LearnIng ObjectIves

• To recognize the importance of a broad differential diagnosis in immunocompromised patients with headache
• To recognize causes of persistent headache and neurological decline in those on targeted treatment for herpes simplex virus (HSV) meningoencephalitis, including acyclovir-induced neurotoxicity

IntrOductIOn

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 as many diseases as they damn well please”) can apply to the challenging scenario of headache in the immunocompromised, especially if the headache and neurological decline continue after targeted treatment is begun.

Case presentatIon

• A 34-year-old man with Type 1 diabetes s/p simultaneous pancreas-kidney transplant on immunosuppressive therapy presented with severe headache, confusion, and somnolence (see figure 1).
• Two weeks earlier, he was diagnosed with antibody-mediated rejection, and he underwent first treatment of plasmapheresis and IVIG several days prior to presentation.
• In the ED, patient had low-grade fever, hypertension (BP 138/107), tachycardia, and leukocytosis. Head CT was unremarkable, and MRI was ordered due to concern for PRES or aseptic meningitis given the association with IVIG. In advance of lumbar puncture, he was empirically started on vancomycin and ceftriaxone due to concern for CNS infection.
• After a traumatic tap, his CSF appeared grossly bloody but did not clear by tube 4 (figure 2A). Cell count on tube 4 revealed 2106 WBCs and 4200 RBVs (figure 2B), prompting immediate addition of acyclovir due to concern for HSV infection.
• On day 2, HSV meningoencephalitis was confirmed as CSF PCR for HSV-1 returned positive. Despite acyclovir, patient’s headache remained prominent and his systolic blood pressure remained elevated at the 170s.
• He had transient improvement on hydrophone PCA, but by day 4, his headache again worsened. Due to concern for acyclovir-induced neurotoxicity (AIN), his dose was reduced by 50%.
• However on day 5, patient became significantly agitated, did not recognize family members, expressed “I feel like I am going to die”, and had continued worsening headache with BP as high as 186/113, which was refractory to IV labetalol.

Case prEsentatIon

Table 1: Frequency of central nervous system effects in 24 patients with acyclovir-induced neurotoxicity (AIN), reported by Haevel et al.

<table>
<thead>
<tr>
<th>Sign/Symptom</th>
<th>Frequency (%)</th>
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<tbody>
<tr>
<td>Tremor, myoclonus</td>
<td>58</td>
</tr>
<tr>
<td>Confusion</td>
<td>50</td>
</tr>
<tr>
<td>Agitation</td>
<td>38</td>
</tr>
<tr>
<td>Lethargy</td>
<td>25</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>25</td>
</tr>
<tr>
<td>Extrapyramidal symptoms</td>
<td>21</td>
</tr>
<tr>
<td>Clouning of consciousness</td>
<td>17</td>
</tr>
<tr>
<td>Dysartha</td>
<td>17</td>
</tr>
<tr>
<td>Unilateral/focal symptoms</td>
<td>13</td>
</tr>
</tbody>
</table>

He was then transferred to the ICU, with differential diagnoses including inadequate CNS source control, suppurated bacterial meningitis (multiple attempts were required before LP was successful), hypertensive emergency, PRES syndrome, intracranial hemorrhage, and still, AIN. Repeat head CT was negative.
• In the ICU, BP normalized with labetalol gtt, and acyclovir was changed to IV ganciclovir as it is less associated with neurotoxicity. By day 7, his hemodynamics normalized, his mental status returned to baseline, and his headache had resolved completely. He was discharged on day 9.

DiscussIOn

The differential diagnosis evolved considerably during this challenging case. Initially, suspicion was high for aseptic meningitis (given recent IVIG) and PRES (given recent IVIG, immunosuppressive therapy, and hypertension). However, the striking CSF appearance and cell count led to rapid initiation of acyclovir. Ultimately, the importance of maintaining a broad differential in immunocompromised patients was demonstrated as the patient was found to likely have two distinct etiologies contributing to his persistent headache and neurological decline: resolving meningoencephalitis and AIN.

AIN is challenging to identify as it can be confused for worsening HSV encephalitis. It typically presents within 24-72 hours with various neurological manifestations (see table 1); visual hallucinations and death delusion (which interestingly was seen in this patient) can also be seen. Most cases occur in those with renal impairment, 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.3

AIN is diagnosed with detection of high serum and CSF levels of CMMG, and can be managed by drug withdrawal, hydration to increase excretion, and/or hemodialysis.4 Most cases show improvement within 5 days after drug withdrawal. Risk of AIN can be reduced with doses adjusted for renal function and body size, pre-hydration, and infusion of acyclovir over at least 1 hour.5 Failure to consider AIN may lead to misinterpretation of neurological symptoms as worsening encephalitis, leading to inappropriate dose increases rather than reduction or withdrawal.

REFERENCES