Efficacy of plasma exchange with a high dose of acyclovir for disseminated varicella infection

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Abstract

In individuals treated with immunosuppressive therapies, the varicella-zoster virus (VZV) infection can become disseminated and lead to a life-threatening condition. There is currently no established treatment strategy for this life-threatening condition. Here, we describe a case where plasma exchange (PE) with a high dose of acyclovir (ACV) ameliorated the severe effects, including VZV-hemophagocytic lymphohistiocytosis (VZV-HLH) and disseminated intravascular coagulation (DIC), in a 9-year-old girl with steroid-dependent nephrotic syndrome. This 9-year-old girl experienced frequent relapse steroid-dependent nephrotic syndrome. She had been treated with steroids, tacrolimus, mizoribine, and rituximab. She had not previously received a varicella vaccine. She was admitted with only one vesicular rash. At admission, a serum test revealed 1.6×10^6 copies/mL of VZV DNA. The patient rapidly developed VZV-HLH and DIC. A combination of a high dose of ACV, immunoglobulin, and steroid pulse therapy could not improve these severe complications. Therefore, PE was applied. PE with a high dose of ACV successfully reduced serum VZV DNA from 7.5×10^6 to 2.8×10^4 copies/mL. This reduction in the VZV DNA copy number suggested that the combination of PE and a high dose of ACV was effective in treating a disseminated VZV infection. To the best of our knowledge, this is the first report showing that PE with a high dose of ACV ameliorated the severe complications of disseminated VZV by reducing the VZV DNA copy number.

Keywords Acyclovir · Disseminated varicella infection · Plasma exchange · Frequent relapse steroid-dependent nephrotic syndrome · Vzv-hemophagocytic lymphohistiocytosis · VZV DNA copy number

Introduction

Primary varicella-zoster virus (VZV) infections cause chicken pox in healthy individuals. Chicken pox is generally a mild form of VZV infection. Although, in individuals treated with immunosuppressive therapies, the VZV infection can become disseminated and lead to a life-threatening condition [1–5]. Intravenous acyclovir (ACV), immunoglobulin, steroid pulse therapy, and plasma exchange (PE) are viable options for treating disseminated VZV infections [1–5]. However, there is currently no established treatment strategy for this life-threatening condition. Here, we describe a case where PE with a high dose of ACV ameliorated the severe effects, including VZV-hemophagocytic lymphohistiocytosis (VZV-HLH) and disseminated intravascular

coagulation (DIC), in a 9-year-old girl with steroid-dependent nephrotic syndrome. To the best of our knowledge, this is the first report that shows PE with a high dose of ACV could reduce VZV DNA copy number and ameliorate the severe effects.

Case report

A 9-year-old girl with frequent relapse steroid-dependent nephrotic syndrome was referred to our hospital with only one vesicular rash on her abdomen and 3-day history of strong low back pain. The first episode of nephrotic syndrome occurred at 4 years of age. She had been treated with 9 mg/day of prednisolone, tacrolimus (trough level at 5.0 ng/mL), and 150 mg/day of mizoribine. Tacrolimus was converted from cyclosporine A previously due to hirsutism which could be a side effect of cyclosporine [6]. Additionally, she was given 375 mg/m^2 of rituximab 2 months before this event. She had not previously received a VZV

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vaccination, but she had come into contact with a child infected with VZV 3 weeks prior to this event.

Her physical examination showed the height of 116 cm, weight of 24.5 kg, a body temperature of 37.2 °C, heart rate of 114 bpm, respiratory rate of 24/min, oxygen saturation of 98% (room air), and blood pressure of 144/88 mmHg. There was no systemic edema and normal urinalysis. Her laboratory data on admission are shown in Table 1. The patient was diagnosed with DIC from VZV infection due to her platelet count, 99,000/ μ L; fibrinogen degradation products,

298.5 μ g/mL; fibrinogen, 98 mg/dL; and prothrombin time-international normalized ratio, 1.37. Her clinical course is shown in Fig. 1. Mizoribine was discontinued, and intravenous ACV was started at 30 mg/kg/day, divided into three doses. In addition, we administered intravenous immunoglobulin (400 mg/kg/day). On day 2, the serum aspartate aminotransferase (AST)/alanine aminotransferase (ALT) levels increased from 431/386 to 751/542 U/mL, the ferritin level increased from 1307 to 4391 ng/mL, and the VZV DNA copy number increased from 1.6×10^6 to 1.6×10^7

Table 1 Overview of laboratory findings on admission, pre plasma exchange, post plasma exchange and follow-up on day 13

Parameters	Admission	Pre PE (day 4)	Post PE (day 9)	Day 13
WBC, / μ L	28,700	26,200	15,500	9200
Hemoglobin, g/dL	16.4	13.7	11.0	5.4
Platelets, / μ L	99,000	23,000	29,000	57,000
Fibrinogen, mg/dL	98	26	166	184
PT-INR	1.37	1.86	1.11	1.14
FDP, μ g/mL	298.5	797.8	71.4	62.2
CRP, mg/dL	0.38	0.99	0.04	0.09
Alb, g/dL	5.0	2.9	3.7	2.7
Creatinine, mg/dL	0.30	0.37	0.37	0.40
AST, U/L	431	3260	37	16
ALT, U/L	386	1547	59	39
LDH, U/L	1913	9248	565	338
Ferritin, ng/mL	1307	15,602	549	366
sIL-2r, U/mL	615	—	—	—
IgG, mg/dL	345	—	—	309
VZV-DNA, copies/mL	1.6×10^6	7.5×10^6	3.1×10^4	2.5×10^3
VZV-IgM, antibody index	Negative	—	—	—
VZV-IgG, IU/mL	Negative	—	—	—

PT-INR prothrombin time-international normalized ratio, FDP fibrinogen degradation products, CRP C-reactive protein, LDH lactate dehydrogenase, sIL-2r soluble interleukin-2 receptor

Fig. 1 Time course of treatments administered for disseminated varicella-zoster virus (VZV) infection. (Left axis) Lines show the VZV DNA copy number (black solid line, copies/mL), aspartate aminotransferase level (AST, black dashed line, U/mL), alanine aminotransferase level (ALT, gray dashed line, U/mL), ferritin level (gray fine solid line, ng/mL), and (right axis) acyclovir concentration (ACV, gray heavy solid line, μ g/L)

copies/mL. The vesicular rash spread throughout the entire body within 3 days. A diagnosis of VZV-HLH was also considered, based on findings of bicytopenia (minimum hemoglobin level of 6.7 g/dL and platelet count of 23,000/ μ L), low fibrinogen level (98 mg/dL), and high serum ferritin (4391 ng/mL) [7]. The elevation of soluble interleukin-2 receptor (sIL-2R) level which is one of the laboratory criteria for the diagnosis of HLH was not observed. We think that the tacrolimus administration might have suppressed elevated sIL-2R levels [8]. Therefore, steroid pulse therapy was started with 20 mg/m² of dexamethasone palmitate for 4 days, and the ACV dose was increased to 60 mg/kg/day with a normal serum creatinine level. The median serum ACV concentration before PE was 2.87 μ g/mL (range 1.23–5.72). On day 4, the serum AST/ALT levels continued to rise up to 3260/1547 U/mL and ferritin levels rose to 15,602 ng/mL.

Administration of high dose of ACV and steroid pulse therapy did not improve this severe condition. Therefore, we used PE (Plasmaflow OP-02W Asahi Kasei, Japan); we replaced 50 mL/kg plasma volume with fresh frozen plasma in one PE treatment. The median hematocrit level was 31% (range 26–43%). The mean plasma separation rate was $27 \pm 2\%$ of the mean blood flow rate, which was 60 ± 13 mL/min. This PE procedure was 2 h. The PE was started at 6 h after the administration of ACV. AS soon as the PE was finished, ACV was added twice every 8 h. After initiating the PE with a high dose of ACV, the patient's vesicular rash stopped exacerbating. The PE with a high dose of ACV effectively reduced the serum VZV DNA copy number, AST/ALT level, and ferritin levels (Fig. 1, Table 1). The PE with a high dose of ACV was applied a total of five times, until day 8. The PE was terminated on day 8 because the AST/ALT and ferritin levels decreased sufficiently and the clinical findings including vesicular rash improved. On day 9, serum AST/ALT levels had declined to 37/59 U/mL, and the VZV DNA copy number had declined to 3.1×10^4 copies/mL. On day 10, serum AST/ALT levels continued to decline to 24/55 U/mL, ferritin levels also continued to decline to 558 ng/mL, and the serum DNA copy number declined to 1.2×10^4 copies/mL. After PE termination, the concentration of serum ACV increased from 6.2 to 19.8 μ g/mL. The ACV administration (60 mg/kg/day) was stopped on day 11. On day 12, we restarted ACV at the conventional dose of 30 mg/kg/day. On day 13, 5 days later after the PE termination, the patient's platelet count rose up to 57,000/ μ L, the serum AST/ALT levels continued to decline to 16/39 U/mL, and the ferritin level continued to decline to 366 ng/mL. The serum VZV DNA copy number declined to 2.5×10^3 copies/mL, and the patient's skin lesions were all fully crusted on day 12, 4 days after termination of PE.

Urinary beta 2-microglobulin (β_2 MG) to creatinine (Cr) ratio peaked on day 4 at 80,488 μ g/gCr and gradually

decreased after the induction of PE. This elevation of urinary β_2 MG to Cr ratio before PE would be induced by VZV-HLH. Urinary β_2 MG to Cr ratio was 13,136 μ g/gCr and serum Cr level was 0.33 mg/dL on day 10 when the concentration of serum ACV increased from 6.2 to 19.8 μ g/mL. On day 11, urinary β_2 MG to Cr ratio elevated from 13,136 to 51,067 μ g/gCr and urinary *N*-acetyl- β -D-glucosaminidase (NAG) to Cr ratio also elevated from 54.5 to 66.7 U/gCr with the elevation of serum Cr level from 0.33 to 0.95 mg/dL. After the interruption of ACV and reduction of ACV dosage, urinary β_2 MG and NAG to Cr ratio decreased to 1021 μ g/gCr and 15 U/gCr, respectively until day 26. The serum Cr level also decreased to 0.18 mg/dL. This result suggested that ACV could induce tubular injury.

The VZV-IgM and -IgG antibodies were checked in her serum every month until now after terminating the PE. The VZV IgM antibodies were not detected through this observational period; however, IgG antibodies were first detectable 5 months after PE. She has continued the oral ACV at a conventional dose until now to prevent from re-activation of VZV because serum VZV DNA copy number has been positive ($\sim 7.0 \times 10^3$ copies/mL) with steroids and tacrolimus. She has not experienced recurrences of the vesicular rash, VZV-HLH, or DIC while on oral ACV treatment, with a VZV-IgG titer of 130 IU/mL. Throughout this period, she had normal creatinine levels.

Discussion

To the best of our knowledge, this is the first report showing that PE with a high dose of ACV ameliorated the severe complications of disseminated VZV, including VZV-HLH and DIC by reducing the VZV DNA copy number. Disseminated VZV can cause HLH, especially in individuals treated with immunosuppression therapy [9]. Therefore, it is important to reduce the VZV copy number to control the HLH. In our case, the serum VZV DNA copy number decreased after PE with a high dose of ACV. This treatment also decreased the AST/ALT and ferritin levels and stopped her vesicular rash from exacerbating. These findings showed that PE with a high dose of ACV reduced the amount of VZV and ameliorated the associated HLH, although high dose ACV treatment itself could not ameliorate these conditions.

Lee et al. reported that PE with a high dose of ACV (1500 mg/day) ameliorated the severe effects of disseminated VZV infection in a 45-year-old man who underwent a bone marrow transplantation [4]. Unfortunately, the report did not show the changes in the amount of VZV. On the other hand, Hirose et al. described a fatal varicella infection, which induced HLH, in a 13-year-old girl with systemic lupus erythematosus [3]. She showed a large amount of VZV DNA (5.2×10^6 copies/ 10^5 peripheral blood mononuclear

cells) with numerous vesicular rashes at diagnosis. She was treated with PE and a conventional dose of ACV (30 mg/kg/day), but those treatments could not ameliorate the VZV-HLH. PE with a conventional dose of ACV might have been insufficient to reduce the amount of VZV.

Our findings showed that PE also reduced the serum ACV concentration. The median serum ACV concentration during PE was 5.61 µg/mL (range 2.19–6.25) and this increased up to 19.8 µg/mL after PE termination (day 10, Fig. 1). The required concentration of ACV to inhibit the VZV replication was reported as 5.00 µg/mL in vitro [10]. Therefore, a high dose of ACV (60 mg/kg/day) and maintaining 5.0 µg/mL of ACV trough levels during PE would be required to suppress the VZV replication. The VZV-IgM antibodies were not detected, but IgG antibodies were first detected 5 months after PE termination. This suggests that the effectiveness of VZV-IgG, which would be in fresh frozen plasma, is quite limited for this patient.

Conclusion

This case demonstrated that PE with a high dose of ACV could decrease the DNA copy number of VZV and improve the severe effects of disseminated VZV infection. More data are needed to establish this as a treatment.

Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

Research involving human participants All procedures performed in studies involving human participants were in accordance with the ethical standards of the ethics committee of Jichi Medical University at which the studies were conducted (IRB approval number A19-009) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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