Linfoma Não Hodgkin com Envolvimento do Colo do Útero

Non-Hodgkin's Lymphoma with Uterine Cervix Involvement

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Resumo:

Os linfomas que envolvem o colo do útero são muito raros. Relatamos o caso de uma mulher de 71 anos apresentando sintomas de diverticulite, com vários achados imagiológicos incidentais sugerindo uma doença linfoproliferativa e uma grande massa no colo do útero. A biópsia profunda do colo do útero diagnosticou um linfoma difuso de grandes células B envolvendo o colo do útero, provável transformação de um linfoma de zona marginal. A doente está atualmente em tratamento com rituximab, ciclofosfamida, doxorrubicina, vincristina e prednisolona e metotrexato em altas doses para profilaxia de envolvimento do sistema nervoso central. Para diagnosticar com precisão um linfoma não-Hodgkin do colo do útero, a equipa médica deve estar atenta a esta hipótese diagnóstica clínica, a fim de proporcionar as melhores condições para a investigação, como biópsia profunda do colo do útero e estudos histológicos e imuno-histoquímicos da amostra.

Palavras-chave: Colo do Útero; Linfoma Difuso de Grandes Células B/diagnóstico; Linfoma Difuso de Grandes Células B/tratamento farmacológico; Neoplasias do Colo do Útero.

Abstract:

Lymphomas involving the uterine cervix are very rare. We report a case of a 71-year-old woman presenting with symptoms of diverticulitis, with various incidental imaging findings suggesting a lymphoproliferative disease and a big cervix mass. Deep uterine cervix biopsy diagnosed a diffuse large B cell lymphoma involving the uterine cervix, presumably transformed from a marginal zone lymphoma. The patient is currently under treatment with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone and high-dose methotrexate to central nervous system involvement prophylaxis. To accurately diagnose a uterine cervix non-Hodgkin's lymphoma, the medical team must be aware of this clinical diagnostic hypothesis in order to provide the best conditions to the work-up, like a deep uterine cervix biopsy and histological and immunohistochemical studies of the sample.

Keywords: *Cervix Uteri; Lymphoma, Large B-Cell, Diffuse/diagnosis; Lymphoma, Large B-Cell, Diffuse/drug therapy; Uterine Cervical Neoplasms.*

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Introduction

Non-Hodgkin's lymphomas (NHL) are a heterogeneous group of hematologic malignancies that derive from B, T or natural killer cells and have a global incidence of about 3%.[1] NHL can affect the lymph nodes, extranodal lymphoid tissue or both, with extranodal sites involved in one-third to 40% of cases.[2,3] Common extranodal locations include the gastrointestinal tract, Waldeyer's ring, nasal cavity, paranasal sinuses and skin. The involvement of the female genital system is rare, with an incidence rate of less than 1%.[4,5] The ovaries are the most affected organs, followed by uterine cervix, corpus uteri, vagina and vulva.[2,5] We report a case of NHL involving uterine cervix and its diagnostic work-up.

Case Report

A 71-year-old woman with primary hypertension, atrial fibrillation and hypothyroidism presented to the hospital with abdominal colicky pain in the left lower quadrant, diarrhea, nausea and vomiting since the day before. Additionally, patient reported anorexia for a month, with no other accompanying symptoms.

Abdominal examination revealed distension and global tenderness, particularly in the left lower quadrant. Her blood workup was unremarkable, despite a hemoglobin of 10.5 g/dL (inflammatory anemia based on the iron kinetics) and a C-reactive protein of 99.1 mg/dL. Since the ultrasound findings did not explain the symptoms, she was submitted to an abdominal computed tomography (CT) scan. This not only revealed diverticulosis of the sigmoid colon with signs of acute diverticulitis in its proximal portion and phlegmonous densification of the pericolic fat, but also an array of other findings: frank enlargement of the uterine cervix (7 cm), that was heterogeneous and irregular, suggesting tumor lesion; a 16.7 cm splenomegaly, suggesting lymphoproliferative disease; perirenal contrast-enhancing masses with perirenal "swaddle" morphology, suggesting bilateral lymphoma; and multiple lumboaortic and iliac adenopathies. She was started on intravenous antibiotics and a liquid diet, and was hospitalized due to Hinchey Ia diverticulitis and probable malignant neoplasm. Regarding the diverticulitis, the patient had significant clinical improvement after treatment and was referred to General Surgery consultation.

During hospitalization, the patient underwent an magnetic resonance imaging (MRI), that better described the cervix

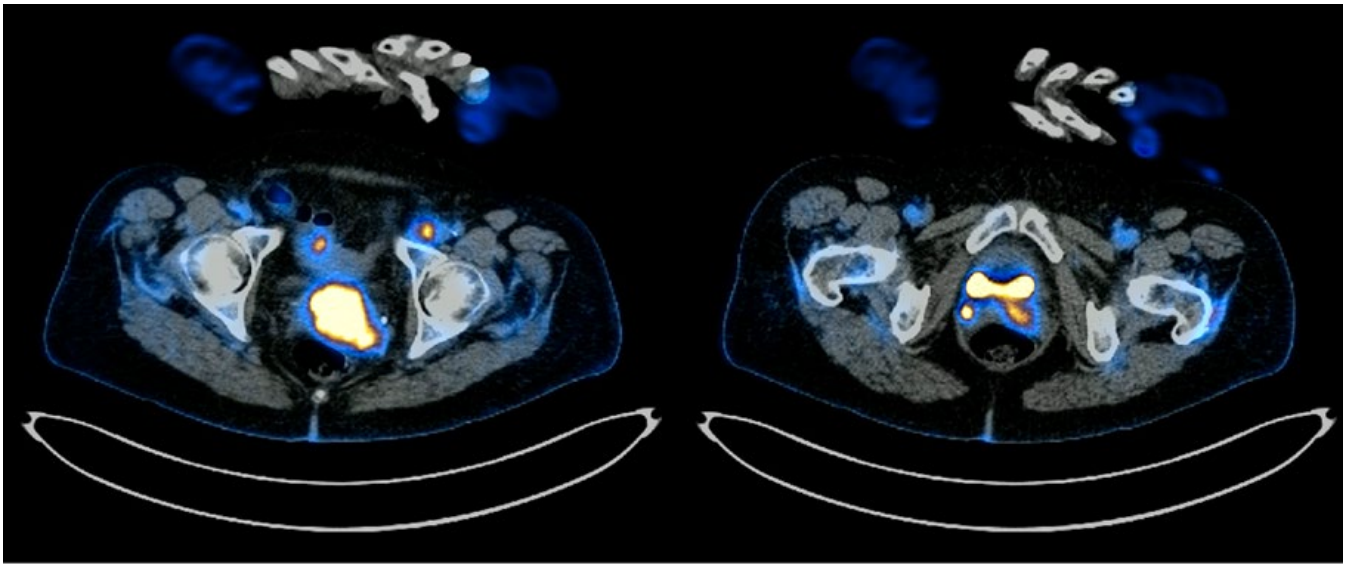

Figure 1 -Positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro- D-glucose integrated with computed tomography (18F-FDG PET/CT) at staging time demonstrating a uterine hypermetabolic mass (SUVmax: 18.8), measuring about 59 x 42 mm of axial axes compatible with a uterine lymphomatous mass.

lesion as an "heterogeneous, clearly thickened uterine cervix, with a mass effect in this topography, in an extension of 55x37x33 mm, occupying the posterior vaginal cul-de-sac and significantly reaching the lower third of the uterine body, suspected of a more aggressive neoformative process"; it also referred left external iliac chain adenopathies and a 16 cm splenomegaly.

At the gynecological exam she had a thickened cervix, with multiple hemorrhagic suffusions; the ultrasound confirmed a 35 mm vascularized cervix and a thin endometrium with anterior and posterior intracavitary fluid. Cervix smear test was negative for intraepithelial lesion or malignant neoplasm.

Since all the findings strongly suggested a lymphoproliferative malignant neoplasm that affected the uterine cervix, we requested a deep cervix biopsy asking to exclude this diagnostic hypothesis. Histological examination of this biopsy specimen demonstrated diffuse cellular infiltrate, comprising predominantly lymphoid cells, with small and medium-sized cells and areas with larger cells. The immunohistochemistry revealed a mixed population of B and T lymphoid cells, with a clear predominance of B cells, translating a diffuse lymphoproliferative process of B cells with positivity for CD20, CD79-alpha, BCL2 and BCL6, supporting the diagnosis of a diffuse large B cell lymphoma. The patient was promptly referred to Hematology-Oncology and submitted to staging. Her Eastern Cooperative Oncology Group (ECOG) performance status was zero (fully active, able to carry on all pre-disease performance without restriction). Her lactate dehydrogenase was normal (205 UI/L). The flow cytometry of bone marrow aspiration demonstrated a phenotype compatible with marginal zone lymphoma. The PET/CT scan demonstrated supra and infra-diaphragmatic ganglion, splenic, renal, uterine, muscular and bone involvement of an active lymphoma (Figs. 1 and 2A). She was then diagnosed with stage IV (by Ann Arbor staging system) diffuse large B cell lymphoma (DLBCL) due to probable transformation from previous marginal zone lymphoma (MZL). The patient was started on chemoimmunotherapy with rituximab plus cyclophosphamide, doxorubicin hydrochloride, oncovin (vincristine sulfate) and prednisolone (R-CHOP) and high dose methotrexate to prevent central nervous system dissemination, being currently under treatment and already showing some improvement (Fig. 2B).

Discussion

Involvement of the female genital tract by lymphoma is usually asymptomatic; in fact, this diagnosis was incidental and our patient only complained about anorexia, with no other B symptoms.[6,7] Symptomatic patients most commonly present with abnormal uterine/vaginal bleeding,[4,3] but also abdominal or pelvic pain, abdominal distension, dyspareunia, postcoital bleeding and vaginal discharge.[2,5]

The cervix smear test rarely diagnoses cervix lymphomas (1.39% of all cases) because they arise from the stroma rather than the mucosa, being only able to diagnose this abnormality once ulceration of epithelial cells had occurred, which justifies the negativity in this clinical case.[3,5] Since anatomopathological and immunohistochemical evaluations of the tissue are fundamental in the characterization of the antibodies and in the classification of the subtype of the lymphoma,[2] the deep uterine cervix biopsy allowed the diagnosis in a minimally invasive manner, accelerating diagnostic timing.

The extranodal involvement may be primary (a localized NHL originating in a gynecologic organ) or secondary (a NHL involving the gynecologic organs as part of systemic

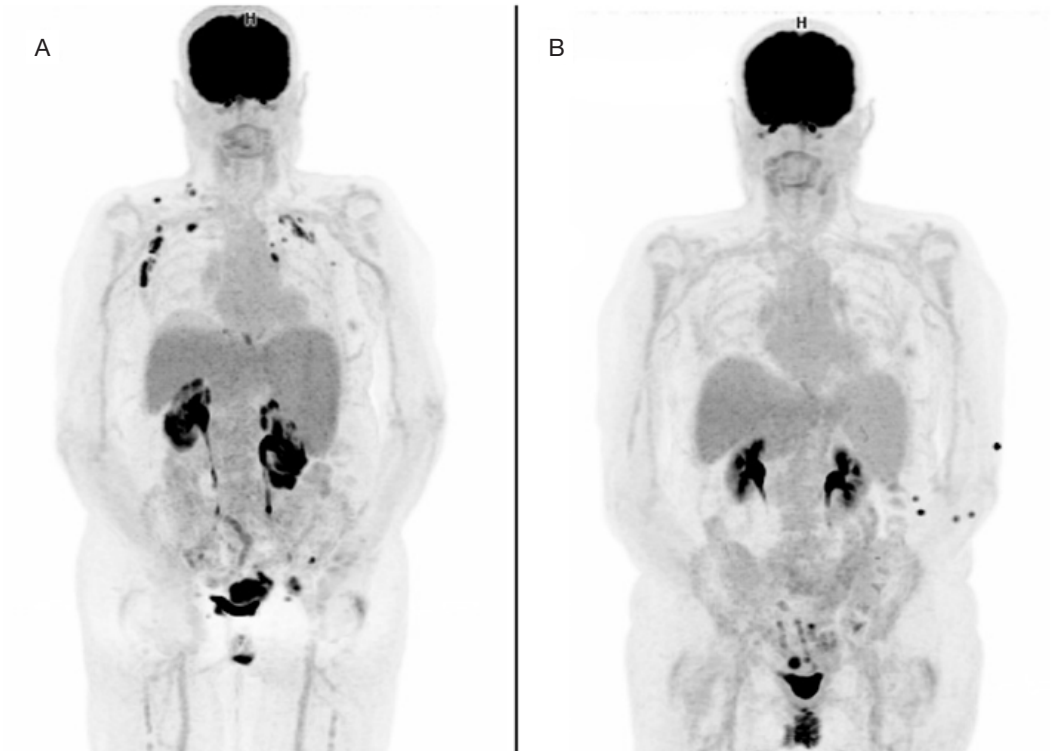

Figure 2 - Positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro- D-glucose integrated with computed tomography (18F-FDG PET/CT). (**A**) At staging time, the study was compatible with active lymphomatous disease with supra and infra-diaphragmatic, splenic, renal, uterine, muscular and osseous involvement. (**B**) Study done after the first cycle of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone, demonstrating favorable evolution of the previously found lymphomatous lesions.

disease).[4,8] In this clinical case, the distinction between primary and secondary uterine cervix lymphoma is challenging, because, despite the spreading, a huge part of the lymphoma manifested in the cervix, impeding us to entirely exclude primary cervix uterine origin.[4,8] According to a recent surveillance, epidemiology, and end results database analysis, patients with uterine DLBCL have more favorable overall survival results as compared to non-uterine DLBCL patients.[9]

MZLs include extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), nodal MZL and splenic MZL.[10] They represent a group of indolent B-cell lymphomas that are derived from the marginal zone of the secondary lymphoid follicles and generally have an indolent course and favorable outcome. However, histologic transformation to DLBCL can occur in any low-grade B-cell lymphoma, with a risk of 5% at 5 and 10 years, and 10% at 12 years, with more unfavorable outcomes than MZL.[10,11] The information concerning histologic transformation of MZL into aggressive entities is thus far very limited.[11]

The most common histologic type of high-stage, presumably secondary, NHL with female genital tract involvement is DLBCL, that has a 5-year survival rate reported to range from 0% to 50%.[4] The International Prognostic Index (IPI) is usually considered the most reliable and reproducible prognostic model to quantify the prognosis of NHL, including extranodal NHL.[5] This patient has an IPI score of 3 points, corresponding to high-intermediate risk, that has a three-year overall survival of 65%, based on a group with CD20-positive aggressive lymphoma treated with R-CHOP.[12,13]

Conclusion

NHL involving the female genital system is rare and commonly asymptomatic. This involvement may be primary or secondary, and the latter is usually diffuse large B cell lymphoma. A deep biopsy with uterine cervix epithelium and mesenchyme is required for diagnosis as surface cytology is frequently negative. Being aware of the existence of lymphomas in this location and having a good communicating system and a multidisciplinary approach may be of vital importance in the work-up of histologically difficult uterine neoplasms, allowing to avoid misdiagnosis and/or delayed diagnosis. R-CHOP chemotherapy is usually an effective treatment. ■

Declaração de Contribuição

RJR, PC – Desenho, elaboração e redação do artigo

FA, MM – Revisão crítica do artigo

RS – Revisão e aprovação final do artigo

Todos os autores aprovaram a versão final a ser publicada.

Contributorship Statement

RJR, PC – Design, drafting and writing of the article
FA, MM – Critical revision of the article
RS – Revision and final approval of the article
All authors approved the final draft

Responsabilidades Éticas

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