

Primary vaginal non-Hodgkin's lymphoma: report of a rare clinical entity

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Abstract

A 52-year-old woman was referred to the gynecology outpatient clinic with a 2 months history of vaginal bleeding with intercourse, and no other symptoms. Vaginal examination revealed a firm, non-tender, mass in the posterior vaginal wall. The initial clinical impression was that of a vaginal carcinoma and a biopsy under local anesthesia was performed, but the result was inconclusive. A deeper biopsy, under general anesthesia, was performed and a histological diagnosis of non-Hodgkin's lymphoma was done. The staging workup permitted to exclude any other site of the body affected by the malignancy. Hematologists reviewed the patient and recommended chemotherapy. A complete tumor regression was observed and the patient has now a disease-free survival of 72 months. This case report intends to create awareness of this rare clinical entity. Although the gynecologist will rarely be faced to extranodal lymphoma, it should be included in the differential diagnosis of gynecologic malignancies.

Introduction

Non-Hodgkin's lymphomas (NHL) arise most frequently in lymph nodes or other lymphatic tissues. Primary extranodal lymphomas account for 20-34% of all cases of NHL¹ nevertheless primary extranodal lymphomas arising in the genital tract are very rare.² The National Cancer database report on NHL in 1997, which includes more than 90,000 NHL patients,³ found 28% of patients presenting a primary extranodal lymphoma, but only 1.5% of those originate in the female genital tract, while older reports showed an incidence even lower (<0.5%) of extranodal NHL.⁴ In those cases, the majority involves the adnexa or the uterus while primary lymphomas of the vagina are extremely rare with a few dozen cases reported,^{5,6} underlining the paucity of data for such uncommon tumors. We report a rare case of primary non-Hodgkin's lymphoma of the vagina successfully treated with chemotherapy.

Case Report

A 52-year-old woman was referred to the gynecology outpatient clinic with a 2 months history of vaginal bleeding with intercourse, and no other symptoms (including fever, night sweats, weight loss or fatigue). There was no past medical history of note and a positive family history of breast cancer. Vaginal examination revealed traces of blood with no visible lesions in the cervix, and a firm, non-tender, mass in the posterior vaginal wall, extending from the posterior vaginal fornix to about 2 cm above the introitus. On digital rectal examination a 6 cm mass was palpable, apparently not invading the rectal mucosa. At this time the clinical impression was that of a vaginal carcinoma and a biopsy under local anesthesia was immediately performed. Because this first biopsy was inconclusive, a deeper biopsy, under general anesthesia, was performed and a histological diagnosis of Non-Hodgkin's lymphoma (diffuse large B-cell lymphoma) was done (Figures 1 and 2). The staging workup (complete blood count, peripheral smear, bone marrow biopsy and body computed tomography scan) permitted to exclude any other site of the body affected by the malignancy and so it was staged as primary extranodal NHL IE. Hematologists reviewed the patient and recommended chemotherapy (R-CHOP regime: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) for 8 cycles. At the end of therapy, a complete tumor regression was observed (clinical and radiological) and the patient has now a disease-free survival of 72 months.

Discussion

Non-Hodgkin's lymphomas, according to the updated 2008 WHO classification of tumors of the hematopoietic and lymphoid tissues,⁷ encompass a large number of lymphoid neoplasms, with different natural histories as well as morphologic, immunophenotypic, and genetic features. The incidence of NHL, especially extranodal lymphoma, has increased in recent decades. NHL rates have steadily increased 3-4% each year in the US from 1973 to the mid 1990s⁸ and most other Western countries have reported similar trends.⁹ The etiology of this increase has been hypothesized to include infectious agents such as HIV and other viruses, immunosuppressive therapies, environmental exposures and improved diagnostic techniques, although the etiology of most types of NHL remains elusive.⁸ Diffuse large B cell lymphoma (DLBCL), is the most common histological subtype accounting for approximately 25 percent of cases of NHL in the developed world. Patients with DLBCL typically present with a rapidly enlarging mass, most

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usually nodal enlargement in the neck or abdomen, but may present as a mass lesion anywhere in the body. It is an aggressive NHL in which survival without treatment is measured in months. The pathologic diagnosis of DLBCL is based on morphology and immunophenotyping. DLBCL is a heterogeneous group of tumors consisting of large, transformed B cells with prominent nucleoli and basophilic cytoplasm, a diffuse growth pattern and a high proliferation fraction. Tumor cells generally express pan B cell antigens (CD19, CD20, CD22, CD79a). The majority has genetic abnormalities, but there is no single cytogenetic change that is typical or diagnostic. The differential diagnosis of DLBCL includes other entities that can result in similar patholog-

ic features, like infectious mononucleosis and large cell malignancies such as carcinoma (distinguished by the demonstration of cytokeratins by immunohistochemistry), melanoma, and other types of lymphoma.¹⁰

NHL arises most frequently in lymph nodes but can also present in other body tissues. Extranodal lymphomas are commonly subdivided as *primary* (primary origin in the organ) and *secondary* (secondary involvement of the organ) although these designations can become ambiguous and arbitrary.¹¹ Primary extranodal lymphomas account for 20-34% of all cases of NHL, depending on the definition used,^{1,4} usually involving the gastrointestinal tract or the skin.^{4,8} Genital tract lymphomas are rare and vaginal primary lymphomas are particularly rare.⁵

The definition of primary lymphomas of the female genital tract has been a subject of controversy for years. A number of authors have discussed cases of lymphomas in different parts of the female genital tract without presenting a definitive selection criterion for primary tumors. While some authors used only stage IE of the Ann Arbor system for definition of primary lymphomas, others considered low stage (IE and IIE) to be primary, allowing a diagnosis of a primary lymphoma, even in the presence of a direct invasion of the tumor to the adjacent tissues or the local lymph nodes.⁶ In the probably largest series of malignant lymphomas involving the female genital organs, that included 117 cases of primary lymphomas based on restrictive criteria (any case with extragenital invasion of either nodal or extranodal was considered secondary) there were only 9 cases (<0.1%) of primary vaginal NHL.⁶ This underlines the paucity of data for such uncommon tumors.

Primary vaginal lymphomas are reported in a wide range of ages with a mean age at presentation of 42 years (range, 26-66 years).^{12,13} As in our report, patients with primary NHL of the vagina most often present with abnormal vaginal bleeding,¹² but they may also complain of a mass at the introitus, dyspareunia, vaginal discharge or irritative urinary symptoms,^{13,14} being the most common clinical finding a vaginal mass.¹² The tumor is usually infiltrative, presenting with thickening of the vaginal wall, frequently with intact endothelium, and colposcopic biopsy may give false negative results.¹⁵ Like in our case report, other reports highlight the need for a second deeper biopsy to be taken for correct diagnosis.¹⁶ A rapid onset of new findings may be also suggestive.¹⁴ Similarly to our case, the most common histologic type of primary vaginal NHL is DLBCL.¹² The differential diagnosis includes other hematopoietic lesions, carcinoma, malignant mixed müllerian tumor, epithelioid leiomyosarcoma, endometrial stromal tumors including endometrial stromal sarcoma, melanoma, extraosseous Ewing's sarcoma/primitive neuroectodermal tumor and chron-

ic inflammation.^{12,15} With the frequent absence of 'B' symptoms (fever, weight loss, night sweat and fatigue, which are often associated with systemic disease), the clinical presentation of primary pelvic lymphoma may be suggestive of more common gynecological malignancies,^{14,17} as it was in our case report.

Lymphomas affecting the female genital tract may be under diagnosed both because they are unexpected in these sites and because they may be misdiagnosed as either inflammatory lesions

or other types of malignant tumor.⁶ In general, the prognosis for extranodal lymphoma is worse than for nodal lymphoma, primarily because of inaccurate or delayed diagnosis (this may be especially true for the rare primary pelvic lymphoma) and inadequate treatment.² Although the gynecologist will rarely experience extranodal lymphoma, it is important for them to be aware of this disease and to include it in the differential diagnosis of gynecologic cancer.² Once a histological diagnosis of NHL is made in the

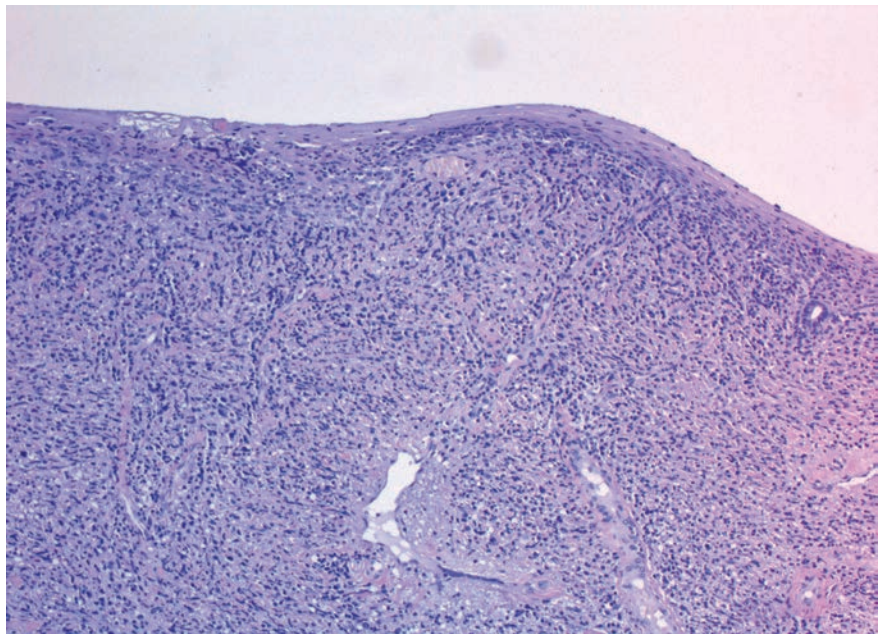


Figure 1. Dense infiltration of sub epithelial connective tissue by the large malignant cells; H&E, x10.

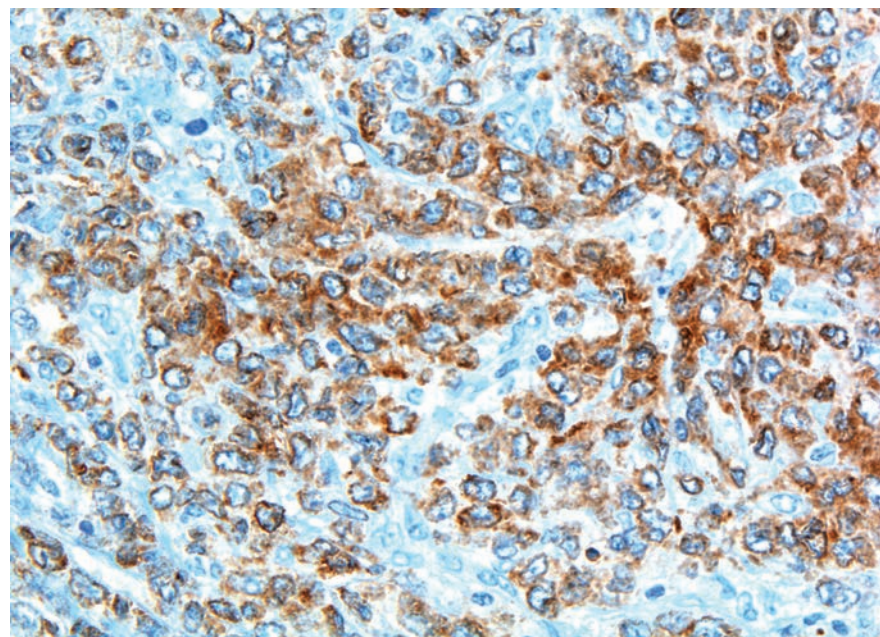


Figure 2. Malignant B cells stained CD79a positive (pan B cell antigen); x40.

female genital tract, referral to hematologist/oncologist is essential for appropriate therapy. Complete staging of NHL includes blood analysis, bone marrow biopsy and imaging studies (computed tomography and/or positron emission tomography scan).^{18,19} Initial imaging both serves to help determine disease stage at diagnosis and to provide a baseline study for comparison to determine response to treatment. The Lugano classification²⁰ is the current staging system used for patients with NHL and is based on the prior Ann Arbor staging system. Our patient was staged as IE (E, extranodal) large B cell NHL. Surgery is not the primary mode of therapy for NHL as these tumors are extremely responsive to chemotherapy.¹⁸ According to recent international guidelines, the treatment for limited stage DLBCL is chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) combined with rituximab (R) (a monoclonal antibody directed against the CD20 antigen) followed, or not, by local radiation therapy.¹⁹ Because of its rarity, there is no established treatment of primary NHL of the vagina. The good outcome in this case report is concordant with the 5-year survival rate of primary pelvic lymphomas of 80 to 90% in the event of early diagnosis and adequate therapy.¹²

Conclusions

Primary lymphomas of the vagina are extremely rare. This case report intends to create awareness of this rare clinical entity. Although the gynecologist will rarely be faced to extranodal lymphoma, it should be included in the differential diagnosis of gynecologic malignancies. Radical surgery does not play a role in the treatment of this malignancy since the mainstays of treatment are cytotoxic chemotherapy, monoclonal antibodies and/or radiation therapy. Histology is essential to reach a correct diagnosis and enable to offer the appropriate treatment for this curable malignancy.

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