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Chapter

Lymphoma and the Microenvironmental Cross-Talk between Sex Hormone Receptors and Epstein-Barr Virus in Predicting Lymphoma Clinical Status

Ahed J. Alkhatib

Abstract

Lymphoma is a significant clinical entity because of its high incidence and complicated etiology and pathology. In this chapter, we discussed lymphoma in general and made focus in our previous studies in which we found unique features linking the interaction of EBV with sex steroid hormones in lymphoma cells. Sex steroid hormones included estrogen receptor and progesterone receptors that were investigated for their expression in malignant lymphoid cells. The localization of EBV in malignant lymphoid cells was also investigated. The two main types of lymphoma, Hodgkin Lymphoma, and non-Hodgkin lymphoma, were investigated for the interaction of EBV with sex steroid hormones. Unique features were obtained in terms of a bridge-linking estrogen receptor with EBV in Hodgkin lymphoma and progesterone receptor with EBV in non-Hodgkin lymphoma. The interactions between EBV and lymphoma are classic, but the reasons beyond this are not well established. The results of our studies highlighted new features by the existence of expressed sex steroid receptors. We think that the dissociation of combination between sex steroid hormones and EBV bears the link to design new therapeutic strategies for lymphoma.

Keywords: lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma, EBV, estrogen receptor, progesterone receptor

1. Introduction

1.1 An overview of lymphoma

Lymphoma is a term used to describe a group of lymphoproliferative malignant disorders that arise from lymphatic T- and B-cells [1]. Lymphoma is a group of malignancies that affect the lymphatic system [2]. The organs, tissues, and veins of the lymphatic system are part of the immune system and are important for battling disease and infection throughout the body [3]. When lymphocytes (the lymphatic

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system's white blood cells) become malignant, they proliferate abnormally, forming tumors and squeezing out healthy cells [3].

1.2 Types of lymphoma

Lymphoma has traditionally been divided into the two types: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). However, it is now recognized that Hodgkin lymphoma is just one of many forms of lymphoma and that non-Hodgkin lymphoma is a largely meaningless phrase that encompasses all the disease's other subtypes [4]. Non-Hodgkin lymphoma is a diverse collection of over 40 lymphoproliferative tumors with varying patterns of behavior and treatment responses [5]. Non-Hodgkin lymphoma has a lower prognosis than Hodgkin lymphoma, and prognosis is determined by histologic type, stage, and treatment [6].

There are over 70 different forms of lymphoma. Some grow slowly (sometimes known as low-grade or indolent), while others grow quickly (referred to as high-grade or aggressive). Lymphoma has no known causes; however, several factors have been linked to an increased chance of having the disease. Hodgkin lymphoma and non-Hodgkin lymphoma are the two types of lymphomas. Hodgkin's lymphoma is a type of cancer that affects the lymphatic system [7, 8].

2. Hodgkin lymphoma

HL is a type of lymphoma that affects roughly 9000 adults and children in the United States each year. Hodgkin lymphoma can occur anywhere lymphocytes are detected in the body. However, lymph nodes in the chest, neck, and beneath the arms are where it usually starts. HL differs from all other kinds of lymphoma in several ways, the most notable of which is the existence of a cell known as the Reed-Sternberg cell. A Reed-Sternberg cell is a big, unusual cell that does not defend the body against infection. It is called for the two scientists who found it. When it multiplies improperly, it creates a tumor within a lymph node and attracts inflammatory cells. Chemotherapy and/or radiation therapy may be used to treat HL. A stem cell transplant may be considered in some circumstances, particularly if the disease does not respond to early treatment or returns after an initial response [9].

Hodgkin lymphoma is also known as Hodgkin's disease. It usually begins in a type of B cell that is found in the bone marrow. Hodgkin's disease is considered one of the most curable forms of cancer, especially if it is diagnosed and treated early. Several types of treatment can be used against Hodgkin lymphoma, including chemotherapy, immunotherapy, and stem cell transplantation [10]. Hodgkin lymphoma, often known as Hodgkin's disease, is a type of lymphoma. It usually starts in a specific type of B cell located in the bone marrow. Hodgkin's disease is one of the most treatable types of cancer, especially when detected and treated early [11]. Chemotherapy, immunotherapy, and stem cell transplantation are among the treatments available for Hodgkin lymphoma [12]. The presence of big aberrant tumor cells known as Hodgkin Reed-Sternberg cells distinguishes it. Hodgkin lymphoma can affect both children and adults; however, it is most diagnosed in young adults aged 20 to 34. Classic Hodgkin lymphoma and nodular lymphocyte-dominated Hodgkin lymphoma are the two primary subtypes of Hodgkin lymphoma. Classic Hodgkin lymphoma affects more than 90% of Hodgkin lymphoma cases [13].

Classical Hodgkin lymphoma is divided into five types as follows [14, 15]:

- Nodular sclerosis.
- Mixed cellularity.
- Hodgkin lymphoma.
- Hodgkin's disease.
- Hodgkin's disease with lymphocyte depletion.

3. Non-Hodgkin lymphoma (NHL)

Non-Hodgkin lymphomas (NHL) are a heterogeneous group of cancers, with B-cell origin in roughly 80% of cases (B-NHL). The presentation, clinical characteristics, prognosis, and therapeutic response of B-NHL are all different. Diffuse large B-cell lymphoma (DLBCL) is the most frequent histologic subtype, accounting for about a third of cases in the United States, followed by follicular lymphoma, which accounts for about a quarter of occurrences [16]. Other histologies are far less prevalent. Rituximab, cyclophosphamide, adriamycin, vincristine, and prednisone are used to treat about 60% of DLBCL patients (R-CHOP). Most patients who relapse after or are refractory to initial therapy, on the other hand, succumb to their condition. Over the last decade, new therapeutic research has concentrated on molecules that target the cell surface, internal pathways, and the microenvironment, rather than cytotoxic chemotherapy drugs. The chimeric anti-CD20 monoclonal rituximab changed B-NHL therapy, extending survival in the majority of subtypes. However, resistance builds with time, necessitating the use of additional techniques aimed at other targets [17].

3.1 Primary central nervous system lymphoma (PCNSL)

PCNSL (primary central nervous system lymphoma) is an uncommon extranodal non-Hodgkin lymphoma that is distinct from systemic diffuse large B-cell lymphomas. PCNSL is diagnosed at a median age of 65 years, and its prevalence is quickly increasing among the elderly. A total of 20% of all PCNSL patients are above the age of 80. Age, in particular, has been recognized as a poor prognostic factor for PCNSL. Elderly patients have a worse prognosis than younger patients and are more susceptible to iatrogenic toxicity; as a result, they are a distinct and vulnerable therapeutic class. The goal of this study was to provide a better understanding of the epidemiology, clinical features, diagnosis, prognosis, and therapy of PCNSL in the aged population by summarizing the current research. Notably, PCNSL is becoming more common in immunocompetent elderly patients, particularly men. Imaging guided stereotactic biopsy is the gold standard for the diagnosis of CNSL. Certain biomarkers have been described that can aid establish a diagnosis when stereotactic biopsy is not possible or conclusive. Even though numerous prognostic grading systems exist, and several prognostic markers have been discovered in PCNSL patients, the elderly have a very dismal prognosis. Furthermore, treating older individuals remains difficult; while a novel agent is unlikely to be utilized as a curative monotherapy, a combination of novel medicines with polychemotherapy or with other innovative therapies may have therapeutic potential [18].

3.2 Cutaneous lymphoma

Primary cutaneous lymphomas are a diverse category of extranodal non-Hodgkin lymphomas that are restricted to the skin at the time of diagnosis [19]. In 2005 [20], the European Organization for Research and Treatment of Cancer (EORTC) and the World Health Organization (WHO) developed a cutaneous lymphoma consensus classification, which was recently updated [21]. Unlike nodal non-Hodgkin lymphoma, which is mostly B-cell originated, about 75% of primary cutaneous lymphomas are T-cell derived, with two-thirds of them being categorized as mycosis fungoides (MF) or Sézary syndrome (SS) [20, 22, 23]. According to the Surveillance, Epidemiology, and End Results (SEER) registry, the incidence of cutaneous T-cell lymphomas (CTCL) has been growing and is now 6.4 per million people, with the greatest incidence rates seen among men and African Americans [23]. When compared to non-Black individuals with MF, there are several major distinctions, including a female predominance, a younger age of onset, and probably worse results [24, 25]. While CTCL can arise in adolescents and young adults, it is a rare occurrence that is generally linked to histopathologic MF variations [26].

4. Lymphoma diagnosis

Lymphoma is diagnosed primarily through pathologic examination of an acceptable tissue specimen in the right clinical situation, which may include morphologic, immunophenotypic, and cytogenetic studies as needed. Individual lymphomas are treated differently, necessitating an accurate and specific diagnosis to provide appropriate patient care [27]. The choice of biopsy procedure and place is a common practical challenge in patients suspected of having lymphoma. For initial diagnosis, surgical biopsy is preferred because the bigger tissue sample collected enables for investigation of processes that may involve the lymph node or extranodal mass in a variety of ways, as well as immunophenotypic, cytogenetic, and molecular analysis [28]. Fine needle aspiration may not allow for the study of histologic architecture, and it may not yield enough tissue for a thorough analysis, including the determination of biologic subtype [29]. In some cases, fine needle aspiration can confirm relapsed illness, although even in these cases, a core needle or surgical biopsy is preferred [30]. Core needle biopsy may allow for nodal architecture study, but it collects less tissue than surgical biopsy, perhaps missing a heterogeneous process and providing less material for thorough testing. Only in clinical scenarios where a surgical biopsy is not possible, a core needle biopsy is suggested for first diagnosis. Despite the WHO classification's established definitions, an experienced hematopathologist will modify about one-fifth of lymphoma diagnoses, with the rate varied among the different forms of lymphoma [31, 32]. Expert pathology review is recommended and should be regarded standard of care because proper therapy is fundamentally dependent on correct pathologic diagnosis. When the diagnosis of lymphoma is unclear, medical imaging can be helpful in staging, but a definitive diagnosis of lymphoma and determination of the histologic subtype require pathological examination [27]. Though not conclusive, [18F]-fluoro-2-deoxyglucose positron emission tomography (FDG-PET) imaging can identify aggressive from indolent lymphomas based on standard uptake value assessment and can help predict indolent lymphoma transformation (usually DLBCL). When transformation is suspected, PET can be used to choose an acceptable biopsy site where the standard uptake value is the highest and thus, transformation is most likely to be present; however, marked FDG avidity does not rule out transformation and does not eliminate the necessity for diagnostic biopsy [33].

5. Viruses and lymphoma

Hepatitis C virus (HCV) is well known for its role in the etiology of chronic non-A, non-B viral hepatitis, liver cirrhosis, and hepatocellular cancer; it has also been linked to a number of extra-hepatic "autoimmune" disease presentations. A causal link between HCV and non-Hodgkin lymphoma (NHL) was proposed just lately, and it has sparked a lot of research and debate. HCV appears to be implicated in the pathogenesis of at least a proportion of patients with NHL, based on epidemiological data, developing scientific investigations, and clinical observations. HCV-associated lymphomas are classified as marginal zone lymphoma (splenic, nodal, and extranodal), small lymphocytic lymphoma/chronic lymphocytic leukemia, lymphoplasmacytic lymphoma, lymphoplasmacytic lymphoma, and diffuse large B-cell lymphoma. Surprisingly, some HCV-associated NHLs appear to respond well to antiviral medication, giving clinical evidence for the link as well as the possibility of innovative therapeutic intervention [34].

Patients with HIV infection have a much higher rate of lymphoma than the normal population. Multiple factors appear to contribute to the increased risk of lymphoma, including the retrovirus's transforming properties, the disease's immunosuppression and cytokine dysregulation, and, most importantly, opportunistic infections with other lymphotrophic herpes viruses such as Epstein-Barr virus and human herpesvirus 8. Lymphomas are classified histologically into three groups: (1) those that occur in immunocompetent people, (2) those that occur more specifically in HIV-positive patients, and (3) those that occur in patients with various types of immunosuppression. The great majority of instances are aggressive lymphomas. They usually present with advanced stage, bulky cancer with a large tumor load and extranodal involvement. Clinical outcomes appear to be worse than those seen in the general population with similar severe lymphomas. The risk of developing lymphoma in the context of HIV infection has decreased, and the clinical result has improved since the advent of highly active antiretroviral therapy [35].

Epstein-Barr virus (EBV) is a common virus that affects over 90% of the world's population [36]. It was discovered to be linked to the development of EBV-associated lymphoproliferative diseases, hemophagocytic lymphohistiocytosis (HLH), and solid tumors, among other things, after being identified as an oncogenic virus in a Burkitt's lymphoma cell line [37]. *In vitro* infection and transformation of quiescent B cells into lymphoblastoid cell lines (LCLs) have proven EBV's carcinogenic potential [36]. The ability of EBV to create a lifelong latent infection in B-lymphoma cells has been established as a key mechanism of EBV-induced lymphomagenesis. During EBV latency, the expression of highly immunogenic proteins is suppressed, while viral lytic proteins are increased, impairing antigen processing by infected cells, and destroying the cellular molecular signaling machinery and metabolism, allowing tumor cells to escape immune surveillance and grow and survive. The most frequent indolent and second most common non-Hodgkin lymphoma subtype is follicular lymphoma (FL) [38]. Follicular lymphoma with EBV is a poorly understood disease that is infrequently reported [39]. Even though Asians have a higher incidence of EBV-associated cancers than Westerners, EBV-positive FL has been observed in the Chinese community on a rare basis. EBV is also the most frequent virus linked to HLH, a rare condition characterized by severe, life-threatening hyperinflammation. The decreased function of cytotoxic T lymphocytes and natural killer (NK) cells is the fundamental pathophysiology of HLH, resulting in uncontrolled immunological activation, hypercytokinemia, and macrophage proliferation. With a fatality rate of up to 50%, EBV-associated HLH is thought to be particularly common in Asia [40]. This may occur prior to, concurrently with, or after EBV-positive lymphoproliferative diseases [40]. T-cell and

NK-cell lymphomas account for the bulk of HLH-related cancers. The majority of B-cell lymphoma associated HLH cases have been observed in Asians [37].

6. Microenvironmental interactions between lymphoma and EBV and sex hormones

The hypothesis of cross-talks between hormone receptors such as the estrogen receptor (ER) and the progesterone receptor (PR) in breast cancer has recently been revealed to have major effects on breast cancer. Many researches, including ours, have previously proven the associations of Epstein-Barr virus (EBV) with lymphoma. We wanted to see if "EBV cross-talk with sex hormones plays a role in dictating the kind of lymphoma, Hodgkin's Lymphoma (HL) or non-Lymphoma Hodgkin's (NHL)" in this work. In lymphoma patients representing HL and NHL, we looked at the expression of sex hormones, ER, and PR, as well as EBV. The expression of these biomarkers in lymphoma cases was assessed using immunoperoxidase staining. Our data revealed that EBV cross-talk with ER is strongly linked with HL ($p < 0.05$), but its cross-talk with PR is significantly associated with NHL ($p < 0.05$). The findings of this study suggest that EBV acts as the conductor of an orchestra, orchestrating the events of lymphoma through various interactions with sex hormones. This could pave the way for novel lymphoma treatment options [41].

Grywalska and Rolinski [42] highlighted in their review study that the Epstein-Barr virus (EBV) has been linked to cancer pathogenesis. EBV is a member of the Herpesviridae family, and through the expression of multiple genes, it has developed ways to maintain the integrity of the viral genome and to escape from the host's immune system during the latent stage of infection. This expression promotes the development of cancers. EBV can infect a wide range of cells, resulting in a variety of diseases, including B-cell lymphoma [43].

Several studies have reported the link between EBV infection and Hodgkin Lymphoma (HL) [42], and the presence of EBV in Hodgkin/Reed-Sternberg (HRS) was confirmed by researchers such as Weiss et al. [44] and Takeuchi et al. [45]. On the other hand, non-Hodgkin Lymphoma (NHL) includes a variety of lymphomas such as Burkitt lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL) [46, 47].

Dolcetti [48] stated in his work that EBV has the power to alter the microenvironment to make it more conducive to cell transformation. EBV can boost the synthesis of a variety of substances that help lymphoid cells grow and/or survive while also allowing them to avoid immune system reactions. There is a complicated interplay between EBV-infected lymphoid cells and the tumor microenvironment that has the therapeutic potential against EBV-driven lymphoid malignancies.

There are few therapeutic alternatives in the treatment of lymphomas caused by EBV that can affect the virus within malignant cells. However, in most instances, no variations in therapy options have been found based on whether EBV is present. As prospective therapeutic methods, existing therapeutic techniques have focused on interfering with biological components of EBV to target lymphomas associated with EBV [49]. EBV-explicit methodologies include reinforcing the antiviral-/antitumor-resistant reaction with antibodies or EBV explicit cytotoxic T-lymphocytes, initiating lytic viral qualities to render tumor cells immune to antiviral treatments, and inhibiting downstream prosurvival or antiapoptotic pathways that may be triggered by dormant EBV proteins. EBV-explicit cytotoxic T-cell imbuements have shown to be effective in EBV-related post-transplantation lymphoproliferative disorder (EBVPTLD) and extending such assenting immunotherapies to additional EBV-related cancers is a hot topic of investigation [49]. Other EBV-related lymphomas, in contrast to EBV-PTLD, have progressively constrained, less immunogenic kinds of

viral antigens to restoratively target with assenting immunotherapy. Furthermore, the threatening EBV-positive tumor cells of HL are dispersed during a thick layer of administrative T-cells, macrophages, and other cells, which may compromise supportive immunotherapy's antitumor efficacy [50]. Continuous preclinical and clinical assessments are areas of continuous methodology to overcome these impediments. Some emerging approaches to treating EBV-related lymphomas include combining specialists that trigger lytic viral replication with anti-herpes virus operators or using small particle inhibitors to block deterioration pathways that are constitutively triggered by EBV. EBV antibodies appear to be generally promising for the treatment or prevention of EBV-related cancers, as opposed to required EBV contamination avoidance [51]. Preliminary EBV vaccination trials in patients with residual or low-mass EBV-related malignancies, or for the counteractive effect of EBV-PTLD in EBV-seronegative patients awaiting strong organ transplantation, are moving forward [52]. In many cases, the treatment of EBV-positive lymphomas is identical to that of EBV-negative lymphomas with similar histologies [53]. Special cases include experimental conventions and situations where a responsive immunotherapy method is available [54, 55]. When EBV-positive lymphomas appear in the context of immunosuppression, boosting the invulnerable deformities can help with lymphoma treatment [56, 57]. Antiretroviral treatment is routinely used in HIV-related lymphomas, but potential pharmaceutical interactions and the effects of chemotherapy on the ability to maintain HAART treatment in terms of sickness, heaving, and mucositis must be considered when antiretroviral treatment is planned [58, 59]. In any case, antiretroviral therapy alone is insufficient for the treatment of EBV-related lymphomas in HIV patients. This contrasts with AIDS-related Kaposi sarcoma, where initiating antiretroviral medication in patients who are asymptomatic or insignificantly symptomatic and antiretrovirally innocent is frequently a regular practice [60, 61]. Select instances with EBV-PTLD may benefit from immunosuppressive reduction as a stand-alone treatment or as part of a therapeutic plan [62, 63]. The therapeutic choices for lymphomas associated with EBV are like those for lymphomas that are EBV-negative. Existing therapy methods, on the other hand, include addressing biological elements of EBV and may require further research to be firmly established.

7. Conclusions

This study showed that new therapeutic strategies are of great potential based on the interactions of EBV, lymphoid malignant cells, and sex steroid hormones, ER or PR. Our studies showed interesting features by identifying the impacts of interaction of progesterone receptors with EBV leading to the development of NHL, while the interaction of EBV with ER led to the development of HL. These features are unique and give the bases of designing new therapeutic lines that inhibit the binding of EBV with sex steroid hormones to participate in lowering the incidence of lymphoma.

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