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CASE REPORT

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Seizure and delirium secondary to carboplatin and pantoprazole therapy-induced hypomagnesemia in a cancer patient

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Abstract

Active surveillance and treatment of hypomagnesemia along with strict avoidance of concurrent offending agents is essential to prevent its grave clinical consequences among patients on carboplatin therapy.

KEYWORDS

carboplatin, delirium, hypomagnesemia, pantoprazole, seizure

1 | INTRODUCTION

Magnesium is an essential intracellular cation critical to multiple biochemical processes and its deficiency can result in a myriad of symptoms. This case illustrates an uncommon etiology and clinical consequence of profound hypomagnesemia, with a follow-up discussion reviewing its biochemical and clinical significance.

Over the past decade, the prevalence of cancer has steadily increased, partly due to better screening but also because of improving diagnostic accuracy and treatment modalities. Estimated worldwide incidence of the three most common cancers for 2020 was a staggering 2.26 million cases for breast cancer, 2.21 million cases for lung cancer, and 1.93 million cases of colon and rectal cancer.[1] As per the national cancer institute, cancer of the oral cavity and pharynx constitutes about 2.8% of all new cancer cases in the United States with an incidence of 54,010 in 2021 with 17,960 being those of the tongue while cancers arising primarily out of the hypopharynx are rare.[2] With time, the use of numerous treatment modalities for various types of cancers has grown exponentially. Chemotherapy, one of the most common of these modalities involves aggressive biological agents which have significant adverse effects on the human body. Platinum-based agents are considered first-line cytotoxic treatment of lung, colorectal, ovarian, breast, head/neck, bladder, and testicular cancers.[3] Here, we shed light on hypomagnesemia which, although commonly seen with cisplatin, is a less common consequence of carboplatin.[3] Deficiency of magnesium, which is involved as a co-factor in more than 300 enzymatic reactions, has wide-ranging effects on the human body and use of platinum-based agents may cause its wasting for up to 6 years after treatment.[3,4] This derangement can be further aggravated if the patient is exposed to other agents which cause hypomagnesemia such as proton pump inhibitors.

2 | CASE

2.1 | Presentation

A 62-year-old male with recently diagnosed squamous cell carcinoma of the tongue and hypopharynx presented to the hospital for a breakthrough seizure at home. The seizure was

generalized tonic-clonic type and spontaneously resolved after 1 min. The patient had a known history of seizure disorder and had been seizure free for 7 years on Levetiracetam. Patient had recently started a chemotherapy regimen with carboplatin, abraxane, and pembrolizumab and his first and only session of chemotherapy was 18 days prior to presentation. Apart from seizure disorder, patient also had a history of gastroesophageal reflux disease for which he was taking oral pantoprazole. On initial encounter, patient was drowsy but oriented to time, place, and person. Patient was able to follow simple commands, but had an attention and memory deficit with good registration but poor recall. Also was observed, generalized weakness with 3/5 strength in all four extremities with preserved deep tendon reflexes. Rest of his neurological examination was unremarkable with no focal sensory or motor deficits. Patient was afebrile and other vitals were also within normal limits. As per patient's sister at bedside, patient had been confused right after the seizure for a short interval but was now back to baseline. However, over the next few hours patient developed gradual worsening confusion and agitation which persisted for over 48 h. During this period apart from cognitive faculties, the patient's neurological examination did not change.

2.2 | Investigations

On presentation, patient's routine laboratory tests were significant for pancytopenia, serum lactic acid of 5.9 mmol/L, serum Bicarbonate of 19 mmol/L, an anion gap of 19, serum calcium of 6.1 mg/dl, (calcium corrected for albumin was 6.82 mg/dl), serum potassium of 3.5 mmol/L, and serum magnesium level of 0.7 mEq/L (Table 1). Computed tomography of head and magnetic resonance imaging of the brain were unremarkable. Patient was also evaluated with video electroencephalogram (vEEG) for 24 h from presentation which revealed 'mild-to-moderate diffuse cerebral dysfunction that is nonspecific in etiology, but may be seen in the context of toxic-metabolic encephalopathies'.

2.3 | Differential diagnoses

At presentation, the patient was afebrile, without elevated white blood cell count and his sepsis screen was unremarkable which included a urinalysis, a chest X-ray, and blood cultures. Additionally, his neurological examination did not reveal any neck rigidity or positive kerning's sign and at this point, infectious causes were deemed less likely. The fact that he did not have any sensory or motor neurodeficits with unremarkable imaging of the brain helped move the differential away from vascular or structural causes such as cerebrovascular accident or metastasis. Continuous vEEG was utilized to rule out non-convulsive seizures. Initial common laboratory reports were significant for hypocalcemia and borderline hypokalemia. At this point, due to the patient's recent exposure to platinum-based chemotherapy agent, serum magnesium level was obtained which was low, at 0.7 mg/dl (Table 1). This hypomagnesemia with existing hypocalcemia and borderline hypokalemia pointed toward severe symptomatic magnesium deficiency. Despite aggressive electrolyte replacement, his serum magnesium levels remained close to 1 Meq/L. The next challenge was confirming the etiology of hypomagnesemia, this required investigating for known offending drugs in addition to recent carboplatin exposure. At this point, it was realized that patient's chronic use of oral pantoprazole was a likely contributor. Urinary electrolytes revealed high magnesium losses and calculated fractional excretion of magnesium in urine was around 25% in presence of normal creatinine, blood urea nitrogen, and estimated glomerular filtration rate. This confirmed our suspicion for renal wasting of magnesium secondary to recent carboplatin exposure since the patient was not taking any other medication

TABLE 1 Laboratory values

Laboratory test	Result	Reference range
Hb	8.9	12.0–16.0 g/dl
WBC	3.4	4.8–10.8 K/ul
Plt	43	150–400 k/ul
Lactic acid	5.9	0.5–1.4 mmol/L
Sodium	138	135–149 mmol/L
Potassium	3.5	3.4–4.8 mmol/L
Chloride	106	93–105 mmol/L
Bicarbonate	19	23–32 mmol/L
Creatinine	0.9	0.3–1.1 mg/dl
BUN	9	7–21 mg/dl
Calcium	6.1	8.2–10.1 mg/dl
Magnesium	0.7	1.6–2.2 mg/dl
Phosphorus	2.6	2.2–5.5 mg/dl
Anion gap	19	3–11 mmol/L
FeMg	24.93%	<3%
Albumin	3.1	3.5–5.2 g/dl
Bilirubin total	0.2	0.2–1.4 mg/dl
AST	28	10–33 IU/L
ALT	31	6–47 IU/L
Alk Phos	71	36–112 IU/L
Total serum protein	5.7	5.6–7.6 g/dl

Note: Patient's laboratory test results with corresponding reference values.

Abbreviations: Alk Phos, Alkaline phosphatase; ALT, Alanine transaminase; AST, Aspartate transaminase; BUN, Blood urea nitrogen; FeMg, Fractional Excretion of Magnesium in urine; Hb, hemoglobin; Plt, Platelet count; WBC, White blood cell count.

(such as diuretics or antifungals) which would cause loss of magnesium in urine.

2.4 | Treatment and follow-up

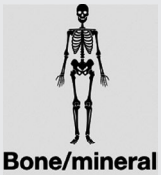
On day 1 of the admission patient was treated with I.V levetiracetam along with aggressive repletion of electrolytes. Two grams of Magnesium sulfate (MgSo4) was administered i.v. immediately after discovering patient's hypomagnesemia. However, next day repeat serum levels of Mg were still low (1.0 mg/dl) and patient was administered additional 4 g of MgSo4 i.v along with 800 mg of magnesium oxide via nasogastric tube. By the third day (after 48 h of initial presentation), his Mg level improved to 1.3 mg/dl and his mental state also began to improve significantly after which the nasogastric tube was discontinued. Apart from magnesium, patient's potassium and calcium were also repleted accordingly. On discharge patient's Mg levels were 1.4 mg/dl and he was prescribed 200 mg of magnesium oxide oral supplements to be taken thrice daily per oral and his PPI was switched to an H-2 blocker. Patient was also advised to follow-up closely with his physician. On speaking to the patient 2 months after discharge, we learnt that he was status post his third round of carboplatin-containing chemotherapy and had been seizure free. He was consistently taking his magnesium supplementation and his H-2 blocker.

3 | DISCUSSION

Platinum-based chemotherapy agents are the first-line cytotoxic modalities for lung, colorectal, ovarian, breast, head/neck, bladder, and testicular cancers.[3] Being cytotoxic, they are not bereft of adverse effects and one of the unwanted implications of their use is electrolyte disturbance, especially hypomagnesemia.[3,4] Most commonly seen with cisplatin use (10%–90%) and less often with carboplatin (10%) magnesium (Mg) depletion can have wide-ranging consequences on human body ranging from minor gastrointestinal side effects to fatal arrhythmias (Table 2).[3,4]

Being the most prevalent intracellular cation and an indispensable co-factor for greater than 300 enzymatic reactions, it is understandable that Mg deficiency can have broad physiological ramifications (Table 2).[3,5] Normally, healthy adults carry around 25 g of magnesium distributed in the intracellular and extracellular compartments.[5] Although Mg is predominantly located intracellularly and in bone, it is also found in serum wherein 55% circulates in the ionized form, with the rest bound to albumin or chelated to anions.[3,5,6] Mg is

TABLE 2 Effects of hypomagnesemia

 Neuromuscular	Muscles: Muscular weakness, tremor, fasciculation, and wasting Neurological: Seizures, Vertigo, ataxia, nystagmus, athetoid, and choreiform movements Neuropsychiatric: delirium, depression, and psychosis Clinical signs such as Positive Chvostek's and Trousseau's sign, Spontaneous carpal-pedal spasm
 Cardiovascular	EKG Changes and arrhythmias: prolonged P-R and Q-T interval, U waves, torsades de pointes, atrial tachycardia, premature contractions and fibrillation, junctional arrhythmias, ventricular premature contractions, tachycardia, fibrillation, and sensitivity to digitalis intoxication Other putative effects—Atherosclerotic vascular disease, Hypertension, and Myocardial ischemia/infarction.
 Bone/mineral metabolism	Hypocalcemia: Believed to be secondary to impaired PTH secretion, renal, and skeletal resistance to PTH and resistance to vitamin D
 Electrolytes & others	Hypokalemia: renal potassium wasting and decreased intracellular potassium. Early signs of magnesium deficiency including loss of appetite, nausea, vomiting, fatigue, and weakness.

Note: Wide range of clinical implications resulting from magnesium depletion.

Abbreviations: EKG, Electrocardiogram; PTH; Parathyroid Hormone.

filtered at the glomerulus and gets reabsorbed primarily at the thick ascending limb of loop of Henley (70%) by passive uptake while only 15% is reabsorbed in the proximal tubule by an active process and around 10% gets absorbed in the distal tubules.[4] With a normal range of 1.7–2.2 mg/dl, hypomagnesemia is defined as serum level less than 1.7 mg/dl.[3,5] On presentation, our patient had a serum Mg level of 0.7 Meq/L and symptoms are believed to usually manifest when levels fall below 1.2 mg/dl (≈1 Meq/L).[7] However, it is noteworthy that serum Mg levels poorly correlate with actual Mg content of the body and profound intracellular Mg deficit has been seen even with normal serum Mg levels.[3–5] Therefore, the term hypomagnesemia is not interchangeable with Mg deficiency and low serum levels of other electrolytes like potassium and calcium may serve as clinical clues to an existing but masked Mg deficiency, especially among patients with known risk factors (Table 3) but otherwise normal serum levels.[3]

The exact mechanism by which platinum-based agents cause hypomagnesemia is unclear but it is believed that the primary route seems to be through renal losses.[3,4] Nephrotoxicity is a well-known side effect of these agents and declining Mg level is believed to be an early sign of cisplatin-induced renal injury while rise in creatinine may occur late.[4] It is hypothesized that platinum agents get filtered at the glomerulus (cisplatin much more than oxaliplatin or carboplatin which are predominately bound to plasma proteins) and reach the renal tubular cells through organic cation transporters to exert nephrotoxicity and interfere with magnesium reabsorption in the ascending limb of loop of Henle, as well as the distal tubule.[3,4] This in turn causes renal Mg wasting.[3,4] Even though our patient did not exhibit them, gastrointestinal side effects of vomiting and diarrhea induced by platinum agents further contribute to Mg loss.[3]

Although the incidence of hypomagnesemia is notably less common among patients being treated with carboplatin as compared to cisplatin, the frequency of hypomagnesemia occurrence in the former has been shown to have a detrimental effect on the overall survival in cancer patients.[8]

Our patient was also exposed to chronic use of proton pump inhibitors (PPIs) which is another class of drugs known to cause hypomagnesemia.[3,9] First described in 2006, PPI-induced hypomagnesemia is now a well-known entity.[9] In fact, PPIs may induce hypomagnesemia which is refractory to oral Mg supplementation and is known to cause generalized tonic-clonic seizures.[3,7] The exact mechanism of PPI-induced hypomagnesemia is unclear but it is believed that PPIs increase the luminal pH in the intestines which reduces the affinity of the Mg influx channel (Transient Receptor Potential Melastatin 6,TRPM6/7) for Mg uptake.[3] It seems apparent that concurrent exposure to carboplatin and pantoprazole predisposed our patient to severe hypomagnesemia. In fact, concurrent use of cisplatin or carboplatin with a PPI is an independent risk factor for PPI-induced hypomagnesemia.[9,10] Our patient, who needed acid suppression for his gastroesophageal reflux would have tolerated histamine receptor-2 (H-2) blocker agents better since studies have found no correlation of these agents with hypomagnesemia.[9]

Apart from co-administration of two offending agents, the patient was also evaluated for other etiologies of hypomagnesemia which may be classified under 2 major categories: renal or gastrointestinal (Table 3) and no other contributor could be identified.[3–5]

Mg deficiency may have various clinical implications ranging from asymptomatic to seizures and fatal arrhythmias (Table 2). Generalized weakness, fatigue, nausea/vomiting, and loss of appetite are commonly occurring early signs. Being such a critical electrolyte with wide-ranging physiological functions, management of Mg deficiency should be prompt. Promptly after discovery of hypomagnesemia, in addition to repletion of magnesium, patient's PPI therapy was halted and instead changed to a H-2 blocker since identification and cessation of offending drugs is an essential component of treating hypomagnesemia.[11] Magnesium may be repleted through oral and/or intravenous formulations. Oral supplementations are preferred among patients who have mild hypomagnesemia, are asymptomatic or have chronic hypomagnesemia which may exist up to 6 years after cessation of platinum-based chemotherapy.[4,11] Several formulations exist for oral supplementation but sulfate and chloride salts are preferred as their absorption is slow with less renal excretion and because they cause diarrhea less frequently.[11] Usual doses for the oral supplements are 400–800 mg per day but doses greater than 400 may cause diarrhea which can actually worsen hypomagnesemia.[3] In case of severe (<1.2 mg/dl) hypomagnesemia, especially if seizures are present (both of which were true for our patient), injection of 1–2 g of magnesium sulfate should be administered over a 5-min period, followed by an infusion of 1–2 g per hour for the next few hours, which may be repeated if seizures persist.[7] However, intravenous administration of Mg is challenging since 80% of the infused Mg load gets excreted by the kidneys in the next 48 h.[11] These phenomena are thought to result from high peak levels of Mg after bolus iv infusions which in turn promotes magnesuria in the thick ascending limb of loop of Henle.[11] Among patients whose Mg levels do not respond adequately to bolus or short iv infusions, alternate may be CMIs (continuous Mg infusions) which involve a 7-day continuous infusion of Mg sulfate.[12] A study by Mateo-Carrasco et al. used infusions prepared in using MgSO4 50% w/v in NaCl 0.9% (final volume 85 ml), and given via a peripherally inserted central catheter using 7-day elastomeric pumps. This technique showed reduction in the number of episodes of severe hypomagnesemia and increase in mean serum Mg concentrations without any impact on safety.[12]

Additionally, research shows that co-administration of intravenous Mg with platinum-based agents is

TABLE 3 Causes of magnesium depletion

Causes of magnesium loss	
Gastrointestinal	**Renal**
Long-standing vomiting or nasogastric suction	Drugs: diuretics (furosemide, ethacrynic acid), aminoglycosides, amphotericin B, viomycin capreomycin, pentamidine, cisplatin, and cyclosporin.
Diarrhea (acute or chronic)	Renal diseases: chronic pyelonephritis, interstitial nephritis, glomerulonephritis, diuretic phase of acute tubular necrosis obstructive nephropathy, renal tubular acidosis, and renal transplantation
Malabsorption syndromes	Metabolic acidosis: starvation, ketoacidosis, and alcoholism
Extensive bowel resection	Genetic: Primary renal hypomagnesemia, Bartter's Syndrome, and Gitelman's Syndrome
Intestinal and biliary fistulae	Others: Chronic parenteral fluid therapy, Osmotic diuresis, and Hypercalcemia
Protein-Calorie malnutrition	
Acute hemorrhagic pancreatitis	
Primary intestinal hypomagnesemia (neonatal)	
Proton pump inhibitors	

Note: Etiology of magnesium depletion broadly classified under renal or gastrointestinal causes.

nephro-protective.[13] However, the dose and duration of Mg administration vary considerably among the studies. Data from meta-analyses recommend co-administration of I.V magnesium with a dose of 1 g (8 mEq) of Mg while higher doses are either inferior or equally effective.[13,14] In these systemic reviews, majority of the studies used magnesium sulfate while some used magnesium chloride.

One also needs to be cautious with Mg supplementation as hypermagnesemia, which although rare among patients with good renal function, can be dangerous among patients with renal insufficiency (known side effect of platinum agents). Clinical features include nausea, vomiting, EKG changes (prolonged PR, QT interval), hypotension, arrhythmias, respiratory depression, and death.[3] In case of severe Mg toxicity causing arrhythmia or respiratory arrest, one may use Calcium gluconate as a Mg antagonist.[3]

4 | CONCLUSION/HIGHLIGHTS

1. Magnesium depletion can cause a wide range of serious clinical consequences
2. Carboplatin can cause long lasting, severe symptomatic hypomagnesemia
3. Patients exposed to carboplatin need close follow-up for electrolyte disturbances
4. Concurrent therapy with other offending agents like PPIs can worsen hypomagnesemia
5. Patient may have profound magnesium depletion despite normal serum levels, where low potassium and calcium levels can be important clinical clues.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTION

SVK, as a member of primary team, was involved in the management of patient, interviewed and examined the patient, collected and compiled data, reviewed relevant research articles, and composed the manuscript. JL reviewed the relevant research articles, contributed to the discussion, and assisted with editing the manuscript. EUE reviewed the relevant research articles, contributed to the discussion, and also assisted in preparing graphics. MM, VSS, and TH reviewed the relevant research articles and contributed to the discussion.

ETHICAL APPROVAL

Ethic committee was not consulted for approval as the case report was written with due permission from the patient and with all possible efforts to maintain complete anonymity.

DATA AVAILABILITY STATEMENT

Not applicable.

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