An Unusual Mimicker of Tumor Lysis Syndrome with Hepatic and Renal Failure

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Submitted: 17 January 2021; Accepted: 21 February 2021; Published: 20 December 2021

DOI: https://doi.org/10.22374/cjgim.v16i4.518

Abstract
A 52-year-old male presented to the emergency department with a 3-day history of malaise, nausea, and pruritic rash. He had a history of treated hepatitis C, primary immune thrombocytopenic purpura (ITP), a monoclonal gammopathy of undetermined significance (MGUS), and a remote history of intravenous heroin use. He had normal vital signs and was jaundiced with a diffuse petechial rash. His laboratory investigations revealed severe transaminitis in the thousands in a hepatocellular pattern and a platelet count of 41 × 10⁹/L; acute kidney injury with a creatinine of 588 µmol/L and potassium of 5.5 mmol/L; a uric acid of 1115 µmol/L and phosphate of 2.36 mmol/L; and white blood cell casts on urine microscopy. His serum toxicology was unremarkable and urine drug screen was positive for opiates and fentanyl.

He was initially managed with intravenous fluids and rasburicase given concern for severe hyperuricemia and potential tumor lysis syndrome. He had a normal computed tomographic scan of his chest and abdomen, as well as portal venous doppler. A thorough workup for hepatopathy was unrevealing, and the patient ultimately endorsed methamphetamine use 5 days prior to presentation. The presentation was ultimately felt to be consistent with methamphetamine toxicity resulting in hepatic injury, rhabdomyolysis, and potential acute interstitial nephritis, despite a negative urine drug screen result on presentation. The patient was managed with N-acetylcysteine for drug-induced hepatic injury shortly after admission, and his hepatic and renal function ultimately recovered after 6 weeks.

Résumé
Un homme de 52 ans s’est présenté à l’urgence après avoir éprouvé pendant trois jours les symptômes suivants : malaise, nausées et éruption prurigineuse. Il avait des antécédents de traitement contre l’hépatite C, de purpura thrombopénique immunologique primaire, de gammopathie monoclonale de signification indéterminée et des antécédents lointains de consommation d’héroïne par voie intraveineuse. Ses signes vitaux étaient normaux et il présentait une jaunisse accompagnée d’une éruption pétéchiale diffuse. Ses analyses de laboratoire ont révélé les éléments suivants : une transaminite grave (taux de transaminases hors de proportion) suivant un motif hépatocellulaire et une numération plaquettaire de 41 × 10⁹/L; une insuffisance rénale aiguë, le taux de créatinine étant de 588 µmol/L et celui de potassium étant de 5,5 mmol/L; un taux d’acide urique de 1115 µmol/L et de phosphate de 2,36 mmol/L; présence de cylindres leucocytaires à la microscopie urinaire. L’analyse toxicologique sérique était sans particularité et le dépistage de drogues dans l’urine s’est révélé positif pour les opiacés et le fentanyl.
An unusual mimicker of tumor lysis syndrome

Case Description

A 52-year-old male presented to the emergency department with a 3-day history of malaise, nausea, and a pruritic petechial rash. His past medical history included being treated for hepatitis C with interferon and a recent undetectable hepatitis C viral load, primary immune thrombocytopenic purpura (ITP) with a most recent platelet count of 219 × 10⁹/L 4 months prior to presentation, and IgG kappa monoclonal gammopathy of undetermined significance (MGUS). He had finished a course of prednisone for his ITP and declined bone marrow biopsy for his MGUS, 3 months prior. He was on no medications or supplements, endorsed smoking with a 20 pack-year history and consumption of approximately seven standard drinks weekly without recent change. He reported a remote history of sporadic intravenous heroin use, but more recently intranasal heroin and cocaine use up to a few weeks prior to presentation.

On exam, he was febrile with a heart rate of 75 beats per minute and a systolic blood pressure of 130 mmHg. He had scleral icterus, was jaundiced, and had a diffuse petechial rash. His cardiac, respiratory, abdominal, and neurologic exams were all unremarkable without evidence of ascites, hepatosplenomegaly, or lymphadenopathy. He had no notable extrahepatic stigmata of liver disease.

The patient's initial bloodwork is shown in Table 1. Notably, he had a sodium of 124 mmol/L, potassium 5.5 mmol/L, creatinine 588 umol/L, calcium 2.05 mmol/L, phosphate 2.36 mmol/L, CK 1873 U/L, and uric acid 1115 umol/L. He was thrombocytopenic with a platelet count of 41 × 10⁹/L. Blood smear was unremarkable with no schistocytes. His liver enzymes were elevated with AST 2028 U/L, ALT 4642 U/L, ALP 139 U/L, INR 1.44, and normal albumin. His urinalysis revealed white blood cell casts. Urine sodium and chloride were over 20 mmol/L. His serum toxicology was unremarkable with normal osmolar gap and an undetectable acetaminophen level. However, his urine drug screen was positive for opiates and fentanyl. There were no traces of cocaine or amphetamines reported initially; however, on further discussion with the laboratory biochemists, the urine amphetamine screen was weakly positive and a small concentration of methamphetamine was detected on confirmatory testing.

During hepatology consultation the following day, the patient disclosed that he had in fact used intravenous methamphetamine as recent as 5 days, and fentanyl 3 days, prior to presentation. The patient was started on N-acetylcysteine for off-label management of drug-induced hepatitis, in addition to intravenous fluid resuscitation. With an otherwise unremarkable work-up, the patient’s hepatic and renal injuries were felt to be most likely secondary to...
methamphetamine-induced hepatic injury and acute interstitial nephritis. His thrombocytopenia recovered spontaneously without any intervention. As he had an unremarkable blood smear with normal abdominal ultrasound, the initial thrombocytopenia was thought to be due to bone marrow suppression secondary to unknown substances mixed with methamphetamine or other narcotics he ingested.

Following hospital admission, the patient’s liver enzymes and creatinine rapidly trended down. He was discharged within a week, and his laboratory values normalized by

Table 1. Laboratory markers at presentation, 2 days after presentation, 5 days after presentation, and at follow-up (27 days after initial presentation)

<table>
<thead>
<tr>
<th>Laboratory test</th>
<th>Normal range</th>
<th>Level at presentation</th>
<th>Level PPD 2</th>
<th>Level PPD 5</th>
<th>Level PPD 27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/L)</td>
<td>130–170</td>
<td>128*</td>
<td></td>
<td></td>
<td>139</td>
</tr>
<tr>
<td>Platelets (x 10^9/L)</td>
<td>140–400</td>
<td>41*</td>
<td>52*</td>
<td>114*</td>
<td>341</td>
</tr>
<tr>
<td>WBC (x 10^9/L)</td>
<td>4.00–11.00</td>
<td>8.73</td>
<td></td>
<td></td>
<td>7.81</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>10–45</td>
<td>4642*</td>
<td>1799*</td>
<td>616*</td>
<td>21</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>7–40</td>
<td>2028*</td>
<td>257*</td>
<td>33</td>
<td>23</td>
</tr>
<tr>
<td>ALP (U/L)</td>
<td>35–125</td>
<td>139*</td>
<td></td>
<td></td>
<td>126</td>
</tr>
<tr>
<td>Bilirubin (total)</td>
<td>0–23</td>
<td>39*</td>
<td>22</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Bilirubin (direct)</td>
<td>0–7</td>
<td>21*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td>0.9–1.1</td>
<td>1.44</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CK (U/L)</td>
<td>5–160</td>
<td>1873*</td>
<td>209*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>35–50</td>
<td>37</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sodium (mmol/L)</td>
<td>135–145</td>
<td>124*</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Potassium (mmol/L)</td>
<td>3.5–5.0</td>
<td>5.5*</td>
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<td></td>
<td></td>
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<tr>
<td>Calcium (mmol/L)</td>
<td>2.10–2.60</td>
<td>2.05</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Phosphorus (mmol/L)</td>
<td>0.80–1.35</td>
<td>2.36</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Uric Acid (umol/L)</td>
<td>260–450</td>
<td>1115*</td>
<td>&lt;90*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine (umol/L)</td>
<td>52–112</td>
<td>588*</td>
<td>686*</td>
<td>390*</td>
<td>89</td>
</tr>
<tr>
<td>Urea (mmol/L)</td>
<td>3.0–7.0</td>
<td>41*</td>
<td>37.9*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate Dehydrogenase (U/L)</td>
<td>100–195</td>
<td>926*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-reactive Protein (mg/L)</td>
<td>0.0–5.0</td>
<td>50.4*</td>
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</tbody>
</table>

*S = Abnormal Value.

PPD = Post-Presentation Day.
follow-up at day 27 post-admission. The patient was encouraged to engage in discussions surrounding methamphetamine use with his addictions and family health teams.

Discussion

This case describes multi-organ dysfunction likely secondary to methamphetamine use. In this case of new multi-system injury, a broad initial differential diagnosis was developed (Table 2). In particular, this patient had multiple preexisting medical conditions such as MGUS, ITP, and Hepatitis C infection possibly contributing to his presentation with acute renal injury and fulminant hepatic failure. Although multiple separate processes could have explained his current medical conditions, given the negative work up, a toxin-mediated cause for organ injury was felt to be most likely.

Methamphetamine use in Canada

Recent data from the Canadian Centre on Substance Use and Addiction suggests that the availability of methamphetamine has been steadily increasing over the past 10 years, with a 590% increase in drug offences related to methamphetamine.1 Approximately 4% of Canadians over 25 years old reported using methamphetamines during their lifetime, and its use is more common in males.1 Methamphetamine use was the third most commonly detected drug relevant to mortality from overdose.1 Death results from psychiatric euphoria resulting in dangerous decisions, as well as from various acute and chronic medical causes.1 In the acute setting, hypertension, tachycardia, and peripheral vasoconstriction leads to a shock state.2 Chronic use results in cardiomyopathy, rhabdomyolysis, pulmonary edema, and seizures.3

Methamphetamine toxicity assays

Methamphetamine's half-life ranges from 8 to 13 h.4 It can be detected using serum and urine drug assays.4 The sensitivity of the assay is also dependent on the concentration of methamphetamine in serum, with a high sensitivity if the concentration is 50 ng/mL.4 Urine-based assays are able to detect methamphetamine use for only up to 48 h after use.4 Therefore, initial toxicology screening may not reflect methamphetamine use prior to 48 h.

Screening assays also have limitations, including false-negative and false-positive results.4 Various psychotropic medications, including bupropion, trazodone, and tricyclic antidepressants, are known to interfere with these assays due to the cross-reactivity with their metabolites. False-negative results are often due to low concentration of the drug in the urine; however, they have been seen due to cross-reactivity of methamphetamine and chlorpromazine metabolites causing a false-negative result.5 When suspecting a toxin-mediated injury, it is important to recognize the limitation of screening assays.

In this case, the immunoassay amphetamine (Roche Cobas Amphetamines II) drug screen used had a cut-off of 1000 ng/mL and has full cross-reactivity with d-amphetamine and d-methamphetamine. The above assay also cross-reacts with methylenedioxymetamphetamine (MDMA) and is reported positive if the concentration is 509 ng/mL.6 However, the confirmatory testing performed using liquid-chromatography mass-spectrometry was found to be positive for methamphetamine. This report was initially negative given the very small signal, but on further review, was felt to be positive.

This case highlights the importance of recognizing the limited sensitivity and variable specificity of drug immunoassay screens. One study found the positive predictive value of this assay to be only 9.3%.7 When a high suspicion exists, a discussion about confirmatory testing can lead to definitive answers.

Methamphetamine hepatotoxicity

Hepatotoxicity has been described after ingestion of several varieties of amphetamines, although the largest number of
reported cases is after ingestion of MDMA. Presentations are divided into two distinct patterns. The first with multi-organ damage (renal, cardiac, and muscular), 3–14 days after ingestion and histopathological similarities to ischemic or hyperthermic hepatitis. The second with isolated hepatitis, akin to autoimmune hepatitis, 7–14 days after ingestion. Both courses are usually self-limited with resolution 1–3 months after time of ingestion. The pathophysiologic mechanism of methamphetamine hepatotoxicity is not well understood; however, in vitro animal models have suggested that it is mediated by oxidative stress and mitochondrial collapse. Methamphetamine has been shown to downregulate cell-cycle genes and induce cell cycle arrest in vitro, which is thought to be the main factor in inducing hepatocellular injury.

In our case, the patient presented 5 days after methamphetamine use and had rapid improvement of his renal and liver function in the days following admission. In the absence of an alternate etiology, the timing and presentation with multi-organ damage was thus felt to be plausibly consistent with methamphetamine toxicity. Based on available evidence, it is expected that urine drug screens may be insensitive at the time of presentation for amphetamine-induced hepatic injury in general.

It should also be noted that sympathomimetic-induced nontraumatic rhabdomyolysis can intuitively confound the diagnosis of liver injury. While a higher ALT to AST ratio in this case may imply a predominantly hepatic source of transaminases, the possibility of rhabdomyolysis with higher AST after methamphetamine ingestion, but faster decline in AST as compared to ALT in the following days, cannot be excluded. A combination may be likely in the reported case.

Methamphetamine nephrotoxicity
Methamphetamine nephrotoxicity is also a well-established phenomenon and can induce injury through a variety of mechanisms. Often patients present in nontraumatic rhabdomyolysis; however, amphetamines are also known to cause acute interstitial nephritis, which was seen in this patient. In patients who also present with fulminant hepatic dysfunction, kidney injury could also be seen from the development of hepatorenal syndrome.

Management
There are no clear guidelines for the management of methamphetamine-induced cellular injury. The initial key principles involve supportive management, and close monitoring of all parameters. If liver failure progresses significantly, liver transplantation may be required. There are also rare cases of acute kidney injury progressing to end-stage renal disease requiring dialysis.

This patient was managed conservatively with fluid resuscitation to manage his acute kidney injury and mitigate further sequelae of rhabdomyolysis. He was also given one dose of rasburicase for the management of hyperuricemia, especially in the context of AKI and biochemical similarities to TLS. Rasburicase has also been shown to be effective in rhabdomyolysis with hyperuricemia. Based on recommendations from our hepatology team, the patient was started on N-acetylcysteine, which has been shown to be effective in cases of drug-induced hepatic ischemia.

This case highlights the multi-system effects of methamphetamine use, resulting in both hepatic and renal injury. Clinicians should be aware of the limitations of serum and urine drug assays, and should always focus on taking a thorough substance-use history when there is an unclear etiology of multi-organ injury. Supportive treatment, including fluid resuscitation, N-acetylcysteine, and rasburicase if hyperuricemia is present, appears to be effective with little risk of harm.

Key Points

1. Methamphetamine use is becoming increasingly prevalent and should be considered in patients with multi-organ injury.
2. Methamphetamine toxicity can present with biochemical similarities to tumor lysis syndrome.
3. Methamphetamine-induced organ injury can present days after ingestion and should be considered even when screening tests are negative.
4. Supportive treatment, including fluid resuscitation, N-acetylcysteine, and rasburicase if hyperuricemia is present, appears to be effective in such cases.

Statement of Informed Consent

Informed consent to use de-identified personal health information for publication with educational intent was obtained from the patient prior to case report drafting. They understood that complete anonymity cannot be guaranteed, given the access of such information to the general public. They understood their right to refuse to consent, and that the act of doing so would not affect their care in any way.
Statement of the Contributions of Authors to the Manuscript

All authors contributed to the conception, design, procurement of data, analysis, drafting, and critical review of the manuscript.

Statement of Funding

Funding for publication of this article was provided by the Department of Medicine at Unity Health, Toronto.

Conflicts of Interest

There are no conflicts of interest to declare.

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