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Investigating the Connection Between Burkitt's Lymphoma and Epstein-Barr Virus-Induced Mononucleosis Through Disruptions in Hematologic and Immune Cell Regulation

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ABSTRACT

Burkitt's Lymphoma (BL) is a rare form of B-cell non-Hodgkin's lymphoma. It is the most aggressive form of lymphoma and is driven by a c-MYC translocation induced by the Epstein-Barr virus (EBV). In endemic regions, malaria is a common cofactor that allows EBV infect host cells for longer periods of time. EBV uses two phases, the latent and lytic cycles, to establish long term infection and invasion of host cells. EBV driven mononucleosis is compared with the B-cell proliferation in BL. Treatment strategies for BL include high-intensity chemotherapy along with stem cell transplantation as a secondary form of treatment. Treatment for EBV is currently being investigated as a method to prevent BL. In this review, a comparison of treatment costs for low-income countries and high-income counties is discussed to emphasize the importance of efficient and affordable healthcare.

Keywords

Burkitt's lymphoma, B-cell non-Hodgkin lymphoma, c-MYC translocation, Latent and lytic EBV cycles.

Introduction

Hematologic malignancies have a large impact on the United States with over one hundred thousand diagnoses which include lymphomas and plasma cells dyscrasias (abnormal or uncontrolled growth of immune cells) each year [1]. Hematologic malignancies, such as leukemias, lymphomas, and plasma cell carcinomas originate from the lymphatic system and the bone marrow rather than viscera. These blood-derived cancers can disrupt many circulatory processes such as hematopoietic generation, and circulation which can cause detrimental effects in the human body [1]. Hematologic malignancies cause the expansion of blasts cells located in the bone marrow. This prevents blasts cells from forming into mature blood cells such as red blood cells, white blood cells, or platelets leading to conditions such as anemia and infection [1]. Hematologic malignancies are known to be driven by genetic mutations and translocations, and environmental factors [1]. Burkitt's Lymphoma (BL) falls under the hematologic malignancy category and is specifically classified as a B-cell non-Hodgkin's lymphoma. Mature B-lymphocytes put BL into the hematologic malignant category because they are a group of white blood cells.

BL is an aggressive form of B-cell non-Hodgkin's lymphoma. BL is caused by a translocation of the c-myc oncogene located on chromosome 8. BL is the first documented cancer known to be linked to the Epstein-Barr Virus. Although BL is very aggressive, it is highly curable with high intensity chemotherapy treatment. There are three main types of BL which are dependent on environmental factors or cofactors. Endemic BL type is commonly found in children from ages 3-12 years old located in Equatorial Africa and Papua New Guinea. Sporadic BL is found worldwide and effects all ages. Immunodeficiency-related BL is commonly found in Sub-Saharan Africa, Eastern Europe, and Central Asia and mostly infects patients who are HIV positive.

Epstein-Barr virus (EBV) also considered herpesvirus 4, is a universal y-herpesvirus omnipresent in over 90% of the human population [2]. There are multiple diseases that are caused by EBV. These diseases include but are not limited to; infectious mononucleosis, chronic active EBV, cutaneous EBV-associated disease, hemophagocytic syndrome, EBV-related cancers, autoimmune diseases, neurologic and vascular diseases [3].

EBV plays a leading role in both BL and infectious mononucleosis. The effects of EBV on the human body include repetitive infection in the throat or pharynx and a dormant infection of B cells that last a lifetime [2]. Children who are infected with EBV typically do not express any symptoms until adolescence where it is usually diagnosed along with infectious mononucleosis (mono or glandular fever). EBV infection is asymptomatic in 70-90% of childhood cases, making it extremely difficult to diagnose [4]. It is often mistaken for a mild cold. Most common symptoms of infectious mononucleosis include fatigue, fever, inflamed lymph nodes, abdominal pain, and rash. Only 30-50% of adolescent infectious mononucleosis cases are symptomatic [4].

This report reviews the effects of EBV on infectious mononucleosis and BL along with cofactors that help drive EBV. This review will also explore the outcome of this virus and disease of high-income countries in comparison to low-income countries.

Discussion

Epidemiology of BL

Burkitt's Lymphoma (BL) is a rare form of non-Hodgkin's lymphoma that is extremely aggressive and fast growing. BL was the first cancer found to be caused by a genetic change, c-myc translocation linked to an oncogenic virus. Specifically, a virus that alters cell growth and differentiation, which is very important to understand when trying to prevent the mutation of protooncogenes. BL is a blueprint disease that represents how the correlation of genetic modifications and environmental infections can alter the outcome of cell proliferation leading to cancer.

A large study with 2,284 adults explored the trends of BL in the United States from the years 1998 to 2009. This study found that the median age for adults with BL in the United States was 49 years of age [5]. More than 50% of the patients in this study presented stage IV BL. This could indicate that the disease is harder to diagnosis at early stages. Tumors and lesions were mostly found in the head/neck and the gastrointestinal tract. This disease is more commonly found in males versus females with a predominance of 2.6:1 [5]. Prognostic factors were identified using the variables, age, race, and stage of each patient. Patients with an older age had a five-time decrease in chances of survival versus patients at a younger age of about 20-39 years of age. There was a trend of improvement of survival rates for age groups 20-39 and 40-59 over the years 1998 to 2007. Those of African-American decent also showed trends of lower survival rates compared to other races with no improvement from years 1998 to 2007. Patients at higher stages (III and IV) showed trends of lower survival rates as well [5].

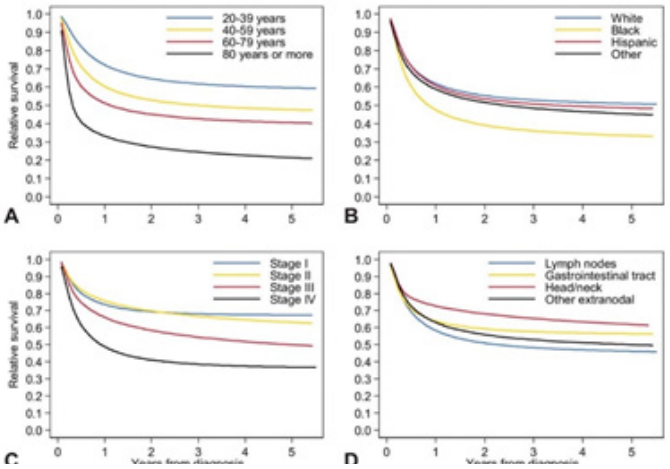

Figure 1: A) survival rates of BL patients categorized by age. B) survival rates of BL patients categorized by race C) survival rates of BL patients categorized by stage. D) survival rates of BL patients categorized by primary anatomical site [5].

Clinical subtypes differ in trends across the world. The main difference between each clinical subtype is the location of tumors and lesions throughout the body. Endemic BL is revealed as a jaw or abdominal tumor, caused by Holoendemic malaria, and presents a 100% Epstein Barr Virus (EBV) correlation; meaning EBV is the leading precursor to genetic mutations of the B-cell eventually causing lymphoma to develop [6]. Sporadic BL is a worldwide phenomenon that differs depending on location. Sporadic BL is shown to have a 15-85% association to Epstein Barr virus, with cofactors being more difficult to pinpoint [6]. AIDS-BL is caused by HIV/AIDS and is extremely common in infected adults who have are untreated. BL is an early symptom of adults infected with HIV/AIDS. AIDS-BL shows the least correlation with Epstein Barr virus with only 30-40 % association. However, with HIV and EBV present in the body, HIV contributed to an increased number of EBV load in the body. HIV is also shown to be a cofactor of BL by stimulating atypical B- cell growth prior to immune collapse [6]. A common trend in all clinical subtypes of BL show an exceedingly high correlation with EBV.

Clinical subtypes of BL *Burkitts Lymphoma*

Subtype	Region/ population	Symptoms	EBV positivity	Relative frequency
Endemic	Africa: children ages 4-7	Jaw/face, kidneys, GI tract, ovaries, and breast tumors	EBV + by almost 100%	50x higher than U.S.
Sporadic	Worldwide: especially U.S./Europe	Abdomen Tumors, kidneys, ovaries, Waldeyer's ring.	Less EBV association by 15%-30%	Make up 1-2% of adult lymphomas; up to 40% pediatric
Immunodeficiency-Related	HIV+, transplant, or congenital immunodeficiency	Bone Marrow/ CNS, lymph nodes, and abdomen	Common, but not uniform	30-40% of HIV related NHL; 1000x higher incidence in HIV+

Figure 2: A table of the clinical subtypes of BL categorized by region, symptoms, EBV positivity, and relative frequency [6].

What is EBV?

Epstein-Barr virus is an extremely common virus that infects human B-cells and epithelial cells. It is the most common cause of infectious mononucleosis. Anthony Epstein and Yvonne Barr made the first discovery of EBV in 1964 identified under a microscope while investigating cells *in vitro* that were extracted from a patient with BL. The structure of EBV consists of a protein core surrounded with the viruses double-stranded DNA. The DNA is surrounded by a protein coat that contains glycoproteins which aid in attaching and entering host cells [2]. The DNA in EBV has a linear double-stranded genome with a length of 172,000 base pairs that are highly repetitive [2]. Repetition of end strands give EBV more stability when infecting human cells. Typical viruses contain 5-20 to genes, however EBV contains around 70 genes giving it the ability to produce a wider variety of proteins compared to other viruses. The proteins being made aid in invasion of human B-cells, limit detection from the hosts immune system, and specifically enhances cell proliferation in BL cases. Examples of proteins made that aid in these functions include BCRF1(viral IL-10 homologue), BARF1(inhibits interferon activity), and BHRF1/BALF1(a viral BCL-2 analogue that blocks apoptosis) [6]. Scientists classified EBV as a gamma-herpesvirus because of the virus' ability to infect B-cells and remain dormant in the cells for such long periods of time although the ability of the herpes simplex virus and its ability to infect and remain in a latent phase for such long periods of time. Early on, scientists used a BamHI restriction map to construct a physical map of the EBV genome [2].

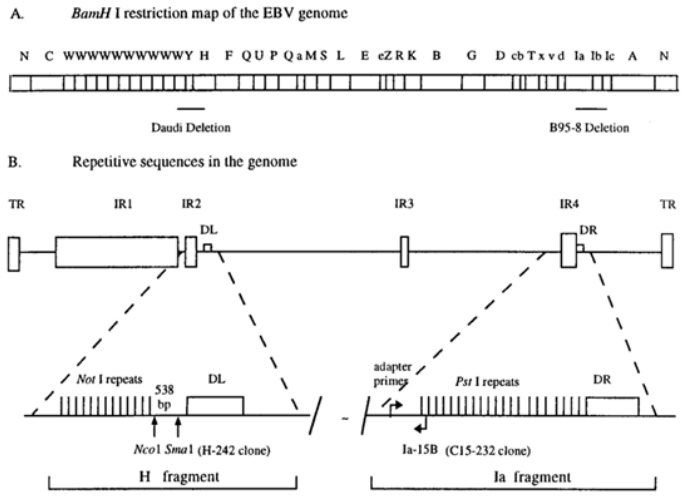

Figure 3: Organizational structure and repetitive sequences of the Epstein-Barr virus (EBV) genome. (A) Structure A represents the BamHI restriction map of the EBV genome. The BamHI fragments are labeled using letter- based biological nomenclature. This structure tags the deletions Daudi, and B95-8. These deletions cause mutations gene expression and regulation. (B) Structure B represents DNA sequence repetition in specific locations on the EBV genome. Terminal repeats (TR) are located at the ends of the genome. There are four internal repeat regions (IR1-IR4). This structure further investigates the repeat patterns of IR1 and IR4 following the dashed lines. IR1 contains NotI repeats and IR4 contains PstI repeats [7].

Pathophysiology

Pathogenesis of EBV

Transmission of EBV induced mononucleosis from human to human is accomplished through saliva transmission. The primary entrance into the body for EBV is the respiratory tract where it infects epithelia cells and immune cells [3]. Due to the virus' ability to survive on moist surfaces it can be transmitted through sharing drinks as well. EBV is one of the most common infections globally with an infection rate of over 90% of the adult population worldwide. Other possible modes of transmission that are less common include blood transfusions, sexual contact, and organ transplantation [8]. EBV can infect host cells such as B-cells, NK cells, T-cells, macrophages, epithelial cells, and muscle cells [6]. Infection can occur in various ways due to the abundant selection of proteins EBV is able to make. EBV can lead to different outcomes depending on what gene expression system is used to further control host cells.

In most cases of BL, EBV prevents malignant B-cells from undergoing apoptosis during viral latency. EBV is responsible for the development of cancer in lymphoid and epithelial cells [2]. EBV can infect B-cells through prolong periods of time due to its ability to switch from two phases, the latent and lytic phases. In the lytic infection cycle, EBV is actively making new proteins to copy and replicate viral DNA allowing the infection to rapidly spread. The genes BZLF1 and BRLF1 begin the process of replication [9]. An increase in viral DNA allows the virus to continue to infect other B-cells. The lytic proteins that damage the stability of the B-cell genome include BNRF1, BGLF5, BALF3, and BGLF4. BamHi N Rightward frame 1 (BNRF1) is a major tegument protein that contributes to chromosome mutations. It is important to recognize that when BNRF1 is removed it reduces damage to the host genes [9]. BamHI G Leftward Frame 5 (BGLF5) is a viral DNase that slices DNA replication of the DNA begins. BamHI A Leftward Frame 3 (BALF3) is a viral terminase protein also breaks DNA causing genomic instability. BamHI G Leftward Frame 4 (BGLF4) is a viral kinase that changes chromosome condensation and intervenes mitosis [9]. When the viral DNA becomes methylated it allows EBV to switch from lytic phase to latent phase [6].

The latent phase allows EBV to remain dormant and undetected inside the B-cells while only expressing a few genes. The latent phase includes stages 0, I, II, and III. It prevents apoptosis by activating a small number of genes that are immunologically silent during a phase known as latency I. Such genes can include EBNA1, EBER, and MicroRNAs, which prevents a signal from being sent to T-cells in the immune system, allowing the cells to continue growing uncontrollably [6]. The most common type of latent infection cycle is called latency III. In latency III, proteins such as Epstein-Barr Nuclear Antigens (EBNA), Latent membrane proteins (LMPs), Leader proteins (LPs) and noncoding RNAs (EBERs) are produced. The latency cycle is important to further investigate because such proteins produced during this phase are known to push the cell into uncontrolled cell proliferation leading to rapid malignant growth.

As previously mentioned, extended exposure to EBV can cause T-cell dysfunction which prevents T-cells from successfully eliminating infected B-cells. The reason T-cells are no longer to detect the infected B-cells is because the EBV drive T-Cells into a state of exhaustion. CD4+ helper T-cells are also affected and can no longer support immune cells. EBV also produces proteins that intervene with immune responses to T-cells, allowing EBV to continue infection without being detected. When the host loses this line of T-cell defense, it increases the chances of mutations and uncontrolled proliferation to occur in the cells [10].

Pathogenesis of Infectious Mononucleosis

Extensive complications in the body due to EBV-driven infectious mononucleosis include splenomegaly, hepatitis, and rare lymphoproliferative disorders. Splenomegaly (enlarged spleen) occurs due to EBV infection putting the immune system into overdrive and over producing lymphocytes. The first documented case of splenomegaly due to EBV infection was an 18-year-old male diagnosed with hereditary spherocytosis, marked hepatosplenomegaly, an acute EBV infection, anemia, atypical lymphocytosis, and jaundice [11]. There was no evidence of splenic rupture. Two months later a splenectomy was performed, and results showed the acute EBV infection (mononucleosis) caused the spleen enlargement by evidence of expansion of infected B cells, a cytokine surge, and increased hemolysis [11]. Spleen enlargement during infectious mononucleosis is not permanent however it can lead to serious injury such as a ruptured spleen. Individuals who are diagnosed with infectious mononucleosis are encouraged to avoid extensive physical exercise until infection subsides.

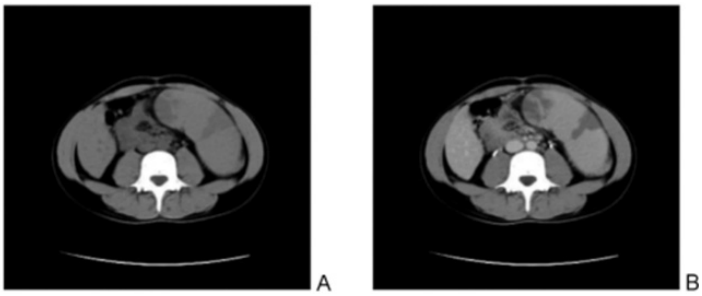

Figure 4: A) A non-contrast CT scan showing an enlarged spleen (splenomegaly) with wedge-shaped regions (showing splenic infraction) of low density. Low density areas show ischemic zone with reduced blood flow. (B)A contrast-enhanced CT scan to highlight blood flow. In this scan, healthy tissue regions will light up, and unhealthy tissue regions will not appearing darker indicating this splenic tissue is not viable [11].

Infectious mononucleosis causes an increase in lymphocytes (specifically T-cells) because the immune system is trying to fight the EBV infection. Transient lymphocytosis is caused by EBV infection of B-cells but subsides once infectious mononucleosis is gone. This increase in lymphocytes is not cancer driven, instead it is driven by an immune response [12]. In contrast, clonal expansion of B-cells in BL are malignant because these cells do not eventually die off like they do with transient lymphocytosis.

Pathogenesis of BL

Although infectious mononucleosis is not a direct contributor to BL, it plays a role in introducing EBV to the host cells creating long-term exposure and infection to the EBV. Cofactors to BL induced by EBV is malaria in endemic regions. The presence of malaria weakens the immune system and allows longer exposure to EBV increasing the chances of developing BL.

In terms of risk factors, in regions such as equatorial Africa where there is a high prevalence of endemic BL, there is also a high prevalence of malaria (*Plasmodium falciparum* infection), making it the leading factor to the overexposure of EBV. Malaria induces the reactivation of the EBV lytic phase which in turn pushes the EBV infection to other B-cells [13]. Overexposure of EBV eventually leads to the progression of BL [13]. There are several mechanisms that cause the uncontrolled B-cell proliferation driven by EBV.

Malaria has been proven to be the cause of the immunosuppression of EBV- specific T-cells leading to the lack of defense from T-cells against EBV infected B-cells. Malaria also plays a role in inducing NK cell dysfunction. When NK cells are suppressed, they cannot kill infected B-cells that are in the EBV lytic phase, further increasing the number of infected B-cells [13]. Malaria also causes an increase in the number of B-cells that can be infected by EBV at a time. By increasing the number of infected b-cells, the likelyhood of malignancy formation increases significantly. Malaria can cause this effect due to its ability to severely weaken the body's immune system [13]. A continued exposure to malaria infection increases the chances of endemic BL in endemic regions.

In rare cases where EBV is not present in the host, other mutations can occur that can lead to the development of BL. TP53 and BIM pathway mutations in IM and BL prevent apoptosis. TP53 is a tumor suppressor protein that controls the c-myc protooncogene by inducing apoptosis or halting the cell cycle all together when a mutation is detected. When the TP53 pathway is mutated, it prevents the ability of p53 to stop overexpression. In other cases, the Bcl-2-interacting mediator of cell death (BIM) becomes downregulated, suppressing the ability for B-cells to undergo programmed cell death. BIM releases cytochrome c to trigger apoptosis [14].

In BL, c-myc is mutated to become continually active by translocating next to immunoglobin genes. A study done on mice models indicate c-myc overexpression can promote the development of lymphoma and can be intensified by supplementary mutations such as suppressing BIM protein and Tp53 pathway. Using Robertsonian (Rb) translocations, it was proven that c-myc gene reorganizes the positioning of the centromere inside the nucleolus, this causes telomeres to fuse. 30 hours later, the activation of the c-myc gene causes new Rb translocations meaning the c-myc gene causes genomic instability on its own which in cases of BL can lead to tumor progression [15].

Not only does the c-myc gene drive cell growth and division, but it also participates in weakening the immune system by, reducing antigen presentation, reducing NF-kB activity, and by reducing interferon response. Mutation in the c-myc reduces antigen presentation on lymphoma cells by downregulating the MHC class I and class II expression which reduced the number of antigens located on the surface of cells [16]. The c-myc gene downregulates MHC expression by interfering with enhancer activity. Transcription factor (H2TF1) is the activator of MHC class I gene transcription. When c-myc gene is involved, H2TG1 cannot properly bind leading to a weakened MHC gene transcription [16].

The c-myc gene interferes with the signaling pathway NF-kB. NF-kB aides in the initiation of immune responses, inflammation, and cell activation [17]. When EBV lowers c-myc activity this weakens immune response. The c-myc gene also suppresses interferon response. An interferon is a protein that defends and protects against cancer cells and infections. c-myc gene is the catalyst in BL. When mutated, the c-myc gene stimulates cancer cell growth along with shielding the detection of BL cells in the immune system.

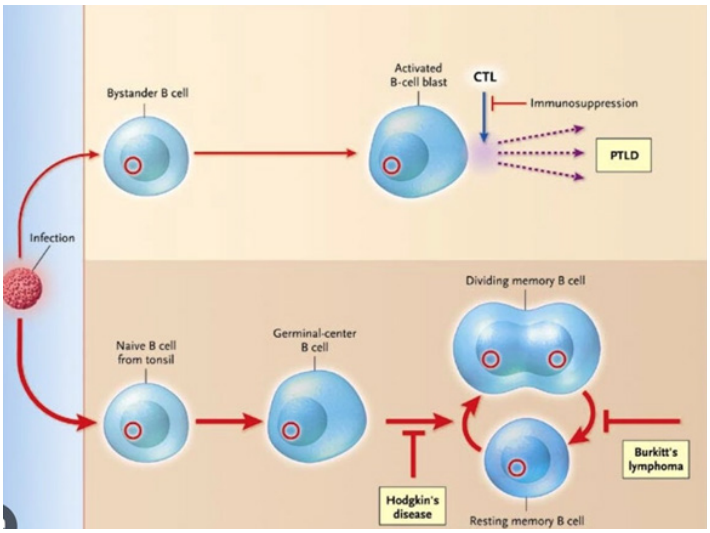

Figure 5: This figure represents the molecular pathogenesis that correlates EBV to lymphoma [18].

Molecular pathogenesis that links infectious mononucleosis and BL

The molecular pathways linking infectious mononucleosis and BL include EBV oncogenic mechanisms, the c-myc translocation mechanism, TP53 and BIM mutations and a role in malaria. It is crucial to understand the importance of viral genes that drive oncogenic mechanisms. Latent genes discussed previously such as EBNA1, LMP1, and LMPA2 work to hijack the signaling pathways of B-cells. Epstein-Barr Nuclear Antigen (EBNA1) is responsible for the viral genome being copied every time a B-cell divides. EBNA1 is a latent protein present in all EBV-positive tumors [19]. EBNA1 aid in the survival of infected B-cells by preventing detection from the immune system. Latent membrane protein 1 (LMP1) falls under the category of an oncoprotein. LMP1 acts as an active CD40 receptor and activates pathways such as NF-kB, JAK/STAT, PI3K/Akt, and MAPK driving B-cell proliferation and regulation. LMP1 also can upregulate bcl-2 genes. Latent Membrane protein 2A (LMP2A) acts as a B-cell receptor signal, preventing infected B-cells from undergoing apoptosis which plays a large role in the survival of infected B-cells [19].

There are 3 types of latency patterns shown in different diseases. Latency I is associated with BL and contains EBNA1 only and is the most silent form of latent EBV phase. Latency II is associated with Hodgkin's lymphoma, and nasopharyngeal carcinomas. Latency II expresses the genes EBNA1, LMP1, and LMP2A and is associated with Hodgkin lymphoma, and nasopharyngeal carcinoma [19]. Latency III is associated with HIV/AIDs-related lymphomas or post-transplant disorders. Latency III expresses EBNA1-6, LMP1, LMP2A, and viral miRNAs [19].

Viral MiRNAs play a major role in BL tumor proliferation allowing long term dysregulation of the c-MYC pathway. BHRF1-miRNAs are involved with fast B-cell growth by enhancing the G1-S cycle. BHRF1-miRNAs also promote c-MYC dysregulation. BART-miRNAs target tumor suppressors and block apoptosis [19].

When the c-myc protooncogene undergoes a mutated translocation mechanism, it is placed under the control of the immunoglobulin heavy and light chain enhancers. the classic translocation t(8;14)(q24;q23) involves moving the c-myc gene on chromosome 8 to a point where it is adjacent with the B-cell immunoglobulin heavy chain (IgH) [20]. This classic translocation makes up about 80% of BL cases. The variant translocation t(2;8)(p12;q24) involves the immunoglobulin kappa light chain (Igk) and makes up about 15% of BL cases. The other variant translocation t(8;22)(q24;q11) involves the immunoglobulin lambda light chain and makes up about 5% of BL cases. The heavy chain enhancer known to be the strongest c-myc gene immunoglobulin enhancer and is located on chromosome 14. The heavy chain immunoglobulin enhancer carries a cis-regulatory enhancer (3'RR) that is supposed to drive immunoglobulin gene transcription, but when place in control of the c-myc gene, it then controls c-myc transcription [20]. The 3'RR cis-regulatory enhancer is what causes the c-myc gene to become permanently expressed leading to uncontrolled B-cell growth. The light chain enhancers are the located-on chromosome 2 and 22. Although the light chain enhancers are not as strong as the heavy chain enhancers, they still cause uncontrolled B-cell proliferation through c-myc activation.

Diagnostics

Diagnostics of EBV and infectious mononucleosis

Clinical manifestations or observable features of infectious mononucleosis can be identified through symptoms and of main feature of infectious mononucleosis is lymphadenopathy, or in other words, swollen lymph nodes. In EBV driven mononucleosis, enlargement of the lymph node is found distinctly in the posterior cervical lymph node [21].

The hallmark diagnostic for infectious mononucleosis is the

presence of atypical lymphocytes. Atypical lymphocytes are T-cells that activate in response to B-cells being infected by EBV [22]. In a study, 97 patients with atypical lymphocytosis were evaluated to determine whether the disease was caused by EBV-positive infectious mononucleosis and what the distinct factors were that made it differ from EBV-negative atypical lymphocytosis. This study used flow cytometry with 26 monoclonal antibodies. Both EBV positive and EBV negative cases shared and increase in activated CD8+ T-cells, a small rise in NK cells, and no change in the number of CD4+ T-cells or B-cells [23]. In patients that were EBV positive presented higher lymphocyte counts, higher atypical lymphocyte counts, a higher activation in CD8+ T-cells, an increase in γδ T-cells, and a light increase in NK cells [23]. This study can conclude that atypical lymphocytosis causes by EBV positive infectious mononucleosis is driven by how EBV infects the host cells and triggers an immune response [23].

EBV induced mononucleosis can be confirmed through a positive heterophile antibody test. However, it is recommended that this test is repeated due to false negative, particularly in children at 4 years old or younger [21]. Infectious mononucleosis in children is often misdiagnosed as an ear infection, a respiratory inspection, and even inflammation of the stomach. If EBV test continue to come back negative, then it is possible that there is another underlying cause such as HIV or cytomegalovirus (CMV) [21].

Along with atypical lymphocytes as previously discussed, hematological findings in individuals infected with EBV associated mononucleosis include an elevated white blood cell count, and thrombocytopenia. Elevated white blood cell counts or leukocytosis is an increase in white blood cells in the bloodstream due to the immune system working in overdrive trying to fight an infection [24]. Thrombocytopenia is considered the destruction of platelets or a decrease in platelet production, leading to a platelet count of less than 150 x 10^6/L [1]. If left untreated, thrombocytopenia can lead to an increased risk of bleeding both internally and externally which can become life threatening. Thrombocytopenia can also lead to iron-deficiency anemia.

Diagnostics of BL

Due to the fast-growing nature of BL, it can be difficult to differentiate it from other types of aggressive B-cell lymphomas such as diffuse large B-cell lymphoma (DLBCL). A diagnostic workup must be done to confirm the BL diagnosis and specify the subtype of BL the patient has. It is important that a full diagnostic workup is done to ensure that the patient receives a proper diagnosis. In the laboratory setting, a tumor biopsy or a peripheral blood smear is taken and analyzed using flow cytometry and immunophenotyping. Immunophenotyping is important when distinguishing BL from other B-cell lymphomas [14]. immunohistochemistry is used to identify makers present such as BCL6, CD10, Ki-67(100% proliferation), and BCL2. Molecular tests can be used to identify c-myc translocations such as t(8;14) (using FISH), and the presence of EBV DNA.

Under the microscope, BL has been classified to have a "Starry Sky" appearance. The Starry Sky appearance is a result of several "tangible-body" macrophages present amidst tightly packed tumor cells. The tangible-body macrophages resemble clear stars and work to ingest apoptotic tumor cells, and debris [14]. Macrophages are leukocytes. BL cells general morphology includes uniform, round, and medium sized B-cells. One of the most distinguishing features of the BL cell that pathologist recognize is that the cells appear to have a basophilic cytoplasm (dark blue appearance) when stained with H&E (hematoxylin and eosin) with square edges due to the rapid growth of the cells [14]. The nucleoli appear to be darker due to how active it is. The BL cells also contain cytoplasmic lipid bubbles which materialize as clear bubbles under a microscope.

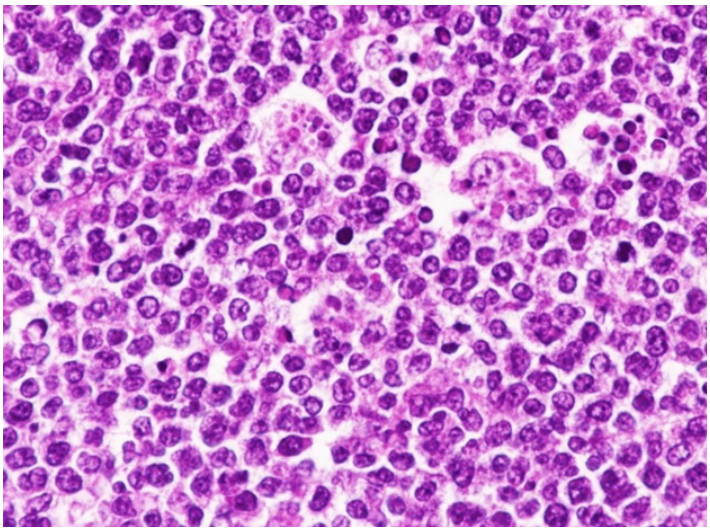

Figure 6: this figure shows the hallmark "starry sky" pattern that is associated with BL. This figure also presents the uniform medium sized B-cells along with some prominent nucleoli. (Magnification x400) [14].

Cytogenetic analysis is used to identify a mutation in the c-myc protooncogene [14]. Patients will always be tested for the presence of EBV when diagnosed with BL. Studies used gene expression microarrays to identify a molecular signature characteristic of Burkitt's Lymphoma. There is a high molecular correlation to high c-myc/lg translocations, and deregulations of c-myc. The transcription factor c-myc is tightly regulated and controls proliferation of cells and programmed cell death (apoptosis).

Being able to differentiate BL from other B-cell lymphomas is an important factor in properly diagnosing and treating patients. The Ki-67 proliferation index measures the nuclear protein Ki-67 which is only expressed in cells that are actively proliferating. Cell that are in the G0 phase do not express the Ki-67 nuclear protein because those cells are at rest. The largest contrast of BL and other forms of lymphomas is in BL, the Ki-67 proliferation index is positive for virtually all cells, reflecting a proliferation index of nearly 100%, which is a significantly higher growth rate than other forms of lymphoma. In Diffuse Large B-cell Lymphoma (DLBCL) the Ki-67 index ranges at approximately 40-90% [25,26]. The ki-67 proliferation index helps researchers assess how aggressive

the cancer is, what the best treatment plan will be, and identify a prognosis.

CD markers also play an important role in differentiation. In BL, the hallmark markers found include CD20+, CD10+, Bcl-6+, and Bcl-2-. CD20 marker confirms the presence of mature B-lymphocytes found in BL and DLBCL. CD10 and Bcl-6 are both proteins that are found in the germinal center of B-cells indicating an antibody gene mutation when they are in the stage of rapid cell division [26]. When both CD10 and Bcl-6 markers are expressed, this indicates that tumor growth will resemble the same phenotype as the original germinal center cells before the presence of malignancies [26]. Meaning the cancer cells will still look like a normal functioning B-cell. The expression of CD10, Bcl-6, and CD20 combined make up the foundation of rapidly growing germinal center B-cells which make BL possible [26]. Bcl-2- indicates the absence of the Bcl-2 protein, further distinguishing BL from other lymphomas. Bcl-2 is a protein that blocks programmed cell death [27]. In other B-cell lymphomas such as DLBCL, Bcl-2 is overexpressed causing uncontrolled cell proliferation leading to malignancies. On the other hand, in BL bcl-2 is negative, meaning there are other factors causing uncontrolled cell proliferation such as EBV [27]. Diagnostic imaging is the next step for BL patients. CT scans are typically used to get a clear image of the chest and abdomen. PET scans are then used to help determine the stage of the disease [14]. Once BL is confirmed, further testing such as bone marrow aspirates and cerebrospinal fluid analysis are imperative for further investigation on how far the disease has spread [14].

Treatment

EBV-specific CTL therapies in BL

The role of cytotoxic T-cells (CD8+T) or cytotoxic T-lymphocytes (CTLs) in healthy individuals is the prevention of uncontrolled proliferation of B-cells. CTLs recognize viral peptides located on Major Histocompatibility Complex class I molecules (MHC class I) that are released from EBV infected B-cells and kill them [28]. MHC class I molecules are proteins located on the cells surface that serve as a signal messenger to T-cells indicating an infection or cancer. In cases such as BL, EBV-infected tumor cells will release a restricted variety of viral peptides, making it more difficult for T-cells to detect and regulate infected B-cells [28]. Studies have shown that it is possible for CTLs to restore antiviral immune control in replacement of failed treatments. One study found significant evidence that reinfused CTLs that are trained to control EBV can specifically target and kill EBV. In this study, CTL lines were successfully grown and administered in 9 out of 13 patients. CTLs can also help aid stem cell transplantations in restoring the immune system for Hodgkin's lymphomas and BL [28]. Patients with no sign of cancer present the largest cell count expansion after CTL infusion. Patients in remission from Hodgkin's lymphoma present the second highest cell count expansions after CTL infusion, indicating a partial immune function recovery. Patients that relapsed showed the lowest cell count expansions, indicating that there is a major dysfunction in T-cells however CTL infusion could be the most beneficial for these patients.

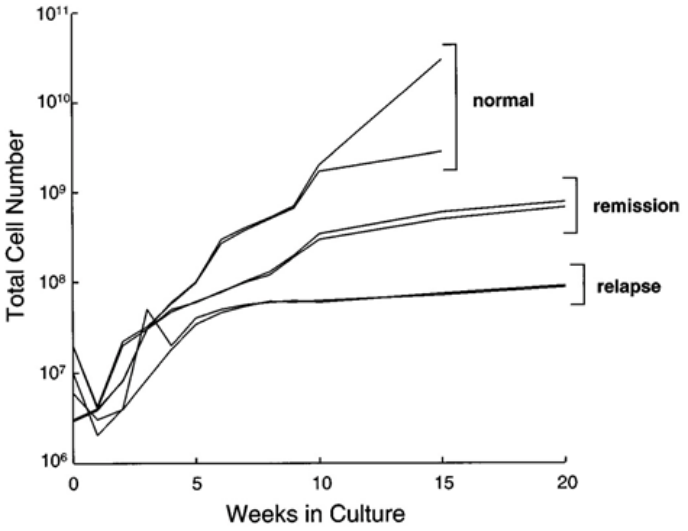

Figure 7: This graph compares EBV-specific CTL expansion of normal patients, patients in remission, and patients who have relapsed with Hodgkin's lymphoma [28].

Chemotherapy treatments for BL

Short but high-intensive chemotherapies are used to treat BL. Due to the aggressive and rapid cell growth of BL, chemotherapy agents such as CTX, VCR, MTX, Ara-c regimens, and high dose MTX are used as the main line of treatment in multidrug chemotherapy regimens. Standard treatment regiments for other lymphomas like DLBCL would not be successful on BL because of how aggressive of a cancer it is [29]. An example of one of the most common chemotherapy treatments for BL is CODOX-M/IVAC which includes a high dose of methotrexate and cytarabine [29]. These high intensity treatments are very effective however they can cause severe infection and damage to many bodily functions such as hematopoiesis which in some cases can result in mortality.

Overall, the survival rates for BL include stage I-II survival rate is >90% with short intensive chemotherapy treatment, stage III-IV survival rate is 70-80%, and BL with CNS involvement survival rates are 50-60% [14]. in endemic regions such as endemic Africa, survival rates drop significantly to less than 50-30%. This low survival rate can be due to a late diagnosis, limited resources or funds, or a correlation to other diseases like malaria or HIV [30].

Stem cell transplantation treatment for BL

Stem cell transplantation therapy allows the body to recover at a faster rate by raising white blood cell count and restoring hematopoiesis. Stem cell transplantation is a secondary form of treatment that is usually administered at complete remission 1 (CR1) or complete remission 2 (CR2). In BL cases, hematopoietic stem cells are used and are derived from either bone marrow or peripheral blood. Peripheral blood stem cells are preferred over bone marrow stem cells because they are more efficient to obtain and administer. To obtain Bone marrow stem cells, they must be collected through aspiration. Bone marrow stem cells are taken directly from the iliac crest (back of the hip bone) while the patient

is under anesthesia. Bone marrow stem cells transplants are most used for pediatric patients. Peripheral blood stem cells are collected through apheresis. G-CSF mobilization is used, and stem cells enter the circulatory system. The blood then enters an apheresis machine which will filter out the stem cells, the blood then returns to the body. Peripheral blood stem cell transplantations also lead to faster engraftment, meaning, it takes less time for the recovery of neutrophils (5 days shorter than BM) and platelets (7 days shorter than BM) [31]. Autologous stem cell transplantation is a safer option to use however there is an increased risk for relapse in cancer patients. Allogeneic stem cell transplantations have a stronger anti-cancer effect.

EBV-Targeted Therapies

Multiple immunotherapy treatments have been used to target EBV to prevent tumors from arising as well as targeting infectious mononucleosis. Research has shown that using BH3 mimetics inhibitors can prevent EBV from inducing survival proteins such as Bcl-2 [32]. Proteasome inhibitors such as bortezomib and ixazomib can induce apoptosis. These proteasome inhibitors have also shown signs of exploiting the EBV lytic cycle [32].

Kempkes and Robertson put an emphasis on the EBV virus uses a cycle of latency mechanisms to infect B-cells. Instead of just depending on one latency phase, EBV relies on switching through many latency phases (latency 0,I,II, and III) [9]. Each latency phase contains a unique combination of latent proteins along with RNAs and promoters. The switch is not an "on and off" switch of EBV activation, instead, it is a constant cycle that allows the EBV virus to invade the host cell persistently and successfully adapt to any environmental changes [9]. EBV promoters are regions that control gene expression. Promoters such as Cp, Wp, ad Qp activate depending on which latency phase is being expressed. The EBV viral genome undergoes histone alteration and DNA methylation during maturation of infected cells [9]. MicroRNAs play a big role in latency stabilization by extinguishing immune signal pathways and suppressing responses that lead to programmed cell death [9]. With this EBV can regulate these processes even with little to no protein production. Kempkes and Robertson reported the importance of chromatin mapping. Although unresearched, it is important for understanding how the EBV virus can control B-cell regulation through super-enhancer networks [26].

Strategies have been discovered for targeting the EBV episome to prevent EBV-associated cancers from developing. The structure of the EBV episome is circular and condensed, giving it a distinct look compared to healthy cells [33]. EBNA1 has been a focus for anti-cancer therapies due to EBVs dependability on to successfully bind to host cells a replicate. CRISPR/Cas9 have been investigated as possible anti-cancer therapy. CRISPR/Cas9 can cut portions of the EBV genome including EBNA1 which would reduce replication and malignancy growth [33]. Another strategy that is highly considered is lytic induction therapy. Lytic induction therapy forces EBV into a constant lytic phase ("awake phase"). In recent clinical trials, EBV is woken up using drugs such as HDAC inhibitors and DNA methylation inhibitors. The reactivation of EBV causes it to produce a higher amount of BGL4. Once this phase is successfully consistent, the drug Ganciclovir is administered and is activated by the BGL4 that is produced. This drug will then kill B-cell infected with EBV leaving normal cells alone because they do not produce the BGLF4 needed to activate the drug [33].

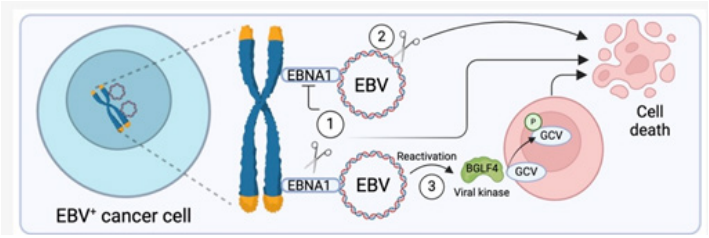

Figure 8: This figure presents a latently infected cell and the three major approaches to the elimination of these EBV-positive cancer cells. (1) EBNA1 inhibition. (2) Direct Genome Cleavage. (3) Lytic Reactivation Therapy [33].

Other advances in immunotherapy such as next-generation sequencing (NGS) is a more cost and time efficient way for doctors to use DNA sequencing technology to detect mutations such as cancer cells [25]. NGS has made it easier for hematologists to identify hematologic malignancies, decide proper treatment, keep track of disease progression, and can also aide in the analysis of a patient's prognosis or cancer- risk [25].

Cost of Treatments

There is a severe problem with costs of treatment in low-income regions such as sub-Saharan Africa. Low-income countries struggle with limited access to healthcare specialists, lack of successful and timely diagnosis, and lack of treatment options available at an appropriate cost. Research has confirmed that there is a 90% mortality rate for children diagnosed with pediatric cancer in sub–Saharan Africa. In contrast, childhood cancer survival rates in high income regions range at 80-85% [34]. Most children in these low-income regions experience infections during treatment due to malnutrition and late diagnosis [34].

Summary and Conclusions

Burkitt's lymphoma falls under the category of a hematologic malignancy due the infection and uncontrolled proliferation of B-cells. BL is a highly aggressive form of lymphoma caused by the c-myc oncogene translocation, under the control of immunoglobulin enhancers. BL has a distinct histology of a "starry sky" pattern along with uniform medium-sized B-cells. This histology demonstrates the outcome of such a fast-growing cancer. BL is also unique in that the Epstein-Barr virus, along with other cofactors, is a main driver for the translocation of the c-MYC oncogene. EBV can infect B-cells for long periods of time due to its ability to switch between latent and lytic phases. The latent phase allows EBV to remain dormant and undetected inside B-cells while the lytic phase allows EBV to express multiple genes and replicate viral DNA causing the spread of the EBV infection to the surrounding B-cells. Infectious mononucleosis is also

driven by EBV and can contribute to the prolonged mutation and uncontrolled cell proliferation that EBV causes in BL. Infectious mononucleosis usually goes undiagnosed due to lack of symptoms.

Treatment for BL include high-dosed chemotherapy to combat the aggressive nature of the disease. It is recommended consider stem cell therapy treatments post-chemotherapy. Stem cell therapies can help improve the immune system and hematopoiesis at a faster rate, reducing the risk of infection and relapse. EBV targeted therapies are currently being researched. Therapies such as HDAC inhibitors, valganciclovir and latency- reversing agents have been proven to significantly reduce the rates of BL by killing the EBV virus and preventing prolonged B-cell infection.

There is a current global health emergency across low-income countries and regions. There have been many prevention strategies put in place to counteract this global health burden.

The Global HOPE program (Hematology-Oncology Pediatric Excellence) is a program that focuses on long-term improvement for healthcare systems located in low-income countries including Uganda, Tanzania, Malawi, Botswana, Kenya, Rwanda, and South Africa [34]. The Global HOPE program is under administration by Texas Children's Hospital and includes hospitals among all countries listed. The Global HOPE program has made a significant impact in Uganda, Tanzania, and South Africa by introducing a unique fellowship opportunity to students to train in these countries as a pediatric Hematology-Oncology physician. This act alone ensures that over 2,800 children in these low-income countries are taken care of each year [34]. The Global HOPE program has also raised the number of trained nurses, surgeons, radiologists, pathologists, intensivists, and pharmacists in each region by collaborating with College of Surgeons of East, Central, and Southern Africa [34]. There is a global initiative for strengthening diagnostic systems in low-income regions. The Global HOPE program contributes to this by providing virtual seminars for pathologist training, donating, and updating diagnostic tools, and introducing new technology. Improving diagnostic tools and technology has made a large impact in Uganda, where a diagnosis once took from a few weeks to months.

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