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CASE REPORT

Burkitt's Lymphoma of the Uterine Cervix in a Woman with Advanced HIV Disease: A Case Report on Challenges with Its Management in a Low Resource Setting

Lisa Erin de Miranda[1,2], Bernard Uzabakiriho[1,2], Melanie Louw[3], Nnabuike Chibuoke Ngene[1,2]

[1]Department of Obstetrics and Gynaecology, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; [2]Rahima Moosa Mother and Child Hospital, Johannesburg, South Africa; [3]School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

Correspondence: Bernard Uzabakiriho; Lisa Erin De Miranda, Rahima Moosa Mother and Child Hospital, Fuel Road & Oudtshoorn St, Coronationville, Johannesburg, 2112, South Africa, Tel +27114709095, Email bernard.uzabakiriho@wits.ac.za; liskrook@gmail.com

Background: Burkitt's lymphoma (BL) affecting the female genital tract is rare.

Objective: The aim of this paper is to report BL of the cervix in an HIV-positive patient to discuss the fatality of the condition and ways to mitigate it through advocacy for improved health care delivery in resource limited settings.

Methods: The patient was a 29-year-old woman, Para 1, with abnormal vaginal bleeding for a month and living with HIV and had a CD4 of 26 cells/μL. The histological examination of the cervical biopsy confirmed an extra-nodal BL. She had International Federation of Gynecology and Obstetrics (FIGO) stage 3B cervical cancer based on presence of hydronephrosis and pelvic wall involvement. The patient was reviewed at the oncology multidisciplinary meeting and required chemoradiation. There was delay in her management due to a long waiting list for chemoradiation at oncology unit in the referral center and the patient demised 43 days after diagnosis and did not receive the treatment.

Results: This case suggests that women living with HIV who have BL should be fast-tracked for treatment as HIV viremia may worsen the prognosis of the malignancy. Following the encounter with the index patient an advocacy action plan has been made by the oncology multidisciplinary team to prioritize the treatment of women with aggressive histological types of cervical cancer.

Conclusion: A long waiting list for chemoradiation in low resource settings may delay management of advanced BL of the cervix. Inadequate cervical cancer screening and delays in diagnosis are other barriers to the care of women with aggressive cervical cancers in low resource settings. Systemic changes in healthcare delivery are therefore required in many low resource settings. Advocacy for patients particularly those with aggressive diseases using the index case as a point of reference is ideal and should be promoted in resource-limited settings to improve health care delivery.

Keywords: Burkitt's lymphoma, cervical cancer, chemoradiation, delay in treatment, non-Hodgkin's lymphoma, patient advocacy

Introduction

Burkitt's lymphoma (BL) is a rapidly growing and highly aggressive B cell non-Hodgkin's lymphoma (NHL) which affects almost every organ system.[1] The World Health Organization (WHO) classifies BL into three clinical subtypes: endemic, sporadic and immunodeficiency-associated. This classification did not change in 5th edition of WHO classification of haematolymphoid tumours.[2] The three clinical subtypes are identical histologically, and their definition is partially based on their pattern of perennial distribution in various geographical settings and the immune status of the patients.[3] Sporadic lymphoma most commonly involves the abdomen and pelvis.[1] The endemic type is associated with either malaria or Epstein-Barr virus (EBV).[4] Immunodeficiency-associated BL is mainly found in people living with HIV, but may also occur less frequently in organ transplant recipients and patients with congenital immunodeficiency.[1]

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HIV-positive patients with BL usually have CD4 counts >200 cells/μL, and the malignancy mainly involves the lymph nodes, bone marrow and central nervous system.[5] Primary lymphoma of the female genital tract is rare and belong to the group of sporadic extra-nodal lymphoma.[6] Extra-nodal lymphomas of the female genital tract account for approximately 1% of all NHL.[7] Of note, the WHO classifies the neoplasm of the mature lymphoid system into B-cell, T-cell, and Hodgkin lymphomas.[8] The diffuse large B-cell lymphomas are the most common histological subtype of extra-nodal lymphoma.[9] A case series of 147 genital tract NHL found 7.5% to be isolated from the cervix as primary or secondary lesions.[10] The age-standardized incidence of cervical cancer in 2020 was 13·3 cases per 100000 women-years (95% CI 13·3-13·3).[11] However, it has also been reported that 0.22% of cervical cancer cases are due to primary lymphoma.[12] Nonetheless, a major significant challenge with comorbid occurrence of BL and HIV is that delays often occur in their management in low resource settings despite the fatal nature of these conditions. Recently, 9.4 weeks' time-to-chemoradiation for cervical cancer was reported in South Africa.[13] This challenge is more likely in the public rather than the private hospitals and other barriers to care in the former are delays in transporting patients, security threats by criminals, overcrowding of health care facilities, inadequate emergency medical services, insufficient drugs and supplies, and shortage of experienced health care professionals.[14] Other limitations specific to oncological services are poor coverage of cervical cancer screening and delays in diagnosis which may be due to patient-, healthcare professional- and administrative-factors.[14] In the present case report, we describe BL of the cervix in an HIV-positive patient to discuss the fatality of the condition and ways to mitigate it through advocacy for improved health care delivery in resource limited settings. To the best of our knowledge, this case is crucial being the first case report on BL of the cervix in a patient with advanced HIV infection (with a low CD4 count).

Case Presentation

A 29-year-old woman, Para 1, with abnormal vaginal bleeding of one-month duration presented to the gynecology outpatient department of a level 2 hospital. She was HIV positive, commenced on antiretroviral treatment following diagnosis, but had defaulted the antiretroviral treatment for one month when she became ill with vaginal bleeding, resulting in virological and immunological failures (viral load 37400 copies/mL and CD4 count 26 cells/μL). Of note, it was unclear when the patient first started showing HIV symptoms. However, she was diagnosed with HIV about a year prior to presentation. Physical examination revealed a large mass on the cervix measuring 8 × 8 cm extending to the parametrium and to the pelvic side walls bilaterally. There was bleeding on contact and foul-smelling vaginal discharge. Ultrasonography detected a bulky cervix and bilateral hydronephrosis. The patient was clinically diagnosed with cervical malignancy stage 3B. She was recommenced on antiretroviral therapy with a treatment change from TLD (Tenofovir-Lamivudine-Dolutegravir combination) to a preferable renal friendly regimen (Lamivudine-Abacavir-Dolutegravir combination). A punch biopsy of the cervix was performed, and the histopathological report revealed the diagnosis of an extra-nodal BL. The immunohistochemical and in situ hybridization confirmed the diagnosis, with CD20, CD75a, CD10, PAX5 and Bcl-6 positive. In addition, the CD44 and c-Myc were positive, with the EBER-ISH demonstrating focal positivity. The Ki67 demonstrated a proliferation index of almost 100% and PAX5 moderately positive BCL6. Figure 1 shows the histopathological images. She had white cell count of 2.67 $x10^9$/L, haemoglobin of 5.7g/dl and platelet count of 71 × 10^9/L. Results of other investigations were serum creatinine 187 mmol/L, urea 11.1 mmol/l, albumin 21 g/l, aspartate transaminase 41 U/l and alkaline phosphatase 100 U/l.

Following histological confirmation of the diagnosis and review at an oncology multidisciplinary meeting, she spent 43 days waiting to start treatment at oncology unit. The delay was due to long waiting list. This delay exceeded the 48 hours waiting period during which oncological treatment for BL should commence following diagnosis.[4] The treatment plan was chemo-radiation therapy, and the patient gave written informed consent for the case to be published. However, she demised in the gynaecological ward on the 43rd day while waiting to start the treatment. During the 43 days, further imaging could not be performed due to poor functionality of the available CT and MRI machines. In addition to antiretroviral therapy, the patient received other supportive care such as blood transfusion and analgesia. Again, the number of days between the diagnosis of the BL and her death was 43 days. Histopathological postmortem was not performed as the diagnoses (BL and retroviral disease) were known. We reckon that the main primary cause of death is challenging to assign because of the multiple principal diagnoses.[15,16] Because BL has rapid progression and

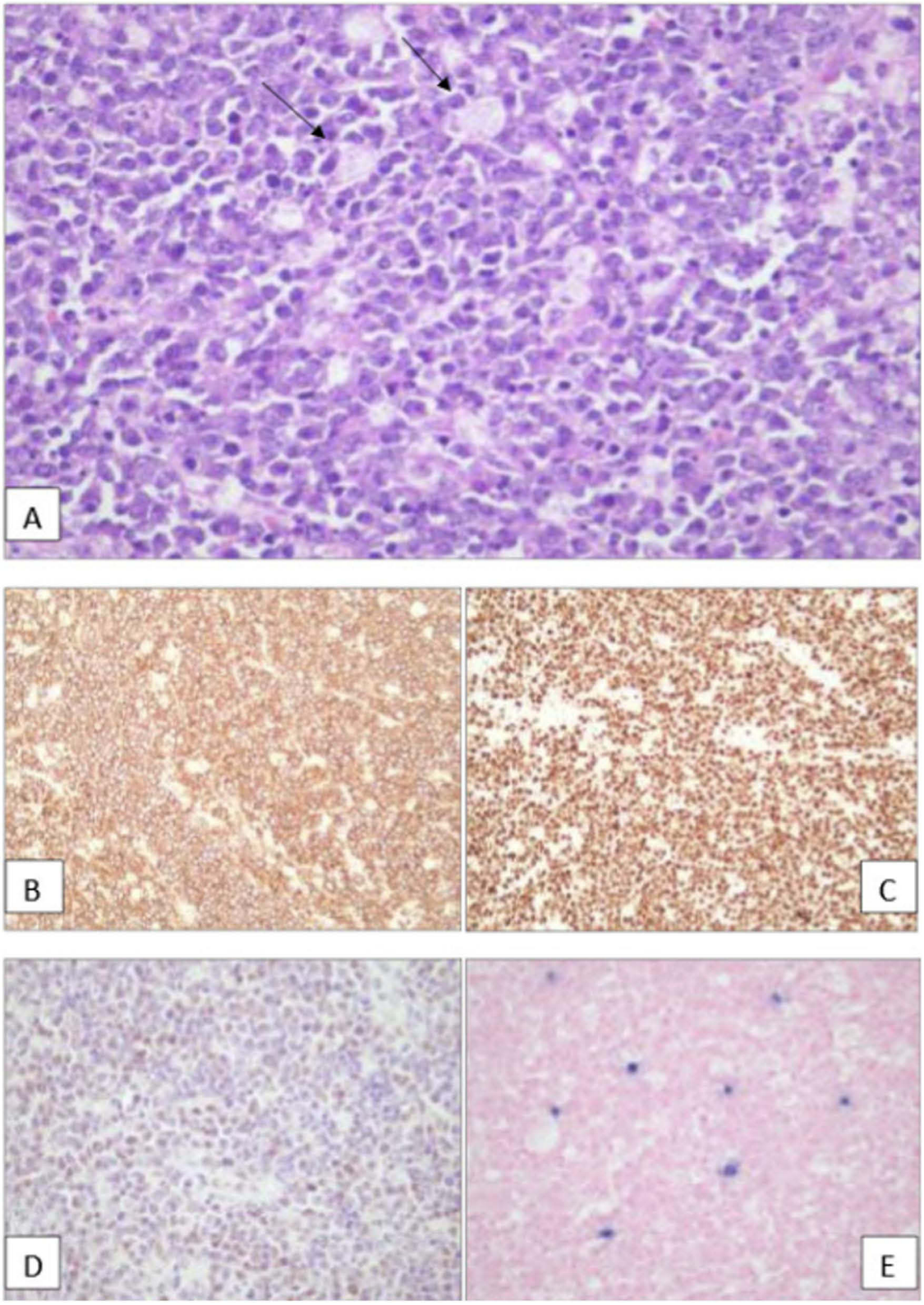

Figure 1 Hematoxylin and Eosin (40x) stained section of biopsy of the cervix with "starry sky" appearance (**A**); CD20 immunohistochemical marker in tumour cells (**B**); Ki67 antibody (20x) demonstrating proliferation index of almost 100% (**C**); c-Myc staining in nuclei of tumour cells (**D**); EBER-ISH present in some of the tumour cells (**E**). Abbreviations: Epstein-Barr virus Encoding Region in situ hybridization (EBER-ISH).

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high mortality rate in persons living with HIV particularly with high viral load,[17] the attending physician certifying the death assigned BL as the most likely cause of death. However, the secondary cause of death was multiple organ failure (renal and haematological inclusive).

Discussion

Non-Hodgkin's lymphomas are second to Kaposi sarcoma among AIDS-defining cancers in patients living with HIV.[17] Additionally, the BL is the second most common subtype of HIV-associated NHL and the first being diffuse large B-cell lymphoma.[18] The term "AIDS-defining lymphoma" refers to aggressive B-cell lymphoma occurring in patients with HIV.[19] A study on AIDS-related BL in the United States demonstrated that the risk for BL declines sharply at very low CD4 count.[3] Specifically, it is also known that the risk for BL peaks at CD4 count above 200 cells/μL, implying that its occurrence may require functional CD4 lymphocytes.[3] It is therefore contradictory that our patient's BL presented during the advanced stages of HIV disease with a CD4 count of 26 cells/μL. Perhaps a different pathogenic pathway occurs in patients with advanced HIV disease although this is difficult to explain and should be a future research agenda. However, it may be because AIDS-defining cancers can generally develop at any level of CD4 count.

The etiology and pathogenesis of lymphomas of the uterine cervix is unknown because few cases have been reported in the literature as the disease occurs rarely. However, chronic inflammation of the cervix has been associated with the disease.[20] The patients typically present with vaginal bleeding, pain and dyspareunia as well as pathological Papanicolaou test or cervical biopsies.[21] This was consistent with the presentation in the index patient. Again, contrary to other forms of HIV-associated NLH, HIV-associated BL occurs more commonly in patients with higher CD4 counts and correlated with cumulative HIV viraemia.[22] It has also been reported that people infected with HIV have a 10–20% lifetime risk of developing BL, irrespective of antiretroviral treatment.[22] HIV viraemia worsens the prognosis of BL.[22] Therefore, irrespective of the CD4 count, once BL has developed, a high HIV viraemia is associated with rapid progression and poor prognosis of the malignancy. One of the suggested pathogenic mechanisms is the chronic antigen stimulation of B-cells by chronic HIV viraemia.[23]

Notably, 80% of cervical and uterine NHL are primary malignancies.[8] The inability to perform further imaging made it difficult to determine the primary origin of the BL in this case. However, the uterus appeared normal on ultrasonography. Certainly, CT scan or MRI is a preferred imaging modality to exclude myometrial involvement.[24] Additionally, the pancytopenia that the woman had was most likely due to HIV (given her markedly low CD4 count). However, we are aware that leukemia can also be a cause of pancytopenia and requires exclusion before concluding that the BL is primarily from the cervix.[25]

Following diagnosis of BL, the disease is preferably staged using the International Federation of Gynecology and Obstetrics (FIGO) system.[26] The oncological treatment is according to the stage of the malignancy. Early cervical cancers (stages 2A and below, but preferably those less than 1B2) are managed surgically while advanced diseases are managed using concurrent chemoradiation.[27] Therefore, the plan to administer chemoradiation to the patient was appropriate.

Understandably, the rarity of BL of the cervix makes the optimal treatment arguably undefined. Given that intensive chemotherapy is effective in general cases of BL, this may be an alternative treatment option in patients with advanced cervical BL if chemo-radiation is not readily available. In general cases of HIV negative adults with BL, for instance, two-year overall survival rate following intensive chemotherapy regimens are hyper-CVAD (hyper-fractionated cyclophosphamide vincristine, doxorubicin, and dexamethasone) 83%, Berlin-Frankfurt-Münster (BFM) protocol 82%, and CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, methotrexate, ifosfamide, etoposide, and cytarabine) 69%.[28] In HIV positive adults, the choice of chemotherapy depends on presence of comorbidity, patient's overall health and CD4 count; therefore, commencing antiretroviral therapy for HIV is crucial. Some of the intensive chemotherapy regimens for BL that may be used in HIV positive patients are CODOX-M/IVAC, hyper-CVAD, and LMB86 (Lymphome Malin de Burkitt 86).[29–31]

Nonetheless, a systematic review and meta-analysis by Kang et al in 2022 showed that the prognostic features of cancer of the cervix are clinicopathological factors which include lymph node involvement, lymph-vascular space invasion, parametrial invasion, FIGO stage, tumor volume, tumor size, tumor grade, histological grade, cell type, squamous cell carcinoma antigen level, hemoglobin level, leukocytosis, thrombocytosis, platelet-to-lymphocyte ratio,

Table 1 Highlights

Serial No	Key Message
1	Burkitt's Lymphoma (BL) of the uterine cervix is rare
2	In people living with HIV, BL typically occurs at CD4 >200 cells/μL
3	Occurrence of BL of cervix in a patient with advanced HIV has not been reported
4	At a high viral load, the occurrence of BL signals rapid disease progression
4	Oncology units should prioritize the care of these women.

neutrophil-to-lymphocyte ratio, resection margin, and the patient's age.[32] However, the poor prognostic features of BL generally are age ≥ 40 years, central nervous system involvement, lactate dehydrogenase three times above the normal limit, and Eastern Cooperative Oncology Group (ECOG) Performance Status ≥2.[33] However, other authors have reported advanced BL stages (based on the Ann Arbor system), age >60 years, and black race as poor prognostic features of BL.[34] Additionally, a nomogram for prognostication has been developed and it is based on the following characteristics: age, race, primary site, stage and whether or not the patient receives chemotherapy.[35]

In the health facility where the woman was managed, there is a high burden of cancer of the cervix due to high HIV prevalence, poor coverage of preventive and screening programs for the cancer. As a result, many women develop cervical cancer and present at advanced stages of the disease. Therefore, there is a long waiting list for cervical cancer treatment amidst insufficient oncology resources such as radiotherapy. Following the demise of the index patient, plans was made by the oncology multidisciplinary team to prioritize the treatment of women with aggressive histological types of cervical cancer such that a specific day of the week will be reserved for their treatment at the referral center. We hope that this will complement the national preventive and screening programs which have been upscaled. The health ministry has also undertaken to expand the oncology treatment centers to relieve the enormous pressure on the existing services. We believe that this advocacy using the index case as a point of reference is ideal and should be promoted in resource limited settings to improve health care delivery. The key messages are provided in Table 1.

Conclusion

Burkitt's lymphoma of the uterine cervix occurring in women living with HIV is an aggressive malignancy. The treatment of women with this type of malignancy should be fast-tracked to improve the quality of life and survival.

Ethical Approval

The patient gave written informed consent for the case to be published. Institutional approval was not required to publish the case details. In our jurisdiction (South Africa), a single case report (not more than 3 patients in number) are exempted from ethical approval. Source: South African National Department of Health. South African Ethics in Health Research Guidelines: Principles, Processes and Structures 2024. page 57. Available from: https://www.witshealth.co.za/Portals/0/2024/Documents/NDoH-2024-Health-Research-Guidelines-3rdEdition-v0.1.pdf (Accessed 30 December 2024).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflict of interest to declare in this work.

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