Case Report

HIV Associated Diffuse Large B-Cell Lymphoma: A Case Study And Literature Review

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ABSTRACT

Human immunodeficiency virus (HIV)-associated lymphomas remain a significant cause of morbidity and mortality, particularly in resource-limited settings. Aggressive B-cell lymphomas may present with extranodal involvement, constitutional symptoms, and multiple co-morbidities, often resulting in delayed diagnosis and poor outcomes. Early recognition and multidisciplinary management are essential for improving survival. The management of lymphoma in HIV rests on three key pillars Combined antiretroviral therapy cART, supportive care and chemoimmunotherapy.

Keywords: HIV-associated lymphoma, aggressive B-cell lymphoma, antiretroviral therapy, immunohistochemistry, chemotherapy; central nervous system involvement, HIV/AIDS

INTRODUCTION

The Human Immunodeficiency Virus (HIV) is a global health problem; as of 2020, 1.5 million people were newly infected and 37.7 million people were living with HIV (PLWHIV) worldwide. In addition, nearly 680,000 people died from diseases associated with Acquired Immunodeficiency Syndrome (AIDS)[1,2]. HIV infection increases the risk of malignancy. More than 28% of HIV-related deaths are attributed to malignant tumors, and a significant proportion of HIV-infected people are eventually diagnosed with acquired immunodeficiency syndrome (AIDS)-related lymphoma[3].

Lymphomas develop in approximately 6% of HIV-positive patients, who are estimated to have a 100–200-fold higher risk of lymphoma and as much as a 1000-fold higher risk of primary cerebral lymphoma (PCL). Lymphoma is the second most prevalent malignancy related to the HIV infection.[4]

The pathogenesis of lymphoma development in the course of HIV infection is complex and not fully understood. Key risk factors however are low CD4 levels, a high HIV load and advanced age. The main factor enhancing the development of malignancy is clonal B-cell proliferation, which is a consequence of stimulation with viral antigens. The duration of the HIV infection is directly related to the increased risk of lymphomas.[4]

We present a case of diffuse large B-cell lymphoma in a known HIV patient who presented with a 6 months history of jaw swelling.

CASE PRESENTATION

The patient was a 61year old male custom officer. Whose presenting complaints were those of jaw and cheek swelling of 6 months prior to presentation. There was history of weakness, headaches, two episodes of convulsions, occasional palpitations, moderate weight loss but no drenching night sweats, no cough or contact with persons with chronic cough. No bone pains, mucosal bleeds or pruritus. The jaw and cheek swelling rapidly increased to the current size and ulcerated spontaneously at the top.

He was a known Retroviral disease (RVD) patient diagnosed about 3 years earlier and commenced on HAART and was compliant with medication. He was also a known Hypertensive for over 10 years, said to be complaint on an unknown drug combination. Review of other systems were essentially normal.

Physical examination findings revealed severe pallor and a left sided jaw swelling measuring 18cm x 17cmx 10cm, hard in consistency, tender with a foul-smelling necrotic ulcer with everted edges. Further examination revealed a poor blood pressure control: BP – 180/90 mmHg.

His Full blood count findings were as follows; PCV – 17%, TWBC – $9X10^9$/L, PLT – $423X10^9$/L.

Other available investigation results were;

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1. Biopsy and histology report:
   Assessment; Diffuse large B-cell lymphoma
   Immunophenotype; CD3 weakly positive, CD20 positive, LCD positive, PCK negative, DESMIN negative and BCl2positive.
   Histologic diagnosis was Diffuse large B-Cell Lymphoma
2. E/U/Cr - was essentially normal
3. Liver function test – was normal
4. ECG – Longitudinal left axis deviation.
   Impression: possible old interior MI
   Recommendation: B – blocker, Antiplatelet, statins, ACEs/ARBs
5. ECHO- Hypertensive Heart Disease with concentric Left ventricular hypertrophy and Grade 1 diastolic dysfunction.
6. Abdominopelvic ultrasound scan was essentially normal
7. Fasting blood glucose was 8.6mmol/L
8. AFB/Genexpert were both Negative
9. CD 4 count was 371cell/m^3
10. HIV viral load was not detectable

An assessment of Diffuse Large B – cell Lymphoma with? CNS infiltration with background HTN, type 2 Diabetes Mellitus and RVD on HAART was made and therapy was commenced which comprised of blood transfusion support, cautious rehydration, IV antibiotics, antihypertensives, hypoglycaemic agent, wound dressing and other optimization necessary for chemoimmunotherapy.

About 1 week on admission, He had an episode of generalized tonic-clonic seizure, lasting about 10 minutes and was aborted with diazepam. Patient also developed cough and pleuritic chest pain.

- A chest X – ray done revealed a mild left pleural effusion
- Fasting blood Glucose – 8.2mmol/L
- Brain CT done a day later showed Right frontal infarct.

The patient received first course of chemotherapy with R-CHOP regime (IV Cyclophosphamide, Adriamycin, oncovin and oral prednisolone) which was well tolerated. 21 days post – 1st course of chemotherapy, he received the 2nd course with R – CHOP.

Following 2nd course of chemotherapy, haematology and medical team reviews revealed marked improvement as the patient was assessed to be in both clinical and haematological remission. The jaw swelling had drastically reduced in size with a healing ulcer. The blood pressure and glucose were also well controlled.

Post chemotherapy full blood count revealed TWBC – $5.6X10^{9/L}$, Hb – 11.3g/dl and PLT – $191X10^{9/L}$. He was subsequently discharged on oral medications: Febuxostat, Rabeprazole, antibiotics and antihypertensives as well as his HAART therapy.

The 3rd and 4th courses of chemotherapy with R-CHOP regime were administered on out-patient basis and were both well tolerated. The jaw swelling completely resolved and ulcer healed.

Patient presented via Accident and Emergency unit few weeks later than the date scheduled for the 5th course of chemotherapy with a history of convulsion, altered consciousness and deviation of the mouth with inability to use the left lower limb or stand without support. His BP was 160/90mmHg and RBS was 15.5mmol/L, haemoglobin concentration of 6.7g/dl necessitating admission for transfusion support with 5 units of packed red cells, BP and glycacemic control. The Neurology team reviewed and made an assessment of Repeat Right hemisphere ischaemic stroke with resolving status epilepticus and Aspiration pneumonitis.

Patient's clinical condition remained unstable and stalled further chemotherapy and he eventually died of cardiopulmonary failure.

DISCUSSION

Human immunodeficiency virus (HIV) infection increases the risk of malignancy.[3] The HIV-associated malignancies are divided into acquired immune deficiency syndrome (AIDS)-defining and non-AIDS-defining cancers based on the incidence among the HIV-infected patients[1]. In HIV-positive individuals, lymphoma accounts for more than 50% of all AIDS-defining cancers and is the most common cause of HIV/AIDS-related cancer deaths[1]. It could be from B or T lymphocytes at various stages of differentiation. Nearly 90% of HIV/AIDS-associated lymphoma originates from B cells, and some distinct subtypes of lymphomas are more common than the other types. Some of these can occur among both HIV-infected and non-infected people, whereas others appear to be more common in HIV-infected people. HIV/AIDS-associated lymphomas are aggressive and invasive and if left untreated, it can lead to death within weeks or months after being diagnosed. In the early times, HIV/AIDS-associated lymphomas had been described by morphology and primary location of lymphomas, such as systemic, primary central nervous system, and body cavity lymphoma.[1,3]

Lymphoma is believed to develop in people with HIV (PWH) through multiple mechanisms. The intricate interplay of direct and indirect mechanisms. Indirect mechanisms based on cytokine dysregulation, HIV-induced immune dysfunction, and co-infections with oncogenic viruses (oncogenic γ-herpes viruses) induce chronic B-cell activation and generation of a suitable environment for malignant transformation and tumor growth. Direct mechanisms arise from oncogenic influences of p17, Tat, and Nef HIV proteins, which generate genomic instability, alteration of cellular signaling, and activation of oncogenic pathways.[5,6,7]

The clinical presentation of HIV/AIDS associated lymphoma (HAL) often involves aggressive disease with rapid progression. Common symptoms are non-specific and can include lymphadenopathy (swollen lymph nodes), fever, night sweats, and weight loss, which are also known as B symptoms. Extra-nodal involvement is a frequent feature particularly in aggressive subtypes.[4, 12] The most

common histological types of HIV-associated lymphomas are diffuse large B-cell lymphoma (DLBCL; 37%), HL (26%) and Burkitt lymphoma (BL; 20%).[6]

Diffuse Large B-Cell Lymphoma (DLBCL)

This is the most common lymphoma in PWH, it presents at an advanced stage of disease with B symptoms.[1] DLBCL is characterised by a diffuse infiltrate of large cells expressing the B-cell markers CD19 and CD20.[3] It can be classified as germinal centre B-cell (GCB) or activated B-cell subtypes based on the cell of origin (COO) determined by gene expression profiling (GEP). Although COO classification based on GEP is preferred, IHC-based classification systems can be used if GEP is not available. DLBCL often presents with nodal or extranodal disease, the gastrointestinal tract being the most common site, mainly in severely immunosuppressed patients. Other commonly involved sites include the central nervous system and bone marrow.[1, 3, 6] HIV-related DLBCL is generally a late event during HIV infection and risk factors for its development include a low $CD4^+$ T-cell count and high HIV viral load. Both profound immunosuppression and prolonged viremia greatly increase the risk and worsen the prognosis of DLBCL.[11]

Burkitt lymphoma (BL)

Burkitt lymphoma is an aggressive non-Hodgkin lymphoma with a molecular hallmark of *MYC* gene translocation with the immunoglobulin heavy-chain loci (80%) or, less frequently, with kappa or lambda light chains. There are three sub-classes of BL: endemic, sporadic, and immunodeficiency-related. In HIV-associated BL (HIV–BL), *TP53* mutations are present in a high percentage of patients. BL usually manifest with extensive mouth swellings, facial asymmetry, dysphagia, and difficulties opening the mouth, especially when the tumour is in the oral and maxillofacial regions. Abdominal involvement is common in HIV-associated BL. Though less common, primary chest wall BL has also been reported in HIV-infected patients, even in those on highly active antiretroviral therapy (HAART) with immune reconstitution.[3,6]

Plasmablastic lymphoma (PBL)

Plasmablastic lymphoma (PBL) is a rare and aggressive entity with diffuse proliferation of large neoplastic cells, mostly resembling B immunoblasts or plasmablasts. PBL typically has a plasma-cell phenotype, which includes CD138, CD38, Vs38c and multiple myeloma 1/interferon regulatory factor 4 (MUM1/IRF4) expression and negativity or weak positivity for CD20 and paired box 5 (PAX5). The biological basis of PBL is not completely understood. In 75%-80% of HIV-positive cases, PBL is associated with EBV infection, which plays an anti-apoptotic role in B cells. Overexpression of the MYC protein is frequently reported. The most frequent genetic alterations are translocations and/or rearrangement of *(IG)/MYC* in approximately 50% of cases, together with amplifications of *MYC*.[6,11]

Primary effusion lymphoma

The discovery of Kaposi sarcoma (KS) herpes virus or human herpes virus 8 (HHV-8), led to the recognition of primary effusion lymphoma (PEL) as a distinct lymphoproliferative disorder. PEL usually presents as serous effusions (ascites, pleuritis and/or pericarditis) without detectable tumour mass (60%-70% of cases) or as an extracavitary mass (extracavitary PEL, 30%-40% of cases). Diagnosis is based on cytological examination of serous fluid or pathological examination of a tumour biopsy specimen. Tumoural cells are polymorphic with immunoblasts, plasmablasts or anaplastic features.[6]

Primary CNS Lymphoma (PCNSL)

HIV-associated primary CNS lymphoma (HIV–PCNSL) occurs in patients who are severely immunocompromised. Nearly all PCNSLs are of B-cell origin. In PLWH, the most frequent histology is DLBCL. Unlike PCNSL in immunocompetent hosts, EBV infection is essential to the pathobiology of HIV–PCNSL. PCNSL presents with acute or subacute neurological signs and symptoms depending on location, size of lesions and surrounding oedema; B symptoms are rare. Full medical and neurological evaluation and Mini-Mental State Examination should be carried out alongside investigations including serum LDH, CSF analysis for EBV DNA using quantitative PCR, cytology and flow cytometry if lumbar puncture can be safely carried out, and contrast-enhanced brain MRI. PCNSL can be multifocal or solitary and most commonly affects deep structures and white matter. FDG–PET–CT scans support the diagnosis of PCNSL by excluding systemic involvement.[6,11]

Hodgkin Lymphoma (HL)

HL is characterised by a small neoplastic infiltration of Hodgkin and Reed–Sternberg (HRS) cells against an inflammatory background of lymphocytes, histiocytes, plasma cells, eosinophils and neutrophils. The neoplastic HRS cells are typically CD30 and CD15 positive, with B-cell markers such as CD20 and CD79a expressed in a minority of cells. EBV infection is almost universal in HIV–HL expressing Epstein–Barr nuclear antigen 1, latent membrane protein 1 and 2 and EBV-encoded RNA.[6] There is a high incidence of unfavorable histological subtypes (Mixed Cellularity and Lymphocyte Depleted) in PWH.[1]

Our patient presented with jaw and facial mass which was overlying the parotid gland. Due to the aggressive growth of the tumour, its acute onset and location we considered a clinical diagnosis of Burkitt lymphoma to rule out a parotid tumour and plasmablastic lymphoma. The diagnosis made from tissue biopsy which was sent for histology and immunohistochemistry. There was CNS symptoms at presentation suggesting either a CNS metastasis or a possible primary CNS tumour. However, further investigations with CT scan and CSF cytology were able to confirm a CVA and rule out CNS metastasis.

The clinical presentation of HIV-associated lymphoma can sometimes mimic disseminated mycobacterial infection, presenting with similar clinical features, laboratory findings, and even granulomatous bone marrow inflammation, which can lead to diagnostic challenges. This was also excluded by doing sputum AFB, Gene-xpert and tissue Histology.

Immunosuppression and high viral load are crucial factors in the development of lymphoma in HIV patients. Co-infection with other lymphotropic viruses, particularly Epstein-Barr Virus (EBV), is strongly associated with the development of certain lymphoma types, including some forms of HIV-DLBCL and PBL. The declining CD4 lymphocyte counts are often noted at the time of diagnosis

in HIV patients, and some studies suggest a downward trend in CD4 counts even a year prior to diagnosis, irrespective of virologic control.[7] This decline in CD4 count serves as an important predictor. Our patient's viral load was undetectable and CD 4 count was more than 371cells/mm^3. Lymphoma may be the presenting manifestation of HIV infection, and all patients with aggressive B-cell lymphoma should be tested for HIV.[11]

Treatment

Life expectancy in the setting of HIV infection treated with antiretroviral therapy (ART) is now 72 to 75 years, depending on the CD4 count at HIV diagnosis.[9] The three key pillars of HIV-associated lymphoma management are cART, supportive care and chemoimmunotherapy. A well-regulated balance is required to administer effective chemotherapeutic regimens while maintaining adequate immune function and preventing infection-related complications.[9]

A combination of chemotherapy and targeted therapy has been approved for the treatment of CD20$^+$ NHL, and the approved chemotherapy regimens include R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone), R-EPOCH (rituximab, etoposide, prednisone, oncovin, cyclophosphamide, and hydroxydaunorubicin), R-CODOX-M/IVAC (rituximab with cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate/ifosfamide etoposide and high-dose cytarabine), and R-hyper-CVAD (rituximab with hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone).[1,9] First-line therapy combines antiretroviral therapy (ART) with chemo-therapy, achieving complete remission rates of 60-70% for DLBCL using R-EPOCH and 50-60% for BL with CODOX-M/IVAC.[8]

Earlier studies suggested that the use of rituximab in HIV-DLBCL was associated with high infection-related mortality, particularly in patients with CD4 counts less than 50 cells/μL. However, recent data reveal that combining rituximab with standard chemotherapy protocols produced more favourable outcomes, resulting in a nearly threefold increase in Complete Remission and a 50% reduction in disease progression. The concomitant use of G-CSF with chemoimmunotherapy further reduces the risk of infection-related deaths[9]

The prognosis is determined by multiple factors, including patient-specific (age, performance status, comorbidity), HIV-specific (history of AIDS, low CD4$^+$ count, viral load, infections, cART history), lymphoma-specific factors (stage, lactate dehydrogenase [LDH] levels, extranodal disease, and a high international prognostic index [IPI]) and practitioner-related factors (experience in lymphoma therapy and experience in HIV therapy). Patients with *Myc* rearrangements, EBV infection, and high-levels of NKp44/NCR2 often have a poor prognosis[1,2]

Our patient had numerous poor prognostic factors (age >60years, hypertension, diabetes, low CD count) but was able to achieve complete remission after two courses of R-CHOP. He was discharged and gradually re-integrated into the general population before he had CVA and other complications from other co-morbidities which subsequently led to his death.

In the relapse or refractory setting high-dose platinum-based salvage regimens [e.g. rituximab–dexamethasone–Ara-C–cisplatin (R-DHAP), rituximab–ifosfamide–carboplatin–etoposide (R-ICE), rituximab–gemcitabine–dexamethasone–cisplatin (R-GDP) and rituximab–etoposide–methylprednisolone–Ara-C–cisplatin (R-ESHAP)] and subsequent autologous stem-cell transplantations (ASCTs) are strategies that have been used.[6,11,13] Nonmyeloablative allogeneic transplantation has been used in select patients[13] and CAR-T therapy is also approved following two lines of treatment.[6]

Newer agents used in management of lymphoma include; Vorinostat (VOR), a histone deacetylase inhibitor, PD-1 inhibitor pembrolizumab, Immunomodulatory drugs (IMiDs), such as pomalidomide and lenalidomide, Brentuximab vedotin (BV), an antibody–drug conjugate (ADC) targeting CD30, combines an anti-CD30 monoclonal antibody with a cytotoxic agent.

CONCLUSION

Life expectancy in HIV-infected persons on ART is approaching that of the general population. Consequently, the incidence of opportunistic infection has decreased drastically making malignancy the commonest cause of death[14]. Lymphoma has also been recorded as the commonest malignancy in PWH[6]. Intensive curative cancer therapies are the standard of care, except in patients with advanced AIDS. These therapies include immunotherapy, targeted therapy and transplant strategies in the setting of relapsed and refractory lymphoma, these have improved the rate complete remission and overall survival in patients with HIV associated lymphoma.[11]

RECOMMENDATIONS

All patients living with HIV who present with persistent lymphadenopathy, rapidly enlarging masses, constitutional symptoms, or extranodal lesions should undergo early evaluation for lymphoma.

Management of HIV-associated lymphoma should involve a multidisciplinary approach including haematologists, oncologists, infectious disease physicians, neurologists, cardiologists, pathologists, and supportive care teams. This is particularly important in patients with multiple co-morbidities such as hypertension, diabetes mellitus, and cerebrovascular disease.

Healthcare institutions in resource-limited settings should strengthen access to diagnostic facilities including immunohistochemistry, molecular studies, neuroimaging, viral load testing, and CD4 monitoring to improve diagnostic accuracy and prognostication.

More multicentre studies are needed in Sub-Saharan Africa to evaluate the clinical characteristics, treatment outcomes, prognostic factors, and survival patterns of HIV-associated lymphomas in resource-constrained environments.

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