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EPSTEIN BARR VIRUS RELATED CANCER IN PEOPLE LIVING WITH HIV: A REVIEW OF THE LITERATURE

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Abstract – *The introduction of Highly Active Antiretroviral Therapy (HAART) has modified the natural history of Human Immunodeficiency Virus (HIV) infection, leading to an increase in life expectancy of the patients living with HIV (PLWH). Similar to other oncogenic viruses, EBV increases the risk of developing cancer in immune-depressed hosts, including HIV-infected people.*

The adherence to anti-retroviral therapy (ART) is important in the management of cancer in HIV-positive patients even if ART has a less favorable impact on EBV related tumors if compared with its impact on AIDS-defining cancers.

This review is focused on the epidemiology, pathogenesis, diagnosis, management and therapy of EBV-associated tumors in the setting of HIV infection.

KEYWORDS: *EBV, HIV, Cancer, Tumorigenesis, Burkitt's Lymphoma, Hodgkin's Lymphoma, Non-Hodgkin's Lymphoma, Nasopharyngeal Carcinoma.*

INTRODUCTION

The introduction of Highly Active Antiretroviral therapy (HAART) has modified the natural history of Human Immunodeficiency Virus (HIV) infection, leading to an increase in life expectancy of the patients living with HIV (PLWH)[1-35]. The incidence of Acquired Immunodeficiency Syndrome (AIDS)-related diseases has declined, while an increase in morbidity and mortality attributable to cancer and cardiovascular, renal, neurological diseases has been documented[36-43].

Malignancies associated with Epstein–Barr virus (EBV) are frequently found in patients infected with HIV[44]. In these patients, EBV is implicated in the development of many lymphoproliferative disorders: most of the Hodgkin's Lymphomas (HL), some Non-Hodgkin's Lymphomas (NHL) such as Burkitt's Lymphoma (BL), Primary Effusion Lymphomas (PEL), Diffuse Large B-Cell Lymphomas (DLBCL), Plasmablastic Lymphomas and Primary Central Nervous System Lymphomas (PCNSL) are caused by EBV infection[15]. Moreover, Nasopharyngeal Carcinoma (NPC) is associated with EBV[40].

This review is focused on the epidemiology, pathogenesis, diagnosis, management and therapy of EBV-associated tumors in the setting of HIV infection.

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MATERIALS AND METHODS

On July 25th, 2019, we performed a review of the literature to identify the link existing between Cancer, Epstein Barr Virus (EBV) infection and Human Immunodeficiency Virus (HIV) infection.

We searched PubMed applying "EBV", "HIV", "cancer", "tumorigenesis", "Burkitt's Lymphoma", "Hodgkin's Lymphomas", "Non-Hodgkin's Lymphomas", "Diffuse Large B-Cell Lymphomas", "Plasmablastic Lymphomas".

We included only recent articles written in English, identifying 83 records. We excluded 11 articles after reading title and abstract. At the end of the assessment we included in our review the 72 full-text articles.

ETIOLOGY

Epstein-Barr virus (EBV), also known as human herpesvirus 4 (HHV4), is a double-stranded DNA virus belonging to the *Gammaherpesviridae* family which asymptomatically infects the majority of population[45].

More than 95% of the world population is seropositive[46]: primary EBV infection is usually acquired during childhood and the virus can establish a lifelong infection in immunocompetent subjects[15]. EBV transmission is through droplets. The virus infects B cells and epithelial cells in the oral cavity. Primary infection may be asymptomatic, or, after an incubation period, it can clinically manifest with fever, lymphadenopathy and pharyngitis[47].

The majority of cases are self-limiting with an excellent prognosis. Serious complications during the acute phase such as hepatitis, splenic rupture or airway obstruction are rare[46,47].

TUMORIGENESIS

EBV infects both B cells and epithelial cells, turning resting B-lymphocytes into proliferative lymphoblastoid cells, eventually immortalizing them[45-47].

Similar to other oncogenic viruses, EBV increases the risk of developing cancer in immune-depressed hosts, including HIV-infected people[46].

Like all herpes viruses, EBV has both latent and lytic replication programs. In the immunocompetent host, virus persists in naïve memory B cells in a non-pathogenic state for the lifetime of the host. Intermittently, these virus-infected memory B cells differentiate into plasma cells, activating the lytic-cycle and promoting infection of other resting B-lymphocytes[48].

EBV needs to express the latent program to drive tumorigenesis. During latent infection, the virus replicates its genome in the host cell chromosomes, but it does not produce infectious virus[46,48].

Latent proteins include latent membrane proteins (LMP-1, -2A and -2B), leader protein (LP) and nuclear antigens (EBNA-1, -2, -3A and -3C). LMP-1 is the main oncogenic protein of EBV and stimulates the proliferation and differentiation of B cells, acting like CD40 (a member of Tumor Necrosis Factor Receptor- TNFR super-family) and leading to the activation of NF-kB and the c-Jun amino-terminal kinase[48].

LMP-1 may directly contribute to the generation of an immunosuppressive microenvironment through its ability to induce/enhance the production of immunosuppressive cytokines such as IL□6, IL-8 and IL-10[49].

HIV may contribute to EBV-driven tumorigenesis by multiple mechanisms: HIV creates an environment in which chronic antigen stimulation, cytokine dysregulation, and coinfection with oncogenic viruses, in the background of genetic abnormalities and disrupted immune surveillance to tumor antigens, can lead to the emergence of monoclonal B cells[50].

Viral proteins such as gp120, Tat and Nef can induce polyclonal B-cell activation. Moreover, immune-activation induced by HIV may influence the expansion of B-cell compartment. The overproduction of B-cells cytokines such as IFNα, IL-6 and TNFα is associated with chronic B-cells hyperactivation: the increased turnover leads to an increased risk of developing B-cell lymphomas[48,50].

HAART is the best weapon to control HIV replication: an adequate control of HIV replication has been associated with decreased plasma EBV DNA; this favorable impact has been observed in patients with viro-immunologic response to HAART and also in virologically suppressed subjects who did not experience adequate CD4+ T-cell recovery[51].

Moreover, an increase in EBV viral load was reported among immunologic responders with detectable HIV viral load. Patients on HAART often have persistent low-level HIV viral load which may cause chronic activation of the immune system, leading to the expansion of EBV-infected cells and, consequently, the onset of EBV-related malignancies. Loss of immune surveillance against EBV probably represents the most important mechanism driving tumorigenesis in the context of severe immunosuppression[52].

HAART has a less favorable impact on EBV related tumors if compared with its impact on AIDS-defining cancers. Although tumors like Primary Central Nervous System Lymphomas (PCNSLs) are favorably influenced by the introduction of HAART, its effect is less impactful on the

incidence of other NHLs, which occur even in the setting of moderate immunosuppression[15,51].

PLWHA have a 60-200-fold and 8-10-fold higher relative risk to develop NHL and HL, respectively, compared to the HIV-negative population[15].

Individuals with normal or slightly decreased number of circulating T CD4+ lymphocytes have a higher risk of BL and centroblastic DLBCL and the risk of PEL and plasmablastic DLBCL is higher among patients with severe immunodeficiency[53].

Engels et al [54] have confirmed that the risk substantially increases in patients with >100,000 HIV-1 RNA copies/ml and/or with <50 CD4+ cells/µl.

NON-HODGKIN'S LYMPHOMA (NHLS)

NHLs are a heterogeneous group of malignant diseases, and they are considered an AIDS-defining cancer (ADC). In the pre-HAART era, PLWHA had a 100-fold increased risk of NHL if compared with general polulation[55]. Currently, NHL still is one of the most important cause of death in HIV-infected patients[15]. However, the incidence of HIV-associated NHLs has significantly decreased after the introduction of HAART: the adjusted incidence rate of NHL was estimated to decline from 6.2% in the pre-HAART era to 3.2% in the HAART era[15,55].

Most NHLs are B-cell neoplasms. Moreover, in PLWHA, they are often found in an advanced stage and are often clinically expressed by the so-called "B symptoms", such as fever, night sweats, weight loss. Clinical manifestation of NHLs depends on location, rate of cancer growth and residual function of any organ compromised by the tumor. In addition, clinical manifestations also depend on the grade of the neoplasia, which can be low, intermediate or high.

When an NHL is suspected, the patient should undergo a series of blood and radiologic tests, such as a complete blood count and at least a total body CT scan and a positron emission tomography (PET)-CT. The workup is completed by bone marrow aspiration, lymph nodes or tumor biopsy and histological examination.

The most frequent morphologic subtypes of NHLs are diffuse large B-cells lymphomas (DLBCL) and BL.

Diffuse large B-cell lymphoma (DLBCL)

NHLs account for 10% of all malignancies in the HIV population and about 70–90% of patients have diffuse large B-cell lymphoma[56].

DLBCL can be divided into centroblastic (CB) and immunoblastic (IB) histological subtypes[54,56].

IB DLBCL usually affects patient with advanced immunosuppression: it is associated with EBV infection in 90% of cases and LMP-1 and EBNA-2 are usually expressed. On the contrary, CB DLBCL usually affects subjects with mild immunosuppression and EBV positivity has been reported in 30% of HIV-positive patients[57].

The majority of DLBCL demonstrates increased expression of the B-cell lymphoma 6 (BCL-6) gene. Overexpression of BCL-6 in B-cell lymphoma cell lines leads to downregulation of BCL-6 target genes, including the p53 tumor suppressor gene. This may be a way in which BCL-6 avoids cells apoptosis in response to DNA damage. Other mechanisms include aberrant somatic hypermutation, BCL-2 activation and c-myc overexpression[58]. The epidemiological characteristics of HIV-related DLBCLs changed after the introduction of HAART, but the overall incidence and EBV association rate of these malignancies still remain significantly higher than the general population[15]. HIV-1 increases the risk for systemic DLBCL by 60–200-fold[59].

At the time of diagnosis, more than half of the patients have evidence of advanced stage and with B symptoms and extra-nodal disease. The clinical presentation can include symptoms like enlarged lymph nodes, night sweats, unusual weight loss, loss of appetite, extreme fatigue, fever and itchiness, abdominal pain, diarrhea, cough and shortness of breath.

Prognosis depends on patient-, lymphoma- and HIV-specific factors[15,51].

Treatment with 6 cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) or R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) is the standard of care for DLBCL. Similar to HIV-negative patients, autologous hematopoietic stem cell transplantation (HSCT) may represent an option in case of relapsing [15,54].

Burkitt lymphoma (BL)

Burkitt lymphoma (BL) is a highly aggressive non-Hodgkin B cell tumor that can be classified into three variants based on clinical features and disease epidemiology: endemic, sporadic and HIV-associated BL[60]. While endemic and sporadic BLs are not important for PLWHA, HIV-associated BL is an important, though rare, cause of disease and death in HIV-infected people. Moreover, HIV infection increases BL incidence by more than 100-fold and the 30–40% of these malignancies are EBV-positive[15,61,62]. BL typically develops early in the context of HIV infection, in patients with preserved immune function. The clinical presentation is characterized

by bulky abdominal masses, lymphadenopathy and B symptoms. It is rapidly progressive.

PLWHA can be treated using the same CTX regimens used for general population (B-ALL regimen, Hyper-CVAD, CODOX/M-IVAC)[53,55].

Dunleavy et al[58] show that dose-adjusted R-EPOCH protocol (rituximab, etoposide phosphate, prednisone, vincristine sulphate, cyclophosphamide and doxorubicin hydrochloride) associated with methotrexate is a good option for the treatment of HIV-positive and negative patients.

The prognosis in PLWHA depends on CD4+ T-cell count, bone marrow involvement and performance status[15,57].

PLASMABLASTIC LYMPHOMA (PL)

HIV-associated PBL is an AIDS-defining cancer, classified by WHO as a distinct entity of aggressive DLBCL, characterized by a diffuse proliferation of large neoplastic cells most of which resemble B-cell immunoblasts[63]. It is a common cancer in HIV-positive patients with CD4+ T-cell counts <200 cells/μL[15,63].

The pathogenesis of PL is poorly understood and determined by a complex biological interplay between HIV-related immunodeficiency, the loss of immune control of oncogenic herpesvirus as EBV, genetic cellular abnormalities and chronic immune activation[63]. HIV-associated PBL is closely linked to EBV infection, and more than 80% of PBL cells express EBV-encoded RNA (EBER-ISH). Molecular analysis of BCL2 and BCL6 are usually negative[64]. Classically, immunophenotype is CD45, CD20, CD79a negative and CD38, CD138, MUM1 positive, EBER and KI67 expression is >80%[63].

Clinically, PBL is an aggressive disease mainly involving the oral cavity even if extraoral and extra nodal sites, including gastrointestinal tract, skin, soft tissue, heart, mediastinum, retroperitoneum, liver, lungs, testes, vulva, parotid gland, breast, central nervous system (CNS), lymph nodes and bone marrow are not infrequent[65]. Prognosis of patients affected by HIV-associated PBL is poor. Castillo et al[65] evaluated the characteristics of 50 patients with HIV-associated PBL and confirmed a poor prognosis regardless of the therapy received.

The diagnosis requires tissue or lymph node biopsy and core needle or fine needle (FNA) biopsy. Standard treatment is, usually, CHOP or CHOP-like regimens while more intensive regimens as CODOX-M/IVAC or DA-EPOCH are possible options[63].

Most guidelines recommend the use of cART during chemotherapy, keeping in mind the possible overlapping toxicities, pharmacokinetic interactions, and adherence problems[65].

HODGKIN'S LYMPHOMA (HL)

HL is the most common non-AIDS-defining cancer[60]. Despite being a NADC, in PLWHA the incidence of HL is 10-fold higher than in the general population[15].

HL can be classified into classical HL (cHL), which accounts for the majority of cases, and nodular lymphocyte predominant HL (NLPHL). cHL can be further subdivided into four histological subtypes: nodular sclerosis, mixed cellularity, lymphocyte depleted and lymphocyte rich[66].

The development of HIV-related HL does not depend on T cell impairment, occurring even in patients with modest reductions in $CD4^+$ T cell counts. A possible explanation is that partial CD4+ T cells suppression is sufficient to elevate EBV loads in the B cell system, contributing to cHL pathogenesis[65]. The association of EBV infection with HL is particularly important in PLWH and infrequent in HIV-negative people. The predominant subtypes of HL in the setting of HIV infection are the mixed cellularity (MC) and the lymphocyte-depleted (LD) ones[15,65]. These subtypes have a particularly unfavorable prognosis and are especially enriched in Reed-Sternberg cells. cART seems to be particularly important for the prognosis of PLWH affected by HL.

HL is characterized by B symptoms and extra-nodal disease and being so non-specific it needs a long differential diagnosis process. At least a chest and abdomen CT-scan is needed in presence of lymphadenopathy to rule out the possibility of HL. Supportive therapy and prophylaxis for opportunistic infection, such as *Pneumocystis carinii* and *Herpes Simplex*, are needed in association with CTX[64]. Well tolerated CTX regimens in PLWH affected by HL are the standard one with doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) and the more intensive one with bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone (BEACOPP). Immunotherapeutic regimens have also been applied more and more frequently in PLWH with HL, with a good rate of complete remission.

PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA (PCNSL)

PCNSL is a rare and aggressive disease, affecting a population of patients who are often elderly or immunocompromised[15]. It usually remains confined to the CNS; however, it can seldomly spread. The etiologic role of EBV in this kind of lymphoma is well known, especially in PLWHA. Its incidence has decreased after the introduction of HAART[54].

Clinical presentation of PCNSL includes changes in mental status, memory loss, focal neurological symp-

toms that can be classified as "mass symptoms"[61,64]. Although being a lymphoma, the treatment challenges it offers make it necessary to classify PCNSL among the brain tumor cancers. Therefore, whole-brain radiation and systemic CTX are the best therapeutic weapons. There is not a single regimen universally accepted as the standard one for the treatment of PCNSL: aggressive regimens are typically used. Examples include dose-adjusted (DA) EPOCH (etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin) or CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)[67].

In PLWHA it is of utmost importance to differentiate PCNSL from any other infectious cause of mass symptoms, such as cerebral toxoplasmosis, even using an "ex iuvantibus" criteria. HAART is important in the management of patients with lymphoproliferative malignancies in the setting of HIV. In a retrospective study of HIV-infected patients diagnosed with PCNSL, Boulanger et al[67] demonstrated a shorter survival for patients with a poor performance status and untreated HIV infection prior to diagnosis.

NASOPHARYNGEAL CARCINOMA (NPC)

NPC is a cancer derived from the epithelial cells of the nasopharynx. It can be classified in: 1) squamous cell carcinoma, typically found in the older adult population; 2) non-keratinizing carcinoma; 3) undifferentiated carcinoma[54-60]. Subtype 2 and 3 are associated with detection of Epstein-Barr virus[56]. The persistence of an infection with EBV in pre-invasive nasopharyngeal epithelium represents an early stage of NPC development[54-57]. Both latent and lytic genes may be involved in the transformation of pre-invasive nasopharyngeal epithelium into NPC[54,58]. EBV, ethnic background and environmental carcinogens seem to play an important role in the pathogenesis of this tumor[56-58]. Lo et al[68] showed that EBV DNA was detectable in the plasma samples of 96% of patients with non-keratinizing NPC, compared with only 7% in controls. Moreover, EBV DNA levels appear to correlate with treatment response[69].

Cervical lymphadenopathy is the initial presentation in many patients. Symptoms related to the primary tumour include trismus, pain, otitis media, hearing loss, cranial nerve palsies, nasal obstruction or bleeding. Metastatic spread may result in bone pain or organ dysfunction[68]. Diagnostic methods include a clinical evaluation of cervical lymph nodes, indirect nasopharyngoscopy, neurological examination of cranial nerves, a Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) scan of the head, biopsy of either the lymph nodes or primary tumor for histological examination[68]. Whereas Burkitt's lymphoma and Hodgkin's disease appears to be influenced by HIV-induced immunosuppression, little has been reported on nasopharyngeal carcinoma. Melbie et al[70] found a relative risk of 2.4 for NPC in HIV-infected subjects who developed AIDS which, however, was not significantly different from general population. In a total of 50,050 patients with AIDS, only 4 NPC were diagnosed. Later studies such as that reported by Frisch et al[71] demonstrate an increased risk of NPC in AIDS patients (SIR 2.6, 95% CI 1.8–3.8). The most recent comprehensive study by Shebl et al[72] also demonstrated an increased risk for NPC for all histologic subtypes (SIR 2.0, 95% CI 1.4–2.7).

CONCLUSIONS

EBV-related cancers are an important cause of disease and death in PLWHA since the first appearance of HIV-infection. The introduction of HAART has led to a better prognosis for EBV-related malignancies, even though they remain the most frequently diagnosed in PLWHA. Moreover, HAART had a smaller impact on EBV-related cancers, both those belonging to ADCs and NADCs, compared with other kinds of NADCs. The control of HIV replication by therapy remains an important step to reduce immune activation and, consequently, it has resulted in dramatically improved clinical responses and outcomes. However, and especially for HLs, it is not clear if an improved immune system can be a triggering factor. Despite this particular situation, HAART allowed PLWHA to be treated with more aggressive CTX and their prognosis has improved, and it is now similar to the HIV-negative people prognosis.

Moreover, more and more frequently, new drugs such as immune-therapeutics and immune checkpoint inhibitors are used in the setting of an EBV-related cancer diagnosed in PLWHA. Currently, their use is only reported in sporadic cases, however it is desirable that in the future large studies will include also PLWHA, as their survival has hugely improved and drugs used for the treatment of HIV-infection are less and less toxic, with a low number of drug-to-drug interactions. Therefore, there should be little concern about their inclusion in clinical studies.

Unfortunately, a screening test for EBV-related cancers is not available. Therefore, they are often diagnosed in an advanced stage, with a worse prognosis. Moreover, this kind of cancer prevalently arise in the setting of late-stage HIV infection. Hence, the best prevention of EBV-related cancers in PLWHA is an early diagnosis of HIV infection. Screening campaigns, information and periodic testing should be implemented, especially for people at high-risk of infection.

Conflict of interest:
The Authors declare that they have no conflict of interests.

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