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Review

Burkitt's Lymphoma: Insights into Etiology, Pathogenesis, Diagnosis and Possible Lines of Management

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Abstract

B-cell lymphomas arise at certain stages of cellular development and maturation, potentially affecting antigen presentation and T-cell recognition. Burkitt's lymphoma (BL) is a highly malignant B-cell lymphoma that is frequently associated with Epstein-Barr virus infection. Although BL can be effectively treated leading to high survival rates, its ability to mask itself from the immune system makes it an interesting disease to study. This review provides an overview of the possible etiology, risk factors, pathophysiology, clinical presentation, diagnosis, prevention and different lines of management of BL.

Key Words: Burkitt's; Lymphoma; Non-Hodgkin's; Cancer; Immune Cells; Chemotherapy

Introduction

Burkitt's lymphoma (BL) is a high-grade malignancy occurring most frequently in children in areas in which malaria is endemic [1]. BL is classified into three different categories according to the epidemiological observations: endemic BL (eBL), sporadic BL (sBL) and HIV-associated BL [2]. About 95% of cases of eBL are associated with Epstein-Barr virus (EBV) and are commonly found in Equatorial Africa where malaria is highly prevalent [3]. In contrast, only 5–15% of sBL and 40% of HIV-associated BL are EBV positive [4]. Worldwide more than 90% of all people become infected with EBV at some point during their lifetime [3]. Though most infected individuals remain healthy, EBV is capable of producing pathologic conditions including malignancies [4]. Also, EBV may transform normal human B lymphocytes into continuously growing cells such as BL and B-lymphoblastoid cells. It is present in approximately 50% of Hodgkin's Lymphoma (HL) and is found with varying frequency in non Hodgkin's Lymphoma (NHL) [5]. EBV is implicated in T-cell lymphoma, infectious mononucleosis, adult T-cell leukemia, nasopharyngeal carcinoma, post-transplant lymphoproliferative disorders and other lymphoid and epithelial malignancies [6]. In most cases, infection of B lymphocytes by EBV is followed by a cytotoxic CD8+ T cell (CTL) response that controls the spread of the virus [7]. In spite of the vigorous CD8+ T cell response, a population of infected B cells escapes immune-mediated elimination [8].

Etiology of Burkitt's Lymphoma

The exact cause of BL is unknown [9]. Risk factors vary according to geographic location. Studies suggest that BL is the most common childhood cancer in regions where there is a high incidence of malaria, like Africa [2]. Elsewhere, the greatest risk factors are human immunodeficiency virus (HIV) and AIDS [10]. The endemic type of BL is almost always linked to a previous infection with the Epstein–Barr virus (EBV) [4]. This is the virus that causes glandular fever. In the type of BL seen in the UK – the sporadic type – the role of EBV is less certain. EBV is a common virus worldwide [11]. Blood tests show that 9 out of 10 adults in the United Kingdom have had this infection at some time in their life [7]. It is not clear why a few people develop lymphoma while most do

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not. Having a weakened immune system also makes some people more likely to develop BL [4]. For example, this might affect people with HIV infection. Most patients with BL will not have HIV infection, but everyone should have a blood test to rule this out [12].

Risk Factors of Burkitt's Lymphoma

There are several factors that may affect a person's liability of getting BL. There are many types of lymphoma, and some of these factors have been linked only to certain types [2].

Age

The old age is a strong risk factor for lymphoma overall, with most cases occurring in patients in their 60s or older. However, some types of lymphoma are more common in younger people [1].

Gender

Generally, the risk of BL is higher in males than in females, but there are certain types of non-Hodgkin lymphoma that are more common in females. The reasons for this are not yet fully understood [13].

Race, Ethnicity and Geography

In the United States, white people are more prone to develop BL than African Americans and Asian Americans. Worldwide, BL is more common in developed countries, with the United States and Europe having the highest rates. Some types of lymphoma that have been linked to specific infections such as Epstein-Barr virus infection are more common in certain areas of the world [2].

Radiation Exposure

Several studies had proven that there is an increased risk of developing several types of cancer, including leukemia, thyroid cancer, and BL between the survivors of atomic bombs and nuclear reactor accidents [14]. Patients treated with radiation therapy for some types of cancer have a slightly increased risk of developing BL later in life and this risk increases in patients treated with both radiation therapy and chemotherapy [15].

Exposure To Certain Chemicals

Certain chemicals such as benzene and certain herbicides and insecticides may increase the risk of non-Hodgkin lymphoma. Some drugs used to treat other types of cancer may increase the risk of developing BL many years later. For example, patients who were treated for Hodgkin disease have an increased risk of later developing BL but it's unclear whether this is related to the disease itself or is an effect of treatment [16,17].

Immune System Dysfunction

Patients with weak immune systems have an increased risk for development of BL. Patients who receive organ transplants are treated with drugs that suppress the immune system to prevent it from attacking the new organ [3]. These people have a higher risk of developing BL. HIV can also weaken the immune system, and people infected with HIV are at an increased risk of BL [18]. Infection with the Epstein-Barr virus (EBV) is an important risk factor for BL in areas of Africa where this type of lymphoma is common. In developed countries such as the United States, EBV is more linked with lymphomas in patients also infected with HIV, the virus that causes AIDS [12].

We collected data from 809 patients who visited the outpatient clinics of the oncology department, faculty of medicine, Tanta university, Egypt. These patients were exposed to the risk factors of BL such as malaria, HIV, Epstein-Barr virus, radiation, chemicals and immunological dysfunction. We determined the incidence of BL among these patients. These data were represented in table 1. These data had proven that the incidence of BL was high in patients exposed to malaria, AIDS and Epstein-Barr virus (22 %, 25 % and 19 % respectively) and was relatively low (7 %) in patients exposed to certain chemicals. These results were in agreement with the results of the previous studies which had proven that the incidence of BL is strongly associated with malaria, AIDS and Epstein-Barr virus infection [3, 10].

Table 1: The incidence of Burkitt's Lymphoma in relation to the risk factors

Patient exposed to	Total No. of patients	Age (Years)	Gender		Incidence of Burkitt's Lymphoma %
			Male	Female	
Malaria	42	45-72	36	6	22 %
AIDS	8	32-51	7	1	25 %
Epstein-Barr virus	53	30-63	39	14	19 %
Radiation exposure	367	32-73	216	151	16 %
Some chemical exposure	218	38-61	156	62	7 %
Immune system dysfunction	121	33-49	73	48	17 %

Pathophysiology of Burkitt's Lymphoma

The exact pathophysiological mechanisms leading to the development of BL are not yet fully understood [4]. Epstein-Barr virus (EBV) and malaria infection as well as C-myc oncogene activation are suggested to be the most important predisposing factors for the development of BL [19]. EBV is a member of the herpes virus family that has been strongly implicated in the endemic form of BL (eBL). Virtually all patients with eBL are EBV positive, whereas only about 20% of sporadic (sBL) cases are associated with EBV. EBV tends to cause a latent infection of B lymphocytes, some of which evade the T-cell-mediated immune response and enter the germinal center. This subsequently results in excessive B cell proliferation [3].

Malaria infection may also play a crucial role in the pathogenesis of eBL, as it may lead to inhibition of EBV-specific immune response [20]. EBV can be detected in 25-40% of immunodeficiency-associated cases. EBV nuclear antigen-1 (EBNA-1) and EBV-encoded RNAs have been shown to have modest anti-apoptotic properties. Furthermore, EBNA-3A and EBNA-3C can inhibit the expression of the anti-apoptotic protein BCL-2 [3]. This may initiate a series of events that lead to activation of the c-myc gene which is responsible for tumor proliferation. Overproduction of the c-myc product may change the lymphocytes into cancer cells, but other gene mutations may be responsible for the progression of BL. Abnormalities in the p53 gene and in death-associated protein kinase had been shown to contribute to inhibition of apoptosis and to the pathogenesis of BL [21].

Clinical Presentation of Burkitt's Lymphoma

Most patients present with advanced disease because of the rapid rate of tumor growth. BL cells have a remarkably short doubling time. Children in equatorial Africa and Papua New Guinea have endemic BL and present with facial tumors in the jaw or orbit, abdominal masses, enlarged gonads or bilateral massive enlargement of breasts, particularly if malignancy onset is associated with puberty, pregnancy or lactation [22].

If the clinical presentation is an African adult with lymphadenopathy and suspected lymphoma, BL is less likely unless the patient is HIV infected. BL is especially suspect worldwide in immune deficiency conditions such as HIV/AIDS, post solid organ transplants, and following chemotherapy for other malignant lymphomas [23]. The anatomical site of presentation in these non- endemic cases is unlikely to be facial and more likely to be abdominal. BL may be primary in the stomach in association with Helicobacter pylori infection and in gastric lymph nodes with erosion into the stomach [24]. The pancreas may be diffusely involved forming a deep abdominal mass along with involved periaortic lymph nodes. Bone marrow involvement is commonly present in late stages of the disease but circulating BL cells with leukemic signs and symptoms are rare [25]. The most common findings in patients with BL include abdominal masses which can cause abdominal pain, distention and ascites. Also, nausea, vomiting, loss of appetite, change in bowel habits, gastrointestinal bleeding and painless lymphadenopathy may be the first presentation of BL [2].

Diagnosis of Burkitt's Lymphoma

It is recommended to use the least invasive procedures to establish the diagnosis of BL. These procedures include pathologic evaluation of the involved tissue biopsy [26]. Patients with more than 25% bone marrow involvement are usually considered as having BL. Diagnosis can sometimes be confirmed by bone marrow aspiration and biopsy if the marrow is involved. If the marrow is not involved, diagnosis will require sampling lymph nodes or the involved extranodal sites [27].

Prevention of Burkitt's Lymphoma

Most people with BL have no risk factors that can be changed. So, it is difficult to protect against these lymphomas. The best way to reduce the risk for BL is to try to prevent the known risk factors such as immunodeficiency [2]. Infection with HIV is a preventable cause of immunodeficiency. Control of the spread of HIV would prevent many deaths from BL. Treating HIV with anti-HIV drugs also lowers the incidence of developing BL [9].

Prevention of the spread of the human T-cell leukemia/lymphoma virus (HTLV-1) is another way that may have a great impact on BL in areas of the world where this virus is endemic. The same strategies used to prevent HIV spread could also help to decrease HTLV-1 transmission [28]. Helicobacter pylori infection has been linked to BL of the stomach. Treating H. pylori infections with antibiotics and antacids may lower this risk, but the benefit of this strategy has not been yet proven [24]. Another risk factor for BL is infection with Epstein-Barr virus but up till now, there is no known strategy to prevent this type of infection [29].

Management of Burkitt's Lymphoma

Burkitt's lymphoma is a fast-growing tumor that has a high sensitivity to chemotherapy. However, sporadic and immunodeficiency-associated BL may be less sensitive than the endemic variant to chemotherapy [2]. Different lines of management of BL have been used with variable success rates. These lines include chemotherapy, radiation therapy, stem cell transplantation and surgical management. These lines may be used in combination with the monoclonal antibody rituximab, with a high success rate [30].

Chemotherapy

Burkitt's lymphoma is always treated with chemotherapy, even if the lymphoma is localized. Intravenous chemotherapy has the best chance of killing most of the lymphoma cells as quickly as possible. The regimens are typically given intravenously as an intravenous infusion [1]. When first starting chemotherapy, many of the tests should be performed to look for signs of 'tumor lysis syndrome', a condition that happens when a lot of lymphoma cells are killed very quickly. The chemicals that were in the lymphoma cells spill out into the bloodstream. The body tries to get rid of the extra chemicals through the kidneys and rebalance the salts in the blood. Serious problems may occur if the levels of salts in the blood

become very abnormal or if the kidneys become overwhelmed by uric acid [31]. In patients with BL, targeting the CNS by chemotherapeutic agents is also needed. Intrathecal chemotherapy is another way to get drugs to the brain and spinal cord. It means giving chemotherapy directly into the cerebrospinal fluid. Only few drugs can be given by this way including methotrexate and cytarabine [32].

Immunotherapy

Immunotherapy is treatment that either boosts the patient's own immune system or uses man-made versions of the normal parts of the immune system. This type of treatment either uses monoclonal antibodies or antibodies that target CD20 to kill lymphoma cells or slow their growth [33]. Monoclonal antibodies may target certain proteins on the surface of cancer cells. They can either potentiate the effect of chemotherapeutic drugs or stimulate the body's immune system to destroy lymphoma cells [34].

Rituximab is one of the first-generation CD20 monoclonal antibody that has been widely used for treatment of BL [35]. It can induce complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC), leading to significant inhibitory effect against lymphoma cells. CDC represents the primary mechanism for cell-killing by rituximab. However, about 10-15% of lymphoid cells was resistant to CDC because of lower levels of complement activation or decreased cytotoxicity of the activated complements [36]. Also, rituximab may induce apoptosis of B cells upon binding to CD20 and therefore can directly inhibit cell growth. Moreover, rituximab was proven to kill lymphoma cells through induction of formation of the cytotoxic reactive oxygen species [1].

Surgical Treatment

In the current clinical practice, effective responses were observed with combination chemotherapy and immunotherapy, making the role of surgical treatment to be considered only for patients with obstruction who cannot begin chemotherapy immediately [37]. Tracheotomy is indicated if the patient's airway is compromised from the physical pressure of a large tumor mass. Exploratory laparotomy may be performed for obstruction of the gastrointestinal tract. Patients with uncontrolled gastrointestinal bleeding may need exploratory laparotomy or endoscopic procedures for hemostasis. An excisional lymph node biopsy may be necessary to reach an accurate diagnosis. Pericardiocentesis is indicated for patients presenting with cardiac tamponade. Paracentesis may be indicated if large ascites is one of the presenting complaints of patients with BL [38].

Radiation Therapy

For the treatment of BL, radiation may be given as a preventive treatment directly to the central nervous system to help stop the spread of the disease in the brain or spinal cord. The efficacy of radiation therapy in management of BL is variable depending on the stage and extent of the disease and the health status of the patients [39].

Stem Cell Transplantation

Some patients with lymphoma may have treatment using stem cells. Stem cells are blood cells at their earliest stage of development. All blood cells develop from stem cells. There are two different types of stem cell treatment, either using the stem cells of the patient himself (Autologous stem cell transplant) or using stem cells from a donor (Allogeneic stem cell transplant) [40]. The choice between these two types of treatment is variable from a patient to another and generally depends on the health status of the patient and his expected response to therapy [41]. Stem cell transplantation is not recommended for patients with BL in first complete remission. High-dose chemotherapy plus autologous stem cell transplantation may be considered for patients whose condition has not responded to or who have relapsed after first-line conventional chemotherapy [42].

Other Lines Of Treatment of Burkitt's Lymphoma

Due to the fact that many cases with BL are refractory to treatment and different lines of treatment are associated with serious adverse effects, clinical trials were carried out to explore new lines of management of this type of lymphoma and to reduce treatment-associated adverse effects [2]. Recent studies suggested that flavonoids such as naringenin may have a promising role in management of BL [43]. Naringenin was proven to kill BL cells, possibly through enhancing natural killer cell lysis activity by increasing the expression of NKG2D ligands on BL cells [44]. Also, Sesamolin and sesamin which are representative lignans found in sesame seed were reported to increase the expression level of NKG2D ligands on Raji cells, which are derived from BL [45]. Moreover, resveratrol which is a polyphenolic natural product had shown chemopreventive properties against BL, possibly through inhibiting the proliferation and survival of Epstein Barr virus-infected BL cells depending on viral latency program [46]. These natural agents may be of great help if combined with the chemotherapeutic agents or radiotherapy to potentiate their effects on BL and decrease the incidence of adverse reactions [17].

Steroids were given with chemotherapy to help treating lymphomas. They help the patient to feel better and can reduce feelings of sickness [2]. Mesna and folinic acid were used to protect against some of the side effects of the chemotherapy drugs used in the chemotherapy regimens of BL [47]. Antiemetics such as metoclopramide, ondansteron and aprepitant are frequently used to reduce chemotherapy-induced nausea and vomiting. Prophylactic antibiotics and antifungals are used to reduce the risk of infection associated with immunosuppression. Also, growth factors such as granulocyte-colony stimulating factors are used to help rapid recovery of the bone marrow [48].

Conclusion

BL is a highly aggressive non-Hodgkin's lymphoma, found primarily in equatorial Africa and Papua New Guinea, but may also be observed with lesser frequency in other parts of the world. Cases of BL may be associated with EBV infection and are widely variable in their clinical presentation. Lines of treatment of BL are variable according to the stage of the disease and the health status of the patient. Future studies are needed for better understanding of the pathogenesis and for exploration of new lines of management of BL.

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