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LYMPHOMAS AND OTHER CANCERS IN HIV-INFECTED PATIENTS

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Absract: *Individuals infected by HIV might develop several types of cancer more frequently than uninfected people. Lymphomas represent the most frequent malignancy among patients with HIV/AIDS (PWHA). Other cancer types that have increased in PWHA include Kaposi sarcoma (KS), cancer of the cervix, anus, lung and liver. Multicentric Castleman Disease (MCD), a lymphoproliferative disorder presenting with heterogeneous pathological and clinical features, comprises disease entities with a complex aetiology and overlapping pathogenesis. MCD can be found in association with HIV infection, KS, primary effusion lymphoma and its solid variant, and Hodgkin lymphoma. This paper focuses on the different type of lymphomas that are generally occurring in PWHA. A comprehensive understanding of the intricacies of viral coinfection will probably lead to additional advances in managements for these disorders.*

KEY WORDS: *Lymphomas, HIV, AIDS, Kaposi sarcoma.*

INTRODUCTION

Despite the introduction of highly active antiretroviral therapy or combination antiretroviral therapy (HAART or cART, respectively) patients infected with HIV might develop certain types of cancer more frequently than uninfected people.

Lymphomas represent the most frequent malignancy among patients with HIV/AIDS (PWHA), displaying a 60-200 fold and 8-10 fold higher relative risk of developing non-Hodgkin lymphoma (NHL) and Hodgkin lymphomas (HL), respectively, compared to HIV uninfected people[1-3]. Diffuse large B-cell lymphoma (DLBCL), in particular, remains the main type of cancer that develops in HIV-positive patients. The incidence of other lymphomas such as Burkitt lymphoma (BL), HL, primary effusion lymphomas (PEL) and plasmablastic lymphoma (PBL) of the oral cavity type still remain high (Table 1)[1,2].

LYMPHOMAS

Lymphomas occurring specifically in HIV-positive patients which are listed in Table 2 display a phenotype related to plasma cell. BL with plasmacytoid differentiation have expression of CD20, CD10, BCL6, absence of BCL2, and a proliferation rate close to 100%. In other HIV-associated lymphomas tumor cells display a plasma cell differentiation-related phenotype. Specifically, plasma cell surface markers, such as CD138, are upregulated, whereas markers of mature B cells, such as CD20 and CD45, are usually downregulated[4]. Similarly, transcription factors associated with B cells in general (such as PAX5 and BCL6) are downregulated, whereas the fact that the transcriptional program has transitioned to that of plasma cells can be demonstrated by the expression of BLIMP1, XBP1, and IRF4/MUM1 proteins (Figure 1)[4-7].

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Table 1. Categories of lymphomas commonly occurring in HIV-infected patients[8].

The same aggressive lymphomas that develop sporadically in the absence of HIV infection
- Burkitt lymphoma
  – *Classical; Plasmacytoid diff.; Atypical*
- Diffuse large B-cell lymphoma
  – *Centroblastic; Immunoblastic*
- MALT lymphoma (rare)
- Peripheral T-cell lymphoma (rare)
- Classical Hodgkin's lymphoma

Unusual lymphomas occurring specifically in PWHA
- Primary effusion lymphoma
- Plasmablastic lymphoma of the oral cavity
- Lymphoma associated with KSHV-associated multicentric Castleman Disease

Lymphomas also occurring in other immunodeficient states
- Polymorphic B-cell lymphoma (PTLD-like)

Table 2. Lymphomas occurring specifically in HIV-infected patients.

- BL plasmacytoid
- Systemic IBL plasmacytoid
- PCNSL (IBL plasmacytoid)
- Hodgkin lymphoma
- PEL and its solid variant
- PBL of the oral cavity
- MCD- associated PBL

Furthermore, lymphomas occurring in patients with HIV are closely linked to other viral infections. GL, DLBCL, plasmablastic lymphoma and HL are associated with Epstein-Barr virus (EBV) infection (Table 3), although this association is not uniform[4,8-11]. By contrast, PEL and its solid variants are consistently linked to Kaposi sarcoma-associated herpesvirus (KSHV) infection[4,8]. Nonetheless, 70-80% of PEL are associated with EBV infection[4].

HIV-associated DLBCL of the immunoblastic type comprises predominantly large lymphoma cells with prominent central nucleoli.

Classic PEL morphologically shows features bridging immunoblastic and anaplastic large-cell lymphomas, and frequently displays a certain degree of plasma cell differentiation. Immunocytochemical staining for ORF73/LANA is the standard assay to detect evidence of KSHV.

PBL of the oral cavity type. PBL consists of a relatively uniform tumor cell population displaying a cohesive pattern and a plasma cell related morphology. The so called plasmablasts display abundant basophilic cytoplasm and eccentric nuclei that are either plasma cell-like or immunoblastic cell-like. PBL are characterized by strong immunostaining with the plasma cell markers MUM1/IRF4 and by high proliferative index.

Other cancers

The risk of Kaposi sarcoma remains substantially increased in HIV-infected patients on effective cART. Other cancers that have a strong association with PWHA include anal, cervical, hepatocellular and lung cancers[12].

Importantly, recent studies have reported a three-fold decrease in the incidence of Kaposi sarcoma and NHL (but not in cervical cancer) after the impact of cART and a substantial increase of the number of non-AIDS-defining cancer (notably cancer of

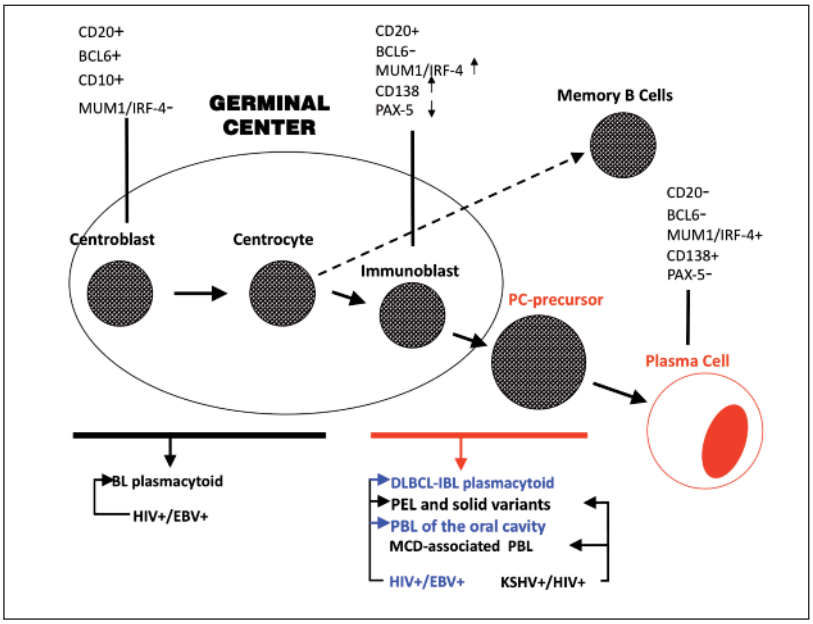

Fig. 1. Lymphomas occurring specifically in HIV-infected patients, their relationship with viral infection and stage of B-cell differentiation. Adapted from ref. 7.

Table 3. The spectrum of HIV-associated NHL and their relationship with gamma herpesvirus infection.

Lymphoma type	*EBV (%)*	*EBV latency*	*KSHV (%)*
Burkitt lymphoma with plasmacytoid differentiation	+ (60%)	I	–
Diffuse large B-cell lymphoma			
• Immunoblastic plasmacytoid variant	+ (90%)	II/III	–
Primary effusion lymphoma and solid variants	+ (90%)	I	+ (100%)
Plasmablastic lymphoma of the oral cavity type	+ (80%)	0/I	–
Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease	–	–	+ (100%)
Polymorphic B-cell lymphoma (PTLD-like)	+ (>90%)	I/II/III	–

the liver, anus, lung, non-melanocytic skin, and HL)[13-17]. However, statistical analyses showed that the increase in non AIDS-defining cancer was mainly driven by the presence of an ageing population with HIV in more-developed countries[14].

As a consequence of effective cART, an increasing number of elderly people with HIV/AIDS reaches an age in which epithelial cancer become frequent.

These cancers are mostly infection-related (Table 4), and exhibit histopathological and immunophenotypical features similar to those observed in HIV-negative patients.

Coinfection of HIV with different viruses represents a common issue in malignancies of immune compromised hosts

Multicentric Castleman disease (MCD)

MCD is lymphoid disorder, presenting with heterogeneous features. CD was first described as a solitary lesion[18], occurring most often in the mediastinum or pulmonary hilus, although its presence in other anatomic sites was subsequently established. Sporadic reports of a "multicentric" variant of CD (MCD) subsequently appeared in the literature[19,20].

Updated definition of Multicentric Castleman disease (after AIDS epidemic). MCD has become increasingly relevant in recent years given its association with HIV and KSHV infections. KSHV-associated MCD is characterized by the presence of plasmablasts harbouring KSHV

Table 4. Other cancer types occurring in patients with HIV/AIDS and relationship with infectious agents

Cancer type	*Infectious agent*
Kaposi sarcoma	KSHV
Cervical cancer, HPV	HPV
Lower female genital tract (vulva and vagina) carcinoma	HPV
Anal carcinoma	HPV
Hepatocellular carcinoma	HBV/HCV
Merkel cell carcinoma	Merkel cell polyomavirus
Lung carcinoma	?
Colorectal carcinoma	?

The coexistence of KS and MCD has been reported in 54%-72% of HIV-infected patients at diagnosis[21,22], whereas the occurrence of B-cell lymphomas has been identified in HIV-infected patients with MCD with incidence 15-fold higher than that in the HIV-infected population without MCD[23].

Recently, a new clinical entity that describes a severe systemic infection/reactivation with KSHV has been proposed within the spectrum of KSHV-associated MCD: KSHV inflammatory syndrome (KICS)[24-26].

The complex interplay between KSHV and HIV have dramatically elevated risk for development of KSHV-induced malignancies, i.e. KS, PEL, and MCD (Figure 2)[27].

Although MCD, KS and PEL are disease entities displaying distinct clinical and pathological features (see above), KSHV-associated MCD is usually a tangle of these different entities which are also commonly associated with HIV and KSHV infection (Figure 2).

Interactions among coinfecting viruses may increase cellular transformation and oncogenesis. A role of viral cooperation in lymphomagenesis is suggested by the simultaneous detection of coinfecting viruses within the same neoplastic cells. This occurs in HIV-associated PEL tumor cells harbouring EBV and KSHV infection. In other cases, non specific mechanisms inducing cellular proliferation and genetic abnormalities are preferentially involved[28].

Concluding remarks

Understanding the involvement of viral infection in specific lymphomas and other malignancies, and defining the molecular mechanisms of viral carcinogenesis are important steps towards better prevention, diagnosis and treatment strategies for HIV-associated cancers.

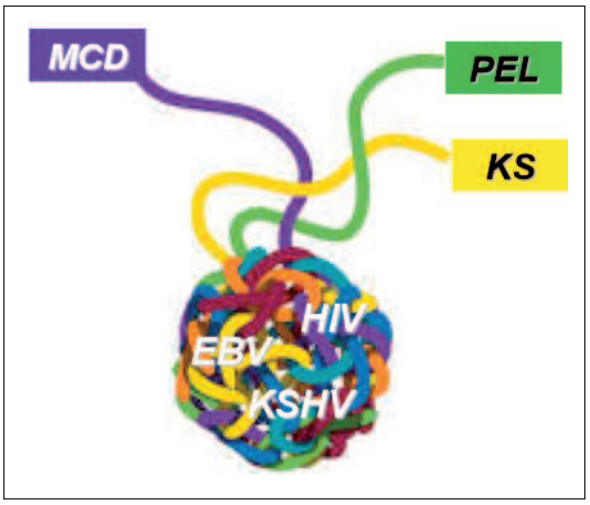

Fig. 2. KSHV-associated multicentric Castleman disease. A tangle of different entities requiring multitarget treatment strategies. Adpated from an illustration created in Adobe Illustrator for The Consumer Associations annual report cover (http://www.graphicnet.co.uk/wp/tangle-3/).

In their interesting paper entitled "Moving Forward in HIV-Associated Cancer", published in Journal of Clinical Oncology, Gopal and colleagues[29] affirm that 1) grouping HIV-associated cancers as infection-related or infection-unrelated is a good strategy in cancer diagnosis and research; 2) characterizing tumors with respect to genomic features is really important to optimize treatment. Besides the relationship of HIV-associated cancers with epidemiological research and diagnosis and patients treatment, the Agenda by Gopal and Colleagues draws the reader's attention on interesting, but still little known key points, such as 1) viral cooperation and tumor pathogenesis, and 2) the interactions between tumor development, cART use, HIV replication and immunosuppression.

In conclusion, we propose that the agenda of HIV-associated cancers should move forward also by defining strict criteria to establish the pathogenetic association between infectious agents and cancer and by designing unique prospective clinical trials on the management of cancer in patients at high comorbidity rate, including drug-drug interaction studies. Prevention/surveillance of cancer in the context of immunosuppression remains a challenge. The agenda should include integrated care practices to proactively monitor patients with long-term viral-immune monitoring and risk-adjusted cancer surveillance programs[30].

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