The Frequency and Importance of Cytomegalovirus and Epstein-Barr Virus Infections in Children with Inflammatory Bowel Disease: Single Center Experience

İnflamatuvar Bağırsak Hastalığı Olan Çocuklarda Sitomegalovirüs ve Epstein-Barr Virüs Enfeksiyonlarının Sıklığı ve Önemi: Tek Merkez Deneyimi

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_____ **Abstract** _____

Objective: Immunosuppressive therapies increase the risk of opportunistic infections in inflammatory bowel disease (IBD). Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) can remain latent in target cells and reactivate when immunity declines. It has been shown that EBV-associated lymphoproliferative disease, EBV and CMV-associated haemophagocytic lymphohistiocytosis can develop in IBD under immunosuppressive therapy. The aim of our study was to evaluate CMV and EBV infections at the admission and attack episodes and discuss the clinical findings in our IBD patients.

Material and Methods: Fifty-six patients who were diagnosed as IBD in the Pediatric Gastroenterology clinic between January 2013 and January 2018 were evaluated retrospectively. Demographic data of patients, classification of IBD and duration of follow-up were recorded. CMV and EBV serologies at the time of diagnosis of IBD, serology results at the colitis attacks in the follow-up, viral load, the treatments that were used for IBD and viral infection were evaluated.

Results: Fifty-five percent of the patients were female, with a mean age of 15.1 ± 4.5 years. 62% of the patients had ulcerative colitis, 30% had Crohn's disease, and 7% had early-onset IBD. Mean diagnosis age of patients was 11 ± 4.5 years, mean follow-up duration was 45 ± 32 months and mean number of attacks was 2.3 ± 1.8 detected. In the follow-up, EBV PCR positivity was observed in two patients and CMV-associated colitis was

_____ **Öz** _____

Giriş: İnflamatuvar bağırsak hastalığı (İBH)'nda immünsüpresif tedaviler fırsatçı enfeksiyon riskini arttırmaktadır. Sitomegalovirüs (CMV) ve Epstein-Barr virüs (EBV) hedef hücrelerde latent kalarak immünite azaldığında reaktive olabilmektedir. İBH'de immünsüpresif tedavi altında EBV ilişkili lenfoproliferatif hastalık, EBV ve CMV ilişkili hemofagositik lenfohistiositoz gelişebildiği gösterilmiştir. Çalışmamızda İBH tanısı ile izlediğimiz hastalarda başvuruda ve atakları sırasındaki CMV ve EBV enfeksiyonlarının değerlendirilmesi ve klinik bulguların tartışılması amaçlanmıştır.

Gereç ve Yöntemler: Ocak 2013-Ocak 2018 tarihleri arasında Çocuk Gastroenteroloji Kliniğinde İBH tanısı ile takip ettiğimiz 56 hasta retrospektif olarak değerlendirildi. Hastaların demografik verileri, İBH sınıflaması ve izlem süreleri kaydedildi. Hastaların İBH tanısı aldığındaki CMV ve EBV serolojileri, izlemde kolit atakları sırasındaki seroloji sonuçları, DNA kopya sayıları, İBH ve viral enfeksiyon için kullanılan tedaviler değerlendirildi.

Bulgular: Hastaların %55'i kız, ortalama yaşları 15.1 ± 4.5 yıldı. Yüzde 62'si ülseratif kolit, %30'u Crohn hastalığı, %7'si erken başlangıçlı İBH tanısı ile izlenmekteydi. Hastaların ortalama tanı yaşı 11 ± 4.5 yıl, ortalama izlem süreleri 45 ± 32 ay ve ortalama atak sayıları 2.3 ± 1.8 saptandı. İzlemde aktif kolit reaktivasyonu döneminde iki hastada EBV polimeraz

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observed in two patients during active colitis reactivation periods. Viral serologies were not compatible with acute disease in two patients with cytomegalovirus related colitis. In one patient, CMV DNA positivity was detected in serum and in the other patient, CMV colitis was diagnosed by histopathological examination of the colon biopsy material. Two patients were also recovered after three weeks of ganciclovir and reduction in the immunosuppressive therapy.

Conclusion: It has been shown that CMV and EBV infection may be a significant problem in patients with IBD in the follow-up and tissue-level studies are necessary in the disease activation, especially even if CMV serology is negative.

Keywords: Child, inflammatory bowel disease, cytomegalovirus, Epstein-Barr virus

zincir reaksiyonu (PCR) pozitifliği ve iki hastada CMV ilişkili kolit izlendi. CMV ilişkili kolit saptanan iki hastada viral serolojiler akut hastalık ile uyumlu değilken, bir hastada serumda CMV DNA pozitifliği, diğer hastada ise kolon biyopsi materyalinin histopatolojik incelenmesi ile CMV koliti tanısı konuldu. İki hastanın da üç haftalık gansiklovir ve immünsüpresif tedavide azaltma sonrası atak bulguları geriledi.

Sonuç: İBH tanısı alan hastalarda izlemde CMV ve EBV enfeksiyonunun önemli bir sorun olabileceği, özellikle CMV serolojisi negatif olsa bile hastalık aktivasyonu durumunda doku düzeyinde incelemelerin gerekli olduğu görülmüştür.

Anahtar Terimler: Çocuk, inflamatuvar bağırsak hastalığı, sitomegalovirüs, Epstein-Barr virüs

Introduction

Inflammatory bowel disease (IBD) is a disease with a course of abnormal inflammatory response in the gastrointestinal tract system resulting from the interaction of environmental factors and the immune response (1). Immunosuppressive agents such as corticosteroids, immunomodulatory agents and biological agents are used in the treatment process of the disease (2). The immune system plays an important role in combating infections and preventing tumor growth. Suppression of the immune system causes an increased risk of infection in patients. Azathioprine and corticosteroid used in conjunction with anti-TNF biologic agents used in the treatment of inflammatory bowel disease have been reported to cause viral infections and tuberculosis tendency (3). Cytomegalovirus (CMV) and Epstein-Barr virus (EBV), which are commonly found in the population, may be reactivated in immunocompromised patients due to their latent characteristics in target cells. Therefore, they may cause significant problems in IBD patients (4,5). It has been reported that low titer positivity of CMV or EBV DNA plays a role in the treatment resistance of patients (6). CMV reactivation, in particular, may lead to deterioration of clinical course in IBD patients, although it is usually reversible (7,8). However, it is aimed to be evaluated in terms of the treatment resistance and reactivation in patients with latent virus. Therefore, rapid and accurate diagnosis of CMV infections is critical in this patient group. In these patients, insufficiency can be observed in natural killer T cell functions, which may be caused by malnutrition in addition to immunosuppressive therapy (4). In this study, we aimed to investigate the frequency of latent viruses, to analyze the laboratory and clinical changes they cause and to determine their effects on clinical results in target cells such as CMV and EBV during diagnosis and attack periods.

Materials and Methods

Before starting the study, approval was obtained from the local ethics committee of our hospital (ethics committee no: 2018 / 8-3). Patients diagnosed with IBD between January 2013 and January 2018 in pediadric gastroenterology clinic and patients diagnosed with IBD before were included in the study. The colitis and intestinal involvement areas of the patients at the time of admission were evaluated according to the Paris classification; cases with ulcerative colitis were rectite (E1); left colon involvement up to the splenic flexure (E2); involvement up to hepatic flexure (E3); Pancolith (E4). For Crohn's disease, ileum 1/3 distal involvement ± cecum involvement was categorized as (L1); colonic involvement was categorized as (L2); ileocolonic involvement was categorized as (L3) (9). Pediatric ulcerative activity index and pediatric Crohn activity index scores were calculated during the diagnosis and attack periods of the patients.

EBV and CMV serology of the patients (CMV IgM, CMV IgG, EBV VCA IgM, EBV VCA IgG, EBV EA IgG, EBV EBNA IgG) was analyzed with Enzyme-linked immunosorbent assay '(ELISA) method in accordance with the recommendations of the company (Abott, USA). CMV DNA and EBV DNA were analyzed with real-time polymerase chain reaction (RT-PCR) (Qiagen, Germany). It was accepted as clinically significant in cases that the CMV DNA was over > 600 copies/mL, EBV DNA > 150 copies/mL in the serum with accompanying colitis findings. Clinical significance for EBV was determined according to laboratory reference value (4). In addition, patients with low titer CMV DNA (< 600 copies/mL)-EBV DNA (< 150 copies/mL) positivity were also recorded. Ulcerative colitis, Crohn's and indetermined colitis diagnoses of the patients were evaluated during the attacks. Laboratory and clinical findings during the disease activation period, treatments for infection detected and immunosuppressive treatments during attacks were recorded.

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Statistical Analysis

Data analysis was conducted using SPSS 21.0 (SPSS Statistics for Windows, IBM Corp.; Armonk, NY, USA). Normal distribution levels of the variables was examined with visual (histogram and probability graphs (PP Plot)) and analytical (the Kolmogorov-Smirnov test due to n > 50) methods. Mean ± standard deviation was used when continuous data had normal distribution, median (min-max) was used when continues data had no normal distribution and number (n) and percentages (%) were used for categorical data. In the comparison of multiple groups, if the standard deviation or variance of the values with normal distribution were homogeneous, one-way analysis of variance (ANOVA) was used. Comparisons for categorical variables were performed using Pearson Chi-square test. p< 0.05 was considered to be statistically significance level to determine whether the observed differences were statistically significant or not.

Results

56 children (55% female) who were followed up for inflammatory bowel disease with a mean age of 11 ± 4.5 years were included in the study. 40 of these patients were diagnosed in this date range and 16 of them were diagnosed before these dates and still followed up. The mean follow-up period was 45 ± 32 months. 62% (n= 35) of the cases were followed up for ulcerative colitis, 30% (n= 17) were followed up for Crohn's disease, and 7% (n= 4) were followed up for IBD with early onset. When the colitis findings of 37 patients with ulcerative colitis were evaluated according to the Paris classification, E1 was 2.7% (n= 1), E2 was 5.4% (n = 2), E3 was 10.8% (n= 4) and E4

was 81% (n= 30). According to the Paris classification of 18 patients with Crohn's disease, L1 was 16.7% (n= 3), L2 was 5.6% (n= 1) and L3 was 77.8% (n= 14). The mean number of attacks of all patients was 2.3 ± 1.8.

Of 39 (69,6%) patients whose EBV virus serology was examined at the time of diagnosis, EBV EBNA IgG was positive in 74% of them, EBV VCA IgG was positive in 67% and EBV EA IgG was positive in 59%. EBV VCA IgM was negative in all patients whose serology was analyzed at the time of diagnosis. EBV DNA positivity was found in serum of two patients who were followed up under immunosuppressive treatment when analysis was conducted due to high fever and colitis. The clinical and laboratory features of these cases are shown in Table 1 and the treatments they received are shown in Table 2. In both patients, clinical findings improved after immunosuppressive therapy was increased, and EBV DNA was negative in the fourth week and no other complications related to EBV were observed in the follow-up.

CMV serology was analyzed in 40 (71.4%) of the patients at the time of diagnosis. While CMV IgG was positive in 66% of these serology cases, CMV IgM was positive in only one (2.5%) patient. Four patients (7%) had low titer CMV DNA positivity at the time of diagnosis. At the time of diagnosis, CMV inclusion body was seen in the colon biopsy material of one patient, and the patient who had also colitis findings was given intravenous ganciclovir for three weeks. And with the help of the treatment, improvement was observed in the clinical findings of the patient.

Table 1. Comparison of the characteristics of cases with EBV-negative and cases with EBV infection during attack

	All patients (n= 57)	EBV negative (n= 37)	EBV positive (n= 2)	p
Age of diagnosis	11 ± 4.5	11.4 ± 4.6	8.5 ± 3.5	0.4
Gender (female)	31 (55%)	22 (59%)	1 (50%)	0.7
Colitis involvement (E4) *	30 (53%)	22 (59%)	2 (100%)	0.7
White cell $10^3/mm^3$	9.8 ± 3	9.9 ± 3.3	11.1 ± 5.6	0.6
Hemoglobin	10.6 ± 1.9	10.5 ± 2	9.2 ± 2.6	0.3
Platelet $10^3/mm^3$	349 ± 149	381 ± 130	654 ± 234	0.08
CRP (mg/dL) median (min-max)	3.2 (0.01-288)	2.7 (0.01-288)	17.9 (10-25.9)	0.6
Sedimentation	31 ± 23	32 ± 25	43 ± 5.6	0.5
AST (IU/L)	25 ± 16	26.6 ± 18.6	18.5 ± 0.7	0.5
ALT (IU/L) median (min-max)	14 (5-138)	13 (5-138)	9	0.48
Globulin	5.1 ± 3	3.1 ± 0.7	3.7 ± 0.14	0.26
Albumin	3.8 ± 0.6	3.9 ± 0.6	3.4 ± 0.2	0.26

CRP: C-reactive protein, AST: Aspattate aminotransferase, ALT: Alanine aminotransfrase, EBV: Epstein-Barr virus.
* According to Paris classification.

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Table 2. Features of patients with positive EBV DNA

	Patient 1	**Patient 2**
Diagnosis	Crohn`s Disease	Unclassified colitis
Colitis involvement	E4 (Pancolitis)	E4 (Pancolitis)
Age	13	7
EBV DNA Level (Copy/mL)	209	12.500
EBV infection time	In the 3rd month of follow-up during the attack	In the 3rd month of follow-up during the attack
Clinical findings	Diarrhea	Fever, diarrhea, lymphadenopathy
Hospitalization period	6 days	8 day
Treatment received at the time of EBV infection	Mesalazine Corticosteroids Azathioprine	Mesalazine Azathioprine Infliximab
Treatment due to infection	Meselazine was continued Corticosteroid was reduced Azathioprine was discontinued	Meselazine was continued Azathioprine was discontinued Infliximab could not be took
Response	Week 4 * Negation of EBV DNA * Clinical response	Week 3 * EBV DNA reduction to 157 copies/mL * Clinical response

* Clinical response.
 EBV: Epstein-Barr virus.

Table 3. Comparison of the characteristics of cases with CMV-negative and cases with CMV infection during diagnosis

	All patients (n= 57)	**CMV negative (n= 38)**	**CMV positive (n= 2)**	**p**
Age of diagnosis	11 ± 4.5	14.6 ± 4.5	17.5 ± 2	0.1
Gender (female)	31 (55%)	21 (55%)	2 (100%)	0.2
Colitis involvement (E4) *	30 (53%)	22 (57%)	2 (100%)	0.2
White cell 10³/mm³	9.8 ± 3	10-3	10.5 ± 0.8	0.8
Hemoglobin	10.6 ± 1.9	10.3 ± 1.9	8.5 ± 2.6	0.2
Platelet 10³/ mm³	349 ± 149	405 ± 150	400 ± 280	0.9
CRP (mg/dL) median (min-max)	3.2 (0.01-288)	3.7 (0.01-288)	1.6 (0.05-3.2)	0.6
Sedimentation	31 ± 23	33 ± 24	16 ± 9	0.3
AST (IU/L)	25 ± 16	25 ± 18	22 ± 7	0.7
ALT (IU/L) median (min-max)	14 (5-138)	12 (5-138)	19.5 (13-26)	0.9
Globulin	5.1 ± 3	3.2 ± 1.6	2.4 ± 1.4	0.9
Albumin	3.8 ± 0.6	3.8 ± 0.5	2.9 ± 1.5	0.05
Disease score UC	49 ± 18	50 ± 17	67 ± 24	0.1

CMV: Cytomegalovirus, CRP: C-reactive protein, AST: Aspartate aminotransferase, ALT: Alanine aminotransfrase.
* According to Paris classification.

During the follow-up of patients under immunosuppressive therapy, 28 of them (50%) had 62 attacks, in which viral examinations were performed, and in the serum of one patient, CMV DNA was positive (7680 copies/mL). The clinical and laboratory findings of two patients with CMV infection and those with negative CMV DNA are shown in Table 3. Although the number of cases was insufficient, albumin was lower espe-cially in patients with CMV colitis. When the attacks of patients with CMV infection were evaluated, It was observed that cas-es did not respond well to immunosuppressive treatment and got worse in clinical condition with high dose corticosteroid treatment. Table 4 shows the clinical features of two patients with positive CMV DNA. Pancolitis picture was observed both in patients whose CMV DNA was positive with low titer and in

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Table 4. Clinical features of patients with positive CMV-DNA

	Patient 1	**Patient 2**
Diagnosis	Ulcerative colitis	Ulcerative colitis
Colitis involvement	E4 (Pancolitis)	E4 (Pancolitis)
Age	18	13
CMV IgM	Negative	Negative
CMV DNA Level (Copy/mL)	7680	18
Inclusion body in colon biopsy	No	Yes
CMV infection time	In the 15rd month of follow-up during the attack	At the time of diagnosis
Clinical findings	Bloody diarrhea, weakness, pallor	Bloody diarrhea, fever, weakness pallor
Hospitalization period	Day 27	Day 22
Treatment received at the time of CMV infection	Mesalazine Corticosteroids Azathioprine	Corticosteroids
Treatment due to infection	Meselazine was continued Corticosteroid was reduced Azathioprine was discontinued Ganciclovir was administrated for 3 weeks Valganciclovir was administrated for 5 weeks	Meselazine was continued Corticosteroid was reduced Ganciclovir was administrated for 3 weeks
Response	Week 3 * CMV DNA reduction to 168 copies/mL * Clinical response	Week 2 * CMV DNA negative * Clinical response
CMV: Cytomegalovirus.		

patients with possible CMV colitis at the same time. Also in our study, patients with low CMV viral load had good response to treatment, and CMV infection was not observed in these patients during follow-up.

Discussion

Some important points such as the prevalence, role, risk factors and treatment approaches of opportunistic viral infections in inflammatory bowel disease have not been solved (3). As a result of our study on the role of viral infections during attack and diagnosis, the most common cause of colitis was CMV virus. Although the number was low, it was observed that these patients were hospitalized for longer period. EBV infection was observed under immunosuppressive therapy but EBV infection did not cause severe colitis in these patients. Patients with low CMV DNA load improved with IBD standard immunosuppressive therapy without antiviral treatment, and CMV infection did not develop in these patients under treatment. Colectomy was not required in patients with CMV and EBV infection and no mortality was observed.

Although data on CMV-associated colitis in children are limited, more severe colitis and resistance to immunosuppressed treatment may be seen in children with IBD with CMV infection (10). These patients have a high risk for colectomy during follow-up. In adult studies including children with inflammatory

bowel disease, the incidence of CMV colitis was reported to be 1.6% (11). The most important risk factors for CMV infection detected in adult studies are being 30 years of age or older, disease period shorter than 5 years and using immunosuppressive therapy (12). In our study, CMV infection was found in two of 57 patients (3%) and the mean age of these patients was 17.5 ± 2 years. In a prospective observational study of Domenech et al. on 114 patients with ulcerative colitis, it was reported that six patients developed CMV colitis and all of these patients were corticosteroid resistant cases, and the majority had disseminated colitis (E3) (6). In our study, both patients with CMV colitis were diagnosed with ulcerative colitis and they had disseminated colitis findings (E4) according to Paris classification. In our study, CMV Ig M was positive in one case at diagnosis but CMV DNA PCR was negative and CMV inclusion was not observed in tissue. In our other patient, while CMV IgM was negative, CMV DNA was positive at low titer which was analyzed because CMV inclusion was observed in the tissue. CMV IgM alone in detecting CMV infection may cause the infection to be unrecognized in IBD patients. Therefore, in patients with IBD, if there is no response to treatment during attacks, analyses should be conducted for CMV and EBV infections. When the attacks of patients with CMV infection were evaluated, it was seen that cases did not respond well to immunosuppressive therapy. The clinical condition deteriorated with high-dose corticosteroid ther-

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apy during induction period of both cases. As mucosal barrier disorder caused by inflammatory bowel disease during active colitis also increases the tendency of infection in patients, the complete interruption of immunosuppressive therapy in these patients is controversial. In patients with IBD, it is reported that antiviral therapy may not be effective alone and that immunosuppressive therapy should be maintained. Patients with low positive viral load have been reported to recover with IBD standard immunosuppressive therapy without antiviral treatment. (13). Also in our study, patients with low CMV viral load had good response to treatment, and CMV infection was not observed in these patients during follow-up. In our patients with CMV infection, clinical findings were improved especially with the reduction of corticosteroid dose and ganciclovir treatment. Meselazine treatment was maintained in both cases. Azathioprine treatment was discontinued in both cases. One of these patients required biological agent (anti-TNF) treatment after CMV DNA became negative due to persistent colitis findings.

Although the potential effect of EBV infection detected in blood and/or colon mucosa on the pathophysiology in inflammatory bowel disease is demonstrated, its effect on the disease course is unclear (14,15). EBV DNA has been shown in intestinal biopsies taken during exacerbation period of the disease compared to patients in remission in the studies. This supports that EBV infection may cause exacerbation in IBD patients (16). The virological behavior of Epstein-Barr virus is similar to CMV and in the literature, it has been detected especially in patients with immunosuppressive therapy, corticosteroid-resistant or with dependent and severe colitis, as in CMV infection. In our study, EBV VCA IgM was negative in all patients whose serology was analyzed at the time of diagnosis. In two patients who were followed up under immunosuppressive therapy, EBV DNA positivity was detected in the serum examinations conducted due to fever and diarrhea, and both patients had pancolititis (E4). As immunohistochemistry or in situ hybridization could not be performed, EBV could not be demonstrated in intestinal mucosa biopsies. One of these patients was diagnosed with Crohn's disease and after EBV DNA positivity was detected, the dose of corticosteroids from immunosuppressive treatments was decreased. The other patient was diagnosed with nonclassified colitis and treated with biological agent (infliximab) treatment. The azathioprine treatment of two patients were discontinued and mesalazine treatment was continued. As in similar studies, clinical findings improved after immunosuppressive therapy decreased (14). It was observed that EBV DNA became negative at the fourth week and no other complications related to EBV were observed in the follow-up of patients. In our study, it is remarkable that these patients had shorter hospitalization period than those with CMV infection. The limitation of our study was that the number of patients with CMV and EBV infection

was low and EBV DNA could not be demonstrated histopathologically. In our patients with EBV and CMV infection, it was observed that decreasing or cutting the dose of corticosteroids and azathioprine treatments positively affected the clinical course. Meselazine, an immunomodulating agent, was continued in these patients. Those with CMV infection also benefited from ganciclovir treatment additionally. Patients with low CMV DNA load were also found to have benefited from conventional immunosuppressive therapy without requiring antiviral treatment. EBV and CMV infections should be kept in mind in cases of inflammatory bowel disease during diagnosis and exacerbation period, especially if there is no response to treatment. And we also emphasize that viral PCR tests should be performed on the patients because disease activation cannot be proved with serologic tests.

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