Acute confusion in a 55-year-old man with end-stage renal disease

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A 55-year-old man with end-stage renal disease secondary to diabetes presented to hospital with a 1-day history of confusion and word-finding difficulties. His medical history included diabetic nephropathy, anemia secondary to renal disease, gout, dyslipidemia, hypertension (baseline blood pressure 150/90 mm Hg) and depression. His regular medications were perindopril, amlodipine, lanthanum carbonate, allopurinol, linagliptin, rosuvastatin, citalopram, insulin and erythropoietin. He had been receiving continuous cycling peritoneal dialysis for 7 months, with no recent changes.

Three weeks earlier, the patient had developed an erythematous and clustered, painless rash on his back and scalp, which was not in a dermatomal distribution. Three days before his hospital visit, his family physician had prescribed oral valacyclovir 1 g three times daily for presumed zoster infection. He had taken 4 doses of valacyclovir by the time he presented to hospital.

We confirmed that the patient had no history of previous cognitive impairment, and he had not recently travelled. On examination, he was afebrile, blood pressure was 189/77 mm Hg and heart rate was 100 beats/min. In addition to the word-finding difficulties, he was confused, agitated and disoriented, and had intermittent multifocal myoclonic movements and asterixis. We noted no nuchal rigidity and no focal neurologic deficits. The patient had small, erythematous, nonvesicular papules with crusting and hemorrhagic centres on his scalp, right arm and left back (Figure 1). Results of his laboratory investigations on presentation are summarized in Table 1. Troponin was elevated at 208 ng/L, consistent with end-stage renal disease in the absence of cardiac symptoms. A brain computed tomography (CT) scan showed no evidence of acute infarction or proximal intracranial arterial branch occlusion. He was admitted to the in-patient nephrology ward for further monitoring and investigations. We continued to observe elevated blood pressure readings (154/93 and 168/75 mm Hg).

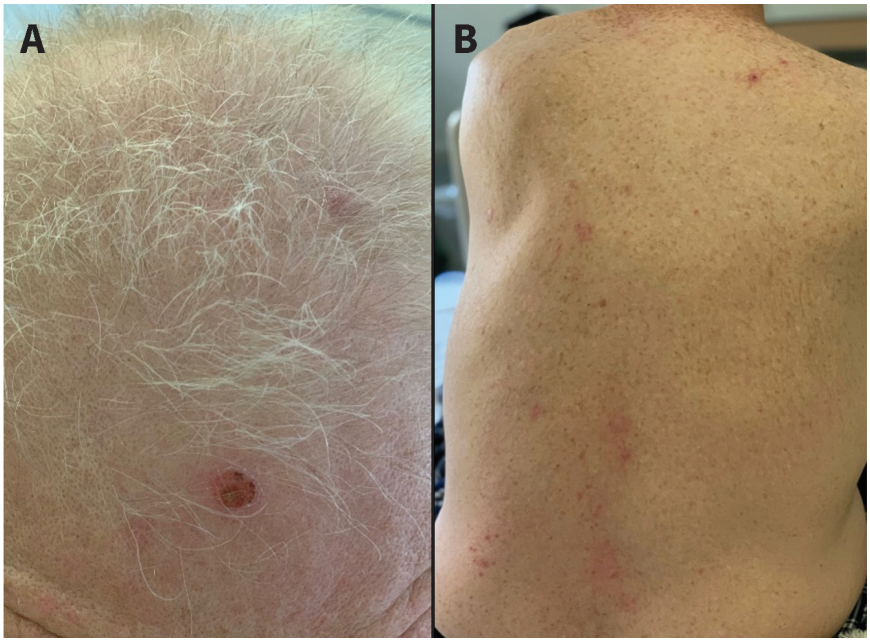

Figure 1: Erythematous, nonvesicular papules with crusting and hemorrhagic centres on (A) the scalp and (B) the back of a 55-year-old man, with no dermatomal distribution.

What is the most likely diagnosis?

a. Uremic encephalopathy
b. Drug-induced aseptic meningitis
c. Valacyclovir neurotoxicity
d. Viral encephalitis
e. Hypertensive encephalopathy

Our primary consideration was valacyclovir neurotoxicity (c). This entity has been well described in patients with underlying end-stage renal disease, particularly when dose adjustment is not performed. In patients receiving peritoneal dialysis, the recommended dosage of valacyclovir is 500 mg every 24 hours.[1,2] The timing of our patient's symptoms aligned with the recent initiation of valacyclovir at 6 times the recommended dose.[3] Our second consideration was viral encephalitis (d), given the combination of rash and altered mental status. The absence of fever and the characteristics of the rash, however, argued against this

Table 1: Laboratory investigations on presentation to hospital and at baseline (1 mo before presentation)

Investigation	At presentation	At baseline	Reference range
Leukocyte count, × 10^9/L	7.9	7.3	4.0–11.0
Hemoglobin, g/L	103	102	130–180
Platelets, × 10^9/L	207	300	150–400
Urea, mmol/L	21.9	17.9	3.0–7.0
Creatinine, µmol/L	947	1040	44–106
Sodium, mmol/L	126	133	135–145
Potassium, mmol/L	4.7	4.6	3.5–5.0
Chloride, mmol/L	89	95	95–107
CO_2, mmol/L	21	22	22–30
Troponin, ng/L	208	NA	< 15
Phosphate, mmol/L	2.19	2.18	0.87–1.52
Calcium, mmol/L	2.29	2.41	2.20–2.60
Magnesium, mmol/L	1.15	1.21	0.70–1.05
ALT, U/L	44	28	< 40
ALP, U/L	173	172	40–120
Bilirubin, µmol/L	4	3	< 20.0

Note: ALP = alkaline phosphatase, ALT = alanine aminotransferase, CO_2 = bicarbonate, NA = not available.

Table 2: Cerebrospinal fluid analysis and microbiologic testing

Investigation	Result	Reference range
CSF tests		
Leukocyte count, × 10^6/L	65	0–10
Neutrophil count, × 10^6/L	3	
Lymphocyte count, × 10^6/L	27	
Monocyte count, × 10^6/L	35	
Erythrocyte count, × 10^6/L	6	
Glucose level, mmol/L	6.6	2.8–4.2
Protein, mg/L	569	150–450
Cryptococcal antigen	Negative	
HSV 1 DNA PCR	Not detected	
HSV 2 DNA PCR	Not detected	
VZV DNA PCR	Not detected	
Enterovirus RNA PCR	Not detected	
CMV DNA PCR	Not detected	
Lyme PCR	Not detected	
Fungal culture	Negative	
Bacterial culture	No growth	
Serum tests		
HIV serology	Non-reactive	
Lyme serology	IgM non-reactive, IgG non-reactive	

Note: CMV = cytomegalovirus, CSF = cerebrospinal fluid, HSV = herpes simplex virus, IgG = immunoglobulin G, IgM = immunoglobulin M, PCR = polymerase chain reaction, RNA = ribonucleic acid, VZV = varicella zoster virus.

diagnosis.[1] Uremic encephalopathy (a) is a plausible explanation for cognitive changes in any patient with chronic renal disease, but our patient's urea level was similar to his baseline, and he had been on a stable regimen of continuous cycling peritoneal dialysis for 7 months, making this unlikely.[3] We also considered drug-induced meningitis and meningitis due to infection were less likely, given the lack of meningeal signs (i.e., nuchal rigidity), fever or symptoms (i.e., headache), despite the presence of confusion and agitation.[3] Hypertension is common among patients receiving dialysis, and patients who have been on dialysis for some time may be more resistant to antihypertensive treatment than patients starting dialysis. Our patient's CT scan did not show hemorrhagic infarct nor edematous areas to suggest posterior reversible leukoencephalopathy syndrome.[4]

What is the most appropriate next step?

a. Start empiric intravenous (IV) acyclovir
b. Order magnetic resonance imaging (MRI) of the brain
c. Perform a lumbar puncture
d. Switch to hemodialysis
e. Order electroencephalography (EEG)

The most appropriate next step in management is lumbar puncture (c), given the importance of viral encephalitis in our differential diagnosis. Cerebrospinal fluid (CSF) analysis showed lymphocytic pleocytosis with normal glucose and mildly elevated protein (Table 2). Microbiologic studies for bacterial and viral encephalitis, HIV, Lyme disease and cryptococcus were negative (Table 2). In addition to performing a lumbar puncture, we discontinued valacyclovir and commenced acyclovir empirically (5 mg/kg IV every 24 hours [425 mg every 24 hours], adjusted for end-stage renal disease) for possible herpes encephalitis. Delayed treatment of this condition is associated with increased morbidity and mortality, and the risks of withholding treatment outweigh the risks of administering acyclovir if appropriately renally dosed.[5] Of note, acyclovir has a smaller molecular weight than valacyclovir and is cleared both by glomerular filtration and tubular secretion, limiting the overall risk of toxic accumulation.[6] The nephrology team intensified his continuous ambulatory peritoneal dialysis regimen with 6 daily exchanges of hypertonic solution (4.25%), from 4 daily exchanges with 2.5% solution.

We ordered a brain MRI to identify features of encephalitis, such as temporal lobe edema in herpes simplex virus encephalitis (Figure 2). The scan showed a subtle signal in the left insular and mesial temporal regions on T_2 fluid-attenuated inversion recovery images. We also performed an EEG to assess for focal or lateralizing abnormalities, which are more frequently seen in herpes simplex virus encephalitis, or seizures.[1] The EEG showed diffuse slowing only.

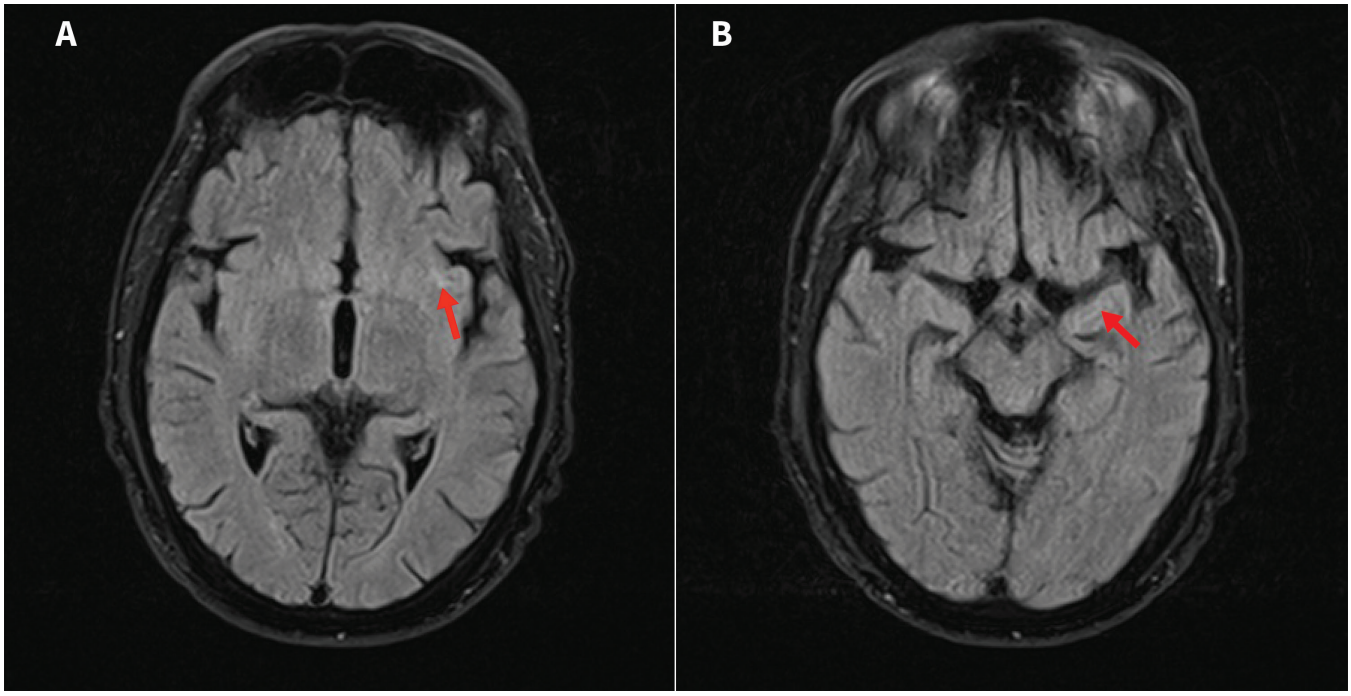

Figure 2: Magnetic resonance imaging scan of the patient's brain, including T_2 fluid-attenuated inversion recovery axial slices showing increased signal in the (A) left insular and (B) mesial temporal regions. Motion artifact present.

Blood cultures were negative, and although the patient did not have residual urine output to allow for urine culture, peritoneal dialysis fluid was negative for microbiological culture. A mid-turbinate swab for SARS-CoV-2 infection was negative. Once polymerase chain reaction (PCR) testing of the patient's CSF returned negative for herpes simplex virus and varicella zoster virus, we discontinued acyclovir, as PCR-based testing is highly sensitive for central nervous system infection secondary to these viruses.[7]

The patient's clinical status improved beginning on hospital day 4, which was the day after intensification of peritoneal dialysis. He continued to improve, and we discharged him 10 days after presentation. Although he improved somewhat when acyclovir was reduced to renal dosing, a dramatic improvement in symptoms occurred with intensification of peritoneal dialysis. This, paired with lack of fever and negative microbiologic testing, suggested a most likely diagnosis of valacyclovir neurotoxicity with atypical radiographic and CSF findings. The Naranjo scale assessment of probability of adverse drug reaction (ADR) related to valacyclovir revealed a score of 5, which represents probable ADR.[8] At follow-up, 3 weeks postdischarge, our patient returned to baseline function and was able to continue peritoneal dialysis independently at home. The rash had completely resolved when he was reassessed after discharge in the outpatient clinic.

Discussion

Valacyclovir is a prodrug of the antiviral agent acyclovir. It is converted to acyclovir and L-valine by first-pass metabolism, and about 60%–90% of acyclovir is renally excreted via glomerular filtration and tubular secretion.[6,9] Acyclovir has a molecular weight of 225 Da, protein binding of 9%–33%, and a volume of distribution of 0.6 L/kg with high water solubility, which are characteristics that allow for clearance via hemodialysis.[6] Both acyclovir and valacyclovir are generally well tolerated, but valacyclovir is often preferred for the treatment of herpes simplex and zoster infections because it requires less frequent dosing.[9,10]

The most common adverse drug reaction associated with acyclovir is renal impairment, caused by precipitation of acyclovir crystals in renal tubules, resulting in impaired clearance and increased accumulation of the agent in the blood.[3,9] Neurotoxicity is an uncommon adverse event associated with acyclovir and valacyclovir use, and literature suggests that neurologic and psychiatric manifestations may be secondary to the metabolite 9-carboxymethoxymethylguanine (CMMG).[9] Predominant risk factors are increased age, renal impairment and malignancy.[1] In a review of 35 published cases of acyclovir neurotoxicity, doses of acyclovir ranged between 600 mg/d and 4000 mg/d.[1] Neurotoxicity can occur even when dosing is appropriately adjusted for renal function.[6] Valacyclovir has been associated with both nephrotoxicity and neurotoxicity.[6] When creatinine clearance is less than 10 mL/min, recommended dosing of valacyclovir is 500 mg every 24 hours.[11]

Clinical manifestations and investigations

Symptom onset with acyclovir and valacyclovir neurotoxicity is acute, typically within 24–72 hours of treatment initiation, but 1 case report described onset 120 days after initiation.[1,3] There is a wide spectrum of neuropsychosis manifestations, including hallucinations, confusion and delirium. The exact mechanism is unclear but is suspected to be a result of accumulation of CMMG metabolite.[9] Fever and headache are typically absent, allowing for possible distinction between antiviral toxicity and infectious encephalitis.[1]

Descriptions of CSF abnormalities with acyclovir and valacyclovir neurotoxicity can be difficult to interpret. In a review of 35 cases of acyclovir neurotoxicity, CSF was abnormal in 8 of 15 patients who underwent lumbar puncture.[1] However, the authors noted plausible alternative explanations for the abnormalities, including concomitant central nervous system tumours, previous meningoencephalitis and receipt of intrathecal medications.[1] In another review of published cases of acyclovir neurotoxicity, only 1 of 18 patients who underwent a lumbar puncture had pleocytosis (30 leukocytes/μL) and for this reason, the authors argued that presence of inflammatory cells may help distinguish acyclovir toxicity from infectious encephalitis.[12] Additional cases of acyclovir neurotoxicity with abnormal CSF findings — namely, pleocytosis (37 leukocytes/μL with 100% monocytes) and elevated protein (640 mg/L) — have been reported.[11] Brain MRI findings in acyclovir neurotoxicity can vary from normal to subcortical bi-hemispheric lesions on T_1-weighted MRI, the latter described in a patient with acyclovir neurotoxicity and seizures after blood stem cell transplantation.[13]

Management and prognosis

Acyclovir and valacyclovir neurotoxicity improve after drug discontinuation or elimination.[1] In some instances, patients may require hemodialysis if symptoms persist,[6] but complete recovery to baseline function is expected within a week.[1,12] Traditionally, peritoneal dialysis is not considered an efficient means for acyclovir clearance;[10] however, case reports of successful management of acyclovir and valacyclovir neurotoxicity via intensification of peritoneal dialysis exist, specifically with increased volume of hypertonic exchanges, without the need to convert to hemodialysis.[2,6]

Conclusion

This case highlights a rare complication of a commonly prescribed antiviral agent. The onset of neurologic symptoms soon after medication initiation in a patient with end-stage renal disease, lack of fever and headache, and rapid resolution of symptoms after intensification of peritoneal dialysis are in keeping with valacyclovir neurotoxicity. Cerebrospinal fluid and MRI findings with acyclovir and valacyclovir neurotoxicity can be variable and may not reliably allow distinction from viral encephalitis. We aim to make clinicians aware that toxicity related to these antiviral agents may mimic infectious presentations clinically, biochemically and radiographically, and that risk is increased in those with impaired renal function.

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