Mediterranean Journal of Hematology and Infectious Diseases

Letter to the Editor

A Case of Fatal Hyperammonaemic Encephalopathy in a Patient with End-Stage Multiple Myeloma

Keywords: High risk Multiple Myeloma; Hyperammonemia.

Published: January 1, 2023 **Received: November 11, 2022** **Accepted: December 21, 2022**

Citation: Passucci M., Fazio F., Petrucci M.T.. A case of fatal hyperammonaemic encephalopathy in a patient with end-stage multiple myeloma. Mediterr J Hematol Infect Dis 2023, 15(1): e2023012, DOI: http://dx.doi.org/10.4084/MJHID.2023.012

To the editor.

We want to comment on a rare and life-threatening neurologic complication of Multiple Myeloma called hyperammonemia encephalopathy.

Despite improved prognosis due to the greater availability of novel agents like proteasome inhibitors, immunomodulatory drugs, and anti-CD38 monoclonal antibodies, multiple myeloma (MM) remains incurable; it is associated with a more aggressive course in about 20-30% of the cases. Disease features related to bone marrow infiltration or paraproteinemia include hypercalcemia, renal insufficiency, anemia and osteolytic bone lesions. Neurologic symptoms like altered mental status, depression/euphoria, and seizures are usually associated with hypercalcemia, renal insufficiency, or hyperviscosity. Hyperammonemia is a rare MM-related condition which may cause a neurologic syndrome in MM patients.

Here we report a case of hyperammonaemic encephalopathy (HE) in advanced relapsed/refractory non-secretory multiple myeloma.

In May 2020, a 61-year-old female came to our hematologic Emergency Department for lower back pain that had progressively worsened for several months. She presented with mild anemia (Hb 10.1 g/dl), hypercalcemia, and hyperuricemia with acute renal failure (calcium 19 mg/dl, uricemia 10.6 mg/dl, creatinine 3.0 mg/dl). A spine magnetic resonance imaging (MRI) showed several osteolytic lesions in the dorsal-lumbar region. A full MM workup was pursued. Serum protein electrophoresis revealed hypogammaglobulinemia; no monoclonal protein was detected; serum free light chain kappa/lambda ratio was 1.34; 24-hour proteinuria was < 200 mg/24h, and urine immunofixation was negative. A bone marrow aspirate revealed 37% of clonal plasma cells; 4% of plasma cells were also identified in the peripheral blood. Fluorescence in situ hybridization (FISH) performed on bone marrow plasma cells showed t(11;14), defining MM as a standard risk by cytogenetics. According to the 2016 International Myeloma Working Group (IMWG) diagnostic criteria, we diagnosed ISS III – R-ISS II non-secretory MM. In June 2020, we started induction treatment bortezomib (1.3 mg/m^2 on days 1, 4, 8 and 11), thalidomide (200 mg/die), and dexamethasone (40 mg on days 1-4 and 8-11) every three weeks – VTd regimen. During the fourth cycle, she developed right lower limb deep vein thrombosis requiring anticoagulants and, according to this condition, she performed the last two cycles without thalidomide. At the end of induction, stem cells were collected by leukapheresis following chemo-mobilization with cyclophosphamide (2.4 mg/m^2), granulocyte colony-stimulating factor, and plerixafor. In January 2021, high-dose melphalan conditioning at 200 mg/m^2 was administered in two separate doses, followed by peripheral blood autologous stem cell transplantation after two days. Based on the International Myeloma Working Group (IMWG) response criteria, the patient obtained a complete response (CR). In July 2021, complete blood counts revealed a progressive increase of peripheral large unstained cells (LUC). Cytomorphological peripheral blood examination showed 21% of plasma cells, diagnostic for end-stage multiple myeloma (secondary plasma cell leukemia). The patient started second-line therapy with a DRd regimen (daratumumab, lenalidomide, dexamethasone). After the first dose of intravenous daratumumab, the patient progressively developed altered mental status, and she came to our Emergency Department (ED). Physical examination showed poor general conditions: the patient was disoriented in space and time with severe lethargy and diffuse muscle hypotonia but no focal deficits. Blood exams showed severe anemia, thrombocytopenia (Hb 9.8 g/dl, PLT 2.000/mm^3), and hyperuricemia (blood uric acid 11.9 mg/dl) with normal liver/renal function and no electrolytic abnormalities. Serum B12 and thyroid hormones were normal. Brain computed tomography (CT) and magnetic resonance imaging (MRI) were negative for intracranial bleeding or space-

occupying lesions; there were no radiological features of brain metabolic or vascular distress. Cytological, chemical-physical and microbiological analyses of cerebrospinal fluid were negative for MM localization or signs of bacterial, viral, or fungal infections (cultural and molecular exams were performed). Considering hyperammonemia in the diagnostic workup, we performed blood ammonium detecting it at a high concentration (179 µmol/l, normal range 11-51 µmol/l). We immediately started antibiotic therapy with vancomycin and evacuation therapy with enemas. Unfortunately, blood ammonium remained stable at > 100 µmol/l, and the patient's neurological condition worsened until coma and death within a few days.

This case shows a rare manifestation of end-stage multiple myeloma presenting with severe hyperammonaemic encephalopathy. Neurologic manifestations in MM often correlate to high calcium levels, drug side effects, hyperviscosity, or infections. Hyperammonaemia is much more frequent in acute or chronic liver failure; uncommonly, high levels of ammonia leading to encephalopathy have been described in multiple myeloma. MM-related hyperammonemia is often associated with advanced disease (International Staging System stage III) and with high risk features such as the presence of plasma cells in the peripheral blood, unfavorable cytogenetics abnormalities, and extra-medullary localization.[1]

The pathogenesis of increased ammonia blood levels in MM has yet to be fully understood. However, it is probably related to MM infiltration of the liver leading to hepatic failure and portosystemic shunts. This hypothesis is in line with the evidence from the case series of increased HE risk in patients with MM and the presence of plasma cells in peripheral blood.[2] In addition, a review of 27 HE cases showed a higher frequency of IgA MM.[3]

Secondary plasma cell leukemia (PCL), nearly 40% of all cases of PCL, is associated with end-stage disease and a worse patient outcome,[4] as in our patient. In the absence of liver failure, recent studies suggest that either aggressive plasma cell clone can produce ammonia or myeloma-related humoral factors can influence amino acid metabolism leading to an increase in blood ammonium. Brain toxicity derives from converting excess ammonium into glutamine by astrocytes, leading to an osmotic transmembrane gradient and subsequent cerebral edema. Moreover, glutamine can negatively regulate lysosomal proteolysis and activate intracellular proteasome activation; this could explain the possible therapeutic effect of proteasome inhibitors in HE.[5] Amino acids L -ornithine- L –aspartate (LOLA) supplementation (together with specific anti-myeloma treatment) could support the hepatic production of urea, reducing ammonia blood levels.[6]

Symptoms of HE are progressive and start with confusion, dizziness, and tremor, leading to irreversible coma in the absence of specific treatment, with a mortality rate of about 40%.[7] First, a proper diagnostic workup of HE requires the exclusion of infective or disease-associated causes of encephalopathy and a blood ammonium measurement. Central nervous system localization of plasma cells is rare both at diagnosis and relapse (1%), but it is associated with a worse prognosis. HE treatment is primarily directed to the cause of increased ammonia production and so in an aggressive therapeutic approach to the underlying MM. Symptomatic treatment tends to reduce pathological ammonia production or to increase its clearance through enemas, osmotic laxatives, and antibiotic therapy acting on the gut microbial environment.

Our patient presented MM end-stage progression in secondary plasma cell leukemia and started a specific treatment with anti-CD38 and lenalidomide-based triplet. There is no clear association between specific treatments and the onset of “iatrogenic” HE. A case of HE after the first dose of daratumumab is reported by Murtaza et al. in a patient with MM.[8] However, there is no clear pathogenic association between the drug and this condition.

Sharma et al. reported a patient with kappa light chain MM developing HE at disease onset and not at progression (or after treatment for progression); the clear evidence is that also in this case the clinical picture was rapidly worsening (the patient required support in Intensive Care Unit), and HE was substantially a diagnosis of exclusion.[9] The authors reported the efficacy of cyclophosphamide combined with new drugs (the so-called VCd regimen, bortezomib/cyclophosphamide/dexamethasone). An aggressive approach that comprises chemotherapy has demonstrated variable efficacy in rapidly reducing disease burden and neurologic symptoms. Also in other case series, VCd is often reported.[10] Nevertheless, the prognosis of this condition in MM remains poor despite chemotherapy.

Our report underlines the importance of considering HE in the differential diagnosis of neurologic symptoms in patients with MM both at diagnosis and at relapse. Despite its rarity, this condition has to be promptly recognized and clinicians should keep MM in the differentials in case of hyperammonaemia.

Mauro Passucci, Francesca Fazio and Maria Teresa Petrucci.

Department of Translational and Precision Medicine, Policlinico Umberto I, La Sapienza University of Rome, Italy

Competing interests: The authors declare no conflict of Interest.

Correspondence to: Dr. Mauro Passucci. E-mail: passucci.mauro@gmail.com

References:

1. Costa, L. J., & Usmani, S. Z. (2020). Defining and Managing High-Risk Multiple Myeloma: Current Concepts, Journal of the National Comprehensive Cancer Network J Natl Compr Canc Netw, 18(12), 1730-1737. Retrieved May 20, 2022. https://doi.org/10.6004/jnccn.2020.7673 PMid:33285523
2. Ikewaki J, Ogata M, Imamura T, Kohno K, Nakayama T, Kadota J. Development of hyperammonemic encephalopathy in patients with multiple myeloma may be associated with the appearance of peripheral blood myeloma cells. Leuk Lymphoma. 2009; Apr;50(4):667-9. https://doi.org/10.1080/10428190902741489 PMid:19373670
3. Jaime Lora-Tamayo, Xavier Palom, José Sarrá, Oriol Gasch, Virginia Isern, Alberto Fernández de Sevilla, Ramón Pujol, Multiple Myeloma and Hyperammonemic Encephalopathy: Review of 27 Cases, Clinical Lymphoma and Myeloma, Volume 8, Issue 6, 2008, Pages 363-369, ISSN 1557-9190, https://doi.org/10.3816/CLM.2008.n.054 PMid:19064403
4. Gertz MA, Buadi FK. Plasma cell leukemia. Haematologica. 2010;95(5):705-707. https://doi.org/10.3324/haematol.2009.021618 PMid:20442443 PMCid:PMC2864374
5. Howman R, Thakerer A, Pitman M, et al. Bortezomib, cyclophosphamide, and dexamethasone: highly effective for rapid reversal of myeloma-associated hyperammonemic encephalopathy. Leuk Lymphoma 2010; 51 : 2299 - 2
6. https://doi.org/10.3109/10428194.2010.518654302. PMid:20929329
7. Amit Patel, Umeer Waheed, Stephen J. Brett, Amin Rahemtulla, Jane F. Apperley & Parind B. Patel. Rapid initial response of myeloma hyperammonemic encephalopathy to L-ornithine-L-aspartate and dexamethasone therapy, Leukemia & Lymphoma, 2014; 55:1, 198-200 https://doi.org/10.3109/10428194.2013.794266 PMid:23573827
8. Anthony Pham, John L. Reagan, Jorge J Castillo; Plasma Cell Myeloma Causing Hyperammonemia Associated with High Inpatient Mortality. Blood 2012; 120 (21): 5002. https://doi.org/10.1182/blood.V120.21.5002.5002
9. Murtaza G, Lu H, Faqah A, Konowitz N, Kuruvilla A, Adhikari S. Multiple Myeloma-Induced Hyperammonemic Encephalopathy. J Hematol. 2017;6(1):29-31. https://doi.org/10.14740/jh322e PMid:32300389 PMCid:PMC7155816
10. Sharma, S. K., Choudhary, D., Handoo, A., Dhamija, G., Kharya, G., Khandelwal, V., Dhamija, M. and Kothari, S. An unusual cause of anemia and encephalopathy, Mediterranean Journal of Hematology and Infectious Diseases, 2015; 7(1), p. e2015036. https://doi.org/10.4084/mjhid.2015.036 PMid:25960864 PMCid:PMC4418384
11. Howman R, Thakerer A, Pitman M, Ding N, Thompson PA, Khot A, Harrison SJ. Bortezomib, cyclophosphamide, and dexamethasone: highly effective for rapid reversal of myeloma-associated hyperammonemic encephalopathy. Leuk Lymphoma. 2010;51(12):2299-2302. https://doi.org/10.3109/10428194.2010.518654 PMid:20929329