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High-Grade B-Cell Lymphoma in a Newly Diagnosed HIV Patient with Near-Normal CD4 Count: A Diagnostic Challenge

Hind Hamid Alrowais[1], Khalid Maddi Alqhatani[1], Hanan Mohamed Moalim Abdullahi[1], Gamal Thabet Aly Ebid[2], Essam Iotfy Abdelhamid Eid[1], Waleed Amasaib Ahmed[1]

[1]Department of Medicine, Security Forces Hospital, Makkah, Saudi Arabia
[2]Laboratory and Blood Bank Department, Security Forces Hospital, Makkah, Saudi Arabia
Email: waleedamasaib@hotmail.com

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Abstract

We present a rare case of a 27-year-old male with newly diagnosed HIV infection who presented with systemic symptoms, generalized lymphadenopathy, hepatosplenomegaly, and multi-organ involvement, ultimately found to have high-grade lymphoma. Notably, despite his advanced clinical presentation, his CD4 count was nearly normal (380 cells/μL), challenging the typical immunopathogenic understanding of HIV-associated lymphomas. This case highlights the importance of maintaining a high index of suspicion for malignancy even in the setting of relatively preserved immune status in HIV-positive individuals.

Keywords

HIV-Associated Lymphoma High-Grade B-Cell Lymphoma, CD4 Count, Diagnostic Challenge, Immune Preservation, Non-Hodgkin lymphoma

1. Introduction

Human Immunodeficiency Virus (HIV)-associated Non-Hodgkin Lymphoma (NHL) remains a notable contributor to morbidity and mortality among individuals living with HIV [1]. NHL most frequently arises in the context of marked immunosuppression, particularly when CD4 counts are below 200 cells/μL [2]. Nonetheless, cases have been documented in patients who retain relatively preserved immune function, although such occurrences are infrequent and may introduce diagnostic complexities [3]. This report details an unusual case of high-grade B-cell lymphoma in a young male with a recent HIV diagnosis, presenting with systemic symptoms and multisystem involvement despite maintaining a near-normal CD4 count.

2. Case Presentation

A 27-year-old male presented in May 2025 with fever (up to 38˚C), night sweats, unexplained weight loss of 10 kg over one month, myalgias, and chills. He had experienced persistent, non-tender cervical lymphadenopathy for a year following tonsillitis, which subsequently involved the axillary and inguinal regions, becoming more noticeable after a tooth extraction.

The patient did not report any genitourinary symptoms, consumption of unpasteurized milk, rash, bleeding, jaundice, early satiety, abdominal pain, dysphagia, voice changes, chest pain, relevant family history, alcohol use, or intravenous drug use.

Initial Physical Examination

- **Vital Signs**: Blood pressure 121/78 mmHg, heart rate 85 bpm, respiratory rate 16 breaths/min, temperature 37˚C, oxygen saturation 98% on room air.
- **General Appearance**: The patient is well-appearing, conscious, alert, and not in pain or distress. Positioned supine, with no pallor, jaundice, or cyanosis noted.
- **Neck**: Cervical lymphadenopathy is palpable.
- **Heart**: Normal rate and rhythm observed; S1 and S2 are audible without murmurs or rubs.
- **Lungs**: Vesicular breath sounds present with bibasilar crackles; no wheezing detected.
- **Abdomen**: Bowel sounds are present. The abdomen is soft and relaxed, with no tenderness. The liver and spleen are palpable.
- **Extremities**: No peripheral edema noted.
- **Neurological**: Grossly intact neurological function.
- **Skin**: No rashes observed.
- **Lymph Nodes**: Lymphadenopathy noted in both cervical and inguinal regions.

Initial Laboratory Findings (Table 1)

Table 1. Initial laboratory workup.

Test	Result	Normal Range	Notes
Hb	10.9 g/dL	12 - 16 g/dL	Hypochromic
Platelets	271 × 10^9/L	150 - 450 × 10^9/L	
WBC	13.09 × 10^9/L	4.0 - 11.0 × 10^9/L	Mainly lymphocytes
CRP	238.4 mg/L	<5 mg/L	elevated
ESR	125 mm/h	<20 mm/h	elevated
Renal Profile	Normal		
ALT	113 U/L	7 - 56 U/L	high
AST	58 U/L	8 - 48 U/L	high
ALP	161 U/L	40 - 129 U/L	high
Total Protein	96.0 g/L	60 - 83 g/L	high
Albumin	40.5 g/L	35 - 50 g/L	
Total Bilirubin	5.22 µmol/L	3 - 21 µmol/L	

Imaging Studies

- **Chest X-ray**: Lungs clear; normal cardiothoracic ratio.

Admission Diagnosis: *Evaluation for possible lymphoma.*

The patient was admitted for further evaluation. The following tests (Table 2) were performed on Day 1:

Table 2. Further specific tests.

Test	Result	Details/Comments
Autoimmune Workup	Negative	
Hepatitis Screen	Negative	
Brucella Test	Negative	
Syphilis Serology	Positive	TPHA positive, RPR positive
Toxoplasma IgG	Positive	
HIV Test	Preliminary positive	Confirmation of Western blot pending
Cytomegalovirus IgG	Positive	
Blood Film	Mild microcytic hypochromic anemia	Moderate rouleaux formation of RBCs, neutrophils shift to left (bands 30%, juvenile cells 5%, myelocytes 1%), few reactive and rare, atypical lymphocytes
Septic screen (blood and urine cultures)	Negative	

Hospital Course

 # Day 2

- The patient experienced pain and tenderness in the right iliac fossa, and a pan CT scan was conducted.

Pan CT Scan Results:

- Hepatomegaly with multiple hypodense lesions
- Splenomegaly
- Retroperitoneal and pelvic lymphadenopathy
- Indeterminate hyper vascular lesions in the left adrenal gland
- Small indeterminate lesion in the medial cortex of the left kidney
- Rounded soft tissue noted within the fat plane anterior to the right gluteus muscle

Day 5

- The patient reported severe headache and visual disturbances. MRI of the brain demonstrated:
- Well-defined soft tissue lesion at the posterior horn of the left lateral ventricle
- Galeal lesion opposite the right parietal region
- Subtle irregularity involving the related skull bones
- Differential considerations included metastasis, lymphoma, and atypical in-

fection

Given the new neurological symptoms and imaging findings, empiric therapy for possible neurosyphilis (Ceftriaxone) and disseminated toxoplasmosis (trimethoprim/sulfamethoxazole) was initiated.

Day 6

- Axillary lymph node biopsy: Reactive lymphoid infiltrate, negative for malignancy.

Day 7

- Lumbar puncture revealed high opening pressure, unremarkable cell count, normal glucose and protein levels, and negative fungal, TB, and bacterial cultures. CSF cytology identified a lymphocytic aspirate, with no evidence of malignancy.

Empirical therapy for suspected cryptococcal meningitis was started with liposomal amphotericin B and fluconazole.

Day 13

- The patient developed weakness in the right lower limb. MRI of the spine showed multifocal, widespread marrow lesions scattered across several vertebral levels, suggestive of a neoplastic process (metastatic or lymphomatous deposits) (**Figure 1**).

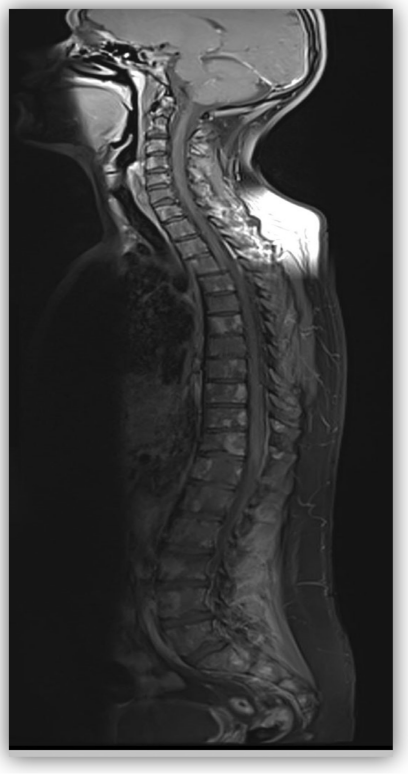

Figure 1. T1 MRI Spine with gadolinium.

- *HIV confirmatory testing returned a positive result*; *CD4 count was* 380 *cells/mm*^{3} (*reference range*: 500 - 1500 *cells/mm*^{3}).

 # Day 15

- Thrombocytopenia was observed. Malaria screening and HIT testing were negative.

 # Day 16

- The patient reported a persistent headache; a lumbar puncture was performed again to lower intracranial pressure.

Day 18

- The repeat blood film showed marked anemia, mild microcytosis, hypochromia, agglutination, nucleated RBCs (2 per 100 WBCs), a left shift in neutrophils (bands = 30%), and increased immature myeloid cells (juvenile = 5%, myelocytes = 3%, promyelocytes = 2%), findings consistent with a leucoerythroblastic reaction.

 # Day 22

- ***Bone marrow aspiration*** demonstrated marked hypercellularity with 80% blasts and significant suppression of granulopoiesis, erythropoiesis, and megakaryopoiesis. Macrophages were observed to exhibit hemophagocytosis. (Figure 2)

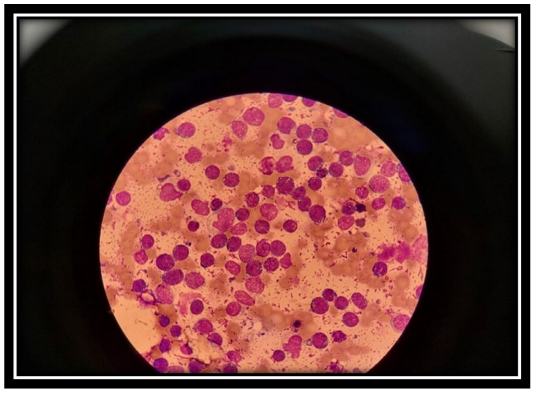

Figure 2. Bone marrow aspiration; oil immersion lens × 100.

Bone Marrow Biopsy Findings:

- A dry tap necessitated a saline-immersed bone marrow biopsy.
- Flow cytometric analysis: Approximately 55% CD19+ cells; positive for CD45, CD20, CD10, CD38; negative for CD34, CD5, CD23, CD103, surface/cytoplasmic light chains.
- Findings indicate a CD5-negative, CD10-positive high-grade B-cell lymphoma.
- Cytogenetic studies (bcl2, bc6, MYC rearrangements) and tissue histopathology are recommended for definitive diagnosis.

Final Diagnosis

- **HIV Infection**: Confirmed via Western blot, with near-normal CD4 count.
- **High-Grade B-Cell Lymphoma**: Supported by bone marrow biopsy and flow cytometry findings.

Treatment and Clinical Course:

Following the diagnosis of high-grade B-cell lymphoma and confirmed HIV infection, the patient was deemed to require specialized multidisciplinary care. Due to the complexity of managing HIV-associated lymphoma—requiring coordinated initiation of Antiretroviral Therapy (ART) and risk-adapted chemotherapy—he was promptly referred to a tertiary HIV and oncology center for definitive management. At the time of referral, ART and chemotherapy had not yet been initiated. The patient was stable for transfer, with ongoing supportive care including intracranial pressure management and discontinuation of antimicrobial therapies upon exclusion of active opportunistic infections. Follow-up information regarding treatment initiation and response is pending due to inter-institutional referral.

Given the need for specialized molecular diagnostics, samples were forwarded to the tertiary oncology center for fluorescence in situ hybridization (FISH) analysis of *MYC*, *BCL2*, and *BCL6* rearrangements to enable definitive classification per WHO criteria. Results are pending due to inter-institutional referral.

3. Discussion

This case highlights several important clinical and pathophysiological insights regarding the development of high-grade B-cell lymphoma in the setting of HIV infection. Most notably, it illustrates that aggressive lymphomas can occur even in patients with relatively preserved immune function, as evidenced by a CD4 count of 380 cells/μL. This challenges the traditional paradigm that HIV-associated lymphomas are primarily diseases of advanced immunosuppression.

3.1. Lymphomagenesis in HIV: Beyond CD4 Count

HIV-associated Non-Hodgkin Lymphoma (NHL) is a well-recognized complication of chronic HIV infection [1]. Historically, NHL was considered an AIDS-defining illness occurring predominantly in patients with CD4 counts <200 cells/μL [2]. However, accumulating evidence suggests that lymphomas may also develop in patients with higher CD4 counts, particularly when other risk factors are present, such as persistent immune activation, chronic inflammation, and co-infection with oncogenic viruses like Epstein-Barr virus (EBV), Kaposi sarcoma herpesvirus (KSHV), or human T-cell leukemia virus type 1 (HTLV-1) [3].

The pathogenesis of lymphoma in HIV-infected individuals with preserved immunity is multifactorial and includes:

1) Chronic Immune Activation and Inflammation

Even in the absence of profound CD4 depletion, untreated HIV leads to persistent immune activation and systemic inflammation. This is driven by continuous viral replication, microbial translocation due to gut mucosal barrier damage, and dysregulated cytokine production [4]. Chronic inflammation creates a permissive environment for malignant transformation by promoting DNA damage, cell proliferation, and resistance to apoptosis [5].

2) Epstein-Barr Virus (EBV) Co-Infection

EBV is strongly implicated in the pathogenesis of many HIV-associated lymphomas, particularly Burkitt lymphoma and Diffuse Large B-Cell Lymphoma (DLBCL). The virus has potent transforming properties via latent gene expression, including the upregulation of anti-apoptotic proteins such as Bcl-2 and LMP-1, which mimic activated CD40 signaling [6]. In our patient, although EBV, KSHV, and HTLV-1 PCR/serology were not performed due to limited local laboratory capacity, the presence of high-grade B-cell lymphoma raises the possibility of underlying EBV-driven oncogenesis.

3) Impaired Immune Surveillance

HIV causes qualitative defects in both adaptive and innate immunity long before CD4 counts fall below critical thresholds. These include:

- Loss of memory in B-cell subsets
- Reduced NK cell function
- Defective antigen presentation
- Exhaustion of cytotoxic T-cells

These impairments allow for unchecked clonal expansion of transformed B-cells and reduced clearance of EBV-infected cells, contributing to lymphomagenesis even in the setting of relatively normal CD4 counts [7].

4) Significance of Antiretroviral Therapy (ART) Initiation Timing

Late initiation of ART allows for prolonged periods of uncontrolled viraemia and immune dysfunction, increasing the risk of malignancy. Our patient had no prior diagnosis or treatment for HIV, suggesting a long-standing untreated infection. Early ART initiation has been shown to significantly reduce the incidence of NHL by restoring immune function and reducing systemic inflammation [8].

5) Persistent Immune Activation and B-Cell Dysregulation in HIV

Even in the era of effective Antiretroviral Therapy (ART), individuals with HIV exhibit persistent immune activation and B-cell dysregulation, which contribute to an elevated risk of non-Hodgkin lymphoma independent of CD4 count. Chronic antigenic stimulation, microbial translocation, and residual viral replication drive a pro-inflammatory milieu that promotes genomic instability and aberrant B-cell proliferation. A recent prospective cohort study by Anastos *et al.* (2022) demonstrated that elevated levels of soluble CD14, IL-6, and B-cell activating factor (BAFF) were independently associated with increased lymphoma risk among HIV-positive individuals, even those with sustained viral suppression and CD4 counts >500 cells/μL. This supports the notion that qualitative immune dysfunction—not just quantitative CD4 depletion—plays a central role in lymphomagenesis, reinforcing the importance of early diagnosis and comprehensive immune profiling in at-risk patients [9].

6) Advances in Risk Stratification and Management of HIV-Associated Lymphoma

Recent advances in the management of HIV-associated lymphomas emphasize the importance of early integration of oncology and infectious disease care, as outcomes now closely mirror those of HIV-negative patients when treated with com-

bined ART and risk-adapted chemotherapy. A 2023 review by Patel *et al.* highlighted that dose-adjusted EPOCH-R and DA-EPOCH regimens have significantly improved survival in aggressive B-cell lymphomas among people living with HIV, particularly when ART is initiated promptly and drug interactions are carefully managed. Furthermore, the authors advocate for routine use of PET-CT and molecular profiling (e.g., MYC/BCL2/BCL6 FISH) to guide risk stratification, although such tools may not be available in resource-limited settings. This underscores the need for equitable access to advanced diagnostics and multidisciplinary care models to improve outcomes globally [10].

3.2. Diagnostic Challenges in Individuals with HIV

HIV-positive patients are susceptible to multiple Opportunistic Infections (OIs) that mimic lymphoma clinically and radiologically, including:

- Toxoplasmosis
- Cryptococcus
- Mycobacterium tuberculosis
- Bartonella species
- Kaposi sarcoma

In this case, the presence of positive Toxoplasma IgG, CMV IgG, and syphilis serology complicated the differential diagnosis. Additionally, the CNS imaging findings were nonspecific, necessitating CSF analysis and bone marrow evaluation for definitive diagnosis.

The empiric initiation of antimicrobials was justified by the high pretest probability of opportunistic infections in a newly diagnosed HIV patient with neurological symptoms and nonspecific CNS lesions. Alternative infections were definitively excluded through negative CSF cultures (bacterial, fungal, TB), lack of response to empiric therapy, and progression of systemic and neurological findings despite antimicrobial coverage, which ultimately shifted the clinical suspicion toward malignancy.

3.3. Involvement of Bone Marrow

Bone marrow involvement occurs in approximately 20% - 30% of HIV-associated NHL cases [11]. Our patient demonstrated extensive marrow infiltration with hemophagocytosis, leading to pancytopenia and a leucoerythroblastic picture. This finding underscores the aggressive nature of the disease despite preserved immunity.

3.4. Clinical Implications

This case emphasizes the need for:

- Early recognition of NHL in HIV patients regardless of CD4 count
- Thorough workup including imaging, bone marrow evaluation, and flow cytometry
- Prompt initiation of ART once diagnosed, as it improves outcomes in HIV-

related lymphoma [12]

4. Limitations

This report is limited by the single-case nature, lack of EBV, KSHV, and HTLV-1 testing, and unavailability of FISH studies for *MYC*, *BCL2*, and *BCL6* rearrangements due to resource constraints. As the patient was referred to an external center, treatment outcomes and long-term follow-up are currently unknown. These factors restrict the generalizability of our observations.

5. Conclusion

This case highlights an uncommon scenario of high-grade B-cell lymphoma occurring in an HIV-positive patient with a near-normal CD4 count. It serves as a reminder that lymphoma should remain in the differential diagnosis for any HIV-infected individual presenting with systemic symptoms, lymphadenopathy, and multiorgan involvement, irrespective of immune status. A high index of suspicion and early referral for specialized diagnostics are crucial for timely management.

Consent

Written informed consent was obtained from the patient for publication of this case report and images. The consent document is available for review by the Editor-in-Chief.

Authors' Contributions

- **H. R.**: Served as the primary physician responsible for patient care and data collection.
- **K. Q.**: Participated in the literature review and provided critical revisions to the manuscript.
- **W. A.**: Responsible for drafting the manuscript.
- **H. M.**: Oversaw case management and contributed to final editing of the manuscript.
- **G. T.**: Oversaw case management and contributed to final editing of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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