



Severe Hyperammonaemic Encephalopathy in a Patient with Secondary Plasma Cell Leukemia Treated with Daratumumab: A Case Report

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Introduction

Despite an improvement in prognosis due to greater availability of novel agents, such as proteasome inhibitors, immunomodulatory drugs and anti-CD38 monoclonal antibodies, Multiple Myeloma (MM) remains an incurable disease and is associated with a more aggressive and resistant course in 20-30% of cases. Disease symptoms are related to the bone marrow clonal plasma cells infiltration and MM patients presents with a variety of disease-related complications; the most common 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 that can cause mental status alteration in MM patients.

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

In May 2020, a 61-years-old female was admitted to our hematologic Emergency Department for lower back pain that has been progressively worsening for several months. Moreover, 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 Magnetic Resonance Imaging (MRI) of the column showed several bone osteolytic dorso-lumbar lesions. A fully MM work up was pursued. Serum protein electrophoresis revealed hypogammaglobulinemia, no monoclonal protein; 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 aspi-



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rate revealed the presence of 37% of clonal plasma cells; in addition, 4% of pathological plasma cells were identified in the peripheral blood. Fluorescence In Situ Hybridization (FISH) performed on bone marrow plasma cells showed t (11;14), defining standard risk cytogenetic abnormalities. According to the 2016 International Myeloma Working Group (IMWG) diagnostic criteria, the patient was diagnosed with ISS III – R-ISS II non-secretory MM. In June 2020, induction therapy based on bortezomib (1.3 mg/m² on days 1, 4, 8 and 11), thalidomide (200 mg/die) and dexamethasone (40 mg on days 1,2-4,5 and 8,9-11,12) every three weeks was immediately started. During the fourth cycle, despite the thromboembolic prophylaxis, she developed right lower limb deep vein thrombosis requiring oral anticoagulants therapy and, according to this condition, she performed the last two cycles of treatment without thalidomide. At the end of the induction therapy, peripheral blood stem cells were collected following chemo-mobilization with cyclophosphamide (2.4 mg/m²), granulocyte colony stimulating factor and plerixafor. In January 2021 high-dose melphalan conditioning at 200 mg/m² was administered in two separate doses, followed by peripheral blood autologous stem cells 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). We performed a cytomorphological examination on peripheral venous blood smear which showed 21% of plasma cells, diagnostic for end-stage multiple myeloma (secondary plasma cell leukemia). The patient started second line therapy according to DRd scheme (daratumumab, lenalidomide, dexamethasone). After the first dose of intravenous daratumumab, the patient progressively developed altered mental status and she was admitted to our Emergency Department (ED). In the ED, physical examination showed poor general conditions: the patient was disoriented in space and time with severe lethargy; moreover, there was diffuse muscle hypotonia without focal neurologic deficits. Blood exams showed severe anemia, thrombocytopenia (Hb 9.8 g/dl, PLT 2.000/mm³) and hyperuricemia (blood uric acid 11.9 mg/dl) with normal liver/renal function and no electrolytic alterations. Serum B12 vitamin 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 not radiological features of brain metabolic or vascular distress. Cytological, chemical-physical and microbiological analysis of cerebrospinal fluid were negative for MM localization or signs of any bacterial, viral or fungal infections (both cultural and molecular exams were performed). Considering hyperammonemia as a rare MM complication, we performed blood serum concentration of ammonium that was found at high concentration, 179 µmol/l (normal range 11-51 µmol/l). We immediately start antibiotic therapy with vancomycin and evacuation therapy with enemas but, unfortunately, the blood ammonium concentration remained stable at > 100 µmol/l and the patient's neurological condition progressively worsened until the onset of irreversible coma and then death within a few days.

This clinical case report shows a rare manifestation of end-stage multiple myeloma presenting with a severe hyperammonaemic encephalopathy. Neurologic manifestations in MM are often correlated to high levels of calcium, side effects of drugs, hyperviscosity related to paraprotein or infections. Hyperammonaemia is typical of chronic liver failure but uncommonly high levels of ammonia leading to encephalopathy have

been also described in multiple myeloma. Hyperammonemia related to multiple myeloma is often a severe condition in advanced stage of the disease (International Staging System stage III) and it can be considered part of “high risk” characteristics, such as the presence of clonal plasma cells in the peripheral blood, unfavorable cytogenetics abnormalities and extra-medullary multiple myeloma localization) [1].

Pathogenesis of increased ammonia blood levels in multiple myeloma is not fully understood but is probably related to MM infiltration of the liver leading to hepatic failure and/or portosystemic shunts. This hypothesis is in accordance with the evidence from case series of an increased risk of HE in patients with MM and presence of plasma cells in peripheral blood [2]. Moreover, in a review of 27 HE cases showed a higher frequency of IgA MM [3]. Secondary Plasma Cell Leukemia (PCL), near 40% of all cases of PCL, is associated with end-stage disease and with a worse patient outcome [4], as in our patient.

In the absence of liver dysfunction, recent studies suggest either aggressive plasma cell clone can produce ammonia or myeloma-related humoral factors can influence amino acid metabolism leading to an increase in ammonia blood levels. Brain toxicity is mainly due to the conversion of excess ammonium in glutamine by astrocytes, leading to an osmotic trans membrane 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 correct diagnostic work-up of HE requires the exclusion of infective or disease-associated causes of encephalopathy and a blood ammonium concentration measurement. In particular, localization of clonal plasma cells in the Central Nervous System (CNS) is rare both at diagnosis and at relapse (1%) but it is associated with a worse prognosis. Therapy of HE is primarily directed to treat the cause of increased ammonia production and consists in immediately starting an aggressive treatment for the underlying MM. Symptomatic treatment tends to reduce pathological ammonia production or to increase its clearance through enemas, osmotic laxatives and antibiotics therapy acting on gut microbial environment.

Our patient presented multiple myeloma end-stage progression in secondary plasma cell leukemia and she started a specific treatment according to monoclonal antibodies (moAbs) anti CD38 and lenalidomide based triplet. To date, there is no clear association between specific treatments and the onset of “iatrogenic” HE. A case of HE following the first dose of anti-CD38 moAbs in a patient with MM is reported by Murtaza et al [8], but no pathogenetic link has been identified.

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 should be rapidly recognized and clinicians should keep MM in the differentials in case of hyperammonemia. Nevertheless, while intensive chemotherapy has demonstrated response in reducing blood ammonia concentration due to MM disease, the prognosis of this condition remains poor.

References

1. Costa LJ, Usmani SZ. Defining and Managing High-Risk Multiple Myeloma: Current Concepts, *J Natl Compr Canc Netw*. 2020; 18: 1730-1737.
2. Ikewaki J, Ogata M, Imamura T, Kohno K, Nakayama T, et al. Development of hyperammonemic encephalopathy in patients with multiple myeloma may be associated with the appearance of peripheral blood myeloma cells. *Leuk Lymphoma*. 2009; 50: 667-669.
3. Lora-Tamayo J, Palom X, Sarrá J, Gasch O, Isern V, et al. Multiple Myeloma and Hyperammonemic Encephalopathy: Review of 27 Cases. *Clin Lymphoma Myeloma*. 2008; 8:363-369.
4. Gertz MA, Buadi FK. Plasma cell leukemia. *Haematologica*. 2010; 95: 705-707.
5. Howman R, Thakerer A, Pitman M, Ding N, Thompson PA, et al. Bortezomib, cyclophosphamide, and dexamethasone: Highly effective for rapid reversal of myeloma-associated hyperammonemic encephalopathy. *Leuk Lymphoma*. 2010; 5: 2299-2302.
6. Patel A, Waheed U, Brett SJ, Rahemtulla A, Apperley JF, et al. Rapid initial response of myeloma hyperammonemic encephalopathy to L-ornithine-L-aspartate and dexamethasone therapy. *Leuk Lymphoma*. 2014; 55: 198-200.
7. Pham A, Reagan JL, Castillo JL. Plasma Cell Myeloma Causing Hyperammonemia Associated with High Inpatient Mortality. *Blood*. 2012; 120: 5002.
8. Murtaza G, Lu H, Faqah A, Konowitz N, Kuruvilla A, et al. Multiple Myeloma-Induced Hyperammonemic Encephalopathy. *J Hematol*. 2017; 6: 29-31.