Differential resistance to antiviral drugs in an immunocompromised patient with cytomegalovirus encephalitis

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Differential Resistance to Antiviral Drugs in an Immunocompromised Patient with Cytomegalovirus Encephalitis

Taizo Wada,* Shintaro Mase, Fumie Shibata, Masaki Shimizu, Tomoko Toma, Akihiro Yachie

Institutional affiliations:
Department of Pediatrics, School of Medicine, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University.
13-1 Takaramachi, Kanazawa 920-8641, Japan

***Correspondence to:** Taizo Wada, MD, PhD
Department of Pediatrics, School of Medicine,
Institute of Medical, Pharmaceutical and Health Sciences,
Kanazawa University
13-1 Takaramachi, Kanazawa 920-8641, Japan
Phone: +81-76-265-2313
Fax: +81-76-262-1866
E-mail: Taizo@staff.kanazawa-u.ac.jp

Abbreviations: human cytomegalovirus, HCMV; cerebrospinal fluid, CSF.

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Figure: 1

Human cytomegalovirus (HCMV) infection is usually inapparent in normal individuals but can cause life-threatening diseases including interstitial pneumonitis, retinitis and meningoencephalitis in immunocompromised hosts.[1] Treatment of these HCMV-associated diseases in immunocompromised patients frequently requires long-term use of antiviral agents such as ganciclovir and foscarnet, which may be associated with the emergence of drug-resistant HCMV strains.[2] Here, we describe a 17-year-old Japanese girl who developed refractory immune thrombocytopenic purpura at the age of 4 years. Despite a series of treatments including steroid, intravenous immunoglobulin, vincristine, vinblastine, cyclosporine, azathioprine, splenectomy, and rituximab, her platelet counts remained low, resulting in 2 episodes of intracranial hemorrhage at the age of 12 and in hemoperitoneum at the age of 13. Due to the immunosuppressive conditions, she developed chronic HCMV viremia and HCMV gastroenteritis leading to recurrent gastrointestinal bleeding at the age of 14, that required multiple and prolonged courses of ganciclovir therapy. At the age of 16, resistance to ganciclovir was clinically suspected because of persistent fever and lack of virologic responses, and foscarnet therapy was initiated. However, the patient showed continued high HCMV viral loads ($>10^6$ copies/mL) in the serum, developed fatal HCMV encephalitis, and died at the age of 17 despite combined use of ganciclovir and foscarnet as well as intravenous immune globulin. The dose of intravenous ganciclovir was 300 mg/day (4.5 mg/kg twice daily) at the time of cerebrospinal fluid (CSF) sample collection.

There are two viral proteins involved in resistance mechanism against these antiviral drugs; the phosphotransferase that is encoded by UL97 and the DNA polymerase encoded by UL54.[2] To determine the presence of drug-resistant HCMV

strains, direct sequence analysis of these genes was performed using her various clinical samples (Figure).[3] We found a ganciclovir-resistant UL97 mutation (C592G) and a foscarnet-resistant UL54 mutation (V781I) in DNA obtained from the peripheral blood, that were consistent with her clinical course. Interestingly, a peak of the foscarnet-resistant V781I mutation was shown to increase over the course of the treatment with foscarnet. In contrast, no mutations in both the UL97 and the UL54 genes were demonstrated in DNA from the patient's CSF. The CSF viral load at the time of drug-resistance assay was 5.0×10^7 copies/mL. Similar observations were described in a patient with severe combined immunodeficiency and a stem cell transplant recipient, both of whom were immunocompromised hosts.[4, 5] One possible explanation for the absence of resistance mutations in the CSF is low penetration of antiviral drugs into CSF. Thus, continued and high-dose antiviral drug therapy may be considered for HCMV encephalitis even though the presence of resistance mutations in the peripheral compartment. These findings highlight the possibility of differential resistance to antiviral drugs at different sites in immunocompromised patients and the importance of genotypic resistance testing with various clinical samples.

Key words: Human cytomegalovirus, Encephalitis, Drug resistance

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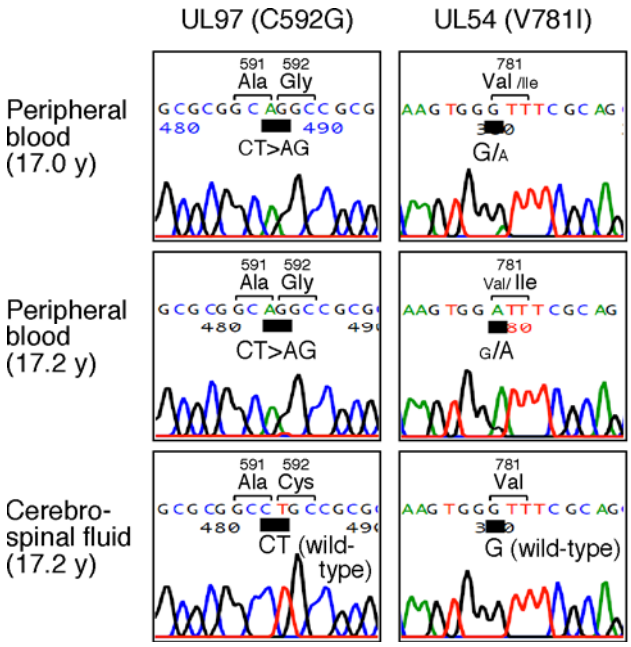
UL97 (C592G)
UL54 (V781I)
Peripheral blood (17.0 y)
Peripheral blood (17.2 y)
Cerebro-spinal fluid (17.2 y)
591 592
Ala Gly
Ala Cys
781
Val /Ile
Val/ Ile
Val
CT>AG
G/A
CT (wild-type)
G (wild-type)