Acute kidney injury and neurological toxicity caused by intravenous acyclovir

İntravenöz asiklovirin neden olduğu akut böbrek hasarı ve nörolojik toksisite

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Abstract

Acyclovir is an effective antiviral agent in herpes simplex and varicella-zoster infections treatments. However, it may cause serious side effects. This case study reports a patient who developed both acute tubular necrosis and neurotoxicity induced by intravenous acyclovir and recovered promptly after hemodialysis. Caution is needed in monitoring patients receiving acyclovir. Eliminating acyclovir with early diagnosis and immediate daily hemodialysis is necessary for successful treatment.

Keywords: acyclovir; acute kidney injury; hemodialysis; neurotoxicity

Öz

Asiklovir, herpes simplex ve varicella-zoster enfeksiyonlarının tedavisinde etkili bir antiviral ajandır. Ancak ciddi yan etkilere neden olabilir. Bu makelede intravenöz asiklovir ile indüklenen, hem akut tübüler nekroz hem de nörotoksisite gelişen ve hemodiyaliz sonrasında klinik tablonun hızla düzeldiği bir hastayı sunuyoruz. Asiklovir ile tedavi edilen hastaların izlenmesinde dikkatli olunmalıdır. Bu hastaların başarılı tedavisi için erken tanı konulmalı ve asiklovirin elimine edilmesi için hızlıca hemodiyaliz uygulanmalıdır.

Anahtar Sözcükler: asiklovir; akut böbrek hasarı; hemodiyaliz; nörotoksisite

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INTRODUCTION

Acyclovir is a widely used antiviral agent for herpes simplex and varicella-zoster infections treatments. Acute renal injury is the well-known toxicity caused by acyclovir. Adverse reactions accompanying acyclovir usage; nausea, vomiting, diarrhea, increased level of serum transaminases, thrombocytopenia, pruritus, and injection site phlebitis might appear. However, in some rare cases, signs of neurological toxicities such as tremors, visual hallucinations, ataxia, and coma, might develop. This case study aims to report a patient who had received intravenous acyclovir treatment and developed acute renal injury and neurotoxicity after three days.

CASE

A 49-year-old man was under regular follow-up by the rheumatology outpatient clinic with a history of complex diagnosis of limited scleroderma, Sjogren syndrome, and silicosis for 13 years. He had been working as a sandblaster for 25 years when he started complaining about dyspnea on exertion in 2008, 13 years ago. Radiological findings were consistent with pleural thickenings and calcified millimetric nodular infiltrations. Consequently, he had been diagnosed first with silicosis In the same year, he had been diagnosed with Sjögren syndrome because of arthralgias in wrists and knees bilaterally; xerophthalmia, and xerostomia along with high ANA titers and a mottled pattern, and positive minor salivary gland biopsy. Six years later, in 2014, he developed severe arthralgias with morning stiffness, photosensitivity, Raynaud's phenomenon, gastroesophageal reflux, and interstitial lung disease. Laboratory parameters including anti-DNA, anti-Ro, anti-Sm, anti-U1-RNP, and anti-Scl-70 had been all found positive, and compatible with a diagnosis of systemic sclerosis. He had been treated with methotrexate, prednisolone, nifedipine, and hydroxychloroquine for 7 years Due to the severe joint and lung involvement, rituximab had been added to his treatment regimen every 6 months for 4 years.

The patient was admitted to our rheumatology outpatient clinic with blurred vision and painful vesicular herpetic lesions around his right eye and right frontal side The patient was diagnosed with herpes zoster ophthalmicus. His treatment started with intravenous (IV) acyclovir 750 mg three times a day, topical treatment consisting of loteprednol ophthalmic suspension, and ganciclovir ophthalmic gel with artificial tears.

He was hospitalized for the proper management of parenteral therapy. On initial examination, the blood pressure was 120/70 mmHg, pulse rate was 75/min, temperature was 36.6 C. The initial findings of neurological examination during the admission were insignificant. In addition, physical examination revealed redness and watering in the right eye as well as painful vesicles on the right eyelid, in the middle of both eyebrows, and on the right forehead.

Laboratory results on admission were as follows; sodium 129 mmol/L, potassium 4.8 mmol/L, urea 30 mg/dL, serum creatinine 1.18 mg/dL, C-reactive protein (CRP) 5.68 mg/L, hemoglobin 15.7g/dL, white cell count (WCC) 10900 per litre, platelets 313000 per litre, aspartate aminotransferase 23 IU/L, alanine aminotransferase 12 IU/L, lactate dehydrogenase (LDH) 219 IU/L (Table1). Seventy-two hours after starting acyclovir, the patient's speech slowed and became unintelligible. He was prescribed no other neurotoxic drug that would cause these findings except acyclovir. Cranial CT, diffusion-weighted MR imaging of the brain, and cranial MRI were negative for any vascular pathology or meningoencephalitis. While evaluating the etiology of his neurological symptoms, it was determined that the patient had a sudden decrease in urine output. His serum BUN and creatinine levels acutely increased to 58 mg/dL and 3.89 mg/dL respectively. Anamnesis, physical examination, and laboratory tests were performed for the etiology of acute kidney injury (AKI). Urinary system ultrasonography, which was done to rule out post-renal causes of AKI, was found to be within the normal limits. The next morning, the BUN level was 66 mg/dL, and the creatinine level was 5.90 mg/dL. Urinary output was measured as 100 cc for 12 hours. Complete blood count showed mild thrombocytopenia (116.000 per liter) and mild anemia (hemoglobin level was 12.8 g/dL). The LDH level elevated to 403 IU/L. There was no history of prerenal factors such as decreased oral fluid intake, diarrhea, and diuretic use. No postrenal pathology was observed in renal ultrasonography. Of the serological tests that were requested for glomerulonephritis from renal patholo-

Table1. Laboratory parameters during the hospitalization of the patient

	On Admission	When toxicity develops	After the first session of hemodialysis	At discharge
WBC (per/μL)	10.900	12.000	18.700	8.400
Hgb (g/dL)	15.7	12.8	13.7	11.7
Plt (per/μL)	313.000	157.500	172.600	435.300
Urea (mg/dL)	31	58	58	18
Serum Creatinine (mg/dL)	1.03	3.89	5.47	1.13
Sodium (mmol/L)	139	132	137	142
Potassium (mmol/L)	4.8	5.2	5.6	4.3
CRP (mg/L)	5.68	101.02	202.82	17.86
AST (IU/L)	23	63	55	28
ALT (IU/L)	12.3	27.3	26.8	38.4
LDH (IU/L)	219	380	488	238

WBC: Leukocyte, Hgb: Hemoglobin, Plt: Thrombocyte, CRP: C reactive protein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase

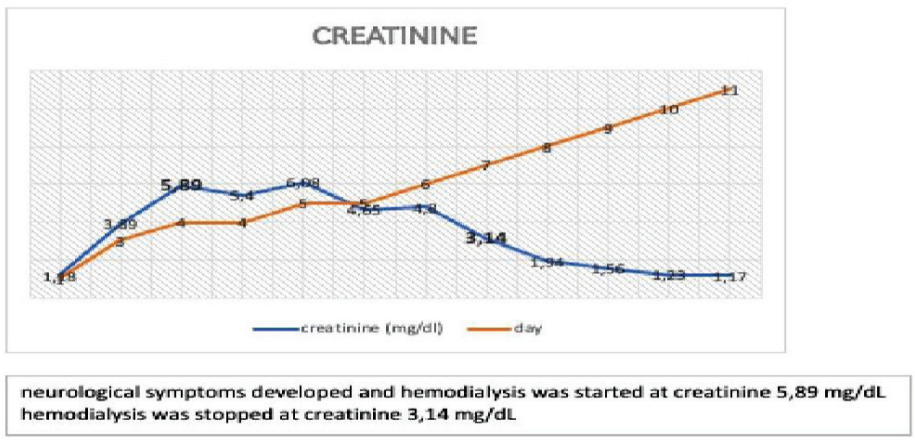

Figure 1: Change of serum creatinine levels in day

gies, the test for ANA was positive at a titer of 1:1280 with a mottled pattern, and anti-dsDNA, MPO-ANCA, and PR-3 ANCA tests were negative. Serum C3 and C4 levels were normal. A kidney biopsy was performed to exclude interstitial nephritis and glomerulonephritis. Kidney biopsy showed signs of acute tubular injury characterized by multifocal hydropic swelling in the proximal tubules and loss of brush border. Peripheral blood smear examination was consistent with thrombocytopenia, and there were no schistocytes in the smear. The patient's blood pressure was normal during all this time. ADAMTS13 level was found to be normal. Consequently, we ruled out scleroderma renal crisis and thrombotic microangiopathy. The clinical situation was consistent with acyclovir-induced AKI and neurotoxicity. Acyclovir therapy was stopped immediately and hemodialysis was started. After one session of hemodialysis, most of the neurologic symptoms improved. Hemodialysis was continued for three consecutive days. On the eighth day of the neurologic symptoms and AKI, the ataxia and slowed speech disappeared, and his serum creatinine level decreased to 1,17 mg/dL. The patient was discharged on the 13th day of admission with improved clinical status and serum creatinine level of 1,03 mg/dL (Figure 1). Additionally, during his hospitalization, his symptoms of painful vesicular eruptions, redness, and watery eyes due to shingles improved.

Report ethics

Written informed consent was obtained from the patients for the publication of this case report and the accompanying images.

DISCUSSION AND CONCLUSION

Acyclovir is an effective antiviral agent in the treatment of herpes simplex and varicella-zoster infections. However, it may cause serious side effects (1). This case study presents a mixed connective tissue disease patient with a previously normal renal function, which was successfully treated with prompt hemodialysis after having developed AKI and neurotoxicity due to IV acyclovir treatment.

Acyclovir is filtered from the renal glomeruli and secreted by the renal tubules (2). Being unable to be dissolved in the urine, it is dialyzable. A continuous 6 hours session of hemodialysis can eliminate approximately 60% concentration of plasma acyclovir (3). IV administration is required to reach high doses in the blood, which explains the frequent occurrence of crystal nephropathy in patients receiving this drug intravenously (2). Intratubular crystal deposition causes occlusion of the nephron, resulting in elevated serum creatinine with increased resistance to renal blood flow. Therefore, daily monitoring of renal function is important. It is useful to give IV fluids and administer acyclovir as an infusion to reduce the risk of AKI (4, 5). It is also necessary to pay attention to neurotoxicity during acyclovir treatment. In the cases of acyclovir neurotoxicity, symptoms such as clouding of consciousness, hallucinations, tremor, agitation, and ataxia may be observed (6, 7). Neurologic symptoms appear as a result of decreased excretion of acyclovir and accumulation of acyclovir and its metabolites. Although the toxic dose for the cerebrospinal fluid (CSF) is not known, the acyclovir level in the CSF is thought to be more important than the serum acyclovir level. In addition, studies show that neurological symptoms are associated with the acyclovir metabolite 9-carboxymethoxymethylguanine (CMMG) (8, 9). It has been shown that with hemodialysis for 3 consecutive days, neurotoxicity findings are completely resolved, serum acyclovir level has reached the therapeutic range, and CMMG level has been detected at an undetectable level (10).

Neurotoxicity is a less common side effect of acyclovir. Neurological symptoms were generally observed when high-dose acyclovir was given or when acyclovir was given to patients with renal insufficiency without dose adjustment. Although neurological toxicity is mostly observed in dialysis patients, it can also be seen in patients without known kidney disease (9, 11). Neurotoxicity findings with or without AKI developing during acyclovir treatment should suggest acyclovir toxicity. Herpes encephalitis should be excluded as the cause of the neurological symptoms. Especially the improvement of neurotoxicity findings with the hemodialysis supports acyclovir neurotoxicity (12). In our patient, neurological symptoms developed approximately 72 hours after the initiation of intravenous acyclovir. There was no evidence of herpes encephalitis on cranial imaging and CSF could not be performed because the patient refused. Simultaneously, the serum creatinine level increased from 1.18 mg/dL to 5.16 mg/dL, suggesting both neurotoxicity and nephrotoxicity secondary to acyclovir. After immediate discontinuation of acyclovir and initiation of hemodialysis, neurological symptoms resolved and renal function improved, supporting the diagnosis of acyclovir-related neuro- and nephrotoxicity. A renal biopsy performed three days after confirmed our initial diagnosis.

Patients treated with intravenous acyclovir should be carefully monitored for acyclovir-related neurotoxicity and nephrotoxicity. If these findings develop, hemodialysis should be started without delay (2, 10-15).

Conflict-of-interest and financial disclosure

The authors declare that they have no conflict of interest to disclose. The authors also declare that they did not receive any financial support for the study.

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