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Cisplatin Chemotherapy for Hepatoblastoma Induced a Carpopedal Spasm due to Hypocalcemia and Hypomagnesemia: A Case Report

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Abstract: ***A two-year-old boy occurs carpopedal spasm seven days after cisplatin and doxorubicin chemotherapy. The physical examination was showed adduction of the thumb over the palm, followed by flexion of the metacarpophalangeal, extension of the interphalangeal, adduction of the hyperextended all fingers, and flexion of the wrist and elbow on both hand. Laboratory data was significant for calcium 5.1 mg/dL (normal, 8.8-10.8 mg/dL) and magnesium 0.46 mg/dL (normal, 1.5-2.5 mg/dL). An electrocardiogram showed sinus rhythm with a rate of 150, normal PR interval, and a normal QTc interval. Other laboratory data showed intact parathyroid hormone (PTH) 33.9 pg/mL (normal, 10-55 pg/mL), total serum 25(OH)-vitamin D of 26.9 ng/mL (normal, 31-60 ng/mL) and calcium urine 5.23 mmol/24 hour (normal, 2.5-4.5 mmol/24 hour). The patient had received a 2300 mg total of intravenous magnesium sulfate and 8300 mg of intravenous calcium gluconate. There was a complete resolution of his clinical symptoms by hospital day three, but the laboratory data still had an imbalance electrolyte. The patient was treated until sixteen days, and the last electrolyte result showed serum calcium 5.6 mg/dL and serum magnesium 0.95 mg/dL when the patient discharge from the hospital. The patient had to continue oral supplementation at discharge.This case emphasizes the importance of the observation side effect of cisplatin and doxorubicin, mostly increase in higher cumulative dose. The patients receiving cisplatin and doxorubicin chemotherapy should be had calcium and magnesium supplement after therapy. An additional oral medication at the time of administration may be given to these patients due to recurrent symptomatic hypocalcemia and hypomagnesemia after chemotherapy.***

Keywords: cisplatin, carpopedal spasm, hypocalcemia, hypomagnesemia

1. Introduction

Chemotherapy with cisplatin for hepatoblastoma seemed to be very effective in the prevention of metastasis and cell cancers eradication. The patient with cisplatin was occurring hypomagnesemia caused by renal tubular damage leading to increased renal wasting of magnesium, and this is a common side effect in 90% patient. Cisplatin causes damage to electrolyte receptors at the ascending loop of henle and distal convoluted tubules, which leads to renal magnesium wasting. Doxorubicin is also thought to possess a similar lowering effect on serum magnesium, although its sole effect has not been fully evaluated. Hypocalcemia may be secondary to hypomagnesemia that was correlated with the parathyroid hormone, which leads to decreased calcium absorption, release, and reabsorption in the body. Here we report a case of hypomagnesemia and hypocalcemia due to cisplatin treatment for hepatoblastoma.

2. Case Report

We present a case of a 2-year-old boy with a history of hepatoblastoma chemotherapy who presented to the emergency room with complaints of stiffness on his fingers. The parents said that symptoms began one hour before admission. These symptoms appeared on the fingers of both hands. He was seven days out from his fifth cycle with cisplatin and doxorubicin chemotherapy. He was treated with an infusion of 9.4 mg (20 mg/m^2 body surface area /day) of cisplatin five times and 11.75 mg (20 mg/m^2 body surface area /day) of doxorubicin three times every three weeks. Total 5th cycle doses of cisplatin and doxorubicin were 47 mg and 34.5 mg, respectively. The patient was not a history taking any drugs like diuretics, glucocorticoids, or calcium supplementation. **As shown in figure 1**, physical examination was showed the adduction of the thumb over the palm, followed by flexion of the metacarpophalangeal, extension of the interphalangeal, adduction of the hyper extended all fingers, and flexion of the wrist and elbow on both hands. The same symptoms another hand was showed carpopedal spasm on the fingers both hands. The average urine output of this patient was 2.05 ml/body weight/hour.

Laboratory result initially showed pancytopenia (white blood cell 1.52 K/uL, hemoglobin 9.24 g/dL, platelet 72.07 K/uL), serum calcium 5.1 mg/dL , serum magnesium 0.46 mg/dL, serum phosphorus 0.96 mg/dL, albumin 4.30 g/dL, glomerular filtration rate 231.57 ml/min/1.73 m^2, intact Parathyroid hormone (PTH) 33.9 pg/mL, total serum 25(OH)-vitamin D of 26.9 ng/mL and high calcium urine 5.23 mmol/24 hour. Magnesium urine and urinary cAMP was not checked. The electrocardiogram showed sinus rhythm with a rate of 150 times/minute, normal PR interval, normal QTc interval. The patient also checks urine analyses were within normal limits. The completed Laboratory data pre and post 5th cycle chemotherapy shown in **table 1.**

Figure 1: The patient finger

Table 1: Laboratory data values 5th cycle chemotherapy

Laboratory result, (normal value)	*Before*	*After*
White Blood Cell, K/uL (5-15.5)	4.83	1.52
Hemoglobin, g/dL (>11.5)	9.10	9.24
Hematocrit, % (>34)	27.30	28.65
Platelet, K/uL (150-350)	387.7	72.07
Calcium, mg/dL (8.8-10.8)	8.8	5.1
Magnesium, mg/dL (1.5-2.5)	1.36	0.46
Sodium, mmol/L (135-145)	135	131
Chloride, mmol/L (97-107)	94.4	95.7
Potassium, mmol/L (3.4-4.7)	3.51	3.25
Albumin, g/dL (3.6-5.2)	4.4	4.3
Intact Parathyroid hormone, pg/mL (10-55)	38.58	33.9
Creatinin, mg/dL (0.3-0.7)	0.19	0.24
GFR, ml/min/1.73 m^2 (>98)	231.57	183.3

Comprehensive management was given, such as 125 ml packed red cell transfusion for the anemia, 100 ml thrombocyte concentrate for the thrombocytopenia, and oral potassium maintenance for hypokalemia. The patient was treated with intravenous magnesium sulfate 25-50 mg/body weight and calcium gluconate 50-125 mg/body weight until the symptoms disappeared. The patient had received a 2300 mg total of intravenous magnesium sulfate and 8300 mg of intravenous calcium gluconate. The patient also had adequate nutrition management in the hospital, approximately containing 552 mg calcium and 187 mg magnesium daily, and had oral supplementation (calcium citrate 500 mg, vitamin D3 200 IU, magnesium 100 mg daily) 7th days hospitalization until patient discharge. Serum calcium and magnesium were checked after electrolyte correction therapy. There was a complete resolution of his clinical symptoms by hospital day three, but the laboratory data still had an imbalance electrolyte. The patient was treated until sixteen days, and the last electrolyte result showed serum calcium 5.6 mg/dL and serum magnesium 0.95 mg/dL when the patient discharge from the hospital. The patient had to continue oral supplementation at discharge.

3. Discussion

Cisplatin and doxorubicin chemotherapy was used to the prevention of metastasis and cell cancers eradication. Cisplatin is an antineoplastic drug used in the treatment of many solid-organ cancers like Hepatoblastoma, and the main dose-limiting side effect of cisplatin is nephrotoxicity. A cumulative dose of cisplatin increased the side effects of Nephrotoxicity inpatient [1,3].

Table 2: Etiologies of Hypomagnesemia [6]

Extra-renal losses	*Renal losses*
Decreased intake	**Genetic (tubular)**
Malnutrition	Autosomal-dominant hypocalcemia, hypomagnesemia, and hypercalciuria
Low-magnesium containing food	Familial hypomagnesemia, hypercalciuria, and nephrocalcinosis
Parenteral fluids with low magnesium content	Isolated hypomagnesemia (autosomal-dominant, autosomal-recessive)
Altered Mg distribution	Gitelman and Bartter syndromes
Rapidly proliferating neoplastic tissue Hungry bone syndrome	**Acquired**
Re-feeding Diabetic ketoacidosis	Massive diuresis (recovery from acute renal failure)
Massive transfusions (citrate effect)	Drugs
Gastrointestinal losses	Loop/thiazide diuretics
Genetic	Aminoglycosides
Primary intestinal hypomagnesemia	Amphotericin B
Acquired	Cisplatinum, carbplatinum
Malabsorptive syndromes (celiac, inflammatory bowel disease)	Calcineurin inhibitors
Diarrhea (of any cause)	Anti-EGFR antibodies
Short bowel syndrome	Pentamidine
Bowel resection	Foscarnet
Drugs	
Proton pump inhibitors	
Laxative abuse	

Plasma magnesium concentrations and glomerular filtration rate decreased after cisplatin chemotherapy. The study has suggested cisplatin doses higher than 50 mg/m2 body surface area (BSA) has been correlated with nephrotoxicity[1,3,11]. In the early and later phases, cisplatin causes damage to magnesium and calcium receptors at the ascending loop of henle and distal convoluted tubules, which leads to renal magnesium wasting[7,8].Cisplatin chemotherapy is associated with hypomagnesemia in a highly significant percentage of patients. Incidence increases with an increase in the cumulative dose of cisplatin[7,14].**In this case,** the patient had a 100 mg/m2 BSA cumulative dose of cisplatin on the 5th cycle chemotherapy, and the glomerular filtration rate was normal on the 7th day after cisplatin chemotherapy. The patient had a hypercalciuria (calcium urine 5.23 mmol/24 hour), which indicated damage to magnesium and calcium receptors at the ascending loop of henle and distal convoluted tubules because there was decreased calcium reabsorption from the kidneys.

Cause of hypomagnesemia may due to absorption or inappropriate intake or increased losses in either the gut or kidney, etiologies of hypomagnesemia as shown in table 2 [6]. Kaplinsky C and Alon US (2013) in a review of magnesium homeostasis and hypomagnesemia in children with malignancy, found that to obtain an indication of the source of the hypomagnesemia is by measuring the fractional excretion of magnesium in a urine specimen obtained concomitantly with serum sample, both analyzed

for magnesium and creatinine [6].

Several Acquired etiologies (table 2) of any kind of polyuria can cause urine magnesium losses. Extra-renal causes may be considered because of the problem in the absorption, intake, and increased losses in the gut. Another possibility is insufficient absorption in the gut, which rarely can be caused by genetic abnormalities in the absorptive mechanism, and is more commonly due to acquired disorders like steatorrhea, short gut, and most frequently prolonged and massive diarrhea. In several reports was found a low amount of calcium and magnesium urine on the intake or gastrointestinal (GI) tract problem [6]. Several Acquired etiologies (table 2) of any kind of polyuria can cause urine magnesium losses. **In this patient**, after chemotherapy, the patient didn't have a good appetite; it's mean a low intake magnesium and calcium source from the food**.** The patient also didn't have a GI tract problem, and the etiologies for this patient may be due to renal losses such as hypercalciuria and cisplatin chemotherapy.

The patient with cisplatin was occurring hypomagnesemia caused by renal tubular damage leading to increased renal wasting of magnesium, and this is a common side effect in 90% patient. Hypomagnesemia was shown after repeated doses of cisplatin, even in the absence of a fall in the glomerular filtration rate [7]. Doxorubicin is also thought to possess a similar lowering effect on serum magnesium, although its sole effect has not been fully evaluated.[4] Nephrotoxicity increases with the dose and frequency of administration and cumulative dose of cisplatin [7]. The glomerular filtration rate and plasma magnesium concentrations decreased after cisplatin doses higher than 50 mg/m 2 body surface area [7,11]. Recovery of renal function usually occurs over a period of 2–4 weeks, though more protracted courses, as well as lack of recovery, are reported. The risk factors for cisplatin nephrotoxicity, as shown in table 3. **In this case**,the risk factor was the frequency and cumulative dose of cisplatin. The patient had chemotherapy every three weeks, and the cumulative dose of cisplatin was 100 mg/m2 BSA.

Hypocalcemia may be secondary to hypomagnesemia that was correlated with the parathyroid hormone, which leads to decreased calcium absorption, release, reabsorption in the body, and relative hypoparathyroidism. Intact PTH assays are sufficiently specific and sensitive to know active PTH for diagnosed the euparathyroid and hypoparathyroid. **In this case,** the patient had an intact PTH of 33.9 pg / mL (euparathyroid), so the cause of secondary hypocalcemia was not related to any abnormalities in the parathyroid hormone. In renal proximal tubule cells, mitochondrial 25-hydroxy-vitamin D 1α-hydroxylase metabolizes 25-hydroxy-vitamin D to the biologically active hormone, 1,25-Dihydroxy-vitamin D. The average circulating level of 25-hydroxy-vitamin D based on Endocrine Society is 31-60 ng/mL[8]. Circulating 1,25-Dihydroxy-vitamin D levels are increased by hyperparathyroidism and phosphate depletion. The 1, 25-Dihydroxy-vitamin D is reduced in hypoparathyroidism, and this is a feedback mechanism for low calcium levels in the blood. The American Academy of Pediatrics recommended minimum daily intake of vitamin D is 400 IU/day for all infants, children, and adolescents beginning in the first few days of life [10]. **In this case,** the levels of 25-hydroxy-vitamin D 26.9 ng/mL were insufficiency because of the hypocalcemia in this patient. This patient had a 200 IU vitamin D3 oral supplement and received approximately 670 IU vitamin D from the food daily.

Table 3: The risk factor for cisplatin nephrotoxicity [2]

Increased risk	*Decreased risk*
Dose Frequency Cumulative dose Older age Female sex Smoking Hypoalbuminemia Pre-existing renal insufficiency (Limited data in humans)	Diabetes (uncertain in humans) Organic cation transporter OCT2 polymorphisms

The clinical symptoms occur when serum calcium levels <8.5 mg/dL and magnesium levels <1.0 mg/dL [2, 13, 14]. Hypocalcemia and hypomagnesemia can appear symptomatic or asymptomatic based on the grade of severity National Cancer Institute–Common Toxicity Criteria Version 5 [15]. Acute symptoms most often seem related to neuromuscular irritability such as chvostek's sign, trousseau's sign, paresthesias, tetany, seizures (focal, petit mal, grand mal), carpopedal spasm, muscle weakness, laryngospasm, bronchospasm [2]. Some patients developed electro-cardiogram abnormalities like arrhythmia, prolonged QTc interval, and ST depression [6].

Carpopedal spasm is neuromuscular of contractions of the hand and foot muscles most often caused by hypocalcemia. Clinical manifestations of carpopedal spasm usually have an extension of the fingers or toes and may be accompanied by pain. Carpopedal spasm is exacerbated by hypomagnesemia, resulting in abnormalities in the regulation of muscle contraction and relaxation [2,4]. Cisplatin chemotherapy-induced peripheral neuropathy on forty-five patient was observed, also have muscle cramps and demyelinating syndromes were each noted in 31% of the patients [16]**. In this case,** the patient was grade 4 based on grades of severity of hypomagnesemia and hypocalcemia. The patient had a carpopedal spasm with calcium serum levels 5.1 mg/dL and magnesium serum levels 0.46 mg/dL, but the electrocardiogram found a normal QTc interval.

The initial bolus injection of elemental calcium can be expected to decrease signs of hypocalcemia [5]. Recommended therapy was 50-150 mg/kg body weight calcium gluconate, and continuous intravenous infusion of calcium is recommended at 5-15 mg/kg/hour until oral medications provide control of serum calcium concentration.[5] Preventing the lowering of Mg levels by giving intravenous (IV) Mg infusions has prevented adverse effects of hypomagnesemia [13].

The study from Netten et al. (1990) found that significantly lower serum magnesium values were present in the unsupplemented group from the third course of chemotherapy. The final conclusion of the study was that hypomagnesemia could be prevented by intravenous supplementation during treatment days [12].For grade 1

hypomagnesemia, no replacement strategy is necessary, as these patients are typically asymptomatic [13]. For patients with grade 2 hypomagnesemia, a weekly IV replacement for Mg levels of 0.9–1.0 mg/dL seems to be effective [13]. Correction of grade 3/4 hypomagnesemia with frequent IV infusions, these patients should receive appropriate replacement [13]. **In this case,** the patient had therapyamagnesium sulfate 25-50 mg/kg body weight/ dose (2300 mg total of intravenous magnesium) and calcium gluconate 50-150 mg.kg body weight/ dose (8300 mg total of intravenous magnesium). This patient didn't have been prevented by intravenous magnesium and calcium supplementation when he had cisplatin chemotherapy.

4. Summary

This case emphasizes the importance of the observation side effect of cisplatin and doxorubicin, mostly increase in higher cumulative dose. The patients receiving cisplatin and doxorubicin chemotherapy should be had calcium and magnesium supplement after therapy. An additional oral medication at the time of administration may be given to these patients due to recurrent symptomatic hypocalcemia and hypomagnesemia after chemotherapy. Periodic monitoring of post-chemotherapy blood electrolytes is needed.

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