Asymptomatic disseminated carcinomatosis of bone marrow presenting as hyperphosphatasia : report of a case

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Abstract

Metastatic involvement of the musculoskeletal system is one of the most significant clinical issues facing orthopaedic oncologists. The number of patients with metastasis to the skeletal system from a carcinoma is 15 times greater than the number of patients with primary bone tumours of all types. However, progression patterns like disseminated carcinomatosis of bone marrow are comparatively rare. The pathophysiology for disseminated carcinomatosis of bone marrow, with a prognosis reported to be very poor, is still unknown. We describe a patient who had no symptoms with hyperphosphatasia. Bone scintigraphy showed a so-called super bone scan and a needle biopsy from the ileum showed adenocarcinoma cells. Additional endoscopic investigation was performed and signet cell gastric cancer was found. From the bone scan and biopsy, we established the diagnosis of disseminated carcinomatosis of the bone marrow. From the experience of this case, we believe that intensive stomach investigation should be considered in cases with hyperphosphatasia, even when the patient has no symptoms. (Acta gastroenterol. belg., **2008**, 71, **271-274**).

Key words : disseminated carcinomatosis of bone marrow, hyperphosphatasia, gastric cancer.

Introduction

Metastatic involvement of the musculoskeletal system is one of the most significant clinical issues facing orthopaedic oncologists. The number of patients with metastasis to the skeletal system from a carcinoma is 15 times greater than the number of patients with primary bone tumours of all types. However, progression patterns like disseminated carcinomatosis of bone marrow are comparatively rare (1). The pathophysiology for disseminated carcinomatosis of bone marrow, with a prognosis reported to be very poor, is still unknown. We report a rare case of asymptomatic disseminated carcinomatosis of bone marrow presenting as hyperphosphatasia.

Case report

A 65-year-old woman was admitted to our hospital for a second opinion, due to a 2-year history of hyperphosphatasia. She had no back pain or any other symptoms.

In 2004, she was found to have a serum ALP level of 800 IU/l by a family practitioner. At that time, from physical examination and laboratory findings, obstructive hepatobiliary diseases, hyperparathyroidism, and hepatotoxic drugs were ruled out. However, osteosclerotic lesions in the thoracic vertebrae and lumbar vertebrae were recognised, so bone diseases were suspected. The patient was referred to a state hospital, where healthcare personnel carried out tumour marker studies (CEA, CA19-9), magnetic resonance imaging (MRI), bone scan, and positron emission tomography (PET). The test results showed increased uptake in the spine and ribs in the bone scan, but tumour markers were negative and there were no abnormal findings with MRI or PET. The logical conclusion at that time was Paget's disease, and the condition was treated with bisphosphonates. The ALP level decreased slightly, but later it increased again. Consequently, the patient was referred to our institution.

She had a past medical history of fatty liver disease, hypertension, gastritis, benign ovarian tumour, and cataract but no history of cancer. At the physical examination, the patient appeared to be a well developed female in no apparent distress (temperature 36.5°C, pulse 69 beats/min, blood pressure 160/63 mmHg), with no deformities in her thoracic to lumbar spine, nor was there local heat or tenderness. The range of motion in her limbs was not restricted. Neurologically, muscle power in both upper and lower extremities was well preserved and there were no sensory disturbances. Reflexes were also normal.

The results of hematological examination and other laboratory tests are shown in Table 1. Although the serum calcium and phosphorus levels were within normal ranges, the ALP level was extremely high, 6267 IU/L. Isoenzyme separation showed a markedly increased amount of bone isoenzyme. Levels of tumour markers CEA and CA19-9 were normal.

Plain radiographs showed multiple osteosclerotic lesions in the spine and pelvis that were not detected eight months earlier (Fig. 1). Magnetic resonance imaging showed low signal intensities on the T1- and T2-weighed images in the lumbar spine, but there was no obvious abnormality. The Tc-99m MDP bone scan showed increased uptake in the whole spine, pelvis, and

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Table 1. — **Laboratory findings**

	Patient's results	Reference interval
White cell count (/μl)	7350	4000-9000
Red cell count ($\times 10^4$/μl)	327	380-480
Haemoglobin (g/dl)	9.1	12.0-17.5
Haematocrit (%)	29.6	35-45
Platelets ($\times 10^4$/μl)	14.8	15-45
Activated partial thromboplastin time (s)	24.7	25-35
Prothrombin time (s)	12.6	11-15
Total protein (g/dl)	7.1	6.0-8.0
Albumin (g/dl)	4.3	3.4-4.7
Asparate aminotransferase (IU/L)	21	0-35
Alanine aminotransferase (IU/L)	16	0-35
Lactate dehydrogenase (IU/L)	290	88-230
Cholinesterase (pH)	0.99	0.8-1.1
γ-gultamyl transpeptidase (IU/L)	232	9-85
Alkaline phosphatase (IU/L)	6267	41-133
Total bilirubin (mg/dl)	0.5	0.1-1.2
Total cholesterol (mg/dl)	228	< 200
Blood urea nitrogen (mg/dl)	13	8-20
Creatinine (mg/dl)	0.7	0.6-1.2
Sodium (mEq/l)	141	135-145
Potassium (mEq/l)	4.3	3.5-5.0
Calcium (mg/dl)	10	8.5-10.5
Phosphate (mg/dl)	3.9	2.5-4.5
Glucose (mg/dl)	103	60-110
Creatine kinase (IU/L)	57	12-170
C-reactive protein (mg/dl)	0.32	0-2
Carcinoembryonic antigen (ng/dl)	4.8	0-5.0
Carbonhydrate antigen 19-9 (U/ml)	1	< 37

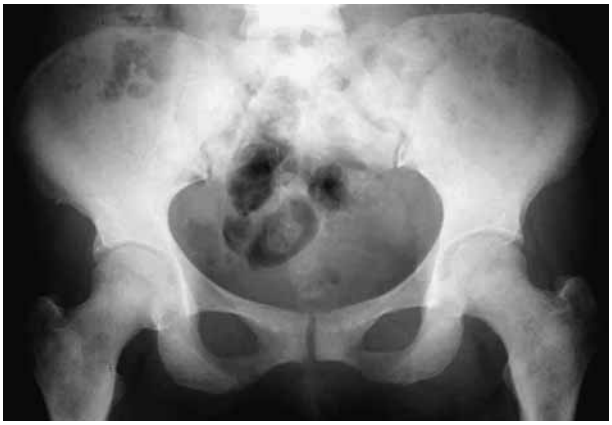

Fig. 1. — Radiograph of the pelvis shows multiple osteosclerotic lesions.

ribs (Fig. 2). On the other hand, no increased uptake was seen in the kidney, which could be interpreted as the so-called super bone scan. Positron emission tomography showed no abnormality. To make a histological diagnosis of the sclerotic bone lesions, needle biopsy was carried out from the ileum (Fig. 3). Microscopically, there were small atypical cells with signet ring cell features. The pathological diagnosis was metastasis of 'signet ring' adenocarcinoma.

Endoscopy was performed and multiple gastric mucosal lesions were found. Biopsy of the lesions showed a poorly differentiated 'signet ring' adenocarcinoma. The tumour was in the form of individual signet ring cells with large mucin vacuoles, resembling the cells seen in the needle biopsy carried out from the ileum.

The patient was moved to the chemotherapy unit and treatment with MTX-5FU commenced. Twenty courses of MTX 100 mg/m^2 and 5-FU 130 mg/m^2 were given and the patient's ALP level decreased to 1708 IU/L. Recently, her ALP level has increased again and weekly paclitaxel (PTX) was started ; the patient has been treated by outpatient care for more than one year.

Discussion

This patient had no past history related to cancer and her tumour markers were negative. Furthermore, she did not report any symptom related to the gastrointestinal system or any pain related to the bone metastases. In many cancer patients, pain is the first symptom, and 75-90% of patients with metastatic or advanced cancer will experience significant amounts of pain (2). In addition, 35-42% of cancer patients have cancer-related bone pain (3,4). The possible mechanisms of bone pain are the release of chemical mediators such as prostaglandin, the increased pressure within the bone, microfractures, and nerve invasion. Typical radiographic features show lytic, sclerotic, or mixed metastases that are responsible for osteoclast activation (5). In bone metastases, osteoclasts secrete acid and cause bone resorption from tumour invasion. In this case showing sclerotic metastases, there may have been little activity of the nociceptor, which senses acid stimulation induced by osteoclasts and mechanical stimulation by bone resorption (2,6).

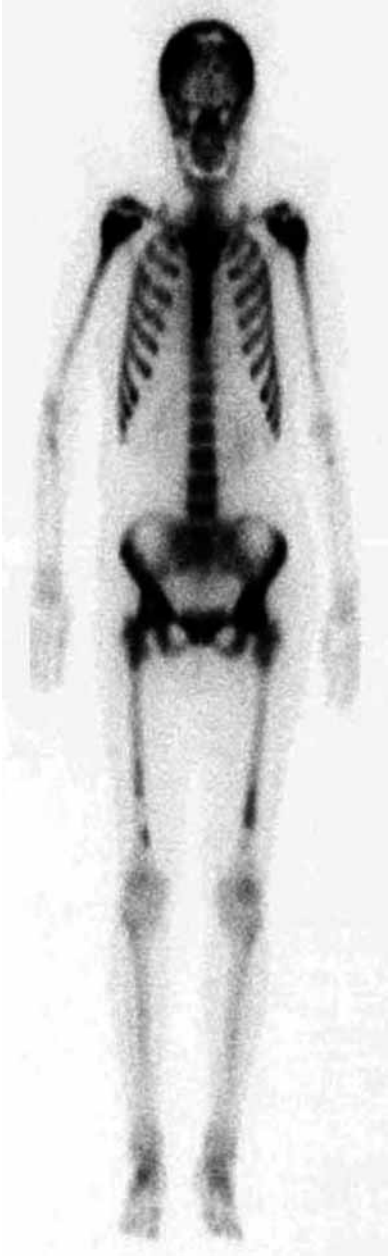

Fig. 2. — Bone scintigraphy shows a so-called super bone scan. Note the markedly increased uptake of the radionuclide in the whole spine and the absence of renal sign.

In this case, the only abnormal finding was hyperphosphatasia. This was the key to diagnosis. Alkaline phosphatase increases in obstructive hepatobiliary disease, bone disease (physiologic bone growth, Paget's disease, osteomalacia, osteogenic sarcoma, bone metastases), hyperparathyroidism, rickets, benign familial hyperphosphatasemia, pregnancy (third trimester), GI disease (perforated ulcer or bowel infarct), and cases of hepatotoxic drugs. Only a few reports have been published concerning multiple metastases of unknown origin with hyperphosphatasia (7-10). Tokushima *et al.* suggested that the cancer cells themselves might produce ALP (10). However, the pathogenesis and pathological

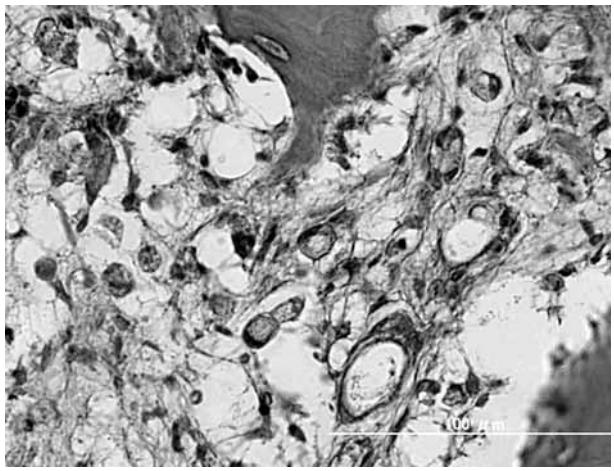

Fig. 3. — Histological examination of the iliac biopsy shows a number of small atypical cells with signet ring cell features (H&E, × 100).

roles of ALP in such cases are still unknown. For the differential diagnosis, a whole body bone scan was performed, which showed abnormal findings, a so-called 'super bone scan'. A super bone scan is defined as intense symmetric activity in the bones and diminished renal parenchymal activity (11). Sy *et al.* hypothesized that the increased uptake of radiopharmaceutical by diseased bone results in reduced phosphate excretion, thereby producing faint renal images in the bone scan (12). Such appearances have been reported to be common in delayed imaging (in normal patients), metastases (most frequently in prostate and breast cancers), and renal osteodystrophy (7). Thrupkaew *et al.* reported that cases of diffuse metastatic disease showed a super bone scan (13). Though rare, there are a few reports about super bone scan due to metastatic gastric cancer (14,15).

In 1936, Jarcho first described a special group of patients with diffusely infiltrating carcinoma of the stomach, showing a number of common features (16). Forty Japanese patients were reviewed by Hayashi *et al.* in 1979 for what was called "disseminated carcinomatosis of the bone marrow" (17). The primary tumour was gastric cancer in 37 of these 40 patients (92.5%). Pathological diagnosis was obtained in 33 patients, 27 of whom showed either poorly differentiated or mucin-producing adenocarcinoma. There were two peaks in age distribution, in the thirties and fifties, and one-fourth of the patients were women under 40 years of age. The triad of symptoms was related to anemia (85%), bleeding tendency (65%), and low back pain (67.5%). Hematological examination often showed severe anemia and leukocytosis with leukoerythoblastosis. Up to 90% of cases were accompanied by microangiopathic hemolytic anemia or disseminated intravascular coagulation. Blood chemical tests revealed marked elevation of ALP and lactate dehydrogenase in most cases.

From the bone scan and biopsy, we established the diagnosis of disseminated carcinomatosis of the bone marrow. The prognosis of this condition has been reported to be very poor (7-10,18). The mean survival after diagnosis is 2.3 months. There are few reports that chemotherapy provides relief in patients with bone carcinomatosis from gastric cancer. Sequential MTX-5FU treatment seems to be one of the most effective regimens for gastric cancer. Chemotherapy with 600 mg/m^2 of 5-FU and 100 mg/m^2 of MTX was more effective for patients with poorly differentiated carcinoma compared with differentiated adenocarcinoma, showing a response rate of 50% (19). Efficacy of chemotherapy can also be expected in cases complicated by disseminated intravascular coagulation, but even so, the patient' survival time is no more than 5-19 months (8).

In this case, we were able to find the cause of the disease and begin chemotherapy. Different chemotherapy regimens were carried out at the primary site. From the experience, we believe that bone scans and intensive stomach investigations should be considered in cases with hyperphosphatasia and multiple osteosclerotic lesions, even when a patient has no symptoms. There is a possibility of disseminated carcinomatosis of bone marrow and if there is a super bone scan, biopsy should be carried out because accurate treatment will prolong the prognosis. The reason why this tumour grows slowly is still unknown and further study is needed.

References

1. HOUGHTON J., STOICOV C., NOMURA S., ROGERS A.B., CARLSON J., LI H., CAI X., FOX J.G., GOLDENRING J.R., WANG T.C. Gastric cancer originating from bone marrow-derived cells. *Science*, 2004, **26** : 1455-1457.
2. MANTYH P.W., CLOHISY D.R., KOLTZENBURG M., HUNT S.P. Molecular mechanism of cancer pain. *Nature Rev. Cancer*, 2002, **2** : 201-209.
3. GROND S., ZECH D., DIEFENBACH C., RADBRUCH L., LEHMANN K.A. Assessment of cancer pain : a prospective evaluation in 2266 cancer patients referred to a pain service. *Pain*, 1996, **64** : 107-114.
4. CARACENI A., PORTENOY R.K. An international survey of cancer pain characteristics and syndromes. IASP Task Force on Cancer Pain. International Association for the Study of Pain. *Pain*, 1999, **82** : 263-274.
5. MERCADANTE S. Malignant bone pain : pathophysiology and treatment. *Pain*, 1997, **69** : 1-18.
6. GHILARDI J.R., ROHRICH H., LINDSAY T.H., SEVCIK M.A., SCHWEI M.J., KUBOTA K., HALVORSON K.G., POBLETE J., CHAPLAN S.R., DUBIN A.E., CARRUTHERS N.I., SWANSON D., KUSKOWSKI M., FLORES C.M., JULIUS D., MANTYH P.W. Selective blockade of the capsaicin receptor TRPV1 attenuates bone cancer pain. *J. Neurosci.*, 2005, **25** : 3126-3131.
7. CHUNG Y.S., CHOI T.Y., HA C.Y., KIM H.M., LEE K.J., PARK C.H., FITZPATRICK L.A. An unusual case of osteoblastic metastasis from gastric carcinoma. *Yonsei Med. J.*, 2002, **43** : 377-380.
8. KOBAYASHI F., IKEDA T., TOZUKA S., NOGUCHI O., FUKUMA T., SAKAMOTO S., MARUMO F., KOMODA T., SAKAGISHI Y., SATO C. A variant alkaline phosphatase found in a case of gastric carcinoma with super bone scan. *Gut*, 1995, **36** : 299-302.
9. UCHIDA T., SHIKATA T., SHIMIZU S., TAKIMOTO Y., IINO S., SUZUKI H., ODA T., HIRANO K., SUGIURA M. Gonadotropin and alkaline phosphatase producing occult gastric carcinoma with widespread metastasis of generalized bone. *Cancer*, 1981, **48** : 140-150.
10. TOKUSHIMA K., IKEDA T., KOBAYASHI F., KUROSAKI M., TOZUKA S., SAKAMOTO S., MARUMO F., KOYAMA I., KOMODA T., SAKAGISHI Y., HIROTA N., SATO C. A variant alkaline phosphatase producing gastric carcinoma with super bone scan. *Dig. Dis. Sci.*, 1997, **42** : 66-73.
11. MANIER S.M., VAN NOSTRAND D. Super bone scan. *Semin. Nucl. Med.*, 1984, **14** : 46-47.
12. SY W.M., PATEL D., FAUNCE H. Significance of absent or faint kidney sign on bone scan. *J. Nucl. Med.*, 1975, **16** : 454-456.
13. THRUPKAEW A.K., HENKIN R.E., QUINN J.L. 3rd. False negative bone scan in disseminated metastatic disease. *Radiology*, 1974, **113** : 383-386.
14. OMI R., HATORI M., SANO H., WATANABE K., WATANABE M., KOKUBUN S. Super bone scan due to bone marrow metastases appearing, 19 years after surgery for early gastric cancer – a case report. *Ups. J. Med. Sci.*, 2004, **109** : 49-56.
15. SAPHNER T., LOVE R.R., PERLMAN S. Super bone scan in metastatic stomach cancer. *Wis. Med. J.*, 1990, **89** : 161-163.
16. JARCHO S. Diffusely infiltrative carcinoma, a hitherto undescribed correlation of several varieties of tumor metastasis. *Arch. Pathol.*, 1936, **22** : 674-696.
17. HAYASHI H., HARUYAMA H., EMURA Y., EMURA F., KAIZUKA I., KOSEKI T. Disseminated carcinomatosis of the bone marrow. *Jpn. J. Cancer Clinics*, 1979, **25** : 329-343 (in Japanese).
18. SOUFLERIS K., PILPILIDIS I., TZILVES D., MOSCHOS J., GATOPOULOU A., PATAKIOUTA F., TARPAGOS A., KATSOS I. A case of early gastric cancer with bone metastases : are bone marrow micrometastases significant ? *Acta Gastroenterol. Belg.*, 2007, **70** : 231-4.
19. KOBAYASHI T., SASAKI T., IBUKA T., IMAI K., MONMA K., - SAKAKI N., TABATA I., ISHIWATARI J., ONOZAWA Y., OHNO T., SHIMOYAMA T. Sequential MTX and 5-FU therapy of gastric cancer with systemic bone metastasis and disseminated intravascular coagulation. *Gan To Kagaku Ryoho*, 1992, **19** : 69-74 (in Japanese with English abstract).