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ACYCLOVIR-INDUCED GLOMERULONEPHRITIS IN A 40-YEAR-OLD WOMAN WITHOUT MEDICAL HISTORY: A CASE REPORT

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ABSTRACT

Well-known side effects of acyclovir are nephrotoxicity and neurotoxicity. We present a 49-year-old woman without pre-existing renal failure, with an acute kidney injury and encephalopathy. Since there was a clear correlation with the intake of acyclovir and the course of illness, findings were attributed to the antiviral agent. Urinalysis showed a proteinuria in nephrotic ranges, which is not described in the currently known causes of acyclovir-induced renal failure. We postulate the hypothesis of a nephritis with podocyte damage induced by acyclovir or, more likely, by an acyclovir metabolite.

KEYWORDS

Acyclovir, encephalopathy, acute kidney disease

LEARNING POINTS

- Presentation of a case of acute kidney injury, with haematuria and proteinuria in nephrotic ranges, after acyclovir administration. These findings suggest glomerular involvement; we postulate a hypothesis of a nephritis with podocyte damage.
- Observation of associated mild encephalopathy in a patient without pre-existing kidney failure.
- Toxic mechanism of glomerular damage and combined encephalopathy. This should be further investigated.

INTRODUCTION

Acyclovir is widely used as an antiviral agent against herpes simplex and varicella. A well-known side effect of acyclovir is nephrotoxicity. The most common manifestation of acyclovir-induced kidney failure is an obstructive nephropathy caused by the intratubular precipitation of crystals and characterised by haematuria, pyuria and crystalluria. Unless the patient has an underlying renal disease, nephrotic proteinuria ranges are not mentioned in literature[1,2]. Other renal side effects of acyclovir are acute tubular toxicity and interstitial nephritis[3]. Additionally, acyclovir can induce encephalopathy. The neurotoxicity is caused by the accumulation of a toxic metabolite of acyclovir, 9-carboxymethoxymethylguanine (CMMG), which occurs

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mostly in patients with pre-existing renal dysfunction[4]. In the following case report, we present a case of acyclovir-induced acute kidney failure and mild encephalopathy in a young and healthy woman without pre-existing renal failure.

CASE REPORT

A 49-year-old woman – without a medical history – presented at the emergency department twelve hours after intake of acyclovir, which was started for an extended herpes labialis. She mentioned general malaise, nausea and vomiting, a frontal headache and mild photophobia. Vital parameters were stable. Neurological examination was normal, with absence of neck stiffness. No fever was measured. Blood results showed a normal kidney function, creatinine 0.38 mg/dl (reference range 0.51–0.95 mg/dl) and eGFR >90 ml/min/1.73m^2 (reference range >90 ml/min/1.73m^2), slightly disturbed liver tests and no inflammation. Brain computer tomography (without contrast) did not detect anomalies. A tentative diagnosis of herpes encephalitis was withheld, and acyclovir was administered intravenously in a higher dose (10 mg/kg/8h). Supportive therapy of intravenous fluid sodium chloride 0.9%, paracetamol 1 g and alizapride 50 mg was started.

Despite the therapy described above, the general condition of the patient was worsening as she vomited repeatedly and continued to suffer from photophobia. Biochemically acute kidney failure was first detected 24 hours after the first intake of acyclovir with creatinine 1.25 mg/dl and eGFR 50 ml/min/1.73m^2 – RIFLE stadium failure. A urine sample showed non-dysmorphic haematuria (RBC 204 µg/l), pyuria (WBC 50 µg/l) and proteinuria in nephrotic range (protein/creatinine ratio 6.68 g/g creatinine) with no metabolic repercussions. No peripheral oedema or hypoalbuminemia (albumin 36 g/l) was observed, and urine output was preserved. An abdominal ultrasound was executed, on which kidneys appeared globular enlarged and postrenal dysfunction was ruled out. We withheld negative titres of anti-nuclear factor and anti-glomerular membrane antibodies. Complement factors (CH50, C3 and C4) were normal. There was no evidence for hantavirus, Puumala virus, leptospira or HIV.

Contrary to tentative diagnosis, a lymphocytic choriomeningitis PCR on a lumbar puncture was negative, which excluded herpes encephalitis and acyclovir therapy was stopped. After interruption of acyclovir, a spectacular amelioration of the kidney function and the general condition of the patient was observed, supporting the hypothesis of an acyclovir-induced kidney failure with encephalopathy. Eighty-four hours after stopping acyclovir therapy, kidney function was recovered – creatinine 0.76 mg/dl, eGFR >90 ml/min/1.73m^2 with an absence of proteinuria – and the patient was asymptomatic *(Fig. 1)*.

DISCUSSION

We present a case of a young and healthy woman with an acute kidney injury and mild encephalopathy. As reported,

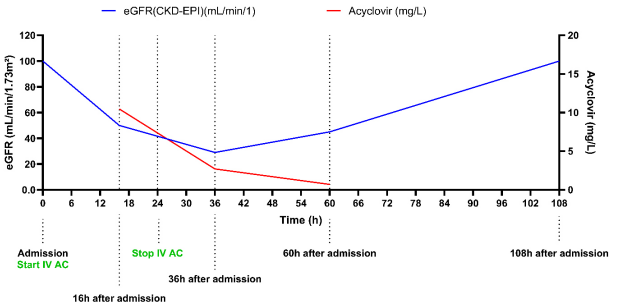

Figure 1. Evolution of kidney function eGFR (ml/min/1.73m2) and acyclovir as a function of time

there was a clear correlation between acyclovir and the course of illness. Clinical symptoms and acute kidney injury started within 24 hours after administration of oral acyclovir. These symptoms were aggravated progressively after administration of a high dose acyclovir intravenously and recovered after interruption of the antiviral agent therapy without the administration of corticosteroids. Additionally, as other possible causes of acute kidney injury – such as auto-immune diseases, ANCA/anti-glomerular basement membrane glomerulonephritis and infectious diseases – were excluded, symptoms were attributed to the use of acyclovir. However, acyclovir blood levels did not exceed normal ranges.

The most common presentations of acyclovir-induced kidney failure are crystal nephropathy and acute tubular necrosis[1,2]. However, urinalysis did not resemble either obstructive nephropathy or acute tubular necrosis as we observed proteinuria in the nephrotic range and haematuria. These findings suggest glomerular damage by inflammation as a primary pathogenic mechanism caused by acyclovir, which is not yet described in literature. Based on the Naranjo Adverse Drug Reaction Probability scale we calculated a score of 6, which suggests the hypotheses is probable.

Further hypotheses are postulated:

1) A direct toxic effect of acyclovir or an acyclovir metabolite on the podocytes: it is possible that the aldehyde metabolite of acyclovir is formed in glomerular cells, causing a similar toxic effect to that described in acute tubular necrosis[5]. Another possibility is that the CMMG metabolite, known for its neurotoxicity, is formed in the glomerulus causing damage to the podocytes[4].
2) Given that neurotoxicity occurred before nephrotoxicity, it can be argued that toxic metabolites of acyclovir, e.g. CMMG, were already in the systemic circulation before damaging the podocytes. As such, these could have precipitated in the glomerulus. However, no biopsy was executed to substantiate the exact pathophysiological mechanism.

Lastly, our patient suffered from headaches, aggravated by the administration of a higher dose of acyclovir. This was interpretated as mild encephalopathy. We report encephalopathy as well as nephropathy occurring simultaneously in a patient without pre-existing kidney failure, which is rarely described in literature. According to

the literature, a rationale of neurotoxicity is the accumulation of an acyclovir metabolite (CMMG) mostly due to a pre-existing kidney injury[4].

Although the clinical image cannot be fully explained, due to the unique nature of this case it was deemed important to share it. Further research of the causative mechanisms of acyclovir-induced nephrotoxicity and neurotoxicity – and the link between the two entities – is needed.

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