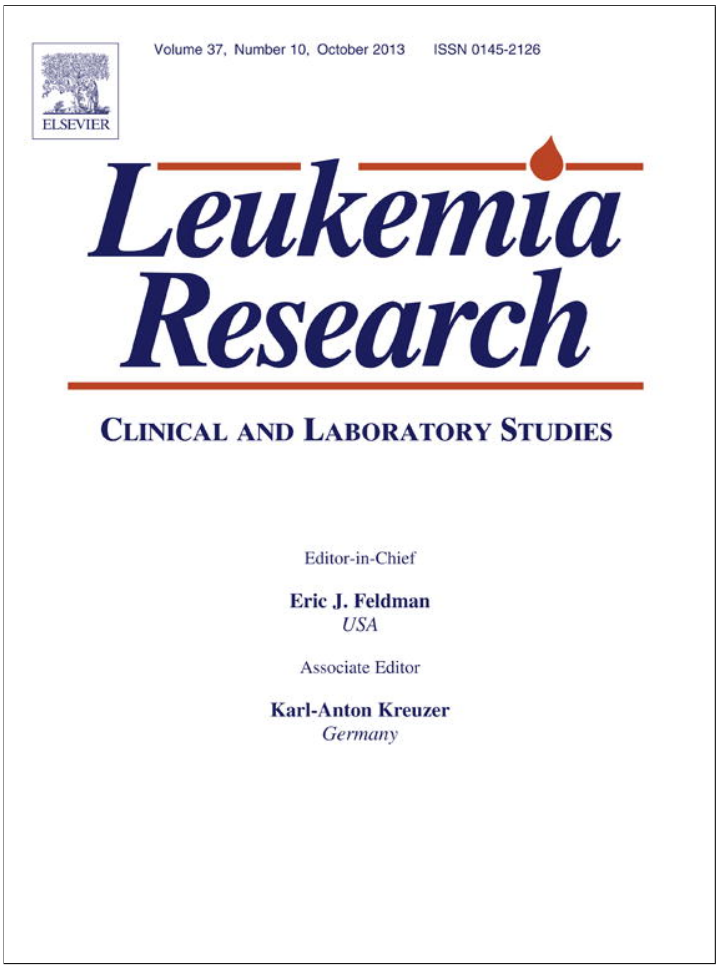

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Multiple myeloma-induced hyperammonemic encephalopathy: An entity associated with high in-patient mortality

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ABSTRACT

Hyperammonemia attributed to multiple myeloma (MM) has been rarely reported. We present 6 patients from our institution and 34 from the literature with MM-induced hyperammonemic encephalopathy. The median age was 67 years with male:female ratio of 1.8:1. The median ammonia level was 114 umol/L. IgG and IgA MM was seen in 40% and 35% of cases, respectively. The in-patient mortality was 48%. The in-patient mortality was 31% in patients who received MM-directed therapy and 100% in those who did not received MM-directed therapy. Hyperammonemic encephalopathy is a rare complication in MM and is associated with high in-patient mortality.

1. Introduction

Hyperammonemia is a common cause of hepatic encephalopathy in patients with severe liver cirrhosis. Multiple factors are thought to lead to hepatic encephalopathy such as decreased oxygen delivery to the cerebral vasculature, relative hypotension associated with severe hepatic dysfunction, and formation of metabolic neurotoxins such as ammonia [1]. The liver normally clears serum ammonia by converting it into glutamine. In liver failure, ammonia accumulates systemically leading to astrocyte dysfunction and encephalopathy [2]. Current treatments of hepatic encephalopathy are aimed at reducing systemic ammonia through the use of lactulose and dietary protein restriction.

There have been a number of reports that describe hyperammonemic encephalopathy induced by multiple myeloma (MM). Here, we present a retrospective case series of six patients identified over a twelve-year period at our teaching institutions with a diagnosis of MM presenting with hyperammonemia and altered mental status but without signs of hepatic dysfunction or other abnormalities. Additionally, we present the results from a systematic review of the literature on patients with MM-induced hyperammonemic encephalopathy.

2. Methods

A retrospective chart review was performed of patients admitted to Rhode Island Hospital and the Miriam Hospital in Providence, Rhode Island, USA, between January 1, 2000 and December 31, 2012. Inclusion criteria were adult patients eighteen years or older, diagnosed with MM based on ICD-9 codes 238.6, and v107.9, presented with altered mental status and had a serum ammonia level drawn showing hyperammonemia. For the systematic review, we performed a literature search using Pubmed from January 1, 1950 to December 31, 2012, looking for case series and reports of patients with a diagnosis of MM who presented with hyperammonemia encephalopathy.

Patient charts and articles were reviewed and data were collected including age, sex, stage of myeloma based on the Durie-Salmon and/or International Staging System, serum ammonia level, complete blood count, serum electrolytes including calcium, brain imaging, treatments administered for hyperammonemia and/or MM, and cause of death, if applicable. A diagnosis of MM-induced hyperammonemia was made in patients with a diagnosis of MM who presented with altered mental status and had concomitant elevated serum ammonia levels. For our institution, hyperammonemia was defined as serum ammonia levels equal or higher than 50 umol/L. Patients with hyperammonemia had further chart review analysis looking for other etiologies for altered mental status including hepatic dysfunction, hyponatremia, hypercalcemia, uremia, infection and/or intracranial processes. Patients who had other etiologies of hyperammonemia and/or encephalopathy, or without a clear-cut diagnosis of MM were excluded from our study. For the systematic review, we used the ammonia normality range for each institution; in most cases, ammonia levels equal or higher than 35 umol/L defined hyperammonemia. In cases in which ug/dL units were reported, we calculated umol/L units by multiplying by 0.6.

The primary outcome was the in-patient mortality rate of MM-induced hyperammonemic encephalopathy. Secondary outcomes were to describe the clinical and laboratory features of patients presenting with MM-induced hyperammonemic encephalopathy. Clinical data were gathered independently by two of the authors. Patients' characteristics are presented using descriptive statistics.

3. Results

The database search of our hospitals revealed 27 individual patients diagnosed with MM found to have elevated ammonia levels in the context of presenting to an inpatient service with confusion or altered mental status. A diagnosis of hyperammonemic encephalopathy was made by ruling out hepatic dysfunction

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Table 1
Selected characteristics of 39 patients who developed plasma cell myeloma-induced hyperammonemia.

Study	Age	Sex	Myeloma type	Stage	Ammonia (umol/L)	Myeloma treatment	Response	Survived hospitalization
Howman [1]	61	M	Light chain Lambda	III	179	DVD	Improved mental status and normalization of ammonia	Yes
Lora-Tamayo [2]	69	F	IgD-Lambda	III	299	None	Died on hospital day 5	No
Benet [3]	89	F	IgG-Lambda	III	211	Cyclophosphamide, methyl-prednisolone, melphalan	Improved mental status and normalization of ammonia	Yes
Caminal [4]	71	M	IgD-Lambda	III	114	IT methotrexate, cytarabine, 6-mercaptopurine	Died on hospital day 15	No
Fine [5]	67	M	IgG-Kappa	III	39,342	None	Died on hospital day 27	No
Frere [6]	62	F	IgA-Lambda	III	>120	Melphalan	Mental status improved	Yes
Furer [7]	78	M	Light chain Kappa	III	106	Cyclophosphamide	Improvement in mental status but died from sepsis	No
	74	F	IgG-Kappa	III	56	Cyclophosphamide, dexametha-sone	Improved mental status and normalization of ammonia	Yes
Holahan [8]	82	F	Light chain Lambda	III	70	Vincristine, dexametha-sone	Normalization of ammonia in four days	Yes
Ikewaki [9]	71	M	IgA-Kappa	III	147	Chemotherapy (unknown)	Improved mental status and normalization of ammonia	Yes
	70	F	Light chain	III	81	Chemotherapy (unknown)	Improved mental status and normalization of ammonia	Yes
	71	M	IgG-Lambda	III	115	Chemotherapy (unknown)	Partial improvement in mental status	Yes
Keller [10]	70	M	IgG	III	86	None	Progressive confusion, respiratory failure.	No
Kuribayashi [11]	23	M	Light chain	NR	108	Chemotherapy (unknown)	Improvement in mental status	Yes
	44	M	IgA-Lambda	NR	77	Chemotherapy (unknown)	Resolution of hyperammonemia	Yes
	65	F	IgA	NR	36	Chemotherapy (unknown)	Died with increasing ammonia levels	No
Kwan [12]	43	F	Light chain	III	172	Cyclophosphamide	Improved mental status and normalization of ammonia	Yes
Martinelli [13]	NR	NR	IgG-Lambda	III	128	VAD	Improved with chemotherapy	Yes
	NR	NR	IgG-Lambda	III	122	VAD	Improved with chemotherapy	Yes
	NR	NR	IgG-Lambda	III	70	None	Hyperammonemia did not improve	No
Matsuzaki [14]	58	M	IgG-Lambda	III	156	CVAD	Deceased soon afterwards	No
	51	F	IgA-Kappa	III	135	CVAD	Resistant to treatment	No
	58	M	IgA-Kappa	III	55	Unknown	Unknown	No
	23	M	IgG-Lambda	III	113	Unknown	Unknown	Yes
	65	F	IgA-Lambda	III	38	Unknown	Unknown	Yes
	57	F	IgG-Lambda	III	50	Unknown	Unknown	Yes
Otsuki [15]	58	M	IgA-Lambda	III	143	Melphalan, vindesine, prednisone, ranimustine	No response from chemotherapy	No
Perez-Retortillo [16]	56	F	IgG-Lambda	NR	100	VAD	Died three months later from hyperammonemia	No
	51	M	IgA-Kappa	NR	137	VAD	Died one month later from hyperammonemia	No

Table 1 (*Continued*)

Study	Age	Sex	Myeloma type	Stage	Ammonia (umol/L)	Myeloma treatment	Response	Survived hospitalization
Shah [17]	76	F	NR	III	182	Melphalan, prednisone	Improvement in mental status and normalization of ammonia	Yes
Shenoy [18]	66	M	IgG-Kappa	NR	74	Chemotherapy (unknown)	Improved mental status and normalization of ammonia	Yes
Takimoto [19]	81	F	IgA-Lambda	III	81	Vindesine	Improvement in mental status however died from pneumonia	No
Weng [20]	70	M	IgA	NR	300	VAD	Improvement in mental status after chemotherapy	Yes
Yamamoto [21]	82	F	IgG lambda	III	125	None	Died on hospital day 40	No
Present report	84	M	IgA	III	91	CyBorD	Improvement in mental status after chemotherapy	Yes
	87	F	Biclonal IgA and IgG	III	50	Bortezomib	Improvement in mental status after chemotherapy	Yes
	65	M	IgG-Kappa	III	79	None	Died on hospital day 16	No
	68	M	IgG-Kappa	III	171	Bortezomib, doxorubicin	Died on hospital day 10	No
	67	M	IgA	III	143	None	Died on hospital day 6	No
	85	M	IgA	III	144	CyBorD	Died on hospital day 5	No

CyBorD: cyclophosphamide, bortezomib, dexamethasone; CVAD: cyclophosphamide, vincristine, doxorubicin, dexamethasone; DVD: doxorubicin, bortezomib, dexamethasone; F: female; IT: intrathecal; M: male; NR: not reported.

and other potential causes of confusion, as detailed in the Methods section. Based on our exclusion criteria, it was determined that 6 out of the 27 (22%) MM patients had hyperammonemic encephalopathy without any other known etiology. The median age at diagnosis was 76 years (range: 65–87 years) with a 5:1 male-to-female ratio. All patients had stage III disease based on the ISS. Prior to admission, 5 patients (83%) were either being treated with or most recently had received bortezomib; 3 patients were actively undergoing treatment with bortezomib at the time of evaluation. IgA MM was seen in 3 out of 5 patients (60%). One patient had IgG and one had biclonal MM. The median ammonia level upon admission was 117 umol/L (range: 50–171 umol/L). All patients had onset of their altered mental status four days prior to admission. Each of these patients had stable hemoglobin, normal electrolytes, liver function tests, and coagulation profile. No intracranial processes were detected on imaging in any of the patients. Three patients had improvement in mental status and decreased ammonia levels after chemotherapy; the other 3 patients declined further interventions. Inpatient mortality resulted in 4 out of 6 patients (67%).

3.1. Systematic review

The search using the keywords *myeloma AND ammonia* rendered 62 articles, and using *myeloma AND hyperammonemia* rendered 35 articles. From the combined 72 entries, 39 were rejected because they did not report on the association between MM and hyperammonemia, 11 because they were not written in English, and 2 were already included in other studies. Twenty articles detailing on a total of 34 patients meeting our criteria were included [1–21] for a total of 40 patients with MM-induced hyperammonemic encephalopathy following the addition of our patient series (Table 1).

Based on 37 patients who had age and sex reported, the median age was 67 years (range: 23–89 years) with a 1.8:1 male-to-female ratio. The median ammonia level amongst these patients was 114 umol/L (range: 35–300 umol/L), after exclusion of one likely outlier patients in whom ammonia levels were reported as 67 mg/dL (39,342 umol/L). Stage was reported in 33 patients; all patients had stage III disease by ISS or DSS. IgG MM was the most common subtype reported in 40% of patients (16/40) followed by IgA MM in 35% (14/40). Light chain MM was seen in 15% of patients (6/40) followed by IgD MM in 5% of patients (2/40). One patient had a biclonal MM and one patient did not have immunoglobulin subtype reported. CNS was evaluated in 68% of patients (27/40). The most common method for assessment of CNS involvement was computed tomography (67%), followed by electroencephalogram (37%), lumbar puncture (33%) and magnetic resonance imaging (19%). Hyperammonemia was identified concurrently with active disease in all cases; at diagnosis of MM in 31% (11/36) and at relapse in 69% of the patients (25/36).

Twenty-nine patients received MM-directed therapy (i.e. melphalan, cyclophosphamide, thalidomide, lenalidomide, bortezomib, steroids, etc.); 16 patients (59%) received conventional chemotherapy, 7 (27%) received an unknown chemotherapy regimen, and 4 (15%) received a bortezomib-containing regimen. Overall, the in-patient mortality was 48% (19/40). From the 29 patients who received some form of MM therapy, 9 (31%) died during hospitalization while 7 of the 7 patients (100%) who did not receive chemotherapy died during the admission. The type of therapy was unknown in 4 patients. Supportive therapy with lactulose was used in 8 patients, from whom none experienced improvement on mental status or ammonia levels. Supportive hemodialysis was used in 5 patients of whom 4 responded, although MM-directed therapy was given concurrently. One patient who received hemodialysis without MM-directed therapy did not respond.

4. Discussion

Hyperammonemic encephalopathy secondary to MM is a rare disease process that, based on our experience and confirmed by our review of the literature, occurs universally with advanced stage disease. Ammonia levels are usually elevated above 100 umol/L, however encephalopathy might also be seen at lower levels. Furthermore, ammonia levels above 100 umol/L appeared to portend

a poorer prognosis in these patients [8], although this is subject to an individual basis. In terms of immunoglobulin subtype, there was a high percentage of patients with IgA MM (35%). In a review from the Mayo Clinic including over 1000 patients with MM, IgA MM comprised 21% of the cases [22]. Given the small sample size of the patients included in the present study, this observation should be considered preliminary.

A notable finding of our study is the high hospitalization mortality, on the order of 48%. To the best of our knowledge, this is the first report that has evaluated such outcome in a systematic manner. One could hypothesize that the high inpatient mortality could have been associated with other conditions and co-morbidities; however, our literature search and inclusion criteria were as stringent as possible to rule out other causes of ammonemia and altered mental status in these patients. Inpatient mortality rates appear lower in those patients who receive MM therapy (31%) compared to those who did not receive any MM therapy (100%). No responses were seen when patients received lactulose or hemodialysis without concurrent MM-directed therapy. Based on these results, we would recommend not treating such patients with lactulose or hemodialysis unless MM-directed therapy is initiated. Interestingly, from four patients who received bortezomib-containing regimens only one died during the hospitalization, although this finding could have been confounded by other factors. Thus far, it is unclear whether or not novel agents such as proteasome inhibitors or immunomodulators improve response rates and decrease inpatient mortality.

The pathophysiology of elevated serum ammonia in these patients is not clearly elucidated; however, there are a number of suggestions of the pathophysiologic mechanism. One potential mechanism is the possibility of plasma cell infiltration of hepatic tissues causing porto-systemic shunting of blood [1,19,20]. There have also been suggestions that some subtypes of MM might undergo a leukemic change which would predispose these patients to hyperammonemia [9]. A third mechanism that has been proposed, and the most likely, is the production of ammonia by the plasma cells themselves. In a study by Otsuki and colleagues, the in vitro production of ammonia by 6 myeloma cell lines was compared with 12 non-myeloma (i.e. leukemia and lymphoma) cell lines [23]. The production of ammonia by the myeloma cell lines was 13.7 umol/L/proliferating cells compared with 4.2 umol/L/proliferating cells in non-myeloma cells ($p < 0.005$). Based on this study, excessive ammonia production from the cells is possibly secondary to increased protein synthesis of immunoglobulins and cytokines. Encephalopathy, however, would not be observed unless the total myeloma burden reaches a critical level that overwhelms the liver ability to metabolize the produced ammonia.

In conclusion, hyperammonemic encephalopathy is a deadly albeit rare development in patients with MM seen most frequently in patients with advanced stage disease. IgG and IgA subtypes are most commonly involved. The diagnosis should be considered in MM patients who present with altered mental status. Treatment, in the form of chemotherapeutics with the addition of novel agents, should be initiated promptly once the diagnosis is determined for patients who have an adequate performance status.

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Authors' contributions:
All the authors designed the study, wrote the manuscript and approved the final version. AP also performed the chart review, gathered the data from the literature and drafted the initial manuscript.

References

[1] 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;51:2299–302.
[2] Lora-Tamayo J, Palom X, Sarra J, et al. Multiple myeloma and hyperammonemic encephalopathy: review of 27 cases. Clin Lymphoma Myeloma 2008;8:363–9.
[3] Benet B, Alexandra JF, Andrieu V, et al. Multiple myeloma presenting as hyperammonemic encephalopathy. J Am Geriatr Soc 2010;58:1620–2.
[4] Caminal L, Castellanos E, Mateos V, et al. Hyperammonaemic encephalopathy as the presenting feature of IgD multiple myeloma. J Intern Med 1993;233:277–9.
[5] Fine P, Adler K, Gerstenfeld D. Idiopathic hyperammonemia after high-dose chemotherapy. Am J Med 1989;86:629.
[6] Frere P, Canivet JL, Gennigens C, et al. Hyperammonemia after high-dose chemotherapy and stem cell transplantation. Bone Marrow Transplant 2000;26:343–5.
[7] Furer V, Heyd J. Hyperammonemic encephalopathy in multiple myeloma. Isr Med Assoc J 2007;9:557–9.
[8] Holahan JR. Hyperammonemia: elevated ammonia levels in multiple myeloma. Am J Med 2004;116:210–1.
[9] Ikewaki J, Ogata M, Imamura 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;50:667–9.
[10] Keller DR, Keller K. Hyperammonemic encephalopathy in multiple myeloma. Am J Hematol 1998;57:264–5.
[11] Kuribayashi N, Matsuzaki H, Hata H, et al. Multiple myeloma associated with serum amino acid disturbance and high output cardiac failure. Am J Hematol 1998;57:77–81.
[12] Kwan L, Wang C, Levitt L. Hyperammonemic encephalopathy in multiple myeloma. N Engl J Med 2002;346:1674–5.
[13] Martinelli G, Peccatori F, Ullrich B, et al. Clinical manifestation of severe hyperammonaemia in patients with multiple myeloma. Ann Oncol 1997;8:811.
[14] Matsuzaki H, Hata H, Sonoki T, et al. Serum amino acid disturbance in multiple myeloma with hyperammonemia. Int J Hematol 1995;61:131–7.
[15] Otsuki T, Nakazawa N, Taniwaki M, et al. Establishment of a new human myeloma cell line, KMS-18, having t(4;14)(p16.3;q32.3) derived from a case phenotypically transformed from Ig A-lambda to BJP-lambda, and associated with hyperammonemia. Int J Oncol 1998;12:545–52.
[16] Perez Retortillo JA, Marco F, Amutio E, et al. Hyperammonemic encephalopathy in multiple myeloma. Haematologica 1998;83:956–7.
[17] Shah AS, Shetty N, Jaiswal S, et al. Hyperammonemia: an unusual presenting feature of multiple myeloma. Indian J Med Sci 2005;59:24–7.
[18] Shenoy C. Hyperammonaemic encephalopathy in plasma cell leukaemia. Intern Med J 2007;37:784–6.
[19] Takimoto Y, Imanaka F, Hayashi Y, et al. A patient with ammonia-producing multiple myeloma showing hyperammonemic encephalopathy. Leukemia 1996;10:918–9.
[20] Weng TI, Shih FF, Chen WJ. Unusual causes of hyperammonemia in the ED. Am J Emerg Med 2004;22:105–7.
[21] Yamamoto Y, Konoike Y, Nakamine H, et al. Multiple myeloma with a variant Burkitt-type translocation, t(2;8)(p12;q24), associated with hyperammonemia. Intern Med 2009;48:1239–42.
[22] Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc 2003;78:21–33.
[23] Otsuki T, Yamada O, Sakaguchi H, et al. In vitro excess ammonia production in human myeloma cell lines. Leukemia 1998;12:1149–58.