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Case Report

A Case of Cytomegalovirus Retinitis during Maintenance Chemotherapy for Acute Leukemia

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

ABSTRACT

Cytomegalovirus (CMV) disease is rare in children who receive anticancer chemotherapy and have no history of stem cell transplantation (SCT). We report a case of CMV retinitis that developed during maintenance chemotherapy for acute leukemia. A 7-year-old boy developed decreased visual acuity and persistent pancytopenia during maintenance chemotherapy. Laboratory investigations initially showed significant CMV antigenemia (51 positive cells/200,000 leukocytes); however, antiviral therapy was not deemed necessary in this patient who had no history of SCT. CMV antigenemia worsened to 170 positive cells/200,000 leukocytes over 3 weeks. Ophthalmological examination revealed multiple bilateral retinal infiltrates and granular lesions. He was diagnosed with CMV retinitis and was treated with a 4-week course of intravenous ganciclovir and intravitreal injection of ganciclovir 6 times, followed by a 1-month course of orally administered valganciclovir. A CMV antigenemia assay showed negative results, and follow-up fundoscopy revealed lesser retinal infiltration after the sixth intravitreal ganciclovir injection. Future studies should focus on the development of standardized screening methods and preemptive therapeutic strategies for CMV disease in high-risk children.

Keywords: Cytomegalovirus; Retinitis; Chemotherapy

INTRODUCTION

Cytomegalovirus (CMV) causes asymptomatic infection or self-limiting febrile illness in most infected children, but it can lead to end organ disease which is an important cause of morbidity and mortality in immunocompromised children.[1] Depression of cell-mediated immunity predisposes to symptomatic cytomegalovirus infection.[2] Among children with hemato-oncologic diseases, CMV disease occurs mostly in patients who have undergone stem cell transplantation (SCT). CMV disease in children who receive anticancer chemotherapy and have not undergone SCT is not well recognized.

Here, we report a case of CMV retinitis that developed during the maintenance chemotherapy for acute leukemia. This study was approved by the Institutional Review Board at Seoul National University Hospital (IRB No. H-1909-012-1061). Requirement for informed consent was waived.

Author Contributions

Conceptualization: Song S, Han MS; Investigation: Song S; Supervision: Han MS, Oh BL, Choi JH; Writing - original draft: Ahn B; Writing - review & editing: Choi EH.

CASE

A 7-year-old boy who was on chemotherapy for acute lymphoblastic leukemia (ALL) was admitted to Seoul National University Children's Hospital (SNUCH) with a chief complaint of decreased visual acuity and CMV antigenemia.

He was diagnosed with common ALL at the age of 4 years and received induction chemotherapy with prednisolone, vincristine, L-asparaginase, and intrathecal (IT) cytarabine. After induction, he received consolidation chemotherapy with vincristine, 6-mercaptopurine, and IT methotrexate. Then he continued maintenance chemotherapy with prednisolone, vincristine, methotrexate, and 6-mercaptopurine till the 7th cycle of maintenance chemotherapy regimen 6 months prior to this admission. He had no other underlying diseases and treatment for ALL had been completed as scheduled without complication that would increase the risk of developing CMV retinitis. At the time of ALL diagnosis, he was seropositive for CMV immunoglobulin (Ig) G and seronegative for CMV IgM.

About 3 months prior to the admission, he was admitted to the Jeju National University Hospital (JNUH) for neutropenic fever and maintenance chemotherapy was halted. At admission to JNUH, his complete blood count results were white blood cell (WBC) count 1,300/μL (56% neutrophils, 17.4% lymphocytes), hemoglobin 10.4 g/dL, and platelet count 119,000/μL. Fever and neutropenia did not improve despite empirical intravenous antibiotics. Routine evaluations for neutropenic fever were all negative, and fever subsided after 2 weeks. There was no evidence for relapse on bone marrow biopsy, so chemotherapy was restarted.

Two months prior to the admission, neutropenic fever occurred and chemotherapy was halted again. He started to complain about decreased visual acuity for the first time and watched TV close by, and the symptom continued until the admission. As he had other symptoms such as cough and abdominal pain, his parents did not pay attention to this new symptom and did not report it to doctors. Abdominal pain persisted for 3 weeks, so evaluations were conducted. There was no specific finding on gastroduodenoscopy, and abdominal computed tomography revealed mild wall thickening on recto-sigmoid colon suggesting mild colitis. CMV antigen level was checked for fever persisting 25 days, and high CMV antigenemia (51 positive cells/200,000 leukocytes) was first detected. At this time, his complete blood count results were WBC count 1,050/μL (52.3% neutrophils, 30.8% lymphocytes), hemoglobin 12.4 g/dL, and platelet count 45,000/μL. However, as the patient was not a SCT recipient antiviral therapy was not administered, and ophthalmological exam was not done. Fever improved since the day of first CMV antigen test, and absolute neutrophil count was recovered to 1,000/μL, so the 8th cycle of maintenance chemotherapy was started after 3 days (**Fig. 1**).

About 2 weeks prior to the admission, neutropenic fever occurred again hence chemotherapy was halted. CMV antigen level was found to have risen to 170 positive cells/200,000 leukocytes in 3 weeks. His CMV serologic status was rechecked, and he was seropositive for CMV IgG and seronegative for CMV IgM. On first ophthalmological examination to check retinal involvement of CMV, multiple retinal infiltrates and granular lesions were found in both eyes. CMV retinitis was diagnosed and ganciclovir induction therapy was initiated. CMV antigen level decreased to 24 positive cells/200,000 leukocytes after 6 days of ganciclovir induction therapy, but the level reached the highest point of 715 positive cells/200,000 leukocytes after nine days of treatment. Therefore, he was transferred to the SNUCH for further management of CMV retinitis.

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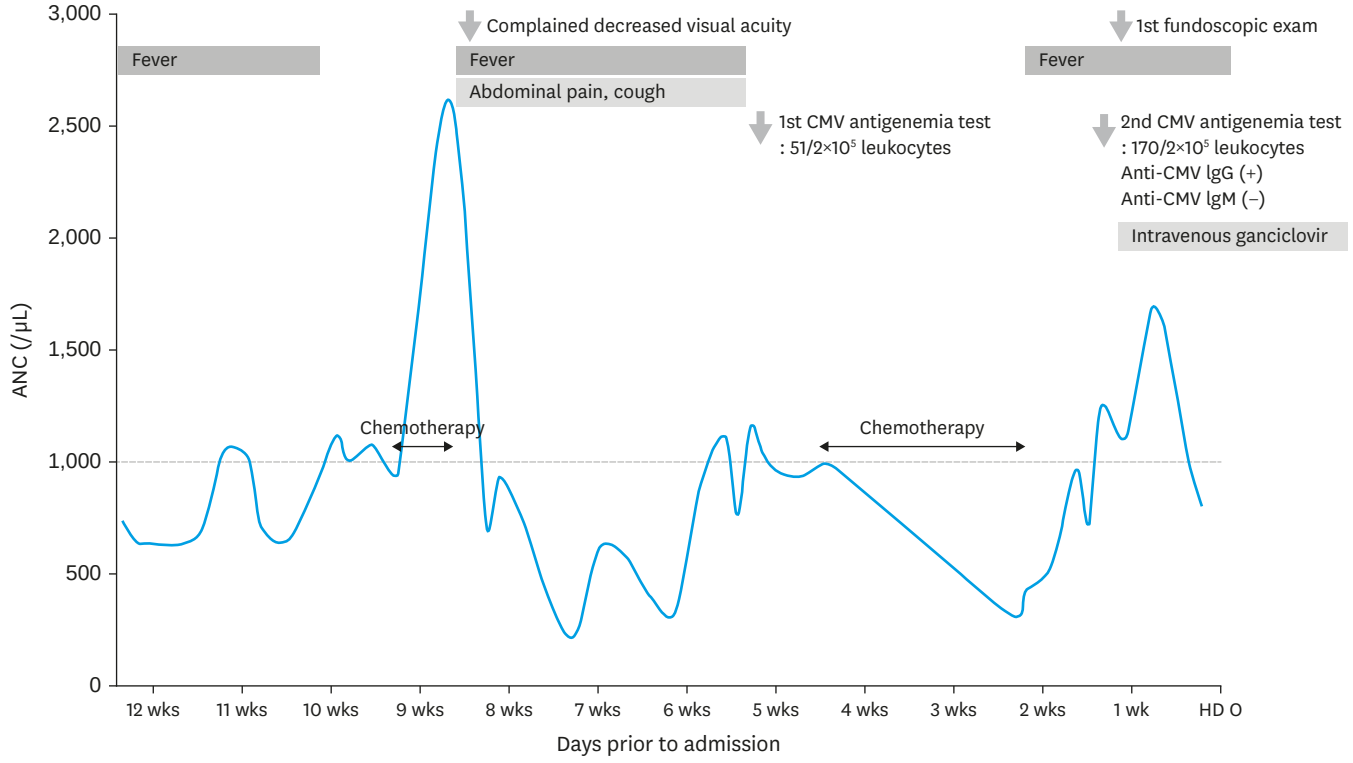

Fig. 1. Clinical symptoms, timing of CMV antigen tests, timing of ophthalmologic exam, duration of chemotherapy together with absolute neutrophil count.
Abbreviations: CMV, cytomegalovirus; ANC, absolute neutrophil count; Ig, immunoglobulin.

At the time of admission, CMV antigen level was of 564 positive cells/200,000 leukocytes (**Fig. 2**). Initial laboratory results were as follows: WBC count 2,300/μL (74% neutrophils, 19% lymphocytes), hemoglobin 9.6 g/dL, platelet count 66,000/μL. Fundoscopic findings showed bilateral granular type of retinal infiltration with blot hemorrhage at post pole and peripheral regions (**Fig. 3A**). Chest CT and abdomen CT did not show abnormal findings.

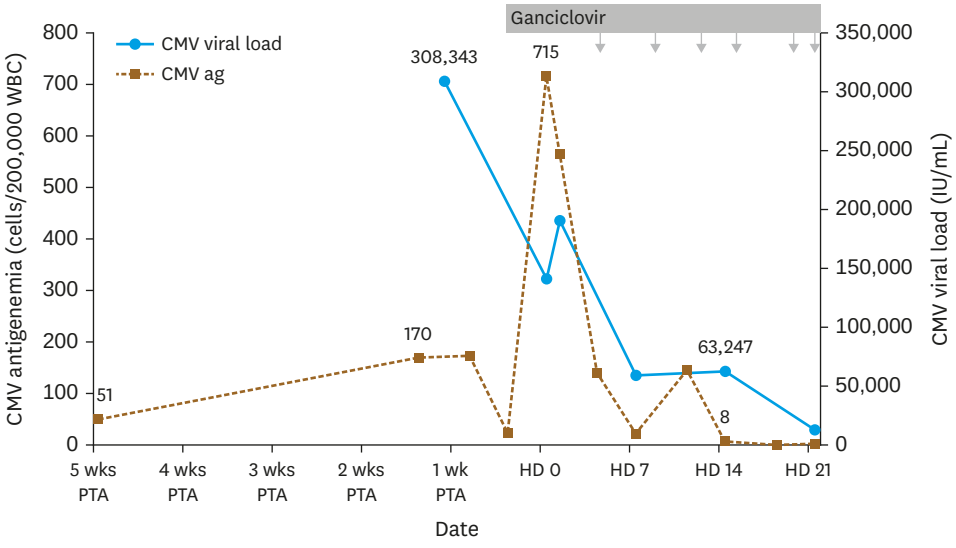

Fig. 2. CMV antigenemia and viral load following intravenous ganciclovir and intravitreal injection of ganciclovir.
Arrows indicates intravitreal injections.
Abbreviations: CMV, cytomegalovirus; WBC, white blood cell; PTA, prior to admission; HD, hospital day.

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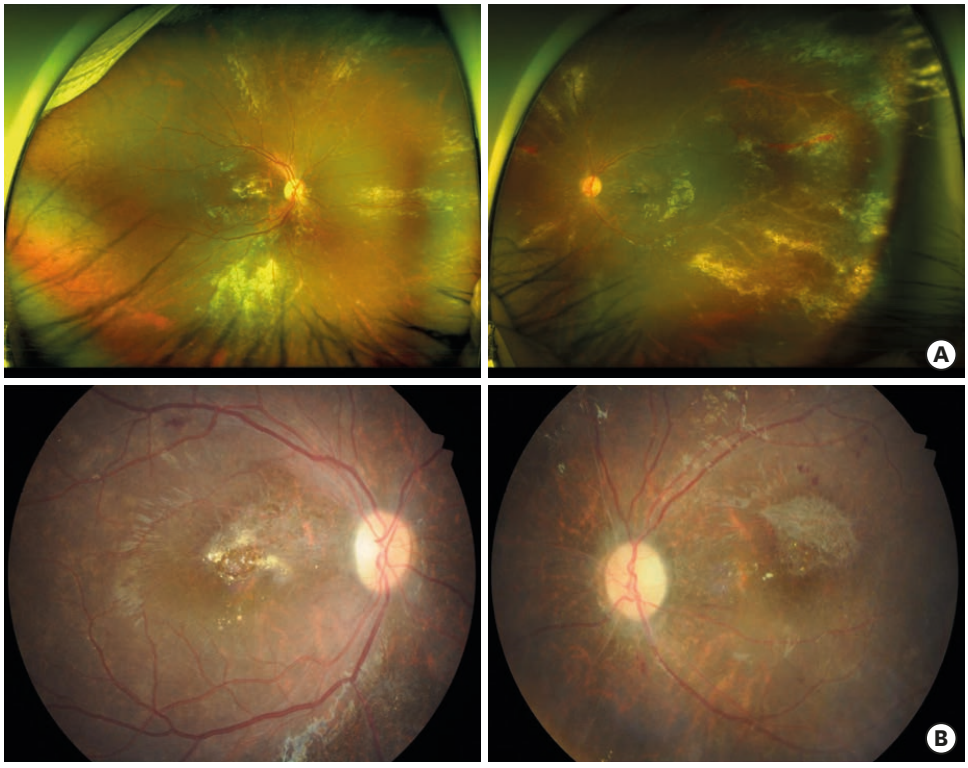

Fig. 3. Fundoscopic findings showed bilateral granular type of retinal infiltration with blot hemorrhage at posterior pole and peripheral regions at 10 days after intravenous ganciclovir treatment (A) and atrophic changes after treatment (B).

Intravenous ganciclovir was administered with an induction dose of 5 mg/kg every 12 hours. Follow-up fundoscopic finding at the third day of admission showed no improvement despite intravenous ganciclovir for 2 weeks, so intravitreal ganciclovir injection was used in conjunction and continued for 6 times. After 4 weeks of intravenous ganciclovir and 6 times of intravitreal ganciclovir, CMV antigen level together with viral load decreased (**Fig. 2**). Retinal infiltration improved on follow-up fundoscopy after completing treatment with intravitreal ganciclovir (**Fig. 3B**). He was discharged with oral valganciclovir (900 mg daily) as maintenance therapy for 1 month.

DISCUSSION

CMV can lead to end-organ diseases in patients with reduced cellular immunity, such as human immunodeficiency virus (HIV)-infected patients, solid organ transplant (SOT) recipients, SCT recipients, and patients receiving immune suppression therapy.[3]

CMV disease can be categorized as viral syndrome (i.e., fever, malaise, leukopenia, and/or thrombocytopenia) or as tissue invasive disease which present as pneumonitis, hepatitis, encephalitis, colitis and retinitis, among others.[4] The most common manifestation of CMV disease in HIV patients is retinitis, which accounts for ≤85% of all cases and is characterized by hemorrhagic retinal necrosis.[3] In SOT recipients, the gastro-intestinal tract is the commonest organ to be involved.[5] CMV tends to involve the allograft depending on the type of organ transplanted.[6]

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Among patients with hemato-oncologic disease, CMV disease occurs mostly in allogeneic SCT recipients, and the most common clinical manifestations of CMV disease are pneumonitis and enterocolitis.[3] CMV retinitis occurs less frequently, but it is a major sight-threatening condition for immunocompromised individuals. CMV retinitis in patients with ALL without SCT has rarely been reported.[7,13]

CMV retinitis is related to the hematogenous spread of the virus to the retina, usually after systemic reactivation of a latent infection.[14] It is usually diagnosed by an experienced ophthalmogist on the basis of typical retina changes. CMV retinitis is a full-thickness necrotizing retinitis, and the characteristic ophthalmologic appearance is that of fluffy, yellow-white retinal lesions, with or without intraretinal hemorrhage, with little inflammation of the vitreous.[15] Bilateral retinal involvement and subsequent reduced visual acuity are more frequent in children and adolescents than in adults.[13]

Most cases of CMV retinitis in patients with ALL were diagnosed during maintenance chemotherapy for ALL.[14] Previous studies have revealed maintenance phase as the most common period of CMV infection in pediatric lymphoblastic leukemia.[16,17] This finding could be explained as the chemotherapeutic agents used in this phase. Moritake et al.[11] assumed that in maintenance therapy, the addition of vincristine and dexamethasone to 6-mercaptopurine and methotrexate remarkably increased the risk of CMV retinitis. Lymphopenia caused by these drugs may contribute to more prevalent CMV reactivation during this phase rather than in the induction or consolidation phases.[18] In this case, the patient used vincristine, prednisolone, 6-mercaptopurine, and methotrexate which could have prolonged immune suppression thus predisposing reactivation of CMV and development of CMV retinitis.

Treatment modalities for CMV retinitis include systemic and intravitreal antiviral medications. The Center for Disease Control and Prevention and the HIV Medicine Association guideline recommend initiation of therapy with one of these medications; oral valganciclovir, intravenous ganciclovir, intravenous ganciclovir followed by oral valganciclovir, intravenous foscarnet or intravenous cidofovir. For sight threatening lesions, intravitreal ganciclovir or foscarnet injections to provide high intraocular levels of drugs with oral valganciclovir is preferred. Intravitreal injections with intravenous ganciclovir followed by oral valganciclovir can also be used,[15] which was the choice of therapy in this case.

Early diagnosis is one of the main prognostic factors for CMV retinitis. The factors that obstruct early diagnosis include the child's inability to express visual symptoms and the absence of external ocular signs of disease. CMV retinitis is more aggressive in children, usually involving both eyes and posterior pole of the eyes[14] as seen in this case, where the risk leading to blindness is high. This case complained of decreased visual acuity 2 months prior to the detection of CMV infection, but his parents did not pay attention to it. CMV retinitis was detected and diagnosed by the doctor who suspected CMV infection which suggests the importance of doctor's awareness.

For children who have undergone chemotherapy without SCT, ophthalmologic examination depends on patient's symptoms, parent's attention, and doctor's awareness. As CMV retinitis could be developed in children who have undergone chemotherapy, doctors should pay more attention to the risk of developing CMV retinitis in these patients. A standardized screening strategy for CMV infection is required for early diagnosis, and regular ophthalmologic examination and appropriate antiviral treatment are important to prevent future visual loss.

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요약

거대세포바이러스병은 혈액종양 질환을 가진 환자군에서는 주로 조혈모세포이식을 받은 환자에게서 발현하는 것으로 보고되고 있으나, 드물게 조혈모세포이식을 받지 않고 항암 치료 중에 발현하는 경우가 있다. 저자들은 발열과 시력 저하를 주소로 입원한 7세 남자에게서 백혈병 유지 치료 중 발현한 거대세포바이러스 망막염을 진단하여 보고하는 바이다. 초기에 거대세포바이러스 항원혈증검사 수치가 51 positive cells/200,000 leukocytes로 높게 보고되었으나 조혈모세포이식을 받은 병력이 없어 항바이러스 치료를 시행하지 않았다가 3주 후 항원혈증검사 수치가 170 positive cells/200,000 leukocytes로 증가하여 시행한 안과 검진에서 양안의 망막 침범 소견과 과립형 병변이 확인되어 거대세포바이러스 망막염으로 진단되었다. 총 4주간의 정맥 내 ganciclovir 치료와 6회의 유리체강 내 ganciclovir 주입술을 시행한 후 경구 valganciclovir 치료를 1달간 더 시행하였다. 치료 시작 1달 후 거대세포바이러스 항원혈증검사가 음성이 되었고 안저검사에서 호전 소견을 보였다. 본 증례와 같이 거대세포바이러스병에 이환되기 쉬운 고위험군 환자들에 대한 선별 검사와 적절한 치료 방침에 대한 논의가 필요하겠다