

## An Unusual Case of Osteoblastic Metastasis from Gastric Carcinoma

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We report an unusual case of osteoblastic metastasis from gastric carcinoma. In this case, bone metastasis was the initial manifestation of the cancer. The laboratory findings revealed mild hypocalcemia and markedly elevated alkaline phosphatase levels. Plain X-ray showed mottled osteoblastic changes in the pelvis. Bone marrow and bone biopsy of the pelvis revealed metastatic adenocarcinoma with increased osteoblastic activity. An extensive search for the primary site revealed advanced gastric carcinoma, which was confirmed by endoscopic biopsy.

**Key Words:** Osteoblastic metastasis, gastric carcinoma

### INTRODUCTION

Bone is a common site of metastasis for carcinoma of the prostate, breast, lung, kidney, bladder, and thyroid, and for lymphoma and sarcoma. Cancer in the bone may produce osteolytic change, osteoblastic change, or both. Prostate and breast carcinomas provide classic examples of osteoblastic metastasis. In contrast, carcinomas of other origins usually show osteolytic metastasis. Gastric carcinoma infrequently metastasizes to the bone and rarely in an osteoblastic way. Hypo-

calcemia and elevated serum alkaline phosphatase levels are more common in osteoblastic metastases than in osteolytic metastasis.

### CASE REPORT

A 40-year-old woman was referred for pains of the lower extremities experienced over a 2-month period. She denied cigarette smoking or alcohol use, and did not complain of any symptom related to the gastrointestinal system. Her past medical history was unremarkable.

On physical examination, her body weight was 65 kg and her height was 163 cm. There was no bone tenderness and no evidence of skull or long bone deformity. Her head and neck examinations were unremarkable, and there was no palpable lymph node on supraclavicular area. A questionable breast mass of about 1 × 1 cm in size was palpable on the left upper outer quadrant. Abdominal examination did not revealed any specific findings.

A laboratory examination revealed hemoglobin 11.6 g/dL, hematocrit 33.7%, white blood cell 8,900/uL, and platelet 138,000/uL. Serum calcium level was 7.9 mg/dL (normal range 8.4 - 10.2), ionized calcium 4.4 mg/dL (4.2 - 5.4), serum phosphorus 3.7 mg/dL (2.5 - 4.5), and magnesium 1.9 mEq/L (1.6 - 2.6). Total protein level was 7.0 g/dL and albumin 4.1 g/dL. Alkaline phosphatase level was 970 IU/L (20 - 120). 24hr urine creatinine was 1093 mg, calcium 13 mg (100 - 300), and phos-

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phorus 718 mg (400 - 1300). Intact PTH level was 85 pg/ml (10 - 64). Her 25 (OH)D level was 2.5 ng/mL (9.9 - 41.5), 1,25 (OH)<sub>2</sub>D<sub>3</sub> 117.4pg/ml (19.9 - 67.0). Osteocalcin was 71.8 ng/mL (8.0 - 36.0), DPD 29.0 nM/ mMCr (3.2 - 7.2), rheumatoid factor < 20 U/mL. Antinuclear antibody and HLA B27 were negative. Stool occult blood was negative. Her TSH level was 2.82 IU/mL, T<sub>4</sub> 114.0 ng/dL, and T<sub>3</sub> 4.06g/dL, and her CEA was 9.2 ng/mL (0.0 - 4.5), CA19-9 3100 U/mL (0 - 29), and CA-125 33.2 U/mL (10.0 - 34.5).

Simple radiographs of the pelvis and sacrum revealed mottled osteoblastic changes (Fig. 1). A whole body bone scan using technetium 99m showed increased uptake in areas of the sternum, ribs, cervico-thoracic-lumbar spine, pelvis, femurs, skull and shoulders (Fig. 2). Bone mineral densities (Expert-XL, Lunar Corp., Madison, Wisconsin, U.S.A.) were 1.398g/cm<sup>2</sup> and T score +2.3 for L<sub>2-4</sub>, 1.000 g/cm<sup>2</sup> and T score +0.8 for femoral neck, 1.129 g/cm<sup>2</sup> and T score +1.6 for total hip, and 1.194 g/cm<sup>2</sup> and T score +1.2 for whole body. Breast ultrasonography, to rule out breast cancer, showed ductal hyperplasia, and fine needle aspiration biopsy was negative for malignant cells.

Bone marrow biopsy revealed metastatic adenocarcinoma with intensive myelofibrosis and osteosclerosis (Fig. 3). The mucicarmine stain and the periodic acid Schiff stain with diastase digestion were both positive. Abdominal CT revealed a thickened gastric wall with invasion of the pancreas and massive lymphadenopathy and liver



Fig. 1. Simple X-ray revealed mottled osteoblastic changes (arrow) in pelvic bone.

metastasis (Fig. 4). Esophagogastroduodenoscopy showed gastric mucosal folds thickening from the upper body to the lower body of lesser curvature, and biopsy showed signet ring cell carcinoma. Transiliac bone biopsy revealed increased osteoblastic activities and new bone formation, marrow fibrosis, and signet ring cell adenocarcinoma metastasis (Fig. 5). The final diagnosis revealed advanced gastric cancer with osteoblastic bone metastasis. The patient refused any specific medical treatment and was lost to follow-up but was reported dead 4 months after the diagnosis.

## DISCUSSION

This case demonstrates that osteoblastic metastasis can occur from gastric carcinoma rather than from the classic sites of the prostate or breast. In fact, in the present case metastatic bone pain was

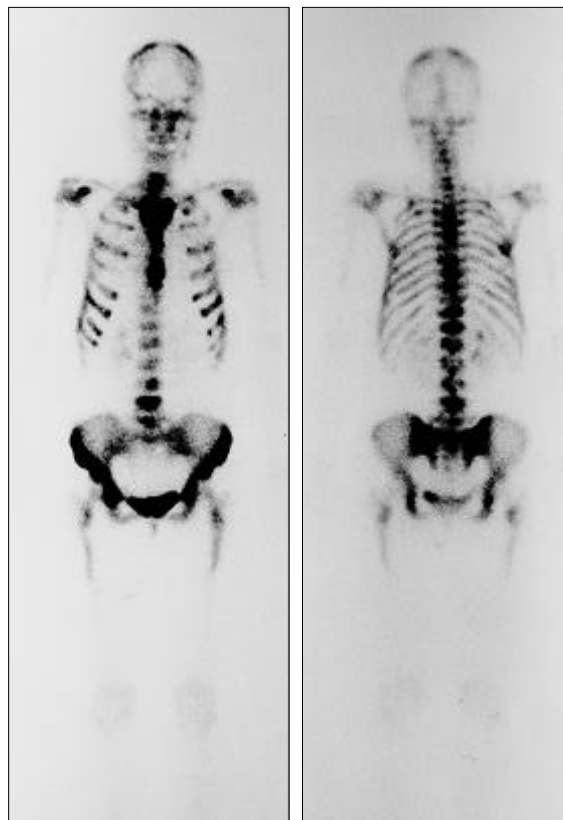


Fig. 2. Whole body bone scan using technetium 99m showed increased uptake in the areas of the sternum, ribs, cervico-thoracic-lumbar spine, pelvis, femurs, skull and shoulders.

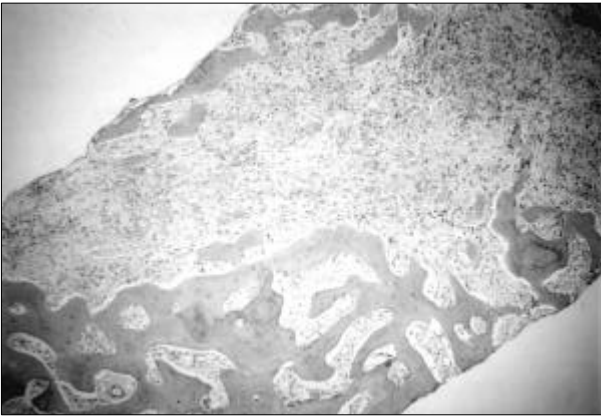


Fig. 3. Bone marrow biopsy revealed metastatic adenocarcinoma with intensive myelofibrosis and osteosclerosis (H&E  $\times 40$ ).

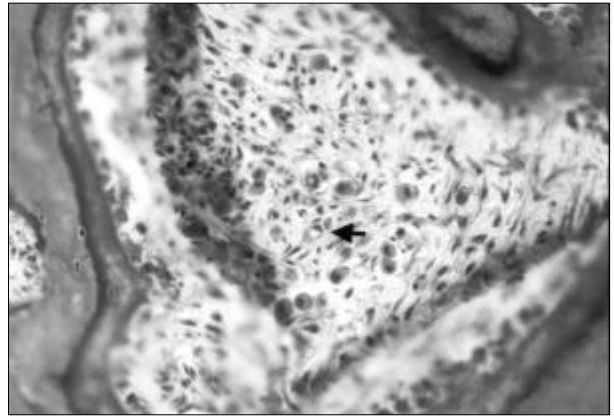


Fig. 5. Transiliac bone biopsy revealed increased osteoblasts and osteoids, marrow fibrosis, and metastatic signet ring cells (Goldner trichrome  $\times 400$ ).



Fig. 4. Abdominal CT revealed a thickened gastric wall (arrow) with pancreatic invasion and massive lymphadenopathy and liver metastasis.

the initial manifestation of gastric cancer, described as a nonspecific generalized ache and uncertain bone pain. The pain increased gradually and soon became intolerable.

In the differential diagnosis of an osteoblastic lesion it is important to distinguish between metastasis and metabolic bone diseases. The absence of a deformity or thickening of the bone, and the symmetrical involvement of the proximal femurs, could have meant the exclusion of Paget's disease. Bone marrow aspiration and biopsy might have been an appropriate next step. Metastatic adenocarcinoma was in fact diagnosed by bone marrow biopsy, and extensive search for the primary cancer followed. Initially, the breast was considered the most likely primary site, and

careful examination revealed a questionable mass on the left mammary gland. However, sonographic and biopsy evaluation, provided no evidence of malignancy in the breast. Furthermore, bone marrow biopsy revealed a mucin-producing metastatic adenocarcinoma, which strongly suggest a gastrointestinal tract origin. An abdominal computed tomography scan revealed a thickened gastric wall, and stomach cancer was confirmed by a tissue diagnosis of stomach cancer.

In this case, the measurement of bone mineral density was not necessary, but the patient complained of back pain, and her primary care physician suggested that she might be suffering from osteoporosis. For that reason, we performed bone mineral density on her first visit to our clinic. In this case, a bone biopsy was not necessary for diagnosis, because the bone marrow biopsy revealed osteoblastic metastasis from signet ring cell carcinoma. Nevertheless, a bone biopsy was performed in order to rule out any possible of metabolic bone disease, including Paget's disease.

Osteoblastic lesions are associated with higher serum levels of alkaline phosphatase, and may produce hypocalcemia.<sup>1</sup> The most common neoplasm associated with hypocalcemia is prostate cancer. Adenocarcinomas of the lung and breast have also been implicated. Pepper et al.<sup>2</sup> have demonstrated similar findings in a patient with breast cancer. Hypocalcemia usually occurs more frequently in patients with osteoblastic metastases (28%) than in those with osteolytic metastases (11%).<sup>1</sup> As might be expected, osteoblastic lesions

are associated more frequently with higher levels of serum alkaline phosphatase than osteolytic lesions.<sup>1</sup> One might then hypothesize that excessive new bone formation, while increasing total body calcium, might result in the depletion of the serum level due to excessive calcium uptake from the blood at sites of osteoblastic activity.

Bone metastasis from stomach cancer relates closely to poorly differentiated adenocarcinoma<sup>3,4</sup> and has a tendency to occur in those with a high lymph node involvement. Usually, it is also associated with invasive cancers such as third or fourth Borrmann types, the so-called scirrhous type.<sup>3,4</sup> Our case also showed extensive lymph node involvement and liver metastasis.

The endoscopic findings revealed an advanced gastric cancer of the Borrmann type IV.<sup>3,4</sup>

The incidence of bone metastasis from gastric cancer ranges from 1.0 to 20.0 percent,<sup>3</sup> and it is usually osteolytic. Osteoblastic metastasis from stomach cancer has only been reported in 4 cases in the English literature. This report is a rare case of osteoblastic bone metastasis due to gastric cancer.

The first reported case involved a 50-yr-old Indian male patient who had experienced persistent abdominal pain for 3 months.<sup>5</sup> He was diagnosed with gastric adenocarcinoma of the antrum with linitis plastica picture. Plain x-rays revealed patchy sclerotic lesions in the pelvis, vertebrae, and skull.

The second case was of a 36-year-old man who was admitted to the Veterans Administration Hospital in San Diego.<sup>6</sup> He experienced symptoms characteristic of peptic ulcer disease and was finally diagnosed with adenocarcinoma of gastric antrum. Plain X-ray revealed diffuse chalky sclerosis of ribs, clavicles, and thoracic and lumbosacral portions of the spine. A bone scan with radioactive technetium demonstrated marked and symmetrical uptake throughout the axial skeleton.

The third case was of a 57-yr-old Japanese male with asymptomatic hematuria.<sup>7</sup> X-ray of vertebrae and pelvis showed diffuse osteosclerosis. Aspiration biopsy of the bone marrow revealed metastatic adenocarcinoma. An extensive search for the

primary site of the adenocarcinoma was unsuccessful. He died of disseminated intravascular coagulation with hemorrhagic diathesis. The autopsy revealed gastric adenocarcinoma of the antrum. The primary and metastatic carcinoma cells were positive for periodic acid Schiff.

The fourth reported case was that of a 64-yr-old Indian male patient who presented with a pain in the neck and back, and weakness of the lower limbs.<sup>8</sup> Clinical examination revealed spastic paraparesis due to extradural compressive myelopathy. Skeletal X-rays revealed multiple osteosclerotic lesions in the lumbar, thoracic and cervical vertebrae, and in the pelvis and ribs. A gastroscopic biopsy revealed Borrmann type III signet ring cell carcinoma of the antrum.

The prognosis of gastric carcinoma with osteoblastic bone metastasis is uniformly poor. All of the cases died within 4 months of diagnosis.<sup>5-8</sup>

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