ISSN: 2581 – 3633

International Journal of Medical Science and Advanced Clinical Research (IJMACR)

Available Online at: https://www.ijmacr.com

Volume – 9, Issue – 6, November – 2026, Page No.: 340 – 349

HIV-Associated Nodal Plasmablastic Neoplasm Favouring Plasmablastic Lymphoma: Pitfalls in a CD45-Negative Large-Cell Malignancy

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How to citation this article: Veena, Nanditha H S, C S B R Prasad, Shilpa S Biradar, Madhuvan H S, "HIV-Associated Nodal Plasmablastic Neoplasm Favouring Plasmablastic Lymphoma: Pitfalls in a CD45-Negative Large-Cell Malignancy", IJMACR– November – 2026, Volume – 9, Issue – 6, P. No. 340 – 349.

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Type of Publication: Case Report

Conflicts of Interest: Nil

Abstract

Background: Plasmablastic lymphoma (PBL) is a rare, aggressive large B-cell lymphoma with plasmablastic morphology and a terminally differentiated B-cell phenotype. It is strongly associated with HIV infection and usually arises at extranodal sites, particularly the oral cavity. Nodal disease that has lost CD45 and CD20 can be mistaken for carcinoma, and PBL is difficult to separate from plasmablastic myeloma.

Case Presentation: A 34-year-old HIV-positive man with incompletely treated tuberculosis presented with a left neck swelling enlarging over 2 months and 1 week of intermittent fever with night sweats. There were no oral lesions, and blood counts, creatinine, calcium and LDH were normal. Fine needle aspiration suggested a high-grade lymphoproliferative disorder or metastatic poorly differentiated malignancy. PET-CT showed hypermetabolic bilateral cervical nodes and FDG uptake in the marrow of multiple bones. An excised cervical

node was effaced by sheets of large cells with eccentric nuclei and prominent nucleoli. These were positive for CD138, weakly positive for MUM1 and BCL2, focally positive for CD56 and partly positive for BCL6 and c-MYC, with a Ki-67 index of 40-50%. They were negative for CD45, CD20, PAX5, CD3, CD10, CD30, ALK, EBV LMP1, pan-cytokeratin and HMB45. The findings favoured PBL, and bone marrow correlation was advised.

Conclusion: In an HIV-positive patient, a CD45-negative, CD20-negative large-cell malignancy in a lymph node should prompt plasma cell markers early in the work-up. Bone marrow examination, serum protein studies and EBER in situ hybridisation are needed to exclude plasmablastic myeloma before the diagnosis is final.

Keywords: Plasmablastic Lymphoma; HIV Infections; Lymphadenopathy; Immunohistochemistry; Diagnosis, Differential

Introduction

Plasmablastic lymphoma (PBL) was first described by Delecluse and colleagues in 1997 in a series of highly malignant diffuse large B-cell lymphomas of the oral cavity. Fifteen of their 16 patients were HIV positive, and the tumours showed minimal or absent expression of CD45 and CD20 despite their B-cell origin.[1] Both the fifth edition of the World Health Organization classification and the 2022 International Consensus Classification recognise PBL as a distinct large B-cell lymphoma.[2,3] The tumour cells have immunoblastic or plasmablastic morphology, lack mature B-cell markers and express plasma cell antigens such as CD138, CD38 and MUM1.[4]

PBL remains most closely linked to HIV infection, although it is also seen in transplant recipients and in immunocompetent patients.[4,5] In a meta-analysis of 277 published cases, half the patients had AIDS, 77% were men and 88% of tumours were extranodal; in HIV-positive patients the median age was 41 years and the oral cavity was the commonest primary site.[5] Indian data are limited. In a 5-year South Indian study of HIV-associated lymphomas, PBL was the second commonest non-Hodgkin lymphoma subtype,[6] and in a separate South Indian series of nine patients with PBL, all were HIV positive and eight had extranodal disease.[7] Outcomes are poor. In a series of 135 patients from the LYSA group, chemotherapy produced complete responses in 55% and the median overall survival was 32 months.[8]

We describe an HIV-positive patient in whom a plasmablastic neoplasm presented as cervical lymphadenopathy. The nodal site, the loss of CD45 and CD20 and PET-CT evidence of marrow uptake each pointed the differential diagnosis in a different direction.

Case Presentation

Clinical history

A 34-year-old HIV-positive man presented with a swelling on the left side of the neck that he had first noticed 2 months earlier and that had gradually increased in size (Figure 1). For 1 week he had also had intermittent fever with night sweats, which was relieved by medication. He had previously been diagnosed with tuberculosis and had discontinued antitubercular treatment, and the clinical impression was tuberculous lymphadenopathy. Examination of the oral cavity showed no lesions. The sequence of events is summarised in Table 1.

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Figure 1: Clinical photograph of the left side of the neck below the mandible showing the swelling. The image has been cropped to protect the patient's identity.

Investigations

Fine needle aspiration cytology of the swelling was reported as a high-grade lymphoproliferative disorder or a metastatic poorly differentiated malignant neoplasm. Complete blood count, serum creatinine, serum calcium and lactate dehydrogenase (LDH) were within normal limits. Whole-body 18F-fluorodeoxyglucose (FDG) PET-CT showed enlarged, hypermetabolic lymph nodes on both sides of the neck and FDG uptake in the bone marrow of multiple bones of the axial and appendicular skeleton, and bone marrow biopsy correlation was suggested. An excision biopsy of a left cervical lymph node was sent for histopathological examination.

Table 1: Timeline of the clinical course

Time point	**Event**
Before presentation	34-year-old man, HIV positive. Diagnosed with tuberculosis; antitubercular treatment discontinued.
2 months before presentation	Swelling noticed on the left side of the neck, gradually increasing in size.
1 week before presentation	Intermittent fever with night sweats, relieved by medication.
Presentation	No oral lesions. Complete blood count, creatinine, calcium and LDH normal. Fine needle aspiration cytology: high-grade lymphoproliferative disorder or metastatic poorly differentiated malignant neoplasm.
Staging work-up	PET-CT: hypermetabolic enlarged bilateral cervical lymph nodes; FDG uptake in the bone marrow of multiple axial and appendicular bones; bone marrow biopsy correlation suggested.
Excision biopsy	Left cervical lymph node sent with a clinical impression of tuberculous lymphadenopathy. Histopathology and an initial immunohistochemistry panel (CD45, CD138, pan-cytokeratin, HMB45).
10 days after biopsy	Final report after additional markers: high-grade B-cell non-Hodgkin lymphoma favouring plasmablastic lymphoma; bone marrow correlation advised.

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Gross examination

The specimen was a single lymph node measuring 3.6 × 3 × 1.3 cm with a congested external surface. The cut surface showed a grey-white area measuring 2.8 × 1.5 cm with congested, reddish-brown tissue at the periphery (Figure 2).

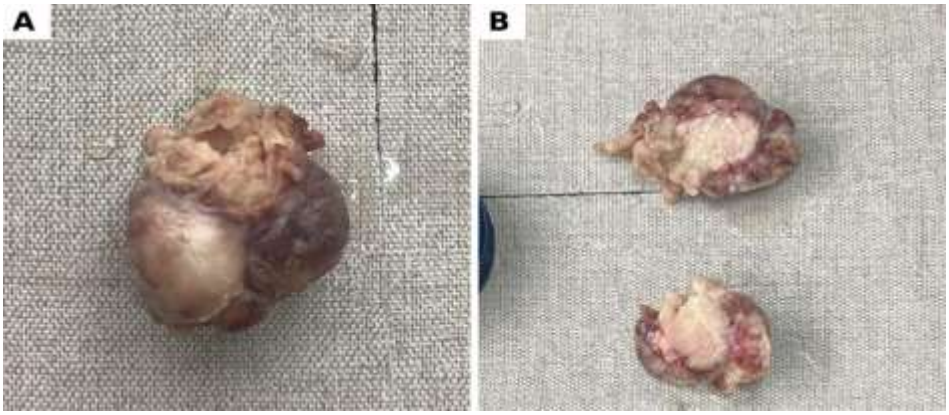


Figure 2: Gross appearance of the excised cervical lymph node. (A) Intact specimen with a congested external surface. (B) Cut surfaces showing a grey-white area measuring 2.8 × 1.5 cm with congested tissue at the periphery.

Microscopic examination

Sections showed a lymph node whose architecture was effaced by an infiltrate of large cells arranged in diffuse sheets (Figure 3A). The tumour cells had enlarged, eccentrically placed nuclei with coarse chromatin and prominent nucleoli (Figure 3B), and many were discohesive with a plasmacytoid appearance (Figure 3C). Small lymphocytes were interspersed among the tumour cells (Figure 3D). No granulomas were seen.

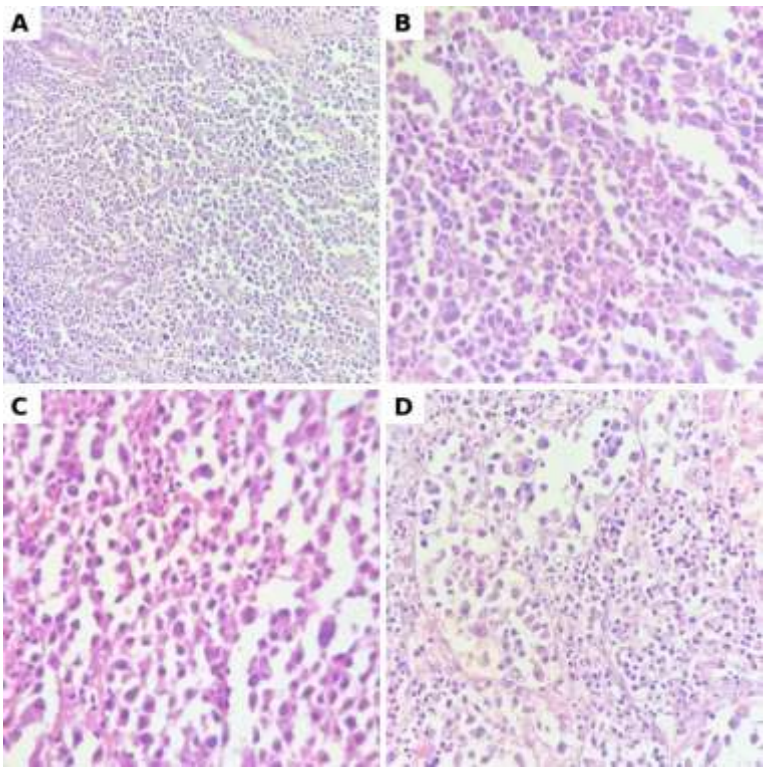


Figure 3: Histopathology of the lymph node (haematoxylin and eosin). (A) Low-power view showing effacement of nodal architecture by diffuse sheets of large atypical cells. (B) Tumour cells with eccentric nuclei, coarse chromatin and

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prominent nucleoli. (C) Discohesive large tumour cells with a plasmacytoid appearance. (D) Tumour cells with interspersed small lymphocytes.

Immunohistochemistry

An initial panel showed that the large cells were positive for CD138 and negative for CD45, pan-cytokeratin and HMB45. Additional markers were then performed. CD45 stained only the background small lymphocytes (Figure 4A), and CD3 was confined to reactive T cells (Figure 4B). The large cells showed membranous positivity for CD138 (Figure 4C) and weak nuclear positivity for MUM1 (Figure 4D). c-MYC showed weak to moderate nuclear staining in 25-30% of the large cells (Figure 4E), and the Ki-67 proliferation index was 40-50% (Figure 4F). BCL2 was weakly positive (Figure 4G), BCL6 showed weak to moderate staining in 35-40% of the large cells and CD56 was weakly and focally positive. CD20 and PAX5 were negative in the large cells and stained scattered background B cells. The large cells were negative for EBV LMP1 (Figure 4H), CD10, CD30 and ALK.

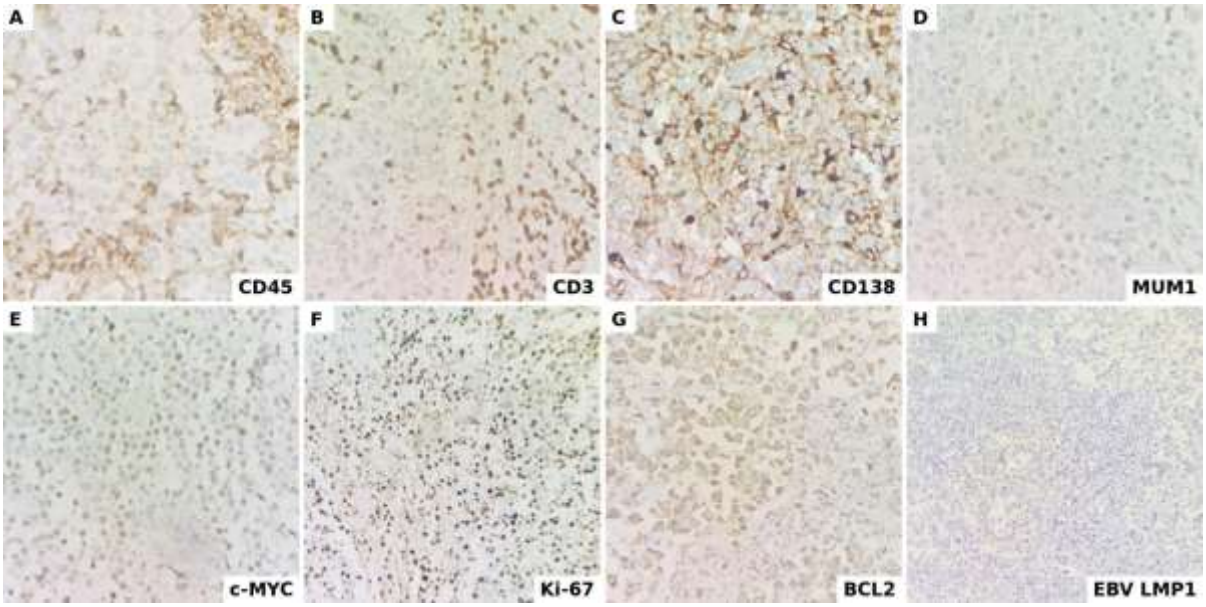


Figure 4: Immunohistochemistry. (A) CD45 negative in tumour cells, with staining of background lymphocytes. (B) CD3 negative in tumour cells, highlighting reactive T cells. (C) CD138 membranous positivity in tumour cells. (D) MUM1 weak nuclear positivity. (E) c-MYC weak to moderate nuclear staining in 25-30% of large cells. (F) Ki-67 proliferation index of 40-50%. (G) BCL2 weak positivity. (H) EBV LMP1 negative.

Diagnosis

The immunohistochemical findings were reported as suggestive of a high-grade B-cell non-Hodgkin lymphoma favouring plasmablastic lymphoma, based on the large-cell morphology, the plasma cell phenotype and the loss of CD45, CD20 and PAX5 in an HIV-positive patient. In view of the marrow uptake on PET-CT, bone marrow biopsy correlation was advised. Because plasmablastic myeloma cannot be excluded on the lymph node biopsy alone, the lesion is described here as a plasmablastic neoplasm favouring plasmablastic lymphoma. The patient was treated with chemotherapy but unfortunately he succumbed to the disease four months after initiation of treatment.

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Discussion

The patient was HIV positive, the setting in which PBL was first described and in which it is still most often seen.[1,4] The unusual feature was the site. Most HIV-associated PBLs are extranodal, and in pooled data the oral cavity was the commonest primary site in this group.[5,7] Our patient had no oral lesions, and the disease was confined clinically to the cervical lymph nodes. Colomo et al found nodal presentation in 13% of PBLs of the oral mucosa type but in 44% of PBLs with plasmacytic differentiation.[9] At 34 years our patient was younger than the median of 41 years reported for HIV-associated PBL.[5] Enlarging neck nodes with fever and night sweats in an HIV-positive man with incompletely treated tuberculosis suggest tuberculous lymphadenitis, and this was the clinical impression when the node was sent for biopsy. The absence of granulomas in the excised node argued against it.

The cytology could not separate a high-grade lymphoproliferative disorder from metastatic poorly differentiated carcinoma. Large cells with prominent nucleoli that are negative for CD45 point first towards carcinoma, a pitfall that Delecluse et al described in the original series.[1] CD138 does not settle the question, because carcinomas can also express it. The initial panel therefore paired CD138 with pan-cytokeratin and HMB45, and their negativity excluded carcinoma and melanoma. Loss of CD45 is not universal in PBL. CD45 was expressed in 31% of HIV-associated cases in pooled data,[5] and all nine biopsies in the South Indian series were CD45 positive.[7] Within the large B-cell lymphomas, the differential diagnosis includes diffuse large B-cell lymphoma (DLBCL) with immunoblastic morphology, ALK-positive large B-cell lymphoma, primary effusion lymphoma and HHV8-positive large B-cell lymphoma.[10] Expression of CD20 or PAX5 favours DLBCL, whereas loss of both with expression of CD138, MUM1, Blimp1 and XBP1 supports PBL.[4,10] ALK-positive large B-cell lymphoma shares the plasmablastic morphology, CD138 and MUM1 expression and can express epithelial markers, but it is ALK positive.[11] The main differential diagnoses and the findings in this case are compared in Table 2.

Table 2: Differential diagnosis of a CD45-negative large-cell malignancy with plasmablastic features, and the findings in this case.

Entity	CD45	CD20 / PAX5	CD138/MUM1	Other markers	Clinical setting
Plasmablastic lymphoma[4,5,10]	Often negative or weak	Negative	Positive	EBER positive in most HIV-associated cases; ALK negative	HIV or other immunodeficiency; usually extranodal, often oral
Plasmablastic myeloma[9,12,13]	Variable	Negative	Positive	EBER negative; CD56 may be positive	Prior or synchronous myeloma; marrow disease, M-protein

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Entity	CD45	CD20 / PAX5	CD138/MUM1	Other markers	Clinical setting
ALK-positive large B-cell lymphoma[10,11]	Positive	Negative	Positive	ALK positive; EBER negative; epithelial markers may be positive	Nodal or extranodal
DLBCL with immunoblastic morphology[4,10]	Positive	Positive	MUM1 variable	Mature B-cell markers retained	Nodal or extranodal
Poorly differentiated carcinoma	Negative	Negative	CD138 may be positive	Cytokeratins positive	Known or occult primary
Melanoma	Negative	Negative	Not a defining feature	HMB45 positive	Cutaneous or mucosal primary
Present case	Negative	Negative	CD138 positive; MUM1 weak	Pan-CK, HMB45, ALK, CD10, CD30 and EBV LMP1 negative; c-MYC 25-30%; BCL6 35-40%	HIV positive; no oral lesions; bilateral cervical nodes; marrow FDG uptake; calcium and creatinine normal

The most difficult distinction was from plasmablastic myeloma, because PET-CT showed FDG uptake in the marrow of several bones. Vega et al found that most AIDS-related PBLs had an immunophenotype virtually identical to plasmablastic myeloma. CD56 was expressed in 5 of 9 PBLs and 3 of 7 myelomas, and the only consistent difference was EBV-encoded RNA (EBER), present in every PBL tested and absent from every myeloma.[12] Colomo et al described extramedullary plasmablastic tumours in patients with myeloma that could not be told apart from PBL on morphology.[9] Ahn et al found no distinctive morphological or phenotypic feature, and EBV in situ hybridisation was the most useful histological test. Lymphadenopathy without complete myeloma-defining findings favoured lymphoma.[13] HIV infection and bulky nodal disease favour PBL in this patient, and focal CD56 positivity does not help in either direction. The normal blood counts, serum calcium and creatinine also mean that anaemia, hypercalcaemia and renal impairment, three of the myeloma-defining features, were absent. The marrow uptake could reflect marrow involvement by either disease. Without bone marrow examination, serum and urine protein electrophoresis with immunofixation, serum free light chains and light chain studies on the tissue, plasmablastic myeloma cannot be fully excluded. We have therefore described the lesion as a plasmablastic neoplasm favouring PBL.

EBV is found in most HIV-associated PBLs, 75% in pooled data.[5] The negative EBV LMP1 stain does not

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exclude it. In the original series, EBER was detected in 9 of 15 tumours tested, and only 5 of these expressed LMP1.[1] EBER in situ hybridisation would add more to this case than any other single test, both for the myeloma question and for prognosis.[12,13]

MYC aberrations were present in 78% of HIV-associated PBLs in pooled data.[5] MYC rearrangements, mostly with immunoglobulin gene partners, were found in 49% of PBLs and were more frequent in EBV-positive tumours.[14] MYC protein overexpression also occurs without rearrangement.[15] In this case c-MYC was expressed in only 25-30% of the large cells, and fluorescence in situ hybridisation would be needed to look for a rearrangement. BCL6 is usually negative or only weakly and partially expressed in PBL,[1,12] which fits the weak to moderate staining in 35-40% of cells seen here. The Ki-67 index of 40-50% is lower than generally described in PBL;[4,12] the South Indian HIV-positive series reported 85-90%.[7]

There is no standard treatment for PBL, and early relapse and chemoresistance are common.[4,10] In the LYSA cohort, HIV-positive status was associated with better overall survival on univariate analysis, and the International Prognostic Index, chemotherapy and complete response were associated with survival on multivariate analysis.[8] In pooled data, Ann Arbor stage I, EBV positivity, CD45 expression and absence of MYC aberrations predicted a better outcome.[5] This tumour was CD45 negative and its EBER status is unknown.

This report has limitations. Bone marrow examination, serum protein studies, kappa and lambda light chain studies and EBER in situ hybridisation were not available, so plasmablastic myeloma could not be fully excluded. The PET-CT images and full report, and treatment and follow-up details, were also not available to the reporting department.

Conclusion

In an HIV-positive patient, a lymph node replaced by large cells that are negative for CD45, CD20 and PAX5 should prompt plasma cell markers early in the work-up, together with epithelial markers and ALK. Cervical lymphadenopathy with fever and night sweats in such a patient, particularly with a history of tuberculosis, may first be taken for infection.

Separating PBL from plasmablastic myeloma depends on clinical, radiological and laboratory correlation more than on morphology. EBER in situ hybridisation, light chain studies, bone marrow examination and serum protein studies complete the work-up and help guide treatment.

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