Primary diffuse large B cell lymphoma of the uterine cervix successfully treated by combined chemotherapy alone

A case report

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Abstract

Rationale: Primary lymphomas of the uterine cervix are a rare disease. They are often misdiagnosed because of their rarity and because they can be easily confused with a squamous cell carcinoma of the cervix, as they are usually presented as exophytic mass with vaginal bleeding as their most common symptoms. Nevertheless, considering that both the prognosis and the treatment are completely different between them, differential diagnosis should be taken into account.

Patient concerns: A case of a 51-year-old woman with a primary diffuse large B-cell lymphoma of the cervix is presented.

Diagnoses: Diagnosis of this tumor was a challenge for pathologists and clinicians, as four biopsies were needed to achieve a final diagnosis.

Interventions: Patient was successfully treated with combined Rituximab and chemotherapy (R-CHOP) alone.

Outcomes: Complete remission, confirmed through biopsy, was reached after six courses of chemotherapy. At 2-years follow up, patient is alive and free of disease.

Lessons: Considering that the prognosis and treatment of primary malignant lymphoma of the cervix are completely different than that of the squamous cell carcinoma, awareness of this disease should be considered in the differential diagnosis.

Abbreviations: CHOP = cyclophosphamide, doxorubicin, vincristine and prednisolone, CT scan = computerized tomography scan, ECOG = Eastern cooperative oncology group, FIGO = International Federation of Gynecology and Obstetrics, IPI = International prognostic index, LLL = lymphoma-like lesions, MALT-lymphoma = mucosa-associated lymphoid tissue lymphoma, MRI = magnetic resonance imaging, NHL = non-Hodgkin lymphomas, R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone.

Keywords: diffuse-large B-cell lymphoma, extranodal lymphoma, non-Hodgkin lymphoma, primary cervix B-cell lymphoma

1. Introduction

Non-Hodgkin lymphomas (NHL) are a miscellaneous group of neoplasms, originating from cells of the immune system. They can affect lymph nodes, extranodal lymphoid tissue or both. The estimated global incidence of NHL is 3\%\textsuperscript{[1]} of that extranodal lymphomas account for 15\%, but only 1\% arises from the genital tract. Because of the rarity of this issue, there are no large series recording clinical data and treatment options, as most cases are presented in the literature as single case reports. There is no consensus on treatment either, although combined chemotherapy appears to achieve better long-term results.

Since the most common clinical presentation of primary cervical NHL is usually the abnormal vaginal bleeding and its macroscopic appearance can be easily confused with squamous cell carcinoma of the cervix, differential diagnosis may be crucial, as prognosis and treatment are radically different between both of them.

Because of the scarce number of cases reported in the literature, there is not an established therapeutic protocol, and different options including surgery, radiotherapy, and chemotherapy are described. Here, we report a case of primary NHL of the uterine cervix successfully treated with combined chemotherapy (R-CHOP) alone.
2. Case report

A 51-year-old gravida 1 para 1 woman with a 1-month history of postmenopausal vaginal bleeding and ECOG performance status of 1 was referred to the Department of Obstetrics and Gynecology in the Hospital Clínico Universitario (Salamanca, Spain). The patient had a routine Pap smear performed 3 years earlier, which was negative.

Gynecological examination revealed a pathological cervix, with a large exophytic lesion with necrotic and bleeding areas infiltrating the upper vagina and both parametria and extending to the pelvic wall. A biopsy of the lesion was taken to be studied by Pathology Department. Since clinical features were all suggestive of squamous cell carcinoma of the cervix, the patient was referred to the Gynecology—Oncology Clinic. Magnetic resonance imaging (MRI) of the pelvis showed a 9 × 10 cm cervical mass with blurred bounds between uterus, bladder, and rectum (Fig. 1A and B) and affecting the inferior portion of the right vaginal wall and right parametrium. Right parametrium seemed to be affected (Fig. 1C) as well as right iliac lymph nodes. A 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET/CT) identified a 10 × 8 × 10 cm mass located in the cervix with intense FDG capitation (SUVmax of 32.12) suggestive of malignancy, inducing bladder compression, and left ureterohydronephrosis (Fig. 2). The iliac lymph nodes identified by MRI did not have FDG accumulation and therefore were considered unspecific.

According to the clinical and radiological findings, the initial diagnosis was cervical cancer, FIGO stage IVa. A Pap smear was done, being negative. Three biopsies of the cervical lesion were carried out, resulting all of them repeatedly inconclusive. Lacking a definitive histological diagnosis, a fourth cervical biopsy was taken. Cervix biopsy showed surface ulceration and effaced architecture by a diffuse proliferation of medium-large lympho-
lymphocytes, often with perivascular distribution. These lymphocytes displayed vesicular-pleomorphic nuclei, centroblastic morphology, and frequent mitosis (proliferative index of 60%). Occasional areas of necrosis and abundant sclerosis with nuclear crush artifact were also observed. These characteristics allow a final diagnosis of diffuse large B cell lymphoma (DLBCL).

Immunohistochemistry showed a CD20+ diffuse large B cell lymphoma pattern. Clonal B cells were CD5+, CD10−, BCL2+, BCL6+, MUM1−, CD45+, CD23+, CD43+, CD30−, Cyclin-D1−, and EBER−. Proliferation markers Ki-67 and p53 were found to be positive in more than 60% of the malignant cells. On the basis of the morphologic and immunohistochemical findings and following the Hans algorithm,[2,3] the definitive diagnosis was germinal center DLBCL (Fig. 3). Fluorescence in situ hybridization (FISH) identified loss of TP53, without alterations in IGH and CMYC. t(14;18)(q32;q21) was also discarded by RQ-PCR. The presence of B-cell clonality was confirmed by PCR.

A bone marrow biopsy was performed as part of the staging protocol, which was found to be negative for tumor infiltration, both by histology and flow cytometry. Routine laboratory analysis showed elevated LDH (285U/L; normal: 135–214U/L) and β2-microglobulin (5.2 mg/L; normal: 1.09–2.53 mg/L) at diagnosis. Therefore, with the final diagnosis of stage IE DLBCL of the cervix with international prognostic index (IPI) 1 (low risk), the patient was referred to the Hematology Department, where decision was made to treat her with the standard dose of R-CHOP every 3 weeks for 6 cycles: 375 mg/m² rituximab, 750 mg/m² cyclophosphamide, 50 mg/m² doxorubicin, 1.4 mg/m² (with a maximum of 2 mg) vincristine, and 100 mg/d prednisone on days 1 to 5. After receiving 6 courses of chemotherapy, repeated PET/CT scan showed no evidence of disease (Fig. 4) and a posttreatment cervix biopsy showed no residual tumor infiltration (Fig. 5). After 2-years follow-up, she is alive and remains disease free.

3. Discussion

NHL is a heterogeneous group of lymphoproliferative disorders with different patterns of behavior and responses to treatment.[4] As NHL often spreads to extranodal sites, the following criteria must be present to be considered a primary genital tract NHL: disease must be limited to just 1 location at the diagnosis, peripheral blood, and bone marrow must be free of tumor cells and there must be no evidence of the disease elsewhere in the body months after the initial diagnosis.[5]

Primary NHL of the female genital tract is a rare malignancy, with an overall estimated incidence around 2%. Most of the cases of primary cervical lymphomas have been described in postmenopausal women,[7] but there are studies reporting cases

Figure 3. Diffuse large B cell type extranodal lymphoma. A, Diffuse tumor infiltration of cervical stroma. B, Atypical lymphoid cells, large/intermediate size, with small cytoplasm, and vesicular nuclei. C, B lymphoid cells population showing CD20 membrane expression. D, Ki-67 staining, showing positivity in 60% tumor cells.

Figure 4. PET/CT scan posttreatment evaluation. Axial PET-CT shows a normal metabolism. PET/CT = positron emission tomography.
in the premenopause as well.\cite{8,9} According to the literature, the median age at presentation is around 44 years.\cite{8,9}

Diagnosis of primary NHL of the cervix is difficult because of its rarity and also because the clinical presentation mimics that of a squamous cell carcinoma. In fact, often the diagnosis of these tumors is not suspected clinically and it is set only after biopsy.\cite{10} Moreover, this type of tumor is rarely diagnosed by cervical smears, as its origin is in the cervical stroma and the overlying squamous epithelium is usually unaffected.\cite{8,9} In the scarce occasions where malignancy could be set through cytology, it has to be necessarily confirmed by histological examination, and even sometimes repeated biopsies may be necessary to confirm the diagnosis.\cite{11} as it happened in our case.

Although abnormal uterine bleeding is the most common presenting symptom, other gynecologic symptoms including vaginal discharge, pelvic pain, and postcoital bleeding have been described.\cite{8,12} Reversely to systemic lymphomas, B symptoms as fever, night sweats, and weight loss are rarely present in cervical NHL. Benign disorders must be also considered in the differential diagnosis.\cite{11,13} Cervical NHL may be sessile, polypoid or appear as a bulky, exophytic cervical mass which increases the size of the cervix, causing pain, abdominal bloating, and compressive symptoms as hydroureteronephrosis. Parametrium, vagina, and pelvic wall can be also invaded.\cite{11,14}

Regarding histology, most tumors are high-grade lymphomas (diffuse large B-cell lymphomas), but low-grade lymphomas have also been described.\cite{6,8,12,13,15} To make a correct histological diagnosis Fox and More criteria\cite{5} must be fulfilled. Immunohistochemistry studies are useful to achieve a correct diagnosis, as some low-grade lymphomas (particularly follicular lymphomas and MALT-type lymphomas) are really difficult to be distinguished from benign reactive issues such as severe chronic cervicitis or follicular cervicitis.\cite{11,13,16}

Here, we describe a case of a NHL of the cervix mimicking cervical carcinoma, clinically presented with vaginal bleeding and with the macroscopic aspect of a bulky, exophytic mass inducing left hydroureteronephrosis. Correct diagnosis was only possible after histopathology and immunohistochemistry. Four biopsies had to be performed to get a definitive diagnosis of NHL, highlighting the difficulty of diagnosis of this disease. Once the NHL has been diagnosed, it must be staged, as staging has proved to be one of the most important factors to predict survival.\cite{14} A clinical examination must be performed to find infiltrated nodes, hepatosplenomegaly, or involvement of the Waldeyer Ring. Other investigations including full blood count, renal and liver function test, bone marrow aspirate, and thoracoabdominal computed tomography must also be done to set the stage of the tumor, following the Ann Arbor staging classification for extranodal lymphomas.\cite{19} Based on this staging classification, the involvement of a single extra-lymphatic organ or site is defined as stage IE. According to the literature, most of the primary cervical NHL are diagnosed at stage IE, as our patient, though more advanced stages have been described.\cite{12,15}

Histologically, primary NHL of the cervix should be distinguished from chronic inflammatory processes, especially from those presenting with dense lymphoid infiltrates, the so-called lymphoma-like lesions (LLL). In contrast to LLL, NHL histology usually shows a monomorphous lymphoid infiltrate, with a preserved epithelium, and diffuse growth in the form of a sclerotic and perivascular mass. Differential diagnosis between primary NHL of the cervix and squamous cell carcinoma is also important regarding prognosis. According to the American Cancer Society, the estimated survival rate for cervical carcinoma at FIGO stage IVa is 16% (http://www.cancer.org/cancer/cervicalcancer/detailedguide/cervical-cancer-survival). Although the prognosis of primary gynecological lymphomas cannot be established considering the scarce number of tumors and their heterogeneity, the estimated overall 5-year survival ranges between 73%\cite{19} and 77%,\cite{20} but it could be even higher due to the new chemotherapeutic drugs.

As cervical NHL is a so rare disease, a standard treatment has not been set and different treatment options are proposed. Substantial changes can be perceived through the literature, from more aggressive approximations years ago, where surgery played a key role in the treatment,\cite{21} to more conservative therapies, where combined chemotherapy with or without radiotherapy seems to be the mainstays of current treatment.\cite{8,9,12} Combined chemotherapy regimens like CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) have proved to be an effective treatment of this disease with 2 additional advantages: first, preventing the micrometastasis and second, preserving the fertility.\cite{9} Considering that a high percentage of these patients are young, fertility preservation is an important issue to be taken into account. As Rituximab, a chimeric monoclonal antibody against the CD20 B-cell antigen, has proved to have therapeutic activity in diffuse large-B-cell lymphoma,\cite{22} its addition to the CHOP chemotherapy regimen has improved overall survival for these tumors.\cite{12,13}

Our patient was treated with a 6-cycles R-CHOP chemotherapy protocol, and achieved a complete response, which was confirmed through a new biopsy of the cervix. Neither surgery nor radiotherapy was administrated after chemotherapy. She is alive and disease free at 2-years follow-up.

**Figure 5.** Posttreatment cervical biopsy. A, Cervical mucosa with preserved glandular component and T-cell-rich areas, without evidence of B-cell lymphoma infiltration. B, CD20 staining was negative in the post-treatment biopsy.
4. Conclusions

Primary malignant lymphoma of the cervix is a very rare disease. The median age at presentation is around 44 years and they can often mimic a squamous cell carcinoma of the cervix, as the most common clinical symptom is vaginal bleeding. Although there is no consensus concerning the optimal treatment options, combined chemotherapy with R-CHOP protocol with or without radiotherapy has proved to achieve good results. Considering that the prognosis and treatment of this entity are completely different than that of the squamous cell carcinoma, awareness of this disease should be considered in the differential diagnosis.

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