUCX) are defined as lymphomas which are localized in the cervix without any myometrial involvement and without any evidence of leukemia at the time of diagnosis (5). The etiology and pathogenesis of primary LUCX are unknown, although there might be a possible association with chronic inflammation (6, 7). The optimal management strategy of female genital tract lymphomas in general and LUCX in particular is not clear due to the rarity of disease, various histopathological subtypes, and a lack of comparative clinical trials. According to the case reports and case series of LUCX published in the literature, treatment regimens used in these cases include

surgery, chemotherapy, radiotherapy, and combinations of these modalities (3-13).

In clinical practice, patients with LUCX initially present to their gynecologists. Presenting symptoms include vaginal bleeding, local pain and dyspareunia as well as pathological PAP smears. In addition, LUCX may be diagnosed by chance. This often leads to the diagnostic delay and uncertainty regarding the appropriate management (5, 11-13). Therefore, the interdisciplinary cooperation between gynecologists, pathologists, and hematologists is important in order to optimally manage patients with LUCX. To highlight the characteristics and pitfalls of female genital tract lymphomas, we report the case of a woman with LUCX and the respective diagnostic challenges and treatment strategies. In addition, we present the case reports and case series of LUCX published in the literature and discuss the current knowledge on diagnosis, management, and prognosis of LUCX.

Case Report

We present the case of a 73-year-old woman who presented in March 2016 to our outpatient dysplasia clinic with recurrent pathological PAP smears of the cervix. She was asymptomatic and reported no pain, discharge or bleeding. She had a history of chronic lymphocytic leukemia (CLL) first diagnosed in 2001. The CLL so far had not required any treatment according to standard recommendations, particularaly the patient had no major lymphadenopathy and no major anemia or thrombocytopenia. Thus, no specific treatment was given between 2001 and 2016. Due to three consecutive pathological PAP smears during the last 9 months which were all categorized as PAP IIIg, ie potentially dyskariotic glandular cells of uncertain origin, colposcopy of the cervix was performed. Colposcopy showed a normally appearing ectocervix with no acetowhite lesion. A test for Human Papillomavirus (HPV) high-risk subtypes (Digene HC2 High-Risk HPV DNA Test, Qiagen, Düsseldorf, Germany) was negative. A cervical biopsy revealed lymphoid aggregates that were positive for CD20 and CD5 whilst negative for CD10, Cyclin D1 and CD23. MIB-1 labeling index was 10%. Thus, a preliminary diagnosis of marginal zone lymphoma was issued. Subsequently, a cervical conization was performed (Large Loop Excision of the Transformation Zone [LLETZ]). Histological sections of the cervix revealed a variable dense lymphoid infiltrate, composed of small, monomorphic cells (Figure 1). Immunhistochemical stains demonstrated the expression of CD20, CD5, and CD23 whilst CD10 and Cyclin D1 were negative (Figure 2). The MIB-1 labeling index was 5%. PCR analysis of immunoglobulin heavy chain detected clonal rearrangement of the IgH gene with three primer sets (FRI, FRII, FRIII). The combined findings led to the final diagnosis of a low-malignant B-Non-Hodgkin lymphoma of the cervix consistent with a manifestation of the formerly known lymphocytic lymphoma (B-CLL) formerly diagnosed in this patient.

The known B-CLL was confirmed by flow cytometry of a peripheral blood sample in order to exclude a leukemic presentation of a second malignancy, *e.g.* marginal zone lymphoma. Subsequently, comprehensive staging was performed and revealed enlarged iliacal, para-aortic, mediastinal, cervical, subclavicular, and inguinal lymph nodes. A subdermal lesion of the right lower extremity with 10 cm in the largest diameter turned out to be the remnant of an old hematoma following a minor traumatic lesion of the tibia. Bone marrow analysis confirmed lymphoid infiltration consistent with B-CLL. Based on this information, the case was diagnosed as an extranodal presentation of a stage IV B-CLL initially diagnosed 15 years before. As recommended by our institutional tumor board, the patient was scheduled for a combined immuno-chemotherapy with obinutuzumab and chlorambucil.

Review of Literature

In a PUBMED literature search (search date 03-05-2016) using the search terms lymphoma, cervix, uterus, B-cell lymphoma, PAP smear, extranodal lymphoma), 91 studies were identified (5, 7-9, 14-101). One study was excluded because it was a double publication (101), leaving 90 studies describing 246 cases of LUCX. Table I shows the study characteristics and findings of these 90 studies. One hundred eight-five (75%) cases were primary LUCX and 61 (25%) cases were recurrent lesions. In the 98 cases of LUCX with a defined tumor stage, stage IE according to the Ann Arbor classification system for extranodal lymphomas (102) was the most prevalent stage (60/98 [61%]), whereas stage II (24/98 [25%]), stage III (4/98 [4%]), and stage IV (10/98 [10%]) were less prevalent. In the pooled analysis of our literature review, individual histology data were reported for 161 women Among these, by far the most common histology was DLBCL, which was the final diagnosis in 99/161 (62%) cases, followed by NHL (16 cases; 10%), FL (12 cases; 7%), CLL (5 cases; 3%), and others (29 cases; 18%). Many treatments and treatment combinations for women with LUCX were used in the 92 studies analyzed in this review. The individual management strategies were outlined in 109 women, demonstrating that there is no standard therapy for women with LUCX. Surgery, radiotherapy, and chemotherapy as well as combinations of these treatment modalities have been used. Apart from local surgical interventions such as cervical biopsy and conization, hysterectomy was performed alone in 13/109 cases (12%) and in combination with chemotherapy in 20 cases (18%). Chemotherapy alone was applied in 25/109 women (23%).

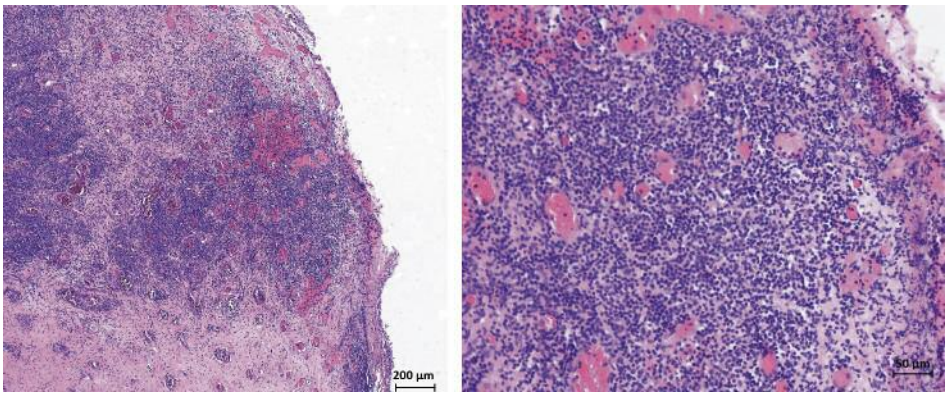

Figure 1. *Histological sections of the cervix demonstrating a variable dense lymphoid infiltrate, composed of small, monomorphic cells.*

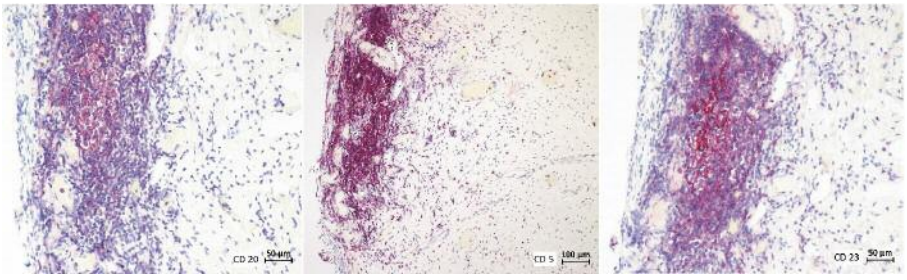

Figure 2. *Immunohistochemical stains demonstrating the expression of CD20, CD5, and CD23.*

Radiotherapy was used in 48/109 cases (44%) as a sole treatment modality (11 cases), in combination with surgery (14 cases), in combination with chemotherapy (19 cases), and in combination with surgery and chemotherapy (4 cases). A minority of women (3 cases) only underwent follow-up monitoring. 68/109 (62%) of women underwent some form of chemotherapy with CHOP with or without rituximab being the most commonly used chemotherapy regimen (23/68 cases).

Despite the wide variation of treatments applied to women with LUCX, the prognosis of this disease is good. In the pooled analysis of our literature review, individual follow-up data were reported for 61 women with a mean follow-up time of 38 months (range=0-228 months). During this follow-up, the disease-specific recurrence rate was 19% (12/61) and the overall survival rate was 81% (49/61). Based on these pooled survival data, we conclude that LUCX in fact has an excellent prognosis despite the lack of a standard treatment, therapeutic uncertainty, and a resulting variability of applied treatments. This is consistent with the 73% 5-year survival rate reported by Harris *et al*. in a series of 21 women with LUCX and with the 86% 5-year survival rate reported by Ahmad *et al*. in their series of 9 women (26). Only Hu *et al*. reported a lower 5-year overall survival rate of 39% in a large Chinese cohort of 44 women (54). However, in this series, the proportion of stage IV patients was unusually high with 43% and this series also included women with extranodal lymphomas of the uterus and adnexae.

Discussion

In this case report and review of the literature, we described a woman presenting to a colposcopy clinic with repeated pathological PAP smears ultimately diagnosed as LUCX. Establishing the diagnosis of LUCX was difficult due to the rare location of a lymphoma in the cervix, the initial interpretation as pathological endocervical glandular cells, and the equivocal immunohistochemical profile. It was not possible to reach a definitive diagnosis based on the cervical biopsy specimen alone due to lack of CD23 expression. With more material being available after conization and after comprehensive immunohistochemical stains and PCR, the diagnosis of LUCX in the form of a low-malignant B-Non-

Table I. *Clinical studies describing cases of primary or recurrent malignant lymphoma of the uterine cervix.*

Author	Year	Number of Cases (n)	Primary/ Secondary LUCX (n)	Stage	Histology	Treatment	Follow-up (m)	Outcomes (Recurrence/ Death) (n)
Dobrosavlje-vic *et al.*	2016	1	Primary	-	FL	-	-	-
Singh *et al.*	2016	2	Primary	IE	DLBCL	R-CHOP+RXT	60;36	0/0
Zhou *et al.*	2016	1	Primary	-	DLBCL	R-CHOP	-	0/0
Hilal *et al.*	2016	1	Primary	IV	BCL	Surgery+CHXT+ Obinutuzumab	3	0/0
Pather *et al.*	2015	6	Primary	-	High Grade B-Cell NHL	-	-	-
Thyagarajan *et al.*	2014	1	Primary	IV	High-Grade B-Cell NHL	CHXT+RXT	7	0/0
Bellevicine *et al.*	2014	1	Primary	IIE	DLBCL	-	-	-
Igwe *et al.*	2014	1	Primary	IIE	DLBCL	R-CHOP	5	0/0
Mandato *et al.*	2014	1	Primary	IVEA	DLBCL	R-CHOP	24	0/0
Ahmad *et al.*	2014	9	Primary/Recurrent	-	DLBCL	Surgery, CHXT, RXT	-	5-YSR 86%
Korivi *et al.*	2014	1	Recurrent	-	Blastic BCL	CHXT+RXT	3	0/0
Cao *et al.*	2014	2	Primary	IEA	DLBCL	CHOP+RXT	47;84	1/0
Hashimoto *et al.*	2013	1	Primary	IIAE	DLBCL	R-CHOP	-	0/0
Bull *et al.*	2013	1	Primary		DLBCL	R-CHOP	-	0/0
Groszman *et al.*	2013	1	Primary	-	DLBCL	CHXT	12	0/0
Kazi *et al.*	2013	1	Recurrent	-	Precursor-B ALL	-	-	-
Parnis *et al.*	2012	1	Primary	IE	DLBCL	R-CHOP+RXT	2	0/0
Binesh *et al.*	2012	1	Primary	IE	DLBCL	R-CHOP	5	0/1
Yalta *et al.*	2012	1	Primary	-	DLBCL	HE	-	-
Kanaan *et al.*	2012	1	Primary	III	DLBCL	CHXT	-	1/1
Vasudev *et al.*	2012	1	Primary	IE	DLBCL	Surgery	20	0/0
Calli *et al.*	2012	1	Primary	-	DLBCL	CHXT+IT	-	0/0
Udupa *et al.*	2012	1	Recurrent	-	CLL	CHXT	-	-
Dyer *et al.*	2011	2	Primary	IE	DLBCL	CHXT, CHXT+RT	-	0/0
Upanal *et al.*	2011	2	Primary	IEA;IIEA	DLBCL	R-CHOP+RXT	20;19	0/0
Parva *et al.*	2011	1	Primary	IEA	DLBCL	R-CHOP	72	0/0
Mainiero *et al.*	2010	1	Primary	-	CLL	Monitoring	-	0/0
Magley *et al.*	2010	1	Recurrent	IV	CLL	-	-	-
Baijal *et al.*	2009	1	Primary	IE	DLBCL	R-CHOP+RXT	15	0/0
Ustaalioglu *et al.*	2009	1	Primary	IEB	DLBCL	CHXT+RXT+IT	10	0/0
Amna *et al.*	2009	1	Primary	IE	FL	CHXT+RXT+IT	12	0/0
Hanprasert- pong *et al.*	2008	1	Primary	IE	DLBCL	CHXT	29	0/0
Köhler *et al.*	2008	2	Primary	-	-	CHXT	-	-
Okudaira *et al.*	2008	1	Primary	IIE	DLBCL	CHOP+RXT	60	0/0
Ab Hamid *et al.*	2008	1	Primary	IE	DLBCL	CHOP	-	-
Coon *et al.*	2008	1	Primary	-	MALT	RXT+Rituximab	28	0/0
Lu *et al.*	2007	16	-	-	DLBCL (n=12); FL (n=4)	-	-	-
Jiang *et al.*	2007	10	Primary	I-III	DLBCL; BL; T-CL	-	-	-
Lorusso *et al.*	2007	1	Primary	IE	LBCL	Surgery+CHXT	60	0/0
Signorelli *et al.*	2007	8	Primary	IE-IIIE	DLBCL	Surgery+/-CHXT	29-228	0/0
Frey *et al.*	2006	4	Primary	IIE	DLBCL	HE+R-CHOP (3x); HE	36;6;28;32	0/0
Ikuta *et al.*	2006	1	Recurrent	-	B-cell ALL	HE, CHXT	1	1/1
Cantu de Leon *et al.*	2006	1	Primary	IIE	DLBCL	CHXT+RXT	6	0/0
Semczuk *et al.*	2006	1	Primary	IE	BCL	Surgery+CHXT	10	0/0
Gonzalez-Cejudo *et al.*	2006	1	Primary	IE	DLBCL	HE+R-CHOP	12	0/0
Huang *et al.*	2005	1	Primary	IE	BL	Surgery	0	1/1
Goker *et al.*	2005	1	Primary	IE	BL	CHXT	14	0/0
Van Renter-ghem *et al.*	2005	2	Primary	-	DLBCL	-	-	-
Kosari *et al.*	2005	17	Primary (16)/ Recurrent	-	DLBCL (11); FL (4); BL (1); MZL (1)	-	-	-
Dursun *et al.*	2005	2	Primary	IE	DLBCL; BCL	HE+CHOP; CHOP	19;22	0/0
Murad *et al.*	2005	1	Primary	-	NHL	-	-	-
Garavaglia *et al.*	2005	2	Primary	IE; IIE	DLBCL	CHXT	120; 84	0/0
Mikami et al.	2004	1	Recurrent	IE	CLL/SLL	Surgery+RXT+CHXT	30	0/1

Table I. *Continued*

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Author	Year	Number of Cases (n)	Primary/ Secondary LUCX (n)	Stage	Histology	Treatment	Follow-up (m)	Outcomes (Recurrence/ Death) (n)
Hu *et al*.	2003	44	Primary/Recurrent	IE - IV	DLBCL; T-CL	-	-	5-YSR 39%
Au *et al*.	2003	3	Primary	IE (2); IIE	DLBCL	CHXT+RXT (n=1); Monitoring (n=2)	96; 12; 60	0/0
Kahlifa *et al*.	2003	1	Primary		Sarcomatoid BCL	CHXT+RXT	10	0/0
Szantho *et al*.	2003	1	Primary	IE	DLBCL	HE+CHOP	60	0/0
Liro *et al*.	2001	1	Primary	-	DLBCL	HE+CHXT	-	-
Rossi *et al*.	2001	1	Primary	IV	MALTL	HE+CHXT	22	0/0
Pomares-Arias *et al*.	2000	1	Primary	-	TCL	RXT	-	-
Kostopoulos *et al*.	2000	1	Primary	IE	DLBCL	HE	-	-
Vang *et al*.	2000	1	Primary	IIEA	DLBCL	Surgery	120	0/0
Wang *et al*.	1999	1	Primary		Low-Grade BCL	Radical HE	-	-
Grace *et al*.	1999	2	Primary	IIIE; IE	DLBCL; FL	CHOP+RXT	-	-
Kaito *et al*.	1998	1	Primary		DLBCL	CHOP+RXT	-	-
Nasu *et al*.	1998	1	Primary	IE	NHL	THP-COP	-	-
Lee *et al*.	1998	2	Primary	IEA	NHL	Surgery+RXT	120	0/0
Biswal *et al*.	1997	1	Primary	IEA	-	-	-	-
Dhimes *et al*.	1996	1	Primary	IE	DLBCL	HE	12	0/0
Abbas *et al*.	1996	1	Primary	IE	Pleomorphic LCL	Surgery+CHXT	1	0/0
Al-Talib *et al*.	1996	2	Primary	IE	High-Grade BCL; DLBCL	CHXT	24;9	0/0
Reynaud *et al*.	1995	1	Primary	-	DLBCL	-	-	-
Winer *et al*.	1995	1	Primary	IE	NHL	HE+CHXT+RXT	-	-
Makarewicz *et al*.	1995	3	Primary	IE	NHL	-	-	-
Figuera *et al*.	1994	1	Primary	-	-	-	-	-
Rodier *et al*.	1993	1	Primary	-	NHL	-	-	-
Aozasa *et al*.	1993	4	Primary	I (2); II (3); III (1)	DLBCL	HE+CHXT	12	4/4
Maryniak *et al*.	1993	3	Primary	IE (2); IV	BCL	RXT+HE (2); RXT+HE+CHXT	38	2/2
Muntz *et al*.	1991	5	Primary	IB (4); IIIA (1)	DLBCL (n=3); FL; Diffuse Small Cell	HE+RXT(3); RXT(2)	120;60;60; 53;53	0/0
Pasini *et al*.	1991	1	Primary	IIE	FL	CHOP	-	-
Sandvei *et al*.	1990	1	Primary	IE	HL	CHOP	72	0/0
Ohta *et al*.	1990	3	Primary	-	-	-	-	-
Mikhail *et al*.	1989	1	Recurrent	-	CLL	CHXT	24	1/1
Cardillo *et al*.	1987	1	Primary	-	PL	-	-	-
Cardillo *et al*.	1987	1	Primary	IE	Primitive Lymphoma	-	-	-
Gharpure *et al*.	1985	2	Primary	-	-	-	-	-
Taki *et al*.	1985	1	Primary	-	BCL	-	-	-
Komaki *et al*.	1984	3	Primary	IVA- (2); IIB (1)	HL; Diffuse Mixed Lymphoma	RXT	36; 84; 156	1/0
Harris *et al*.	1984	21	Primary	IE (16);IIE (3); IV (2)	-	Surgery (5); Surgery+ RXT (7); Surgery+ CHXT (2); RXT (4); CHXT (1)	10-168	73% 5-YSR
Carr *et al*.	1976	2	Primary	-	Reticulum CL	RXT	-	-
Pooled Analysis	-	246	185 (75%)/ 61 (25%)	IE 60 (61%); II 24 (25%); III 4 (4%); IV 10 (10%)	DLBCL 99 (62%); NHL 16 (10%); FL 12 (7%); CLL 5 (3%): Others 29 (18%)	-	Mean 38 m	12 (19%)/ 12 (19%)

LUCX, Lymphoma of the uterine cervix; m, months; CLL, chronic lymphatic leukemia; CHOP, cyclophosphamide, hydroxydaunorubicine, vincristine, prednisolone; R, rituximab; 5-YSR, 5-year survival rate; RXT, radiotherapy; BCL, B-cell lymphoma; PL, primitive lymphoma; HE, hysterectomy; HL, histiocytic lymphoma; MALT, marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue; FL, follicular lymphoma; SLL, small lymphocytic lymphoma; T-CL, T-cell lymphoma; THP-COP, pirarubicin, cyclophosphamide, vincristine sulfate, prednisolone; BL, Burkitt's lymphoma; IT, immunotherapy; MZL, marginal zone lymphoma.

Hodgkin lymphoma was established. This was based on the expression of CD20, CD5, and CD23 and the lack of expression of CD10 and Cyclin D1. In addition, PCR analysis of immunoglobulin heavy chain detected clonal rearrangement of the IgH gene with three primer sets (FRI, FRII, FRIII). After local surgery and the establishment of the diagnosis of LUCX in the course of the above described histopathological, immunohistochemical, and molecular analyses, systemic staging revealed multiple manifestations of this disease and combined chemo-immunotherapy was initiated. In addition to the rarity of LUCX, this case is interesting due to a remarkably long latency period with a CLL diagnosed in this patient in 2001 and the manifestation of a stage IV low-malignant B-Non-Hodgkin lymphoma 15 years later. This case highlights the necessity of an interdisciplinary cooperation between gynecologists, hematologists, and oncologists in order to optimally diagnose and manage patients with LUCX.

Therapy. Because of the rarity of the disease, there is no established standard treatment for women with primary LUCX. Surgery and radiotherapy, either alone or in combination, are the mainstay of treatment (1, 2, 4, 5, 9). Other treatment options include oral alkylating agents, purine nucleoside analogues, combination chemotherapy, interferon, monoclonal antibodies, or even watchful waiting. Historically, radiotherapy was used as the treatment of choice for stage IE LUCX until the 1990s (12, 25, 29, 36, 45). For example, more than two thirds of patients treated between the 1970s and 1990s received radiotherapy either alone or in combination with surgery and/or chemotherapy (86). There are no comparative trials addressing the value of adjuvant treatment modalities after local surgery for early stage LUCX. While systemic chemotherapy is usually applied in cases of disseminated disease, it is unclear if chemotherapy can be used as the sole treatment in young women with stage IE LUCX. Some have advocated combination chemotherapy alone in order to preserve reproductive function in young women and to treat regional or distant micrometastasis as well (93, 95, 96, 98). If radiotherapy to the pelvis is applied in young patients, ovarian transposition to preserve reproductive and gonadal function has been recommended (86).

In our review of the literature, the treatments used for LUCX were variable and there was no consensus regarding the optimal management. Specifically, most patients reported in the literature were treated with radiotherapy (44%) either as the sole treatment modality or in combination with surgery and/or chemotherapy. Thirty percent of the patients underwent hysterectomy, followed by chemotherapy in 18% of cases. Chemotherapy alone was applied in 23% of women. Therefore, based on data available in the literature, radiotherapy, either alone or in combination with surgery and chemotherapy is the most commonly used treatment for women with LUCX. CHOP with or without rituximab was the most commonly used chemotherapy regimen (23/68 cases; 34%). Key issues in the treatment of women with LUCX are a specialized pathological assessment with experience in lymphoma pathology. This may require a second opinion by a reference pathologist. In our view, local surgery is the most reasonable therapy in women with early-stage LUCX both for diagnostic and therapeutic reasons. This should be followed by a comprehensive staging. In case of localized disease, there is no evidence for an adjuvant treatment and therefore, adjuvant radiotherapy, chemotherapy or targeted therapies cannot be recommended outside of clinical trials. In case of systemic disease, treatment should be guided by established lymphoma treatment protocols.

Immunohistochemistry. Immunohistochemistry is important in the diagnosis and differential diagnosis of LUCX. Although no commonly accepted standard set of immunohistochemical markers for the diagnosis of LUCX exists, typical immunohistochemical marker profiles are used to differentiate between certain histological lymphoma subtypes. For example, Yalta *et al.* describe a case of LUCX where the imunohistochemical profile showed positivity for LCA, vimentin, CD20, CD30, Bcl6, Bcl2. The Ki-67 index was found to be 80% (35). Based on the histopathological appearance of LUCX the most important histopathological differential diagnoses include follicular or chronic cervicitis, small cell carcinoma, endometrial stromal sarcoma, and granulocytic sarcoma (35). Dyer *et al.* described positivity for CD20, BCL6, IgMk and negativity for CD10, MUM1, and BCL2 as typical for diffuse large B-cell LUCX (88). In our case of low-malignant B-Non-Hodgkin lymphoma, we found expression of CD20, CD5, and CD23 whilst CD10 and cyclin D1 were negative. MIB-1 labeling index was 5%.

Prognosis. Prognosis of female genital lymphomas in general and LUCX in particular has been described to be poorer than that of the more common nodal lymphomas (11, 13, 25, 26). This has been attributed to inaccurate initial diagnoses and subsequently delayed or failed therapy. However, the prognosis of LUCX when diagnosed at an early stage and treated appropriately, seems to be excellent (12, 88, 103). Some even proposed that diffuse large B-cell LUCX may be considered a benign disease or a very early stage of classical diffuse large B-cell lymphoma that is curable by local excision alone (88). This is consistent with our finding of an excellent prognosis of women with LUCX reported in the literature. Specifically, in our pooled analysis of survival data, the overall survival rate was 81%. Of note, this is despite the lack of a standard treatment, therapeutic uncertainty, and a resulting variability of applied treatments. Others have also found high survival rates in smaller, single-institution series. For example, Harris *et al.* had a 5-year

survival rate of 73% in a series of 21 women and Ahmad *et al*. had a 86% 5-year survival rate in their series of 9 women (86, 26). One of the largest series was published by Anagnostoupoulos *et al*. (103). In their review of 118 cases of LUCX, they observed no evidence of recurrence within a median follow up time of 40.5 months (range 2-240 months) in 85.2% of patients. Recurrence is documented in 2% of patients within 12-48 months, while 8.6% died of their disease within 0-40 months.

In women with LUCX, disease stage is the most important predictor of survival. Based on our literature review, >60% of cases of LUCX are diagnosed at an early stage, ie stage IE. This might be the reason for the excellent outcome observed in the literature with an overall survival rate of 81%. Others have found comparable results in monocentric series. For example, in case series, survival was found to be better in stage IE compared to higher stages (stage IE, 89% *versus* stages IIE and IV, 20%) (103). Besides tumor stage, the grade of the disease is also important when comparing the survival between low-grade and high-grade diffuse lymphomas (66, 98, 103), whereas the prognostic impact of the various histological types of LUCX is unknown (1, 2, 103). Based on the data we have extracted from the literature and the combined data of other studies, the 5-year survival rate of patients with LUCX is approximately 80%.

Conclusion

In conclusion, we describe the case of a woman with a low-malignant B-Non-Hodgkin lymphoma of the cervix and discuss the clinical and histological characteristics as well as the management and prognosis of patients with lymphomas of the cervix. Based on the data available in the literature, LUCX is rare and accounts for only 0.5% to 1% of lymphomas. Most cases are occurring at an early stage, have the histological appearance of a DLBCL, and a good 5-year overall survival rate >80%.

Conflicts of Interest

Authors declare that they have no conflict of interest.

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Received June 14, 2016
Revised July 6, 2016
Accepted July 8, 2016