



Italian Journal of Gynæcology & Obstetrics

March 2023 - Vol. 35 - N. 1 - Quarterly - ISSN 2385 - 0868

Recurrent Non-Hodgkin's Lymphoma in the uterine cervix: a case report and a review of the literature

Vanessa Paladini, Allegra Mazzeo*, Ida Faralli, Marianna Deroma, Marco Monti, Mariagrazia Piccioni

Department of Maternal and Child Health and Urological Sciences, Sapienza University of Rome, Rome, Italy.

ARTICLE INFO

History

Received: 22 March 2022

Received in revised form: 27 April 2022

Accepted: 27 May 2022

Available online: 21 March 2023

DOI: 10.36129/jog.2022.39

Key words

Lymphoma; Non-Hodgkin Lymphoma; uterine cervix; recurrent; relapse.

*Corresponding author: Allegra Mazzeo, M.D.
Department of Maternal and Child Health and Urological Sciences, Sapienza University of Rome, Policlinico Umberto I Hospital, viale del Policlinico 155, 00161 Rome, Italy.
Email: allegra.mazzeo@uniroma1.it.
ORCID: 0000-0001-8185-1971.

INTRODUCTION

Lymphomas are a heterogeneous group of malignant lymphoproliferative diseases and represent 3-4% of all neoplastic processes [1].

Lymphoma can be divided into two types: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). NHL are further subdivided into nodal and extranodal. The extranodal form occurs in approximately 40% of all NHL, considering this, the extranodal lymphomas of the female genital tract account for only 0.5% to 1% of all NHL [2].

ABSTRACT

Background. Lymphomas are a heterogeneous group of malignant lymphoproliferative diseases. As primary localization, the most common histological subtype of female genital lymphomas is a Non-Hodgkin Lymphoma (NHL), the diffuse large B-cell type. However cervical relapse of NHL is a very rare condition (0.3%).

Case presentation. A 42-year-old Peruvian woman experienced relapse of NHL with uterine localization. She complained at first of abnormal vaginal bleeding and stranguria. The cervical biopsy performed showed a diffuse large B-cell lymphoma in the uterine cervix. The lack of clinical studies on this topic and its rarity make this type of recurrence very difficult to treat.

Conclusions. In case of a woman with vaginal bleeding and history of NHL, a disease relapse should always be considered, and a biopsy should be performed to confirm the diagnosis.

The most common histological subtype of female genital lymphomas is diffuse large B-cell lymphoma. 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: considering this the ovary is the organ most often affected [2].

We present a case of a patient with a recurrent NHL in the uterine cervix. Considering its rarity, the aim of this case report is to emphasize the possibility of a disease relapse in case of a woman with vaginal bleeding and history of NHL.

CASE PRESENTATION

A 42-year-old Peruvian woman complaining of abnormal vaginal bleeding was admitted to our hospital. She had a history of NHL diagnosed in July 2018. She also reported hypothyroidism and a generalized anxiety syndrome. She did not take drugs, denied smoking, use of alcohol and any family history of cardiovascular diseases and neoplasia. In July 2018, she presented with swelling of the right maxillary sinus: its biopsy diagnosed a diffuse large B-cell lymphoma (DLBCL) with double expressor (translocation of cMyc and Bcl-2, Bcl-6 negative). Treatment consisted of chemotherapy with CODOX-M (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate) and IVAC (ifosfamide, etoposide and cytarabine) for four cycles. In March 2019, she underwent chemotherapy with FEAM (fotemustine, cytarabine, etoposide, melphalan) sequenced by infusion of autologous peripheral stem cells.

She had regular negative follow-up until July 2019 when she complained abnormal vaginal bleeding and stranguria. The patient was admitted to our department for a gynaecological evaluation.

At the pelvic examination the cervix appeared hard, large, and hyperaemic without exophytic or erosive components. At the transvaginal ultrasound the uterine cervix appeared highly vascularized with no evidence of a tumour mass. Subsequently, a cervical biopsy was performed showing neoplastic cells with a positive test result for CD20, CD79a, Bcl2, CD10, cMyc, and negative test for CD3. These findings confirmed a recurrent DLBCL with cervical localization. Moreover, a PET-CT scan was performed showing a skeleton relapse of the disease without clear image on relapse of the uterine cervix. The patient was referred to the haematology department and, in consideration of the disease recurrence, was started on P-VABEC (adriamycin, etoposide, cyclophosphamide, vincristine, bleomycin and prednisolone) for eight cycles and three doses of Ritux-

imab. Following this, the patient received therapy with Pixantrone, but only for three doses due to severe thrombocytopenia as collateral effect.

Finally, a body CT scan was performed confirming progression of the disease only interesting the maxillary sinus. Considering this and the poor general condition of the patient, she was discharged to continue with palliative care. Differently from other cases reported in literature the diagnosis of the relapse in our case was diagnosed by vaginal biopsy without any finding of bulky mass at a diagnostic exam. Moreover, the biopsy was performed without evidence of exophytic mass of the cervix but considering the anamnesis and the vaginal bleeding complained by the patient.

Review of literature (Table 1)

A PUBMED literature search was conducted from January 2000 to April 2021, using the key words "lymphoma", "cervix", "uterus", "Non Hodgkin lymphoma", identifying a total of 168 studies. Only the ones related to NHL recurrence of the uterine cervix were included for a total of 7 articles [3, 4]. The other 161 cases were excluded because they were related to primary lymphomas of the cervix. The 7 articles included appeared to be all case reports. All cases included were B-cell lymphomas and the most common histologies were: Chronic Lymphocytic Leukaemia (3 cases - 43%) [4-6], Blastic B-cell lymphoma - Acute Lymphoblastic Leukaemia (3 cases - 43%) [7-9] and Mantle Cell Lymphoma (1 case - 14%) [3]. Surgery, radiotherapy and chemotherapy as well as combinations of these treatment modalities have been used. In particular, chemotherapy was used in almost all cases (7 cases – 87.5%).

There is only little data regarding the prognosis of these patients, however the main prognostic factor seems to be the initial stage of the disease: as later is the diagnosis as worse is the prognosis. Due to the rarity of extranodal cervical NHL, there is no consensus in the literature concerning the optimal management of cervical extranodal NHL [10].

Table 1. Clinical studies describing cases of recurrent malignant lymphoma of the uterine cervix.

Authors	Year	Number cases	Histology	Stage	Treatment
Santangelo <i>et al.</i> [3]	2020	1	Mantle Cell Lymphoma	IIIA	R-CHOP, R-DHAP, FEAM
Korivi <i>et al.</i> [4]	2014	1	Blastic B-cell lymphoma	-	EPOCH; IMRT
Kazi <i>et al.</i> [5]	2013	1	Acute Lymphoblastic Leukaemia	-	CHXT
Udupa <i>et al.</i> [6]	2012	1	Chronic Lymphocytic Leukaemia	-	CHXT
Magley <i>et al.</i> [7]	2010	1	Chronic Lymphocytic Leukaemia	IV	-
Ikuta <i>et al.</i> [8]	2006	1	Blastic B-cell lymphoma- Acute Lymphoblastic Leukaemia	-	HE, CHXT
Mikami <i>et al.</i> [9]	2004	1	Chronic Lymphatic Leukaemia	IE	Surgery+RXT+CHXT

Rchop: Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone; R-Dhap: Rituximab, Cisplatin, Cytarabine, Dexamethasone; Feam: Fotemustine, Cytarabine, Etoposide, Melphalan; Epoch: Etoposide, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin; Imrt: Intensity Modulated Radiation Therapy; CHXT: Chemotherapy; He: Hysterectomy; Rxt: Radiotherapy.

DISCUSSION

The lymphoma involving the uterine cervix is very rare, and it accounts for only 0.3% of cervical malignancies [2, 11, 12]. Non-Hodgkin's lymphoma (NHL) can involve extranodal sites. Common extranodal locations include the gastrointestinal tract and the skin. Female genital tract involvement can represent a site of origin [2].

Cancers involving the genital tract represents tumours with high psychological impact for a woman, especially during the reproductive age. Diagnosis alone represents a very stressful experience for a woman and its treatment often leads to physical and sexual changes that severely compromise the female identity [13].

For these reasons, fertility preservation options have greatly improved in recent years, including embryo and oocyte cryopreservation and fertility-sparing surgery [14]. These techniques aim to reduce as much as possible the impact of a tumour of the genital tract on the sexual and physiological functioning of the affected patient [15]. Great results are described in the literature, in fact, despite its aggressiveness, several cases of preservation of fertility after treatment for a lymphoma of the cervix, show the possibility to conceiving and giving birth vaginally even after treatments [16].

Looking in the literature, in addition to pregnancies obtained after surgery for cervical cancer, cases of diagnosis of this tumour in pregnancy are also described: it is clear that this condition also finds problems in the diagnosis, as well as in the timing of treatment [17].

Even more rare is the NHL relapse of uterine cervix. The majority of relapses in NHL occur two years after the end of the treatment, they are frequently asymptomatic and hard to identify by the only imaging surveillance. Standard therapeutic regimen has not been established. According to the current literature, treatment options for non-Hodgkin's lymphoma of the cervix include chemotherapy, radiation, or radiation combined with either chemotherapy or surgery.

CONCLUSIONS

Cervical relapse of NHL is a very rare condition and has a variable and nonspecific presentation. Nevertheless, in case of vaginal bleeding in women with NHL history, relapse of NHL should always

be considered, helping for an early diagnosis of the relapse, obtained by biopsy or surgical resection. The best treatment hasn't been found yet, leaving a poor prognosis for these patients.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contributions

M.G.P.: Conceptualization, design, coordination. I.F., M.D.: Data collection. V.P., A.M., G.P. Writing – original draft, writing – review & editing. G.P., M.G.P.: Critical review & editing. M.G.P.: final approval. The authors read and approved the final manuscript.

Funding

None.

Study registration

N/A.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

N/A.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Data sharing

N/A.

REFERENCES

1. Snowden JA, O'Connell S, Hawkins J, Dalley C, Jack A, Mannari D, et al. Haematological cancers: improving outcomes. A summary of updated NICE service guidance in relation to Specialist Integrated Haematological Malig-

- nancy Diagnostic Services (SIHMDS). *J Clin Pathol.* 2017;70(6):461-8. doi: 10.1136/jclinpath-2016-204029.
2. Kosari F, Daneshbod Y, Parwaresch R, Krams M, Wacker HH. Lymphomas of the female genital tract: a study of 186 cases and review of the literature. *Am J Surg Pathol.* 2005;29(11):1512-20. doi: 10.1097/01.pas.0000178089.77018.a9.
 3. Santangelo G, Palaia I, Perniola G, Di Pinto A, Musella A, Tomao F, et al. Recurrent mantle cell lymphoma in the uterine cervix: a case report. *J Med Case Rep.* 2020;14(1):138. doi: 10.1186/s13256-020-02487-6.
 4. Mikami Y, Maehata K, Fujiwara K, Sasano H. Squamous cell carcinoma of the uterine cervix in association with stage 0 chronic lymphocytic leukemia/small lymphocytic lymphoma. *Gynecol Oncol.* 2004;92(3):974-7. doi: 10.1016/j.ygyno.2003.11.021.
 5. Korivi BR, Jensen CT, Patnana M, Patel KP, Bathala TK. A rare presentation of lymphoma of the cervix with cross-sectional imaging correlation. *Case Rep Radiol.* 2014;2014:157268. doi: 10.1155/2014/157268.
 6. Kazi S, Szporn AH, Strauchen JA, Chen H, Kalir T. Recurrent precursor-B acute lymphoblastic leukemia presenting as a cervical malignancy. *Int J Gynecol Pathol.* 2013;32(2):234-7. doi: 10.1097/PGP.0b013e31825bd828.
 7. Udupa K, Ganesan P, Majhi U, Sagar TG. Unusual involvement of cervix and vulva in a case of chronic lymphocytic leukemia. *J Gynecol Oncol.* 2012;23(3):205-6. doi: 10.3802/jgo.2012.23.3.205.
 8. Magley J, Moyers C, Ballard KS, Tedjarati S. Secondary cervical cancer in a patient with chronic lymphocytic leukemia and recurrent chronic lymphocytic leukemia mimicking recurrent cervical dysplasia: a case report. *J Reprod Med.* 2010;55(3-4):175-8. Available at: <https://pubmed.ncbi.nlm.nih.gov/20506683/>.
 9. Ikuta A, Saito J, Mizokami T, Asano M, Nakamoto T, Nakajima T, et al. Primary relapse of acute lymphoblastic leukemia in a cervical smear: a case report. *Diagn Cytopathol.* 2006;34(7):499-502. doi: 10.1002/dc.20519.
 10. Elsayed WSH, Harb OA, Balata R, Ahmed RZ, Abd El Fattah AR, Abd-Elmohsen Alnemr A. NR2F6, LOXL2 and DMBT1 expression in cervical cancer tissues, prognostic and clinicopathological implications. *Ital J Gynaecol Obstet.* 2021;33(3):170-80. doi:10.36129/jog.33.03.05.
 11. Hilal Z, Hartmann F, Dogan A, Cetin C, Krentel H, Schiermeier S, et al. Lymphoma of the Cervix: Case Report and Review of the Literature. *Anticancer Res.* 2016;36(9):4931-40. doi:10.21873/anticancer.11059.
 12. Gardella B, Dominoni M, Morsia S, Gritti A, Soso C, Arrigo A, et al. Multiple human papillomavirus infection and ASCUS-LSIL progression: a review. *Ital J Gynaecol Obstet.* 2021;33(3):145-54. doi: 10.36129/jog.33.03.02.
 13. Laganà AS, La Rosa VL, Rapisarda AM, Platania A, Vitale SG. Psychological impact of fertility preservation techniques in women with gynaecological cancer. *Ecancermedicalscience.* 2017 8;11:ed62. doi: 10.3332/ecancer.2017.ed62.
 14. Vitale SG, La Rosa VL, Rapisarda AMC, Laganà AS. Fertility preservation in women with gynaecologic cancer: the impact on quality of life and psychological well-being. *Hum Fertil (Camb).* 2018;21(1):35-8. doi: 10.1080/14647273.2017.1339365.
 15. Vitale SG, La Rosa VL, Rapisarda AM, Laganà AS. Comment on: "The consequences of gynaecological cancer in patients and their partners from the sexual and psychological perspective". *Prz Menopauzalny.* 2016;15(3):186-7. doi: 10.5114/pm.2016.63501.
 16. Quaresima P, Saccone G, Zuccalà V, Guarascio G, Leo L, Amendola G, et al. Successful Vaginal Delivery after Induction of Labour in a Patient Treated for Non-Hodgkin's Lymphoma of the Cervix: A Case Report and Literature Review. *Case Rep Obstet Gynecol.* 2022;2022:3541046. doi: 10.1155/2022/3541046.
 17. Cucinella G, Rossi C, Granà R, Lentini VL, Calagna G, Chiantera V. Burkitt's lymphoma in pregnant woman: Difficult management of a rare case. *Int J Surg Case Rep.* 2020;77S(Suppl):S147-51. doi: 10.1016/j.ijscr.2020.10.071.