

Hyperammonemic Encephalopathy: A Rare Presentation of Relapsed Multiple Myeloma

Sasmith R. Menakuru^{a, c}, Mona Atta^a, Nischala Ammannagari^b,
Mohamad Younes^b

Abstract

Hyperammonemia is a rare cause of encephalopathy in multiple myeloma in the absence of hepatic involvement. This is the only reported case of a 74-year-old man who presented with multiple myeloma and achieved complete remission but developed hyperammonemia afterward. He was aggressively treated with a combination of chemotherapy and immunotherapy, with a resolution of his encephalopathy; however, within one month, he relapsed with encephalopathy. He ultimately decided to pursue comfort-care measures. The authors conclude that hyperammonemia in multiple myeloma is a rare but important differential in patients with encephalopathy of unknown causes. Aggressive treatment is of the utmost importance due to the high mortality associated with the condition.

Keywords: Hyperammonemia; Encephalopathy; Multiple myeloma; Treatment

Introduction

Multiple myeloma (MM) is the second most common hematologic malignancy, characterized by the neoplastic proliferation of plasma cells, which in turn produces a monoclonal immunoglobulin [1]. MM can cause a wide spectrum of diseases with high mortality rates, ranging from skeletal destruction from plasma cells to renal dysfunction due to immunoglobulin deposition [2, 3]. Most patients will present subacutely; however, a small number of patients will present with acute findings such as spinal cord compression or hyperviscosity. MM defying events include calcium elevation, renal insufficiency, anemia, and bone disease. Diagnostic workup includes a blood count with smear, serum protein electrophoresis (SPEP) and

immunofluorescence, serum free light chains, renal and liver function testing, calcium level, lactate dehydrogenase (LDH), albumin, B2 microglobulin, urinalysis for proteinuria, urine electrophoresis and immunofluorescence, next generational testing, cytogenetics, and imaging, including a whole body computed tomography (CT) and a whole body magnetic resonance imaging (MRI) if CT is negative to reveal bone lesions [4]. A definitive diagnosis involves bone marrow aspiration and biopsy for analysis of marrow cellularity, with possible additional study of cytogenetics and specific protein production. Upon diagnosis, patients can seek medical treatment with chemotherapy, targeted therapy such as enzyme inhibition and monoclonal antibodies, immunomodulatory medications, steroids, and bone-modifying drugs to significantly improve symptom development and overall mortality [5].

One of the rare complications associated with MM is encephalopathy, which is attributed to hyperammonemia in the absence of liver involvement, as seen in this case. Based on studies published thus far, it is proposed that ammonia is produced and released from myeloma cell lines themselves [6]. Another theory is that myeloma-related humoral factors influence ammonia acid metabolism, leading to hyperammonemia [7]. A persistent finding in cases of hyperammonemia due to MM is that lactulose and hemodialysis do not lower ammonium levels, and therefore, the mainstay of treatment is chemotherapy with high-dose cyclophosphamide, bortezomib, and dexamethasone [7-9].

In this report, we present a case of a patient who had achieved remission with medical management of MM before he eventually returned to the hospital with altered mentation. The evaluation revealed elevated levels of ammonia as well as an increase in the free light chain ratio after prior improvement, and a repeat bone marrow biopsy demonstrated recurrent marrow overgrowth with plasma cells. After chemotherapy was initiated, ammonia levels normalized, and the patient's mentation returned to baseline. Delays in treatment can lead to a poor prognosis, and without treatment, there is a 100% mortality rate, according to a study done by Pham et al [9].

Case Report

In June 2019, a 74-year-old man with no significant past medical history was noted to be anemic with a hemoglobin of 9.2 g/dL (13.8 - 17.2), white cell count of $6.4 \times 10^3/\text{mm}^3$ (4.5 - 11.0), platelets $96 \times 10^9/\text{L}$ (150 - $450 \times 10^9/\text{L}$), mean corpuscular vol-

Manuscript submitted January 27, 2023, accepted April 20, 2023
Published online April 30, 2023

^aDepartment of Internal Medicine, Indiana University School of Medicine, Muncie, IN, USA

^bHematology Oncology, New York Oncology Hematology, Albany, NY, USA

^cCorresponding Author: Sasmith R. Menakuru, Department of Internal Medicine, Indiana University School of Medicine, Muncie, IN, USA.
Email: smenakur@iu.edu

doi: <https://doi.org/10.14740/jh1097>

ume (MCV) 98 fL (80 - 100) and elevated total protein of 9.6 g/dL (6.0 - 8.3). The patient was not taking any medication at that time and lived a healthy lifestyle. The patient's laboratory testing revealed a calcium of 9.6 mg/dL (8.6 - 10.2) and a creatinine of 1 mg/dL (0.7 - 1.3). Further evaluation revealed beta-2 microglobulin of 6.68 μ g/mL (0.70 - 1.80), albumin of 3.9 g/dL (3.4 - 5.4), and his LDH of 158 IU/L (105 - 333). His kappa/lambda ratio was 31.1 (0.26 - 1.65) with kappa light chains of 92.2 mg/L (3.3 - 19.4) and lambda light chains of 2.7 mg/L (5.7 - 26.3). Immunoglobulin testing revealed immunoglobulin G (IgG) of 5,250 g/L (6.0 - 16.0), SPEP revealed a paraprotein of 4.1 g/dL (6.4 - 8.3), and immunofixation revealed IgG kappa. A skeletal survey did not reveal lytic lesions, but a bone marrow aspirate and biopsy confirmed the diagnosis of MM and 90% involvement of the bone marrow. Cytogenetics showed loss of chromosome Y, deletion of 13q, and gain of 1q. Given these findings, the patient was classified as having an International Myeloma Working Group (IMWG) uniform response criteria stage 3.

The patient was treated with lenalidomide, bortezomib, and dexamethasone (RVD) and attained complete remission after a total of 12 cycles. The patient was referred for autologous stem cell transplantation, but he declined. He continued lenalidomide maintenance with follow-up every month. By June 2022, his laboratory results for SPEP, kappa light chains, kappa/lambda ratio, calcium, hemoglobin, and creatinine were within normal limits, and the patient was doing remarkably well. According to the IMWG uniform response criteria, the patient was defined as having a complete response.

However, in September 2022, he was admitted to the hospital for altered mental status with rapid deterioration. On physical examination, the patient had an increased respiratory rate, slurred speech, tremors of the hands, and marked confusion. His SPEP revealed an increased paraprotein of 1.1 g/dL, his kappa light chains increased to 47.7, his kappa/lambda ratio was 5.1, and he was found to have hyperammonemia of 62 μ mol/L ($<$ 30 μ mol/L). His calcium had increased to 11.9 mg/dL, hemoglobin had dropped to 9.1 g/dL and his creatinine was 1.3 mg/dL. A bone marrow biopsy revealed 100% involvement of the bone marrow with sheets of aberrant plasma cells. According to the IMWG uniform response criteria, the patient relapsed from a complete response.

His ammonia levels continued to increase, and his encephalopathy continued to worsen despite treatment with lactulose and rifaximin. His aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, gamma-glutamyl transferase (GGT) were unremarkable and a MRI of the liver showed no concerning findings. A lumbar puncture and MRI of the brain were unrevealing. Given that all testing was unrevealing, his confusion was attributed to hyperammonemia secondary to MM. He was started on bortezomib and dexamethasone without significant improvement in his symptoms. He was transferred to a higher center and then started on daratumumab, carfilzomib, and dexamethasone. The patient developed an allergic reaction to carfilzomib, necessitating its discontinuation. He was continued on daratumumab combined with dexamethasone with the addition of bortezomib to his regimen, which led to the resolution of his encephalopathy, a decline in serum ammonia levels, and a significant improvement in his kappa light chains and

monoclonal protein after 5 weeks of treatment.

By November 2022, his SPEP was 0.25 g/dL, his kappa light chains were 14.6, and the kappa/lambda ratio was 6.08, and the patient was doing well. The patient's ammonia levels were recorded after discharge during his follow-up appointments (Fig. 1). Unfortunately, he was admitted to the hospital 1 month later with altered mental status, again with marked elevation of ammonia levels (114 μ mol/L) and an increase in the free light chain ratio (26.1). His ammonia level peaked at 212 μ mol/L 5 days later, and given his rapid deterioration and poor performance status, he was transitioned to comfort care.

Discussion

MM can rarely present as encephalopathy due to hyperammonemia in the absence of liver involvement; however, it has never been reported as the presenting sign of a relapse occurring after a patient had been in remission for several years [10]. In most cases, neurological manifestations of MM are due to hypercalcemia, hyperviscosity, infection, or medication side effects. Hyperammonemia due to MM is often associated with advanced stages of disease (International Staging System (ISS)-3), plasma cells in the peripheral circulation, cytological abnormalities, and extramedullary locations [11, 12]. Patients with an advanced stage of the disease and poor prognostic factors such as 1q gain are more susceptible to the development of hyperammonemia. Hyperammonemia encephalopathy due to MM has been associated with high mortality and is characterized by lethargy, confusion, and asterixis, with reported cases progressing rapidly to coma and subsequent death [13].

The pathophysiology of hyperammonemia in patients with MM is not well understood, but according to a study done by Otsuki et al, human myeloma cell lines produce an elevated amount of ammonia *in vitro* compared to non-MM cells [5]. Toxicity arises from the conversion of excess ammonia into glutamine by astrocytes, which leads to an osmotic transmembrane gradient and the ensuing cerebral edema. The overproduction is possibly due to mutations in the enzymes involved in the urea cycle. Another theory is thought to be due to excess protein synthesis in myeloma cells, including the synthesis of immunoglobulins and cytokines that induce excess ammonia biosynthesis [6]. Ikewaki et al postulated that the mechanism of hyperammonemia is the hepatic infiltration by MM cells, leading to liver failure, coupled with the presence of myeloma cells in the peripheral blood [13]. Howman et al theorized that liver infiltration of the plasma cells could result in portal hypertension and a portosystemic shunt that results in hyperammonemia [14]. Gaiani et al suggested an alteration in urea metabolism that would increase protein synthesis and subsequent catabolism of plasma cells, leading to hyperammonemia [15]. In our case, we suspected hyperammonemia was due to the MM cells themselves without hepatic involvement, as the patient's liver function tests were within normal limits, his MRI of the liver was normal, and he did not respond to lactulose or rifaximin.

A review by Pham et al [9] presented 40 patients with MM-induced hyperammonemia-induced encephalopathy and showed that the median age was 67 years with a male-to-female ratio of

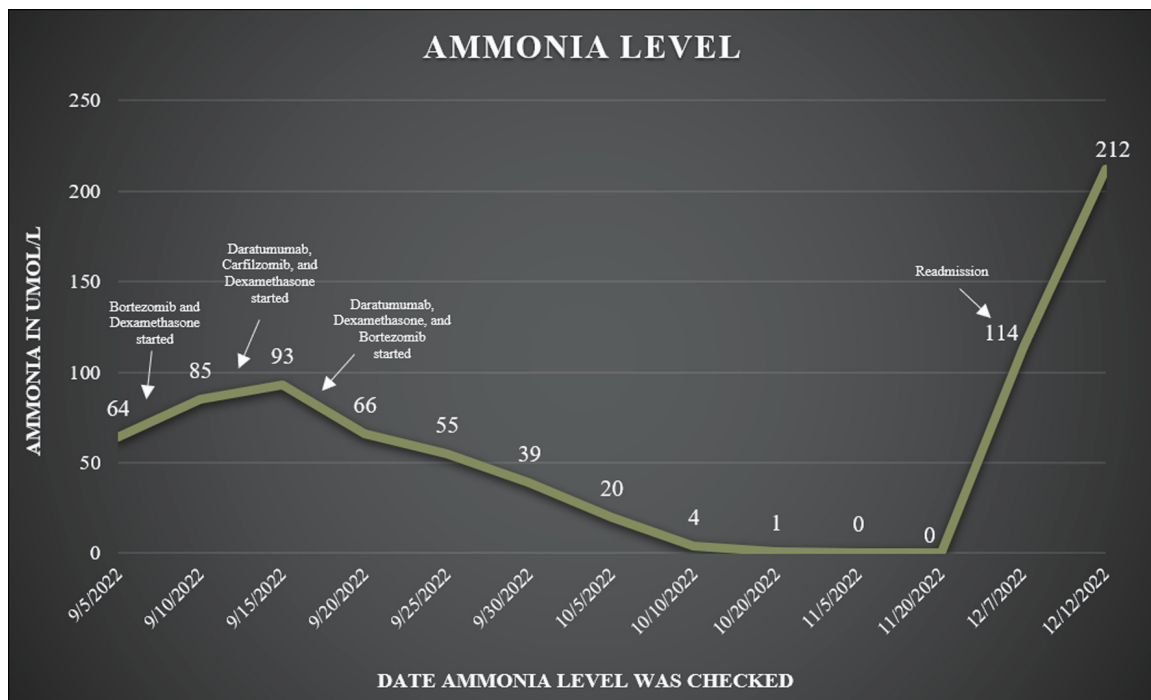


Figure 1. Patient's ammonia levels recorded after discharge during his follow-up appointments.

1.8:1. The median ammonia level was found to be 114 $\mu\text{mol/L}$, and IgG was the most common type, followed by IgA. Inpatient mortality was 48%, with 31% mortality in patients with hyperammonemia who received MM-directed treatment versus 100% mortality in those who did not [16]. In cases of hyperammonemia, aggressive treatment with chemotherapy and immunotherapy is the mainstay. It has also been found that ammonia levels and a patient's state of consciousness return to baseline when the underlying MM responds to treatment. A similar review by Lora-Tamayo et al showed that 22 of the 25 patients with hyperammonemia due to MM had lower ammonia levels after treatment, and 15 of the 25 survived [17].

A review performed by Talamo et al [18] of 279 patients with encephalopathy due to MM found that 70 patients had hyperammonemia due to liver dysfunction. Of the 279 patients, only eight had serum ammonia greater than 47 $\mu\text{mol/L}$, which is the upper limit of normal, and only two patients were found to have encephalopathy due to MM as they did not have concomitant cause factors such as hypercalcemia, central nervous system disease, or plasma hyperviscosity. These two patients had a rapid improvement in their neurological function after therapy, with normalization of their ammonia levels [18].

In current literature, most patients with hyperammonemia due to MM have an initial presentation or a refractory case (Table 1) [12, 19, 20]. The case reported here is rare, as our patient was in remission but thereafter relapsed, and the initial presentation was of hyperammonemia and not typical MM symptoms. The patient responded well to daratumumab, dexamethasone, and bortezomib therapy and eventually had his mental status return to baseline. However, he relapsed again with higher levels of ammonia than before, and due to his rapid

deterioration, he was transitioned to comfort care. The authors urge physicians to consider MM in cases of hyperammonemia of unknown cause, as timely management with aggressive treatment is of the utmost importance. It also underscores the gain of 1q as an aggressive and poor prognostic sign in MM.

Acknowledgments

None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

No conflict of interest to declare.

Informed Consent

Informed consent has been taken from the patient.

Author Contributions

SRM and MY saw the case. SRM did research on the topic and wrote the paper. MA and NA edited the paper.

Table 1. Hyperammonemia Due to MM in Current Literature

Source	Initial treatment	Presenting symptom upon relapse	Ammonia levels	Outcome
Douedi et al, 2021 [19]	A 51-year-old male was diagnosed with MM 6 years prior to relapse. He underwent four cycles of chemotherapy with ixazomib, darzalex, venetoclax, and stem cell transplant two years prior to relapse. He was on maintenance therapy with daratumumab weekly with chronic dexamethasone.	After 6 years in remission, he presented to the emergency department with radiating chest pain for 1 week and was found to have a hemoglobin of 8 and platelets of 20. He was hospitalized and developed encephalopathy after 6 days.	The patient's ammonia level was 118 µg/dL at the time of encephalopathy, and it eventually rose to 256 µg/dL.	He was intubated for airway protection due to encephalopathy and ultimately chose to go to hospice after 2 weeks as he was unable to be weaned off the ventilator.
Murtaza et al, 2017 [12]	A 73-year-old male was on hemodialysis at the time of diagnosis with hemodialysis to manage his renal failure and was treated with bortezomib and dexamethasone. He had relapsed one year later and was treated with second-line chemotherapy with thalidomide and dexamethasone, but his disease continued to progress. He then started third-line therapy with lenalidomide and dexamethasone. Lenalidomide was held due to cytopenia. He continued to worsen over the next 2 years. He resumed on lenalidomide, but the disease progressed, so he was started on daratumumab with dexamethasone, acetaminophen, and diphenhydramine.	He became lethargic after the first dose of daratumumab. Daratumumab was selected because of the patient's cytopenia, and renal disease, which precluded alternatives. The patient rapidly declined and became unresponsive.	The patient's ammonia level was 120 µg/dL initially; and rose to 127 µg/dL despite treatment.	He was treated with lactulose, rifaximin, vancomycin, cefepime, and acyclovir, but his ammonia level worsened. The authors contemplated using cyclophosphamide, but due to the patient's poor prognosis with severe cytopenia and lack of response to treatment thus far, he was a poor candidate. The family decided to withdraw care, and the patient passed after 5 days of disease progression.
Nakamura et al, 2023 [20]	A 75-year-old female was initially treated with bortezomib-melphalan-prednisolone (VMP), lenalidomide-dexamethasone (Ld), pomalidomide-dexamethasone (Pd), bortezomib-dexamethasone (Bd), and panobinostat-bortezomib-dexamethasone, but had disease progression.	After disease progression on the initial five therapies over 2 years and 3 months, the patient was started on carfilzomib-lenalidomide-dexamethasone (KRd). She developed encephalopathy one day later.	The patient's ammonia level was 286.6 µg/dL.	The patient was treated with branched-chain amino acid (BCAA) agent for hyperammonemia and continued on KRd treatment. Despite improvement in ammonia levels, her MM progressed, and the patient ultimately died 7 days later.
Nakamura et al, 2023 [20]	A 61-year-old female had relapsed after 3 years following an MM diagnosis at age 55. The patient was initially treated with an autologous peripheral blood stem cell transplant. She was then managed consecutively with Ld, Pd, daratumumab-bortezomib-dexamethasone, carfilzomib-dexamethasone, and ultimately elotuzumab-pomalidomide-dexamethasone (EPd), but still had disease progression.	The patient presented with altered mental status 5 days after EPd treatment.	The patient's ammonia levels were 212.1 µg/dL on presentation with AMS. The patient was treated with BCAA agents, and the ammonia level decreased to 56.7 µg/dL after 11 days.	The patient continued two additional cycles of EPd after developing hyperammonemia but ultimately deteriorated due to infectious complications, due to which she could not continue chemotherapy. She died 4 months after the presentation of hyperammonemia.
Nakamura et al, 2023 [20]	A 48-year-old woman was initially treated with Bd, Ld, and Pd but continued to have disease progression. She then started on elotuzumab-lenalidomide-dexamethasone (ERd).	One day prior to starting on ERd, the patient developed altered mentation. She was started on ERd as planned and concomitantly treated for hyperammonemia with BCAA agents.	The patient's ammonia level was 67.7 µg/dL	The patient had an improvement in ammonia levels and a corresponding improvement in encephalopathy after two days of treatment with BCAA agents. After one cycle of ERd, she developed massive ascites and was found to have multiple metastases to the liver. She died from complications of refractory ascites 32 days following her diagnosis of hyperammonemic encephalopathy.

MM: multiple myeloma; AMS: altered mental status.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin.* 2022;72(1):7-33. [doi pubmed](#)
2. Kyle RA, Rajkumar SV. Multiple myeloma. *N Engl J Med.* 2004;351(18):1860-1873. [doi pubmed](#)
3. Bataille R, Harousseau JL. Multiple myeloma. *N Engl J Med.* 1997;336(23):1657-1664. [doi pubmed](#)
4. Dimopoulos MA, Moreau P, Terpos E, Mateos MV, Zweegman S, Cook G, Delforge M, et al. Corrigendum to 'Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up': [Ann Oncol 2021; 32(3): 309-322]. *Ann Oncol.* 2022;33(1):117. [doi pubmed](#)
5. Otsuki T, Yamada O, Sakaguchi H, Ichiki T, Kouguchi K, Wada H, Hata H, et al. In vitro excess ammonia production in human myeloma cell lines. *Leukemia.* 1998;12(7):1149-1158. [doi pubmed](#)
6. Leon-Ruiz M, Oliva-Navarro J, Alonso-Singer P, Castaneda-Cabrero C, Benito-Leon J. Multiple myeloma-induced hyperammonemic encephalopathy: another important potential cause of triphasic waves. *J Clin Neurophysiol.* 2022;39(7):647. [doi pubmed](#)
7. Vahora I, Panneerselvam E, Deoker A. Hyperammonemic encephalopathy in multiple myeloma: a case report. *Cureus.* 2023;15(1):e33626. [doi pubmed pmc](#)
8. Jaruvongvanich V, Spanuchart I, P OC, Kitamura C, Sumida L, Roytman M. An unusual cause of altered mental status in multiple myeloma: an extrasosseous manifestation. *Hawaii J Med Public Health.* 2016;75(4):109-112. [pubmed pmc](#)
9. Pham A, Reagan JL, Castillo JJ. Multiple myeloma-induced hyperammonemic encephalopathy: an entity associated with high in-patient mortality. *Leuk Res.* 2013;37(10):1229-1232. [doi pubmed](#)
10. Costa LJ, Usmani SZ. Defining and managing high-risk multiple myeloma: current concepts. *J Natl Compr Canc Netw.* 2020;18(12):1730-1737. [doi pubmed](#)
11. Passucci M, Fazio F, Petrucci MT. A case of fatal hyperammonemic encephalopathy in a patient with end-stage multiple myeloma. *Mediterr J Hematol Infect Dis.* 2023;15(1):e2023012. [doi pubmed pmc](#)
12. Murtaza G, Lu H, Faqah A, Konowitz N, Kuruvilla A, Adhikari S. Multiple myeloma-induced hyperammonemic encephalopathy. *J Hematol.* 2017;6(1):29-31. [doi pubmed pmc](#)
13. 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;50(4):667-669. [doi pubmed](#)
14. 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. [doi pubmed](#)
15. Gaiani A, Pompanin S, Zambello R, Briani C, Cagnin A. Steroid-responsive hyperammonemic encephalopathy as first manifestation of multiple myeloma. *Neurol Sci.* 2017;38(3):503-505. [doi pubmed](#)
16. Issa N, Blondeau B, Dimicoli-Salazar S, Marit G, Morlat P, Camou F. [Hyperammonemic encephalopathy as the presenting feature of a relapsing multiple myeloma]. *Rev Med Interne.* 2016;37(8):567-569. [doi pubmed](#)
17. Lora-Tamayo J, Palom X, Sarra J, Gasch O, Isern V, Fernandez de Sevilla A, Pujol R. Multiple myeloma and hyperammonemic encephalopathy: review of 27 cases. *Clin Lymphoma Myeloma.* 2008;8(6):363-369. [doi pubmed](#)
18. Talamo G, Cavallo F, Zangari M, Barlogie B, Lee CK, Pineda-Roman M, Kiwan E, et al. Hyperammonemia and encephalopathy in patients with multiple myeloma. *Am J Hematol.* 2007;82(5):414-415. [doi pubmed](#)
19. Douedi S, Kapadia S, AlAzzawi M, Sen S. Hyperammonemic encephalopathy: a unique presentation of multiple myeloma. *Cureus.* 2021;13(1):e12781. [doi pubmed pmc](#)
20. Nakamura H, Takada K, Murase K, Ikeda H, Iyama S, Manabe T, Kobune M. Multiple myeloma with hyperammonemia treated with novel agents: a case series of three patients. *Intern Med.* 2023;62(5):775-778. [doi pubmed pmc](#)