

Paraneoplastic Hypocalcemia Developed in Gastric Cancer Accompanied by Osteoblastic Metastasis

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Abstract

Paraneoplastic syndromes are generally defined as clinical disorders associated with malignant diseases, and hypocalcemia associated with cancer is a rare condition. A woman in her 60s was referred to our hospital for the further examination of massive ascites due to carcinoma of unknown primary origin. She complained of numbness around her lips, and marked hypocalcemia of 5.0 mg/dL was noted. After two courses of chemotherapy, computed tomography showed a decrease in the ascites, and her serum calcium level increased. Although hypocalcemia is a very rare condition in patients with gastric cancer, serum calcium values should be evaluated when neurological symptoms are observed.

Key words: hypocalcemia, gastric cancer, bone metastasis

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Introduction

Paraneoplastic syndromes are generally defined as clinical disorders associated with malignant diseases and are not directly related to the physical effects of the primary or metastatic tumors (1, 2). Among the symptoms or laboratory disorders that have been reported relating to this broad spectrum of conditions, hypercalcemia is one of the most common paraneoplastic syndromes, occurring in up to 30% of cancer patients (3). In contrast, hypocalcemia is a rare condition that is sometimes observed in the advanced stage of prostatic cancer due to abnormal calcium influx in developing bone metastasis. To date, however, cases of severe hypocalcemia associated with gastric cancer have not been reported. This report describes a very rare case of persistent hypocalcemia that developed in a patient with advanced gastric cancer and bone metastasis.

Case Report

A woman in her 60s visited a hospital because of increasing abdominal pain. She underwent esophagogastroduodenoscopy (EGD) and abdominal CT in which findings were unremarkable. Four months later, she developed massive ascites and an abdominal puncture was performed. A cytological examination of the ascites showed no malignancy, and positron emission tomography (PET)-CT demonstrated no abnormal accumulation of ¹⁸F-fluorodeoxyglucose. Diagnostic laparoscopy was carried out as a further examination, and multiple disseminated nodules were revealed in the abdominal cavity. Histopathologically, the nodules were diagnosed as adenocarcinoma. Eventually, the patient was referred to our hospital for the further examination of the primary lesion and therapy. When she visited our hospital, she complained of numbness around her lips. Her medical history consisted of a post-thyroidectomy state due to thyroid cancer in her 50s, myoma of the uterus, and ovarian cyst.

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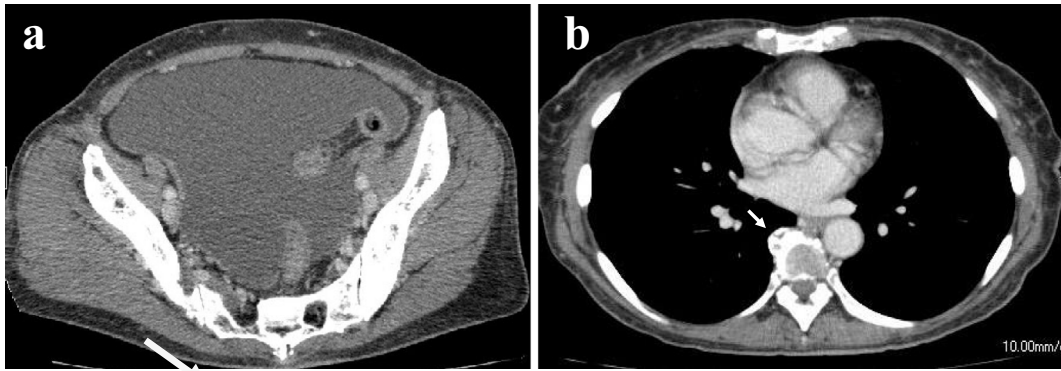


Figure 1. Contrast-enhanced CT showed massive ascites (a) and an abnormal bone formation adjacent to the thoracic spine (b, arrow).

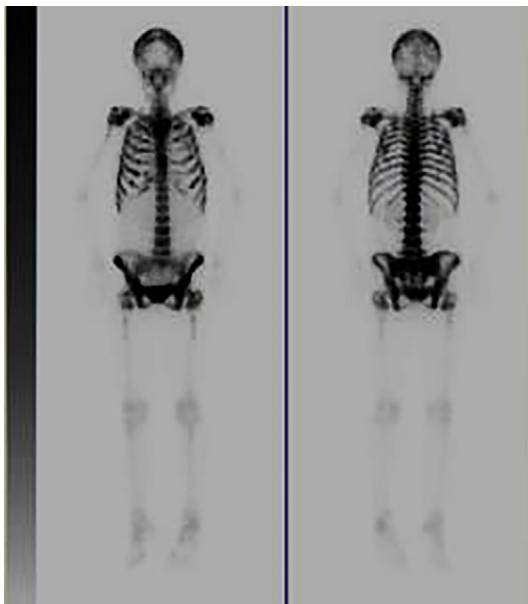


Figure 2. Bone scintigraphy demonstrated the increased uptake of 99m -technetium diffusely throughout the skeleton, showing a 'beautiful bone scan'.

She was not a smoker or alcohol drinker. She had no fever or abdominal pain. In a general examination, her blood pressure and heart rate were normal. No lymphadenopathy was noted. Her abdomen was slightly distended due to ascites, but there was no tenderness. Paresthesia was noted in the extremities and lips. The laboratory data (complete blood count, chemistry, urinalysis, tumor markers, and coagulation) showed mild anemia (11.8 g/dL of hemoglobin), and the tumor markers carcinoembryonic antigen (CEA) and CA 19-9 were elevated to 8.3 ng/mL and 4,510 U/mL, respectively. The lactate dehydrogenase (LDH) and alkaline phosphatase (ALP) were also elevated to 339 IU/L and 9,668 IU/L, respectively. Marked hypocalcemia of 5.0 mg/dL was also noted, and the corrected calcium value was 5.9 mg/dL by the correction formula applying 3.1 g/dL of serum albumin. She had been taking tablets of Bifidobacterium, esomeprazole, furosemide, and spironolactone, none which were

considered to have caused her hypocalcemia.

Given the above findings, the patient was admitted immediately to our hospital due to severe hypocalcemia. Contrast-enhanced CT demonstrated massive ascites (Fig. 1a), but there were no lung or liver tumors. It also revealed an abnormal bone formation adjacent to the thoracic spine (Fig. 1b arrow). Bone scintigraphy using technetium 99m (99m Tc) showed an increased uptake of the radio-labeled agent diffusely throughout the skeleton: cervical-thoracic-lumbar spine, pelvis, femurs, skull and shoulders. There was no increased uptake in the kidneys (Fig. 2). Additional endocrinological studies were performed, and the following results were recorded: inorganic phosphorus (IP) 6.0 mg/dL (normal range: 2.4-4.6 mg/dL), magnesium 2.7 mg/dL (1.6-2.3 mg/dL), intact parathyroid hormone (PTH) 78 pg/mL (10-65 pg/mL), bone-specific alkaline phosphatase 848.0 μ g/L (3.8-22.6 μ g/L), carboxy-terminal telopeptide of type I collagen (ICTP) 42.5 ng/mL (<4.5 ng/mL), 1,25-(OH) $_2$ vitamin D 148 pg/mL (20-60 pg/mL), urine N-terminal telopeptide 731 nmolBCE/nmolCr (14.3-89.0 nmolBCE/nmolCr), urine calcium 12.8 mg/gCr, and maximum tubular reabsorption of phosphate per glomerular filtration rate (GFR) (TmP/GFR) 6.0 mg/dL. Based on these findings, she was diagnosed with cancerous peritonitis and diffuse bone metastasis derived from cancer of unknown primary (CUP). The prolonged hypocalcemia was considered a paraneoplastic syndrome, presumably due to the exhaustion of calcium by diffuse osteoblastic bone metastasis.

Treatment with intravenous administration of paclitaxel and carboplatin was started in accordance with the therapeutic guidelines for CUP. After two courses of chemotherapy, a CT scan showed a gradual decrease in the ascites as well as a decrease in the CEA. The serum calcium level was also increased (Fig. 3). During chemotherapy, she complained of abdominal discomfort, and EGD was performed. A slightly depressed pale lesion with fold convergence was found in the upper body (Fig. 4a-c). A histopathological examination of a biopsy specimen from the lesion revealed a poorly differentiated tubular adenocarcinoma (Fig. 4d), which was consistent with the histopathology of the disseminated nod-

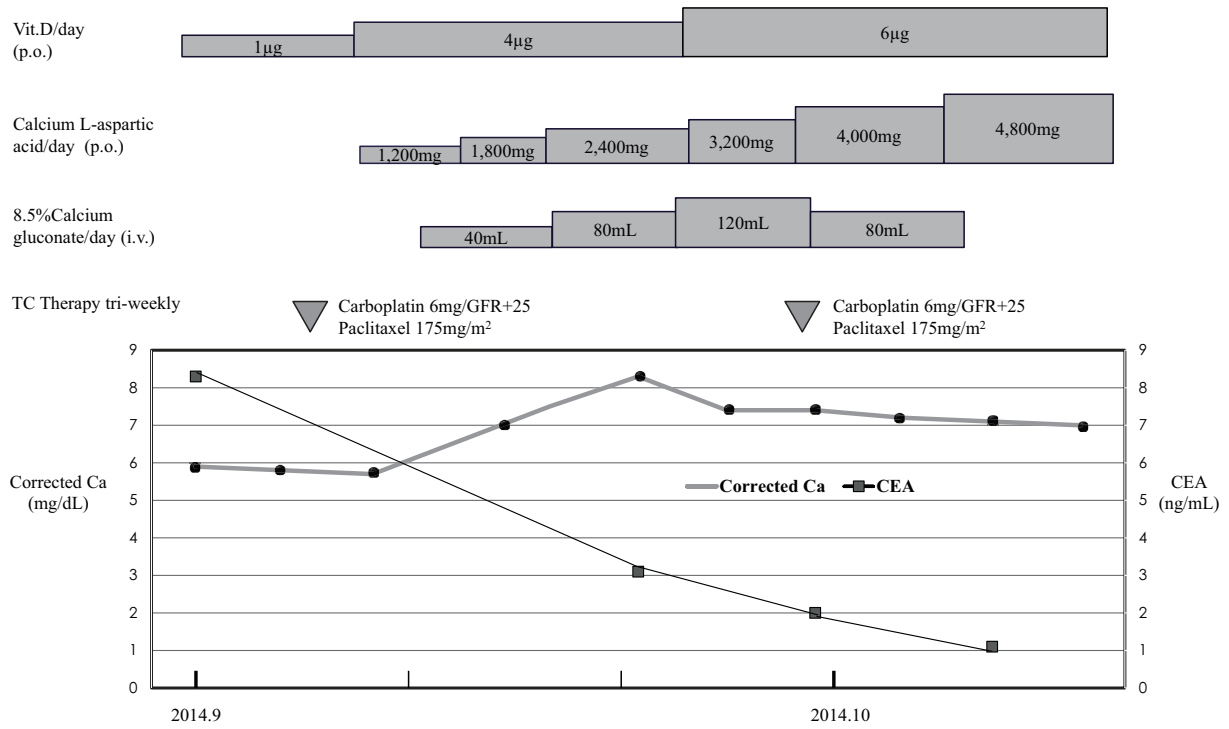


Figure 3. Clinical course of the case. The serum calcium level was increased and the CEA level decreased due to chemotherapy.

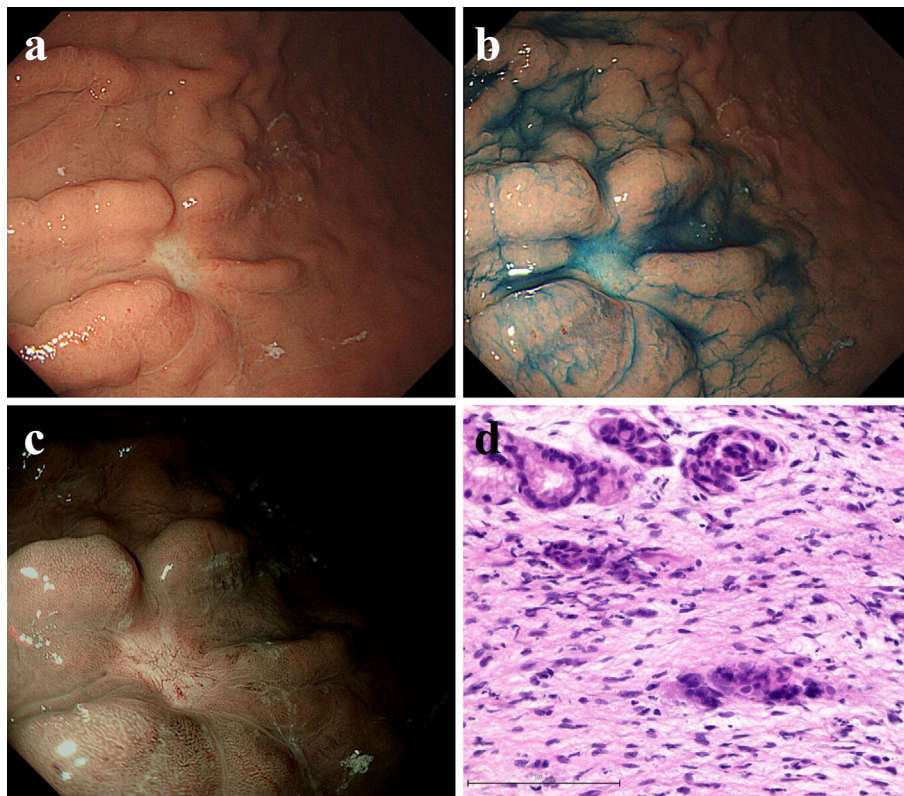


Figure 4. EGD demonstrated a slightly depressed pale lesion with fold convergence (a). In images with indigocarmine spray (b), encroachment and swelling of the converging folds were enhanced, and narrow band imaging with magnification (c) showed irregular microvessels on the surface of the lesion. Histopathology of a biopsy specimen showed a poorly differentiated tubular adenocarcinoma (d).

Table. Cases of Osteoblastic Metastases Due to Primary Gastric Cancer.

Age	Sex	Histology	Endoscopic appearance	Serum calcium	Prognosis	Reference
21	M	sig	Erosion	7.8 mg/dL	2 months	16
65	M	diffuse	Linitis plastica	9.1 mg/dL	-	15
45	F	sig	Micro-nodular	-	-	14
71	M	sig	Small erosion	-	-	13
41	F	por	Slight depression	-	8.5 months	12
64	M	por/sig	Slight depression	-	-	12
40	F	sig	Folds thickening	7.9 mg/dL	4 months	11
60	M	sig	-	normal	-	10
64	M	por/sig	Borrmann-III	-	3 months	9
57	M	mod	Tiny erosion	8.6 mg/dL	3 months	8
36	M	-	Ulceration	10 mg/dL	1 month	7
50	M	-	Linitis plastica	9.2mg/cent	2 weeks	6
69	F	por	Small depression	5.0 mEq/L	Alive	Our case

diffuse: diffuse pattern adenocarcinoma, mod: moderately differentiated adenocarcinoma, por: poorly differentiated adenocarcinoma, sig: signet ring cell carcinoma, -: data were not shown

ules. Ultimately, this patient was diagnosed with primary gastric cancer with abdominal dissemination and bone metastases. The chemotherapy regimen was changed to S-1 plus docetaxel in accordance with the therapeutic strategy for gastric cancer. Oral calcium intake was discontinued after six months of administration, but the serum level of calcium remained stable. She has been receiving chemotherapy as an outpatient and is in stable condition with normal serum calcium levels.

Discussion

Bone metastases often occur during the clinical course of prostate cancer, breast cancer, and lung cancer. However, the incidence of bone metastases in gastric cancer is relatively low, ranging from 1.0% to 20.0% (4), and osteoblastic metastases are extremely rare. Osteoblastic metastases are associated with higher serum levels of alkaline phosphatase and hypocalcemia (5). Hypocalcemia occurs more frequently in patients with osteoblastic metastases (28%) than in those with osteolytic metastases (11%) (5). Osteoblastic metastases from gastric cancer have been reported only in 12 cases from 1,977 until now (Table) (6-16). Among these reported cases, only 2 showed hypocalcemia, and their serum calcium values were 7.8 mg/dL and 7.9 mg/dL, respectively (11, 16), while our case showed severe and intractable hypocalcemia (6.0 mg/dL).

In our case, the patient underwent thyroidectomy previously, which may have caused potential hypoparathyroidism and impaired the regulation of serum calcium. The condition also showed the characteristic diffuse uptake of the radioisotope throughout the skeleton that is called a 'beautiful bone scan' in bone scintigraphy terminology. It is speculated that increasing new bone formation caused the excessive calcium uptake from the blood, regardless of the continuous supply of calcium and vitamin D. Additionally, hungry bone syndrome might have developed as a cause of severe hypocal-

cemia in this case. Although the serum phosphate was slightly increased, it was likely due to the effect of tumor lysis resulting from the extensive bone metastasis.

Among gastric cancer cases accompanied by osteoblastic metastases, 80% (10 out of 11) were poorly differentiated adenocarcinoma or signet-ring cell carcinoma (Table). In bone metastasis of cancer cells, various molecular mechanisms seem to be active and involve, for example, insulin-like growth factor (IGF), transforming growth factor-beta (TGF- β), bone morphogenetic proteins (BMP), and platelet-derived growth factor (PDGF) (17). However, whether or not these molecules cause hypocalcemia is unclear. In our case, no definite key molecule was identified, so it might be possible that other osteoblastic factors are associated with the patient's marked osteoblastic bone metastasis and severe hypocalcemia. The prognosis for gastric cancer with osteoblastic bone metastases is generally poor (18). However, our case has remained alive for more than two years since the initial diagnosis without disease progression, probably owing to aggressive chemotherapy.

In conclusion, we experienced a case of prolonged hypocalcemia that developed in a patient with advanced gastric cancer and bone metastasis. Although hypocalcemia is a very rare condition in patients with gastric cancer, serum calcium should be evaluated when neurological symptoms are observed.

The authors state that they have no Conflict of Interest (COI).

References

1. Kanaji N, Watanabe N, Kita N, et al. Paraneoplastic syndromes associated with lung cancer. *World J Clin Oncol* 5: 197-223, 2014.
2. Spiro SG, Gould MK, Colice GL; American College of Chest Physicians. Initial evaluation of the patient with lung cancer: symptoms, signs, laboratory tests, and paraneoplastic syndromes: ACCP evidenced-based clinical practice guidelines (2nd edition).

- Chest **132** (3 Suppl): 149S-160S, 2007.
3. Farolfi A, Ferrario C, Aquilina M, et al. Paraneoplastic hypocalcemia-induced heart failure in advanced breast cancer: A case report and literature review. *Oncol Lett* **10**: 773-777, 2015.
 4. Yoshikawa K, Kitaoka H. Bone metastasis of gastric cancer. *Jpn J Surg* **13**: 173-176, 1983.
 5. Raskin P, McClain CJ, Medsger TA Jr. Hypocalcemia associated with metastatic bone disease. A retrospective study. *Arch Intern Med* **132**: 539-543, 1973.
 6. Banerjee AK, Banerjee K, Bhattacharya B. Osteosclerotic bony metastases from carcinoma stomach. *J Indian Med Assoc* **68**: 38-39, 1977.
 7. Carstens SA, Resnick D. Diffuse sclerotic skeletal metastases as an initial feature of gastric carcinoma. *Arch Intern Med* **140**: 1666-1668, 1980.
 8. Uchida T, Shikata T, Shimizu SI, et al. Gonadotropin and alkaline phosphatase producing occult gastric carcinoma with widespread metastasis of generalized bone. *Cancer* **48**: 140-150, 1981.
 9. Mohandas KM, Swaroop VS, Krishnamurthy S, et al. Unusual bone metastasis as the initial symptom of gastric cancer—a report of four cases. *Indian J Cancer* **30**: 146-150, 1993.
 10. Narváez JA, Narváez J, Clavaguera MT, Juanola X, Valls C, Fiter J. Bone and skeletal muscle metastases from gastric adenocarcinoma: unusual radiographic, CT and scintigraphic features. *Eur Radiol* **8**: 1366-1369, 1998.
 11. Chung YS, Choi TY, Ha CY, et al. An unusual case of osteoblastic metastasis from gastric carcinoma. *Yonsei Med J* **43**: 377-380, 2002.
 12. Koyama M, Koizumi M. Two cases of diffuse osteoblastic metastases from early type gastric cancer. *Clin Nucl Med* **32**: 545-547, 2007.
 13. Kang SH, Kim JI, Moon HS, et al. Overt bone marrow metastasis from early gastric cancer. *Endoscopy* **40** (Suppl 2): E34-E35, 2008.
 14. Anagnostopoulos G, Sakorafas GH, Kostopoulos P, Margantinis G, Tsiakos S, Pavlakis G. Early (mucosal) gastric cancer with synchronous osteosclerotic bone metastases: a case report. *Eur J Cancer Care* **19**: 554-557, 2010.
 15. Santos VM, Vieira TA, Marinho CS, Loures TP, Brandao BB, Botan RN. Infiltrating gastric adenocarcinoma with disseminated osteoblastic metastases. *An Sist Sanit Navar* **36**: 153-157, 2013.
 16. Ermiş F, Erkan ME, Besir FH, Oktay M, Kutlucan A, Aydın Y. Osteoblastic metastasis from signet ring cell gastric cancer in a young male. *Turk J Gastroenterol* **25** (Suppl 1): 284-286, 2014.
 17. Iguchi H. Recent aspects for disseminated carcinomatosis of the bone marrow associated with gastric cancer: What has been done for the past, and what will be needed in future? *World J Gastroenterol* **21**: 12249-12260, 2015.
 18. Kim HS, Yi SY, Jun HJ, et al. Clinical outcome of gastric cancer patients with bone marrow metastases. *Oncology* **73**: 192-197, 2007.

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