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CASE REPORT

Hypomagnesemia because of nedaplatin for cervical cancer: A case report

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Abstract

A 76-year-old woman with cervical cancer was treated with nedaplatin, a platinum-based drug. After the initiation of the treatment, she became aware of numbness, dizziness, and loss of appetite. Exploration of the causes revealed no clues, but blood tests revealed hypocalcemia and hypomagnesemia. She was treated with intravenous calcium and magnesium, which resolved calcium, magnesium levels, and her symptoms. She was diagnosed with hypomagnesemia because of nedaplatin. Regular follow-up is necessary for patients during or after nedaplatin. Awareness of electrolyte disturbances may elucidate the accurate diagnosis even in patients with obscure symptoms, particular in undergoing or following anticancer therapies.

KEYWORDS
hypomagnesemia, nedaplatin, uterine cervical neoplasms

1 | BACKGROUND

Nedaplatin is a type of platinum drug developed in Japan and used mainly in Japan for uterine and lung cancer. Cisplatin, another platinum drug, has been reported to cause hypomagnesemia in up to 90% of patients.[1] Nedaplatin has shown fewer side effects than cisplatin,[2] and there have been no reports of hypomagnesemia after starting nedaplatin therapy. We report a rare case of hypomagnesemia after starting nedaplatin.

2 | CASE PRESENTATION

A 76-year-old woman with hypertension, dyslipidemia, and chronic kidney disease presented with dizziness. Three months ago, she was diagnosed with cervical cancer (TNM classification T4N0M0, clinical stage IVA) with bladder invasion and left hydronephrosis at our hospital. Two months ago, she was admitted to a gynecology department of another hospital for chemoradiation therapy. Weekly nedaplatin therapy (40 mg/sq) was started, receiving four courses. Radiotherapy consisted of whole pelvis irradiation (50.4 Gy/28 f) and a remote after-loading system (12 Gy/2 f). After the start of chemotherapy, there was a temporary increase in serum creatinine levels, which was thought to be nedaplatin-induced nephrotoxicity. She showed improvement over time and was discharged from the hospital. One month prior, however, she developed a loss of appetite for an unknown reason, and 2 days prior, numbness and dizziness as well. She was referred to the general medicine department for evaluation. She was only taking 2.5 mg of rosuvastatin and 2.5 mg of amlodipine. She seldom drank alcohol. She denied any family history of electrolyte disturbances. She denied a history of recent intake reduction, diarrhea, and aggressive hydration. Physical examination revealed a

positive Trousseau sign. Laboratory results showed normal findings, except for hypomagnesemia of 0.5 mg/dL, hypocalcemia of 4.4 mg/dL, and elevated FECa 4.4% and FEMg 150.3% (Table 1). There was no electrocardiogram change.

Since the patient developed hypomagnesemia after nedaplatin treatment, an adverse event of nedaplatin was suspected. Other platinum drug could cause Fanconi's syndrome, but investigations were negative. The cause of hypocalcemia was thought to be vitamin D deficiency because of insufficient intake or lack of sunlight, and a decrease in 25(OH)D with normal P. No association with hypomagnesemia was suspected. The patient was urgently hospitalized on the same day, and intravenous calcium gluconate and magnesium sulfate were started. On the next day of admission, subjective symptoms improved, and Trousseau sign disappeared. After confirming that serum magnesium and calcium levels improved to the normal range, the patient was switched to oral magnesium oxide and calcium aspartate on the fourth day of hospitalization and discharged home on the eighth day (Figure 1). After the discharge, we followed up with her monthly and performed blood tests. While oral magnesium oxide and calcium aspartate dosages were adjusted according to serum magnesium and calcium levels, resulted in a decrease in FEMg to 3.41 at 15 months after the start of treatment, with no recurrence of hypomagnesemia, hypocalcemia, and subjective symptoms.

3 | DISCUSSION

Nedaplatin is a type of platinum drug developed in Japan and used mainly in Japan for various malignancy treatment.[2] According to the package insert of AQUPLA® for Intravenous Injection (Nichi-Iko Pharmaceutical Co., Ltd.), after nedaplatin enters the cell, the bond between the alcoholic oxygen of the glycolate ligand and platinum, the other glycolate ligand changes to various ionic species and binds to DNA. It is believed to exhibit antitumor activity by binding to DNA through the same pathway as cisplatin, resulting in the inhibition of DNA replication. Reported side effects include nausea, vomiting, anorexia, alopecia, and nephrotoxicity. There are reports suggesting that nedaplatin in combination with chemoradiation therapy for cervical cancer does not differ in efficacy from cisplatin and may show reduced nephrotoxicity compared with cisplatin.[3,4] Therefore, nedaplatin is listed as an alternative drug in Japanese guidelines when renal function is impaired.[5]

TABLE 1 Laboratory data on admission.

					Reference range
WBC	14,190/μL	(3500–9100)	PTH-intact	189 pg/mL	(10–65)
Hb	11.3 g/dL	(11–16)	25(OH)D	<4.0 ng/mL	
Plt	28.8×10^4 μL	($13.0–37.0\times10^4$)			
TP	6.6 g/dL	(6.7–8.3)	Blood pH	7.412	(7.350–7.450)
Alb	3.3 g/dL	(3.7–5.3)	PvCO2	40.2	(35.0–45.0)
AST	34 mg/dL	(7–38)	PvHCO3	25.0	(20.0–26.0)
ALT	16 IU/L	(4–43)			
LDH	569 IU/L	(107–220)	Urinalysis		
ALP	107 IU/L	(38–113)	Urine pH	7.0	
γ-GTP	35 IU/L	(–73)	Glu	Negative	(Negative)
BUN	13.7 mg/dL	(8.0–20.0)	Protein	(+ –)	(Negative)
Cr	1.56 mg/dL	(0.30–1.20)	Blood	Negative	(Negative)
eGFR	25.4 mL/min/1.73 m^2	(90–)	Acetone	Negative	(Negative)
Na	142 mmol/L	(135–147)	Specific gravity	1.010	
K	3.1 mmol/L	(3.0–5.0)	Cr	35.7 mg/dL	
Cl	104 mmol/L	(98–108)	Ca	4.45 mg/dL	
Ca	4.4 mg/dL	(8.4–10.2)	Mg	17.2 mg/dL	
P	3.9 mg/dL	(2.5–4.5)			
Mg	0.5 mg/dL	(1.8–2.3)			
Glu	137 mg/dL	(70–110)			
HbA1c	6.3%	(4.6–6.2)			

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Ca, calcium; Cl, chlorine; Cr, creatinine; eGFR, estimated glomerular filtration rate; Glu, glucose; Hb, hemoglobin; HbA1c, hemoglobin A1c; K, potassium; LDH, lactate dehydrogenase; Mg, magnesium; Na, sodium; P, phosphorus; Plt, platelet; PTH, parathyroid hormone; TP, total protein; WBC, white blood cell; γ-GTP, γ-glutamyl transpeptidase.

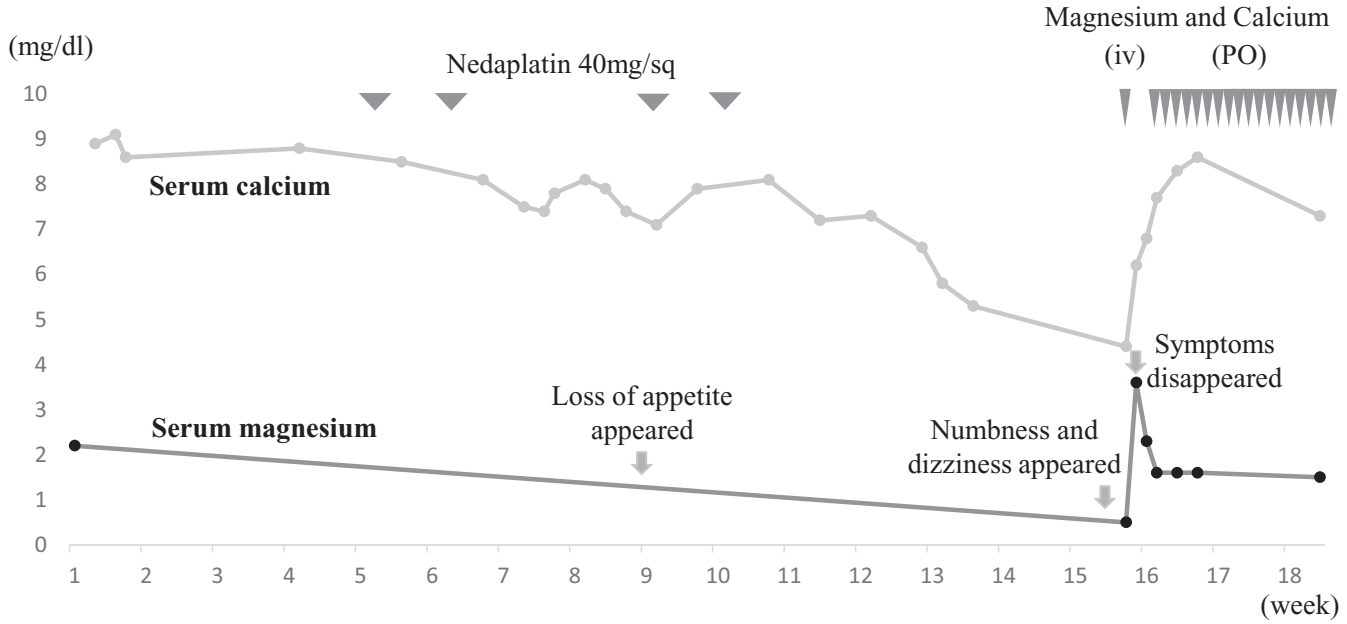

FIGURE 1 Clinical course of this case, hypocalcemis, hypomagesemia, and replenishment.

A search of the literature for cases of hypomagnesemia associated with nedaplatin did not reveal any similar case reports in the past. Cisplatin accumulates in renal proximal tubular cells through basolateral uptake via organic cation transporter (OCT)2, which is one of the major determinants of cisplatin-induced proximal tubular injury. On the contrary, magnesium is reabsorbed mainly at the loop of Henle and distal convoluted tubules. The exact mechanism by which cisplatin causes hypomagnesemia is not clear, but it is thought to cause increased magnesium excretion by direct damage to the ascending limb of the loop of Henle and distal convoluted tubule.[1] Nedaplatin is considered less nephrotoxic than cisplatin since it does not interact with OCT2.[6] Therefore, nedaplatin may induce urinary magnesium wasting by acting on the distal nephron, as cisplatin does, irrespective of its effect on the proximal tubules. This hypothesis is supported by the fact that carboplatin, which does not interact with OCT2, does induce hypomagnesemia in 10% of those who receive this drug.

Hypomagnesemia, an adverse event associated with platinum drugs, is also treated by magnesium supplementation as in general therapy,[7] either by intravenous magnesium sulfate or by oral magnesium oxide. Mild cases can be treated orally, but severe cases require intravenous administration.

Our case is a rare case of decreased serum magnesium level because of renal magnesium excretion of 481.8 mg/gCr after initiation of chemotherapy with nedaplatin. The limitation is that serum magnesium levels were not measured during nedaplatin administration, and the duration of hypomagnesemia is unknown at this time. In this case, 12 months after the completion of nedaplatin administration, serum magnesium levels were stable at 1.7–2.3 mg/dL with the same dose of magnesium oxide as at discharge, but drug-induced hypomagnesemia because of cisplatin was reported to persist for up to 6 years after administration.[7,8] Hypomagnesemia can cause long-term reduction in activity of daily life and quality of life because of symptoms such as decreased appetite and fatigue, with associated loss of therapeutic opportunities. In addition, sudden death because of lethal arrhythmias can affect short-term prognosis. Considering that carboplatin, a second-generation platinum drug, caused hypomagnesemia in 10% of patients,[9] the same degree of hypomagnesemia is possible and should be carefully monitored by periodic blood tests. As generalists increasingly treat patients with cancer, electrolyte disturbances should be suspected in patients with obscure symptoms and are of particular importance in undergoing or following anticancer therapies.

4 | CONCLUSION

We report a case of hypomagnesemia after nedaplatin administration. Measurement of serum magnesium levels should be considered in patients during or after nedaplatin administration.

AUTHOR CONTRIBUTIONS

JK, TH, KS, KK, and TS drafted the manuscript, and TS revised and edited the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

ETHICS APPROVAL STATEMENT

Ethical approval was not required for this study.

PATIENT CONSENT STATEMENT

Written informed consent was obtained from the patient for the publication of this case report.

CLINICAL TRIAL REGISTRATION

No clinical trials were performed in this study.

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