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CASE REPORT

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Lung squamous cell carcinoma with severe hypomagnesemia due to cisplatin plus gemcitabine in combination with necitumumab therapy: A case report

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Abstract

A 72-year-old man, diagnosed with advanced lung squamous cell carcinoma, was administered of cisplatin plus gemcitabine with necitumumab, a human monoclonal antibody that binds to the epidermal growth factor receptor (EGFR), as a sixth-line treatment. Tumor shrinkage was observed, but asymptomatic grade 4 hypomagnesemia occurred on day 8 of the second cycle. He received magnesium replenishment and hypomagnesemia recovered on day 40, but tumor progression was observed during the period of magnesium correction. Hypomagnesemia is known as a major adverse event of treatment with anti-EGFR antibodies, but there have been no case reports of severe hypomagnesemia or its clinical course.

KEYWORDS

cisplatin, gemcitabine, hypomagnesemia, necitumumab, squamous cell lung cancer

INTRODUCTION

Personalized medicine is being gradually incorporated into clinical practice for the treatment of non-small cell lung cancer (NSCLC). The epidermal growth factor receptor (EGFR) pathway has been explored as a druggable target with monoclonal antibodies, including cetuximab and necitumumab. Necitumumab is a humanized immunoglobulinG1 (IgG1) antihuman EGFR monoclonal antibody. In the phase III SQUIRE trial, necitumumab used as first-line therapy in combination with cisplatin and gemcitabine was associated with an improvement in overall survival and progression-free survival in patients with squamous cell NSCLC.[1] Necitumumab is associated with adverse events, including infusion reactions, hypomagnesemia, diarrhea, and dermatological toxicities. The clinical utility of necitumumab may be limited due to the high cost of the drug as well as the additional toxicity when combined with cisplatin-based combination chemotherapy.

Hypomagnesemia is defined as a condition in which the serum magnesium (Mg) concentration is <1.8 mg/dl. It causes severe convulsions and arrhythmias in some cases.[2] Treatment of drug-induced hypomagnesemia by chemotherapy is limited to symptomatic treatment by replacement, but the rate of grade 4 hypomagnesemia was reported to be as low as 2.4%.[1] We present here an unusual case of severe hypomagnesemia and describe its successful treatment and clinical course.

Case report

The patient was a 72-year-old man with a history of Hashimoto's disease, old myocardial infarction, and disseminated nontuberculous mycobacteriosis. He was taking aspirin, tiladine, losartan, and atorvastatin. He had no drinking habit, but had a 26 pack-year history of smoking. The patient had been introduced to our hospital 3 years previously, and was diagnosed with squamous cell carcinoma of the lung with multiple bone metastases to the spine and a high programmed cell death 1- ligand 1 expression level in tumor tissues. He was treated with pembrolizumab

monotherapy, carboplatin plus nab-paclitaxel, docetaxel plus ramucirumab, tegafur/gimeracil/oteracil (S-1), and nivolumab therapy. Although he had achieved long-term survival (>3 years), tumor progression was observed soon after the start of treatment with nivolumab. Since his performance status was 1, with a good general condition at the end of the nivolumab therapy as a fifth-line therapy, we decided to perform cisplatin (CDDP) plus gemcitabine (GEM) in combination with necitumumab (every 3 weeks on days 1 and 8) therapy. Significant shrinkage of the tumor relative to baseline partial response was observed after the administration of one course (Figure 1). The adverse events he experienced were as follows: grade 1 skin eruption, grade 2 anemia, and grade 3 neutropenia. The second course was initiated 1 week later than planned due to prolonged myelosuppression. When he was examined prior to the administration of chemotherapy a week after the second cycle of chemotherapy, there were no subjective symptoms or significant changes in the electrocardiogram, but but a blood test revealed a serum Mg level of 0.5 mg/dl (grade 4 hypomagnesemia), which required urgent hospitalization. Table 1 shows the findings of the blood analysis on admission. Hypokalemia and hypocalcemia were also present. The Mg level was replenished intravenously according to the proper use guide of necitumumab. As for diarrhea, he reported experiencing grade 1 diarrhea a few days before admission. Even though diarrhea did not recur during hospitalization, hypomagnesemia recurred when Mg supplementation was stopped. Based on this clinical course, we judged the diarrhea to be an adverse event of CDDP plus GEM in combination with necitumumab therapy. The patient was hospitalized for the correction of his Mg level for 11 days. With only Mg replenishment, both hypocalcemia and hypokalemia were recovered on days 4 and 9 after admission. He then attended frequent outpatient visits, and Mg correction was continued according to the serum Mg level. Recovery was confirmed on day 40 from the onset of hypomagnesemia and admission, and Mg supplementation was no longer necessary (Figure 2). The chemotherapy regimen was terminated because computed tomography images on day 57 showed tumor regrowth with disease progression.

DISCUSSION

Chemotherapy for lung cancer has made remarkable progress due to recent active clinical trials.[3] In squamous cell lung cancer, necitumumab in combination with CDDP and GEM is now a new standard treatment option for squamous NSCLC, although other standard combination chemotherapy with immune checkpoint inhibitors has recently emerged.[4,5]

Hypomagnesemia often causes other electrolyte abnormalities, include somnolence, tremor, muscle weakness, tetany, convulsions, and arrhythmias, which can be severe in some cases.[2] Clinical symptoms are often caused by associated electrolyte abnormalities, such as hypocalcemia and hypokalemia. Hypomagnesemia is known to be frequently accompanied by other electrolyte abnormalities. In particular, hypokalemia is known to be an essential factor in the management of hypomagnesemia since it does not improve unless hypomagnesemia is corrected.[6] Replacement therapy cannot be effective for accompanying electrolyte imbalance such as hypokalemia or hypocalcemia in this case without Mg correction for any of the electrolytes. As both CDDP and necitumumab can cause hypomagnesemia, careful monitoring of Mg during this combination regimen would be required. Orally ingested Mg is absorbed in the small intestine, with an absorption rate of 30–50%,[7] excretion mainly occurs via the kidneys, and approximately 70–80% of serum Mg is filtered from the glomeruli. Although there is little evidence to support the efficacy of Mg replacement therapy, oral replacement is generally considered to be ineffective due to the low rate of absorption in the intestinal tract.

Hypomagnesemia induced by CDDP plus GEM in combination with necitumumab therapy was frequently reported

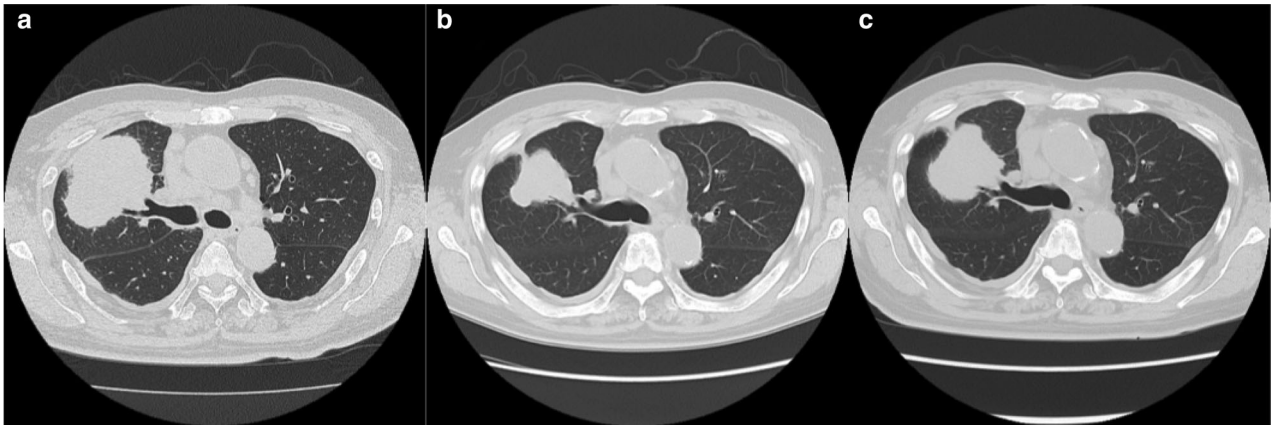

FIGURE 1 Chest computed tomographic scans before intravenous administration of CDDP plus GEM in combination with necitumumab (a). Three weeks after therapy, tumor shrinkage was observed (b). On day 57 from the first admission of CDDP plus GEM in combination with necitumumab therapy, the tumor progressed (c)

TABLE 1 Laboratory data on admission

Hematology		Biochemistry		Serological examination	
WBC	5100/μl	TP	6.7 g/dl	CRP	3.73 mg/dl
Neut	60.80%	Alb	3.2 g/dl		
Eosino	2.20%	T-bil	0.5 mg/dl		
Baso	0.00%	AST	32 IU/L		
Lymph	33.10%	ALT	40 IU/L		
Mono	3.90%	LDH	244 IU/L		
RBC	340 × 10^4/μl	ALP	202 IU/L		
Hb	9.3 g/dl	γ-GTP	66 IU/L		
Hct	29.50%	BUN	15 mg/dl		
MCV	86.8 fL	Cr	0.88 mg/dl		
MCH	27.4 pg	Na	141 mmol/L		
MCHC	31.50%	K	3.0 mmol/L		
Plt	46.4 × 10^4 μl	Cl	99 mmol/L		
		Ca	8.5 mg/dl		
		P	3.3 mg/dl		
		Mg	0.5 mg/dl		
		CK	109 IU/L		
		Glu	141 mg/dl		

Abbreviations: Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Baso, basophil; BUN, blood urea nitrogen; Ca, calcium; CK, creatine kinase; Cl, chlorine; Cr, creatinine; CRP, c-reactive protein; Eosino, eosinophil; Glu, glucose; Hb, hemoglobin; Hct, hematocrit; K, potassium; LDH, lactate dehydrogenase; Lymph, lymphocyte; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin consentration; MCV, mean corpuscular volume; Mg, magnesium; Mono, monocyte; Na, sodium; Neut, neutrophil; P, phosphorus; Plt, platelet; RBC, red blood cell; T-Bil, total; TP, total protein; WBC, white blood cell; γ-GTP, γ-glutamyl transpeptidase.

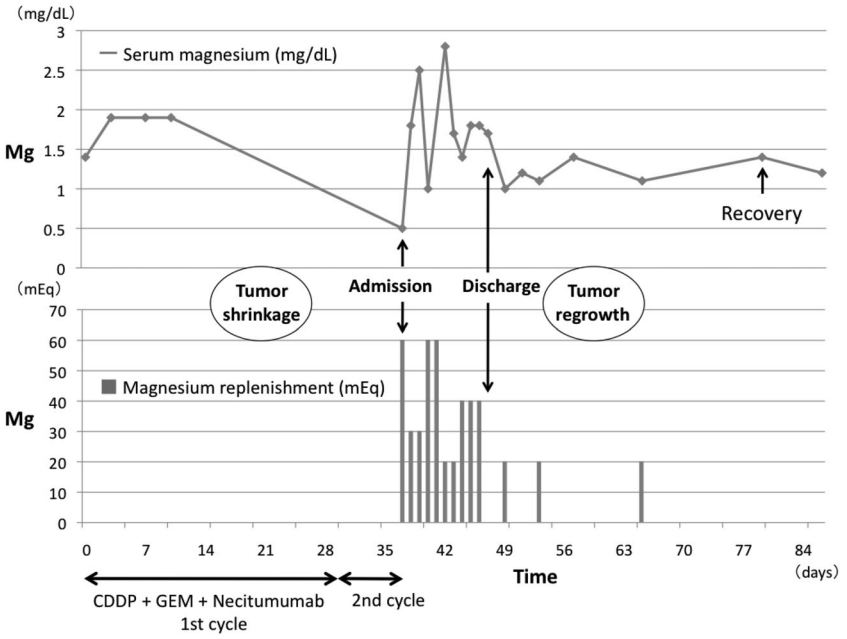

FIGURE 2 Clinical course of this case, hypomagnesemia and replenishment. The upper graph shows the careful monitoring of serum magnesium levels observed in a lung cancer patient receiving chemotherapy treatments with CDDP plus GEM in combination with necitumumab. The lower graph shows a time course of doses of intravenously administered magnesium levels (mEq) during the same treatment

(31.2% in all grades) in the SQUIRE study[1] and in 38.9% of the patients in the JFCM study.[8] We searched the relevant literature for cases associated with the chemotherapeutic agents used in this case, but the search yielded no reports on GEM-related hypomagnesemia. In contrast, CDDP is known to cause hypomagnesemia. Some studies reported that CDDP monotherapy resulted in hypomagnesemia in cervical cancer patients.[9] Hypomagnesemia is also known as an adverse event in uses of other

anti-EGFR antibodies, cetuximab,[10] and panitumumab.[11] Importantly, hypomagnesemia has been reported to correlate with the therapeutic effect in colorectal cancer patients treated with cetuximab or panitumumab,[12] emphasizing the importance of the management of hypomagnesemia.

Although CDDP plus GEM in combination with necitumumab therapy showed a prominent antitumor effect, with a response rate of 51.1% in the JFCM study,[8] we recognized that there are limited opportunities to use this combination chemotherapy because some patients may be unfit for treatment with immune checkpoint inhibitors. Our case report could be important, as the tumor response may be expected even in late-line treatments, with the adequate management of severe hypomagnesemia by intravenous Mg replenishment.

This case was asymptomatic despite severe hypomagnesemia, thus it could be necessary to consider screening by blood sampling and prophylactic administration of Mg before use of necitumumab. Regarding the timing of blood sampling, the median onset of hypomagnesemia is reported to be around 1–2 months in clinical trials, but others reported that the onset occurs from 1 week after administration to over a year in practice. Therefore, we presume that evaluation of Mg might be required for each patient visit. On the other hand, there is no evidence or consensus on the effectiveness of prophylactic administration of Mg. However, it has been reported that supplementation of Mg at the low grade stage may prevent the aggravation of hypomagnesemia, suggesting the significance of prophylactic administration.[13]

This is the first case in which the course of correction from the onset to recovery of grade 4 hypomagnesemia in the treatment for squamous NSCLC and the importance of the management of hypomagnesemia via intravenous supplementation was reaffirmed.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest in association with the present study.

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