A rare case of primary vulvar diffuse large B-cell lymphoma: A case report

Moushami Singh[1], Sajan Ngakhusi[1], Akriti Shrestha[1], Prajna Subedi[1], Karuna Khadka[1], and Hari Dhakal[1]

[1]Nepal Cancer Hospital and Research Center Ltd.

August 24, 2024

Title Page

TITLE: A rare case of primary vulvar diffuse large B-cell lymphoma: A case report

Authors:

Singh M[1], Ngakhusi S[1], Shrestha A[1], Subedi P[1], Khadka K[1], Dhakal HP[1]

Department of Pathology and Laboratory Medicine, Nepal Cancer Hospital and Research Center Ltd.

Corresponding author:

Dr. Moushami Singh

MBBS, MD

Department of Pathology and Laboratory Medicine

Nepal Cancer Hospital and Research Center Ltd.

Harisiddhi, Lalitpur

Bagmati Province, Nepal

Email ID: moushamisingh123@gmail.com

Authors :

Dr. Moushami Singh

MBBS, MD

Department of Pathology and Laboratory Medicine

Nepal Cancer Hospital and Research Center Ltd.

Harisiddhi, Lalitpur

Bagmati Province, Nepal

Email Id: moushamisingh123@gmail.com

Responsibilities: Compilation of the contents, editing, and manuscript review

Dr. Sajan Ngakhusi

MBBS

Department of Pathology and Laboratory Medicine

Nepal Cancer Hospital and Research Center Ltd.

Harisiddhi, Lalitpur

Bagmati Province, Nepal

Email Id: drsajan.ngakhusi@gmail.com

Orcid Id: 0009-0007-7483-3530

Responsibilities: Manuscript writing, compilation of the contents, and manuscript reviewing

Dr. Akriti Shrestha

MBBS

Department of Pathology and Laboratory Medicine

Nepal Cancer Hospital and Research Center Ltd.

Harisiddhi, Lalitpur

Bagmati Province, Nepal

Email Id: akritishrestha117@gmail.com

Responsibilities: Manuscript writing, compilation of the contents, and manuscript reviewing

Prajna Subedi

B. Tech in Biotechnology

Department of Pathology and Laboratory Medicine

Nepal Cancer Hospital and Research Center Ltd.

Harisiddhi, Lalitpur

Bagmati Province, Nepal

Email Id: prajna.subediii@gmail.com

Responsibilities: Manuscript writing, compilation of the contents, and manuscript reviewing

Dr. Karuna Khadka

MBBS, MD

Department of Pathology and Laboratory Medicine

Nepal Cancer Hospital and Research Center Ltd.

Harisiddhi, Lalitpur

Bagmati Province, Nepal

Email ID: karunakhadka13@gmail.com

Responsibilities: Manuscript review

Dr. Hari Prasad Dhakal

MBBS, MD, PhD Senior Consultant Pathologist Head, Department of Pathology and Laboratory Medicine Nepal Cancer Hospital and Research Center Ltd. Harisiddhi, Lalitpur, Nepal Email: drhari.dhakal@nch.com.np

Responsibilities: Manuscript review

DATA AVAILABILITY STATEMENT

The data supporting the findings in this case report is available within the article and its supplementary materials.

FUNDING

This case report received no specific grant.

CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest.

ETHICS STATEMENT

None

WRITTEN CONSENT FROM THE PATIENT

Written informed consent was obtained from the patient before the submission of the report. The patient understands that his name and initials won't be mentioned.

DETAILED AUTHORS' CONTRIBUTIONS

SN, AS, and PS collected the required case information, images, slides, and reports, and contributed to writing the original draft of the manuscript. MS, KK, and HPD examined and interpreted the pathology. MS, SN, and AS were involved in conceptualizing and describing the case. MS, SN, AS, PS, KK, and HPD contributed to reviewing and editing the manuscript. All authors read and approved the final manuscript.

TITLE: A rare case of primary vulvar diffuse large B-cell lymphoma: A case report

KEY CLINICAL MESSAGE

Primary vulvar diffuse large B-cell lymphoma is an exceptionally rare entity, presenting diagnostic challenges due to its low incidence and varied clinical manifestations. Despite its rarity, early recognition and treatment can lead to favorable outcomes with low recurrence rates and good long-term survival. We present a rare case of primary diffuse large B-cell lymphoma of vulva in a 78-year-old elderly woman.

KEYWORDS

B-cell lymphoma; Non-Hodgkin's lymphoma; vulva

INTRODUCTION

Non-Hodgkin's lymphomas (NHL) comprises 70–80% of all lymphoma cases.[1] They are generally found in lymph nodes or other lymphoid tissue like the spleen and bone marrow.[2] However, around 20–24% of NHL cases are extranodal and mostly originate from areas like the gastrointestinal tract, lungs, central nervous system, skin, thyroid, and salivary glands.

Although the secondary involvement of the female genital tract, especially the ovaries is common, primary genital tract lymphomas are exceptionally rare, accounting for less than 0.5% of genital cancers and 1.5% of all NHL cases. These tumors are anatomically reported in the following order of prevalence: ovary (49%), uterus (29%), fallopian tube (11%), vagina (7%), and vulva (4%).[2,3]

Diffuse large B cell lymphoma (DLBCL) is a subtype of non-Hodgkin lymphoma that comprises around 30% of total NHL cases. DLBCL can be further classified into three subtypes; germinal center B-cell, activated B-cell, and unclassified subtype.

So far only a couple of dozen cases of DLBCL of vulva are reported in the medical literature and is hence a very rare entity.[4]

We present a rare case of DLBCL of the vulva in a 78-year-old elderly patient.

CASE HISTORY/EXAMINATION

A 78-year-old female patient presented with a history of a small, hard lump on labia majora that appeared in 2022, and according to her, it disappeared after using topical antibiotics for 1 week. However, as per her, one month later it reappeared. The patient is currently under Levothyroxine 100mcg for hypothyroidism. She is G10P4L4A2 and her last childbirth was 44 years ago. Menopause occurred about 40 years ago. The patient provided no family history of carcinoma.

METHODS

Transvaginal sonography was done in another center which revealed a well-defined mass lesion of homogeneous echogenicity measuring 6.0 x 4.0 cm in the anterior vaginal wall completely filling the vaginal lumen with increased intrinsic vascularity. Fine needle aspiration and cytology (FNAC) of periurethral mass done was suspicious of lymphoma. Biopsy of the mass revealed chronic nonspecific inflammation.

Magnetic resonance and imaging (MRI) of the pelvis revealed well defined solid encapsulated smooth outlined lesion measuring 7.0 x 5.1 x 4.8cm in size in the perineal region inferior to the pubic symphysis, extending cranially in between the urethra anteriorly and vagina posteriorly. The lesion is extended up to the bladder neck and anterior vaginal fornix level superiorly and extended up to the introitus inferiorly. Posteriorly, it is abutting the anal canal with a distinct fat plane in between and displacing the bulb of the vestibule and crura of the clitoris. The vaginal lumen is compressed posteriorly by the lesion.

The patient then presented to the gynecology unit of our center for further evaluation and management. On examination, a huge ulcerative growth periurethral mass was noted. Cystoscopy revealed a periurethral mass, with external compression at distal 1 cm of the urethra. Subsequently, a multiple-punch vulvar biopsy was taken. Histomorphological examination of sections revealed show ulcerated tissue revealing infiltrating discohesive sheets of atypical lymphoid cells in the subepithelial stroma. These atypical lymphoid cells exhibit pleomorphism and have a high nucleo-cytoplasmic ratio, large nucleus, irregular nuclear contours, conspicuous nucleoli, and scant cytoplasm. Mitosis noted. Fibrinoid necrosis of vessels seen. **(Figure 1)** IHC analysis was done.

Immunohistochemistry (IHC) analysis showed tumor cells positive for CD20, BCL6, MUM1, CMYC, and BCL2 and negative for CK, CD3, CD10, SOX11, and Ki67 70%. **(Figure 2a-2c)** The overall histomorphological features combined with the immunohistochemical profile were suggestive of Diffuse large B-cell lymphoma, active B-cell immunophenotype.

CONCLUSION AND RESULTS

The patient was then admitted for further management. Her laboratory findings showed an increased level of Lactate Dehydrogenase level of 219 U/L (reference range: 100-210) and the rest findings were within normal limits. Peripheral blood smear was within normal limits. Multi-detector Computed Tomography (MDCT) of the neck and chest revealed bilateral sub-centimeter cervical lymph nodes and prominent mediastinal lymph nodes in the paratracheal, pre-carinal, AP window, and pre-vascular; the largest measuring 1.6x1.7 cm in the pre-carinal region. Bone marrow aspiration and bone marrow biopsy revealed marrow showing no involvement with atypical lymphoid cells.

Subsequently, an R-CVP chemotherapy cycle was initiated which included Inj. Rituximab 500mg on Day 1, Inj. Vincristine sulphate 2 mg on Day 2, Inj. Cyclophosphamide 1000mg on Day 2 and Tablet prednisolone 60mg for Day 1-5.

Following the completion of 6 cycles of chemotherapy, PET CT of the whole body with contrast was done after 2.5 months which revealed ill-defined soft tissue thickening of the vulva/ lower vagina with minimal f-18 fluorodeoxyglucose uptake (Deauville score 2), likely treated disease.

The purpose of this case report is to highlight a highly uncommon and exceptionally rare vulvar condition. Primary vulvar NHL is exceedingly uncommon, which can make its diagnosis challenging if not considered.

DISCUSSION

Based on one of the recent studies, primary vulvar DLBCL is bi-modally distributed between the age group of 25 to 43 and 62 to 79 with a mean age of 58. Our patient is a 79-year-old elderly woman. Clinically, the patient with vulvar DLBCL may present with complaints of tender to non-tender mass with or without ulceration. Erythema, edema, and pruritus may also be present.[4] Our patient presented with the complaint of a hard nodule in the right labia majora, which appeared to be an ulcerative peri-urethral mass on examination.

Since there are only a few reported cases of primary vulvar DLBCL in medical literature, it might be diagnostically challenging. The differential diagnosis for vulvar DLBCL ranges from inflammatory lymphoid conditions (lichenoid dermatoses, extramedullary myeloid cell tumor, Langerhans cell granulomatosis) to carcinomas (Neuroendocrine carcinomas like Merkel cell or metastatic, lymphoepithelioma-like, poorly differentiated squamous cell, Bartholin's gland adenocarcinoma) and other conditions like melanoma, rhabdomyosarcoma, extraosseous Ewing's sarcoma/primitive neuroectodermal tumor, lipoma, and Bartholin gland cyst or abscess.[5] Pelvic MRI emerges as the most effective imaging tool for this purpose.[6,7]

In cases of DLBCL, the typical IHC analysis findings involve large, abnormal lymphocytes that are negative for CD3 but positive for CD20, exhibiting a Ki-67 labeling index surpassing 80%. To determine the cell of origin, staining for CD10, Bcl-6, and MUM-1 is conducted using the Hans algorithm.[8] Confirmation of the double-expression phenotype involves staining for Bcl-2 and c-myc.[9]Additionally, Epstein-Barr virus in situ hybridization staining assists in identifying EBV-positive DLBCL. In some instances, DLBCL may be suspected despite negative findings for CD3 and CD20 in H&E staining. In such scenarios, it's important to entertain the likelihood of a poorly differentiated carcinoma or a small round-cell tumor as part of the standard diagnostic process. Nevertheless, the spectrum of potential diagnoses broadens to include CD20-negative DLBCL and anaplastic large-cell lymphoma (ALCL) when lymphoma is under consideration.[10]

In our case, immunohistochemistry analysis revealed the tumor cells were positive for CD20, BCL6, MUM1, CMYC, and BCL2 and negative for CK, CD3, CD10, SOX11, and Ki67 70%.

The primary treatment used for vulvar lymphoma is typically R-CHOP therapy, sometimes followed by radiotherapy. Recent studies have highlighted the significance of the cell type causing DLBCL, with Activated B Cell (ABC) and Germinal Centre B Cell (GCB) DLBCLs showing varying responses to standard treatment like rituximab and CHOP chemotherapy (R-CHOP). Patients with GCB-DLBCL usually respond well to R-CHOP, while those with ABC-DLBCL may not.[11,12]

In comparison to nodal NHL, genital lymphomas seem to be less aggressive and show a very low incidence of recurrence. The prognosis of the genital lymphomas appears to be very good with a 5-year survival rate occurring between 80 and 90%.[13–15]

REFERENCES

1. Sehn LH, Salles G. Diffuse Large B-Cell Lymphoma. *N Engl J Med* . 2021;384(9):842-858. doi:10.1056/NEJMra20276122. M S, A M, S C, et al. Conservative management in primary genital lymphomas: the role of chemotherapy. *Gynecol Oncol* . 2007;104(2). doi:10.1016/j.ygyno.2006.08.0243. Bagella MP, Fadda G, Cherchi PL. Non-Hodgkin lymphoma: a rare primary vulvar localization. *Eur J Gynaecol Oncol* . 1990;11(2):153-156.4. Ye AL, Willis MS, Link BK, Naridze RL, Syrbu SI, Liu V. Primary diffuse large B cell lymphoma of the vulva—Two new cases of a rare entity and review of the literature.*JAAD Case Rep* . 2018;4(9):962-967. doi:10.1016/j.jdcr.2018.06.0235. Vang R, Medeiros LJ, Fuller GN, Sarris AH, Deavers M. Non-Hodgkin's Lymphoma Involving the Gynecologic Tract: A Review of 88 Cases: *Adv Anat Pathol* . 2001;8(4):200-217. doi:10.1097/00125480-200107000-000026. Shetty AS, Menias CO. MR Imaging of Vulvar and Vaginal Cancer. *Magn Reson Imaging Clin N Am* . 2017;25(3):481-502. doi:10.1016/j.mric.2017.03.0137. Onyiuke I, Kirby AB, McCarthy S. Primary gynecologic lymphoma: imaging findings.*AJR Am J Roentgenol* . 2013;201(4):W648-655. doi:10.2214/AJR.12.89078. Choi WWL, Weisenburger DD, Greiner TC, et al. A new

immunostain algorithm classifies diffuse large B-cell lymphoma into molecular subtypes with high accuracy. *Clin Cancer Res Off J Am Assoc Cancer Res* . 2009;15(17):5494-5502. doi:10.1158/1078-0432.CCR-09-01139. Riedell PA, Smith SM. Double hit and double expressors in lymphoma: Definition and treatment. *Cancer* . 2018;124(24):4622-4632. doi:10.1002/cncr.3164610. Cho J. Basic immunohistochemistry for lymphoma diagnosis. *Blood Res* . 2022;57(Suppl 1):55-61. doi:10.5045/br.2022.202203711. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma.*N Engl J Med* . 2002;346(4):235-242. doi:10.1056/NEJMoa01179512. Clemente N, Alessandrini L, Rupolo M, et al. Primary Non-Hodgkin's Lymphoma of the Vulva: A Case Report and Literature Review.*Medicine (Baltimore)* . 2016;95(10):e3041. doi:10.1097/MD.0000000000000304113. Harris NL, Scully RE. Malignant lymphoma and granulocytic sarcoma of the uterus and vagina. A clinicopathologic analysis of 27 cases. *Cancer* . 1984;53(11):2530-2545. doi:10.1002/1097-0142(19840601)53:11<2530::aid-cncr2820531127>3.0.co;2-j14. Vang R, Medeiros LJ, Ha CS, Deavers M. Non-Hodgkin's lymphomas involving the uterus: a clinicopathologic analysis of 26 cases. *Mod Pathol Off J U S Can Acad Pathol Inc* . 2000;13(1):19-28. doi:10.1038/modpathol.388000515. Stroh EL, Besa PC, Cox JD, Fuller LM, Cabanillas FF. Treatment of patients with lymphomas of the uterus or cervix with combination chemotherapy and radiation therapy.*Cancer* . 1995;75(9):2392-2399. doi:10.1002/1097-0142(19950501)75:9<2392::aid-cncr2820750932>3.0.co;2-y**FIGURE LEGENDS**

Figure 1: Hematoxylin and eosin-stained section show discohesive sheets of atypical lymphoid cells have large nucleus, irregular nuclear contours, conspicuous nucleoli and scant cytoplasm. Mitosis noted. (400x)

Figure 2a: IHC shows tumor cells are positive for BCL2

Figure 2b: IHC shows tumor cells are positive for CD20

Figure 2c: IHC shows tumor cells are negative for Ki67