Title page; Uterine Cervical Involvement of Non-Hodgkin Lymphoma; Rare Cause of Postcoital Bleeding

Running Title; Uterine Cervical Involvement of Non-Hodgkin Lymphoma

1. **Özer Birge,** M.D. Nyala Sudan Turkey Training and Research Hospital, Department of Gynecology Obstetrics, Nyala-Darfur-Sudan.

   Ozbirge@gmail.com

2. **Mehmet Sait Bakır,** M. D. Akdeniz University, Department of Gynecology Obstetrics, Division of Gynecologic Oncology. Antalya, Turkey.

   sabakcil@gmail.com

3. **Ceyda Karadag,** M. D. Akdeniz University, Department of Gynecology Obstetrics, Division of Gynecologic Oncology. Antalya, Turkey.

   drceydakaradag@gmail.com

4. **, Can Dinc,** M. D. Akdeniz University, Department of Gynecology Obstetrics, Antalya, Turkey.

   Candinc00@hotmail.com

5. **Ahmet Boduroglu**, M. D. Akdeniz University, Department of Pathology. Antalya, Turkey.

   ahmet-boduroglu@outlook.com

6. **Tayup Simsek,** M. D. Akdeniz University, Department of Gynecology Obstetrics, Division of Gynecologic Oncology. Antalya, Turkey.

   tsimsek@akdeniz.edu.tr

   Corresponding author; **Ozer Birge,** M. D.. Nyala Sudan Turkey Training and Research Hospital, Department of Gynecology Obstetrics, Nyala-Darfur-Sudan.

   ozbirge@gmail.com

   Adress: Southern Nyala - West Alezza Distrik - Nyala, Sudan.

Uterine Cervical Involvement of Non-Hodgkin Lymphoma; Rare Cause of Postcoital Bleeding

Abstract

Objective: Non-Hodgkin's lymphoma of the female genital system is extremely rare. It may be confused with cervix uteri malignancies when being diagnosed.

Case Presentation: A 40-year-old female patient who HAD presented with postcoital bleeding, dyspareunia and vaginal discharge with a foul odor preliminarily diagnosed with a cervical malignant mass was diagnosed as non-Hodgkin lymphoma cervix uteri infiltration as a result of the pathological examination. PET CT revealed pathological involvement, and the medical oncology department administered chemotherapy. Cure was achieved in the patient with chemotherapy.

Result: In presentations with the clinical findings of cervix uteri cancer, it should be kept in mind that non-Hodgkin lymphoma, which rarely involves the cervix uteri, may be diagnosed after biopsy; massive lesions detected in any organ or system could also be malignancies that cause systemic invasion and the treatment of such cases should be planned after performing a multi-system screening.

Keywords: Cervix uteri cancer, non-Hodgkin lymphoma, B-cell lymphoma.

Key Clinical Message: In final words, with multidisciplinary efforts in systemic lymphomas that mimic genital system malignancies and involve the female genital system and cause gynecological complaints, unnecessary genital organ losses can be prevented.

Introduction

Lymphoma is a disease with various subtypes. It tends to vary from region to region. Non-Hodgkin lymphoma (NHL) is a diverse collection of malignant neoplasms of lymphoid cell origin that includes all malignant lymphomas not classified as Hodgkin. NHL is one of the most common cancer types diagnosed in men and women in developed countries (1). In women, malignant lymphomas comprise 3.5% of all malignant neoplasms. Most of these are NHL (73%). NHL is a heterogeneous group of malignancies originating from different differentiation stages of two distinct types of lymphocytes, namely B or T lymphocytes (2). The World Health Organization’s (WHO) classification is currently the most used system (3). The WHO classification's 2016 revision includes more than 50 NHL types defined and a few temporary types (4).

While 60-75% of NHLs develop in lymphoid tissues such as the lymph nodes, spleen and the bone marrow, they may develop in almost any tissue. It may range between a more occult follicular lymphoma, a more aggressive diffuse large B-cell, and Burkitt lymphoma (5).

Primary extranodal involvement of non-Hodgkin lymphoma is rare. While the rate of primary extranodal disease is near 30% in Europe, it has been identified as 22-25% in America. Based on differences in geographical regions, this rate increases to nearly 50% in Middle Eastern

and Asian countries (6,7). The most common extranodal involvement areas of non-Hodgkin lymphomas are the stomach, skin, small intestines and the tonsils, but they can involve almost any system (6,7). In particular, extranodal involvement may occur in many genitourinary regions such as the kidneys, testes, ovaries, ureters, bladder, uterus and the cervix uteri in the form of infiltration of the lymphoma or primary lesions (6,7,8). Nearly 1% of the lymphomas originating from the testicular region are primary. The clinical findings are similar regardless of whether it is primary or due to infiltration, and there are complaints of feeling pressure, pain, vaginal bleeding, hematuria and organ failures secondary to obstruction. Although rare, severe clinical conditions such as hypercalcemia, hyperuricemia, severe hypoglycemia and renal failure can develop as complications secondary to non-Hodgkin lymphomas.

Case Presentation:

After a mass was detected in the gynecological examination of the 40-year-old female patient who had presented with bleeding after sexual intercourse, dyspareunia and watery vaginal discharge, and who had a history of 3 healthy normal vaginal births, a biopsy was obtained from the mass. The pathology was reported as cervical squamous type non-keratinizing carcinoma and the patient was referred to our tertiary hospital for advanced tests and treatment. The patient had no complaints other than postcoital bleeding, dyspareunia and watery vaginal discharge with a foul odor. The gynecological examination revealed a normal vulva and vagina consistent with age; however, speculum examination revealed a massive lesion approximately 2 cm in size with irregular borders and fragile bleeding outside the transformation zone on the upper pole of the uterine cervix. The uterus was normal on ultrasound examination, and the ovaries bilaterally and tubas had normal anatomical structure. However, transvaginal ultrasonography showed a normal uterine canal and a massive lesion approximately 16x17mm with irregular borders on the anterior surface of the uterine cervix that did not extend into the endocervical canal. A colposcopic examination was performed to obtain biopsy samples. The biopsies obtained from the uterine cervical mass in the external center also underwent the consultation of our hospital's pathology department. As a result of the pathological examination, CD 20-positive high-grade B-cell lymphoma infiltration was determined. In the immunochemical examination of the preparations, the neoplastic cells were CD20, LCA, vimentin-positive and CD3, CEA, P63, CD56, and Pan-CK negative (Figure 1 and 2).

The positron emission tomography (PET-CT) performed while waiting for the patient's pathology results revealed a right inferior jugular hypermetabolic millimetric lymph node, intense FDG uptake, hypometabolic in the center with hypermetabolic surroundings in the middle of the cervix, multiple hypermetabolic areas in the corpus uteri, multiple hypermetabolic lymph nodes in the abdomen, increased FDG uptake in the lesions observed close to the antral region of the stomach wall small curvature and fundus, intense FDG uptake in the liver areas that appeared hypodense, focal increased FDG uptake in the areas of filling defects in the bowel loops in the abdomen, and increased FDG uptake in the lytic areas observed in the left acetabulum, left femur head, and the anterior end of the left first rib.

After imaging and pathology studies, the medical oncology department administered systemic rituximab, cyclophosphamide, vincristine, and prednisone (R-CHOP) chemotherapy and radiotherapy to the right humerus and pelvic region. The control PET-CT performed four months later revealed low FDG uptake in the lytic area observed in the right humerus head and a non-metabolic millimetric nodule in the superior of the left lung lower lobe and this was reported as findings consistent with response to treatment. In the comparative PET-CT repeated six months later, the lytic hypermetabolic area in the right humerus head was similar, no pathological lymph node involvement was observed, and complete cure was achieved after chemotherapy treatments. It was also observed that the case's cervix uteri lesion had regressed, and the complaints had resolved.

Discussion

Hematological malignancies are rarely a primary gynecological problem. They usually occur as a result of systemic spread of tumor cells rather than primary tumors. Extranodal NHL often involves the gastrointestinal system and bone marrow. Less than 1% of all extranodal NHLs affect the female genital system (9). NHL rarely infiltrates the female genital tract. Female genital tract lymphoma has an extremely low prevalence. Multicentric and interdepartmental joint studies are required to investigate these lymphomas. (6) An interdisciplinary medical approach is required to diagnose, treat and follow-up this disease. Misdiagnosis of the primary tumor or infiltration of the female genital system should be prevented. Our case was also diagnosed with a cervix uteri tumor, and after a detailed evaluation, she was diagnosed with infiltration of the systemic malignant disease non-Hodgkin lymphoma and cured with an appropriate treatment regimen. Furthermore, it is evident that morbidity and mortality would have increased if our case had been treated directly based on the external center preparations.

In the study conducted by the International Workshop Group (IWG) in 2007, after analyzing the response criteria, FDG-PET became the standard method of evaluating the response in both Hodgkin and non-Hodgkin lymphomas (10). Due to the fat that NHLs are extremely sensitive to chemotherapy, the first treatment method is chemotherapy. CHOP-R is the first treatment for this type of cancer. However, less is known about the follow-up protocol and recurrence management. Radiation therapy may or may not be added at all (11).

In final words, with multidisciplinary efforts in systemic lymphomas that mimic genital system malignancies and involve the female genital system and cause gynecological complaints, unnecessary genital organ losses can be prevented. Furthermore, most importantly, it is seen that the best results can be obtained by making the actual diagnosis timely and starting treatment.

Declaration of competing ınterest

None declared.

Acknowledgments

The authors thank all the staff members involved in this case. Published with written consent of the patient.

Author contrıbutıons

MSB and ÖB: wrote the manuscript; AB, CK and CD contributed to clinical follow−up; TS: revised the manuscript.

References

1) Sağlam A, Esin E, Hayran M, Boyraz B, Üner A. Distribution of lymphomas in Turkey: data of 4239 cases from a single institution using the WHO classification. Turk J Med Sci. 2018;48(5):1013-1023.
2) Swerdlow SH, Campo E WHO classification: pathology and genetics of tumors of haematopoietic and lymphoid tissues. IARC Press, 2008, Lyon.
3) Pratap S, Scordino TS. Molecular and cellular genetics of non-Hodgkin lymphoma: Diagnostic and prognostic implications. Exp Mol Pathol. 2019 Feb;106:44-51.
4) Swerdlow SH CJ, Sohani AR, Pileri SA, Harris NL, Jaffe ES, Stein H. Lymphoplasmacytic lymphoma. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, revised 4th edn: IARC Press, Lyon; 2017:232-235.
5) Shankland KR, Armitage JO, Hancock BW. Non-Hodgkin lymphoma. Lancet.2012 380 (9844):848–857.
6) Roman E, Smith AG. Epidemiology of lymphomas. Histopathol 2011;58:4-14.
7) http://seer.cancer.gov/statfacts/html/nhl.html (date accessed: 10.08.2013).
8) Schultz A, Maruschke M, Leithäuser M, et al. Genitourinary manifestations of lymphomaAktuelle Urol 2007;38:324-327.
9) Contreras-Chavez P, Aliaga R, Samee M, Anampa-Guzmán A. Primary Vaginal Non-Hodgkin Lymphoma. Cureus. 2018;10(12):e3713.
10) Tamayo P, Martín A, Díaz L, et al. 18F-FDG PET/CT in the clinical management of patients with lymphoma. Revista Espanola de Medicina Nuclear e Imagen Molecular. 2017;36(5):312-321.
11) Tilly H, Gomes da Silva M, Vitolo U, et al.: Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015, 26:v116-25.

Figure Legends

Figure 1: Diffuse neoplastic lenfoid infiltration composed of atypical neoplastic cells with large cytoplasm and hyperchromatic nuclei in the cervical stroma. Endocervical glands are entrapped in the neoplastic infiltration.

Figure 2: Neoplastic cells show diffuse and strong positive staining for CD20.