Acute kidney injury and acyclovir-associated encephalopathy after administration of valacyclovir in an elderly person with normal renal function

A case report and literature review

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Abstract

Introduction: Acyclovir (ACV)-associated encephalopathy is related to an increase in plasma levels of 9-carboxymethoxymethylguanine, an ACV metabolite, and is often reported in patients with renal dysfunction. We report a case of ACV-associated encephalopathy with rapid progression of renal dysfunction after oral administration of valacyclovir (VACV) and review literature of previous ACV-associated encephalopathy cases.

Patient concerns: An 88-year-old man was diagnosed with herpes zoster. VACV (3000 mg/day) treatment was initiated. Serum creatinine (Cr) level was 0.80 mg/dL. However, irritability, memory impairment, and decreased responsiveness occurred after 3 days. The Cr level was 6.76 mg/dL on admission.

Diagnosis: He was diagnosed with ACV-associated encephalopathy with acute kidney injury.

Interventions: VACV was discontinued, hemodialysis was initiated on the day of admission, and then the signs and symptoms improved approximately 72 hours after the admission.

Conclusion: Worsening of renal function and encephalopathy should be a focus when using VACV or ACV, regardless of age and original renal function. Acute kidney injury and ACV-associated encephalopathy may particularly occur in the elderly even when renal function is normal. Therefore, regular monitoring of renal function and consciousness is necessary during VACV treatment.

Abbreviations: ACV = acyclovir, VACV = valacyclovir.

Keywords: acute kidney injury, acyclovir neurotoxicity, case report, herpes zoster, valacyclovir

1. Introduction

Acyclovir (ACV) associated encephalopathy is a very rare case induced by ACV and valacyclovir (VACV), a prodrug of ACV.[1] Rashiq et al reported that several neuropsychiatric symptoms, such as consciousness disturbance, tremor, and myoclonus, usually occur within 2 days of administering VACV.[1] Hallucination frequently occurs in addition to consciousness disturbance and involuntary movements.[1–3] However, headache, fever, convulsions, and focal symptoms are rare.[2] Abnormalities in cerebrospinal fluid examinations or head computed tomography (CT)/magnetic resonance imaging are generally not observed, and symptoms disappear 48 to 72 hours after discontinuing ACV. However, dialysis may be necessary.[4]

ACV-associated encephalopathy is related to an increase in plasma levels of 9-carboxymethoxymethylguanine, a metabolite of ACV, and is often reported in patients with renal dysfunction.[5] However, there are few reports of the onset of ACV-associated encephalopathy in patients in whom renal dysfunction was not indicated.[4] Here, we report a case of ACV-associated encephalopathy with the rapid progression of renal dysfunction after oral VACV administration, although serum creatinine (Cr) levels were normal. In addition, we report a review of previous ACV-associated encephalopathy cases.
2. Case report
An 88-year-old man who could independently perform activities of daily living visited the hospital with a primary complaint of consciousness disturbance. The patient had a history of radical resection for prostate cancer (T1c N0 M0, stage I). His history of varicella-zoster infection was unknown. A painful vesicular eruption appeared in the right axilla 8 days before admission, and he visited a nearby clinic the following day. The Cr level was 0.80 mg/dL. He was consequently diagnosed with herpes zoster. Thus, VACV administration (3000 mg/d) was initiated. Pregabalin (75 mg/d) and meclozabalin (1500 μg/d) were also administered for analgesic purposes without the concomitant use of nonsteroidal anti-inflammatory drugs. The patient experienced pain that led to reduced food intake and dehydration. He urinated about 4 times daily. Also, irritability, memory impairment, and decreased responsiveness occurred after 3 days, and the patient was admitted to our hospital for emergency treatment due to exacerbated symptoms.

Physical findings on admission were as follows: E3V3M6 on the Glasgow Coma Scale, body temperature of 35°C, blood pressure of 110/60 mm Hg, pulse rate of 60 beats/min, respiratory rate of 20 breaths/min, and oxygen saturation level of 96% (room air). The patient had xerostomia. Herpes zoster scarring on the right upper limb (TH-1/TH-2 areas) was noted in the extremities. Furthermore, examination of meningeal irritation symptoms showed no neck stiffness, negative Kernig sign, and negative Brudzinski sign. The diameter/light reflex of the pupils was 2+/2+. Myoclonus was observed with no clear paralysis. Hematologic examination results were as follows: white blood cell, 6530/μL; C-reactive protein, 1.07 mg/dL; blood urea nitrogen, 58.4 mg/dL; Cr, 6.76 mg/dL; and blood glucose, 91 mg/dL (Table 1). The urinal sediment showed muddy brown casts of epithelial cells, indicating acute tubular necrosis. Cerebrospinal fluid test results revealed an initial pressure of 13 cm H₂O, cell count of 71/μL, protein level of 147 mg/dL, and glucose level of 48 mg/dL (Table 2). However, blood, urine, and cerebrospinal fluid cultures were negative.

The hemodynamics were maintained, but ultrasounds showed that the inferior vena cava collapsed, suggesting dehydration. Abdominal CT revealed no obstruction, and postrenal renal failure was ruled out. The maximum diameter of the kidney was 62 mm on the right and 65 mm on the left, and there was no prominent renal swelling. However, urinary retention of about 250 mL in the bladder was observed. Moreover, head magnetic resonance imaging did not reveal any findings suggestive of encephalitis.

Table 3 shows the comparison of ACV-associated encephalopathy and varicella zoster virus encephalitis.⁶⁻⁷ Our elderly patient had taken VACV for a sufficient period and was thus suspected to have ACV-associated encephalopathy based on the absence of fever, stiff neck, and headache, and normal imaging findings. The clinical course is shown in Fig. 1. VACV was discontinued, hemodialysis was initiated from the day of admission to day 3, and then the signs and symptoms improved approximately 72 hours after the admission. The Glasgow Coma Scale score was 14 points, and hemodialysis was discontinued on hospital day 4. The plasma concentration of ACV level at the time of examination, which was discovered later, was markedly elevated (34.6 μg/mL), and results of polymerase chain reaction analysis of the cerebrospinal fluid were negative for herpes simplex virus and varicella zoster virus DNA. The plasma concentration of ACV level was <0.5 μg/mL (normal range <2.0) when the consciousness level became normal on day 10 of hospitalization. Negative blood, urine, and cerebrospinal fluid cultures ruled out bacterial consciousness disorder. Furthermore, the consciousness level did not improve immediately after the dialysis on day 1; however, it improved after the dialysis was performed for 3 days. Therefore, the consciousness disorder due to uremia was ruled out. Thus, a definitive diagnosis of ACV-associated encephalopathy was made based on the patient’s course. The increase in cell count in the cerebrospinal fluid could have been due to the effects of ACV-associated encephalopathy, although this finding was atypical.

| Parameter | Recorded value | Standard value |
|-----------|----------------|----------------|
| White blood cell count | 65/μL | 4500–7500/μL |
| Neutrophils | 68% | 42%–74% |
| Hemoglobin | 11.7 g/dL | 11.3–15.2 g/dL |
| Hematocrit | 34.2% | 36%–45% |
| Platelet count | 17.0 x 10^11/μL | 13–35 x 10^11/μL |
| International normalized ratio | 0.93 | 0.80–1.20 |
| Activated partial thromboplastin time | 23.3 s | 26.9–38.1 s |
| Fibrin degradation products | 10.4 μg/mL | 2.0–8.0 μg/mL |
| C-reactive protein | 1.07 mg/dL | <0.14 mg/dL |
| Estimated glomerular filtration rate | 6.6 | |
| Total protein | 6.6 g/dL | 6.9–8.4 g/dL |
| Albumin | 3.5 g/dL | 3.9–5.1 g/dL |
| Total bilirubin | 0.3 mg/dL | 0.2–1.2 mg/dL |
| Aspartate aminotransferase | 25 U/L | 11–30 U/L |
| Alanine aminotransferase | 8 U/L | 4–30 U/L |
| Lactate dehydrogenase | 227 U/L | 109–216 U/L |
| Creatine phosphokinase | 252 U/L | 40–150 U/L |
| Blood urea nitrogen | 58.4 mg/dL | 8–20 mg/dL |
| Creatinine | 6.76 mg/dL | 0.63–1.03 mg/dL |
| Sodium | 130 mEq/L | 136–148 mEq/L |
| Potassium | 6.4 mEq/L | 3.6–5.0 mEq/L |
| Glucose | 91 mg/dL | 70–109 mg/dL |
| Hemoglobin | 3.5 g/dL | 11.3–11.7 g/dL |
| Hematocrit | 34.6 g/dL | 41.5–47.5 g/dL |
| pH | 7.359 | 7.350–7.450 |
| Partial pressure of arterial carbon dioxide | 37.3 mm Hg | 35–45 mm Hg |
| Partial pressure of arterial oxygen | 88.6 mm Hg | 80–100 mm Hg |
| Bicarbonate | 21.6 mEq/L | 22–26 mEq/L |
| Lactate | 1.07 mmol/L | <2.0 mmol/L |

ACV = acyclovir.

| Parameter | Recorded value | Standard value |
|-----------|----------------|----------------|
| Cell count | 70/μL | 0–5/μL |
| Mononuclear count | 70/μL | 0–5/μL |
| Polynuclear count | 1/μL | 0–5/μL |
| Total protein | 147 mg/dL | 10–40 mg/dL |
| Glucose | 46 mg/dL | 50–75 mg/dL |
| Lactate dehydrogenase | 39 IU/L | 0–25 IU/L |
| Creatine phosphokinase | 3 IU/L | <6 IU/L |
| HSV DNA PCR | Negative | |
| VZV DNA PCR | Negative | |

HSV = herpes simplex virus, PCR = polymerase chain reaction, VZV = varicella zoster virus.
Subsequently, ambulatory discharge was possible on hospital day 35 without any sequelae.

2.1. Search strategy

The terms “acyclovir neurotoxicity” or “acyclovir encephalopathy” were searched in the MEDLINE database. Fifty-one cases have existed in the literature since 1988. Among those 51 cases, 35 reported acyclovir neurotoxicity when limited to the English and Japanese literature.

3. Discussion

We report a case of ACV-associated encephalopathy with rapid progression of renal dysfunction after oral VACV administration despite normal serum Cr levels (0.80 mg/dL). The patient experienced pain that led to reduced food intake and dehydration. Moreover, the use of VACV, which has a high oral bioavailability and a long plasma half-life, caused renal dysfunction, leading to ACV-associated encephalopathy. Furthermore, as shown in Table 4, ACV-associated encephalopathy may occur even under normal renal function or prophylactic administration of antiviral drugs. ACV-associated encephalopathy is commonly observed in patients with impaired renal function but may develop even when renal function is normal.[1]

Two mechanisms of ACV-induced acute kidney injury exist. One is renal dysfunction due to dehydration and the use of nonsteroidal anti-inflammatory drugs, as well as tubular obstruction due to ACV itself,[5] and the other is renal dysfunction caused by a direct mechanism of ACV aldehyde.[6] The serum ACV level increases due to dysuria when renal dysfunction occurs, which further exacerbates renal dysfunction and causes ACV-associated encephalopathy.[8] Elderly people are prone to dehydration and potentially impaired renal function. The aforementioned mechanism causes acute renal damage and a tendency for the onset of ACV-associated encephalopathy. Moreover, VACV is a prodrug of ACV and has better gastrointestinal absorption than ACV. Consequently, the oral bioavailability of ACV is 10% to 20% (54.2% for VACV), and its serum half-life is approximately 5 times longer. Hence, VACV is simpler to administer than ACV because the number of doses is smaller and characteristically tends to result in increased serum levels.[1]

In total, 43 cases of ACV-associated encephalopathy have been reported in 35 studies. A summary of the literature review is presented in Table 4. The age range of the patients with ACV-associated encephalopathy was from 0.5 to 88 years (mean age, 55.0 years; median age, 62 years). Among the patients, 24 (55.8%) were aged ≥60 years, and 6 (13.9%) were aged ≥18 years. The sex ratio was almost equal (18 females and 24 males [55.8%]; 1 unknown). ACV-associated encephalopathy occurred following the treatment of herpes zoster in 27 cases (62.7%), treatment of herpetic simplex in nine cases (20.9%), and for the purpose of suppressing the onset of virus associated with chemotherapy in 5 cases (11.6%).

ACV-associated encephalopathy occurred in 24 patients (55.8%) using oral medication only. The administered antiviral agent was ACV in 37 cases (86.0%). The duration of antiviral administration was known in 40 patients, and the time of onset was 1 to 36 days (median, 4 days). Moreover, an NSAID was concomitantly used in only 2 patients (4.7%).

Many patients had an underlying disease, especially 27 dialysis patients (62.7%); 22 undergoing hemodialysis and 5 undergoing peritoneal dialysis. However, 4 patients (9.3%) had no underlying disease, and the presence of the underlying disease was unknown in 4 patients (9.3%).
| Case | Author | Reference number | Age | Sex | Cause | Medication (dosing period, days) | Total dosing period (days) | Dosage (mg/day) | Comorbidity | Serum acyclovir measurement | Dialysis treatment for underlying disease | Normal Creatinine (mg/dL) | Onset Creatinine (mg/dL) | Concomitant drug |
|------|--------|-------------------|-----|-----|-------|-------------------------------|--------------------------|----------------|-------------|----------------------------|-------------------------|------------------|------------------|----------------|
| 1    | Umoru GO et al | 9 | 57 | Man | Herpes Zoster | Oral ACV (4) | 4 | 4000 mg/d | hemodialysis, type 2 diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, congestive heart failure, shingles, and multiple incision and drainage procedures for bilateral recurrent abscesses in his thighs | Yes | HD | Unknown | Unknown | Unknown |
| 2    | Kawabe Matsukawa M et al | 10 | 77 | Man | Herpes Zoster | Oral ACV (2) | 2 | 800 mg/d | Angina after stenting, Hyperuricemia, Dyslipidemia, hypertension | No | CAPD | 9–10 | 12.58 | Unknown |
| 3    | Belz A et al | 11 | 86 | Unknown | Herpetic simplex keratitis | Oral VACV (4) | 4 | 800 mg/d | chronic heart failure Class II NYHA (ejection fraction 40%), moderate mixed aortic valve disease, mild mitral and tricuspid insufficiency, paroxysmal atrial fibrillation, and type 2 diabetes mellitus | No | HD | Unknown | 8.48 | Unknown |
| 4    | Ikuta K et al | 12 | 27 | Man | Herpes simplex virus–1 | intravenous ACV (6)→intravenous ACV (12) | 18 | 30 mg/kg/d (6 days)→15 mg/kg/d | Hepatitis A infection, Hepatitis B infection | Yes | None | 1.4 | None | None |
| 5    | Patel J et al | 13 | 63 | Man | Herpes Zoster | Oral ACV (5)→intravenous ACV(2)→oral ACV(1) | 5 | 4000 mg/d | Abscesses in his thighs | No | None | 1 | None | 1.2 | Unknown |
| 6    | Sadjadi SA et al | 14 | 80 | Man | Herpes Zoster | Oral ACV (5) | 5 | 5 mg/kg/d→200 mg/d | Hypertension, congestive heart failure and end stage renal disease | Yes | CAPD | None | 9.73 | Unknown |
| 7    | Goritsky BR et al | 15 | 60 | Man | Herpes simplex virus–2 | Oral VACV (4) | 4 | 800 mg/d | hypertensive nephrosclerosis and diabetes | Yes | None | HD | None | 9.73 | Unknown |
| 8    | Watson WA et al | 16 | 62 | Man | Herpes Zoster | Oral VACV (14)→intravenous ACV (2)→intravenous ACV (6) | 16 | 3000 mg/d | Goodpasture syndrome complicated by end-stage renal disease requiring a living donor kidney transplant 11 years prior to presentation, chronic allograft glomerulopathy, and a recent diagnosis of collagenous colitis. | No | None | None | 1.2 | 2.5 |
| 9    | Thind GS et al | 17 | 82 | Man | Herpes Zoster | Oral VACV (5)→intravenous ACV (6) | 11 | 3000 mg/d→5 mg/kg | type 2 diabetes mellitus, a history of coronary artery disease, chronic atrial fibrillation, gastro-esophageal reflux disease and gout | No | HD | None | None | None |
| 10   | Chowdhury MA et al | 18 | 69 | Woman | Herpes simplex virus | Intravenous ACV (1.5) | 1.5 | 1500 mg/d | hypertension, diabetes, chronic obstructive pulmonary disease, and end-stage renal disease on hemodialysis was admitted with a diagnosis of pneumonia and right breast cellulitis | Yes | HD | None | None | None |

(continued)
| Case | Author | Reference number | Age | Sex | Cause | Medication (dosing period, days) | Total dosing period (days) | Dosage (mg/day) | Comorbidity | Serum acyclovir measurement | Dialysis treatment for underlying disease | Normal Creatinine (mg/dL) | Onset Creatinine (mg/dL) | Concomitant drug |
|------|--------|------------------|-----|-----|-------|---------------------------------|--------------------------|----------------|-------------|-----------------------------|-------------------------------|------------------|------------------|---------------------|
| 11   | Sacchetti D et al | [4] | 69   | Woman | Herpes zoster | Oral ACV (2) → intravenous ACV (1) → intravenous ACV (2) | 5 | 1500 mg/d → 550 mg/d | uncontrolled diabetes and asthma | No | None | Unknown | 3.94 | NSADs |
| 12   | Adair JC et al | [3] | 70   | Woman | Herpes zoster | Oral ACV (2) | 2 | 1400 mg/d | Granulomatosis with polyangiitis | Yes | HD | Unknown | 8.8 | Unknown |
| 13   | Adair JC et al | [3] | 64   | Woman | Herpes simplex virus | Oral ACV (2) | 2 | 600 mg/d | Hemolytic uremic syndrome | No | None | Unknown | 0.3 | Unknown |
| 14   | Tomori K et al | [18] | 30   | Woman | Herpes simplex virus | Intraocular ACV (2) | 2 | 1000 mg/d | None | No | None | Unknown | None | Unknown |
| 15   | Itoh M et al | [19] | 7    | Woman | Herpes zoster | Oral ACV (2) | 2 | 1000 mg/d | None | No | None | Unknown | 0.8 | Unknown |
| 16   | Gómez Campderá FJ et al | [20] | 59  | Woman | Herpes zoster | Oral ACV (7) | 7 | 300 mg/d | Secondary to chronic interstitial nephropathy, hypertension, diabetic nephropathy | Yes | HD | Unknown | Unknown | None |
| 17   | Hoskote SS et al | [21] | 52  | Man | Herpes zoster | Oral VACV (7) → oral ACV (2) | 2 | 1000 mg/d | End-stage renal disease on hemodialysis 3 times a week, hemorrhagic stroke | No | HD | Unknown | Unknown | None |
| 18   | Sagawa N et al | [22] | 83  | Man | Herpes zoster | Oral ACV (5) | 5 | 1250 mg/d | Type 2 diabetes mellitus | Yes | None | 0.8 | 5.11 | NSADs |
| 19   | Strong DK et al | [23] | 5    | Woman | Epstein-Barr virus-induced lymphoproliferative disease | Intravenous ACV (2) → intravenous ACV (12) | 14 | 460 mg/m²/d | End-stage renal failure due to cystinosis | No | None | Unknown | Unknown | None |
| 20   | Blohm ME et al | [24] | 12  | Woman | Prevention | Intravenous ACV (8) → intravenous ACV (18) | 26 | 30 mg/kg → 20 mg/kg | CML | Yes | None | 0.8 | 1.7 | Unknown |
| 21   | Peces R et al | [25] | 44  | Man | Herpes zoster | Oral ACV (2) | 2 | 4800 mg/d | Unknown | No | HD | Unknown | Unknown | None |
| 22   | Mesar I et al | [26] | 78  | Man | Herpes zoster | Oral ACV (2) | 2 | 4000 mg/d | Unknown | No | HD | Unknown | Unknown | None |
| 23   | Mesar I et al | [26] | 61  | Man | Herpes zoster | ACV (Unknown) | Unknown | Uncontrolled diabetes and asthma | No | HD | Unknown | Unknown | None |
| 24   | Mesar I et al | [26] | 72  | Man | Herpes zoster | Oral VACV (4) | 3 | 1600 mg/d | Nuclear amyloidosis, arterial hypertension, hypothyroidism | No | HD | Unknown | Unknown | None |
| 25   | Asahi T et al | [2] | 78  | Woman | Herpes zoster | Oral VACV (5) | 5 | 3000 mg/d | Alzheimer’s disease | No | None | Unknown | 3.2 | Unknown |
| 26   | Asahi T et al | [2] | 73  | Man | Herpes zoster | Oral ACV (2) | 2 | 3000 mg/d | Chronic renal failure | No | HD | Unknown | Unknown | None |
| 27   | Hussein MM et al | [27] | 51  | Man | Anti-GMV prophylaxis | Oral GCV (5) | 5 | 1.25 mg/d every 48 h | End-stage renal disease of uncertain etiology, diabetes mellitus | No | HD | Unknown | 10.45 | Unknown |
| 28   | Yang HH et al | [28] | 70  | Man | Herpes zoster | Intravenous ACV (1.5) | 1.5 | 500 mg/d | Rectal cancer status post-colectomy and end-stage renal disease | Yes | HD | 5.7 | 6.2 | Unknown |
| 29   | Chevret L et al | [29] | 0.5 | Woman | Prevention | Intravenous ACV (2) → intravenous ACV (1) | 3 | 750 mg/m² | Acute liver failure, related to neonatal enterovirus infection, occurred within a few days after birth, liver transplantation at 6 months of age | Yes | None | Unknown | Unknown | None |
| 30   | Peyrâne H et al | [30] | 13  | Man | Prevention | Intravenous GCV (14) + VSCG (Unknown) → oral ACV (2) → oral VSCG (Unknown) | 16 | 450 mg/d | Acute lymphoblastic leukemia | Yes | None | Unknown | Unknown | None |

(continued)
| Case | Author                  | Reference number | Age | Sex | Cause                      | Medication (dosing period, days) | Total dosing period (days) | Dosage (mg/day) | Comorbidity                                                                 |
|------|------------------------|------------------|-----|-----|---------------------------|---------------------------------|---------------------------|-----------------|-----------------------------------------------------------------------------|
| 31   | Rajan GR et al         | [31]             | 73  | Man | Herpes simplex labialis   | Intravenous ACV (2)             | 2                          | 400 mg/d        | amiodarone pulmonary toxicity, coronary artery bypass grafting, chronic atrial fibrillation, non-sustained ventricular tachycardia, and congestive heart failure due to long-standing renal failure and poor blood pressure control |
| 32   | Beales P et al         | [32]             | 51  | Man | Herpes zoster              | Oral ACV (1.5)                  | 1.5                        | 1600 mg/d       | end-stage renal failure due to IgA nephropathy, poor blood pressure control |
| 33   | Beales P et al         | [32]             | 56  | Woman | Herpes zoster            | Oral ACV (9)                  | 9                          | 1600 mg         | end-stage renal failure of uncertain cause, tuberculosis, lumbar osteomyelitis, and recurrent continuous ambulatory peritoneal dialysis peritonitis |
| 34   | Krieble BF et al       | [33]             | 77  | Woman | Herpes zoster              | Intravenous ACV (2)            | 2                          | 3000 mg/d       | None end-stage renal failure due to chronic pyelonephritis |
| 35   | Davenport A et al      | [34]             | 72  | Woman | Herpes zoster              | Oral ACV (1)→ intravenous ACV (1)→ oral ACV (1) | 1                          | 800 mg/d→4 mg/kg/d→4 mg/kg/d+800 mg/d | None end-stage renal failure secondary to focal glomerular sclerosis |
| 36   | Davenport A et al      | [34]             | 41  | Man | Viral pneumonia           | Oral ACV (5)                  | 5                          | 1600 mg/d       | end-stage renal failure secondary to focal glomerular sclerosis |
| 37   | MacDiarmaid-Gordon AR et al | [35]         | 62  | Man | Herpes zoster              | Oral ACV (Unknown)             | Unknown                    | 2000 mg/d       | None end-stage renal failure secondary to focal glomerular sclerosis |
| 38   | MacDiarmaid-Gordon AR et al | [35]         | 47  | Man | Herpes zoster              | Oral ACV (5)                  | 3                          | 4000 mg/d       | None end-stage renal failure secondary to focal glomerular sclerosis |
| 39   | MacDiarmaid-Gordon AR et al | [35]         | 30  | Man | Herpes zoster              | Oral ACV (3)→oral ACV (5)      | 8                          | 2000 mg/d→1000 mg/d | Granulomatosis with polyangiitis |
| 40   | MacDiarmaid-Gordon AR et al | [35]         | 56  | Man | Herpes zoster              | Oral ACV (9.2)                | 9                          | 2000 mg/d       | None end-stage renal failure secondary to focal glomerular sclerosis |
| 41   | Swan SK et al          | [36]             | 76  | Woman | Herpes zoster              | Oral ACV (4)                  | 4                          | 1000 mg/d       | Unknown metastatic ovarian germ cell tumor |
| 42   | Feldman S et al        | [37]             | 17  | Woman | Herpes simplex virus      | Intravenous ACV (2)            | 2                          | 4000 mg/d       | Unknown metastatic ovarian germ cell tumor |
| 43   | Sugimoto K et al       | [38]             | 70  | Man | Prevention                | Oral VACV (36)                | 36                         | 500 mg three times a wk | multiple myeloma |

ACV = acyclovir, VACV = valacyclovir, GCV = ganciclovir, VGCV = valganciclovir, HD = hemodialysis, CAPD = continuous ambulatory peritoneal dialysis.
Serum ACV concentration was measured in 21 of 43 cases (48.8%). The serum concentration of 9-carboxymethoxymethylguanine was measured in only 1 case (case 28). VACV is a produg of ACV, which becomes ACV in the blood; thus, there were no cases with VACV concentration measurement.

For many patients, the precritical serum Cr levels were unknown, and in 2 patients (4.7%), the levels were <1.0 mg/dL. Moreover, serum Cr levels at the time of onset were often unknown. The serum Cr level at the time of onset, when known, was elevated except in 1 patient, a 7-year-old child (0.3 mg/dL).

In conclusion, based on our case findings, it is important to focus on the worsening of renal function and encephalopathy when using VACV or ACV regardless of age and original renal function. Acute kidney injury and ACV-associated encephalopathy may particularly occur in the elderly even when renal function is normal. Therefore, regular monitoring of renal function and consciousness is necessary.

Author contributions
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