Anti-Cancer Drugs 2001, **12,** pp. 731–734

Case report

Pamidronate-induced remission of pain associated with hypertrophic pulmonary osteoarthropathy in chemoendocrine therapy-refractory inoperable metastatic breast carcinoma

Takaomi Suzuma,[1] Takeo Sakurai,[1] Goro Yoshimura,[1] Teiji Umemura,[1] Takeshi Tamaki,[1] Tatsuya Yoshimasu[2] and Yasuaki Naito[2]

[1]Department of Surgery, Affiliated Kihoku Hospital, Wakayama Medical University and [2]First Department of Surgery Wakayama Medical University, Wakayama 649-7113, Japan.

We describe an extremely rare case of a woman with pulmonary metastatic disease from breast cancer, who presented with features of hypertrophic pulmonary osteoarthropathy (HPOA). Pain associated with HPOA may be extremely disabling and resistant to treatment. Treatment with pamidronate, an inhibitor of osteoclastic bone resorption, given every 2 weeks by i.v. drip infusion, led to rapid disappearance of uncontrolled pain caused by HPOA. [© 2001 Lippincott Williams & Wilkins.]

Key words: Breast cancer, hypertrophic pulmonary osteoarthropathy, pamidronate.

Introduction

Hypertrophic pulmonary osteoarthropathy (HPOA) is an uncommon, poorly understood syndrome usually seen with bronchogenic carcinomas,[1–3] but also in rare cases with pulmonary metastases from extrathoracic malignancies.[2–4] It is characterized by clubbing of the digits with painful swelling of the distal extremities, arthralgias of distal extremities and periosteal bone formation.[1,2,4,5] Pain associated with HPOA may be extremely disabling and resistant to treatment.[6] We describe an extremely rare case of a woman with pulmonary metastatic disease from breast cancer who presented with features of HPOA, and report that pamidronate led to the rapid disappearance of uncontrolled pain caused by HPOA and prolonged palliation for the patient.

Correspondence to T Suzuma, 219 Myouji, Katsuragicho, Itogun, Wakayama 649-7113, Japan.
Tel: (+81) 736 22 0066; Fax: (+81) 736 22 8305;
E-mail: suzuma@mail.wakayama-med.ac.jp

Case report

A 44-year-old woman had a right radical mastectomy for T2 infiltrating ductal carcinoma in August 1989. She was premenopausal. Axillary lymph node status was negative; estrogen receptors were negative. A chest X-ray film was normal at this time. She had no postoperative irradiation or chemoendocrine therapy. In July 1993, she had bilateral multiple pulmonary tumors. On bronchoscopic examination, the appearance of the biopsy specimen was compatible with metastatic breast carcinoma. The patient received two courses of combination chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil, two courses of combination chemotherapy with cyclophosphamide, epirubicin and 5-fluorouracil, and two courses of chemotherapy with docetaxel until May 1994, but indicated no response. The patient further received endocrine therapy with tamoxifen citrate and medroxyprogesterone acetate, again with no response.

In September 1996, she had swelling of the lower extremities, with pain in the knees, ankles and feet, which interfered with her ability to walk and do her daily activities. She had no respiratory symptoms. She also had swelling of the fingers and pain in the wrists. A chest X-ray film showed bilateral multiple pulmonary tumors, growing compared to previously (Figure 1). Roentgenograms of the extremities showed lineal periosteal new bone formation in the tibias and fibulas (Figure 2). Radionuclide bone scan images showed diffuse, symmetrically increased uptake along the pericortices of the tibias and fibulas demonstrating changes characteristic of HPOA (Figure 3). In May 1997, non-steroidal anti-inflammatory

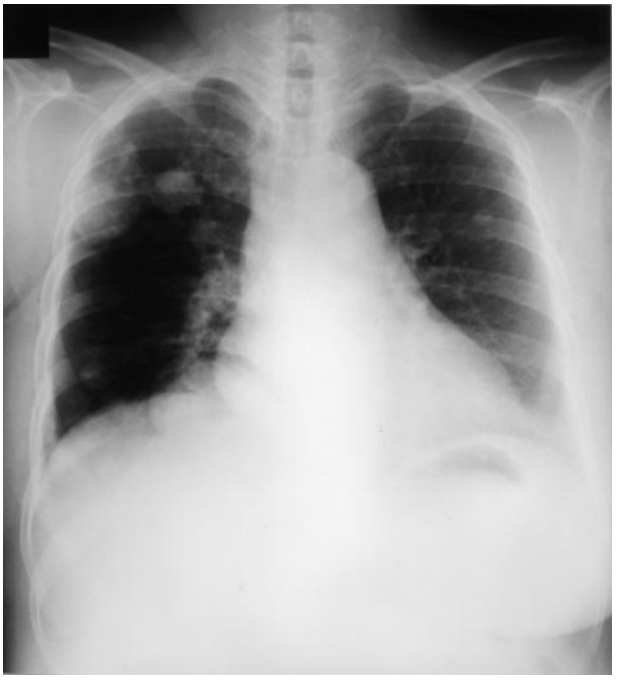

Figure 1. A chest X-ray film showed bilateral multiple pulmonary tumors.

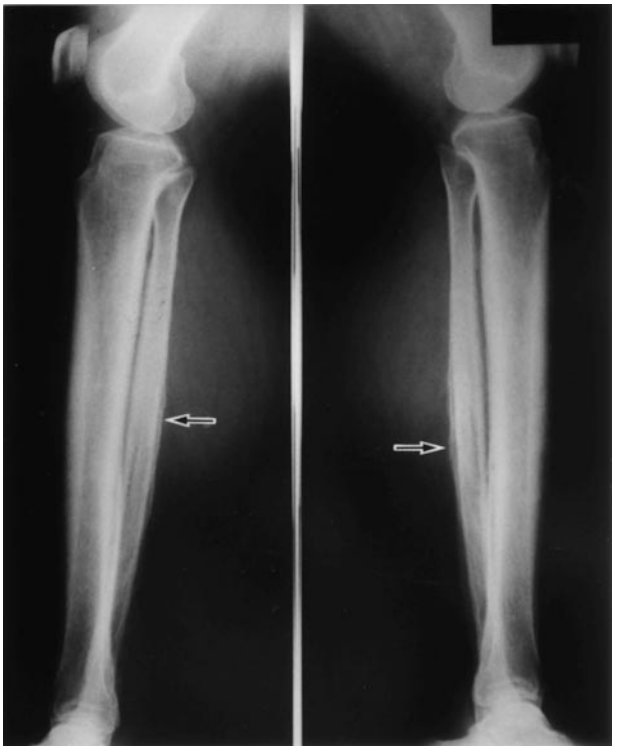

Figure 2. Roentgenograms of the extremities showed lineal periosteal new bone formation (arrows) in the tibias and fibulas.

drugs (NSAIDs) at full dosage (loxoprofen, diclofenac) as well as steroids and oral morphine had been

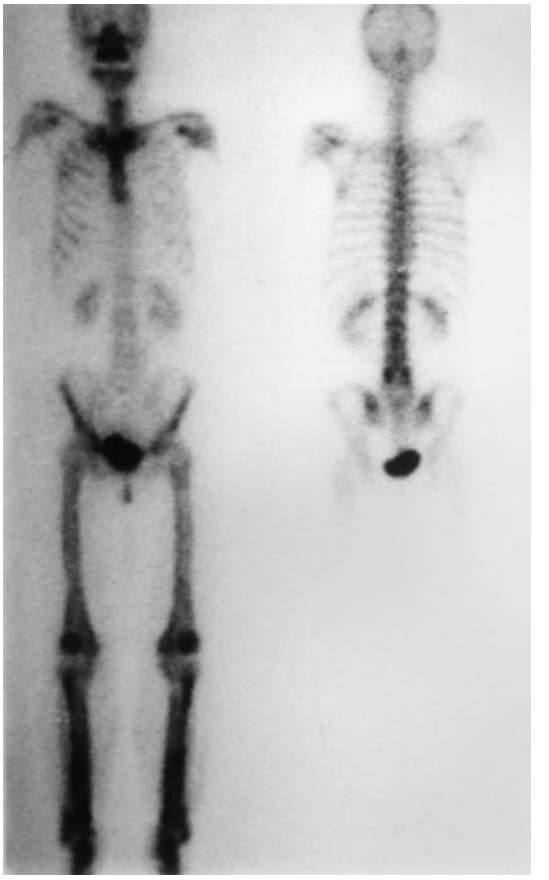

Figure 3. Radionuclide bone scan images showed diffuse, symmetrically increased uptake along the pericortices of the tibias and fibulas without any focal increased uptake of the spine and rib cage suspected of bone metastases from the breast.

unsuccessful in relieving her pain and swelling. From May 1997, treatment was commenced with pamidronate, at a dose of 30 mg in 500 ml of 0.9% saline over 3 h by i.v. drip infusion. Within 7 days the patient's pain had completely resolved and she was able to walk unaided. However, after 21 days the pain recurred. Reintroduction of pamidronate led to symptom relief, but X-ray findings of the lower extremities show no alteration and the abnormal subperiosteal bone formations remained. Following the administration of pamidronate at 2-week intervals she became pain free and remained so until her death 5 months later.

Discussion

Hypertrophic osteoarthropathy is classified as primary (idiopathic/hereditary) or secondary (various thoracic, cardiovascular and gastrointestinal diseases). However,

more than 90% of secondary cases are associated with intra-thoracic pathology (neoplasm, chronic sepsis) and so that syndrome is often called HPOA.[29]

Primary lung tumors account for 80% of HPOA cases[30] and the incidence of HPOA in primary lung tumors varies from less than 1 to 10%.[8] HPOA is rarely associated with pulmonary metastases from extrathoracic malignancies,[3–5] the majority of which are sarcomas.[9] Only six other cases due to metastatic breast cancer have been recorded,[3,11–13] comprising a roughly equal incidence of sarcoma and carcinoma, with melanoma and miscellaneous tumors making up the remainder.[3,11] Allowing for its overwhelming prevalence, breast carcinoma may be remarkably under-represented in these cases, compared to osteosarcoma, a much rarer tumor.[12]

HPOA is characterized by clubbing of the digits with painful swelling of the distal extremities, arthralgias of distal extremities and periosteal bone formation.[14] Typical bone scan findings in HPOA are symmetrically increased uptake along the cortical margins of the long, tubular bones.[31–33] Since our patient had extensive pulmonary metastases from breast cancer, it was unclear whether her pain of the distal extremities was caused by metastatic bone disease or HPOA. Her pain is highly likely to have been caused by the latter possibility. First, based on clinical, typical X-ray and bone scan findings, our patient's condition was diagnosed as HPOA. Second, her bone scan images do not show any focal increased uptake of the spine and rib cage suspected of bone metastases from the breast. It is not conceivable that she had symmetrical metastases of bilateral distal extremities.

Like HPOA, pachydermoperiostitis, thyroid acropachy and unusual cortical reaction with venous insufficiency also show periosteal new bone formation.[34,35] Hypertrophic pulmonary osteoarthropathy should be differentiated from these entities with clinical and laboratory findings.[36]

The etiology and pathogenesis of HPOA is unknown, but is presumed to be mediated by neurohormonal factors elaborated by the underlying disease process.[14]

HPOA is a relatively uncommon cause of symptoms in patients with primary and metastatic pulmonary malignancies, but it can limit independence and mobility at a time when respiratory symptoms are minimal. A commonly seen peculiarity of HPOA is often dramatic remission of symptoms, sometimes within hours or days, after surgical resection of the lesion or interruption of neural fibers in the thorax, or even abdomen,[1,7–10,17,18] or effective treatment to pulmonary lesions with radiation[1,20] or chemotherapy[12,15,16] in selected cases. In patients presenting with HPOA, however, with no indication of radiotherapy or chemoendocrine therapy-refractory inoperable metastatic breast carcinoma, analgesics, steroids and NSAIDs remain the mainstay of conventional symptomatic management. However, they have been variably effective in HPOA,[1,9,10,19] as responses tend to be incomplete and transient.[6]

Bisphosphonates such as pamidronate are inhibitors of osteoclastic bone resorption, playing an important role in various types of bone disorders such as osteoporosis,[21] hypercalcemia of malignancy[22] and bone metastasis.[23,24] Most experience with bisphosphonates for bone pain is from their use for skeletal metastases from advanced breast cancer.[28] The majority of early studies were open uncontrolled studies; however, subsequent randomized controlled trials of i.v. bisphosphonates have all demonstrated useful pain relief.[25–27] This is the first known report of the successful use of bisphosphonates such as pamidronate, a highly potent new drug, in providing symptom control in a patient with HPOA.

Conclusion

We believe that bisphosphonates will be an important addition to the therapeutic options available for the relief of pain in HPOA and therefore merit further evaluation.

References

1. Semple T, McCluskie RA. Generalized hypertrophic osteoarthropathy in association with bronchial carcinoma. *Br Med J* 1955; **1**: 754–9.
2. Firooznia H, Seliger G, Genieser NB, *et al*. Hypertrophic pulmonary osteoarthropathy in pulmonary metastases. *Radiology* 1975; **115**: 269–74.
3. Aufses AH, Aufses BH. Hypertrophic osteoarthropathy in association with pulmonary matastases from extrathoracic malignancies. *Dis Chest* 1960; **38**: 399–403.
4. Yacoub MH, Simon G, Ohnsorge J. Hypertrophic pulmonary osteoarthropathy in association with pulmonary metastases from extrathoracic tumors. *Thorax* 1967; **22**: 226–30.
5. JustViera JO. Clubbed digits: an enigma. *Arch Intern Med* 1964; **113**: 122–8.
6. Blackwell N, Bangham L, Hughes M, *et al*. Treatment of resistant pain in hypertrophic pulmonary arthropathy with ketorolac. *Thorax* 1993; **48**: 401.
7. Shneerson JM. Digital clubbing and hypertrophic osteoarthropathy: the underlying mechanisms. *Br J Dis Chest* 1981; **75**: 113–31.
8. Goldstrow P, Walbaum PR. Hypertrophic pulmonary osteoarthropathy and its occurrence with pulmonary metastases from renal carcinoma. *Thorax* 1976; **31**: 205–11.

9. Lokich JJ. Pulmonary osteoarthropathy: association with mesenchymal tumor metastases to the lung. *J Am Med Ass* 1977; **238**: 37–9.
10. Sethi SM, Saxton GD. Osteoarthropathy associated with solitary pulmonary metastasis from melanoma. *Can J Surg* 1974; **17**: 221–4.
11. Booth BW, Nostrand DV, Graeber GM. Hypertrophic pulmonary osteoarthropathy and breast cancer. *Southern Med J* 1987; **80**: 383–6.
12. Davies RA, Darby M, Richards MA. Hypertrophic pulmonary osteoarthropathy in pulmonary metastatic disease. A case report and review of the literature. *Clin Radiol* 1991; **43**: 268–71.
13. Gregory RK, Chang J, Singh R, *et al*. Clubbing, arthralgia and haemoptysis in a patient with metastatic carcinoma of the breast. *Ann Oncol* 1996; **7**: 756–7.
14.. Bunn PA, Ridgway EC. Paraneoplastic syndromes. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer: principles and practice of oncology*. Philadelphia, PA: Lippincott 1993: 2026–71.
15. Uchivama G, Ishizuka M, Sugiura N. Hypertrophic pulmonary osteoarthropathy inactivated by antitumor chemotherapy. *Radiat Med* 1985; **3**: 25–8.
16. Dalgleish AG. Hypertrophic pulmonary osteoarthropathy: response to chemothrapy without documented tumour response. *Aust NZ J Med* 1983; **13**: 513–6.
17. Hollis WC. Hypertrophic osteoarthropathy secondary to upper-gastrointestinal-tract neoplasm. *Ann Intern Med* 1967; **66**: 125–30.
18. Greco FA, Kushner I. Loss of symptoms of hypertrophic pulmonary osteoarthropathy after laparotomy. *Ann Intern Med* 1974; **81**: 555–6.
19. Zorroza J, Cangir A, Green B. Osteoarthropathy associated with nasopharyngeal carcinoma. *Am J Rheumatol* 1977; **128**: 679–81.
20. Atkinson MK, McElwain TJ, Peckham MJ, *et al*. Hypertrophic pulmonary osteoarthropathy in Hodgkin's disease: reversal with chemotherapy. *Cancer* 1976; **38**: 1729–34.
21. Liberman UA, Weiss SR, Bröll J, *et al*. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. *N Eng J Med* 1995; **333**: 1437–43.
22. Body JJ, Pot M, Borkowski A, *et al*. Dose/response study of aminohydroxypropylidene bisphosphonate in tumor-associated hypercalcemia. *Am J Med* 1987; **82**: 957–63.
23. Hortobagyi GN, Theriault RL, Porter L, *et al*. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 Aredia Breast Cancer Study Group. *N Engl J Med* 1996; **335**: 1785–91.
24. Theriault RL, Lipton A, Hortobagyi GN, *et al*. Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions. Protocol 18 Aredia Breast Cancer Study Group. *J Clin Oncol* 1999; **17**: 846–54.
25. Body JJ, Bartl R, Burckhardt P, *et al*. Current use of bisphosphonates in oncology. International Bone and Cancer Study Group. *J Clin Oncol* 1998; **16**: 3890–9.
26. Body JJ, Lichinitser MR, Diehl I, *et al*. Double-blind placebo controlled trial of ibandronate in breast cancer metastatic to bone. *Proc Am Soc Clin Oncol* 1999; **18**: 575A.
27. Berenson JR, Lipton A, Rosen LS, *et al*. Phase I clinical study of a new bisphosphonate, zoledronate (CGP-42446), in patients with osteolytic bone metastases. *Blood* 1998; **88**(suppl 1): 586a.
28. Coleman RE. Optimising treatment of bone metastases by Aredia and Zometa. *Breast Cancer* 2000; **7**: 361–9.
29. Charan NB, Carvalho P. Cardinal signs and symptoms in respiratory disease. In: Pierson DJ, Kacmanek RM, eds. *Foundations of respiratory care*. New York: Churchill Livingstone 1992: 663–78.
30. Coury C. Hippocratic fingers and hypertrophic osteoarthropathy. *Br J Dis Chest* 1960; **54**: 202–9.
31. Spencer RP, Daju JA. Bilateral lower limb uptake of bone scanning agents. *Semin Nucl Med* 1980; **10**: 314–6.
32. Rosenthall L, Kirsh J. Observation of radionuclide imaging in hypertrophic pulmonary osteoarthropathy. *Radiology* 1976; **120**: 359–62.
33. Donnelly B, Johnson PM. Detection of hypertrophic pulmonary osteoarthropathy by skeletal imaging with ^{99m}Tc-labeled disphosphonate. *Radiology* 1975; **114**: 389–91.
34. Scalon GT, Clemett AR. Thyroid acropachy. *Radiology* 1964; **8**: 1039.
35. Ediken J, Hodges PJ. New bone production and periosteal reaction. In: *Roentgen diagnosis of diseases of bone*. Baltimore, MD: Williams & Wilkins 1973: 39–54.
36. Uchisako H, Suga K, Tanaka N, *et al*. Bone scintigraphy in growth hormone-secreting pulmonary cancer and hypertrophic osteoarthropathy. *J Nucl Med* 1995; **36**: 822–5.

(Received 20 March 2001; revised form accepted 5 August 2001)