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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/m^2, Melphalan 140 mg/m^2 and rabbit antithymocyte globulin (rATG)-conditioned matched unrelated donor AlloHSCT. She was treated previously with hydroxyurea, anagrelide and ruxolitinib. Comorbidities included gastro-oesophageal reflux disease and depression. She was an ex-smoker with a mildly reduced diffusing capacity. Consequently, her Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) was 3, with a high risk of non-relapse mortality. Graft-versus-host disease prophylaxis included ciclosporin, methotrexate and rATG. Antimicrobial prophylaxis comprised posaconazole 300 mg orally daily and aciclovir 250 mg IV three times daily.

The transplant was delayed one week due to symptomatic rhinovirus infection. It was complicated by pyrexia and hypoxia during conditioning, thought to be rATG-mediated, which resolved with hydrocortisone, and stem cell infusion proceeded without delay. On day one post-infusion she again developed pyrexia, tachypnoea and hypoxia with neutropenia, and examination did not reveal any focal signs of infection. Meropenem and vancomycin were commenced and the patient was transferred to ICU for respiratory support. The C-reactive protein was 17.3 mg/L (<10 mg/L). Severe mucositis led to the institution of total parenteral nutrition (TPN) with day six and eleven methotrexate omitted.

Extensive investigation did not identify a source of infection, comprising blood cultures, urine microscopy and culture, and herpes multiplex PCR on blood (including HSV 1/2, CMV, EBV, adenovirus, enterovirus). Additional investigations for viral (SARS-CoV-2, influenza, adenovirus/enterovirus, parainfluenza virus, metapneumovirus, RSV) and bacterial infections (*Bordatella*, *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. Empiric 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 eosinophilic 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

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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 m^2)	>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 (x10^9 cells/L)	4.0–12.0	0.2	0.0	0.0
Neutrophils (x10^9 cells/L)	2.0–8.0	0.1	0.0	0.0
Platelets (x10^9 cells/L)	150–400	78	11	20

†36 μmol/L on day 15.

immunocompromised hosts are protean 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 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 beneficial, 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. Shipton[1], Paul M. Kinsella[2], Thomas Davis[1], Francesca Azzato[3], George Taiaroa[4], Jeff Szer[1], David Routledge[1] and Olivia Smibert[5,6]✉

[1]*Department of Clinical Haematology, Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, VIC, Australia.* [2]*Department of Microbiology, Royal Melbourne Hospital, Melbourne, VIC, Australia.* [3]*Victorian Infectious Diseases Reference Laboratory, The Peter Doherty Institute for Infection and Immunity, Melbourne, VIC, Australia.* [4]*Department of Microbiology and Immunology, The Peter Doherty Institute for Infection and Immunity, Melbourne, VIC, Australia.* [5]*Department of Infectious Diseases, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia.* [6]*Department of Infectious Diseases, Austin Health, Melbourne, VIC, Australia.*
✉*email: liv.smibert@austin.org.au*

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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.

COMPETING INTERESTS

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.