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Plasmablastic Lymphoma: The 'Rare' Frequency Among Immunocompromised Patients

Radu Bogdan FLORESCU[1,2*], Mihai Emilian LAPADAT[1,2], Alexandra MARCOCI[1,2], Miruna IOVAN[1,2], Madalina Deliana SELAGEA[1,2], Irina Nicoleta TRIANTAFYLLIDIS[1,2], Anca Mariana CIOBANU[2], Oana STANCA[1,2]

Abstract

Limfoproliferations associated with HIV infection/AIDS are rare conditions, with an incidence of malignant lymphomas of approximately 10% among the 25-40% malignancies that can occur in these immunosuppressed patients (1). Plasmablastic lymphoma (PBL), with an incidence of only 2% (out of the total lymphomas), is a borderline form (morphologically and immunophenotypically) between lymphoma and myeloma, defined by its high aggressiveness and unfavorable prognosis (2). Objectives: identifying the clinical, histopathological, and biological characteristics of PBL that require a differential diagnosis within other malignant hematological conditions associated with HIV infection. Materials and Methods: We present three comparative cases of PBL that were observed at the Colțea Hematology Clinic in a short time window (4 months). All patients were diagnosed with PBL in the context of HIV/AIDS infection, with an average age of approximately 41 years, predominantly male (66.6%), and with a symptomatology onset characteristic of immunocompromised individuals (manifesting at the oral, lymph node, and cutaneous levels), but with specific aspects related to associated comorbidities (e.g., psychiatric pathology, dilated cardiomyopathy), risk behaviors (e.g., intravenous drug use for 20 years), and infectious/ non-infectious complications, which influenced the patients' evolution. Conclusions: Plasmablastic lymphoma still represents a highly aggressive condition with an unfavorable prognosis, possibly having a higher clinical incidence than that described in the literature and requiring a adequate multidisciplinary approach.

Keywords: plasmablastic lymphoma, HIV, AIDS related lymphoma, incidence, aggressive disease, cytogenetic studies

[1] University of Medicine and Pharmacy "Carol Davila" – Hematology Department- Coltea Clinical Hospital, Bucharest, Romania

[2] Hematology Clinic- Coltea Clinical Hospital, Bucharest, Romania

Corresponding author:
***Radu Bogdan Florescu,** MD, Resident Doctor, Hematology Clinic, Coltea Clinical Hospital, I.C. Bratianu Bvd. No.1, Bucharest, Romania
email: radu-bogdan.florescu@rez.umfcd.ro

Case series:

We hereby present 3 patients who presented at Hematology department of Coltea Clinical Hospital with plasmablastic lymphoma between March and June of 2023 (for simplification reasons we will tag this patients from P1 to P3 and the cases are going to be displayed by comparison). The average age was 41 years and the sex distribution shows a predominance of male sex (66.6%). All patients show an immunosuppressed status associated with HIV infection (added to other risk factors and comorbidities that are more frequently encountered in this group of patients). (Table 1)

	Age	Sex	Risk factors	Other comorbidities	HIV infection status	ART
P1	53	F	None	Anxiety- depressive syndrome (on psychiatric treatment)	AIDS C3 (from March 2023) CD4: 42 cells/mm^3 CD 4/CD 8 = 0.37 RNA HIV: 523 x10^3 copies/ml	Bictegravir/ emtricitabine/tenofovir alafenamide 1cp/day (from March 2023)
P2	35	M	Heavy smoking Drug user (Cannabis)	Hepatitis B	AIDS C3 (with uncertain onset) CD4: 45 cells/mm^3 CD4/CD 8 = 1,46 RNA HIV: 160 x10^3 copies/ml	Bictegravir/ emtricitabine/tenofovir alafenamide 1cp/day (from March 2023)
P3	36	M	Heavy smoking Drug addict (iv user for 18 years) – currently in rehab	Hepatitis C Dilatative cardiomyopathy Secundary syphilis	AIDS C3 (from March 2023) CD4: 13 cells/mm^3 CD4/CD 8 = 0.06 RNA HIV: 293 copies/ml	Emtricitabine/tenofovir 1 cp/day, Raltegravir 1cp x2/day (from March 2023)

Table 1. iv – intravenous; AIDS – acquired immune deficiency syndrome; ART- Antiretroviral Treatment

All three patients had a typically PBL onset with a mass in oral cavity, which presented a rapid increase in size, with central necrosis and suprainfection, along with progressive extension to maxillary sinus and left orbit in one case. (P1 – Image 1). Other involvements with a higher frequency in immunosuppressed patients that were found in our cases are nodal disease (P2, P3 – Image 2), skin involvement (P3) and, with a lesser frequency, bone marrow involvement (P2). – Table 2

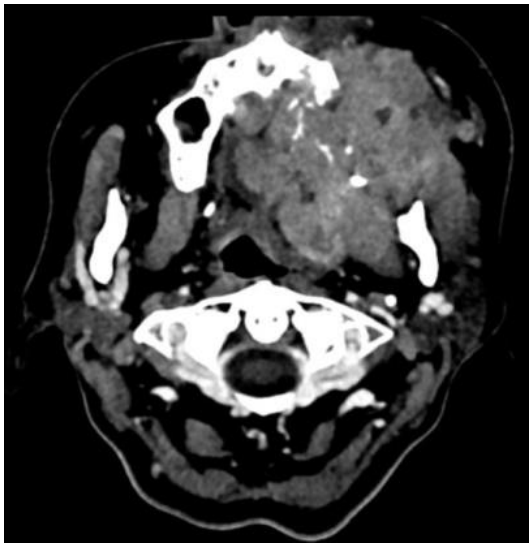

Image 1 (P1) – CT scan with contrast, cervical region, coronal section – maxillary sinus extension of the oral mass

Image 2 –Laterocervical lymph nodes involvement

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	Date of diagnosis	Constitutional symptoms	Onset involvement	Ann Arbor Staging	IPI score (less relevance in HIV + patients)
P1	March 2023	None	Oral cavity – with maxillary sinus extension	IV A, X, E	3 – High-intermediate risk
P2	May 2023	Sweating Fever Weight loss	Oral cavity Left laterocervical mass (over 8 cm) Bone marrow	IV B, X	4 – High risk
P3	June 2023	None	Oral cavity Bilaterally laterocervical masses (over 8 cm) Skin (mostly upper body)	IV A, X	4 – High risk

Tabel 2

The biopsy was performed on the oral cavity mass (P1, P3) and the laterocervical lymph node (P2), with histopathologic exam and immunohistochemical staining (IHC), which established the PBL diagnosis. IHC stains showed a typically PBL immunophenotype profile: positive - CD138, CD38, CD30, MUM1; negative - CD20, CD56, CD10, bcl-2, bcl-6, HHV8; ki67 > 70%.; particularly: P1 – LMP1 positive (Epstein Barr Virus - EBV expression), P3 - c-myc overexpression.

Due to the high aggressiveness of the disease (bulky masses, dysphagia, difficulties breathing, rapid extension, and pancytopenia in P2) we opted for dose adjusted HYPER-CVAD/MA chemotherapy protocol (hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone/ methotrexate, cytarabine) for all 3 patients, which was started as soon as possible. It is important to mention that P2 presented with fever, severe pancytopenia, elevated LDH, elevated ferritin, hypofibrinogenemia, hypertriglyceridemia, and abnormal liver function tests. A bone marrow aspiration was performed which underlined hemophagocytosis. Based on clinical and paraclinical criteria the diagnosis of hemophagocytic syndrome was confirmed. It was managed with low dose etoposide and steroids, with favorable outcome. Despite the advanced stage disease and these complications, the early clinical response to the treatment was favorable (Image 3).

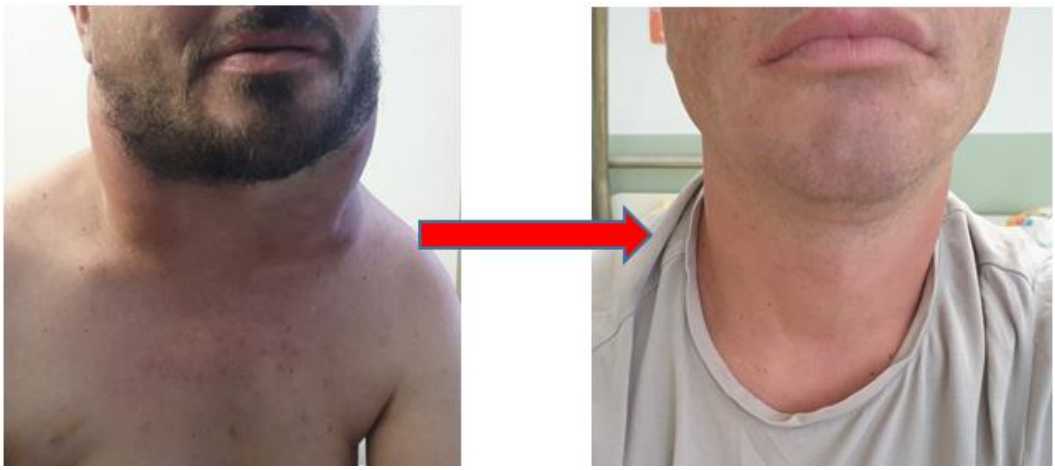

Image 3 – massive reduction (by size and number) of laterocervical masses)

However, due to the frailty of HIV + patients, P1 and P2 developed a long period of aplasia secondary to first and subsequent chemotherapy regimens (despite neutropenic fever prophylaxis with GCSF). Prolonged aplasia was accompanied by multiple infectious complications (sepsis, skin abscess, anal abscess, and viral retinitis – table 3) which were either managed in our clinic or by collaboration with HIV department of Infectious Disease hospital. It's very important to mention that with all 3 patients we had a difficult collaboration (due to depressive episodes, being in rehab period or by requesting hospital discharge contrary to medical advice).

The patients were followed up for a short period of time between 4 to 6 months. The current status of the patients is not encouraging: all 3 patients suffered multiple complications, which resulted in exitus. P1 was admitted to infectious diseases department with fever, anal abscess and severe neutropenia. After large spectrum antibiotherapy and granulocytic colony-stimulating factors, her clinical status improved, but the patient refused further hospitalization and suffered exitus at home.

P2 presented in the emergency room of Coltea Clinical Hospital with right vision impairment, fever, generalized mucocutaneous bleeding and severe pancytopenia (after 3 days from a personally requested hospital discharge). He was admitted to the hematology department. Despite supportive treatment, the clinical status was gradually deteriorating and culminated with acute respiratory distress, mechanical ventilation and exitus.

P3 had a favorable clinical evolution, with no significant complications during the first two cycles of chemotherapy regimen. An intermediate imaging evaluation by PET-CT scan was planned, but the patient was positive for SARS-COV2 infection. Because of the severe respiratory impairment he was admitted to the ICU department and consequently non-invasive ventilation was required. After a period of stable clinical status, he developed sudden massive hemoptysis and exitus.

	COMPLICATIONS (chronological order)	**CLINICAL EVOLUTION (months)**
P1	bronchopneumonia with K. pneumoniae, Sepsis, DIC CMV retinitis – treated with valganciclovir C. Difficile Enterocolitis Anal fistula complicated with anal abscess and sepsis with E. Coli	6 months
P2	hemophagocytic syndrome, DIC , Gastroenterocolitis right axillary abcess, subconjunctival hemorrhage Staph. Haemoliticus sepsis, acute respiratory distress	4 months
P3	SARS-COV2 infection with severe pulmonary impairment and massive hemoptysis	4 months

Table 3 – DIC = disseminated intravascular coagulation, CMV = cytomegalovirus

Discussions

HIV prevalence in Europe and Central Asia averages 0.9 %, with a rising tendency for east European countries. AIDS defining malignancies had a progressively decreasing incidence (since 2002 - late ART period) of 25-40% among HIV positive people. Less than 10% develop non-Hodgkin lymphoma (NHL). PBL represents approximately 2% AIDS defining NHL (around 0.5 cases/ 100.000 people/ year) – figure 1 (3) (4) (5). It is important to underline that this 3 new cases of PBL have presented in a very short period of time (4 months) which raises the question: is real life incidence higher than the one described in literature or is this occurrence just a coincidence?

Arguments in favor of first theory may be that PBL is associated with high aggressiveness and high mortality (which leave a short time window for diagnosis work-up). Also, the profile of a PBL patient (drug user, HIV positive, etc.) may delay the diagnosis (either by refusing medical attention or by complex differential diagnosis). Moreover, the diagnosis may be easily overlooked because of the extensive pathology assays required- specifically adequate immuno-histochemically staining.

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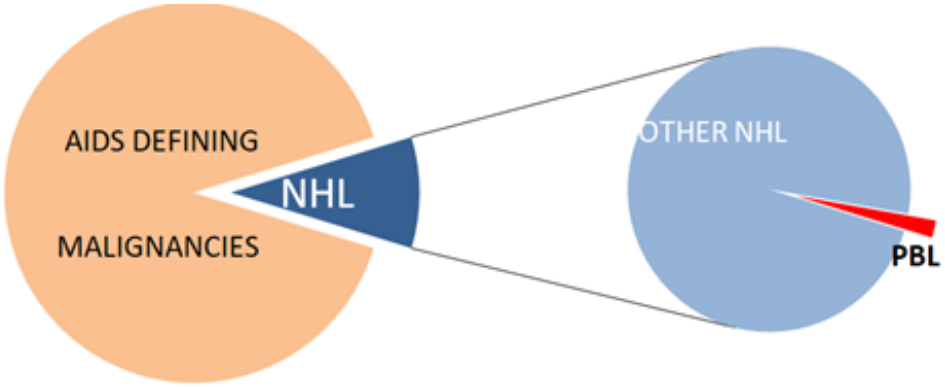

Figure 1 – PBL incidence (adapted from Lawrence D Kaplan- HIV-related lymphomas: Epidemiology, risk factors, and pathobiology).

In terms of managing AIDS related lymphomas (ARL), we are confronting with several problems due to the poor assessment of these patients' disease prognosis. The most common tool used for risk stratification in patients with aggressive lymphomas is International Prognostic Index (IPI). However, some studies have suggested that only ECOG performance status ≥ 2 and advanced stage disease are reliable indicators for a poor prognosis AIDS associated PBL (6) (7).

Furthermore, we are overlooking some features of HIV positive patients that may be independent risk factors for ARL (CD4+ count, CD4+/CD8+ ratio, viral load, type of ART, other AIDS related malignancies). The importance of a standardized scoring system for ARL was also underlined by the US researchers. They combined HIV scores (based on viral load, CD4+ count and prior history of AIDS), number of involved extranodal sites and age adjusted IPI. The new scoring system (ARL-IPI) proved to be more accurate for the assessment of overall survival (OS) in ARL patients, than aaIPI (8) (9).

Various studies have described a median overall survival of 12-18 months for PBL patients (10). The fact that these case reports show an OS reduced by half is attributed to infectious complications and not necessarily to disease aggressiveness. However, these aspects may raise another important question: which chemotherapy protocol is more suitable for our patient? Due to the lack of prospective studies it's difficult to establish a standardized protocol. There are some retrospective studies along with several case reports and case series that suggested a more targeted approach for PBL treatment (11).

Based on the results of retrospective studies, the current tendency in first line PBL treatment is to combine molecules from multiple myeloma (MM) protocols with a less aggressive lymphoma treatment. The most common combination was V-EPOCH (bortezomib, etoposide, vincristine, cyclophosphamide, doxorubicin, and prednisone), with promising results in terms of complete remission (CR) (10) (12). Another therapeutic combination of interest is Daratumumab (because of the high expression of CD38+ by plasmablasts) with dose adjusted EPOCH as a front line therapy (13) (14). The second or subsequent line of treatment in PBL may be improved by using of specific myeloma protocol. Regimens based on Daratumumab, like DRd (Daratumumab, Lenalidomide, Dexamethasone), were used in refractory/ relapsed PBL. The CR was achieved in few case reports, but no major study was conducted (15). These encouraging results may widen the spectrum of molecules which can be used for further research. Brentuximab vedotin (an anti CD30+ monoclonal antibody) and Pembrolizumab (PD1 inhibitor) are also promising therapeutic agents, which may be used even in monotherapy (16) (17). However, the major setback of this targeted treatment is that all this molecules can be used only as off-label therapy. The high costs of this agents will play a major deciding factor for not using this drugs.

The pathogenesis of PBL is slowly but gradually explained by cytogenetic studies (conventional karyotype, FISH, next generation sequencing). These tests are mandatory, especially in highly aggressive hematological malignancies, and can prove useful for disease prognosis assessment, novel treatment choice and even for making an accurate differential diagnosis. More than 60% of PBLs are associated with MYC translocations or amplifications which are reflected by MYC protein overexpression. MYC aberrations and TP53 mutations are associated with a poor prognosis and low OS (18) (19).

Other important findings in PBL are STAT3 mutations – SH2 domain (16-40%), IRF4 amplifications,

amplification of chromosome 1q21.3 (MCL1 anti-apoptotic protein), PRDM1 mutations and NOTCH signaling pathways. Some of them have therapeutic use (JAK inhibitors, Lenalidomide - downregulation of IRF4, anti MCL1 agents – currently in trials for MM). Differential diagnosis with extramedullary plasmocytoma may be challenging (even by immunohistochemically staining). STAT3 mutations may prove crucial for diagnosis (18) (19) (20).

One of the main characters of PBL pathogenesis is EBV infection. It main porpoise is to elude the immune system by any means (overexpression of PD-1/PD-L1, downregulation of MHC II on the tumor cells, apoptosis inhibition through NF-KB and NOTCH signaling pathway, IL-10 and TGF-B overproduction). EBV positive disease has a better event free survival, but has no influence on OS. However, negative EBV PBL is highly associated with TP53 mutation. This association may partially explain the poor prognosis and low OS of our patients (1/3 positive for EBV) (18) (21).

A multidisciplinary approach of AIDS related PBL is absolutely mandatory because of the complexity of these cases. However, there is a need for trained specialists in hemato-oncology (cardio-hematology, gastro-hematology, etc.) for a more personalized and targeted approach, with focus on the specific complications these patients may face.

Hematologic malignancies have a negative impact on the patients' quality of life. There are multiple scores and scales useful for this assessment (Karnofsky Performance Status, Edmonton Symptoms Assessment, EQ-5D-5L Quality of Life Questionnaire). Psycho-oncology is a new psychotherapeutic branch, which comes to spotlight in order to improve mental health and the quality of life of these patients. This therapeutic approach can provide support in addressing some physical and mental challenges that may have a negative impact for these patients wellbeing (cancer related pain and fatigue, fear of disease progression, fear of death) (22) (23).

Conclusions:

Plasmablastic lymphoma still represents a highly aggressive condition with an unfavorable prognosis, possibly having a higher clinical incidence than that described in the literature and requiring an adequate multidisciplinary approach.

Proper scoring system for AIDS related lymphoma and cytogenetics studies are indispensable tools for an individualized treatment and prognosis assessment.

Medical education of patients living with HIV infection and adequate training regarding differential diagnosis for health care providers may reduce the time window to a PBL diagnosis and also improve disease prognosis.

Abbreviations list:

AIDS – acquired immune deficiency syndrome
ARL - AIDS related lymphomas
ART- Antiretroviral Treatment
CMV – cytomegalovirus
CR - complete remission
DIC - disseminated intravascular coagulation
EBV - Epstein Barr Virus
GCSF – granulocyte colony sitmulating factor
IHC - immunohistochemical staining
MM - multiple myeloma
NHL - non-Hodgkin lymphoma
OS - overall survival
PBL - Plasmablastic lymphoma

Conflict of Interest

The authors declare no conflict of interest.

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