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Review Article

Review Malaria and Endemic Burkitt's Lymphoma: Effects of the Parasite on the Pathogenesis of the Malignancy

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Abstract

Burkitt lymphoma is the most common childhood cancer in equatorial Africa. A major risk factor in the development of endemic Burkitt lymphoma is Plasmodium falciparum malaria and Epstein-Barr virus exposure. EBV seropositivity in most African children is by three years of age with some infected before six months of age. EBV reactivation and Chronic or repeated P. falciparum coinfection.

Malaria transmission intensity can affect the age at which children become infected with EBV and contribute to a greater EBV burden in infected children. The frequency of EBV and BL co-infection varies depending on the patient group and geographical location. By deregulating the oncogene c-MYC via chromosomal translocation, EBV may have a role in the pathogenesis of BL.

Since its discovery, the epidemiological link between eBL and P. falciparum malaria has been frequently proven. Antigens specific to P. falciparum activate polyclonal B cells and improve the survival of EBV-infected B cells. Learning how to suppress or divert signaling pathways that interfere with normal EBV immune surveillance, as well as gaining a better knowledge of how chronic malaria contributes to eBL pathogenesis, could help avoid this pediatric malignancy in Africa. There will also be a discussion of unanswered topics and preventative techniques.

Keywords: *Epstein-Barr Virus; Plasmodium Falciparum; Endemic Burkitt's Lymphoma; B-Cell*

Introduction

Burkitt lymphoma (BL) is a type of non-Hodgkin lymphoma that affects the lymphatic system. It is named after Denis Burkitt, an Irish surgeon who first characterized the disease while working in equatorial Africa in 1958 [1]. Burkitt observed that the geographic distribution of BL is similar to that of malaria, particularly the most severe type caused by *Plasmodium falciparum*, a protozoan parasite spread by female Anopheles mosquitos [2].

According to WHO classification -2008, there are three clinical/epidemiological variations of the disease: endemic "African" (eBL), sporadic (sBL), and acquired immunodeficiency syndrome (AIDS)–related BL. Burkitt's lymphoma is typically associated to EBV pre-infection, which has been shown to play a key role in disease etiology [3]. The most common sites of presentation are the jaws and belly. eBL peaks at 6–7 years of age, is more common in males, and the most common sites of presentation are the jaws and abdomen. *P. falciparum* endemic locations are the only places where eBL can be found [4].

In 2019, there were an estimated 229 million malaria cases worldwide, spread among 87 malaria-endemic countries [5]. Malaria's acute complications are well-known, but there is growing evidence that, in addition to direct malaria-related morbidity and mortality, malaria has a number of long-term consequences. Burkitt lymphoma, the most frequent malignancy among children in Sub-Saharan Africa, is one such result [6].

Two proposed theories emerged from studies conducted to clarify the function of P. falciparum malaria in the eBL etiology. According to the first theory, *P. falciparum* malaria causes polyclonal B-cell proliferation and lytic Epstein-Barr virus (EBV) infection to reactivate, resulting in the expansion of latently infected B-cells and therefore increasing the risk of c-myc translocation. According to the second theory, EBV-specific T-cell immunity is harmed during *P. falciparum* malaria co-infection as a result of – or maybe as a result of – EBV replication, which finally leads to viral control loss [7].

Malaria and EBV co-infections are widespread in children living in high-risk eBL locations, despite eBL having a low yearly incidence of 1 - 5 per 100,000 children. Co-infection during primary EBV infection sets the basis for EBV latency dysregulation, and recurring malaria infections worsen EBV homeostasis and T-cell immunity, suggesting that Pf-malaria may play numerous roles in eBL pathogenesis [7].

In regard to the pathogenesis of eBL, the International Agency for Research on Cancer classified *P. falciparum* infection as a potential carcinogen (category 2A) [8]. In equatorial Africa, BL is the most common children cancer, accounting for 74% of all pediatric malignancies [9]. In Sub-Saharan Africa, nearly all BL harbors EBV, and tumor cells are latently infected, carrying the viral DNA as a clonal extrachromosomal episome [10].

Malaria and endemic Burkett's lymphoma

Malaria is a life-threatening disease caused by the protozoan parasite Plasmodium in many tropical and subtropical areas. *Plasmodium falciparum, Plasmodium malariae, Plasmodium ovale,* and *Plasmodium vivax* are the four Plasmodium species that cause human malaria. There are currently over 100 countries and territories where malaria transmission is a problem, with over 125 million foreign tourists visiting each year [11].

The parasite *Plasmodium falciparum* has also been linked to eBL. The start of endemic BL may be linked to the genetic complexity of *P. falciparum* malaria infections and the immunological response they elicit [12]. Malaria's function in eBL is due to malaria's massive impact on the immune system, which leads to a rise in EBV burden [13]. Malaria suppresses T cell responses, including those that target EBV (14). However, increasing EBV load and immunosuppression may not be enough to develop eBL. Malaria must be involved in the pathophysiology of eBL in some way [10].

The discovery that *P. falciparum* induces expression of the gene for activation-induced cytidine deaminase (AID), [15] an enzyme that is mainly expressed in germinal center (GC) B cells and plays a pivotal role in both immunoglobulin class switch recombination and somatic hypermutation for antibody maturation, has recently clarified the link between malaria and BL. Antibodies that protect against a variety of infections are produced by these two genetic pathways. On the other hand, abnormal AID expression, such as the c-myc translocation seen in BL, can be a risk factor for cell leukemias and lymphomas. The underlying mechanism of AID activation, as well as why BL is only associated with *P. falciparum* and not with other Plasmodium species, remained unknown [16].

The World Health Organization (WHO) classifies BL as a kind of hematological and lymphoid tissue malignancy [17]. B cells at various phases of development are hypothesized to give rise to the three clinical subtypes of BL. The MYC gene, which encodes for the c-myc protein transcription factor and is found on chromosome 8q24, governs cell proliferation, differentiation, and apoptosis, is required for BL development [18].

Burkitt's lymphoma was discovered throughout tropical Africa, with the exception of high altitudes and locations with a mild environment. The likelihood of occurrence was higher in places with more rainfall. These geographical and meteorological correlations pointed to a link with falciparum malaria. Burkitt's lymphoma continues to be the leading cause of childhood cancer in Africa [19].

BL is defined by abnormally high amounts of c-myc, which can be caused by a variety of causes, the most prevalent of which is translocation of chromosome 8's long arm (which contains the MYC gene) and chromosome 14's Ig heavy chain gene. Overexpression of c-Myc causes rapid B cell proliferation, which accounts for the BL tumor cells' rapid doubling time (between 24 and 48 hr) [20].

EBV is implicated in the pathogenesis of eBL, according to epidemiological studies, as nearly all eBL tumors are EBV-positive [21]. Furthermore, those who were infected early in life and had the greatest EBV antibody titres had the highest risk of acquiring the tumor. Only cycling memory B cells produce the EBV latent gene EBNA1, which has a gene expression pattern similar to that of BL tumor cells [22].

EBV may have a role in the pathogenesis of BL via deregulating c-MYC activity and clonal growth, as well as direct mutagenesis and immunological inactivation, allowing malignant clones to escape. Resting B cells are known to be transformed into latently infected lymphoblastoid cells by EBV. The immune system regulates the increase of the B-cell pool produced by co-infection with EBV; immunosuppression induced by illnesses like HIV and malaria could lead to prolonged stimulation of B-cells, increasing the chance of c-MYC translocation and other alterations [23].

Interaction between malaria, EBV and B-cell

It's critical to remember that *P. falciparum* spends the most of its existence in the bloodstream, right in the middle of the immune system, in order to fully comprehend how the parasite and EBV interact. Immunosuppression, hyperactivation, and growth of atypical memory B cells are all promoted by Pf parasites, which modify host defenses. Subversion of immunity could possibly be aided by parasite genetic diversity. If this is the case, parasite genetic diversity could increase children's vulnerability to EBV infection or cause EBV reactivation in children with latent infection [24].

Almost everyone in the world is infected with the Epstein-Barr virus at some point in their lives. Once infected, the virus normally remains latent in the host for the rest of its life, causing no symptoms. However, this dormant EBV can reactivate and contribute to certain human malignancies, including Burkitt's lymphom [25]. The virus produces three different types of latencies (latency I, II, and III) based on the differential expression of EBV-specific genes, and throughout each program, the virus expresses a set of latency linked genes (Tempera I, Lieberman PM, 2014). The virus produces three different types of latencies (latency I, II, and III) based on the differential expression of EBV-specific genes, and throughout each program, the virus expresses a set of latency linked genes [26].

The fact that Pf-malaria infection occurs before eBL indicates a temporal relationship with EBV. The average age of eBL patients in malarious areas was 8.1 years, while it was 16.2 years in low-risk malarious areas. The greatest age-related incidence of eBL is when a child is between the ages of 4 and 9 [27,28]. Pf-malaria linked morbidity, mortality, and parasite density are highest at this age. Even though these children get their primary EBV infection before the age of three, it is highly rare for a child to acquire eBL before the age of two, implying that these co-infections need to interact for a long time to promote carcinogenesis [29].

The role of *P. falciparum* on the pathogenesis of eBL

Retinoid toxicity

The fact that *P. falciparum* parasites selectively take vitamin A from the host in a parasitemia-dependent way, with absorption increasing with parasite maturation, is another possible hint to understanding the involvement of malaria in Burkitt's lymphoma. The parasite's biological processes appear to be dependent on vitamin A. [30]. As a result of the widespread distribution and release of vitamin A from damaged RBCs throughout the body, individuals who have had multiple episodes of malaria may be exposed to repeated toxic doses of retinoic acid (RA), the main biologically active metabolite of vitamin A, delivered by merozoite-stage P. falciparum emerging from the liver and entering the RBCs [31].

It is believed that P. falciparum infection raises the risk of BL by increasing retinoic acid exposure to lymphatic tissue, which leads to EBV activation. Long-term exposure to high retinoid concentrations in lymphatic tissues may cause B-cell translocation and raise the risk of Burkitt's lymphoma [31].

Pf erythrocyte membrane protein 1 (PfEMP1)

PfEMP1 is a P. falciparum-specific antigenic protein produced on the surface of infected red blood cells. The main polypeptide, PfEMP1, is an adhesin that allows erythrocytes infected with mature stages to stick in the microvasculature, sequester, and evade splenic clearance [32]. PfEMP1, a *P. falciparum*-specific protein, has been linked to polyclonal B cell activation and higher survival in recent research, leading to speculation of a possible relationship to eBL [33]. PfEMP1-like proteins are not found in other human pathogenic malaria parasite species [34].

Malaria's influence on B-cells

Malaria appears to directly regulate B-cell differentiation as an immune evasion strategy, inhibiting the production of long-lived memory B-cells while permitting the generation of atypical short-lived memory B-cells [35]. Transitional B-cells are found in significantly higher numbers in the peripheral circulation of children with acute clinical malaria, and this subset is more susceptible to EBV infection than other memory B-cell subsets, as well as expressing elevated levels of microRNA, which is important in blocking B-cell differentiation. [36,37].

Infection with *P falciparum* grows a subset of immature transitional B cells *in vivo,* resulting in the activation of the activation-induced deaminase (AID), which causes alterations in immunoglobulin class switching [38]. *In vitro,* the cysteine-rich interdomain region 1 (CIDR1) domain of the Pf erythrocyte membrane protein 1 (PfEMP1) domain has been demonstrated to activate proliferation of B-cells from people who have never had malaria, selectively targeting memory B-cells and protecting them against apoptosis [14]. B-cell proliferation may thereby increase the EBV-infected compartment, but B-cell activation can reactivate latent EBV, which has been proven to boost AID activity directly [39].

Malaria deregulates EBV-specific T-cell immune

EBV-specific T-cells inhibit viral replication and reduce the number of B-cells that are latently infected. EBV persistence is a balance between viral immune evasion mechanisms and control mediated by CD8+ and CD4+ T-cells specific to latent and lytic EBV antigens in immunological competent individuals [40,41].

The decrease of EBV-specific T-cell immunity was caused by both acute and chronic malaria infection. In comparison to children from a hypoendemic location, children 5-9 years old displayed decreased response to both lytic and latent EBV CD8+ T-cell epitope-peptides after recurrent Pf-malaria infections [42]. Pf-malaria co-infections during EBV latency establishment may have a deleterious impact on EBV-latent antigen specific T-cell lineage commitment, and recurrent Pf-malaria infections over time reduce EBV-lytic antigen-specific T-cell functional capacity [7].

Conclusion

Burkitt's lymphoma and other extremely aggressive lymphomas demand rapid attention and should begin therapy as soon as possible following diagnosis. BL is still primarily lethal in Africa, and diagnosis is still done clinically. In the West, BL treatment is highly effective now, with response and cure rates of > 90% for current regimens [43]. Long-term cure rates in Africa have remained low, with rates of 25 - 30 percent reported in the early days [44]. While poor outcomes may be attributable to a lack of resources and capacity, it's also probable that many cases go unnoticed or are detected late, and that once recognized and treated, patients drop out [45].

Since its discovery, the epidemiological link between eBL and P. falciparum malaria has been frequently proven. Although the molecular details are yet unknown, *P. falciparum* infection appears to have an indirect and direct impact on eBL etiology [46].

Finally, malaria appears to play a number of roles in the development of eBL tumors, with EBV acting as the promotor and human mutations forming the backdrop. Pf parasites and EBV are acknowledged as co-factors in the origin of eBL on a biological level, although the precise mechanisms of interaction between Pf parasites, the B cell compartment, and EBV are unknown. Malaria-induced changes in B-cell differentiation, as well as the identification of alternate EBV reservoirs, have yet to be thoroughly studied. A better knowledge of the events that occur during Pf-malaria and EBV co-infections would aid in the development of eBL prevention measures. The risk of BL from malaria or EBV infection has not been estimated. Efforts to see if BL might be avoided by avoiding malaria or early EBV infection were abandoned.

Conflict of Interest

The author has no competing interest.

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