Abstract. Hypermagnesemia is often an under reported finding in critically ill patients with cancer. Hypomagnesemia is a commonly encountered electrolyte abnormality in patients with cancer that is primarily caused by a reduced intake, secondary to chemotherapeutic drugs and malnutrition. Hypermagnesemia is rarely observed in patients with normal renal function, as excess intake can be compensated by renal excretion. However, in critically ill patients with reduced renal function, hypermagnesemia can add further to complications and increase mortality. Drugs such as lactulose, antacids, fentanyl and peptide hormones, including vasopressin, can further increase chances of hypermagnesemia, particularly when patients demonstrate decreased renal function and multiple organ failure. Prudence and caution must therefore be exercised while using these agents in critically ill patients with cancer to avoid increased complications and mortality. Herein, the current study reports three cases of critically ill patients with cancer admitted into intensive care who had refractory hypermagnesemia.

Introduction

Electrolyte disorders are commonly present in cancer patients. Such disorders can be attributed to mainly cancer specific or treatment related factors. Cancer associated electrolyte imbalances are chiefly due to para-neoplastic syndromes or treatment related adverse-effects secondary to chemotherapeutic agents and other supportive medication. Abnormalities in magnesium are reported far less when compared to sodium and potassium in cancer patients (1). Deheinzelin et al (2) conducted a study in 226 critically ill cancer patients and reported that 45.6% had hypomagnesemia and none had hypermagnesemia. Hypomagnesemia in cancer patients is due to several etiologies such as cancer related anorexia, diarrhea, malnutrition, vomiting, malabsorption, chemotherapy such as cisplatin, anti-EGFR antibodies and concomitant diseases like hyperparathyroidism, hyperthyroidism and diabetes mellitus (1). Hypermagnesemia in cancer patients is most commonly caused due to tumor lysis syndrome where rapid amount of cellular destruction leads to efflux of multiple ions (including magnesium and potassium) into the blood stream. Hypermagnesemia is a rare electrolyte imbalance as compared to hypomagnesemia. The rarity can be attributed to the fact that normally functioning kidney has the ability to eliminate excess magnesium. Felsenfeld et al reported that hypermagnesemia occurs in ~10-15% of hospitalized patients with renal dysfunction (3). Hypermagnesemia commonly occurs due to excessive administration of magnesium salts or magnesium-containing drugs like antacids and laxatives, especially in patients with reduced renal function with glomerular filtration rate (GFR) of <30 milliliters/minute (ml/min) (4). Even normal quantities of magnesium consumption can lead to elevated serum magnesium levels in patients with chronic renal insufficiency (5). Recent evidence suggests that even mild hypermagnesemia is associated with increased in-hospital mortality and that risk of mortality increases with increasing serum magnesium levels (6). We report three cases of grade 3 hypermagnesemia in critically ill cancer patients which was treatment refractory.

Case reports

Case 1. A 77 year old male, a case of stage IV non-small cell lung cancer with metastases to liver, adrenal and bone presented with complaints of fever, cough, breathlessness and burning micturition. The patient was a known case of type 2 diabetes mellitus since 15 years. On examination, the patient was semi-conscious, drowsy and arousable to vocal commands. His vital signs included Blood Pressure: 120/60 mmHg, Pulse: 118 beats per minute, Temperature: 1010F, SPO2 of 72% in room air, GRBS 93 mg/dl and Respiratory Rate of 28 per min. Patient was shifted to ICU, put on ventilatory support and blood investigations sent showed hypercalcemia (13.1 mg/dl), deranged liver functions and high ammonia levels suggestive of hepatic encephalopathy. KOH mount sputum for fungus was positive for yeast like budding cells with pseudomycelium. Parathyroid
hormone levels were within normal range (iPTH: 14 pg/ml). Patient was symptomatically managed with antibiotics, lactulose (15 ml), antacids and hypercalcemia was managed with Calcitonin (100 IU) and aggressive hydration. Patient was also receiving midazolam/fentanyl (50 mcg) infusion as part of ventilatory management. Post 3 days of treatment serum magnesium levels and creatinine levels started to rise. His calculated eGFR was 30 ml/min (Cockcroft-Gault method). Standard treatment guidelines were followed for treating hypermagnesemia with intravenous calcium gluconate and aggressive hydration along with loop diuretics. Grade 3 hypermagnesemia persisted despite best conservative measures and patient succumbed due to multiorgan dysfunction.

**Case 2.** A 58 year old male patient with stage IVa squamous cell carcinoma of tongue underwent anterior 2/3 rd glossectomy + marginal mandibulectomy + bilateral neck dissection + free flap reconstruction. Patient was a known case of type 2 diabetes mellitus and chronic liver disease. Post-surgery, secondary to sepsis, patient developed coagulopathy and hypotension for which aggressive care was initiated. In view of persistent hypotension refractory to fluid challenge, he was started on vasopressor support which included noradrenaline and fentanyl administration. Patient had acute kidney injury with deranged sodium and calcium levels. Culture/sensitivity of swab taken from surgical site was reported as gram negative bacilli Stenotrophomonas maltophilia. The patient also developed rhabdomyolysis (CPK: 25205.0 U/l) which further aggravated acute kidney injury resulting in need for dialysis. Patient developed multiorgan dysfunction syndrome with new onset liver dysfunction and patient was initiated on hemodialysis, vasopressor support (vasopressin 40 units), antibiotics, lactulose (15 ml) and other hepato-protective measures. Persistent grade 3 hypermagnesemia was observed despite the above measures and patient continued to deteriorate leading to death.

**Case 3.** A 57 year old female diagnosed with locally advanced cholangiocarcinoma underwent Open Cholecystectomy with T tube insertion and was on adjuvant chemotherapy. 10 days post completion of 3rd cycle of combination chemotherapy, patient had complaints of coffee-ground-colored vomitus with difficulty in breathing. Chest X-ray showed pleural effusion and pleural fluid aspiration was done despite which patient continued to desaturate, developed hypotension, acute kidney injury, liver dysfunction, hypokalemia, hypocalcemia, hyponatremia and encephalopathy. Patient was put on ventilator support and treated with antibiotics, inotropes, lactulose and hepato-protectants. Dialysis was initiated and electrolyte disturbances were corrected. Post addition of lactulose 15 ml thrice daily, patient developed persistent grade 3 hypermagnesemia which did not resolve with treatment and patient collapsed due to multiorgan failure. The complete case details of cases 1, 2 and 3 are enlisted in Table I.

**Table I. Electrolyte and creatinine levels of cases 1, 2 and 3.**

| Case | Sodium | Potassium | Calcium | Magnesium | Creatinine | Sodium | Potassium | Calcium | Magnesium | Creatinine |
|------|--------|-----------|---------|-----------|------------|--------|-----------|---------|-----------|------------|
| 1    | 142    | 4.5       | 13.1    | 2.1       | 1.3        | 133    | 3.9       | 8.2     | 4.4       | 1.5        |
| 2    | 150    | 3.4       | 4.7     | 2.3       | 0.7        | 144    | 3.4       | 6.4     | 6.7       | 1.6        |
| 3    | 152    | 3.6       | 7.7     | 2.1       | 1.4        | 139    | 3.1       | 7.3     | 6.6       | 1.2        |

**Discussion**

Hypermagnesemia is an uncommon electrolyte disorder as compared to hypomagnesemia especially in cancer patients. Multiple etiological factors are associated with cancer related hypomagnesemia such as cancer associated diarrhea, vomiting, malnutrition, anorexia, cancer therapy, comorbidities and concomitant supportive drugs. However, hypermagnesemia is a very rarely reported electrolyte abnormality in cancer patients and manifested mainly in tumor lysis syndrome along with other abnormalities like hyperkalemia, hyperphosphatemia and hypocalcemia. High magnesium concentrations have been reported in patients with cardiovascular disease and levels of 2.3 mg/dl or higher were associated with increased hospital mortality (6). The major etiological factors for hypermagnesemia are decreased renal excretion, increased magnesium intake and compartment leak or shift. Hypermagnesemia between 7 to 12 mg/dl causes decreased reflexes, confusional state, drowsiness, bladder paralysis, flushing, headache and constipation. A slight reduction in blood pressure and blurred vision caused by diminished accommodation and convergence may manifest. For higher values (>12.0 mg/dl) muscle paralysis, paralytic ileus, decreased breathing rate, low blood pressure, electrocardiogram (ECG) changes including an increase in PR and QRS interval with sinus bradycardia, atrioventricular block, coma and cardiac arrest (exceeding 15.0 mg/dl) may ensue. We observed elevated magnesium levels in presence of acute kidney disease especially post administration of lactulose in the above mentioned cases. Impurity test in the batch of lactulose used for these patients revealed no evidence of magnesium in it (Fig. S1). Despite the patient having multiple complications like sepsis, hepatic and renal dysfunction along with other electrolyte disturbances, the chief reason for persistent hypermagnesemia even after correction of other electrolyte imbalances was most probably due to acute kidney injury. The other factors which could have possibly contributed to hypermagnesemia are lactulose and fentanyl administration.

Seki et al (7) reported that lactulose enhances the intestinal absorption of calcium and magnesium. Decrease in
gastro-intestinal motility also results in increased absorption of magnesium. All of the above 3 patients were given intravenous fentanyl which could have decreased gastro-intestinal motility leading to enhanced absorption of magnesium. Peptide hormones such as parathyroid hormone, calcitonin, glucagon and vasopressin can increase magnesium reabsorption in distal convoluted tubule. These hormone acts through cAMP dependent protein kinase A, Phospholipase C and protein kinase pathways in both distal convoluted tubule and thick ascending limb of Henle's loop (8,9). Calcitonin was administered along with fentanyl and lactulose in cases 1 and 2 and case 3 received vasopressin along with lactulose and fentanyl. Therefore we hypothesized that hypermagnesemia in the above reported cases was chiefly due to acute kidney injury which was further compounded by increased intestinal absorption of magnesium due to fentanyl and lactulose administration. Increased renal reabsorption of magnesium mediated by calcitonin and vasopressin in presence of decreased renal function could have contributed further to hypermagnesemia.

Hypermagnesemia though rarely seen and reported in clinical practice could possibly contribute to increased mortality in critically ill patients. The main reason for hypermagnesemia in critically ill patients is decreased renal function. Concomitant administration of lactulose, fentanyl and ionotropes like vasopressin could further accentuate the hypermagnesemia and complicate clinical management in these patients who already have other electrolyte imbalances and multiple organ dysfunctions. Hence, caution and prudence must prevail when administering lactulose or opioids to these critically ill patients, fully aware of the possible complication of hypermagnesemia which could contribute to increased mortality.

Acknowledgements

The authors would like to express their sincere gratitude to Dr Walter Anthony (Nephrologist, Healthcare Global Enterprises Limited) for identifying the ideal patients for the present study. The authors would also like to thank Dr Priyank Tripathy (Pharmacologist, Healthcare Global Enterprises Limited) for providing valuable pharmaceutical assistance for the study.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

VRK provided treatment and designed the current study. HV acquired the data, designed the current study and provided pharmacological input. YS performed the literature review and acquired the data. RN has provided cancer related scientific inputs. VS and RN confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The current study was conducted upon Institutional Ethics Committee approval. All three subjects provide their or their relatives informed consent for participation.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Berardi R, Torniai M, Lenci E, Pecci F, Morgese F and Rinaldi S: Electrolyte disorders in cancer patients: A systematic review. J Cancer Metastasis Treat 3: 79, 2019.
2. Deheinzelin D, Negri EM, Tucci MR, Salem MZ, Da Cruz VM, Oliveira RM, Nishimoto IN and Hoelz C: Hypomagnesemia in critically ill cancer patients: A prospective study of predictive factors. Braz J Med Biol Res 33: 1443-1448, 2000.
3. Felsenfeld AJ, Levine BS and Rodriguez M: Pathophysiology of calcium, phosphorus, and magnesium dysregulation in chronic kidney disease. Semin Dial 28: 564-577, 2015.
4. Swaminathan R: Magnesium metabolism and its disorders. Clin Biochem Rev 24: 47-66, 2003.
5. Cascella M and Vaqar S: Hypermagnesemia. In: StatPearls [Internet]. StatPearls Publishing, Treasure Island, FL, 2021.
6. Cheungpasitporn W, Thongprayoon C and Qian Q: Dysmagnesemia in hospitalized patients: Prevalence and prognostic importance. Mayo Clin Proc 90: 1001-1010, 2015.
7. Seki N, Hamano H, Iyama Y, Asano Y, Kokubo S, Yamauchi K, Tamura Y, Uenishi K and Kudou H: Effect of lactulose on calcium and magnesium absorption: A study using stable isotopes in adult men. J Nutr Sci Vitamol (Tokyo) 53: 5-12, 2007.
8. Dai LJ, Bapty B, Ritchie G and Quamme GA: Glucagon and arginine vasopressin stimulate Mg2+ uptake in mouse distal convoluted tubule cells. Am J Physiol 274: F328-F335, 1998.
9. Quamme GA, Schlingmann KP, Konra M S: Mechanisms and disorders of magnesium metabolism. In: Seldin and Giebisch's The Kidney. Alpern RJ, Herbert SC (eds). Volume 2. 4th edition. Academic Press. pp 1747-1767, 2008

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.