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CASE REPORT

Successful treatment of acyclovir-resistant herpes simplex virus infection with amenamevir in a patient who received umbilical cord blood transplantation for T-cell prolymphocytic leukemia

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Abstract

A 34-year-old woman received umbilical cord blood transplantation for refractory T-cell prolymphocytic leukemia after salvage therapy with alemtuzumab. She developed right angular cheilitis on the 46th day after transplantation, which worsened after receiving systemic steroid therapy for extensive chronic graft versus host disease. The treatment dosage of acyclovir (ACV), ganciclovir, and vidarabine ointment was not effective due to ACV-resistant mutations of the herpes simplex virus type 1 (HSV-1) in the thymidine kinase domain. Foscarnet is expected to be effective against ACV-resistant HSV-1 infection. However, it could not be used because the patient developed renal dysfunction. Several viral thymidine kinase mutations related to ACV resistance were found in the patient's sample. Nevertheless, amenamevir, a helicase-primase complex inhibitor, was effective in our patient who was significantly immunocompromised after allogeneic hematopoietic stem cell transplantation (allo-HSCT). ACV-resistant HSV infection after allo-HSCT is an rare but important complication in the era of low-dose long-term ACV prophylaxis. To date, there is no established treatment against ACV-resistant HSV infection. This case report showed that amenamevir could be a promising treatment option for ACV-resistant HSV infection in patients with renal failure after allo-HSCT.

KEYWORDS
acyclovir, alemutuzumab, amenamevir, cord blood stem cell transplantation, foscarnet, herpes simplex, homologous, leukemia, prolymphocytic, simplex virus, T-Cell, transplantation

1 | INTRODUCTION

Herpes simplex virus (HSV) infection after allogeneic hematopoietic stem cell transplantation (allo-HSCT) rarely occurs with low-dose long-term acyclovir (ACV) prophylaxis. The prevalence rate of HSV type 1 (HSV-1) resistance to ACV among patients who are immunocompromised, including allo-HSCT recipients, is 3.5%–10%. To date, there is no established treatment for ACV-resistant HSV infection.

2 | CASE PRESENTATION

In August 2021, a 34-year-old woman diagnosed with T-cell prolymphocytic leukemia (T-PLL) underwent three cycles of CHOP (cyclophosphamide, doxorubicin, vincristine and predonisone) therapy. Nonetheless, the disease remained stable, and the patient was transferred to our hospital for allo-HSCT.

The use of alemtuzumab for T-PLL is not approved by public insurance in Japan. However, after obtaining institutional ethical board approval and consent from the patient, alemtuzumab was administrated 11 times from day −39 to −21 before umbilical cord blood transplantation. The patient's peripheral blood lymphocyte count decreased immediately, and the bone marrow lymphocyte ratio remarkably reduced. After treatment, cytomegalovirus antigenemia (CMV-ag) was observed on day −9. Hence, ganciclovir (GCV) treatment was continued until peripheral blood leukocyte disappearance on day 3 after transplantation.

In January 2022, umbilical cord blood transplantation was performed from male donor with 5/6 of human leukocyte antigen matched in both rejection/graft versus host direction. The conditioning treatment comprised cytarabine 2 g/m^2 (day −6 and− 5), cyclophosphamide 60 mg/kg (day −4 and −3), and 12 Gy of the total body irradiation in four fractions (day −2 to −1). Tacrolimus (Tac) and short-term methotrexate were used for graft versus host disease (GVHD) prophylaxis. To prevent viral infection, oral ACV (1000 mg/day [day −7 to day35] and 200 mg/day thereafter) and letermovir (day 6–97) were administered.

Neutrophils were engrafted on day 24. However, on day 28, bone marrow examination showed that 30.8% of cells were derived from the recipient in fluorescence in situ hybridization for sex chromosome. On day 49, it reached 49.8%. Furthermore, a newly complex karyotype abnormality emerged. Nevertheless, T-cell receptor rearrangement at diagnosis was not observed. Hence, we could not confirm T-PLL relapse. To resolve mixed chimerism, Tac was discontinued on day 59 (Figure 1A).

Thereafter, the mixed chimerism was fixed. Nonetheless, renal failure and fluid retention, which could be related to chronic GVHD, progressed gradually from day 132. On day 262, prednisolone (PSL) 0.5 mg/kg was administered for extensive chronic GVHD (NIH criteria, severe, skin score of three, and suspected serosal lesion). With systemic steroid therapy, the skin eruption subsided, and the deterioration of renal function was inhibited. The PSL dose was reduced. However, renal dysfunction worsened again. Thus, moderate-dose PSL was continually administered (Figure 1B).

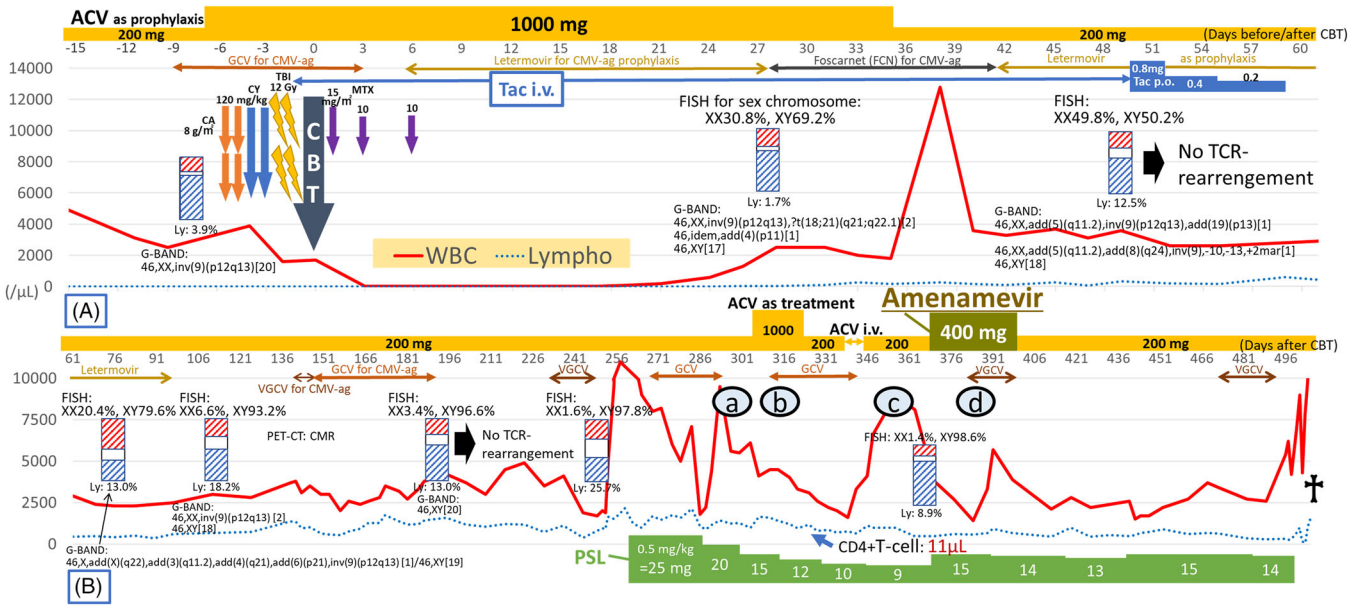

FIGURE 1 (A) Clinical course before and after CBT. (B) Long-term follow-up after CBT. ACV, acyclovir; CA, cytarabine; CBT, cord blood transplantation; CMR, complete metabolic remission; CMV-ag, cytomegalovirus antigenemia; CY, cyclophosphamide; FCN, foscarnet; FISH, fluorescence in situ hybridization; G-BAND, chromosome G-banding; GCV, ganciclovir; i.v., intravenous; Ly, lymphocyte; Lympho, lymphocyte count in the peripheral blood; MTX, methotrexate; PET-CT, positron emission tomography-computed tomography; p.o., per orem; PSL, prednisolone; Tac, tacrolimus; TBI, total body irradiation; TCR, T-cell receptor; VGCV, valganciclovir; WBC, white blood cell count.

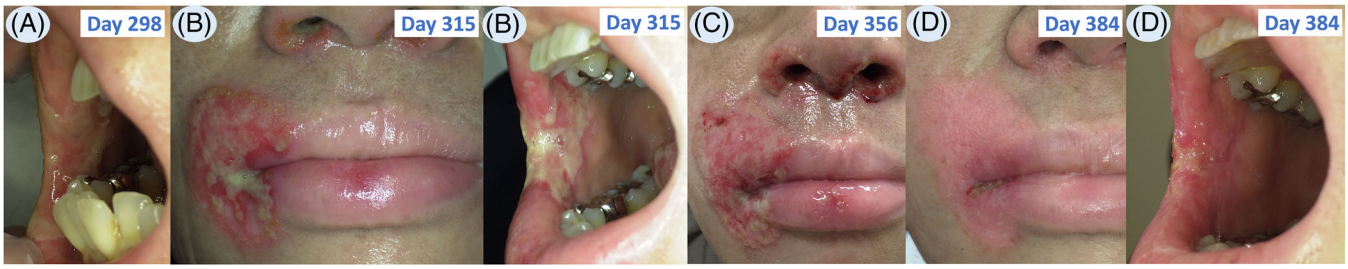

FIGURE 2 Changes in right angular cheilitis and erosion of the nasal ala caused by ACV-resistant HSV-1. (a) This is the image of HSV-1 angular cheilitis at day 298 after transplantation. (b) The images are at day 315. treatment dose of ACV administration started due to severe pain around that time. (c) At day 356, this indicates that the ACV administration is ineffective. Therefore, we suspected the emergence of resistance to ACV. (d) At day384. The image shows immediate response to amenamevir. ACV, acyclovir; HSV-1, herpes simplex virus type 1.

The patient developed right angular cheilitis on day 46, and cytological examination showed HSV-1 infection. It improved temporarily on day 76 but relapsed after PSL initiation (Figure 2A). Despite the concurrent pre-emptive GCV administration against CMV-ag, the application of vidarabine ointment, and ACV dose escalation, the erosions spread to the tongue and nasal ala, resulting in severe pain (Figure 2B,C).

The peripheral lymphocyte count and the immunoglobulin level were within normal level. Nevertheless, the peripheral lymphocytes were mostly B-cells, and the CD4-positive T-cell counts were extremely low (11 cells/μL) on day 321 (Figure S1). The mutation and drug susceptibility analysis of the HSV-1 isolated from the patient's sample was performed at the National Institute of Infectious Diseases. For sequencing, DNA was extracted from the buccal mucosa, oral mucosa, and nasal ala swab and virus isolate samples (High Pure Viral Nucleic Acid Kit, Roche). PCR targeting the thymidine kinase (TK) gene was performed (KOD FX neo, Toyobo), and amplified products were sequenced (3500xL Genetic Analyzer, ABI). The sequences were analyzed with DNA Dynamo. The TK sequences of specimens and isolated viruses were identical, respectively. Susceptibility testing was conducted using the plaque reduction assay with Vero cells. Results showed two mutations (T287M, F289S) in the TK domain (Figure S2). T287M is a known mutation related to ACV resistance. F289S mutation is an unknown mutation, and it is resistant to ACV based on the drug susceptibility test (Table S1). After obtaining informed consent, treatment with AMNV was initiated at a dose of 400 mg/day at day 370. The erosions significantly improved on the following week (Figure 2D), and AMNV was discontinued on day 398. The erosions did not recur with prophylactic ACV (200 mg) until the patient died of pulmonary complications on day 506.

3 | DISCUSSION

A recent study has reported ACV-resistant HSV infections after allo-HSCT [1]. That is, all patients were presented with T-cell depletion due to some medications such as alemtuzumab, ibrutinib, and Tac. The CD4-positive T-cell counts of the patients were extremely low. Under severe immunosuppression, the risk of HSV infection, regardless of ACV effect, could not be ruled out.

Several HSV-1 mutation variants, which were resistant to ACV based on the drug susceptibility analysis, were isolated. ACV is phosphorylated by viral TK in HSV-infected cells and incorporated into the 3′ end of the viral DNA as a nucleic acid analog. Moreover, it inhibits DNA replication and exhibits antiviral activity [2]. Approximately 95% of ACV-resistant HSV isolates are associated with low-producing or altered variants of the virus TK enzyme. Further, 5% are associated with mutations in the viral DNA polymerase. Cross-resistance may occur due to nucleotide sequence mutations, including GCV and famciclovir, which have similar pharmacological mechanisms. Foscarnet, which inhibits DNA polymerase, is effective against ACV-resistant HSV in a previous trial targeting acquired immunodeficiency syndrome [3]. However, its nephrotoxicity can be an issue. AMNV exhibits antiviral activity by inhibiting the helicase-primase complex required for viral double-stranded DNA cleavage and RNA primer synthesis [4]. AMNV was first approved for herpes zoster infection in Japan in 2017. In 2023, it was additionally approved for recurrent herpes simplex. Pritelivir, a similar helicase-primase complex inhibitor, is now currently developed, and it has been found to be effective against ACV-resistant HSV-1 infection after allo-HSCT [5]. However, the efficacy of AMNV has not been elucidated, and this report first showed its efficacy and safety in this setting.

In conclusion, AMNV can be a promising treatment option for ACV-resistant HSV infection in patients with renal failure after allo-HSCT.

AUTHOR CONTRIBUTIONS

Yuma Kawamura performed the initial clinical observation and wrote the first draft. Nako Uchibori provided the clinical images of angular cheilitis for the figures. Souichi Yamada, Yoshiko Fukui, and Shuetsu Fukushi isolated the herpes simplex virus from the specimens, analyzed nucleotide sequences, and investigated the drug susceptibility of the virus to antiviral drugs. The other authors edited and drafted the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data of this case and study are available from the corresponding author upon request.

ETHICS STATEMENT

The authors have confirmed ethical approval statement is not needed for this submission.

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

PATIENT CONSENT STATEMENT

The authors have confirmed patient consent statement is not needed for this submission.

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REFERENCES

1. Anton-Vazquez V, Mehra V, Mbisa JL, Bradshaw D, Basu TN, Daly ML, et al. Challenges of aciclovir-resistant HSV infection in allogeneic bone marrow transplant recipients. J Clin Virol. 2020;128:104421.
2. Safrin S, Crumpacker C, Chatis P, Davis R, Hafner R, Rush J, et al. A controlled trial comparing foscarnet with vidarabine for acyclovir-resistant mucocutaneous herpes simplex in the acquired immunodeficiency syndrome. the AIDS Clinical Trials Group. N Engl J Med. 1991;325:551–555.
3. Bacon TH, Levin MJ, Leary JJ, Sarisky RT, Sutton D. Herpes simplex virus resistance to acyclovir and penciclovir after two decades of antiviral therapy. Clin Microbiol Rev. 2003;16:114–28.
4. Chono K, Katsumata K, Kontani T, Kobayashi M, Sudo K, Yokota T, et al. ASP2151, a novel helicase-primase inhibitor, possesses antiviral activity against varicella-zoster virus and herpes simplex virus types 1 and 2. J Antimicrob Chemother. 2010;65:1733–41.
5. Bosetti D, Bernardi C, Maulini M, Giannotti F, Mamez AC, Masouridi-Levrat S, et al. Salvage treatment of refractory HSV oral lesions with pritelivir in allogeneic hematopoietic cell transplant recipients. Antimicrob Agents Chemother. 2023;67:e0173222.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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