Hyperammonemic Encephalopathy in Multiple Myeloma

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Multiple myeloma is a neoplastic monoclonal proliferation of bone marrow plasma cells characterized by lytic bone lesions, plasma cell accumulation in the bone marrow, and the presence of monoclonal protein in the serum and urine. Disturbances in level of consciousness are frequent in MM, with hypercalcemia and hyperviscosity syndrome being the most common culprits. Hyperammonemic encephalopathy in the absence of documented liver dysfunction appears to be a rare entity responsible for altered sensorium in patients with progressive MM. Excess ammonia production *in vitro* by myeloma cells was found [1], suggesting that the clinical manifestations of hyperammonemia are due to the myeloma itself. Although the precise mechanism of the phenomenon remains unclear, therapeutic interventions targeting MM may normalize serum ammonia levels and lead to increased level of consciousness.

We report the development of hyperammonemic encephalopathy in two patients with advanced MM in whom serum ammonia levels and cognitive state returned to normal, or at least some improvement in the latter, following treatment for MM.

Patient Descriptions

Patient 1

A 78 year old male patient with stage IIIA (Durie-Salmon classification) kappa light-chain MM was admitted to our department with shortness of breath and cognitive deterioration. Three months prior to his admission he was diagnosed with advanced MM that manifested as diffuse bone lesions, massive infiltration of bone marrow by myeloma cells, and high levels of κ free light chain in urine. No paraprotein in the serum was detected. Treatment with high dose dexamethasone, cyclophosphamide and pamidronate, as well as local radiotherapy was initiated without significant improvement.

On admission, physical examination revealed respiratory distress, normal oxygen saturation, normal body temperature, bilateral basilar rhonchi and bilateral pitting edema on both legs. The neurological examination was normal except for somnolence. Laboratory examination demonstrated normal white blood count and primary respiratory alkalosis with metabolic compensation (pH 7.52, CO_2 23.6 mmHg, bicarbonate 22 mmol/L). The workup for dyspnea including chest X-ray, lung scan, chest computed tomography, bronchoscopy, blood pulmonary profile, echocardiography and brain CT were unremarkable apart from a small consolidation in the left lower lobe of the lung on chest CT. Ceftriaxone and azythromycin were introduced. Consequently, new normocytic anemia and thrombocytopenia developed, accompanied by elevation in lactate dehydrogenase serum level. Peripheral blood smear revealed plasma cells and plasmoblasts. New lytic bone lesions were detected. The patient was treated with cyclophosphamide, which led to cognitive improvement but he still felt respiratory discomfort. He was discharged and therapy with cyclophosphamide, pamidronate and thalidomide was continued in our ambulatory care unit. Gradually, the respiratory discomfort resolved.

Three months later the patient was readmitted due to a fall accompanied by head injury and an acute confusional state that developed a few hours later. On admission he was afebrile, agitated, confused and tachypneic. The neurological exam revealed no neck stiffness and no focal neurological signs. White blood cell count, renal function tests and liver enzymes were within normal limits. No hypercalcemia was noted. Head CT did not reveal any abnormality. Intravenous cefepime and IV vancomycin were initiated empirically. During the next 24 hours the patient developed progressive shortness of breath and became stuporous. A primary respiratory alkalosis and metabolic acidosis were found on blood gas analysis (pH 7.51, CO_2 17.4 mmHg, bicarbonate 15.1 mmol/L). Multiple purple and raised nodules appeared over his trunk. No meningeal signs or focal neurological signs were found on repeated examination. White blood cell count, renal and liver function tests, and blood calcium were within normal limits; blood LDH was elevated (2914 IU/L). Lumbar puncture was performed and the cerebrospinal fluid analysis revealed the following: no cells, glucose 47 mg/dl, total protein < 1 g/dl, LDH 249 IU/L, chloride 128 mEq/L. An electroencephalogram was consistent with the pattern of encephalopathy. Magnetic resonance imaging of the brain did not show any abnormalities. A skin biopsy was performed and revealed massive skin infiltration by multiple myeloma cells (monoclonal κ chains). In the search for reversible causes of encephalopathy, serum ammonia level was measured on the 10th day of hospitalization and found to be high – 106 µmol/L in the presence of otherwise completely normal liver function tests. A trial of hemodialysis in combination with cyclophosphamide was performed to decrease serum ammonia levels, which was successful: ammonia levels returned to normal range and a significant improvement in the patient's

MM = multiple myeloma

LDH = lactate dehydrogenase

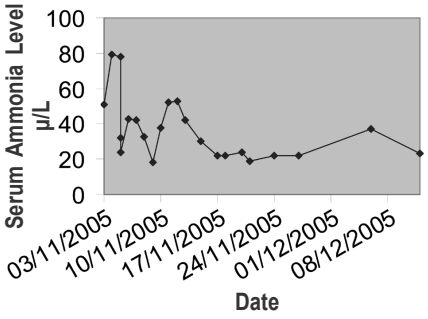
mental and respiratory status was observed. Unfortunately, the patient developed sepsis and died.

Patient 2

A 74 year old female patient with immunoglobulin G κ light chain MM stage IIIA (Durie-Salmon classification) was transferred to the hematology department from the orthopedics department due to fever and acute confusional state. She had been suffering from MM resistant to treatment for 1 year. Her treatment included eight courses of VAD (vincristine, doxorubicine, dexamethasone), thalidomide, four courses of plasmapheresis, pamidronate, and intravenous immunoglobulin. Prior to her admission, the patient was a candidate for the trial treatment with bortezomib and doxorubicin.

The patient was admitted to the orthopedics department due to fracture of the femoral neck following a fall. Closed reduction and fixation of the fracture were performed. One week after the surgery the patient developed fever accompanied by acute confusional state. IV cefepime was initiated covering presumed hospital-acquired pneumonia. CT of the head revealed multiple skull lytic lesions but no brain structural lesions.

On admission to the hematology ward the patient was afebrile, drowsy and tachypneic. Oxygen saturation was normal. Neurological examination did not reveal meningeal or focal signs. During the next few hours she became increasingly confused. Blood electrolytes, blood urea nitrogen, creatinine and calcium levels as well as liver function tests were unremarkable. Primary respiratory and metabolic alkalosis was noticed on blood gas analysis (pH 7.53, CO_2 29.6 mmHg, bicarbonate 26.8 mmol/L). Chest X-ray was normal. Evaluation of MM activity revealed high blood levels of IgG and κ light chains, 8360 and 2270 mg/dl respectively. Hyperviscosity syndrome was excluded based on fundus examination. At this point, serum ammonia level was checked and found to be high – 56 µmol/L, rising to 78 µmol/L over the next 24 hours. A trial of high dose IV dexamethasone 40 mg in combination with one dose of IV cyclophosphamide 600 mg was started. This led to a striking improvement in the patient's cognitive and respiratory status following a decline in the serum ammonia level. A regimen of two courses of high dose IV dexamethasone 40 mg per day for 3 days was begun, with an interval of 1 week between the courses. The patient's mental and respiratory status returned to normal. Consequently, the serum ammonia level returned to normal concurrently with a decline in serum IgG level [Figure]. Ammonia levels remained under 40 µmol/L for 4 weeks.



Serum ammonia levels before and after the treatment in patient 2. Dates of treatment: 3/11/2005 – dexamethasone and cyclophosphamide, 6 to 8/11/2005 – first course of high dose dexamethasone, 15 to 18/11/2005 – second course of high dose dexamethasone.

Comment

Hyperammonemia occurs in a diverse range of disorders such as liver failure, Reye's syndrome, inborn errors of urea synthesis, and following stem cell transplantation and intensive chemotherapy for hematological malignancies. It may also occur as a complication of urinary tract infection, asparginase therapy, valproic acid therapy and systemic carnitine deficiency. Recently, several cases of hyperammonemia associated with MM were reported [2-5] and, interestingly, most of the patients were Japanese. Liver function was not considered to be the cause of the hyperammonemia in these patients, since hepatic function was normal in most cases and the pattern of distribution of serum amino acids differed to that seen in hepatic failure in some cases [2]. The principal manifestations are neurological, with confusion, agitation, somnolence and lethargy which can evolve into encephalopathy and coma. These symptoms are accompanied by hyperventilation and respiratory alkalosis. The syndrome resembles Reye's syndrome or inherited defects of the urea cycle. There was a close temporal relationship between the onset of symptoms and serum ammonia levels, with resolution of symptoms occurring upon reduction of serum ammonia, possibly due to tumor response.

To the best of our knowledge, all the patients reported to develop hyperammonemic encephalopathy suffered from advanced MM, suggesting an association between the two. The diagnosis might be deferred when the physician is not alert to this entity, as demonstrated in our first patient. Following this patient, the diagnosis in our second patient was reached promptly, permitting immediate medical intervention and a better outcome. Revision of the medical histories of both patients from the time of MM diagnosis revealed transient unexplained episodes of somnolence and confusion. In some cases, the improvement followed the beginning of treatment for MM, which consisted mostly of cytotoxic agents or dexamethasone. It could be speculated that at least some of these episodes were the first manifestations of hyperammonemia.

The precise mechanism of the development of hyperammonemic encephalopathy in MM remains unclear. Excess ammonia production *in vitro* by myeloma cells has been observed [1]. Myeloma cell lines produce and secrete ammonia into culture medium more than other hematological malignant cells [1]. However, examination of RNA expression levels for the genes of the enzymes related to ammonia metabolism failed to detect any differences between the myeloma cell lines and the other lines studied [1]. Possibly, excess ammonia production accompanies excess protein synthesis in myeloma cells. In addition, mutations in the genes of the enzymes related to ammonia synthesis, such as those known in inherited hyperammonemia in childhood, may occur in myeloma.

There is no consensus regarding the therapeutic approach to hyperammo-

Ig = immunoglobulin

nemic encephalopathy in these cases. Clearly, lactulose and neomycin are not appropriate despite their role in hepatic encephalopathy [5]. Rapid serum ammonia level reduction could be achieved by treatment regimens focusing on MM. Escalating doses of cytotoxic agents or second-line chemotherapy for resistant disease might be necessary. In addition, renal dialysis could be utilized to clear blood ammonia excess, as in our first patient and as already reported [3,4]. Since our second patient responded promptly to the treatment with dexamethasone and cyclophosphamide, there was no need for dialysis in her case.

There are many questions to be answered regarding hyperammonemic encephalopathy in MM patients. What is the real incidence of the phenomenon? Which patients are prone to develop it? What are the mechanisms responsible for the excess ammonia production in these patients? We present these cases in order to alert physicians to the risk of encephalopathy in multiple myeloma patients with altered mental status without a clear cause. Serum ammonia level should be examined promptly in these instances.

References

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