Syndrome of Inappropriate Antidiuretic Hormone Due to Multiple Myeloma

by Ashley Abraham, Fariha Shafi, MD, Maaz Iqbal, Ramya Kollipara & Emran Rouf, MD

The association between multiple myeloma and SIADH must be noted in order for physicians to be aware of this rare, but possible cause of SIADH.

Fariha Shafi, MD, FACP, is an Assistant Professor of Medicine in the Section of General Internal and Hospital Medicine at the University of Missouri - Kansas City. Ashley Abraham, MSMA member since 2003, Maaz Iqbal, and Ramya Kollipara, MSMA member since 2003, are all medical students at the University of Missouri - Kansas City. Emran Rouf, MD, FACP, is in the Division of General Internal Medicine at the Center for Diagnostic Medicine at Scott and White Healthcare.
Contact: shafif@umkc.edu

Abstract

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) has been linked to many malignancies. However, literature noting multiple myeloma as a possible cause of SIADH is lacking. Although there is a plethora of literature reporting multiple myeloma induced spurious hyponatremia, our review revealed only one case report, in 1983, describing multiple myeloma induced SIADH.[1]

Here we report another case of multiple myeloma induced SIADH, where secondary causes of SIADH, including pseudohyponatremia, were ruled out.

Introduction

The syndrome of inappropriate antidiuretic hormone (SIADH), characterized by hyponatremia, in which the urine osmolality exceeds the serum osmolality, has been attributed to many malignancies, ranging from small-cell lung carcinoma to Hodgkin's lymphoma.[7] However, literature noting multiple myeloma as a possible cause of SIADH is lacking. Although there is much literature reporting multiple myeloma induced spurious hyponatremia, our review of the literature showed only one case report, dating back to 1983, describing multiple myeloma induced SIADH.[1] Here we report a case of SIADH in a 61-year-old Hispanic patient, diagnosed with multiple myeloma, in whom secondary causes of SIADH, including pseudohyponatremia, hypothyroidism, medications, and adrenal insufficiency, were ruled out. This association between multiple myeloma and SIADH must be noted in order for physicians to be aware of this rare, but possible cause of SIADH.

Case Presentation

A 61-year-old Hispanic female presented to the emergency department for progressive weakness over the past six weeks. The patient also reported decreased appetite along with significant weight loss. She denied any nausea, vomiting or diarrhea.

The patient's past medical history was significant only for diabetes complicated by diabetic retinopathy, causing bilateral blindness, hyperlipidemia and depression. Her home medications included Metformin, Insulin Glargine, Atorvastatin and Clopidogrel. Her medication list also included Filgastrim for presumed thrombocytopenia, diagnosed in

Mexico, where she previously received care. She was no longer taking it at the time of admission.

On initial physical examination, she was afebrile, her blood pressure was 123/65mmHg with no orthostatic changes, pulse rate was 79, respirations were non-labored and 20 per minute. She was found to have mild jugular venous distention, mild hepatomegaly, but no appreciable peripheral edema. Patient was both alert and oriented and further detailed mental status exam was unremarkable.

Initial review of her laboratory studies showed a hemoglobin level of 7.7g/dL, MCV (mean corpuscular volume) 92.5fL, white blood cell count 8,500/μL, reticulocyte count 2.86%, platelet count 424/cmm, and TSH (Thyroid Stimulating Hormone) 0.73uIU/mL. She was hyponatremic with sodium of 127mmol/L, potassium 4.0mmol/L, chloride 94mmol/L, serum bicarbonate 27mmol/L, glucose 138mg/dL, creatinine 0.5mg/dL, calcium 8.9mg/dL. Albumin was low at 2.4g/dL, total bilirubin 1.6mg/dL, alkaline phosphatase 544IU/L, AST 116IU/L, ALT 50IU/L, INR 1.23. Troponins were negative, but BNP (Brain Natruretic Peptide) was elevated at 2,259pg/mL. Her serum osmolality was 274mmol/kg, urine creatinine 61mg/dL, urine sodium 20mmol/L and urine osmolality 435mOsm/kg, with urine sodium and urine osmolality peaking at 77mmol/L and 651mOsm/kg, respectively, over the course of her hospitalization.

Urine chemistries and serum sodium levels were consistent with a picture of syndrome of inappropriate antidiuretic hormone secretion (SIADH). The patient's presenting complaint of weakness was attributed to anemia. Each of these issues was subsequently investigated in detail.

Elevated BNP levels prompted an echocardiogram, which revealed grade 2 diastolic dysfunction, with an ejection fraction of 55%. The patient received diuresis, management of diastolic dysfunction and a cardiology consultation. However there was no improvement in the hyponatremia. Due to elevated transaminases, a liver biopsy was performed, which revealed passive edema, likely due to the diastolic heart failure.

The patient was placed on a fluid restriction, which resulted in minimal improvement. The administration of salt tablets also did not result in any improvement. Further workup consisting of an MRI of the brain and chest X-ray did not reveal any possible causes of SIADH. Other common causes of hyponatremia were ruled out, including pseudohyponatremia, hypothyroidism, medications, and adrenal insufficiency. During the hospital course, the patient's sodium levels continued to drop, with levels reaching as low as 119mmol/L. The patient remained euvolemic with no changes in mental status despite severe hyponatremia.

The patient's initial peripheral blood smears showed a hypochromic normocytic anemia. Additionally, stool guaiac was found to be positive. Therefore, there was a high suspicion for a gastrointestinal bleed and the patient underwent a thorough gastrointestinal evaluation, with an EGD (esophagogastroduodenoscopy) and colonoscopy, neither of which revealed an active source of bleeding. During the hospital course, the patient's status continued to decline. Her hemoglobin levels dropped as low as 4.4mg/dL, for which she received multiple blood transfusions. A Serum Protein Electrophoreis (SPEP) was done which showed Alpha-1 Globulin of 0.25 g/dl, (normal 0.10-0.20), Alpha -2 Globulin of 0.69 g/dl (0.50-0.80), Beta-1 Globulin 0.61g/dl (0.40-0.60), Beta-2 Globulin 1.91 g/dl (0.10-0.40), Gamma Globulin at 0.57g/dl (0.60-1.2). Flow Cytometry was also performed. She had an IgA lambda spike of 1.8g/dl on her SPEP and an IgA monoclonal light chain spike on her Urine Protein Electrophoresis (UPEP) which was positive for Bence Jones Proteins. Subsequently, a bone marrow biopsy was done, which revealed normocellular bone marrow with active trilineage hematopoiesis, but plasma cells were enumerated at 31%. Cytogenetic testing confirmed the diagnosis with hypodiploidy and loss of chromosome 13 which has an unfavorable prognosis. This result was consistent with IgA monoclonal gammopathy.

With the above results, the patient was diagnosed with multiple myeloma with secondary SIADH. The patient was subsequently started on dexamethasone and bortezomib therapy for multiple myeloma, which resulted in a complete resolution of her hyponatremia and anemia; supporting the diagnosis of multiple myeloma induced SIADH. The patient successfully completed one cycle of chemotherapy but after discussion with family decided on pursuing palliative care instead.

Discussion

Frequently, the hyponatremia found in myeloma is a spurious hyponatremia secondary to elevated serum paraprotein concentrations. These paraproteins displace serum water resulting in an artificially low serum sodium level.[5] However, when urine osmolality exceeds serum osmolality in the context of hyponatremia, SIADH must be considered.

The first step in differentiating a true hyponatremia (i.e. SIADH) from a pseudohyponatremia is to calculate the effective serum osmolality (serum osmolality minus urea

concentration). From this calculation, an effective serum osmolality greater than or equal to 280mOsm/kg signifies a pseudohyponatremia; whereas levels less than 280mOsm/kg signify a true hyponatremia. In those with a true hyponatremia, an increased urine osmolality (greater than 100mOsm/kg) indicates impaired water excretion; and if in addition, urine sodium levels are greater than or equal to 20mmol/L, the diagnosis of SIADH is probable.[8] These criteria were consistent with our patient's presentation. Typically, SIADH is a diagnosis of exclusion and should not be diagnosed without properly excluding salt wasting, diuretic use, thyroid, adrenal and pituitary insufficiency.[5]

Although the link between multiple myeloma and SIADH is not definitively established, the association has been recounted sporadically in literature for as far back as 1983.[3] One potential mechanism for the development of SIADH in myeloma implicates the increased IL-6 production induced by myeloma cells. IL-6 is a potent stimulator of arginine vasopressin (AVP) secretion.[6] Physiologically, AVP is released from the posterior pituitary in response to hypothalamic osmoreceptor stimulation if serum osmolality exceeds 285 mOsm/kg. AVP subsequently increases intracellular cAMP(cyclic adenosine monophosphate) levels via induction of adenylate cyclase in aquaporin-2, resulting in water channel incorporation into the apical plasma membrane of the renal collecting duct and thus increased water retention.[5]

This IL-6 theory is further supported by the observation that IL-6 suppression has been effective in terminating the cycle of stimulation and differentiation of B-cells, and thus allowing for normalization of vasopressin levels.[4] This theory lends itself to the use of corticosteroids in the treatment of multiple myeloma.[4,6] By altering gene transcription, corticosteroids are potent inhibitors of inflammatory cytokine production.[4] As evidenced in our patient, the administration of dexamethasone, a potent corticosteroid, resulted in complete resolution of the patient's hyponatremia.

References

1. Nanji AA. "Multiple Myeloma and Syndrome of Inappropriate Secretion of Antidiuretic Hormone." Southern Medical Journal. 1983 Feb;76(2):270.
2. Raftopoulos H. "Diagnosis and Management of Hyponatremia in Cancer Patients." Support Care Cancer. 2007;15(12):1341-347.
3. Alexander DD, Mink PJ, Adami H, et al. "Multiple Myeloma: A Review of the Epidemiologic Literature." International Journal of Cancer. 2007; 120.S12: 40-61.
4. Klein B, Zhang X, Lu Z, Bataille R. "Interleukin-6 in Human Multiple Myeloma." Blood. 1995;85(4):863-72.
5. Hoorn EJ, Zietse R. "Hyponatremia Revisited: Translating Physiology to Practice." Nephron Physiology. 2008;108 (3):46-59.
6. Papanicolaou DA, Wilder RL, Manolagas SC, et al. "The Pathophysiologic Roles of Interleukin-6 in Human Disease." Ann Intern Med.1998; 128:127-37.
7. Jameson JL, Johnson BE. "Paraneoplastic Syndromes: Endocrinologic/Hematologic." In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, Loscalzo J, eds. Harrison's Principles of Internal Medicine. 17th ed. New York, NY: McGraw Hill Medical; 2008:617-622.
8. Milionis HJ, Liamis GL, Elisaf MS. "The Hyponatremia Patient: a systemic approach to laboratory diagnosis." CMAJ2002;166:1058.

Disclosure

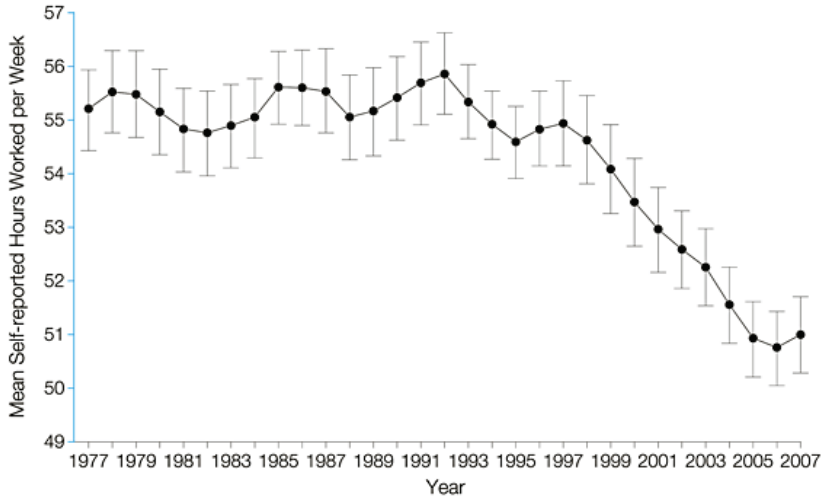
None reported.

MM

1 PICTURE = THOUSAND WORDS

Figure 1
Mean Self-reported Hours Worked per Week by Physicians Between 1977 and 2007

Current Population Survey data based on hours worked in the previous week. Data represent three-year moving averages for each year plotted (eg, 1977 represents 1976-1978 and 2007 represents 2006-2008) and are weighted using sampling weights. Error bars indicate 95% confidence intervals.



Reprinted with permission. Trends in the Work Hours of Physicians in the United States by Douglas O. Staiger, PhD; David I. Auerbach, PhD; Peter I. Buerhaus, PhD, RN . JAMA. 2010;303(8):747-753.