CLINICAL VIGNETTE

A Case of Resistant Hypomagnesemia

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A 67-year-old male was seen in the Emergency Department (ED) with fatigue, dyspnea, and a productive cough. He reported being in his usual state of health until the day prior. Prior medical history was significant for recurrent marginal zone lymphoma originally treated with Rituximab, Cyclophosphamide, Doxorubicin, and Prednisone (R-CHOP) more than 15 years prior and Rituximab upon recurrence two years ago with good clinical response. He was also diagnosed with early stage papillary thyroid carcinoma treated with total thyroidectomy a year prior. Subsequently that same year, he developed human papilloma virus (HPV) positive tonsillar squamous cell carcinoma treated with left radical tonsillectomy, resection of base of the tongue, pharyngectomy, and modified left neck dissection. He received concurrent adjuvant chemoradiation. The therapy included thirty-three sessions of radiation therapy as well as carboplatin. His other medical history included non-ischemic cardiomyopathy and hypertension. His home medications were Lisinopril 5 mg daily, Metoprolol tartrate 12.5 mg twice a day, Aspirin 81 mg daily, Atorvastatin 80 mg daily, Oxycodone as needed and Ondansetron as needed. He denied any significant family history. He has never smoked, drank alcohol only rarely and denied using any recreational drugs.

On physical exam he required six liters of supplemental oxygen via nasal cannula to maintain adequate oxygenation. He was febrile at of 37.8 degrees Celsius and tachycardic with heart rates of 100 beats per minute. His head and neck exam revealed post-surgical changes with no wound dehiscence or cellulitis. Examination of his chest revealed coarse crackles diffusely over his left chest. Laboratory findings were concerning for acute kidney injury with a blood urea nitrogen (BUN) of 45 and creatinine of 1.8 mg/dl), lactic acidosis (lactic acid of 4.5 mmol/l). Chest radiograph revealed left upper lobe and left lower lobe infiltrates. A diagnosis of sepsis due to pneumonia was made in the ED and he was treated with intravenous fluid resuscitation and broad-spectrum intravenous antibiotics (Vancomycin and Piperacillin-Tazobactam). He remained on intravenous vancomycin and piperacillin-tazobactam while hospitalized with clinical status during the early phase of his hospitalization. Blood cultures, sputum cultures and viral respiratory panel were all reported negative. Swallow evaluation was concerning for aspiration, so his diet remained strictly NPO. Multiple electrolyte imbalances including hypokalemia (potassium levels of 3.1 mmol/L), hypocalcemia (corrected calcium of 6.8 mg/dl) and hypomagnesemia (magnesium level of 1.3 mg/dl) was particularly concerning and thought to be contributing to his prolonged QT interval. A percutaneous gastrostomy (PEG) tube was inserted, and feeding was started through the PEG tube. He was started on calcium carbonate 3000 mg three times a day and calcitriol 0.5 mg twice a day, potassium chloride 40 meq, and magnesium oxide 500mg twice daily which resulted in improvement of his hypocalcemia and hypokalemia. His magnesium level, however, remained low despite enteral supplementation. Although he was receiving QT prolonging agents, and his potassium and calcium levels had normalized, his QT interval remained prolonged. Despite improvement in his overall status, the patient sustained a sudden cardiac arrest due to Torsades de pointes. He was successfully resuscitated and extubated after two days. Torsades de Pointes was felt to be caused by the prolonged QT interval and refractory hypomagnesemia. Post cardiac arrest laboratory studies showed normal potassium level but his magnesium was still persistently low at 1.3 mg/dl. His hypomagnesemia required multiple daily dosing of intravenous magnesium sulfate (average requirement of 6-8 mg of intravenous magnesium sulfate per day).

His enteral magnesium supplementation through gastrostomy tube was increased to magnesium oxide 800 mg four times a day but could not be increased further due to development of diarrhea. He required multiple doses of intravenous magnesium per day to maintain his magnesium level above 2. Evaluation of his profound and prolonged hypomagnesemia, was felt most likely to be due to cisplatin induced nephrotoxicity. He had significantly elevated 24-hour urinary magnesium wasting of 456 mg per day. His fractional excretion of magnesium was also significantly elevated at 29%. His hospital stay was prolonged and he remained an inpatient for forty days. On discharge, his magnesium level was measured three times per week and he received three grams of intravenous magnesium sulfate three times per week at an infusion center for two months. The frequency of his visits was gradually reduced and six months later his magnesium levels were stable enough on enteral supplementation that intravenous magnesium infusions were stopped.

Discussion

Hypomagnesemia can have a myriad of clinical presentations but these symptoms and signs are usually due to coexistent electrolyte abnormalities, such as hypokalemia or hypocalcemia. Cardiovascular symptoms include ventricular tachycardia, ventricular fibrillation, atrial fibrillation, multifocal atrial

tachycardia, ventricular ectopic beats, hypertension, enhancement of digoxin-induced dysrhythmias, and cardiomyopathies. Neurologic signs include hyper-reactivity to sensory stimuli, tremors, seizures, weakness, ataxia, increased tone, carpo-pedal spasm and tetany, reversible failure of respiratory musculature, confusion, psychosis, agitation, and delirium.

The prevalence of cisplatin nephrotoxicity is high and affects nearly one-third of patients undergoing cisplatin treatment.[1] It occurs after about ten days of drug administration and results in lower glomerular filtration rate (GFR), high serum creatinine, and reduced serum magnesium and potassium levels.[2] Some of this toxicity may be prevented by pre-hydration and the use of diuretics. At the cellular and molecular level, after exposure of tubular cells to cisplatin, signaling pathways are stimulated which lead to renal tubular cell injury and death. A significant inflammatory response is also generated which contributes to more renal tissue damage. Cisplatin may also induce injury in renal blood vessels and result in reduction in blood flow and ischemic injury to the kidneys, further reducing glomerular filtration rate. These events, together, culminate in the loss of renal function during cisplatin nephrotoxicity, triggering acute renal failure. It is believed that cisplatin treatment may lead to subclinical but also a permanent reduction in glomerular filtration rate. Numerous approaches have been reported to afford renoprotection during cisplatin treatment. Most of these tests have been conducted only in cultured cells or laboratory animals.[3] The effectiveness in patients remains unclear.

In our patient, the most clinically significant aspect of his presentation was hypomagnesemia induced by cisplatin renal tubular injury. Plasma magnesium concentration is the major regulator of magnesium reabsorption in the loop of Henle and distal convoluted tubule. Any abrupt elevation in the plasma magnesium concentration will partially remove the stimulus to magnesium retention, and up to 50% of infused magnesium will be excreted in the urine. Furthermore, magnesium uptake by the cells is slow, and repletion requires sustained correction of the hypomagnesemia.[4] For these reasons, oral replacement should be given in the asymptomatic patient, preferably with a sustained-release preparation. In severe cases of magnesium depletion, for example, when plasma level is <1.0 mg/dL, magnesium repletion should be achieved by intravenous administration of 2 g of magnesium sulfate in 100 mL of five percent dextrose water [D5W] over ten minutes. A continuous infusion of 4–6 g/day for three to five days can be used, presuming renal function is normal. Ongoing repletion with oral administration of magnesium oxide (400 mg 2-3 times daily) for the duration of magnesium deficiency. Oral magnesium gluconate (500 mg 2-3 times daily) can also be used.[5]

Distally acting diuretics (e.g. amiloride) are used as magnesium-conserving agents in Bartter's or Gitelman's syndrome, or platinum-induced nephrotoxicity (as in our case). All three of these diseases are associated with resistant urinary magnesium wasting.[6] However, only magnesium repletion is partially effective because raising the plasma magnesium levels lead to increased magnesium excretion. In addition to oral and parenteral supplementation we also recommended that our patient increase his dietary intake of magnesium. It is known that magnesium is widely distributed in plant and animal-based foods. Green leafy vegetables, such as spinach, as well as legumes, nuts, seeds, and whole grains, are good sources. In general, foods containing dietary fiber also provide magnesium.[7]

Finally, differentiating between gastrointestinal and renal loss of magnesium can be made by measuring the fractional excretion of magnesium or 24-hour urinary magnesium excretion. The former can be calculated using the following formula: FEMg = Urine magnesium x Plasma creatinine /0.7 x Plasma magnesium x Urine creatinine x100 percent. Daily excretion above 10 to 30 mg in 24-hour urine or a fractional excretion of magnesium above 3 to 4 percent in a person with hypomagnesemia and normal renal function as in our case, is consistent with renal magnesium wasting.[8]

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