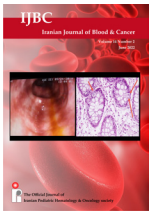
Iranian Journal of Blood & Cancer

Journal Home Page: www.ijbc.ir



CASE REPORT

CMV-colitis in a pediatric non-transplant ALL patient receiving chemotherapy; A case report

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ARTICLE INFO

Article History:
Received: 4/12/2021
Accepted: 4/6/2022

Keywords:
Acute Leukemia
Colitis
Cytomegalovirus

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Abstract

Cytomegalovirus (CMV) is the leading cause of viral-associated congenital infections. Moreover, it can also be acquired. Between 50 to 80 percent of the world's population is seropositive for CMV and most clinical disease occurs in individuals previously infected with CMV. Rarely, serious CMV infection has occurred in individuals with healthy immune system. In contrast to immunocompetent patients, higher morbidity and mortality of CMV end organ disease is considered in immunocompromised patients. According to available evidence, gastrointestinal (GI) disease has lower prevalence in case of CMV-induced organ involvement, especially in pediatric non-transplant acute leukemia. In this report, we present a 12-year-old girl, known case of acute lymphoblastic leukemia (ALL) receiving maintenance chemotherapy with manifestations of gastroenteritis and significant weight loss. Initial laboratory data, demonstrated mild pancytopenia especially lymphopenia and thrombocytopenia. After excluding more common etiologies, colonoscopy with multiple biopsies were taken which was indicative of CMV-colitis. Intravenous (IV) ganciclovir for 3 weeks and oral valganciclovir for about 9 months were initiated. Follow-up courses for CMV surveillance included blood qualitative CMV polymerase chain reaction (PCR) and colonoscopy with biopsy which were negative for CMV but tissue qualitative CMV PCR was positive for CMV in about 7 months after initiation of treatment. Oral treatment was decided to be continued. To sum up, plenty of guidelines have been developed in stem cell transplantation and human immunodeficiency virus (HIV) patients but non-transplant leukemic setting, is a neglected area in the field of CMV infection management.

Please cite this article as: Darbandi B, Niyasti P, Maleknejad S, Baghersalimi A, Hashemian H, Karimzadeh A. CMV-colitis in a pediatric non-transplant ALL patient receiving chemotherapy; A case report. IJBC 2022; 14(2): 49-57

1. Introduction:

Cytomegalovirus, a member of herpesviridae family, is a double-stranded DNA virus [1, 2] which can be a leading cause of viral-associated congenital infections [3] or either can be acquired [1]. Between 50 to 80 percent of the world's population is seropositive for CMV [4]. Most clinical disease occurs in individuals previously infected with CMV (seropositive) and therefore represents either re-activation of latent infection or re-infection (de novo) with a novel strain [5]. In immunocompetent host, it is typically asymptomatic or is responsible for mild undifferentiated viral symptoms and mononucleosis-like syndrome [4]. Rarely, serious CMV infection has occurred in individuals with healthy immune system [6]. In contrast to immuno-competent patients, immuno-compromised patients may experience systemic and end-organ disease primarily due to virus reactivation as a result of impaired immune system consistency. Systemic CMV disease is characterized by fever, pancytopenia, and inflammatory changes in multiple organs [4].

CMV infection is controlled by virus-specific CD4+ and CD8+ cytotoxic T- lymphocytes [7]. Previously, it was demonstrated that conditions like HIV infection, hematopoietic stem cell transplantation (HSCT), solid organ transplantation [8], and some immunosuppressive agents like ibrutinib [9], dasatinib [4], alemtuzumab [10], steroids, fludarabin, and high-dose cyclophosphamide [11] can impair T-cell mediated immunity but standard chemotherapy alone for pediatric leukemia mainly depletes humoral rather than cellular immunity [12]. Therefore, CMV disease development is rare in pediatric non-HSCT ALL being on chemotherapy regimens [11] and data regarding incidence, manifestations [13], optimal management, and outcome of the disease in such condition are limited [11].

According to available literature [5, 14, 15], GI disease has lower prevalence in case of CMV-induced organ involvement, especially in pediatric non-transplant acute leukemia.

Herein, we present a 12-year-old non-transplant ALL patient receiving maintenance chemotherapy, admitted with symptoms of gastroenteritis which was diagnosed CMV-colitis after extensive workups including colonoscopy and biopsy study along with qualitative CMV PCR on biopsy samples for both diagnosis and follow-up of the patient which yielded considerable outcomes.

2. Case presentation:

A 12-year-old girl, known case of Down syndrome and hypothyroidism under treatment with levothyroxine and also known case of acute B-lymphoblastic leukemia which was under treatment with ALL-BFM 2002 protocol, admitted to our center due to deterioration of general condition and fluctuation in bowel habit in September 19th, 2019. At the time of admission she was in her maintenance phase of chemotherapy and she had not undergone a bone marrow transplant. Her chief complaint was bulky loose diarrhea and steatorrhea which was started since 7 months ago and was under supervision of a gastroenterologist. During this period of time, she was hospitalized 2 times due to gastroenteritis, 6 and 5 months earlier, respectively. No specific pathogen was isolated as a known cause of her gastroenteritis in both admissions. At admission, abdominal physical examination was normal. Initial laboratory data revealed mild pancytopenia, coagulation tests were in normal range, other laboratory findings are shown in **Table 1.**

Table. 1: Initial laboratory data

Indicators (Normal range)	Results
White blood cell count (3.5-10 $\times10^3$/cumm)	0.90×10^3
Red blood cell count (3.80-5.80$\times10^3$/cumm)	3.38×10^6
Hemoglobin (12-16 g/dl)	8.4
Platelet (135-450$\times10^3$/cumm)	66×10^3
Erythrocyte sedimentation rate 1st hour (≤20 mm/hr)	50
Blood urea nitrogen (5-23 mg/dl)	5.3
Creatinine (0.3-0.9 mg/dl)	0.9
Sodium (135-145 mEq/L)	135
Potassium (3.5-5.5 mEq/L)	4
Total protein (Adult 6.6-8.3 & Infant 5.2-9.1 g/dl)	5.8
Serum Albumin (3.5-5.3 g/dl)	3.7
Aspartate aminotransferase (< 37 IU/L)	97
Alanine aminotransferase (< 40 IU/L)	137
Alkaline Phosphatase (180-1200 U/L)	275
Amylase (< 90 U/L)	54
Lipase (21-128 IU/L)	27
C-reactive protein	Positive (1+)

Stool examination was normal. Stool culture was negative for Salmonella and Shigella. Other laboratory evaluations including anti-transglutaminase antibodies, anti Strongyloides Stercoralis antibody, anti-saccharomyces cerevisiae antibody and perinuclear anti-neutrophil cytoplasmic antibody, wright and widal tests were negative. Stool calprotectin was

67 (borderline, according to laboratory reference). There was a slight to moderate increase in liver enzymes during the course of the disease, which also could have been due to chemotherapy medications including 6-mercaptopurine and methotrexate. An abdominal sonography revealed splenomegaly (spleen size 135mm) while liver, biliary tract, and kidneys were normal. Upper GI endoscopy with biopsy was performed and was normal. Further evaluations for celiac disease and Giardia infection in biopsy samples were negative. A colonoscopy showed edematous mucosa, erythema, loss of vascular markings with longitudinal ulcers, and skip lesions throughout the colonic mucosa (**Fig. 1**).

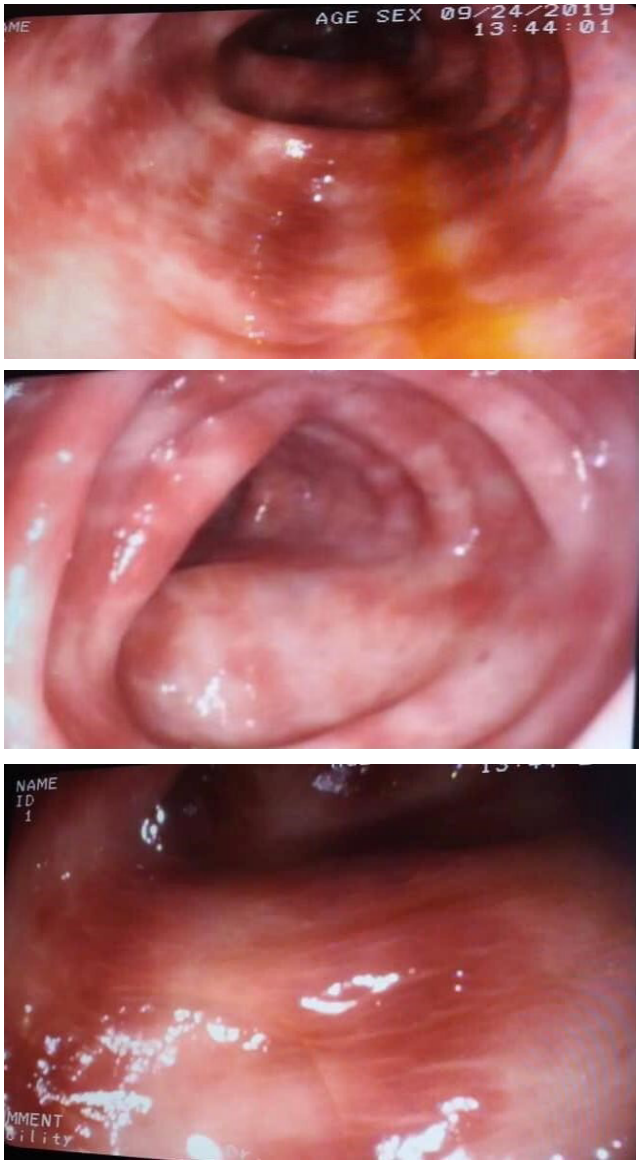

Figure 1: Colonoscopic view. Edematous mucosa, linear erythema with loss of vascular markings throughout colonic mucosa.

Biopsy samples were taken from ascending colon and recto-sigmoid area to evaluate inflammatory bowel disease and CMV infection. Biopsy samples showed nonspecific inflammation in colonic mucosa and basophilic intranuclear inclusion bodies surrounded by a clear halo in few endothelial cells (**Fig. 2**).

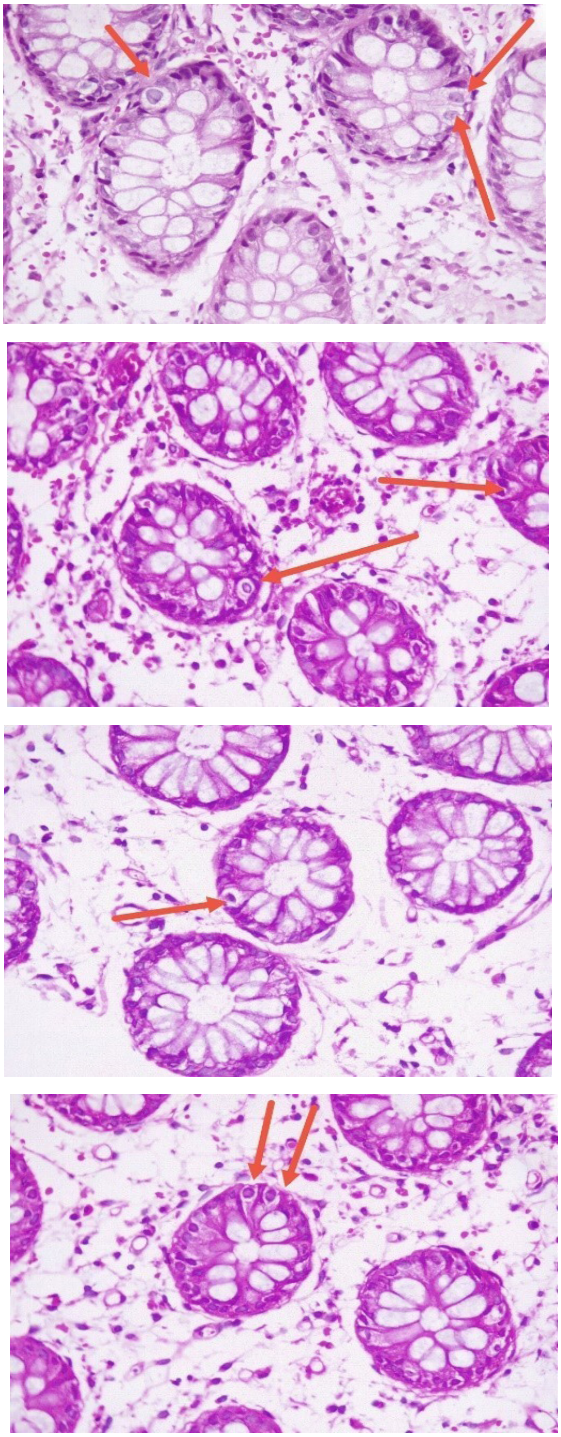

Figure 2. Microscopic view of colonic biopsy specimens in hematoxylin and eosin staining (H&E). Giant cells with inclusion bodies (arrows) characteristic of CMV-colitis.

Tissue qualitative CMV PCR was positive. After 25 days of extensive work ups, the patient admitted again with the diagnosis of CMV-colitis in our tertiary care center. The treatment started at the first day of her admission with IV ganciclovir (160 mg, every 12 hours) for 21 days. Patient's complete blood counts (CBC) before, during, and after treatment with IV ganciclovir are listed in **Table 2.** Blood qualitative real time CMV PCR (RT-PCR) in day 7 after initiation of treatment showed a negative result. After completion of IV ganciclovir, the patient's general status improved and became asymptomatic without any signs & symptoms of fever, diarrhea, and abdominal pain. After 3 weeks of hospitalization, the patient discharged with oral valganciclovir (900 mg tablets every 12 hours) while she was on her last 3 months of chemotherapy regimens and recommended for about 6-12 months after the end of chemotherapy by our infectious specialist. About 6 months after initiation of outpatient oral treatment, a follow-up colonoscopy with biopsy was performed. It revealed no sign of edema, erythema or ulceration throughout colonic mucosa. Nonspecific inflammation with no typical viral cytopathic effect was reported in biopsy samples taken from ascending, descending colon, and recto-sigmoid area but tissue qualitative CMV PCR was still positive. Oral treatment continued for up to 7 months after the end of chemotherapy. The first follow-up visit was 1 month after starting the treatment and subsequent visits were carried out every 4 to 5 months. Each follow-up visit included history taking & physical exam, weight measuring, CBC, stool calprotectin antigen, and stool exam along with blood CMV RT-PCR in the first and last follow-up visits. During follow-ups, absolute neutrophil count (ANC) decreased to less than 500 cells/cumm, which was resolved by temporary discontinuation of chemotherapy agents and daily G-CSF administration. Eventually in the last follow-up, our patient remained asymptomatic, without recurrence of fever, diarrhea, abdominal pain, and a weight gaining trend along with normal laboratory data and a negative blood qualitative CMV RT-PCR which taken together led to termination of oral treatment.

Discussion:

In this report, we are presenting a 12-year-old girl, known case of non-HSCT ALL admitted to our center in September 19th, 2019 presented with gastroenteritis in her maintenance phase of chemotherapy (ALL-BFM 2002 protocol).

Prevalence of end-organ involvement in systemic CMV disease can be various based on underlying immune deficiency condition. For example in HIV patients, retinitis, colitis (5 to 10%), esophagitis, pneumonitis, and neurologic disease (dementia, ventriculoencephalitis and polyradiculomyelopathies) are organs involved with respect to their prevalence [5]. In non-transplant pediatric ALL, retinitis (50%), pneumonia (40%), GI tract (20%), and hemophagocytic lymphohistiocytosis (7%) were CMV disease manifestations with respect to their prevalence [14]. Another prospective study performed on ninety five patients with non-transplant acute leukemia (AML & ALL) undergoing chemotherapy, prevalence of gastroenteritis in active CMV mono and co-infection with other human herpesviruses (HHV-6 , HHV-7, and EBV) was reported 17.9% and 15.8%, respectively (p=0.084) [15].

In our patient, in both previous admissions due to her gastroenteritis, diagnostic work ups except endoscopic and biopsy procedures, revealed no certain pathogen as a known cause of her gastroenteritis and her symptoms had periodic full response to supportive treatment and antibiotics. Therefore, no suspicion and work up for CMV was considered, due to complete recovery with antibiotics.

Tormo et al. published a prospective cohort consisted of 50 consecutive CMV-seropositive adult patients undergoing cytotoxic chemotherapy for de novo AML.

Table 2: CBCs before, during, and after treatment with IV ganciclovir

CBC before treatment	CBC during treatment	CBC at the time of discharge
WBC: 3600 Neutrophil: 60% Lymphocyte: 18%	WBC: 4300 , 2700, 700 Neutrophil: 64%, 62%, no differential Lymphocyte: 31%, 26%, no differential	WBC: 28900 Neutrophil: 49% Lymphocyte: 7%
Hemoglobin: 9.7	Hemoglobin: 9.7, 8.8, 8.3	Hemoglobin: 9.8
Platelet: 111000	Platelet: 119000, 61000, 50000	Platelet: 114000

patients enrolled had CMV DNAemia. CMV DNAemia was detected most frequently during periods of consolidation therapy (in 10 of the 11 patients). The episodes of CMV DNAemia lasted a median of 7 days (range, 7–103 days) and resolved spontaneously (without the need for antiviral therapy) [16]. Also, Jong et al. in a case report presented a 71-year-old non-transplant AML patient undergoing salvage chemotherapy and reported resolution of CMV-colitis in their patient without using antiviral treatment. The explanation was the role of immune system recovery in resolution of CMV disease without antiviral therapy [17].

Therefore, in our patient, CMV-induced GI tract involvement could not be ruled out despite periodic response to antibiotics in that period of time.

According to literature, predisposing factors for CMV infection in such conditions include: prolonged (>7 days) febrile neutropenia (ANC<500/μL), lymphopenia (ALC<1000/μL) [14], CD4+ count<50 cells/mm^3 [5], thrombocytopenia (platelet count<100 ×10^3 cells/cumm) [18], male sex, lower body mass index [17], certain immunosuppressive agents as mentioned earlier, CMV seropositivity, hypoalbuminemia, bacterial pneumonia and sepsis [19, 20], high levels of CMV viremia (≥1000 copies/mL) [5], red blood cell transfusion within 1 month prior to CMV disease [21] and granulocyte infusion from unscreened donors [11].

CMV is not a usually investigated pathogen in a child on standard chemotherapy with manifestation of only prolonged febrile neutropenia but one study suggested it to be as a standard investigation in prolonged febrile neutropenia protocol, especially if associated with lymphopenia [14].

A cross-sectional study taken on 50 non-transplant ALL pediatrics receiving chemotherapy demonstrated that all patients with high level CMV DNAemia (≥1000 copies/mL) were in maintenance phase of chemotherapy. Elevated ALC was associated with prevention from high level CMV DNAemia (odd ratio: 0.997, p=0.02). It was concluded that quantitative CMV PCR may be considered in ALL patients who are in maintenance phase with ALC<800 cells/mL as a cut off for presence of high level CMV DNAemia with 88.9% sensitivity and 50.4% specificity (p=0.001) [8].

In our case, mild pancytopenia especially lymphopenia and thrombocytopenia along with prednisolone administration as a part of ALL-BFM 2002 protocol could be potential risk factors for CMV disease.

At her first day of admission on September 19th, 2019, due to reduced blood counts and clinical manifestations of possible GI infection, chemotherapy agents were held temporarily, G-CSF and broad-spectrum antibiotics were initiated but no response to treatment was observed. After excluding more common etiologies for gastroenteritis in that context like sepsis work up, Giardia and Strongyloides stercoralis infection, celiac disease, inflammatory bowel disease, brucellosis and Salmonellosis, we decided to investigate CMV infection due to suspicious clinical picture along with coordinated para-clinic risk factors suggestive of CMV disease by CMV serology and endoscopy with biopsy procedures.

CMV serology assay has a negative predictive value and is not diagnostically useful [4]. In our case, CMV serology was not prepared, therefore we could not identify whether CMV infection was present prior to or after initiation of chemotherapy.

Upper GI endoscopy with biopsy was normal but colonoscopy with multiple biopsies showed macroscopic features of CMV-colitis and eventually the microscopic examination with H&E staining confirmed the diagnosis. Also, a tissue qualitative CMV PCR was taken which gave positive results.

According to literature, CMV-colitis is usually diagnosed based on demonstration of mucosal ulcerations in endoscopic examination, combined with histopathologic demonstration of characteristic intranuclear and intracytoplasmic inclusions as a gold standard method [4, 5]. Colonic biopsy has very high specificity (92-100%) but low sensitivity (10-87%) making the need for taking multiple biopsy samples and evaluation by a trained pathologist [22, 23].

In biopsy samples, immunocytochemical techniques have demonstrated that typical intranuclear inclusions (Cowdry type A) detected by H&E staining are far less common than atypical cytopathic effect [24]. Moreover, histological staining using immunohistochemistry (IHC) has shown higher sensitivity than H&E staining (78% -93%) [25, 26]. However, IHC can lead to an equivocal interpretation due to atypical

staining patterns. Also, detection depends on the observer which contributes to inter- and intralaboratory variability. It is suggested that in such cases, molecular methods like tissue CMV DNA PCR could be complementary [27, 28].

Blood CMV levels can be detected by PCR, antigen assays or culture. Due to their poor positive predictive value, they are not recommended for CMV end-organ disease diagnosis [5]. In general, the detection of CMV by antigenemia or PCR analysis has not been a reliable predictor of CMV end-organ disease in the settings outside transplantation [29, 30] or HIV patients with low CD4 cell counts as viremia detected by one of these assays in such settings, can be present in disease-free patients. Also, a negative serum or plasma PCR assay does not exclude CMV end-organ disease [5]. Therefore, we did not try blood or plasma CMV PCR for diagnosis of CMV-colitis in our patient.

Quantitative PCR can give important prognostic information [31]. However, serum or plasma PCR should examined together with clinical findings for excluding false-positive results [4]. Unfortunately, quantitative blood CMV PCR was not available in our center and therefore, qualitative CMV blood PCR was requested in all paraclinic investigations.

After about 25 days of extensive work ups, the patient was admitted again with diagnosis of CMV-colitis for initiation of antiviral treatment. IV ganciclovir (160 mg, every 12 hours) was started and continued for 21 days. CBC before starting treatment showed an acceptable WBC count of 3600 cells/cumm but ALC count was 648 cells/cumm (lymphopenia). During treatment, lymphopenia resolved. However, WBC count decreased to 700 cells/cumm with no differential reported. At this time, chemotherapy agents were held temporarily and G-CSF initiated which resulted in WBC count of 28900 cells/cumm (Neutrophil: 49% & lymphocyte: 7%) at the end of IV antiviral treatment course.

According to the center for disease control and prevention, the national institutes of health, and the HIV medicine association guideline recommendations, IV ganciclovir 5mg/kg q12h should be initiated for 21-42 days or until the signs and symptoms resolve [5].

Jain et al. in a prospective case series study on 10 non-transplant pediatric ALL patients being on chemotherapy reported that children who had recurrent CMV infection had a non-significant lower median ALC compared with those who did not have recurrent CMV infection (P=0.13). ANC was not significantly different between two groups (P=0.75). Calculation of median ALCs for a period of 2 months before and after CMV disease showed that the group with recurrent CMV was more lymphopenic as compared with other group (P=0.019 and P=0.06, respectively). For patients with recurrent CMV infection, reinduction with IV ganciclovir for 14-21 days showed full response in same doses with negative follow-up blood PCR for all of the patients. It was concluded that CMV disease was associated with periods of prolonged lymphopenia with a higher likelihood of recrudescence in the presence of persistent lymphopenia and ganciclovir therapy duration of <14 days [14].

In our case, a follow-up qualitative blood CMV RT-PCR at week one after initiation of IV antiviral treatment showed negative results.

According to literature, recommended treatment for CMV pneumonia is combination of ganciclovir and intravenous immunoglobulin (IVIg). However, there is no strong evidence to support the routine use of IVIg. It is noteworthy that IVIg is not recommended in other manifestations of CMV disease [32] and prompt treatment with ganciclovir guided by viral titers can save patient's life even if IVIg is unavailable [33]. Therefore, it may needed to be decided per cases by physicians. We did not use IVIg in our patient.

Response to treatment is defined as complete resolution of clinical features of CMV and documentation of negative CMV PCR performed on blood samples according to clinical profile of the patient [14]. Recurrent infection is defined if blood viral DNA levels resolve then become positive in a later time point [15] and antiviral treatment resistance is defined as increasing / persistence of viral load despite administration of adequate antiviral therapy for

more than 2 weeks and is confirmed based on genotyping and/or phenotyping tests [34, 35].

We did not check quantitative viral load but qualitative result was negative 1 week after starting the treatment and patient was symptom-free at the end of IV ganciclovir treatment course which excluded resistant CMV disease.

After 3 weeks of hospitalization, our patient discharged with oral valganciclovir (900 mg tablets every 12 hours) as maintenance therapy recommended for about 6-12 months after the end of chemotherapy.

In HIV patients, chronic maintenance therapy is usually not necessary for CMV GI disease unless there is concurrent retinitis or disease relapses [5]. Among 6 similar reports in non-transplant ALL patients with CMV-colitis under chemotherapy, from 4 related case reports [11, 13, 17, 36], only 1 case report used maintenance therapy with valganciclovir (10mg/kg twice daily) for a few days until negative results for CMV were achieved [13]. Also, from 2 related case series [14, 15], one of them used a median of 16 weeks (range: 2-28weeks) of maintenance therapy with valganciclovir (doses not mentioned) on 10 patients. 4 children who had a 7-10 days IV ganciclovir treatment, had relapse of CMV within 12 weeks while receiving oral antiviral treatment [14].

Our patient was followed-up in a total of 3 visits.

In patients receiving ganciclovir, CBC, serum electrolytes (including potassium, magnesium, calcium, and phosphorus), and renal function should be monitored twice weekly during induction and at least once weekly during maintenance therapy due to possible adverse effects of ganciclovir/valganciclovir [5].

In follow-up visits, blood qualitative CMV RT-PCR in first and last visits were negative but colonoscopy with biopsy and tissue qualitative CMV PCR in second visit yielded considerable outcomes in about 6 months after initiation of outpatient oral treatment.

Colonoscopy was normal but biopsy samples showed colonic mucosa with nonspecific inflammation with no typical viral cytopathic effect in H&E staining. CMV qualitative DNA PCR on biopsy samples was positive.

According to literature, CMV DNA load quantified with RT-PCR in whole blood and plasma is a useful tool for diagnosis and monitoring disease activity for CMV disease [37]. Also, quantitation of CMV-DNA on GI biopsies seems to be useful for monitoring GI CMV disease [38]. Yan et al. demonstrated that isolated CMV infected GI cells identified by IHC was associated with atypical cytopathic changes on H&E. It was concluded that, CMV IHC stain should be considered as a part of evaluation in any case where there is a high suspicion either clinically or histopathologically, especially in immunocompromised individuals whose GI specimens have no morphological evidence of typical CMV cytopathic changes [1, 22].

IHC was not performed in our biopsy samples and this might be a reason for negative typical viral cytopathic effects despite positive PCR results on biopsy samples. But instead, we used qualitative CMV PCR on our biopsy samples as previously demonstrated to have the same sensitivity (100%), specificity (98%), positive (93%) and negative predictive value (100%) as CMV-IHC [39].

On the other hand, we have not checked blood CMV RT-PCR at the time of checking tissue PCR simultaneously but as literature previously proved, there is a poor correlation between the burden of CMV infection in tissue and the peripheral blood viral load [1]. Therefore, tissue detection of CMV by CMV DNA PCR or IHC is of high priority.

Data regarding usage of tissue CMV PCR for therapeutic goals and monitoring response to treatment in non-transplant leukemic patients are limited. In contrast, some authors performed studies in post-allogeneic HSCT [39] and HIV infection settings [38].

Ljungman et al. established 3 definitions of CMV disease as proven, probable, and possible CMV disease as discussed in detail, previously [40].

In our case, positive CMV PCR on biopsy samples in about 6 months after initiation of maintenance therapy along with no GI symptoms and negative macroscopic findings, indicates a low probability for our patient to be categorized as proven, probable or possible CMV disease at this moment.

Furthermore, as previous literature described, the severity of immunodeficiency, the shedding status for CMV and GI inflammation triggered by other pathogens like Giardia intestinalis and Isospora belli are conditions associated with false positive results of tissue CMV PCR [22]. In our case, immunosuppression as periods of neutropenia which resulted in transient chemotherapy discontinuation and G-CSF prescription due to chemotherapy, could result in shedding status for CMV and false positive results.

It is not known whether a delay of 25 days for starting anti-CMV treatment could be a potential risk factor for positive tissue CMV PCR in about 7 months after starting IV antiviral treatment despite previous negative blood CMV RT-PCR results.

To the best of our knowledge previously, 4 case reports [11, 13, 17, 36] and 2 case series [14, 15] presented GI CMV disease in non-transplant acute leukemia being on chemotherapy until November 2019 and this study is the first case report considering tissue CMV PCR for diagnosis, follow-up, and monitoring response to antiviral treatment which yielded considerable outcomes.

Conclusion:

Further studies need to be done to investigate the role of tissue CMV PCR in follow-up and monitoring response to treatment in leukemic patients, defining treatment goals and resistancy/recurrency of CMV disease in follow-ups based on CMV PCR results preformed on biopsy specimens.

Also, the role of IVIg in CMV disease management especially in end organ disease other than pneumonia needs to be more clarified.

With keeping in mind that CMV infection could result in tumor resistance to some

chemotherapy agents, taken together with higher morbidity and mortality of CMV end organ disease in immunocompromised patients, more studies need to be performed for designing protocols in treatment and follow-up of CMV disease for leukemic patients outside HSCT and HIV infection settings.

Conflict of interest:

None to declare.

Acknowledgements:

Thanks to Pediatric Diseases Research Center, Guilan University of Medical Sciences, Rasht, Iran

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