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Etiology of Lymphoma in Western Sudan: Role of Cytomegalovirus, Human Immunodeficiency Virus, and Epstein-Barr Virus

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ABSTRACT

Background: *The potential involvement of viruses in lymphoma development remains uncertain. This study investigates the role of cytomegalovirus (CMV), human immunodeficiency virus (HIV), and Epstein-Barr virus (EBV) in the development of lymphoma among Sudanese patients.*

Materials and Methods: *This study examined 55 blocks of formalin-fixed, paraffin-embedded (FFPE) tissue previously diagnosed as lymphoma. Immunohistochemical staining was employed to detect Epstein-Barr virus, human immunodeficiency virus, and cytomegalovirus. Data were collected from El-Obeid histopathology laboratories from January 2023 to July 2024.*

Results: *Of the 55 FFPE blocks examined, 36 (65.4%) belonged to men. Most participants (43.6%) were between 40 and 60 years old. EBV is the most common virus in lymphoma patients, accounting for 18% (10/55), with the majority being Hodgkin (4/5) 80% and non-Hodgkin (6/50) 12%. HIV positivity in lymphoma is 16.3% (9/55), while CMV positivity is 5.5% (3/55), both of which are only identified in non-Hodgkin lymphoma.*

Conclusion: *These findings suggest a strong relationship between EBV, HIV, and CMV and lymphoma, with CMV appearing to have a smaller impact. We need further research with a larger sample size to determine how these viruses contribute to lymphoma development.*

Keywords

Lymphoma, Epstein-Barr virus (EBV), Cytomegalovirus (CMV), Human immunodeficiency virus (HIV), Hodgkin Lymphoma (HL), Non-Hodgkin Lymphoma (NHL).

Introduction

Lymphoma, a category of hematologic malignancies primarily impacting the lymph nodes, presents a significant global health challenge, with an estimated 627,000 new cases and 283,000 deaths reported worldwide in 2020. There are two main types of lymphomas: [1] non-Hodgkin lymphoma (NHL), which includes B cell NHLs, T cell NHLs, and natural killer (NK)-cell NHLs and makes up 80–85% of cases; and [2] Hodgkin lymphoma (HL), which makes up 10–15 percent of cases and is identified by Reed–Sternberg cells. The incidence of lymphoma, particularly non-Hodgkin lymphoma (NHL), has increased significantly over the past few decades, by approximately 3-4% [3,4]. Hodgkin lymphoma (HL) accounts for approximately 83,000 new cases annually, significantly contributing to the global cancer burden. Failure to promptly identify and treat both NHL and HL can result in significant health risks [5]. There is a pressing requirement for effective diagnostic tools and therapeutic interventions. Modern treatments for lymphoma include chemotherapy, radiation therapy, immunotherapy, and targeted therapies [6]. These treatments need to be tailored to each type and stage of lymphoma. Virus-related lymphoma is harder to treat and has a worse outlook because it is both a hematologic cancer and a viral infectious disease in one [7]. The replication of viruses can lead to various detrimental effects on the host's nuclear material. Oncoviruses account for approximately 20% of all human oncogenesis. To fully understand how lymphoma grows and spreads, which involves oncogenic viruses, we need both clinical data and experimental studies. Investigating oncogenic viruses aids in elucidating pathophysiology and formulating targeted antiviral therapies. This review looks at the pathophysiology of lymphomas connected to Epstein-Barr, CMV, and human immunodeficiency viruses. It shows what we know now and what we've learned recently.

Materials and Methods

This study retrospectively screened lymphoma block samples for the presence of human immunodeficiency virus, Epstein-Barr virus, and cytomegalovirus. Following standard procedures, immunohistochemical staining methods were used on 55 FFPE tissue blocks that had been fixed in formalin and embedded in paraffin. Specimens were acquired from the histopathology laboratories in El-Obeid. The collection period spanned from January 2023 to July 2024.

Ethical Approval

The study protocol received approval from the ethical committee of the Faculty of Medicine at Kordofan University and the Prof. Medical Research Consultancy Center.

Data Analysis

The acquired data was compiled on a data sheet and then entered into the computer software SPSS. The data was then evaluated for frequencies and cross-tabulations.

Results

This study investigated 55 FFPE blocks that had previously been diagnosed as lymphoma. Of these individuals, 36 (65.5%) were men and 19 (34.5%) were women. We discovered CMV in three of the 55 patients (5.4%), evenly distributed across males and females. EBV was found in ten out of 55 individuals, accounting for 18.2% of the total. Out of the 55 cases, seven (70%) were men, three (30%) were women, and nine (16.4%) had HIV. In terms of age distribution, 15 instances were under the age of 40, while 24 (43.6%) were between the ages of 40 and 60, with 18 (75%) men and 6 (25%) females. As demonstrated in Table 1 and Figure 1, there are only five cases of Hodgkin lymphoma, with males and females equally represented.

Table 1: Displays the distributions of EBV (+ve/-ve), CMV (+ve/-ve), HIV (+ve/-ve), age, and lymphoma types among the research participants.

Variables	Males	Females	Total
EBV			
Positive	7	3	10
Negative	29	16	45
Total	36	19	55
CMV			
Positive	2	1	3
Negative	34	18	52
Total	36	19	55
HIV			
Positive	8	1	9
Negative	28	18	46
Total	36	19	55
Age			
<40 years	9	6	15
40-60	18	6	24
>61	9	7	16
Total	36	19	55
Lymphoma types			
Hodgkin	2	3	5
Non-Hodgkin	34	16	50
Total	36	19	55

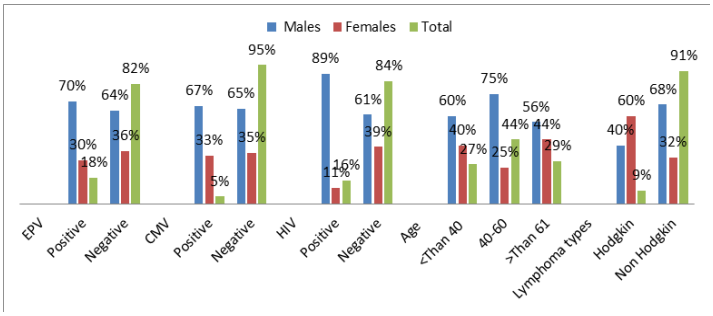

Figure 1: Exhibits the distributions of EBV (+ve/-ve), CMV (+ve/-ve), HIV (+ve/-ve), age, and lymphoma type among the research participants.

45 of the 55 patients tested negative for EBV, while 10 tested positive, with men accounting for the majority of the positive cases (7). Most people who test positive for EBV are between the ages of 40 and 60. Only two out of every ten (70%) EBV positive findings occur in people under the age of 40, and one in those over the age of 61. The extra nodal site had the highest percentage of EBV positive case comprise 60%, distributed as nasopharyngeal was most common 30% and another 30% went to breast, cutaneous and nephrectomy 10% for each one 40% went to the nodal site.

Table 2: Distribution of EBV (positive or negative) by Sex, Age, Sample Site, and Lymphoma Types.

Variable	EBV positive	EBV negative	Total
Sex			
Males	7	29	36
Females	3	16	19
Total	10	45	55
Age			
< 40 years	2	13	15
40-60	7	17	24
> 61	1	15	16
Total	10	45	55
Sample site			
Lymph node	4	20	24
Abdominal mass	0	21	21
Breast	1	3	4
Skin biopsy	1	1	2
Nasopharyngeal	3	0	3
Nephrectomy	1	0	1
Total	10	45	55
Lymphoma types			
Hodgkin	4	1	5
Non-Hodgkin	6	44	50
Total	10	45	55

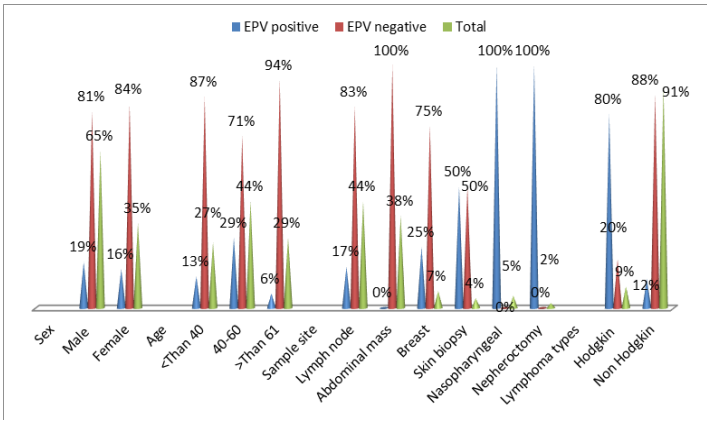

Figure 2: Distribution of EBV (positive or negative) by sex, age, sample site, and lymphoma types.

Table 3 shows the CMV-positive cases: Males accounted for two out of the 55 instances (5%) compared to females with one case. The majority of instances are negative (52 out of 55, or 95%). The majority of CMV-positive cases were found in people between the ages of 40 and 60, with the last instance being in someone under 40. Two cases of abdominal masses and one case of lymph node tested positive for CMV. All CMV-positive cases were diagnosed with non-Hodgkin lymphoma.

Table 3: Distribution of CMV (positive or negative) by sex, age, sample site, and lymphoma type.

Variable	CMV positive	CMV negative	Total
Sex			
Males	2	34	36
Females	1	18	19
Total	3	52	55
Age			
<40 years	1	14	15
40-60	2	22	24
>60	0	16	16
Total	3	52	55
Sample site			
Lymph node	1	23	24
Abdominal mass	2	19	21
Breast	0	4	4
Skin biopsy	0	2	2
Nasopharyngeal	0	3	3
Nephrectomy	0	1	1
Total	3	52	55
Lymphoma types			
Hodgkin	0	5	5
Non-Hodgkin	3	47	50
Total	3	52	55

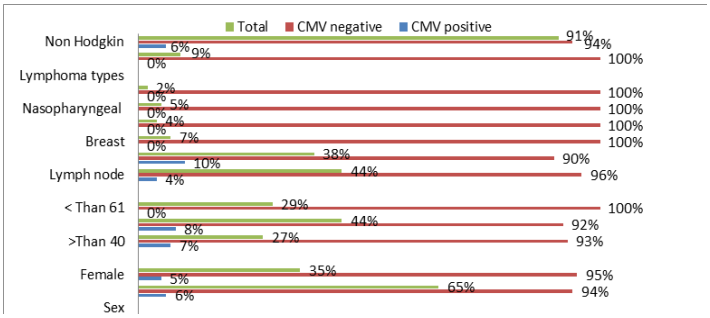

Figure 3: CMV (positive or negative) by sex, age, sample site, and lymphoma type.

Table 4 shows that males have a greater HIV positivity rate than females, with males 8/36 (22%) and females 1/19 (5%). Age groups of less than 40 (27%) and more than 61 (24%) had a higher frequency of HIV positivity. While 40–60% of cases had HIV, only 4% were positive. Abdominal mass samples are most commonly detected in HIV-positive cases, with a positive rate of 33% (7 positive) vs. 14 negatives, a positivity rate for lymph nodes of 8%, and no positive cases at other sites. Only non-Hodgkin lymphoma (9/50, 18%) is associated with HIV in this sample.

Table 4: HIV distribution (positive or negative) by sex, age, sample site, and lymphoma type.

Variable	HIV positive	HIV negative	Total
Sex			
Males	8	28	36
Females	1	18	19
Total	9	46	55
Age			
< 40 years	4	11	15
40-60	1	23	24
> 61	4	12	16
Total	9	46	55
Sample site			
Lymph node	2	22	24
Abdominal mass	7	14	21
Breast	0	4	4
Skin biopsy	0	2	2
Nasopharyngeal	0	3	3
Nephrectomy	0	1	1
Total	9	46	55
Lymphoma types			
Hodgkin	0	5	5
Non-Hodgkin	9	41	50
Total	9	46	55

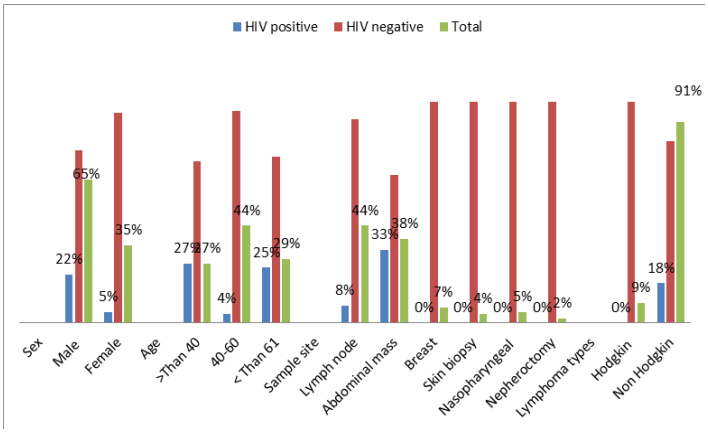

Figure 4: Showing the distribution of HIV (positive or negative) by sex, age, sample site, and lymphoma type.

Table 5: Showing how cytomegalovirus (CMV), human immunodeficiency virus (HIV), and Epstein-Barr virus (EPV) are spread in people with lymphoma.

Virus	Hodgkin's lymphoma	Non-Hodgkin lymphoma	Key Finding
CMV	0%	6%	Rarely found
HIV	0%	18%	Strongly linked to NHL
EBV	80%	12%	Strongly linked to HL

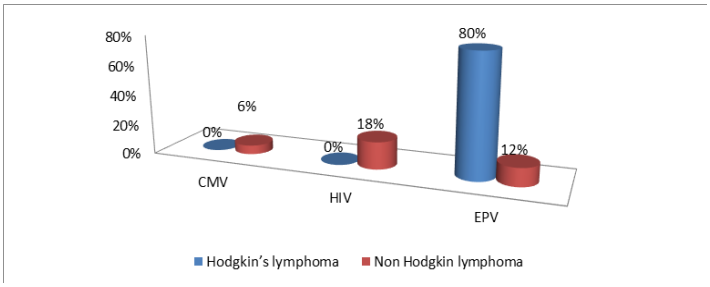

Figure 5: Showing how cytomegalovirus (CMV), human immunodeficiency virus (HIV), and Epstein-Barr virus (EPV) are spread in people with lymphoma.

Discussion

Lymphoma is a common disease that affects people of all ages and genders around the world; we still have a lot to learn about its causes. There could be numerous risk factors leading to the vast regional variability in lymphoma incidence. There is evidence to support the hypothesis that contracting cancer-causing organisms increases the risk of developing lymphoma. Some researchers investigate oncogenic viruses to gain a deeper understanding of the pathogenesis of lymphoma, and identifying associations between lymphoma and known and unknown viruses should lead to cellular and pharmacologically targeted antiviral strategies for treating malignant lymphoma [9]. The current study's findings indicate that males have a much higher prevalence rate of lymphoma than females, with 56% and 44%, respectively. The study found comparable results, with 36,795 lymphoma cases (56.4%) in men and 43.6% in women [10]. Our study found that the majority of cases occurred in the 40-60 age group, with males having a higher prevalence, which is consistent with an epidemiological study finding that NHL is more common in men, those over 65, and those with autoimmune disease or a family history of hematological malignancies [11]. A lot of people in this study were infected with EBV, which is strongly linked to Hodgkin lymphoma (4 out of 5 cases), which is 80% of all Hodgkin patients. Furthermore, this conclusion is consistent with previous research indicating that Hodgkin lymphoma is distinguished by the presence of Hodgkin and Reed-Sternberg cells, which originate from germinal center B-cells altered in the IgV gene. EBV's major oncoprotein, latent membrane protein, promotes the production of multinucleated RS cells through telomere organization. 1. Downregulation of LMP-1 recovers pro-apoptotic B-cells [12]. Another study found that EBV can cause some types of cancer, including Hodgkin's lymphoma, Burkitt's lymphoma (mostly found in Africa), diffuse large B-cell lymphoma, extra-nodal natural killer/t-cell nasal type, and nasopharyngeal carcinoma [13]. On the other hand, lymphomas are thought to be a primary source of morbidity and mortality among HIV-positive patients. In 1982, researchers first observed a connection between HIV and aggressive lymphoma [14]. According to another study, non-Hodgkin's lymphoma is the most common kind of lymphoma in HIV-positive patients. [15] This conclusion is consistent with our findings: We exclusively detect HIV in the non-Hodgkin lymphoma positivity rate of 16.3% (9/55), not in any Hodgkin lymphoma cases. And these HIV-NHL

lymphomas are very bad because they show up late, spread to other parts of the body, and tend to affect the digestive system, central nervous system, liver, bone marrow, and soft tissues per node [16]. For example, our study found that abdominal mass samples have the highest percentage of HIV-positive cases. CMV positive is uncommon; just three of 55 instances are male; lymph node and abdominal samples are the most prevalent, and all appear to be related to non-Hodgkin lymphoma. The modest positive result is statistically insignificant, potentially due to sample size limitations. The study found that people with non-Hodgkin's lymphoma were more likely than people with Hodgkin's disease to have cytomegalovirus antigenemia and CMV-D (P = 0.01) [17]. We can attribute Sudan's inequality to the absence of preventive and surveillance initiatives. Thus, it is critical to execute these programs and conduct future studies with a larger sample size to determine the impact of these viruses on the development of lymphoma. It is critical to recognize that viruses play an important role in approximately 20% of all human oncogenesis [18]. Oncogenic virus research can help us learn more about how lymphoma works and how it spreads. Finding both known and unknown viral links between lymphoma and other diseases could lead to the creation of new ways to treat malignant lymphoma that target viruses specifically in cells and with drugs.

Conclusion

This study emphasizes the critical involvement of EBV, CMV, and HIV in the pathogenesis of lymphoma. The higher rate of EPV and HIV-positive lymphoma in men is in line with previous research showing that immunocompromised individuals have a higher risk of lymphoma. More research with a bigger sample size is needed to look into how EPV, CMV, and HIV might affect lymphomagenesis when they are all present at the same time.

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