

MORNING REPORT

# OCCAM'S RAZOR VERSUS HICKAM'S DICTUM: HEADACHE IN AN IMMUNOCOMPROMISED PATIENT

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A 34-year-old man with a history of simultaneous pancreas-kidney transplant for Type I diabetes and associated nephropathy, requiring chronic immunosuppressive therapy with tacrolimus, prednisone, and mycophenolate, presented with acute onset headache and subjective confusion. Two weeks prior, he had been diagnosed with antibody-mediated kidney transplant rejection, undergoing first treatment of plasmapheresis and intravenous immunoglobulin (IVIG) several days prior to his acute presentation.

*We have a medically complex patient whose headache differential starts out broadly. We should immediately be concerned about infection causing meningitis, encephalitis, or meningoencephalitis given his chronic immunosuppression as well as recent acute rejection treatment. Bacterial, viral, or fungal infections are concerning. Medication adverse effect and intracranial bleed should also be considered early.*

On examination, his temperature was 37.8°C, and he was hypertensive to 183/107 mmHg with mild tachycardia. He was intermittently somnolent, agitated, and disoriented. Neck pain and stiffness were present.

*Meningitis due to infection remains high on the differential given his nuchal rigidity. His normal temperature does not exclude the possibility. His hypertension and chronic tacrolimus also raise concern for posterior reversible encephalopathy syndrome (PRES). His recent IVIG therapy could also cause an aseptic meningitis.*

He was started on empiric vancomycin and ceftriaxone for bacterial meningitis coverage; acyclovir was not empirically initiated. Urgent head CT was unremarkable. MRI was also subsequently unremarkable. Lumbar puncture (LP) was performed urgently as soon as the head CT showed no signs of impending herniation, although this was a difficult bedside procedure with multiple attempts needed to access the cerebrospinal fluid (CSF) space. The

CSF initially appeared red in color. The intensity of the color did not lessen with subsequent sampling; vials one through four were identical in their dark red appearance.

*The stable CSF appearance between vials one and four made trauma from needle insertion less likely, as this is typically associated with a bloody CSF appearance that lessens over time as fluid is collected. CSF appears cloudy with RBC concentrations between 500-6000 K/cu mm and begins to appear grossly bloody when the concentration exceeds 6,000 K/cu mm (K/cu mm or K/mm<sup>3</sup> is equivalent to cells/μL.) The differential for grossly bloody CSF includes traumatic LP, subarachnoid haemorrhage, and hemorrhagic meningoencephalitis. SAH seems less likely here given negative imaging and absence of head trauma.*

Because of the association between HSV encephalitis with CSF erythrocytosis in combination with his immunosuppressed status, he was immediately started on empiric intravenous acyclovir. Subsequent CSF analysis revealed WBC count of 2,106 K/cu mm (76% neutrophils), RBC count of 42,000 K/cu mm, protein 249 mg/dL, and normal glucose relative to serum levels (64 mg/dL).

*In HSV encephalitis, CSF erythrocytosis occurs in approximately 80% of cases and is attributed to the necrotizing and hemorrhagic nature of the infection.<sup>1</sup> CSF HSV polymerase chain reaction (PCR) is associated with a sensitivity of 98% for detecting infection, but can be falsely negative in the setting of significant erythrocytosis due to presence of porphyrin (a heme-degradation product) which can interfere with the assay.<sup>2</sup> Therefore, in such a setting, negative PCR results should be interpreted with caution. Peripheral blood contamination of CSF after traumatic LP artificially increases WBC count. However, this CSF pleocytosis appears "real" as the pro-*

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	Cerebrospinal Fluid	Peripheral Blood
WBC count (K/cu mm)	2,106	14,750
RBC count (K/cu mm)	42,000	4,600,000
WBC:RBC ratio	0.05	0.003

portion of CSF WBC to RBC is larger than the peripheral blood WBC / RBC ratio (see table on page 9).

His CSF HSV-1 by PCR ultimately returned positive on hospital day 2, and he was continued on intravenous acyclovir with antibiotics discontinued. However, despite acyclovir, he experienced only minimal improvement in his headache severity before manifesting acute worsened headache and agitation with hypertension to 180/110s mmHg on hospital day 5. His delirium included the inability to recognize family members and paranoid delusions of dying (repeatedly stating “I feel like I’m going to die”).

*Our differential for this clinical setback includes inadequate CNS source control, superimposed bacterial meningitis given his difficult lumbar puncture, hypertensive emergency, PRES syndrome, new intracranial hemorrhage, and acyclovir-induced neurotoxicity. Acyclovir-induced neurotoxicity typically presents within 24-72 hours of drug initiation with neurologic manifestations such as tremor, myoclonus, delirium, agitation, lethargy, hallucinations, and extrapyramidal symptoms.<sup>3</sup> Visual hallucinations and death delusions, which interestingly was one of the most striking features for this patient, are reported.<sup>4</sup>*

*Acyclovir-induced neurotoxicity can be challenging to identify, as it can be confused for worsening HSV*

*encephalitis or meningoencephalitis. Most cases occur with renal impairment,<sup>5</sup> leading to accumulation of acyclovir and its metabolite 9-carboxymethoxymethylguanine (CMMG), which is believed to act at the blood-brain barrier by inhibiting transporter proteins and increasing susceptibility to uremic toxicity.<sup>5</sup> Our patient’s graft function had normalized by the time of this adverse event. AIN can be managed by drug withdrawal, hydration to increase excretion, and/or hemodialysis.<sup>6</sup> Most cases show improvement within 5 days after drug withdrawal.*

His hypertension normalized with intravenous labetalol, and acyclovir was changed to intravenous ganciclovir with subsequent dramatic improvement. On hospital day 7, his mental status had returned to baseline with complete headache resolution. He was discharged on hospital day 9 and ultimately made a full recovery.

*Failure to consider AIN may lead to misinterpretation of neurological symptoms as worsening encephalitis, leading to inappropriate dose increases rather than reduction or withdrawal. This case highlights the importance of maintaining a broad differential diagnosis in immunocompromised patients presenting with headache. It also illustrates the importance of recognizing causes of persistent headache and neurologic decline in those on targeted therapy for HSV meningoenceph-*

*alitis, including acyclovir-induced neurotoxicity. The opposing philosophies of Occam’s Razor (strive to find the fewest possible causes to explain a patient’s presentation) and Hickam’s Dictum (patients can have multiple diagnoses simultaneously) can apply to the challenging scenario of headache in an immunocompromised patient, especially if the headache and neurologic decline continue after targeted treatment is begun.*

**References**

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