CORRESPONDENCE

Infective hyperammonaemic encephalopathy after allogeneic stem cell transplant

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TO THE EDITOR:
Currently allogeneic haematopoietic stem cell transplantation (AlloHSCT) is the only curative therapy for primary myelofibrosis (PMF), but the inherent risks include a transplant-related mortality of 20%. Ultimately 20% of patients die from infection secondary to ongoing immunosuppression and potentially due to a greater incidence of poor graft function and failure [1].

A 65-year-old female with high-risk PMF (Dynamic International Prognostic Scoring System of 5) underwent a Fludarabine 25 mg/m², Melphalan 140 mg/m² and rabbit antithymocyte globulin (rATG)-conditioned matched unrelated donor AlloHSCT. She was treated previously with hydroxyurea, anagrelide and ruxolitinib. Comorbidities included gastro-oesophageal reflux, metapneumovirus, RSV) and bacterial infections (SARS-CoV-2, influenza, adenovirus, enterovirus, parainfluenza virus, metapneumovirus, RSV) and bacterial infections (Bordetella, Legionella, M. pneumoniae) were also negative. Although positive pre-transplant, rhinovirus PCR was not detected. Imaging was unremarkable including chest X-ray, CT pulmonary angiography and transthoracic echocardiography.

Despite lack of engraftment, the patient remained stable until day 22 post-transplant when she developed an acute reduction in her conscious state, with hallucinations and suicidal ideation. A non-contrast CT scan of her brain revealed no intracranial haemorrhage, cerebral oedema nor evidence of opportunistic infection. Bloods were notable for a remarkably elevated serum ammonia concentration of 946 µmol/L (normal < 60 µmol/L, Table 1).

Several differential diagnoses for hyperammonaemia were considered, including hepatic failure, urea cycle disorder (UCD), drug-induced, and Ureaplasma/Mycoplasma hominis infection. On discussion with the Metabolic Diseases Unit, a urease-producing bacteria was thought to be the most likely cause. Empirc treatment was initiated for Ureaplasma spp. and M. hominis with azithromycin 500 mg IV daily and ciprofloxacin 400 mg IV twice daily, pending further investigations. Hyperammonaemia was addressed with cessation of TPN and replacement with 10% dextrose IV, 10% Intralipid IV and sodium benzoate 12 g IV daily. Haemodialysis was instituted owing to the risk of fatal cerebral oedema. A serum amino acid panel demonstrated low levels of citrulline, arginine and other amino acids, but a urine metabolic screen was non-diagnostic for UCD such as deficiency of carbamoylphosphate synthetase 1 or ornithine transcarbamylase.

Despite a reduction in the serum ammonia, there was no evidence of clinical improvement. In the absence of engraftment and in keeping with the patient’s wishes she was transitioned to end-of-life care and died on day 27. Given the strong clinical suspicion of infection with a urease-producing organism, additional investigations were requested. Blind subculture of blood cultures to Ureaplasma spp./Mycoplasma media produced no growth. PCR on EDTA blood sample four days prior to death detected Ureaplasma parvum, and confirmed using a stored DNA extract from the preceding day. To further investigate this, novel primers and probes specific for Ureaplasma parvum were designed as described previously [2]. This assay was also positive on both samples, excluding non-specific amplification as a cause of the previous positive PCR. Ureaplasma parvum PCR of urine was also positive, suggesting a possible portal of entry. A posthumous liver biopsy (within ten hours of death) revealed zone three necrosis but no visualised organisms (on Gram and silver stains) nor esoinophilic inclusions on periodic acid Schiff stain, negative immunohistochemistry for EBV, CMV, HSV and hepatitis B, and negative trichome stain. Multiple microbiological tests on liver tissue were negative including bacterial and fungal culture, Ureaplasma/Mycoplasma culture and broad target PCR techniques (16 S ribosomal RNA for bacteria and internal transcribed spacer for fungi).

Ureaplasma spp, including U. parvum and U. urealyticum are commensal bacteria which commonly reside in the urogenital tract [3]. Ammonia is released during metabolism to generate ATP through urea hydrolysis by urease. Ureaplasma spp lack a cell wall and therefore cannot be visualised by Gram stain; diagnosis is reliant on a high index of suspicion with subsequent inoculation of enriched media, or molecular methods such as PCR. Presentations in
immunocompromised hosts are prone to protein including disseminated infection with septic arthritis, endocarditis or central nervous system infection, and hyperammonaemia syndrome.

The clinical manifestations of hyperammonaemia are variable, ranging from irritability and headache to encephalopathy, seizures and coma, especially with ammonia levels >200 µmol/L. Optimal treatment entails removal of excess ammonia with urgent and coma, especially with ammonia levels >200 µmol/L. Optimal treatment entails removal of excess ammonia with urgent continuous renal replacement therapy, and enhanced endogenous elimination via administration of substrates such as L-arginine, L-citrulline and L-ornithine, which promote the urea cycle [4]. Sodium benzoate reduces ammonia production by preventing metabolism of glutamine and glycine. IV dextrose decreases protein catabolism through provision of calories. Cessation of offending agents, for example sodium valproate and calcineurin inhibitors, is warranted. Efforts to limit ammonia intake are paramount, including reduction of dietary protein and restriction or modification of TPN.

Hyperammonaemia syndrome is a well-described complication of solid organ transplantation, particularly of the lung, and portends a poor prognosis [4]. The focus of infection may be either donor-derived [5] or via translocation of the host’s endogenous flora, presumably in the setting of urinary catheterisation [6]. In the context of AlloHSCT, historical cohorts indicate an incidence of <1% of idiopathic hyperammonaemia occurring early post-transplant with a high mortality [7]. Hyperammonaemia syndrome associated with Ureaplasma spp. has been described post-AlloHSCT [8] and promptly following chimeric antigen receptor T-cell therapy in two patients who had received AlloHSCT within twelve months, potentially mimicking immune effector cell-associated neurotoxicity syndrome [9, 10]. While pre-emptive screening and empiric treatment of those colonised with Ureaplasma spp. and Mycoplasma spp. has been promoted [11], the authors believe this approach would be of limited clinical benefit and may increase resistance rates given the low frequency of infection with these commensal organisms.

Most Ureaplasma species are susceptible to macrolides and fluoroquinolones [12], but resistance to these agents has been described. Importantly, antibiotics which target the cell wall have no activity, including all beta-lactams, which remain the cornerstone of treatment for febrile neutropenia in haematology patients.

Despite antimicrobial prophylaxis, AlloHSCT recipients remain at high risk of opportunistic infection. Given the inability for Ureaplasma spp./M. hominis to be cultured conventionally, a high index of suspicion is required. In immunocompromised patients who develop features of encephalopathy, it is prudent to consider assessment of serum ammonia levels in addition to other appropriate investigations. Confirmation of hyperammonaemia should prompt further investigation for Ureaplasma spp./M. hominis concurrent with hyperammonaemia-directed management. Empiric administration of antibiotics with activity against these organisms should take into consideration local resistance profiles.

Michael J. Shipton1, Paul M. Kinsella2, Thomas Davis3, Francesca Azzato1, George Taiaroa4, Jeff Szer5,6

David Routledge1 and Olivia Smibert5,6

1Department of Clinical Haematology, Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, VIC, Australia.
2Department of Microbiology, Royal Melbourne Hospital, Melbourne, VIC, Australia.
3Victorian Infectious Diseases Reference Laboratory, The Peter Doherty Institute for Infection and Immunity, Melbourne, VIC, Australia.
4Department of Microbiology and Immunology, The Peter Doherty Institute for Infection and Immunity, Melbourne, VIC, Australia.
5Department of Infectious Diseases, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia.
6Department of Infectious Diseases, Austin Health, Melbourne, VIC, Australia.

Correspondence

✉email: liv.smibert@austin.org.au

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Table 1. Trend of blood results from day 0 of AlloHSCT to day 25.

| Parameter                      | Reference range | Day 0 | Day 22 | Day 25 |
|-------------------------------|----------------|-------|--------|--------|
| Sodium (mmol/L)               | 135–145        | 140   | 145    | 138    |
| Potassium (mmol/L)            | 3.5–5.0        | 3.2   | 4.4    | 4.1    |
| Creatinine (µmol/L)           | 60–110         | 72    | 119    | 73     |
| Urea (mmol/L)                 | 4.0–9.0        | 8.9   | 22.5   | 3.4    |
| eGFR (mL/min/1.73 m²)         | >90            | 76    | 41     | 75     |
| Bilirubin (µmol/L)            | <21            | 13    | 9      | 6      |
| Alanine transaminase (U/L)    | 5–40           | 40    | 35     | 14     |
| Aspartate transaminase (U/L)  | <35            | 28    | 17     | 12     |
| Alkaline phosphatase (U/L)    | 30–110         | 42    | 64     | 57     |
| Gamma glutamyltransferase (U/L)| <50           | 36    | 76     | 42     |
| Albumin (g/L)                 | 35–50          | 27    | 18     | 14     |
| Ammonia (µmol/L)              | <60            | 946   | 547    |        |
| C-reactive protein (mg/L)     | <10            | 17.3  | 66.2   | –      |
| Haemoglobin (g/L)             | 120–170        | 75    | 73     | 63     |
| White cell count (x10⁹ cells/L)| 4.0–12.0      | 0.2   | 0.0    | 0.0    |
| Neutrophils (x10⁹ cells/L)    | 2.0–8.0        | 0.1   | 0.0    | 0.0    |
| Platelets (x10⁹ cells/L)      | 150–400        | 78    | 11     | 20     |

†36 µmol/L on day 15.
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AUTHOR CONTRIBUTIONS
MJS, PMK and TD wrote the manuscript. FA and GT performed laboratory analysis. JS, DR and OS provided feedback on the report. All authors read and approved the final manuscript.

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JS has received funding for consulting fees from Takeda and Alexion; has received honoraria from Takeda, Alexion and Pfizer; and is on an advisory board for Prevail Therapeutics and Novartis. DR has received honoraria from Amgen, BMS, Pfizer, Janssen and Sandoz; and financial support for attending meetings from Amgen and BMS. All others authors report no conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

CONSENT FOR PUBLICATION
The patient’s next of kin provided informed consent for the publication of this case presentation.

ADDITIONAL INFORMATION
Correspondence and requests for materials should be addressed to Olivia Smibert.

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