

# Multiple Myeloma-Induced Hyperammonemic Encephalopathy

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## Abstract

Multiple myeloma (MM) typically presents with hypercalcemia, renal insufficiency, anemia, and bone lesions. Elevated ammonia level manifesting as altered mental status is a rare complication in MM. We report an interesting case of hyperammonemic encephalopathy in a 73-year-old male with advanced relapsing kappa-light chain MM.

**Keywords:** Abdominal pain; Pancreatitis; Renal cell carcinoma; Pazopanib

## Introduction

Multiple myeloma (MM) is a neoplastic, monoclonal proliferation of terminally differentiated plasma cells. It is characterized by plasma cell bone marrow infiltration and accumulation of monoclonal protein in the serum and urine [1]. MM is the second most common hematologic neoplasm, with a 1 in 143 lifetime risk and 5-year survival rate of 47%. In 2015, an estimated 30,300 people were diagnosed with the disease and an estimated 12,650 deaths resulted directly from MM and its complications [2]. Treatment for MM in the past decade has improved dramatically with the advent of three novel targeted agents: proteasome inhibitor bortezomib, immunomodulatory agent, thalidomide, and its analog lenalidomide. With these novel agents, the total healthcare cost of MM amounts to a mean estimate of \$118,353 per treatment episode [3]. While MM presents with a variety of disease-related complications, the most common complications include the following: hypercalcemia, renal insufficiency, anemia, and bone lesions [2, 3]. The complication of altered mental status in MM is usually

secondary to hypercalcemia, hyperviscosity, or uremia; hyperammonemia is a rare reported cause of altered mental status in an MM patient.

Hyperammonemia is typically found in chronic liver diseases with portal-systemic shunts and acute fulminant hepatic failure [4]. It has also been described in hematologic malignancies such as acute leukemia and following bone marrow transplantation [5, 6]. We report a rare case of hyperammonemic encephalopathy in a 73-year-old African American male with advanced relapsing kappa-light chain MM.

## Case Report

Three years ago in June 2013, our patient with no relevant medical history presented with worsening fatigue, and was diagnosed with kappa-light chain MM. At the time of diagnosis, he was anemic (8.4 g/dL), hypercalcemic (14.4 mg/dL), thrombocytopenic (88,000/ $\mu$ L), and had acute kidney injury (BUN 52 mg/dL and creatinine 5.7 mg/dL). He had low serum immunoglobulins (IgA 27 mg/dL, IgG 376 mg/dL, and IgM 9 mg/dL), high serum kappa free light chain (1,082.50 mg/dL), normal serum lambda free light chain (0.98 mg/dL), low protein electrophoresis (5.3 g/dL), high M protein (0.1 g/dL), low C3 (85 mg/dL), normal C4 (19.6 mg/dL), and high kappa/lambda ratio (1,104.59). He was placed on hemodialysis to manage his renal failure and treated with proteasome inhibitor bortezomib and dexamethasone. He responded well to the therapy, with a reduction of kappa-light chain from 1,082.50 to 505 mg/dL. In February 2014, his MM relapsed, and he began second-line chemotherapy with immunomodulatory agent thalidomide and dexamethasone. His MM continued to progress, and after achieving an inadequate response, he was started on third-line therapy with immunomodulatory agent lenalidomide and dexamethasone. By April 2016, his MM continued to worsen and he was requiring frequent transfusions. Lenalidomide had been on hold for several months due to his severe cytopenia. After restarting lenalidomide, his platelet counts improved, but his disease progressed and now showed plasma cell leukemia. Having already failed three other drug treatments, the patient was started on a fourth chemotherapy treatment, monoclonal antibody daratumumab, with dexamethasone, tylenol, and benadryl. His end-stage renal failure and cytopenia excluded the option of other chemotherapy treatments.

Manuscript accepted for publication March 06, 2017

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doi: <https://doi.org/10.14740/jh322e>

**Table 1.** Published Treatment Regimens and Outcomes for MM-Induced Hyperammonemic Encephalopathy

Treatment	Outcome
Bortezomib + cyclophosphamide + dexamethasone [11]	Patient released home after 11 days.
Bortezomib + high dose dexamethasone + bendamustine [6]	Patient died 2 weeks after treatment due to aspiration pneumonia.
Simultaneous continuous venovenous hemodialysis and extended daily hemodialysis Vincristine + high dose dexamethasone [12]	Patient with medically refractory hyperammonemia survived and was discharged home.

After his first dose treatment of daratumumab, the patient became progressively lethargic. Prior to treatment, he was oriented to self and place, and ambulated to the hospital.

Vitals showed that the patient was afebrile 36.9 °C, normotensive BP 101/55, pulse 92, and saturating 90% on room air. Laboratory findings revealed leukocytosis (white blood cell count 25,700/ $\mu$ L, with a differential of 35% plasma cells), anemia (8 g/dL), thrombocytopenia (49,000/ $\mu$ L), and hypercalcemia (10.6 mg/dL). Blood sodium and glucose levels were normal, as were liver function tests (bilirubin 0.7 mg/dL, ALT 53 units/L, AST 56 units/L, and alkaline phosphatase 80 units/L) and prothrombin time. Consistent with the patient's end-stage renal disease, BUN (31 mg/dL) and creatinine (7.62 mg/dL) were elevated. Rapid neurologic deterioration ensued and the patient became confused and unresponsive to verbal stimuli. He did not have neck stiffness or signs of meningismus. In evaluation of the patient's altered mental status, a CT scan of the head and MRI of the brain were performed and were negative for acute infarct, hemorrhage, mass, or midline shift. Liver function tests and abdominal CT scan showed no evidence of hepatic dysfunction. The patient had not received salicylates and blood and urine cultures were found to be negative. Ammonia levels were sent and he was confirmed to have an encephalopathic picture with elevated ammonia of 120 mg/dL (normal value < 47 mg/dL). The patient was promptly started on lactulose, rifaximin, empiric antibiotics vancomycin and cefepime and antiviral treatment acyclovir. Through the next 4 days, his elevated ammonia levels did not resolve: 120 mg/dL  $\rightarrow$  95 mg/dL  $\rightarrow$  120 mg/dL  $\rightarrow$  127 mg/dL. With findings suggestive of MM-induced hyperammonemic encephalopathy, our next step in treatment would have been aggressive chemotherapy with high dose cyclophosphamide. But, considering his severe cytopenia and failure to respond to prior chemotherapy, the patient was deemed a poor candidate for further aggressive treatment. After discussion with the family, the decision was made to withdraw active treatment and our patient died within 5 days from disease progression.

## Discussion

Hyperammonemic encephalopathy in the absence of liver disease is a rare complication of advanced MM that has a high mortality. It is usually characterized by lethargy, confusion, and asterixis, with rapid progression to coma and death. Literature review suggests that most cases of hyperammonemic encephalopathy are MM IgA subtype and chemotherapy-resistant. The

etiology of this disease has yet to be determined. Currently, there is no consensus on management (Table 1) [7-9].

Some studies report beneficial effects in using hemodialysis to remove excess ammonia [9, 10]. Several others suggest that the initiation of aggressive chemotherapy is the most effective measure to achieve normal ammonia levels and clinical improvement [7]. Unfortunately, our patient was severely cytopenic and a poor candidate for chemotherapy treatment when he presented with hyperammonemic encephalopathy.

Little is known about the underlying pathophysiology of hyperammonemic encephalopathy as a complication of MM. One study demonstrated excess production of ammonia *in vitro* by human myeloma cell lines, although the mechanism is unclear. Whether this overproduction is due to mutations in the enzymes involved in ammonia synthesis or due to excess protein synthesis remains unknown [11]. Hyperammonemic encephalopathy has also been infrequently reported to occur after high dose chemotherapy for treatment of hematologic malignancies [6]. No cases have been reported to specifically describe daratumumab-induced hyperammonemia, but considering our patient's acute change in mental status following chemotherapy treatment, its contributions to the clinical presentation cannot be ignored.

The characteristics of hyperammonemic encephalopathy secondary to MM have also not been well studied. One review reports three cases that show an association of the appearance of peripheral blood myeloma cells to the development of hyperammonemic encephalopathy [12]. Our case supports this rare association, with our patient's altered mental status developing shortly following his progression to plasma cell leukemia (plasma cells comprising 35% of the white blood count).

## Conclusion

We emphasize the need for a better understanding of the etiology of the hyperammonemic encephalopathy, its prognostic factors, and alternate treatment modalities for MM patients unable to undergo chemotherapy. Most importantly, patients with relapsing MM who present with altered mental status without a clear cause should be promptly evaluated for primary hyperammonemic encephalopathy as a potential cause.

## Financial Disclosures

We do not have any financial disclosures nor have we received any funding.

## Conflicts of Interest

There are no conflicts of interest.

## Consent

Consent was obtained.

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