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Retrospective Investigation of Cytomegalovirus and Epstein–Barr Virus Positivity in Inflammatory Bowel Disease Patient Biopsies

Enflamatuvar Bağırsak Hastalığı Hasta Biyopsilerinde Sitomegalovirüs ve Epstein-Barr Virüs Pozitifliğinin Retrospektif Araştırılması

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ABSTRACT

Objective: Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory conditions affecting the gastrointestinal tract. The aim of this study was to investigate the distribution of cytomegalovirus (CMV) and Epstein-Barr virus (EBV) in the intestinal tissue of patients with IBD.

Methods: The study included tissue samples taken from 50 IBD (32 male, 18 female, between the ages of 18-76) patients. Thirty of the patients had CD and 20 had UC. The control group consisted of 31 patients who underwent routine colonoscopy and whose biopsies were extracted from suspicious sites, but no evidence of IBD was found. In these samples, the presence of CMV and EBV viruses was investigated by real-time polymerase chain reaction in our medical virology laboratory.

Results: In mucosal tissues, EBV positivity was 50% in UC and 40% in CD; CMV positivity was 35% in UC and 17% in CD. EBV positivity in the control group was 16%, and CMV was not detected. The presence of EBV and CMV in CD (p=0.049; p=0.024) and in UC (p=0.013; p=0.001) patients was statistically significantly higher than that in the control group. We analyzed the differences between the groups in terms of age, clinical features, biopsy locations, surgery type, medical treatment, and biochemical marker results. There was no significant difference in patients with CD compared with the control group. However, there was a statistically significant decrease in albumin and hemoglobin levels in patients with UC compared with the control group.

Conclusion: We believe that these viruses may play a role in the pathogenesis of IBD and exacerbation of the disease, and this study shows that patients with IBD undergoing surgery have a high prevalence of EBV and CMV.

Keywords: Inflammatory bowel diseases, cytomegalovirus, Epstein-Barr virus, surgery

ÖZ

Amaç: Crohn hastalığı (CH) ve ülseratif kolit (ÜK) dahil olmak üzere enflamatuvar barsak hastalıkları (İBH), gastrointestinal sistemi etkileyen kronik enflamatuvar durumlardır. Bu çalışmanın amacı İBH hastalarının bağırsak dokusunda sitomegalovirüs (CMV) ve Epstein-Barr Virüsü'nün (EBV) dağılımını araştırmaktır.

Yöntemler: Çalışmaya 50 İBH (32 erkek, 18 kadın, 18-76 yaş arası) hastadan alınan doku örnekleri dahil edildi. Hastaların 30'u CH, 20'si ÜK idi. Kontrol grubunu ise rutin kolonoskopi yapılan, şüpheli yerlerden biyopsi alınan ancak İBH bulgusuna rastlanmayan 31 hasta oluşturdu. Bu numunelerde CMV ve EBV virüslerinin varlığı Tıbbi viroloji laboratuvarımızda real-time polimeraz zincirleme reaksiyonu ile araştırılmıştır.

Bulgular: Mukozal dokularda EBV pozitifliği ÜK'de %50, CH'de %40; CMV pozitifliği ÜK'de %35, CH'de %17 idi. Kontrol grubunda EBV pozitifliği %16 idi, CMV saptanmadı. EBV ve CMV, CH (p=0,049; p=0,024) ve ÜK (p=0,013; p=0,001) hastalarında kontrol grubuna göre istatistiksel olarak anlamlı derecede yüksekti. Gruplar arasında yaş, klinik özellikler, biyopsi açısından farklılıklar analiz edildi. ÇH'li hastalarda kontrol grubuna göre anlamlı bir fark yoktu. Ancak ÜK'li hastalarda albümin ve hemoglobin düzeylerinde kontrol grubuna göre istatistiksel olarak anlamlı azalma görüldü.

Sonuç: Bu virüslerin İBH patogenezinde ve hastalığın alevlenmesinde rol oynayabileceğini düşünüyoruz ve bu çalışma, ameliyat edilen İBH hastalarında EBV ve CMV prevalansının yüksek olduğunu göstermektedir.

Anahtar Sözcükler: İnflamatuar barsak hastalığı, sitomegalovirüs, Epstein-Barr Virüsü, ameliyat

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INTRODUCTION

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory conditions affecting the gastrointestinal tract that progress with relapses and remissions. UC causes inflammation in the superficial mucosa of the colon, whereas CD is characterized by transmural inflammation affecting any part of the gastrointestinal tract. Indeterminate colitis, a third subtype of IBD with features common to UC and CD, causes mucosal inflammation (1). The pathogenesis of IBD remains unclear. Leading theories about the pathogenesis of the diseaseare that they cause uncontrolled chronic inflammation by promoting an immunopathological process in the intestinal mucosa because of the interactions of genetic and environmental factors (diet, immunological, infectious, vascular and psychological) (2-4).

Infections with Epstein-Barr virus (EBV) and cytomegalovirus (CMV) are typically acquired in early childhood (5). Globally, approximately 83% of adults are CMV-positive and over 90% are EBV-positive (2,6). CMV and EBV viruses belong to the Herpesviridae and remain latent in the body. In the case of immunosuppression, they can reactivate and proliferate (6). Immunosuppressive therapies have beneficial effects for treating IBD, but they also increase the risk of developing severe opportunistic infections, such as those caused by EBV and CMV (2,7). Some studies found that CMV and EBV positivity in IBD patient tissue samples was substantially higher than that in healthy control groups (8-10).

CMV reaction often occurs in the colon mucosa of patients with IBD, causing toxic megacolon, requiring colectomy, and can contribute to high morbidity and mortality (8). For CMV, early antiviral treatment may enhance IBD prognosis and reduce the colectomy rate (11). EBV reactivation is also often described in the inflammatory gastrointestinal mucosa of patients with IBD (4,8). When EBV is reactive, it can aggravate the clinical course by causing lymphoproliferative diseases such as EBV-positive mucocutaneous ulcer, lymphomatoid granulomatosis, hemophagocytic lymphocytomatosis, and diffuse large B-cell lymphoma (4). Patients with IBD should be screened for viral agents before initiating immunosuppressive therapy and monitored during treatment. Thus, the repair process can be accelerated by directing the treatment (2,4).

Although surgery in CD is mainly based on complication management (fistula, obstruction, etc.), ileocecal resection is recommended in patients with disease limited to the ileocecal region (12). For treating UC, surgery is more prominent. Although emergency surgery may be required because of conditions such as hemorrhage, toxic megacolon, and perforation, total proctocolectomy and ileal pouch anal anastomosis are recommended in patients with chronic active symptoms despite optimal medical treatment (13). Complications such as fistula and pouchitis are frequently encountered after these surgeries (14).

In our study, we aimed to investigate the presence of CMV and EBV in intestinal tissue samples obtained surgically from patients with IBD using molecular virological methods and the effects of these results on perioperative outcomes.

MATERIALS AND METHODS

The study was approved by the Gazi University Clinical Research Ethics Committee (approval number: 651, date: 31.07.2023). Our study included tissue samples taken from 50 patients with IBD and 31 controls that were sent to the Gazi University Faculty of Medicine Pathology Laboratory between 2014 and 2023. A total of 50 patients, 32 males and 18 females, between the ages of 18 and 76 years, were included in the study. Thirty of the patients were CD and 20 were UC. All specimens were obtained from patients with IBD undergoing surgery. In our study, the control group consisted of 31 patients who underwent routine colonoscopy and whose biopsies were extracted from suspicious sites, but no evidence of IBD was found.

In these samples, the presence of CMV and EBV viruses was investigated by real-time polymerase chain reaction (PCR) at Gazi University, School of Medicine, Medical Virology Laboratory.

Deparaffinization

Deparaffinization is the elimination of tissue-penetrating paraffin; for this purpose, we used xylene, which removes paraffin from the tissue. The paraffinized tissue was initially subjected to xylene. The tissue was then exposed to 100%, 80%, 60%, and 40% alcohol to remove xylen. Finally, the tissue was hydrated with distilled water.

Nucleic Acid Isolation and DNA Replication

The QIAamp DNA Mini Kit (Qiagen, Germany) was used to isolate nucleic acids from paraffin-embedded tissue samples after deparaffinization. The isolated DNA was kept at -80 °C until amplification. The isolated DNA was amplified using EBV RG PCR (Qiagen, Germany) and the CMV QS-RGQ Kit (Qiagen, Germany) on a Rotor-Gene Q 5plex HRM (Qiagen, Germany) instrument. The device permits reading on five distinct channels: green, yellow, orange, red, and purple. Both investigations used a 45-cycle PCR program. In the Green channel, the EBV reagent detected a region of 97 bp in the EBV-DNA genome. The yellow channel monitors internal study control. The outcomes were measured using four distinct standards (5x101 copies/L, 5x102 copies/L, 5x103 copies/L and 5x104 copies/L) and a negative control. Using the CMV reagent, a 105-bp region of the CMV-DNA genome was detected in the Green channel. The internal study control was monitored in the yellow channel. The results were analyzed using four distinct standards (1x101, 1x102, 1x103 and 1x104 copies/L) and a negative control.

Surgical Method

Crohn's patients who underwent ileocecal resection, ileal resection, and total colectomy because of complications (obstruction and intestinal fistula) were included in the study. Patients who underwent total proctocolectomy and J-pouch ileoanal anastomosis because of UC complications and resistance to medical treatment were included in the UC group.

RESULTS

Of the 50 IBD patients in our study, 30 had CD and 20 had UC. Thirty-two (64%) IBD patients were male and 18 (36%) were female. The control group consisted of healthy colonic mucosa of 31 patients who

underwent colonoscopy for diseases other than IBD. In the control group, 20 (64.5%) patients were female and 11 (35.5%) were male. The rate of male patients in the IBD patient group was significantly higher than that in the control group (Table 1). The mean age of the CD patients was 41.74±14.99 (22-76) and the mean age of the UC patients was 46.65±17.37 (18-74). The mean age of the control group was 52.3±17.65 (21-81). We divided the ages of the patients into three parts: 18-40, 41-65, and over 65 years, and there was no difference between the IBD patients and the control group in terms of age (p>0.05) (Table 1, 2).

All specimens from IBD patients were obtained during surgery. Of the 20 samples from CD patients, 11 were small intestinal mucosa and 19 were colonic mucosa. All 30 specimens from patients with UC belonged to the colonic mucosa. The presence of EBV and CMV in mucosal tissues was examined using real-time PCR. In mucosal tissues, EBV positivity was 50% (10/20) in UC and 40% (12/30) in CD; CMV positivity was 35% (7/20) in UC and 17% (5/30) in CD. EBV positivity in the control group was 16% (5/31), and CMV was not detected. The presence of EBV and CMV in CD patients was statistically significantly higher than that in the control group (p=0.049; p=0.024; Table 3). The presence of EBV and CMV in UC patients was statistically significantly higher than that in the control group (p=0.013; p=0.001; Table 3).

Of the 30 CD patients, 8 (26.7%) were EBV positive, one (3.3%) was CMV positive, 4 (13.3%) were both EBV and CMV positive, and 17 (56.7%) were both EBV and CMV negative. Of the 20 UC patients, 6 (30%) were EBV positive, 3 (15%) were CMV positive, 4 (20%) were both EBV and CMV positive, and 7 (35%) were both EBV and CMV negative. We analyzed the differences between the groups in terms of age, clinical features, biopsy locations, surgery type, medical treatment, and biochemical marker results. There was no significant difference in patients with CD compared with the control group (Table 4). However, there was a statistically significant decrease in albumin and hemoglobin levels in patients with UC compared with the control group (Table 5).

Table 1. Comparison of EBV and CMV positivity rates in the Crohn's disease, ulcerative colitis, and control groups

	Mean age	Gender			EBV			CMV		
		Male	Female	p	Positive	Negative	p	Positive	Negative	p
CD, (n=30)	41.74±14.99	20 (66.7%)	10 (33.3%)		12 (40%)	18 (60%)		5 (17%)	25 (83%)	
UC, (n=20)	46.65±17.37	12 (60%)	8 (40%)		10 (50%)	10 (50%)		7 (35%)	13 (65%)	
Control group, (n=31)	52.29±17.65	11 (35.5%)	20 (64.5%)	**0.040***	5 (16%)	26 (84%)	**0.027***	-	31 (100%)	**0.003***

*Pearson chi-square analysis, CD: Crohn's disease, UC: Ulcerative colitis, EBV: Epstein-Barr virus, CMV: Cytomegalovirus.

Table 2. Evaluation of EBV and CMV positivity in the Crohn's disease and ulcerative colitis groups according to age

CD	EBV +	EBV -	p	CMV +	CMV -	p
22-40 (n=16)	7	9		4	12	
41-65 (n=11)	3	8	0.422*	-	11	0.165*
>65 (n=3)	2	1		1	2	
UC	**EBV +**	**EBV -**	**p**	**CMV +**	**CMV -**	**p**
18-40 (n=8)	3	5		3	5	
41-65 (n=9)	4	5	0.164*	3	6	0.982*
>65 (n=3)	3	-		1	2	

*Pearson chi-square analysis, CD: Crohn's disease, UC: Ulcerative colitis, EBV: Epstein-Barr virus, CMV: Cytomegalovirus.

Table 3. Comparison of EBV and CMV positivity in the Crohn's disease and ulcerative colitis groups with the control group

	EBV			CMV		
	EBV +	EBV -	p	CMV +	CMV -	p
CD (n=30)	12 (40.0%)	18 (60.0%)	**0.049***	5 (16.7%)	25 (83.3%)	**0.024***
Control group (n=31)	5 (16.1%)	26 (83.9%)		0 (0%)	31 (100%)	
	EBV			**CMV**		
	EBV+	**EBV-**	**p**	**CMV +**	**CMV +**	**p**
UC (n=20)	10 (50.0%)	10 (50.0%)	**0.013***	7 (35%)	13 (65%)	**0.001***
Control group (n=31)	5 (16.1%)	26 (83.9%)		0 (0%)	31 100%)	

*Pearson chi-square analysis, CD: Crohn's disease, UC: Ulcerative colitis, EBV: Epstein-Barr virus, CMV: Cytomegalovirus.

DISCUSSION

The prevalence of EBV and CMV, which belong to the Herpesviridae, is relatively high in healthy people worldwide, and they can be reactivated in immunosuppressed individuals. These viruses may play a role in the pathogenesis and exacerbation of the disease in patients with IBD (2).

The epidemiology of IBD is complex. The prevalence of IBD depends on the type of disease (UC or CD), patient age, and geography of the region examined (15). Autoimmune diseases are typically more common in women, but this is not the case for IBD (16). There was no significant gender difference in UC. The incidence of UC is similar between men and women up to the age of 45years. After this age, the frequency of UC is higher in men. On the other hand, there is a gender difference in CD. While CD is more common in men in Asian countries, it is more common in women in European and US countries. This shows that environmental factors such as

Table 4. Clinical features of patients with Crohn's disease infected with Epstein-Barr virus and cytomegalovirus

	EBV and CMV positivity				
	EBV CMV (n=17, 56.7%)	**EBV + CMV (n=8, 26.7%)**	**EBV CMV + (n=1, 3.3%)**	**EBV + CMV + (n=4, 13.3%)**	**p**
Gender					
Male	9	6	1	4	0.242[a]
Female	8	2	0	0	
Age (years)*	41.58±13.21	44.50 ± 14.90	24.0	41.0 ± 24,39	0.470[b]
Illness duration (month)*	71.05±88.71	78.37±120.12	192.0	50.75± 39.57	0.568[b]
Location**					
C1	1	0	0	0	0.923[a]
C2	1	0	0	0	
C3	13	8	1	3	
C4	2	0	0	1	
Clinical disease activities					
Asymptomatic	3	2	0	0	0.060[a]
Mild	2	1	0	1	
Moderate	11	5	0	3	
Severe	1	0	1	0	
Clinical disease activity score*	271.64±110.18	268.25±108.46	516.0	277.90±108.34	0.433[b]
Clinical classification					
Incipient	3	2	0	1	0.188[a]
Chronic	14	6	1	3	
Surgical urgency					
Urgent	9	4	1	3	0.670[a]
Elective	8	4	0	1	
Surgery type					
Total colectomy	3	0	1	0	0.129[a]
Ileocaecal resection	11	7	0	4	
Ileal resection	3	1	0	0	
Preoperative medical treatment					
Steroid	11	5	0	2	0.605[a]
Biological agent	2	4	0	2	0.131[a]
Immunosuppressive therapies	10	6	0	3	0.461[a]
Laboratory examination*					
C-reactive protein (mg/dL)	82.69±80.60	47.81±62.05	61.70	120.75±59.03	0.647[b]
Albumin (g/L)	2.91±0.88	3.25±0.66	3.11	2.38±0.35	0.138[b]
Hemoglobin (g/L)	10.52±2.07	11.11±1.55	9.70	10.62±0.97	0.623[b]
White blood cell (x10^9/L)	10.07±2.67	10.77±4.59	12.6	16.74±6.02	0.104[b]

*Mean ± standart deviation, **C1: Terminal ileum, C2: Colon, C3: Ileocolon, C4: Upper gastrointestinal location, [a]Pearson chi-squared test, [b] Kruskal-Wallis test, EBV: Epstein-Barr virus, CMV: Cytomegalovirus.

westernization of lifestyle play an important role in the pathogenesis of IBD (15). In our study, we did not find a significant difference in terms of age between CD and UC patients. We found the frequency of IBD to be significantly higher in men. We assumed that this was due to the disproportionate gender of the patients in the control group.

There are many studies on the prevalence of EBV and CMV in IBD patients. According to those studies, the reported prevalence of EBV in patients with IBD varies between 33.3% and 79.4%, and the prevalence of CMV varies between 21% and 43.4% (11,17-23). In our study, the prevalence of EBV was 44% (22/50) and the prevalence of CMV was 24% (12/50) in patients with IBD. The differences in

Table 5. Clinical features of ulcerative colitis patients infected with Epstein-Barr virus and cytomegalovirus

	EBV and CMV positivity				**p**
	EBV CMV, (n=7, %35.0)	**EBV + CMV, (n=6, %30.0)**	**EBV CMV +, (n=3, %15.0)**	**EBV + CMV +, (n=4, %20.0)**	
Gender					
Male	3	5	1	3	0.323[a]
Female	4	1	2	1	
Age (years)*	44.71±12.29	51.33±22.97	32.66±13.31	53.50±17.33	0.361[b]
Illness duration (month)*	158.14±157.47	103.83±69.40	77.00±19.51	46.50±31.77	0.494[b]
Location**					
U1	3	1	1	0	0.396[a]
U2	2	2	0	3	
U3	2	3	2	1	
Clinical disease activities					
Mild	4	2	1	0	0.299[a]
Moderate	3	4	2	4	
Clinical disease activity score*	4.71±2.36	7.00±2.82	6.00±2.00	8.00±1.41	0.133[b]
Endoscopic activity index score*	5.85±2.34	7.33±3.26	7.33±4.16	9.50±1.00	0.227[b]
Clinical classification					
Incipient	0	0	0	1	0.240[a]
Chronic	7	6	3	3	
Surgical urgency					
Urgent	1	2	0	0	0.420[a]
Elective	6	4	3	4	
Preoperative medical treatment					
Steroid	6	6	2	3	0.246[a]
Biological agent	3	1	1	3	0.323[a]
Immunosuppressive therapies	3	5	2	4	0.196[a]
Malignancy					
Positive	2	1	1	0	0.638[a]
Negatif	5	5	2	4	
Pouchitis					
Positive	3	1	2	2	0.486[a]
Negative	4	5	1	2	
Laboratory examination*					
C-reactive protein (mg/dL)	58.19±75.52	41.78±46.01	38.59±30.57	36.70±34.14	0.898[b]
Albumin (g/L)	3.30±0.52	2.57±0.71	2.27±0.69	3.82±0.66	**0.031[b]**
Hemoglobin (g/L)	11.62±1.03	10.51±3.32	11.33±2.37	13.45±3.31	**0.031[b]**
White blood cell (x10^9/L)	14.52±7.02	15.26±8.72	10.50±5.37	10.89±6.81	0.676[b]

*Mean ± standart deviation, **U1: Ulcerative proctitis, U2: Left-sided UC, U3: Extensive UC, [a]Pearson chi-squared test, [b]Kruskal-Wallis test, EBV: Epstein-Barr virus, CMV: Cytomegalovirus.

the rates reported in other studies might be related to the samples belonging to different patients and the use of different diagnostic methods. In previous studies, the immunohistochemistry method was mostly used. Nevertheless, in recent research, the real-time PCR technique has often been preferred.

In our study, there were 30 CD and 20 UC patients. EBV positivity was detected as 40% (12/30) and 50% (10/20) in CD and UC patients, respectively. CMV positivity was 16.7% (5/30) in CD patients and 35% (7/20) in UC patients. When the presence of EBV and CMV in the intestinal mucosa of CD and UC patients was compared with the results of the control patients, we found that the EBV and CMV positivity in both CD and UC patients were significantly higher. In a study conducted by Wang et al. (21) under similar conditions, EBV and CMV positivity was reported to be significantly higher in IBD patients than in the control groups.

We found that both EBV and CMV positivity rates were higher in UC patients than in CD patients. Results of similar studies also showed that the prevalence of EBV and CMV was higher in UC patients; for example, in a study by Ryan et al. (18), EBV DNA was detected in 55% of CD patients and 64% of UC patients. In another study, Wethkamp et al. (23) reported that CMV-DNA was detected in 10% of CD patients and 33% of UC patients. Takahashi and Tange (24) and Nakase et al. (25) also stated that the prevalence of CMV was lower in CD patients. Additionally, another result of our study was that the EBV positivity rate in IBD patients was higher than that of CMV. Similarly, Wang et al. (21) detected EBV-DNA in 79.4% and CMV-DNA in 34.5% of the colonic mucosa of 287 IBD patients.

In our study, serum albumin and hemoglobin levels in patients with UC were significantly lower than those in the control group. In a study conducted with IBD and non-IBD patients, the serum albumin value in IBD (CD and UC) patients was significantly lower than that in non-IBD patients (23). Since serum albumin is the main protein in human serum, it reflects nutritional status and is an acute phase reactant. The level of serum albumin decreases in inflammation (26). In a study by Liu et al. (27), comparing patients in remission and active IBD, serum hemoglobin and albumin values in the active IBD group were significantly lower than those in remission.

Detection of lower hemoglobin and serum albumin levels in patients with IBD having CMV and EBV infection in our study suggests that that patients with EBV and CMV infection may have more serious clinical findings. In addition, it is known that low hemoglobin and albumin levels in the pre-operative period increase surgical complications (28,29). From this perspective, care should be taken regarding postoperative complications after surgery in IBD patients with EBV and CMV infection.

The incidence of developing colorectal cancer in patients with UC is approximately 3% (30). The effect of EBV and CMV on the development of malignancy in IBD is not yet clearly understood. In our study, we detected colorectal cancer in 20% of patients who underwent total proctectomy. However, EBV and CMV infections were not significantly different in the UC group with malignancy.

Clinical symptoms play an important role in the diagnosis of EBV and CMV infection in patients with IBD. Although Wang et al. (21) showed a correlation between clinical disease activities and EBV/CMV infection, we did not detect a relationship between EBV and CMV infection and clinical activity and endoscopic activity index scores.

CONCLUSION

In conclusion, this study shows that patients with IBD undergoing surgery have a high prevalence of EBV and CMV. In addition, although it has not been shown to directly affect surgical outcomes, caution should be exercised regarding perioperative surgical complications that may be caused by low serum hemoglobin and albumin levels in patients with UC.

Ethics

Ethics Committee Approval: The study was approved by the Gazi University Clinical Research Ethics Committee (approval number: 651, date: 31.07.2023).

Informed Consent: Retrospective study.

Peer-Review: Externally peer-reviewed.

Authorship Contributions

Concept: H.B., Design: S.E., Supervision: K.Ç., Resources: G.B., Materials: A.D., Data Collection or Processing: A.Ç.B., Analysis or Interpretation: A.Ç.B., Literature Search: K.D., Writing: S.E.

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