LETTER TO THE EDITOR

Pegylated asparaginase as cause of fatal hyperammonemia in patients with latent urea cycle disorder

To the editor:
The manuscript by Steiner and colleagues describes hyperammonemia caused by pegylated asparaginase (PEG-ASNase) in pediatric patients with acute lymphoblastic leukemia (ALL).1 While ammonia levels were found to be strikingly elevated—up to seven times normal—the authors did not find evidence of central nervous system toxicity in their cohort. We report the case of a teenaged male with ALL and an undiagnosed urea cycle disorder (UCD) who presented with severe hyperammonemic encephalopathy induced by PEG-ASNase.

1 CASE
A 14-year-old male with new diagnosis of T-cell ALL presented for induction therapy. One day after PEG-ASNase administration, he displayed progressive encephalopathy. Elevated ammonia levels were detected and medical therapy was initiated without clinical improvement. With the development of cerebral edema, the patient was transferred to a tertiary-care facility where he progressed to brain death despite dialysis. Peak ammonia level prior to the transfer was 466 umol/l. Magnetic resonance imaging (MRI) showed elevated glutamine on proton spectroscopy, which raised suspicion for urea cycle disorder. Urine orotic acid was 1123.9 mmol/mol Cr (RR 0.4–1.2), pathognomonic for ornithine transcarbamylase deficiency (OTCD).2

Patient’s DNA was not available for molecular DNA testing. Testing of the asymptomatic biological mother revealed a pathogenic mutation in the OTC gene, c.830 G>A; p. Arg277Gln, previously reported with late-onset OTCD.3–5

2 DISCUSSION
This case of hyperammonemic encephalopathy precipitated by PEG-ASNase in a patient with an underlying late-onset UCD demonstrates that patients with inborn errors of metabolism like OTCD are at risk for life-threatening complications with PEG-ASNase. Early recognition by routine monitoring of ammonia is critical and can be lifesaving.

PEG-ASNase, a mainstay for the treatment of childhood ALL, has not previously been reported as a stressor leading to presentation of OTCD. Although drug mechanism involves ammonia production from the hydrolysis of plasma asparagine, life-threatening complications from hyperammonemia are rare.1,6 There are currently no protocols to screen for at-risk patients prior to induction therapy. The only intervention for dosage monitoring in response to hyperammonemia is with fatigue, known as “ASNase blues,” where a 25% reduced dose is recommended.7 Studies suggest monitoring ammonia levels as a marker for PEG-ASNase activity, but not toxicity.8 Our case highlights the need for routine ammonia monitoring with drug administration.

Late-onset mutations and females with OTCD may be asymptomatic and therefore undiagnosed. This population may benefit from preinduction screening to stratify risk for hyperammonemia-related adverse events. A molecular panel including urea cycle genes prior to chemotherapy could identify late-onset UCD and lead to modifications in treatment prior to induction. Several hyperammonemia gene panels are commercially available, but results take several weeks. With rapid next-generation sequencing (NGS) currently approaching 48 hr turnaround, potential for timely molecular screening will be increasingly possible.9

To our knowledge, this is the first-reported fatal case of hyperammonemic encephalopathy caused by PEG-ASNase. Implementing ammonia monitoring at the onset of induction could minimize time to detection and treatment of symptomatic patients particularly for patients who have underlying predisposition to hyperammonemia such as OTCD. OTCD and other pathologies associated with hyperammonemia should be considered in patients with adverse events to PEG-ASNase.

ACKNOWLEDGMENTS
We would like to acknowledge this patient’s family for their willingness to present this case to advance the medical community’s understanding of urea cycle disorders and the rare complications that can result from chemotherapy.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

ORCID
Everett Lally http://orcid.org/0000-0002-1706-3783
Jessica Scott Schwoerer http://orcid.org/0000-0001-6106-8242
Megan Peters
Ashley Kuhl
Jennifer Orozco
Everett Lally
Jessica Scott Schwoerer

Abbreviations: ALL, acute lymphoblastic leukemia; OTCD, ornithine transcarbamylase deficiency; PEG-ASNase, pegylated asparaginase; UCD, urea cycle disorder

Received: 31 October 2017    Accepted: 13 April 2018
DOI: 10.1002/pbc.27239
LETTER TO THE EDITOR

1Department of Pediatrics–Critical Care Medicine, University of Wisconsin, Madison, Wisconsin
2Department of Pediatrics, Gundersen Health System, La Crosse, Wisconsin
3Department of Pediatrics–Medical Genetics, University of Wisconsin, Madison, Wisconsin
4Department of Pediatrics–Hematology & Oncology, Gundersen Health System, La Crosse, Wisconsin
5Department of Integrated Oncology and Genetics, ARUP Laboratories, Salt Lake City, Utah

Correspondence
Jessica Scott Schwoerer, 1500 Highland Ave., Rm 341, Madison, WI 53705.
Email: jscottschwoerer@pediatrics.wisc.edu

REFERENCES

Fatal presentation of OTCD with use of PEG-ASNase.