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PRIMARY LYMPHOMA OF THE UTERINE CERVIX: CASE REPORT

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Palabras clave: Cuello uterino; Linfoma; Neoplasias.

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RESUMEN

Introducción. El linfoma primario del cuello uterino es una patología infrecuente, de síntomas inespecíficos y que pocas veces altera el examen de citología del cuello uterino dado que se desarrolla en el estroma cervical. Para su tratamiento existen varias opciones, incluyendo quimioterapia, radioterapia y cirugía, así como combinaciones de estas. La localización única del linfoma en el cuello uterino se considera un factor de buen pronóstico.

Presentación del caso. Paciente femenina de 49 años, quien consultó por dolor pélvico y flujo y sangrado genital. Se ordenó colposcopia por reporte de ASC-H (células escamosas atípicas que no excluyen lesiones intraepiteliales de alto grado) en citología vaginal. La biopsia reportó linfoma difuso de células B grandes, el cual se trató con rituximab, ciclofosfamida, doxorrubicina, vincristina y prednisolona por tres ciclos, y con rituximab, ifosfamida, carboplatino y etopósido por dos ciclos; este cambio se hizo debido a una mala respuesta con el primer esquema. Se realizó nueva biopsia después del último ciclo de quimioterapia con reporte de pólipo de tipo endocervical y abundantes grupos de células glandulares con atipia focal. Los estudios de imágenes diagnósticas posteriores al tratamiento reportaron engrosamiento concéntrico de la unión entre cuello uterino y vagina. A los 7 años del diagnóstico del linfoma se realizó otra biopsia que resultó negativa para displasia o malignidad. Al momento de la elaboración del presente reporte, 10 años después del diagnóstico, la paciente se encontraba asintomática y libre de enfermedad.

Conclusiones. El linfoma primario del cuello uterino es una patología rara que en pocas oportunidades se evidencia con anormalidad en la citología vaginal como en el caso reseñado. Dado este hallazgo se realizó una colposcopia mediante la cual se confirmó el diagnostico de linfoma difuso de células B grandes. Se presenta un caso con evolución satisfactoria y supervivencia libre de enfermedad después de 10 años.

ABSTRACT

Introduction: Primary lymphoma of the uterine cervix is a rare disease, with nonspecific symptoms, that seldom alters Pap smear results since it develops in the cervical stroma. Chemotherapy, radiation therapy, and surgery, as well as their combination, are some of the medical options available for treatment. The unique location of the lymphoma in the cervix is considered a good prognostic factor.

Case presentation: A 49-year-old female patient consulted due to pelvic pain and vaginal discharge and bleeding. She underwent a colposcopy due to cytology findings of ASC-H (atypical squamous cells that do not exclude high-grade squamous intraepithelial lesions). The biopsy reported diffuse large B-cell lymphoma, which was initially treated with three cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone, and was then switched to two cycles with rituximab, ifosfamide, carboplatin and etoposide due to a poor response with the first scheme. A new biopsy was performed after the last cycle of chemotherapy with a report of endocervical polyp and abundant clusters of glandular cells with focal atypia. Post-treatment diagnostic imaging studies reported concentric thickening of the cervix-vagina junction. Seven years after being diagnosed with lymphoma, another biopsy was performed. The result was negative for dysplasia or malignancy. At the time of writing this case report, 10 years after diagnosis, the patient is asymptomatic and disease-free.

Conclusions: Primary lymphoma of the uterine cervix is an unusual condition that is rarely detected through an abnormal Pap smear result, as in this case. A colposcopy was done because of this finding, confirming the diagnosis of diffuse large B-cell lymphoma. This case report describes the satisfactory evolution of the patient and disease-free survival after 10 years.

INTRODUCTION

Lymphomas are hematologic malignancies that are subdivided into Hodgkin's lymphomas and non-Hodgkin's lymphomas. The latter are the most frequent (1) and, depending on their primary location, are further subdivided into nodal and extranodal (2).

Lymphomas usually grow in the lymphoid organs and can cause systemic symptoms such as fever, night sweats, and weight loss (3). However, non-Hodgkin's lymphomas affect extranodal regions, including the female genital tract, in about a third of patients (4).

Primary lymphoma of the uterine cervix is a rare disease that accounts for only 0.008% of cervical tumors and 2% of female extranodal lymphomas (5.6). Symptoms are usually nonspecific and include vaginal bleeding (70%), perineal discomfort (40%) and persistent vaginal discharge (20%) (7).

The diagnosis of primary lymphoma of the cervix can be made when there is no nodal involvement and no other site of extranodal involvement is established at the time of presentation. Mandate *et al.* (8) suggest that these conditions may occur three months before and three months after diagnosis. The most common histological subtype of female genital lymphomas is diffuse large B-cell lymphoma, which is difficult to diagnose. Its detection may be delayed due to the rarity of the disease and the lack of clear clinical symptoms (8). Most cases are presented in the literature as individual reports and no standard treatment for its management has been established (9).

CASE PRESENTATION

A 49-year-old female patient, Hispanic, from Bogotá, retired from the Colombian Armed Forces, with no relevant medical history other than two full-term pregnancies (one by vaginal delivery and one by cesarean section), consulted due to clinical symptoms consisting of pelvic pain and genital discharge and bleeding that she associated with a Pap smear. Given these symptoms, a transvaginal ultrasound was requested, showing normal findings. No cervical abnormality was found during the gynecological examination.

Due to the persistence of symptoms and a cytology report that indicated ASC-H (atypical squamous cells that do not exclude high-grade intraepithelial lesions), a colposcopy was requested, yielding unsatisfactory results due to incomplete visualization of the transformation zone. However, it was possible to identify a prominent lesion on the anterior lip of the cervix that was described as a dense acetowhite lesion with raised borders.

The biopsy reported diffuse large B-cell lymphoma, and the microscopic report noted: "The sections show endocervical fragments with benign-looking epithelium with focal atypical repair and a diffuse stroma extensively compromised by an intermediate and large size lymphoproliferative lymphocytic neoplasm with small nucleoli and irregular nuclear membrane." The tissue was positive for immunohistochemistry markers CD20, ACL (diffusely), and BCL6 (focally). Furthermore, CD3, CD43, and BCL2 were positive in the accompanying lymphocytes; CD22, KAPPA and Lambda were non-contributory; CD10 and cyclins were negative; and Ki-67 showed a cell proliferation index of approximately 60%.

In the general clinical examination, the patient was in good condition (ECOG 0 scale) and no adenopathies were reported, whereas the gynecological examination revealed a cervix with easy and abundant bleeding and the presence of a raised lesion on the anterior lip. Vaginal examination revealed a 4x4cm diameter lesion in the cervix and pelvic examination showed no alterations or masses in the body of the uterus, nor nodules in the parametria. Liver and kidney function tests were normal.

A computed axial tomography (CAT) scan was requested, which reported a retrouterine, pararectal and left lower retrovesical soft tissue lesion of homogeneous appearance measuring 5.7x7.5x5cm. The bladder did not show any alterations and no other findings of masses, adenopathies or fluid collection were reported. No changes were observed on chest x-ray.

The patient was diagnosed with primary lymphoma of the uterine cervix and was treated with three cycles of rituximab + CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone), which was switched to salvage chemotherapy with two cycles of RICE (rituximab, etoposide, carboplatin, ifosfamide) after obtaining an inadequate response with the first scheme, considering that the CAT scan showed that the size of the lesion had not changed since the previous study. Adverse events to these treatments were mild.

Eight days after completing the second cycle with RICE, a new colposcopy was performed. The biopsy reported acute, chronic, and ulcerated exocervix cervicitis, while the endocervix biopsy showed endocervical polyp and abundant clusters of glandular cells with focal atypia. The patient did not return for consultation with hemato-oncology.

CAT scan images in the following three years reported concentric thickening of the cervicovaginal junction. Seven years after the diagnosis of primary lymphoma of the cervix, a biopsy was performed, reporting endocervix with muco-hemorrhagic material with loose endocervical glands without atypia, exocervix with mild chronic cervicitis, and negative results for dysplasia or malignancy. The endocervical polyp biopsy was also negative for malignancy.

At the time of writing this report (10 years after diagnosis), the patient was still undergoing gynecologic oncology follow-ups and was asymptomatic and disease-free. Gynecological assessment, Pap smear and ultrasound of the abdomen were normal at her last check-up.

DISCUSSION

Although the reported patient consulted for pelvic pain accompanied by genital bleeding and discharge, which are symptoms of primary lymphomas of the uterine cervix (bleeding is the most common symptom) (7,9), initial assessments showed no abnormality in the cervix. The Pap smear report prompted to perform colposcopy and biopsy and request additional diagnostic imaging scans.

Finding cytological anomalies in this condition is extremely uncommon since diffuse large B-cell lymphoma of the cervix is a stromal disease, and a cytological diagnosis would only be expected when there is ulceration of epithelial cells (5,10).

Primary lymphomas of the uterine cervix are most common in women between the ages of 40 and 59 (11), which is the age range of the reported patient. The correct diagnosis of this condition is often delayed, so the disease is detected in advanced stages mainly due to its low prevalence and the absence of specific clinical symptoms (8).

The most common finding in gynecologic examination of patients with primary lymphomas of the uterine cervix is diffuse thickening of the cervix wall without mucosal abnormality, which

is voluminous and shaped like a "champagne cork" (>4cm in diameter in 50% of cases) and without vegetations or necrosis. It is worth mentioning that squamous carcinoma does present with vegetations and necrosis (12).

The differential diagnosis, besides squamous carcinoma (especially in barrel-shaped presentations), may include cervical myomas, cervical sarcomas, and small-cell carcinomas (13). A biopsy is needed to confirm the diagnosis (14), but it is important to consider that, on occasions, a reactive lymphoma-like lesion can distort the diagnosis (15-17).

Primary lymphomas of the uterine cervix are treated in a variety of ways, and there is no established standard approach (3,8). However, depending on the situation, they have been treated with radiotherapy alone or in combination with surgery and/or chemotherapy, following the general principles of treatment for non-Hodgkin's lymphomas (1,18-20). They have also been effectively treated with combination chemotherapy in regimens such as CHOP, which has two additional advantages: it prevents micrometastases and can preserve fertility in young women (9,21). Rituximab, a chimeric monoclonal antibody that targets the B-cell CD20 antigen, is added to this chemotherapy. It is a human immunoglobulin G1 with a CD20 binding region derived from a mouse monoclonal antibody through genetic engineering (22,23). This addition to the CHOP scheme improves overall survival (24,25).

Approximately 40-60% of patients with low-grade non-Hodgkin lymphoma treated with anthracycline regimens fail to achieve a complete response or relapse after achieving a complete response (26,27), but the addition of RICE has proven to be successful in these cases (28).

Female genital lymphomas, in general, and cervical lymphomas, in particular, have a worse prognosis than the most common nodal lymphomas (8,29-31). This is explained by inaccurate initial diagnoses and late-onset or failed therapies. However, the prognosis of primary lymphoma of the uterine cervix, when diagnosed early and treated properly, tends to be excellent (24,32,33), with overall five-year survival between 73-86% (31,34).

CONCLUSIONS

Abnormal findings on Pap smear in the reported case led to the diagnosis of cervical neoplasm, allowing for an early diagnosis of primary lymphoma of the uterine cervix. Two chemotherapy regimens were used to treat what appeared to be a stable disease based on medical imaging, but biopsies revealed a full pathological response, and the patient exceeded 10 years of disease-free survival.

ETHICAL CONSIDERATIONS

The patient's informed consent was obtained for the preparation of this case report.

CONFLICTS OF INTEREST

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