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Acute Confusional Syndrome in Patient with Relapsed/Refractory Multiple Myeloma

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Abstract

Acute confusional syndrome in a patient with multiple myeloma (MM) opens a wide range of diagnostic possibilities, from infectious diseases, endocrine metabolic disorders and drug toxicity, to more infrequent causes such as hyperviscosity syndrome, among many others.

Hyperammonemia is an infrequent but known complication of multiple myeloma. Its etiology is not yet clear, and it's associated with advanced disease and poor prognosis.

We present here a case of a patient with relapsed/refractory multiple myeloma (RRMM) treated in our hospital. He was admitted for disease progression and a third line treatment was started, developing acute confusional syndrome shortly after.

We reproduce the clinical reasoning carried out, ruling out etiological causes according to their frequency and relation to the clinical case in particular, finally arriving to the diagnosis of hyperammonemic encephalopathy due to advanced and progressive MM.

Hyperammonemic encephalopathy is a rarely reported complication of MM. There are 27 cases reported in the literature so far, and IgA heavy chain isotype and advance disease with multiple lines of previous treatment are the more frequent factors associated with it.

Its diagnosis requires a high level of suspicion, and chemotherapy should be promptly initiated, as it´s the only treatment that has shown to be effective in this setting.

Keywords: Multiple Myeloma; Confusional Syndrome; Hyperammonemia; Hyperammonemic Encephalopathy

List of abbreviations: CBC: Complete Blood Count; CRP: C-Reactive Protein; CSF: Cerebrospinal Fluid; CyBorD: Cyclophosphamide, Bortezomib and Dexamethasone; DRD: Daratumumab, Lenalidomide and Dexamethasone; IGA: Immunoglobulin A; KPD: Carfilzomib, Pomalidomide and Dexamethasone; LDH: Lactate Dehydrogenase; MM: Multiple Myeloma; MRI: Magnetic Resonance Imaging; PET/CT: Positron Emission Tomography/Computed Tomography; PRES: Posterior Reversible Encephalopathy Syndrome; R-ISS: Revised Multiple Myeloma International Staging System; RRMM: Relapsed/Refractory Multiple Myeloma; SUV: Standard Uptake Value; TMA: Thrombotic Microangiopathy; TSH: Thyroid-Stimulating Hormone; TTP: Thrombocytopenic Thrombotic Purpura

Introduction

Confusional syndrome in cancer patients is frequent. The incidence of delirium in this population ranges from 57-85%, compared to 15-30% in medically ill hospitalized patients [1].

Delirium is associated with increased morbidity and mortality, prolonged hospital and intensive care unit stays, as well as increased distress in patients, families, and caregivers [2].

The clinician must recognize the predisposing risk factors for confusion (old age, dementia, psychiatric disorder, substance abuse, hypoalbuminemia, cachexia, advanced cancer, bone metastases) and determine the more immediate precipitating factors which may be modifiable.

Frequently, multiple causes are identified in patients with cancer, including metabolic abnormalities (electrolyte abnormality, hypercalcemia of malignancy, tumor lysis syndrome, endocrine dysfunction, end organ failure), metastatic disease (mainly those involving the brain and the leptomeninges), vascular disorders (thrombotic microangiopathy and vasculitis), paraneoplastic and autoimmune syndromes, hyperviscosity, direct drug toxicity, and systemic infections in the context of immunosuppression and immunoparesis [3].

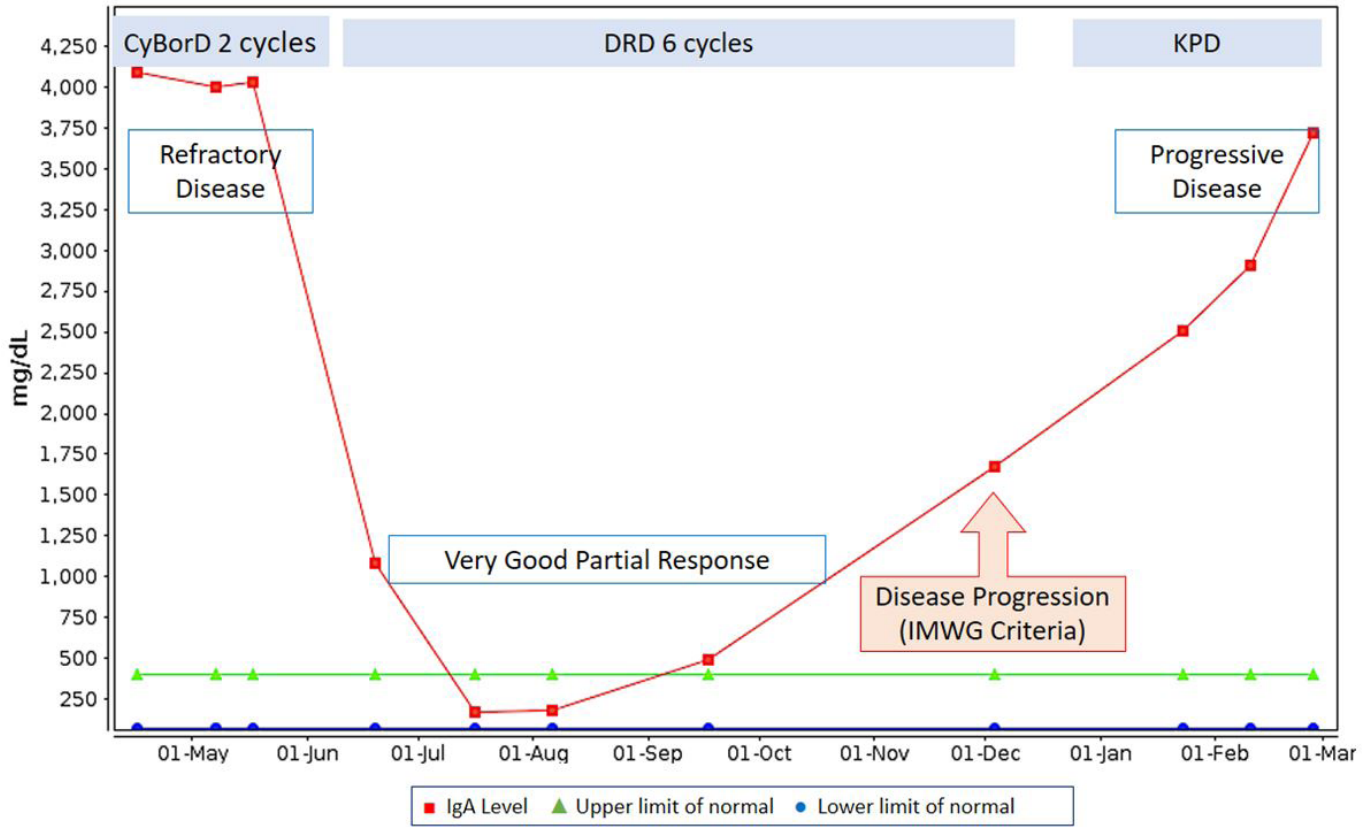
Hyperammonemic encephalopathy is usually seen in patients with hepatic dysfunction as a result of malignant infiltration, chemotherapeutic toxicities, targeted anticancer therapies, reactivation hepatitis, portosystemic shunting, and transarterial chemoembolization (TACE) [4].

In a few cases, such as in MM, is the direct production of ammonium by plasma cells what causes the elevation of serum ammonia levels. Hyperammonemic encephalopathy in patients with MM is associated with disease progression and poor short-term prognosis. Chemotherapy should be promptly initiated, as it´s the only treatment that has shown to be effective in this setting.

Methodology

A patient's medical history was examined and summarized in order to elucidate the chronology of events. Then we reproduced the clinical reasoning carried out to finally arrive to the diagnosis. We reviewed bibliography to generate a theoretical framework and support our decision making.

A timeline demonstrating the disease progression of the patient was made (Figure 1).



CyBorD: Cyclophosphamide, bortezomib and dexamethasone; DRD: Daratumumab, Lenalidomide and Dexamethasone; IMWG: International Myeloma Working Group; KPD: Carfilzomib, pomalidomide and dexam ethasone

The Figure shows the response to chemotherapy and the progression of the disease, through IgA levels, from diagnosis to patient discharge

Figure 1: Disease progression timeline

Laboratory results were summarized in tables (Tables 1,2 and 3).

Parameter	Patient's values	Reference values
Hemoglobin	8 (L)	13 - 17 g/dl
Hematocrit	23.5 (L)	40 - 53 %
White cell count	3629 (L)	5000 - 1000 /mm3
Platelet count	255500	158000 - 478000 /mm3
Total calcium	9	8.5 - 10.5 mg/dl
Ionic calcium	1.14	1 - 1.35 mmol/L
Creatinin	1.51 (H)	0.6 - 1.3 mg/dL
Urea	59 (H)	20 - 50 mg/dl
Phosphorus	5 (H)	2.5 - 4.5 mg/dL

Parameter	Patient's values	Reference values
Glucose	176 (H)	70- 110 mg/dL
Total bilirubin	0.36	0.1 - 1.4 mg/dl
DIrect bilirubin	0.09	0.00 - 0.4 mg/dl
Alkaline phosphatase	56	31 - 100 UI/L
AST	15	10 - 42 UI/L
ALT	30	10 - 40 UI/L
Total colesterol	82 (L)	110 - 200 mg/dl
Total protein	9.38 (H)	6.3 - 7.8 g/dL
Albumin	2.64 (L)	3.2 - 5 g/dl
Prothrombin time	67 (L)	70 - 120 %
Sodium	130 (L)	135 - 145 mmol/L
Potassium	5.9 (H)	3.5 - 5 mmol/L
Chlorine	90 (L)	95 - 106 mmol/L
Magnesium	1.9	1.9 - 2.5 mmol/L

Laboratory results are summarized. (H): High. (L): Low
Table 1: Laboratory results

Parameter	Patient's values	Reference values
Glucose	130 (H)	40 - 70 mg/dl
Total protein	49 (H)	15 - 40 mg/dl
White cell count	0	0 - 5 /mm3
Red cell count	500	- /mm3
Bacteriological culture	Negative	-
Indian Ink (cryptococcus)	Negative	-
Herpes simplex 1 and 2 (RCP)	Negative	-

Cerebrospinal fluid analysis results are summarized: (H): High; (L): Low
Table 2: Cerebrospinal fluid analysis

Parameter	Patient's values	Reference values
Reticulocytes - Relative count	2.9 (H)	0.5 - 1.5 %
Corrected reticulocyte count	1.5	0.5 - 1.5 %
Reticulocytes - Absolute count	89610 (H)	28000 - 84000 / mm3
Haptoglobin	>500 (H)	16 - 200 mg/dl
LDH	116	100 - 210 UI/L
Uric acid	5.3	2.5 - 7.5 mg/dl
Peripheral blood smear	Anisocytosis	-

Parameters of hemolysis and tumor lysis syndrome are summarized: (H): High; (L): Low
Table 3: Parameters of hemolysis and tumor lysis syndrome

Clinical Case

A 76-year-old male patient with a history of relapsed/refractory multiple myeloma was admitted to the hospital for low back pain and disease progression. He started a new chemotherapy scheme, and developed acute confusional syndrome.

The patient had been diagnosed with IgA Lambda Multiple Myeloma 10 months before, while he was being evaluated for low back pain. He presented anemia and multiple osteolytic bone lesions with normal creatinine and calcium levels. In the initial workup, his M Spike was 4.91 g/dl, IgA level 4090 mg/dl and free serum lambda light chains 42.73 mg/l (with a free light chain ratio <100) and normal LDH levels. Bone marrow biopsy showed 90% infiltration by clonal plasma cells. PET/CT scan showed multiple osteolytic bone lesions (T10, L1, 11th left posterior costal arch, 10th lytic right costal arch with soft tissue component, right proximal humerus, left scapula, right acetabulum) and ganglionar involvement (retroperitoneal adenomegalies, SUV 11,8). The R-ISS stage was II, with a high-risk cytogenetic (complex karyotype with gain of Chromosome 1q) [5].

He was refractory to first line induction treatment with CyBorD (cyclophosphamide, bortezomib and dexamethasone) and started treatment with DRD (Daratumumab, Lenalidomide and Dexamethasone) achieving partial response and progressed on treatment after 7 months [6].

New bone lesions were diagnosed (left iliac, T1, left clavicle, 7th left rib) and he was readmitted for pain treatment (Figure 1).

An analgesic scheme was initiated and once pain was controlled, a third line treatment with KPD [7] (carfilzomib, pomalidomide and dexamethasone) was started.

After first infusion of carfilzomib the patient presented tumor lysis syndrome and was referred to the intensive care unit. Non lithiasic cholecystitis was diagnosed and required antibiotics, vassoprresive drugs and renal replacement for 48 hours.

The patient was fully recovered and 14 days later chemotherapy was restarted.

Twenty-four hours later, the patient presented acute confusional syndrome

He was awake but drowsy, hyporesponsive, and disoriented. His blood pressure was 110/60 mmHg, heart rate 56 bpm, saturation 86% breathing ambient air that improved 95% with 2 liters of inhaled oxygen. The axillary temperature was 36 ºC. He presented adequate ventilatory mechanics, and hypoventilation and bibasal crackles were heard. Heart sounds were present and normophonic. The jugular veins were difficult to assess due to the physical build of the patient. The abdomen was soft, depressible and painless. Catharsis was negative in the previous 2 days. Diuresis was preserved, with no urinary symptoms. The limbs were symmetrical, without edema nor phlebitis. There were no signs of neurological deficit. When raising the arms, he presented spontaneous bilateral flapping. He did not report dyspnea, and tolerated supine position adequately.

His laboratory results showed anemia and leukopenia. The liver function tests were normal. There was evidence of an increase in total protein levels with low albumin levels. Creatinine and urea were slightly increased (Table 1).

Infection was suspected, so blood cultures samples were taken and empiric antibiotics (vancomycin and imipenem) and acyclovir were administered. A lumbar puncture was performed (Table 2). Sample for bacteriological culture, Cryptococcus and herpes virus were sent. Serologies for HIV and syphilis were negative.

Metabolic and endocrine causes of encephalopathy were suspected, but TSH, vitamin B12, folic acid and calcium blood level were within normal limits.

Drug toxicity was suspected, as our patient had received a new chemotherapy regimen recently. Cases of posterior reversible encephalopathy syndrome (PRES), thrombotic microangiopathy (TMA) (including cases of thrombocytopenic thrombotic purpura - TTP) and tumor lysis syndrome have been reported (<1%) with the use of Carfilzomib [8].

Parameters of hemolysis, phosphorus and uric acid, were all within the normal range (Table 3). A peripheral blood smear was requested, showing anisocytosis. Schistocytes were absent.

An emergency MRI was performed (protocols T1, T2, FLAIR, DWI, ADC and Gre) without showing areas of edema, space-occupying lesions, ischemic or hemorrhagic lesions.

A non-convulsive epileptic status was suspected, and an electroencephalogram was performed, which showed an activity compatible with generalized moderate slowing.

As the patient seemed to present no habitual cause of confusional syndrome, less frequent causes were suspected. Due to his history of RRMM and the presence of spontaneous flapping, hyperammonemia was suspected. A serum ammonium dosage was requested, showing elevated blood levels (103 ug/dL, for normal values of 19 to 82).

An electrophoretic proteinogram, immunoglobulin dosage and free light chains were requested, all evidencing rapid serological disease progression (monoclonal M spike increased, IgA increased, lambda light chain increased).

A liver ultrasound was performed and a serum Factor V measurement was requested, both within normal limits, which made liver disease or failure unlikely to be the cause of hyperammonemia.

Confusional syndrome due to hyperammonemia secondary to advanced and progressive multiple myeloma was diagnosed

Antibiotics and acyclovir were suspended. Blood cultures, CSF cultures, Indian ink (Cryptococcus) and herpes CRP were negative.

The case was discussed with the treating hematologist, and together with the patient and the family, the decision to continue with chemotherapy treatment in intensive care unit was made.

The patient presented progression of hyperammonemia and later added hypercalcemia, both refractory to chemotherapy and hemodialysis.

Due to lack of response despite the complete intensive treatment and the patient's clinical conditions, it was decided to suspend treatment and start palliative care.

The patient was finally discharged with hospice care at his hometown, and died ten days later.

Discussion

Hyperammonemic encephalopathy presents a wide range of symptoms that vary from subtle alterations in attention and changes in the sleep-wake rhythm, to deterioration of the sensory, confusion, and flapping, and may even progress to coma and death.

Hyperammonemia normally comes from portal hypertension and/or hepatic insufficiency, impaired metabolism disorders (i.g. ornithine transcarbamylase deficiency), and use of valproic acid.

In situations of high blood ammonia levels, it converses to glutamine in the astrocytes, leading to an osmotic gradient, cerebral edema and increase of intracranial pressure, that leads to a state of neurotoxicity clinically similar in all etiologies. Other theories of ammonia toxicity point to the role of ammonium in neurotransmitter release, in the redox processes of mitochondrial respiration, in cerebral metabolism and in the self-regulation of cerebral circulation [9].

There are multiple case reports in the literature describing hyperammonemic encephalopathy in cancer patients, usually caused by drug toxicity (Hyper CVAD in Burkitt's lymphoma / ATRA and idarubicin in AML M3 [10], fluorouracil/oxaliplatin in colorectal cancer [11], gemcitabine/oxaliplatin in pancreatic cancer [12]).

In MM patients, on the other hand, the mechanism of elevation of ammonium levels occurs differently. It is an inherent complication of disease progression. Up to date, 27 cases of hyperammonemic encephalopathy in MM patients have been reported in the literature, and in a retrospective study the estimated prevalence in patients with MM and altered mental status was <1% [9,13].

The direct production of ammonium by plasma cells and the secondary increase in metabolism and degradation of large amounts of immunoglobulins that overcome hepatic clearance, are postulated as the main physio pathogenic mechanisms of this condition

The production of hepatic portosystemic shunts secondary to infiltration by plasma cells or amyloid, among others, are thought to be secondary causes in this scenario [13,14].

In the published case series, IgA heavy chain isotype, and advance disease with multiple lines of previous treatment were the more frequent factors associated with hyperammonemia [9,13].

Hyperammonemic encephalopathy is a serious complication in the course of MM. The overall mortality is high (48-44%), the diagnosis needs a high level of suspicion, and treatment should be initiated as soon as possible [9,13].

Chemotherapy is the only treatment that has shown to be effective in this setting. In a small case series, all patients who were not treated with chemotherapy died, though only 68% of patients treated with chemotherapy survived the episode [9,13,14].

Other general measures to decrease serum ammonia can be used, like dialysis, the use of carnitine, antibiotics to decrease intestinal bacterial load, and optimization of catharsis with laxatives or enemas. Though they only seem to gain time, as they do not reduce ammonium levels in a sustained way.

Taking effective action on this case, using available resources to quickly rule out the most frequent causes of confusional syndrome, were the basis to finally continue with studies of other less frequent causes. The absence of positive data in the initial complementary studies, the antecedent of MM and the spontaneous flapping presented by the patient, helped to include hyperammonemic encephalopathy as a differential diagnosis of his confusional syndrome.

This experience helps us think about how to face the case of a patient with confusional syndrome and multiple myeloma.

An initial approach would be to rule out the classic causes of confusional syndrome initially described (infection, hydro electrolytic and metabolic disorders, organ failure, etc.), and then think of hyperammonemia as a probable causal agent, even more if the patient presents advanced disease (RRMM) and IgA heavy chain isotype.

Conclusion

Hyperammonemia should be suspected in patients with RRMM and acute confusional syndrome, especially when the involved immunoglobulin heavy chain isotype is IgA. Treatment and early control of the disease are essential tools for the reversal of symptoms.

Conflicts of Interest

- Natalia Schütz
  - Honoraria: Takeda, Janssen, Tecnofarma, Amgen
  - Advisory Board: Takeda, Janssen
  - Research Funds: Janssen, Takeda, Helsinn, Abbie.
- Dorotea Fantl
  - Honoraria: Janssen, Tecnofarma, Amgen, Takeda
  - Advisory Board: Takeda, Janssen
  - Research Funds: Janssen, Takeda, Helsinn, Abbie.

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