Journal of Communicable Diseases
Volume 55, Issue 4 - 2023, Pg. No. 119-125
Peer Reviewed & Open Access Journal

Research Article

Epstein–Barr Virus and Rheumatoid Arthritis in Cancer Patients Undergoing Chemotherapy in Al-Najaf Province, Iraq

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DOI: https://doi.org/10.24321/0019.5138.202364

I N F O

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How to cite this article:
Al-Nafakh RT, Aldawmy FAAK, Mubark HA, Al-Fadhul SAL, Abdulrazzaq HI, Almealawy YF, Atyaa FN, Yasir NJ, Yasir SJ. Epstein–Barr Virus and Rheumatoid Arthritis in Cancer Patients Undergoing Chemotherapy in Al-Najaf Province, Iraq. J Commun Dis. 2023;55(4):119-125.

Date of Submission: 2023-08-27
Date of Acceptance: 2023-12-29

A B S T R A C T

Background: Some studies suggested a link between Epstein–Barr Virus (EBV) and rheumatoid arthritis, although the exact mechanism of this is not yet established. Cancer patients undergoing chemotherapy are more immunocompromised. Hence this study has demonstrated the role of EBV in rheumatoid arthritis in these patients.

Objective: To study the relationship between Epstein–Bar viral infection and rheumatoid arthritis in cancer patients undergoing chemotherapy

Patients and Methods: A cross-sectional study was conducted from September 1, 2021 to March 1, 2022. The study participants included 200 cancer patients who reported to the Middle Euphrates Cancer Center in Al Najaf for chemotherapy treatment. Cancer patients were diagnosed with cases of rheumatoid arthritis, according to rheumatologist physicians and serological tests. Five ml of blood was collected from every cancer patient. Each sample was screened for the presence of anti-EBV antibodies. The chi-square test was used to test the significance of the relationship between qualitative variables. A p value of less than or equal to 0.05 indicated a statistically significant difference.

Results: Two hundred cancer patients were included in this study. Their age ranged from 17 to 73 years. Nearly half of them (47.5%) aged 30–50 years. Most of them were females (67.0%) and 60.5% of the participants lived in urban areas. More than one-third of participants (40.0%) had rheumatoid arthritis. More than half of them (53.0%) were EBV-positive. Statistical analysis showed a highly significant association between EBV and rheumatoid arthritis ($p < 0.00001$). No significant differences ($p > 0.05$) were found between different age groups regarding anti-EBV-IgM and IgG antibodies in rheumatoid and non-rheumatoid patients. On the other hand, PCR testing showed a statistically significant difference ($p < 0.001$) in non-rheumatoid patients and no significant difference in rheumatoid patients.

Conclusion: A significant association was detected between EBV and rheumatoid arthritis in cancer patients treated by chemotherapy and this association was not related to EBV antibody levels.

Keywords: EBV, RA, Cancer Patients, Chemotherapy, ELISA, IgM, IgG

Introduction

One of the most common human herpes virus types is Epstein–Barr virus (EBV), also called Human Gamma herpes virus 4. EBV is a double-stranded DNA virus and is one of nine recognised types.[1] It is an asymptomatic infectious agent that affects 95% of the world's population,[2] though it is transmitted from host to host only through salivary contact[3]. Infection, differentiation, persistent infection, reactivation, and reinfection are all aspects of EBV persistence exploited by mature B cells.[4] Following primary infection, EBV can cause memory B cells to become latently infected with the virus.[5] Thus, patients with latent EBV infections are at risk of reactivating the infection when stressed, infected, or immunosuppressed. It is of concern if the latent EBV is reactivated, but more concerning are the long-term consequences, which are malignancies. During latency, EBV becomes different from other viruses as it encodes genes that differentiate it from others. A variant of the EBV gene, known as Epstein–Barr virus nuclear antigen 1 (EBNA) or latent membrane protein 2a (LMP-2A), may be responsible for the differentiation of primary B cells into lymphoblastoid cells.[6]

Rheumatoid arthritis (RA) is one of the utmost communal systemic autoimmune diseases (SADs), also called rheumatic connective tissue diseases. Synovitis of the peripheral joints, characterised by peripheral joint destruction, may cause loss of function if left untreated. Most patients' aetiology is unknown, but environmental triggers are believed to be infections in up to 20% of cases.[7] An autoimmune disease characterised by chronic pain and inflammation, RA affects up to 1% of the population around the world.[8] Since EBV has been associated with several autoimmune diseases, including RA, it has long been suspected that EBV may contribute to the pathogenesis of RA.[9]

In patients with RA, infection control with EBV is impaired. They appear to have high-titer antibodies against EBV antigens.[10] Peripheral blood T lymphocytes of EBV-infected individuals are less effective at controlling B cell growth. RA cases have an increased susceptibility to B-cell lymphomas compared to the general population. They have more EBV-infected B cells than normal controls.[11] The exact mechanism by which EBV causes RA is not fully understood, therefore, the current study aims to assess the relationship between EBV and RA in cancer patients undergoing chemotherapy.

Materials and Method

Study Design and Setting

This is a cross-sectional analytical study of cancer patients. It was conducted at the Middle Euphrates Cancer Center in Najaf from September 1, 2021 to March 1, 2022.

Study Participants

This study included 200 cancer patients undergoing chemotherapy. The involved patients suffered from different types of cancers, including Wilms tumour, lymphoma, vulva, stomach, rectum, prostate, breast, lung, rectum, bladder, pancreas, liver, bone, and brain cancers. The age of the patients varied from 17 to 73 years.

Exclusion Criteria

The study excluded patients with any acute or chronic disease or other autoimmune diseases.

Sample Collection

5 ml of blood was collected from every cancer patient. Each sample was divided into two tubes. Four ml blood samples were drawn in sterile plain tubes and were left for 30 minutes at room temperature, after which, the tubes were centrifuged for 5 minutes at 3000 rpm for immunological testing. One ml of blood was drawn in ethylenediamine tetraacetic acid (EDTA) as an anticoagulant preserved at -20^{o} for extraction of DNA.

Serology

Cancer patients were diagnosed with rheumatoid arthritis, according to a rheumatologist physician and serological tests. Antibodies against Cyclic Citrullinated Peptide (ACCPs) kit (Favogen, Korea) was used for quantitative detection by enzyme-linked immunoassay. The serum screenings for the presence of EBV-IgM and EBV-IgG were done by ELISA Anti-EBV-CA IgM kit (Euroimmun, Germany) and Anti-EBV-CA ELISA IgG kit (Euroimmun, Germany) respectively while PCR kit (Sacace Company of Biotechnologies, Italia) was used for DNA extraction and amplification. All procedures were accomplished according to the recommendations of the manufacturer.

Ethical Approval

All procedures were performed in compliance with The Ethics of the World Medical Association (Declaration of Helsinki). The Kufa Medical College Ethics Committee approved the protocol of this study. Informed consent was obtained from each cancer patient.

Statistical Analysis

The chi-square test (χ2-test) was used to test the significance of the relationship between categorical variables. A p value of less than or equal to 0.05 indicated statistical significance.

Results

The current study enrolled a total of 200 cancer patients with ages ranging from 17 to 73 years. Nearly half of them (47.5%) were from the age group of 30–50 years.

ISSN: 0019-5138
DOI: https://doi.org/10.24321/0019.5138.202364

Most of the patients were female (67.0%) and 60.5% of the participants lived in urban areas. More than one-third of the participants (40.0%) were diagnosed with RA, and 53.0% of them were serologically positive for EBV (Table 1).

The current study included patients diagnosed with various types of cancer; maximum number of participants suffered from lung cancer (32.5%), followed by those who suffered from breast cancer (22.0%) (Table 2).

Figure 1 shows that more than one-third of RA cases (43.75%) were within the age group of 30–50 years. However, statistical analysis recorded no significant difference in the distribution of RA cases, according to the age groups.

A higher number of females were diagnosed with RA as compared to males (65% vs 35%), but there was no statistically significant difference ($p > 0.05$) (Figure 2).

The results demonstrated a higher percentage of EBV detected in RA patients than those not having RA (82.5% vs 33.3%). This difference was statistically significant ($p < 0.00001$) (Figure 3).

Statistically non-significant differences were found between different age groups according to the result of anti-EBV-IgM and IgG antibody and PCR testing for detection of EBV in rheumatoid patients ($p > 0.05$) (Table 3).

The results showed highly statistically significant differences between different age groups of non-rheumatoid patients and EBV by PCR testing ($p < 0.001$). However, the results reported statistically non-significant differences in the level of anti-EBV-IgM and IgG antibody testing in non-rheumatoid patients according to the age groups (Table 4).

Table 1.Demographic and Clinical Features of Cancer Patients (N = 200)

Features	Values	Number	Percentage
Age groups (years)	< 30	45	22.5
	30–50	95	47.5
	> 50	60	30.0
Gender	Male	66	33.0
	Female	134	67.0
Residency	Urban	121	60.5
	Rural	79	39.5
Rheumatoid arthritis	RA +	80	40.0
	RA -	120	60. 0
Epstein-Barr virus	EBV +	106	53.0
	EBV -	94	47.0

Table 2.Types of Cancers of the Studied Patients according to Their Gender

Type of Cancer	Female n (%)	Male n (%)	Total N (%)
Wilms tumour	3 (2.2)	4 (6.1)	7 (3.5)
Vulva	6 (4.5)	2 (3.0)	8 (4.0)
Stomach	2 (1.5)	4 (6.1)	6 (3.0)
Rectum	2 (1.5)	3 (4.5)	5 (27.5)
Prostate	0 (0.0)	13 (19.7)	13 (6.5)
NHL	10 (7.5)	9 (13.6)	19 (9.5)
Lung	22 (16.4)	14 (21.2)	36 (18.0)
Breast	47 (35.1)	0 (0.0)	47 (23.5)
HL	12 (9.0)	7 (10.6)	19 (9.5)
Cervix	10 (7.5)	0 (0.0)	10 (5.0)
Bladder	3 (2.2)	5 (7.6)	8 (4.0)
Pancreas	6 (4.5)	2 (3.0)	8 (4.0)
Brain	3 (2.2)	1 (1.5)	4 (2.0)
Liver	4 (3.0)	0 (0.0)	4 (2.0)
Bone	4 (3.0)	2 (3.0)	6 (3.0)
Total	134 (67.0)	66 (33.0)	200 (100.0)

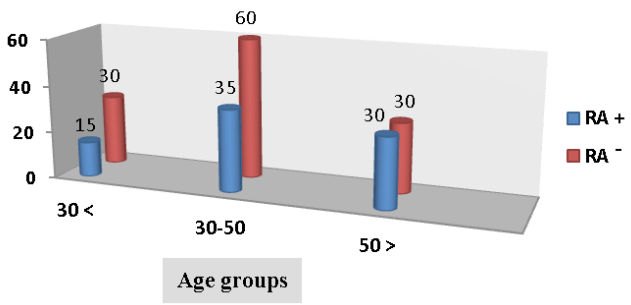

Figure 1.Detection of Rheumatoid Arthritis Cases by ACCP Antibodies according to the Age Groups ($p = 0.155$)

ISSN: 0019-5138
DOI: https://doi.org/10.24321/0019.5138.202364

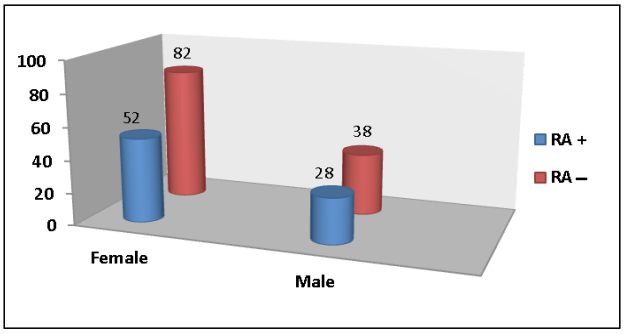

Figure 2.Detection of Rheumatoid Arthritis Cases by ACCP Antibodies according to Gender (p = 0.623)

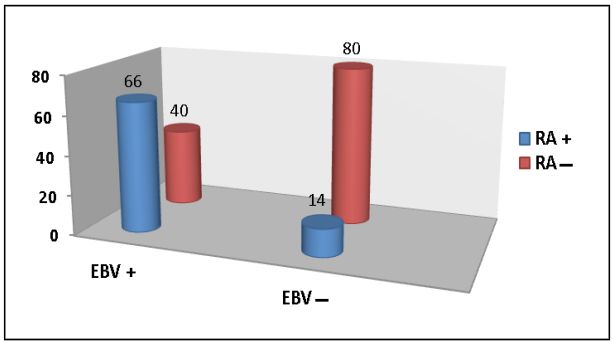

Figure 3.Association Between Epstein-Barr Virus and Rheumatoid Arthritis in Cancer Patients (p < 0.001)

Table 3.Distribution of Anti-EBV-IgM and IgG Antibody and PCR in Rheumatoid Patients according to Age Groups

Age Groups (Years)	< 30 n (%)	30–50 n (%)	> 50 n (%)	Total N (%)	p Value
IgM+	13 (16.25)	30 (37.50)	23 (28.75)	66 (82.50)	0.566
IgM-	2 (2.50)	5 (6.25)	7 (8.75)	14 (17.50)	
IgG+	15 (18.75)	33 (41.25)	29 (36.25)	77 (96.25)	0.838
IgG-	0 (0.00)	2 (2.50)	1 (1.25)	3 (3.75)	
PCR+	13 (16.25)	23 (28.75)	25 (31.25)	61 (76.25)	0.144
PCR-	2 (2.50)	12 (15.00)	5 (6.25)	19 (23.75)	
Total	15 (18.75)	35 (43.75)	30 (37.50)	80 (100.00)	160

Table 4.Distribution of Anti-EBV-IgM and IgG antibody and PCR in Non-rheumatoid Patients according to Age Groups

Age Groups (Years)	< 30 n (%)	30–50 n (%)	> 50 n (%)	Total N (%)	p Value
IgM+	12 (10.0)	20 (16.7)	8 (6.6)	40 (33.3)	0.343
IgM-	16 (13.3)	40 (33.3)	24 (20.0)	80 (66.6)	
IgG+	15 (12.5)	35 (29.2)	15 (12.5)	65 (54.2)	0.838
IgG-	13 (10.8)	25 (20.8)	17 (14.2)	55 (45.8)	
PCR+	3 (9.1)	12 (36.4)	18 (54.5)	33 (27.5)	< 0.0001
PCR-	25 (28.7)	48 (55.2)	14 (16.1)	87 72.5)	
Total	28 (23.3)	60 (50.0)	32 (26.7)	120 (100.0)	-

Discussion

Epstein–Barr virus is one of the most commonly found DNA-containing herpes viruses with more than 80% of adults showing serological evidence of a prior infection.[12] Several studies have suggested that EBV is related to autoimmune diseases such as RA.[13] Our study reported that the highest rheumatoid factor positivity (RA^+) was seen in the age group of 30–50 years and was more common among females (65%) than males (35%). This result is similar to other studies[14,15] that showed that most cases of the disease occurred among the elderly. This may be because the immune system slows down in the elderly and they suffer from weakness. Physically, females are weaker than males, and they also experience different hormonal fluctuations and changes in body structure throughout their lives. This may make them more susceptible to RA.

Our result revealed the presence of anti-EBV-IgM^+ and IgG^+ antibodies, as well as PCR^+ in 82.5%, 96.25% and 76.25% of RA^+ cases respectively out of 80 patients. This study agrees with the results of a study conducted by Marzoq and Yaser[16] and another study in Iraq, which revealed the presence of a significantly higher level of EBV-IgG and IgM

ISSN: 0019-5138
DOI: https://doi.org/10.24321/0019.5138.202364

in the serum of RA patients[17]. Who referred the immune antibody has a direct relationship with acute and chronic infections.

The current study found a highly significant association of EBV with RA ($p < 0.00001$). This result is similar to other studies that demonstrated a link between EBV infection and RA pathogenesis.[16–19] One of the chronic autoantibody responses related to the development of RA is the anti-EBV antibody response.[20] Other studies have provided evidence about the association of EBV with RA, and have shown EBV to be the cause of RA.[21] Another study revealed significantly higher levels of variation in serum antibodies against EBV in patients suffering from RA.[8] In a study, it was found that EBV infection may be a risk factor for the development of RA in an environment.[22] This study supports previous research that EBV may act as a triggering factor in the pathogenesis of reactive arthritis,[23] while another study indicated a favourable association between inflammatory arthritis and EBV[24]. Additionally, a study demonstrated that EBV plays a significant role in the aetiology of RA and molecular mimicry in RA initiation is one mechanism responsible for this role.[25] Synovial B cells and joint epithelial cells via inherent activation effects or chronic recurring infection. It has been found that a significant fraction of RA patients' distinctive ACPAs are antibodies to a citrullinated region of EBNA2, a significant transcription factor of EBV expressed in lyric phases.[8]

It is currently understood that between 15% and 20% of all human cancers are caused by viral infections.[26] These oncogenic viruses consist of a variety of complex strategies used to destroy biological processes in the infected host cells. These viruses' genetic materials pass a number of mechanisms, including cell division-synchronised replication, immune surveillance defeat, and apoptosis inhibition.[27] EBV is one of the eight unique human pathogens in the family of enveloped DNA viruses known as Herpesviridae, which causes diseases ranging from mild and seldom symptomatic to severe and potentially lethal.[28] EBV is the main reason for glandular fever, or infectious mononucleosis and is linked to a number of cancers, including Hodgkin lymphoma, Burkitt, nasopharyngeal cancer and stomach cancer, as well as a number of autoimmune diseases.[29] EBV-infected tumours are mostly made up of latently infected cells. The host cell's DNA polymerase replicates the virus while it is still in the nuclear episode form.[4]

In the current study, we found that cancer patients receiving chemotherapy frequently had EBV co-reactivation. EBV co-reactivation has been demonstrated to be associated with ageing, as previously described, and EBV DNAs were often found in older patients.[30] The biological and epidemiological data for the relationship between EBV and various cancers have been reviewed in a number of studies.[31] The prevalence of EBV-associated post-transplant lymphoproliferative disease (PTLD) varies from 1% to 20%, with the incidence varying according to the allograft type, age, and the transplant recipient's pre-transplant EBV-serostatus. The incidence of PTLD is greatest (32%) in small intestine transplant patients and ranges from 3% to 12% in heart, lung, liver, and pancreas transplant recipients. Renal transplant recipients have the lowest incidence (1%–2%).[32] Viral infections are responsible for around 13% of the global cancer burden, which varies depending on sociodemographic characteristics.[33] Long-term viral genome persistence in the host is required for virus-driven cancer.[34]

There are several studies demonstrating how EBV affects cancer. A previous study supported the relationship between EBV and thymic epithelial tumours in the Iranian population.[35] Another study indicated that the genesis of EBV-associated cancers is likely the consequence of a complex intersection of genetic, clinical, environmental, and nutritional variables.[36] Currently, EBV is linked to 1% of all cancers worldwide, most of which are lymphomas and carcinomas; every year, 140,000 people die from cancers linked to EBV.[37] In a recent study, it was shown that EBV is linked to epithelial tumours such as gastric and nasopharyngeal carcinomas.[38] In addition, EBV has been found in some cases of breast, oral, and cervical cancer, while the aetiology of the virus in these cancers is still debatable.[39]

Conclusion

A significant association was detected between Epstein-Barr Virus and rheumatoid arthritis in cancer patients treated by chemotherapy and this association was not related to the EBV antibody levels.

Source of Funding: None

Conflict of Interest: None

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ISSN: 0019-5138
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ISSN: 0019-5138
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