Tetany due to Hypomagnesemia Induced by Cisplatin and Doxorubicin Treatment for Synovial Sarcoma

Tomoatsu MUNE, Keigo YASUDA, Mitsukazu ISHII*, Takanobu MATSUNAGA* and Kiyoshi MIURA

Hypocalcemic crisis developed in a patient with monophasic synovial sarcoma after amputation of the right leg, followed by long-term treatment with cisplatin and doxorubicin. Laboratory data revealed severe hypomagnesemia and hypocalcemia. High normal intact parathyroid hormone (PTH), elevated mid-region PTH and undetectable osteocalcin levels had already been found before the appearance of obvious symptoms concomitantly associated with moderate hypomagnesemia and hypocalcemia. Further, both PTH levels measured by two different methods gradually decreased until the initiation of magnesium supplementation. The magnesium supplement immediately relieved the tetany, and induced striking increases in both intact and mid-region PTH levels transiently and continuous elevations of osteocalcin levels. These results suggest that magnesium depletion has dual effects on PTH secretion, from stimulation to inhibition, as hypomagnesemia progresses. Both relative hypoparathyroidism and refractoriness of bone to PTH were thought to be responsible for hypocalcemia due to hypomagnesemia.

Key words: hypocalcemia, parathyroid hormone, functional hypoparathyroidism, parathyroid hormone-related protein

Introduction

Cisplatin (cis-diamminedichloroplatinum)-induced hypomagnesemia and hypocalcemia have been reported in several patients (1-3), and the renal magnesium wasting due to its nephrotoxic effect is suggested to be pathogenic (4). Doxorubicin hydrochloride is also thought to possess a similar lowering effect on serum magnesium (3, 5, 6), although its sole effect has not been fully evaluated. Regarding the mechanisms involved in the development of hypocalcemia in magnesium deficiency, several conflicting data have been reported in various conditions (7-19). Here we report a case of hypomagnesemia and hypocalcemia due to cisplatin and doxorubicin treatment for monophasic synovial sarcoma, and evaluate the detailed changes in parathyroid function and bone turnover using sensitive assays of parathyroid hormone (PTH) and bone Gla protein [(BGP) osteocalcin].

Case Report

A 15-year-old boy was admitted to our hospital in 1990 for the evaluation of a tumor, measuring 11x10x5 cm, in his right leg and was diagnosed to have a monophasic fibrous synovial sarcoma. He was preoperatively treated with an intraarterial infusion of 20 mg of cisplatin three times a week and 100 mg of doxorubicin hydrochloride monthly for 4 months. Total doses of cisplatin and doxorubicin were 1,110 mg and 380 mg, respectively. From the day after the operation (above-knee amputation of the right leg) on Dec. 17, he manifested symptoms of tetany and paresthesia on his fingers and lips. There were positive Trousseau’s sign as well as Chvostek’s sign and hyperactive deep tendon reflexes. Investigation on Dec. 18 revealed low serum calcium corrected with serum albumin (20) (cCa) of 5.6 mg/dl (normal, 8.3-10.3), high serum inorganic phosphate (Pi) of 5.8 mg/dl (normal, 2.0-4.4), low serum magnesium (Mg) of 0.4 mEq/L (normal, 1.3-1.9) and low serum potassium (K) of 3.0 mEq/L (normal, 3.4-4.8). Acid-base balance showed metabolic alkalosis. Complete blood count showed pancytopenia due to chemotherapy which had continued from October. Creatinine clearance was 79.3 ml/min. The patient was given a total of 1,700 mg of calcium gluconate per day until Dec. 22. As the intravenous administration of calcium gluconate did not relieve the symptoms effectively, an infusion of 2,000 mg of magnesium sulfate per day was started in the evening of Dec. 22. Laboratory data just before the magnesium supplementation showed cCa of 6.2 mg/
dL, Pi of 6.6 mg/dL, plasma ionized calcium of 0.760 mM (normal, 1.067–1.283), Mg of 0.4 mEq/L and creatinine phosphokinase of 5,042 IU/L (normal, 40–200). Serum PTH levels were 0.6 ng/ml with c-terminal assay (normal, <0.5), 540 pg/ml with mid-portion assay (mid-PTH; normal, 160–520) which detects PTH (44–68) (21) and 35 pg/ml with 2-site immunoradiometric intact PTH assay (int-PTH; normal, 15–50) which detects only intact molecules of PTH (1–84) (22), and serum PTH-related protein-like immunoreactivity was not detected (normal, not detected) (23). Serum 25(OH)-vitamin D and 1,25(OH)₂-vitamin D were 18 ng/ml (normal, 10–30) and 32 pg/ml (normal, 20–76). Serum calcitonin and BGP (24) were 54 pg/ml (normal, <100) and 13 ng/ml (normal, 2.5–13), respectively. The symptoms improved immediately after magnesium supplementation, and Mg began to increase, following normalization of cCa as shown in Fig. 1, which outlines the changes in serum levels of cCa, Mg, Pi, mid-PTH, int-PTH, BGP and calcitonin during the clinical course. Before the development of apparent hypocalcemic symptoms following the operation, cCa had been decreased. The preoperative Mg, later measured from a frozen sample stored on Dec. 11, had been low (0.8 mEq/L). The int-PTH and mid-PTH levels in the same sample had been high normal and 2-fold elevated, respectively, and serum BGP had been undetectable. Postoperatively,
both int-PTH and mid-PTH decreased in spite of progressive hypomagnesemia and hypocalcemia, and increased strikingly soon after magnesium supplementation. This increase in PTH after magnesium supplementation was transient. Although serum cCa and Mg were almost restored to normal levels during the course of the magnesium supplementation, int-PTH and mid-PTH were restored to values within the normal range 5 days and 14 days later, respectively. BGP, which was normal under hypomagnesemia, increased after magnesium supplementation. The patient is now well.

Discussion

Long-term treatment with cisplatin and doxorubicin for malignant synovial sarcoma seemed to be very effective in the prevention of metastasis. Both cisplatin (1–4) and doxorubicin (3, 5, 6) have already been shown to cause hypomagnesemia due to magnesium leaking from the kidney.

Regarding the cause of hypocalcemia secondary to hypomagnesemia, several possible mechanisms have been suggested (7): diminished end organ responsiveness to PTH (8–10), decreased release of calcium from bone (19), or relative hypoparathyroidism (5, 6, 11–18). In these reports, the measurement of PTH in hypomagnesemia caused by combined chemotherapy containing doxorubicin revealed mostly low values (5, 6). In the present patient, the values of mid-region PTH (44–68) (21) and intact PTH, a recently developed sensitive assay of intact molecules of PTH (1–84) (22), did not show low levels. The mid-region and intact PTH were elevated and high normal, respectively, under asymptomatic mild hypomagnesemia on Dec. 11, and tended to decrease, followed by progressive hypomagnesemia until the initiation of magnesium supplementation. Previous reports (14–16, 25) revealed that serum PTH levels during hypomagnesemia due to chronic alcoholism or malabsorption were not always low. Allgrove et al (16) showed that amino-terminal PTH values were elevated under mild or moderate hypomagnesemia and became lower or undetectable as magnesium depletion became more profound. Our present result was consistent with this finding. The level of serum magnesium showing a change from a suppressive effect to a stimulative effect on intact PTH secretion was estimated to lie at about 0.4 mEq/L (0.2 mmol/L) or more in our patient, which was almost equal to the level described in the previous in vivo report (16) or in vitro report (26). These findings suggest that previously reported variances in serum immunoreactive PTH levels are due to differences in the degree (and duration to some extent) of hypomagnesemia and hypocalcemia. Magnesium supplementation induced a striking increase in mid-region PTH and intact PTH in the present patient as in the previous reports (11–17) in which serum values of PTH were measured with traditional assays. This increase indicates that the stimulating drive for PTH secretion in response to severe hypocalcemia was suppressed by magnesium depletion.

Interestingly, there were some dissociations between serum mid-region and intact PTH levels. Mid-region and intact PTH were high and within the normal range, respectively, in the symptomatic condition, and the mid-region PTH took more time to normalize compared with the intact PTH after magnesium supplementation. Regarding the dissociation during the latter period, the difference in restoration time from the transient increase between mid-region and intact PTH might be due to a difference in degradation time, because it has been shown that the half-life (rate of disappearance from the circulation) of intact PTH was 5–10 min in normal humans (27) and 21 min in patients after parathyroid adenomectomy (28), while that of mid-region PTH was 1–2 hours (27). However, the dissociation in the pretreatment period cannot be explained solely by the difference in degradation time. A recent report on a hypomagnesemic patient whose condition was due to chronic alcoholism (29) also revealed a similar dissociation between mid-region and intact PTH, and assumed that magnesium depletion enhanced the metabolism of PTH and reduced the secretion of bioactive intact PTH by increasing the sensitivity of parathyroid cells to calcium via the mimetic/antagonistic action of magnesium against calcium (26, 29). Magnesium depletion might have influenced the metabolic process of PTH in our patient as well. Further evaluation will be necessary in various conditions.

Serum bone Gla protein ([BGP] osteocalcin) has been shown to reflect bone remodeling (30). The preoperative BGP level under asymptomatic mild hypomagnesemia was undetectable despite a high normal intact PTH level, but was found to be high normal under symptomatic severe hypomagnesemia. It is supposed that the amputation activated local bone remodeling, as reported in patients with fractures (31). The further increase in serum BGP levels after the magnesium supplementation and the preoperative low BGP level implied that magnesium depletion attenuated the bone turnover. These findings suggest that a refractoriness of target organs to PTH contributes to the hypocalcemia due to hypomagnesemia as an additional mechanism (7–10, 14, 29).

In the present patient, mild hypomagnesemia and hypocalcemia were already present without obvious symptoms prior to amputation, and apparent symptoms of hypocalcemia appeared only after amputation surgery. The stress of amputation, alterations in the electrolyte balance by intravenous fluids during the operation, and/or progressive metabolic alkalosis were considered to trigger the apparent symptoms of hypomagnesemia and hypocalcemia. The restoration of serum calcium after magnesium supplementation seemed to occur earlier than that of magnesium in our young patient, in contrast to the previous reports which described the later normalization of serum calcium (9–11, 14, 16, 17). Our patient’s amputation surgery might have accelerated bone remodeling, which was suggested by the postoperative increase of BGP, resulting in sufficient mobilization of calcium from bone. The postoperative immobilization status (32) of the patient might also have contributed to the earlier restoration of serum calcium.

In summary, the present report describes the development and restoration of functional hypoparathyroidism caused by hypomagnesemia due to cisplatin and doxorubicin. Our findings suggest that magnesium depletion affects PTH secretion in
a biphasic fashion: from stimulation to inhibition as hypomagnesemia progresses. It is also suggested that magnesium depletion causes the refractoriness of bone to PTH, which is partly responsible for the hypocalcemia.

References