

Leukaemia Section

Short Communication

HIV-associated lymphomas

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Abstract

Lymphoma remains the most frequent neoplastic cause of death among HIV-infected individuals. Lymphomas in patients infected with HIV are heterogeneous, not only pathologically but also in terms of pathogenetic pathways and cellular derivation. This CARD summarizes the association of the different types of HIV-associated lymphomas with known genetic lesions and/or oncogenic viruses. In the setting of HIV infection different, but not mutually exclusive, pathogenic pathways might occur. For a distinct pathway of AIDS-related lymphomagenesis there can be multiple associated genetic lesions in the tumor. Several of the HIV-associated lymphomas are also related to EBV and/or KSHV (HHV-8) infection.

Keywords: AIDS-related lymphoma; HIV-associated lymphoma; HIV; lymphoma, gamma herpesviruses

Identity

Other names: AIDS-related lymphomas, HIV-related lymphomas, Lymphomas associated with HIV infection

Clinics and pathology

Disease

The most common lymphomas arising in HIV-infected individuals include Burkitt lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL).

Classical Hodgkin lymphoma (cHL) is also common. Other lymphomas include primary effusion lymphoma (PEL) and its solid variants, lymphoma associated with Kaposi sarcoma herpesvirus (KSHV)-related multicentric Castleman Disease (MCD), and plasmablastic lymphoma (PBL) (Table 1) (IARC 2012; Dolcetti et al., 2016;). The latter three types of lymphomas rarely occur in the general population.

Epidemiology

Lymphoma is still the most frequent neoplastic cause of death among HIV-infected individuals (Grulich et al., 2015). Young and middle-aged people afflicted with HIV infection are most often affected.

The age of lymphoma occurrence is dependent on the patient's age of HIV infection. Although the incidence of HIV-associated non-Hodgkin lymphomas has declined after the introduction of combination antiretroviral therapy (cART), these lymphomas remain the main type of cancer to be detected in HIV-infected people.

Curiously, the incidence of cHL has increased since the Highly Active Antiretroviral (HAART) era whereas the incidence of other HIV-associated lymphomas remains stable. This high incidence of lymphomas, despite the immunoreconstitution promoted by cART, strongly suggests that factors other than HIV-related immunosuppression are probably still acting as lymphomagenic factors in the HIV setting (Pantanowitz et al., 2015; Dolcetti et al., 2016;).

Burkitt lymphoma- mostly plasmacytoid
Primary central nervous system lymphoma
Diffuse large B-cell lymphoma, including primary central nervous system lymphoma (immunoblastic, plasmacytoid and centroblastic)
Plasmablastic lymphoma
Primary effusion lymphoma (PEL) and its solid variant (Classic PEL - in the absence of tumor masses; Solid PEL with or without serous effusion)
Multicentric Castleman Disease (MCD)-associated large cell lymphoma
Hodgkin lymphoma
Other histotypes (rare)
Marginal zone lymphoma
Unclassifiable lymphomas with features intermediate between Burkitt lymphoma and diffuse large B-cell lymphoma
Polymorphic B-cell lymphoma (PTLD-like)

Table 1. Categories of HIV-associated lymphomas

Clinics

Sex. There is an apparently higher risk of HIV-associated lymphomas in men than women.

Site. Lymphomas that develop in HIV-infected patients are predominantly aggressive B-cell malignancies.

These lymphomas display a marked propensity to involve extra-nodal anatomic sites such as the central nervous system, gastrointestinal tract, liver, bone marrow, and perinodal soft tissue. At diagnosis, most patients with HIV-associated HL present with advanced stages of disease with involvement of such extranodal sites.

Pathology

Macroscopy.

Most HIV-associated lymphomas present with extra-nodal tumour masses, lymphadenopathy with necrosis, and/or effusion.

Microscopy

Burkitt lymphoma (BL). HIV-associated BL includes cases that exhibit classic BL features, as well as cases that show plasmacytoid differentiation (Gloghini et al., 2013).

Diffuse large B-cell lymphoma (DLBCL). DLBCL can be morphologically heterogeneous. The different morphological variants of DLBCL include the centroblastic variant, immunoblastic variant (which requires there to be at least 90% of

immunoblasts with plasmacytoid features), and the anaplastic variant (Carbone et al., 2001; Gloghini et al., 2013).

Primary DLBCL of the central nervous system (PCNSL) associated with HIV infection usually belongs to the immunoblastic type.

Primary effusion lymphoma (PEL). Lymphoma cells range from large tumor cells showing anaplastic morphology to cells with immunoblastic or plasmablastic morphology.

These lymphomas frequently display a certain degree of plasma cell differentiation (Carbone et al., 2001; Cesarman et al., 1995).

Plasmablastic lymphoma (PBL).

These lymphomas can be subdivided into two morphologic subgroups: 1) lymphomas comprised of a monomorphic population of plasmablasts with no/minimal plasmacytic differentiation, and 2) lymphomas with plasmacytic differentiation, composed of plasmablasts and cells showing plasma cell differentiation (Delecluse et al., 1997; Stein et al., 2008).

Classical Hodgkin lymphoma (cHL). cHL is currently the most common type of non-AIDS-defining cancer.

Common encountered histological subtypes in HIV-positive patients include mixed cellularity and lymphocyte depleted cHL (Carbone et al., 2014; Uldrick and Little, 2015).

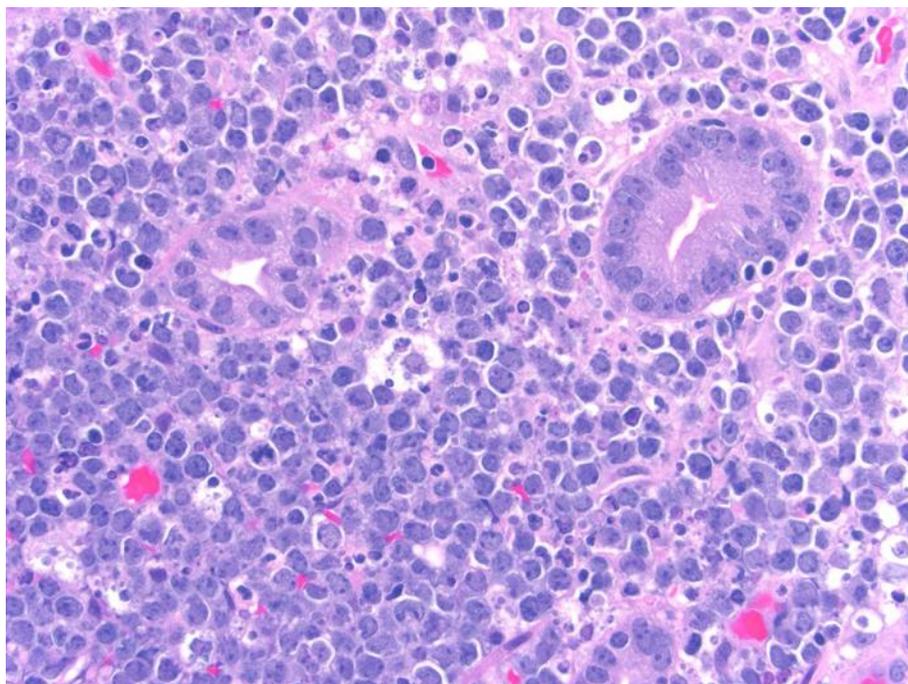


Figure 1. HIV-associated Burkitt lymphoma involving the colon (H&E stain, 40x magnification).

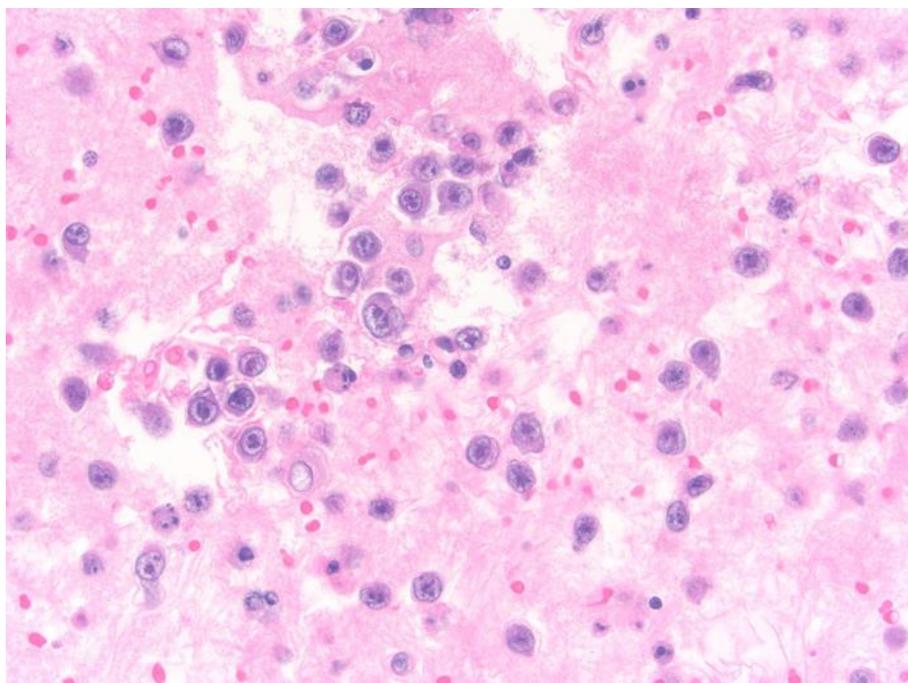


Figure 2. HIV-associated pericardial primary effusion lymphoma (cell block preparation, H&E stain, 40x magnification).

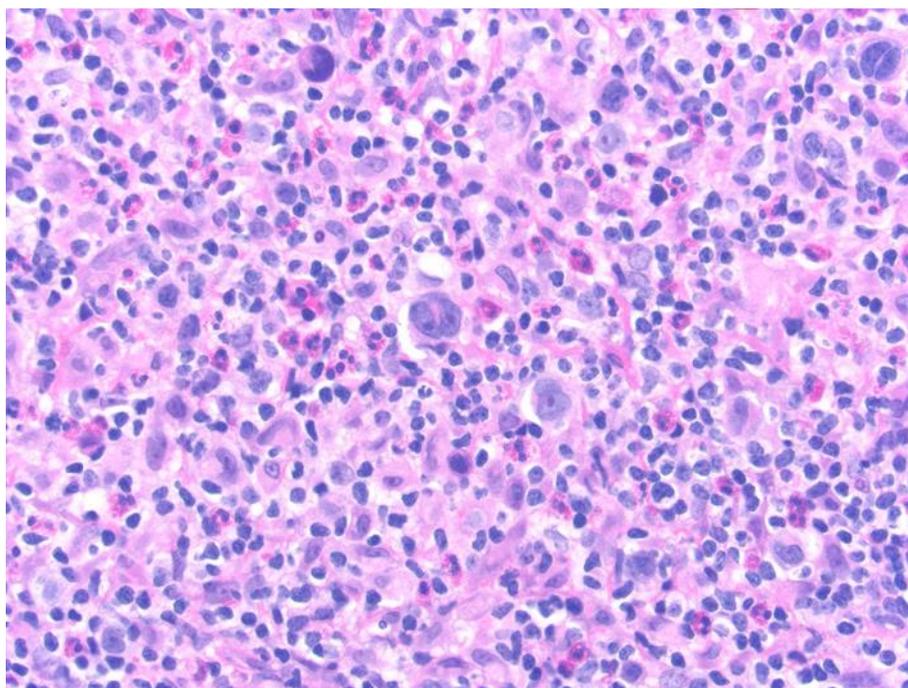


Figure 3. HIV-associated classical Hodgkin lymphoma of mixed cellularity subtype (H&E stain, 40x magnification).

Immunophenotype

BL: CD45+, CD20+, CD10+, BCL6+, BCL2-, MYC+, Ki67+ 100%
 DLBCL (CB): CD45+, CD20+, BCL6+, MUM1/IRF4-, CD138-
 DLBCL (IB): CD45+, CD20-/, BCL6-, MUM1/IRF4+, CD138-
 DLBCL (IB with plasmacytoid features): CD45+/-, CD20-/, BCL6-, MUM1/IRF4+, CD138+
 PEL: CD45+, CD20-, T/NK markers+/-, CD30+, CD138+, EMA+/-, LNA-1+
 PBL: CD45+/-, CD20+/-, CD79a+/-, PAX5-, CD138+, EMA+/-, CD31-/, LNA-1-
 cHL (Reed Sternberg cells): CD45-, CD20-/, PAX5+, CD30+, CD15+/-, OCT-2+, BOB.1-, LMP1+

Treatment

The combination of cART and chemotherapy treatment has resulted in a remarkable prolongation of survival among HIV-infected patients with lymphoma. Safety and efficacy of combined treatment including rituximab plus chemotherapy (R-CT) has been documented (Dunleavy and Wilson, 2012; Carbone et al., 2014). HIV-associated Hodgkin lymphoma shows unusually aggressive clinical behaviour, which mandates the use of specific therapeutic strategies. The combination of cART with better supportive therapy has made standard ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) and intensive chemotherapy regimens feasible in patients with HIV-associated Hodgkin lymphoma (Carbone et al., 2014; Uldrick and Little, 2015).

Prognosis

The outcome of HIV-associated lymphomas including Non-Hodgkin and Hodgkin lymphomas has dramatically improved since the introduction of cART with intensive chemotherapy regimens (Carbone et al., 2014; Uldrick and Little, 2015).

Immunodeficiency states usually increase susceptibility to cancer as a result of reduced immune surveillance and enhanced chances for viral-driven oncogenesis. The viral contribution to the development of HIV-associated malignancies has been extensively studied (IARC 2012); but only two oncogenic viruses -i.e., Epstein Barr virus (EBV) and Kaposi sarcoma-associated herpesvirus (KSHV)/Human Herpesvirus-8 (HHV8) - have been pathogenically associated with specific lymphomas occurring in the HIV setting (Carbone et al., 2009).

Table 2 lists those lymphoid proliferations occurring in HIV-infected patients that are known to be associated with infection by EBV and/or KSHV.

Importantly, these co-infected lymphomas are frequently associated with single or multiple genetic lesions, as shown in Table 2 (Carbone et al., 2001; Chadburn et al., 2013). The HIV virus itself is thought to contribute to lymphomagenesis through induction of chronic B-cell activation, due to HIV-mediated immune dysfunction. In summary, the pathogenesis of HIV-associated lymphomas is the result of different factors including impaired immune surveillance, genetic alterations, viral infection and chronic B-cell activation.

Histotype	BL	DLBCL-CB	DLBCL-IB	PBL	PEL
Viral Infection					
EBV	+/-	-/+	+	+/-	+/-
KSHV	-	-	-	-	+
Genetic abnormalities					
<i>BCL2</i>	-	-	30%	20%	-
<i>BCL6</i>	100%	>75%	-	<10%	-
<i>TP53</i>	50-60%	Rare	-	-	-
<i>MYC</i>	100%	0-50%	-	40%	-

Table 2. Co-infected lymphomas in people with HIV/AIDS S

Abbreviations. BL, Burkitt lymphoma; CB, centroblastic; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein Barr virus; HIV, human immunodeficiency virus; IB, immunoblastic; KSHV, Kaposi sarcoma-associated herpesvirus; PEL, primary effusion lymphoma; PBL, plasmablastic lymphoma; +, positive in 100% of cases; -, negative in 100% of cases; +/-, positive in less than 50% of cases; +/+, positive in more than 50% of cases

References

. A Review of Human Carcinogens. Part B: Biological Agents IARC Monograph on the Evaluation of Carcinogenic Risk to Humans. Vol. 100. IARC, Lyon, France, 2012.

Carbone A, Cesarman E, Spina M, Gloghini A, Schulz TF.. HIV-associated lymphomas and gamma-herpesviruses. *Blood*. 2009 Feb 5;113(6):1213-24 (REVIEW)

Carbone A, Gloghini A, Larocca LM, Capello D, Pierconti F, Canzonieri V, Tirelli U, Dalla-Favera R, Gaidano G. Expression profile of MUM1/IRF4, BCL-6, and CD138/syndecan-1 defines novel histogenetic subsets of human immunodeficiency virus-related lymphomas. *Blood*. 2001 Feb 1;97(3):744-51

Carbone A, Vaccher E, Gloghini A, Pantanowitz L, Abayomi A, de Paoli P, Franceschi S.. Diagnosis and management of lymphomas and other cancers in HIV-infected patients. *Nat Rev Clin Oncol*. 2014 Apr;11(4):223-38 (REVIEW).

Cesarman E, Chang Y, Moore PS, Said JW, Knowles DM.. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in AIDS-related body-cavity-based lymphomas. *N Engl J Med*. 1995 May 4;332(18):1186-91

Chadburn A, Abdul-Nabi AM, Teruya BS, Lo AA.. Lymphoid proliferations associated with human immunodeficiency virus infection. *Arch Pathol Lab Med*. 2013 Mar;137(3):360-70 (REVIEW).

Delecluse HJ, Anagnostopoulos I, Dallenbach F, Hummel M, Marafioti T, Schneider U, Huhn D, Schmidt-Westhausen A, Reichart PA, Gross U, Stein H. Plasmablastic lymphomas of the oral cavity: a new entity associated with the human immunodeficiency virus

infection. *Blood*. 1997 Feb 15; 89(4):1413-20.

Dolcetti R, Gloghini A, Caruso A, Carbone A.. A lymphomagenic role for HIV beyond immune suppression? *Blood*. 2016 Mar 17;127(11):1403-9 (REVIEW).

Dunleavy K, Wilson WH. How I treat HIV-associated lymphoma. *Blood*. 2012 Apr 5;119(14):3245-55 (REVIEW).

Gloghini A, Dolcetti R, Carbone A.. Lymphomas occurring specifically in HIV-infected patients: from pathogenesis to pathology. *Semin Cancer Biol*. 2013 Dec;23(6):457-67 (REVIEW).

Grulich AE, Vajdic CM.. The epidemiology of cancers in human immunodeficiency virus infection and after organ transplantation. *Semin Oncol*. 2015 Apr;42(2):247-57 (REVIEW).

Pantanowitz L, Carbone A, Dolcetti R.. Microenvironment and HIV-related lymphomagenesis. *Semin Cancer Biol*. 2015 Oct;34:52-7 (REVIEW).

Stein H, Harris NL, Campo E. Plasmablastic lymphoma Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele H, Vardiman JW (eds.) World Health Organization Classification of Tumours, Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues, Lyon: IARC Press, 2008:256-257

Uldrick TS, Little RF.. How I treat classical Hodgkin lymphoma in patients infected with human immunodeficiency virus *Blood*. 2015 Feb 19;125(8):1226-35 (REVIEW).

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