Case report

Mantle cell lymphoma in HIV infection: First reported case in Sri Lanka

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Abstract

Non Hodgkin's Lymphoma (NHL) in Human Immunodeficiency Virus (HIV) infection is an Acquired Immunodeficiency Syndrome (AIDS) defining malignancy which can present with generalized lymphadenopathy. HIV itself has a 60-to-200-fold increase in risk for NHL, and most of the NHL in HIV infection are aggressive B cell-type with wide histological variation. Primary Central Nervous System lymphoma (PCNSL) and Burkitt lymphoma (BL) are the two most common types of Diffuse Large B-cell Lymphomas (DLBCL) associated with HIV infection. Mantle Cell Lymphoma (MCL) is a rare and aggressive form of NHL arising from the "Mantle Zone" of the lymph nodes. MCL is not a common type of NHL described in HIV infection. We report a case of MCL in 34-year-old HIV-infected women presented with generalized lymphadenopathy and hepatosplenomegaly in Sri Lanka. Failure to adhere to antiretroviral therapy leading to uncontrolled HIV viral load and low CD4 count as risk factors for developing rare MCL is discussed.

Keywords: Human Immunodeficiency Virus, Lymphadenopathy, Mantle cell lymphoma, Non Hodgkin's Lymphoma, Sri Lanka

Funding: None
Competing interest: None
Received: 04.08.2023 **Accepted revised version:** 21.04.2024 **Published:** 30.04.2024

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Cite this article as: Ratnayake C. *et al*, Mantle cell lymphoma in HIV infection: First reported case in Sri Lanka. Anuradhapura Medical Journal 2024; 18 (1): 23-28, DOI: https://doi.org/10.4038/amj.v18i1.7796

Introduction

Non Hodgkin's Lymphoma (NHL) in Human Immunodeficiency Virus (HIV) infection is considered an Acquired Immunodeficiency Syndrome (AIDS) defining malignancy, often reported in the late stage of HIV when the immune system is severely damaged. HIV-positive patients have a 60 to 200-fold increase in risk for NHL [1,2]. Most NHL in HIV are aggressive B cell type and histologically can have wide variation. Common HIV-associated lymphomas are diffuse large B-cell Lymphoma (DLBCL), which includes Primary CNS Lymphoma (PCNSL) and Burkitt Lymphoma (BL). Other less common types reported in HIV include

Primary Effusion Lymphoma (PEL), Plasmablastic Lymphoma and classic Hodgkin lymphoma (HL) [1]

Mantle Cell Lymphoma (MCL) is a rare, aggressive form of NHL arising from the "Mantle zone" of the lymph nodes and not commonly reported in HIV infection.

Case report

A 34-year-old HIV-infected woman, while on antiretroviral therapy (ART) presented with generalized lymphadenopathy to the Sexual Health Center, Anuradhapura, in October 2021. She was first diagnosed with HIV in 2011 and had a baseline CD4 count of 295 cells/ul. She received Zidovudine (AZT), Lamivudine (3TC) and Nevirapine (NVP) as the first line ART regimen, but later, NVP was replaced with Efavirenz (EFV) due to severe allergic reaction.

Her adherence to ART was poor, and there was a documented virological failure in 2016, with a high viral load of 26679 copies/ml and intermediate resistance to EFV. A second-line ART regimen with Tenofovir(TDF), Emtricitabine (FTC) and Atazanavir/ritonavir (ATV/r) helped to get the viral load down to 4700 copies but never reached the undetectable level. The patient continued to default treatment despite all supportive counselling.

In 2021, the patient presented with enlarged cervical lymph nodes, which were firm and non-tender and subsequently became generalized, associated with fever and hepatosplenomegaly. (Figure 1) At the time, the HIV viral load was recorded as 1.38 X104 copies/ml, which continued to increase to 3.08 X104 copies/ ml, with a CD4 count of 273 cells/ul (Table 1).

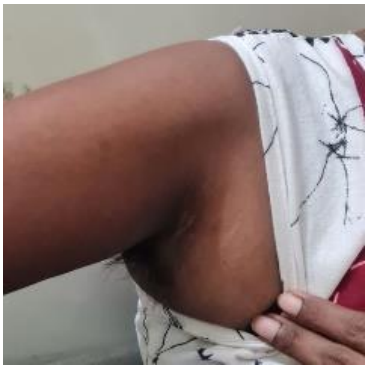

Figure1: The enlarged axillary lymph nodes, as part of generalized lymphadenopathy

Her chest X-ray showed bilateral hilar and para-tracheal lymphadenopathy without lung parenchymal lesions or pleural effusions (Figure 2). Contrast-enhanced CT scan showed extensive lymphadenopathy and moderate hepatosplenomegaly (Figure 3). All the cervical nodal groups from level I to VI were involved bilaterally. Axillary, hilar and mediastinal lymph node masses were seen in the chest with no lung parenchymal lesions or pleural effusion. Extensive abdominal lymph node masses involving para-aortic, celiac, mesenteric, iliac, and inguinal groups encase the vessels. However, there was no evidence of bowel wall involvement or ascites. All lymph nodes showed homogeneous enhancement with no cavitation, necrosis or calcification in favour of untreated lymphoma over tuberculosis or Castleman's disease. Extensive iliac and bilateral inguinal nodal involvement and the absence of lung parenchymal lesions and ascites also favoured the lymphoma than tuberculosis.

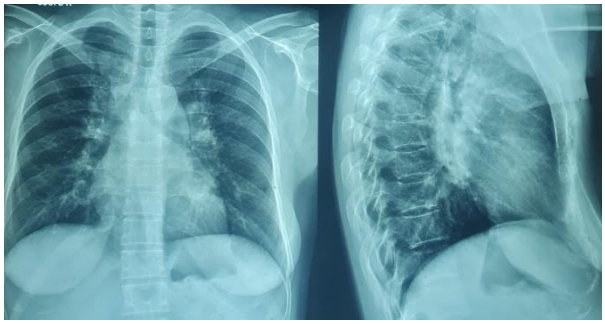

Figure 2: Chest X-ray showing bilateral hilar and para-tracheal lymphadenopathy

A total white cell count of 19 $X10^3$ with relative lymphocytosis with low Hb and platelet count strongly indicated lymphoproliferative disease in our patient. Blood picture showed atypical lymphoid cells, high nuclear/cytoplasm ratio, increased rouleaux formation, elevated LDH, calcium levels and prominent monoclonal gamma globulins in serum electrophoresis further suggested lymphoproliferation pushing diagnosis more towards AIDS-related malignancies. At this point, Multicentric Castleman's Disease(MCD) and NHL were at the top of the list of differential diagnoses. However, positive antibodies for Epstein Bar virus was a strong clue for NHL.

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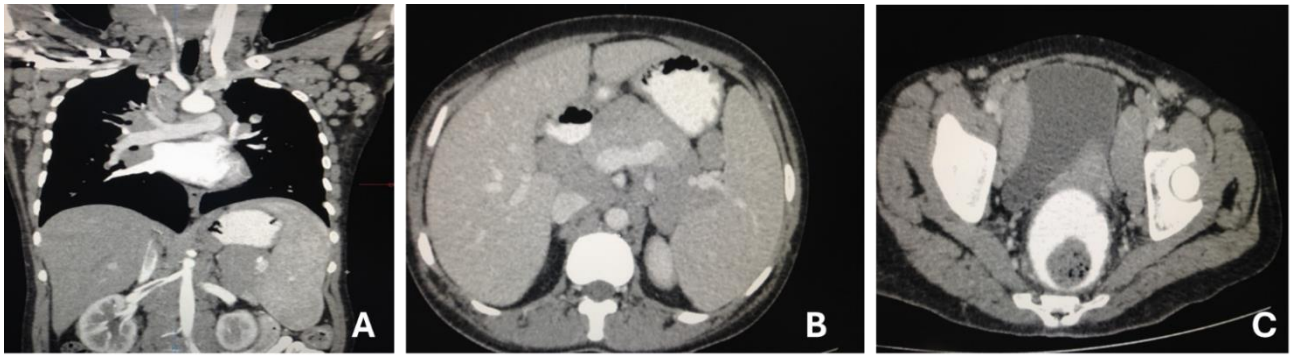

Figure 3: CT Scan of the thorax and abdomen: A, Coronal image showing bilateral cervical, axillary, hilar and mediastinal lymphadenopathy and moderate hepatosplenomegaly; B, Axial image showing extensive para-aortic, celiac and mesenteric lymphadenopathy; C, Axial image with iliac and bilateral inguinal lymph adenopathy

Table 1: Haematological, biochemical, virological and other investigations of the patient at the acute presentation (October 2021)

Test	**Result (normal range)**
CD4 count	273 cells/ul
HIV Viral Load	3.08 X 104 copies/ml
Full Blood Count	21X 103 (4.00-10.00) neutrophil –19% lymphocyte-72.5%
Hb	8.1g/dl (11.0-17.0)
Platelet Count	69X103 (150.0-400.0)
C- Reactive Protein (CRP)	111.46mg/l(0.00-5.00)
Liver Function Tests (LFT)	SGPT -5U/L (13-40) SGOT-26U/L (10-35) ALP-58U/L(30-120) Albumin-28g/L(35-52) Globulin-86g/L(25-35), GGT-17U/L(7-50)
Serum creatinine	74umol/L(60-120)
Sodium	134mmol/L(135-148)
Potassium	3.8mmol/L(3.6-5.0)
Total calcium	2.5mmol/L(2.15-2.65)
Corrected calcium	2.78
Toxoplasma antibodies IgM and IgG	both negative
Cyto Megalo Virus (CMV) antibodies	IgM- equivocal, IgG- positive
Epstien Bar (EB) virus antibodies IgM and IgG	both Positive
Lactate Dehydraganate (LDH)	348U/L(225-450)
Blood Picture	Suspected lymphoproliferative disorder With numerous atypical lymphoid cells with high nuclear/cytoplasm ratio. Low neutrophils. red cells normochromic, normocytic and hypochromic with increases Rouleau formation. Platelets were seen with many aggregates.
Protein electrophoresis	Monoclonal band is seen in the gamma region with a paraprotein level of 19.6g/l. Immunoassay showed Kappa light chain level of 339.9mg/l(2.37-20.73)
Ultra Sound Scan(USS) Abdomen	Hepatosplenomegaly with enlarged intra abdominal lymphnodes

Lymph node biopsy and histology showed effaced architecture with follicles and expanded mantle zones (Figure 4; A and B), which suggested MCL. Further diffuse proliferation of small to medium-sized lymphoid cells is evident with vesicular chromatin.

Immunochemistry studies concluded the features consistent with Mantle cell lymphoma Classic variant with the following findings: (Figure 4; C and D) cells diffusely and strongly positive for CD20 markers indicating B cell lymphoma; Positive CD3 in reactive lymphoid cells; BCL2 –Positive in CD20-positive cells; CD5- positive for tumour cells; CD10 negative in tumour cells; CD23 highlights the residual follicular dendritic meshwork of germinal centres; Cyclin D1 strongly positive in tumour cells; CD138-Positive for some scattered cells at the periphery and Ki 67 index to be 35%.

Genetic confirmation of chromosome 11 and 14 translocation was not possible due to a lack of facilities at the local level at the time of writing.

It was decided to start standard chemotherapy before the bone marrow biopsy and CT scan, considering the clinical situation and Covid 19 pandemic, where delays were unavoidable for the best interest of the patient. The patient completed a full course of standard chemotherapy with R- CHOP (Rituximab with Cyclophosphamide Doxorubicin, Vincristine and Prednisolone) and recovered fully without recurrences at the end of one year.

Discussion

MCL is a rare, aggressive variety of NHL reported in HIV-infected women with uncontrolled viral load and low CD4 count. Histology and imaging studies were useful in diagnosing and correcting chemotherapy in time, saving the patient.

NHL is an AIDS-defining malignancy, and low CD4 has an increased risk of 60-200 than that of HIV-negative [1].

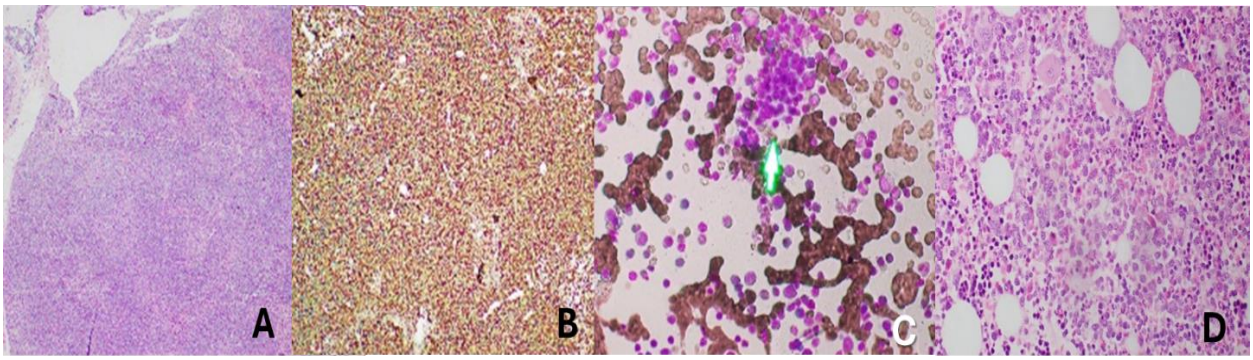

Figure 4: A, The lymph nodes show effaced architecture with expanded mantle zones and diffuse areas (x40); B, The cells are diffusely and strongly positive for cyclin D1 (x40); C, Bone marrow aspirate – showing collections of abnormal lymphoid cell; D, Bone marrow trephine-show focal and interstitial infiltration of abnormal lymphoid cells and few scattered plasma cells.

Pathogenesis of B cell lymphomas in HIV infection is related to chronic antigen stimulation, which leads to polyclonal B-cell expansion and the later emergence of uncontrolled monoclonal B-cell proliferation. Circulating free light chains are elevated in HIV-infected patients who have a high risk of developing lymphoma and could be a useful marker to identify HIV patients at risk [1].

Oncogenic viruses have a role in the pathogenesis of certain types of NHL. EB virus (EBV) is the commonest and is reported in 40% of NHLs. Almost all PCNSL, 30-50% of BL and 50% of plasmablastic lymphomas are known to be associated with EBV. Human Herpes Virus 8 (HHV-8) is associated with almost all cases of PEL in HIV infection [1,2]

MCL is a rare NHL which accounts for 3-10% of all NHLs. It is common among the 35-85 year age group

with a median age of 68 years. Male to female ratio of MCL occurrence is 3:1 [3]. The most common initial presentation is lymphadenopathy 75% of the time [4] Patients may also present with B symptoms (loss of weight, fever, night sweats reported in 40%), Hepatomegaly (30%), splenomegaly (60%) and nervous system, lungs and gastrointestinal involvement are less common [2].

Pathogenesis of MCL is associated with a genetic abnormality, which is a reciprocal translocation between chromosomes 11 and 14 (11;14) and is observed among 85% of patients with MCL [2]. This translocation results in short segments of chromosome 11 and chromosome 14 exchanging places at the site of the cyclin D1 gene on chromosome 11, resulting in an overproduction of cyclin D1, a protein that has a major role in cell cycle regulation. Cyclin D1 controls the progression of cells from G1 phase to S phase by activating cyclin-dependent kinases. Overproduction of D1protein leads to uncontrolled cell division and accumulation of a large number of cells in lymph nodes, including tonsils. Neutropenia, anaemia and thrombocytopenia are results of marrow infiltration. Leukocytosis could be a feature of the disease growing in peripheral blood vessels in the leukaemic phase [2]. MCL has not been reported as a common variant of HIV infection.

Characteristic histological features of MCL are described as an expansion of the Mantle Zone of the lymphoid follicles with atypical lymphocytes, which contain irregular and indented nuclei with coarse chromatin and increased mitosis. The blastic subtype is more aggressive than the classic type. Immunophenotyping is useful in differentiating MCL from other small B-cell lymphomas. In MCL, cells are positive for CD5 and pan B cell antigens(CD20, CD22) and lack the expression of CD10 and CD23. Characteristically, cyclin D1 is overexpressed [3].

Cytogenetic studies are useful in demonstrating chromosome translocation between chromosomes 11 and 14, which is the characteristic genetic predisposition for MCL [3]. Imagine studies and bone marrow biopsy are useful in staging the disease. Level of LDH may correlate with tumour burden [3].

Prognosis depends on the stage and subtype of MCL, and recommended standard chemotherapy includes R-CHOP (Rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone) in most practices. Rituximab is a monoclonal antibody that destroys cells with CD20. [3,4] initial chemotherapy is combined with autologous stem cell transplantation where the patient's own stem cells are collected, stored then returned to the patient after chemo. Stem cell transplantation enhances the response to therapy and prolongs the remission. Relapses are common, and median survival is 5 to 7 years [3,4]. Difference in treatment response between HIV-positive and HIV-negative has not been described.

The exclusion of Multicentric Castleman's Disease (MCD) which is a lymphoproliferative disease found in higher numbers in HIV with low CD4 and present with similar symptoms of generalized lymphadenopathy fever and hepatosplenomegaly is also important. MCD has a strong association with HHV 8, and histology is typically described as having an onion skin appearance due to the concentric arrangement of lymphocytes, which helps differentiate it from mantel cell lymphoma [5]. Opportunistic infections in HIV, such as *Mycobacterium tuberculosis*, *Mycobacterium avium* complex(MAC) and disseminated fungal infections, are possibly differential diagnoses. [6-8] Inability to maintain a good CD4 count and controlled viral load with ART in HIV are risk factors for developing NHL, including rare varieties of NHL in HIV.

Our patient's poor adherence to ART would have been the main reason for her low CD4 count and high viral load, which in turn made her at risk of developing MCL. Therefore its important to maintain a good adherence to ART throughout in order to protect the immune system and prevent NHLs. Further, when HIV patients with low CD4 count present with lymphadenopathy and B symptoms, investigations should be directed to exclude NHL, including rare varieties.

Acknowledgement

Dr Thanuja Vitharana and the staff of the sexual health clinic, Anuradhapura are acknowledged for their help.

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