

## A Case of Hypertrophic Osteoarthropathy Associated with Nasopharyngeal Carcinoma in a Child

Hypertrophic osteoarthropathy is characterized by clubbing of the digital tips and periosteal reaction of long bones. Most of the cases are associated with malignancy or other conditions such as congenital heart disease, liver cirrhosis, pulmonary fibrosis, biliary atresia, and gastrointestinal polyps. Hypertrophic osteoarthropathy associated with malignancy is rare in children. A few cases of hypertrophic osteoarthropathy in children with nasopharyngeal carcinoma have been reported, however, there has been no report of such case in Korea. We present a case of hypertrophic osteoarthropathy associated with nasopharyngeal carcinoma with lung metastasis in a 14-yr-old boy. In this case, hypertrophic osteoarthropathy regressed after intensive chemotherapy, but subsequently the patient died of progressive lung metastasis.

**Key Words :** *Osteoarthropathy, Secondary Hypertrophic; Nasopharyngeal Neoplasms*

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Received : 18 September 2002  
Accepted : 3 December 2002

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## INTRODUCTION

Hypertrophic osteoarthropathy (HOA) is a condition characterized by periosteal reaction of tubular long bones, characteristic bulbous deformity of the digital tips, and synovial effusion (1). HOA in malignancy is very rare in children. To date, only 30 cases of HOA in association with childhood neoplasia have been published (2-5). Among them 12 patients had carcinoma of the nasopharynx, 8 had an osteosarcoma, 5 had Hodgkin's disease, 3 had a carcinoma of the thymus, 1 had a periosteal sarcoma, and 1 had a mesothelioma of the pleura. Most of the patients had abnormalities of the lung, mediastinum, or pleura during the course of the disease but only 6 had no abnormalities. We experienced a case of HOA, associated with nasopharyngeal carcinoma with lung metastasis in 14-yr-old boy, which regressed after intensive chemotherapy. Here we report our case with a short review of the literature.

## CASE REPORT

A 14-yr-old boy was admitted in October 2000 with a diagnosis of undifferentiated nasopharyngeal carcinoma. There was no evidence of metastasis on chest radiographs or bone scintigraphy. The patient staged as III and treated with combination of radiation (125 cGy twice a day, for a total of 7,000 cGy) and chemotherapy (five days of treatment with 12 mg/m<sup>2</sup> of cisplatin per day and 600 mg/m<sup>2</sup> of fluorouracil per day during weeks 1 and 6 of irradiation). In addition, two cycles of cisplatin and fluorouracil were given to him after the comple-

tion of radiotherapy according to the protocol of the Duke Comprehensive Cancer Center (6). With these treatments the tumor size decreased partially.

In February 2001, the patient visited our hospital for polyarthralgia. On physical examination, swelling and tenderness of both lower legs and hands, local heat on both lower legs, and clubbing of the fingers and toes were noted (Fig. 1). There was no evidence of synovial effusion. Laboratory findings were as follows; serum alkaline phosphatase 606 IU/L, erythrocyte sedimentation rate 62 mm/hr, C-reactive protein 5.7 mg/dL, weakly positive (1:40) result for antinuclear antibody, and negative for rheumatoid factor. In radiography of the long bones, periosteal reaction was seen along the bones of both legs (Fig. 2). Bone scintigraphy showed increased uptake along the cortical margins of long bones (Fig. 3). Regular follow-up for malignancy showed no evidence of recurrence or metastasis. One month later, on the subsequent chest radiography, pleural effusion was noted. Histological examination of pleural fluid was negative for malignancy. However, computed tomography (CT) of the chest showed significant pleural effusion, metastatic lymphadenopathy in the right supraclavicular area, and multiple nodular densities in left lower and right upper lungs, which would represent metastatic lesions probably.

The chemotherapy protocol was changed to paclitaxel and carboplatin for lung metastasis. After 4 cycles of chemotherapy, chest CT and bone scintigraphy were done. Chest CT revealed mixed response by decreased size of multiple metastasis and increased size and extent of lymphadenopathy on the left para-aortic and AP window area. But the previous parallel tract sign was not shown by follow-up bone scan (Fig. 4), and the

patient did not complain of arthralgia. Digital clubbing was still noted. Chemotherapy protocol was further changed 3 times, but lung metastasis progressed. In March 2002, the patient died of progressive disease.

## DISCUSSION

HOA is a rheumatic disorder characterized by digital clubbing, periostosis of tubular bones, and synovial effusions, which are most prominent in large joints. Periostosis is usually accompanied by tenderness of the involved area. It can be divided into primary HOA, which is not associated with any other medical conditions and secondary HOA, which can be further divided into pulmonary and non-pulmonary causes. Primary HOA is known as pachydermoperiostosis and trans-



Fig. 1. Clubbing deformity. There was clubbing of fingers.

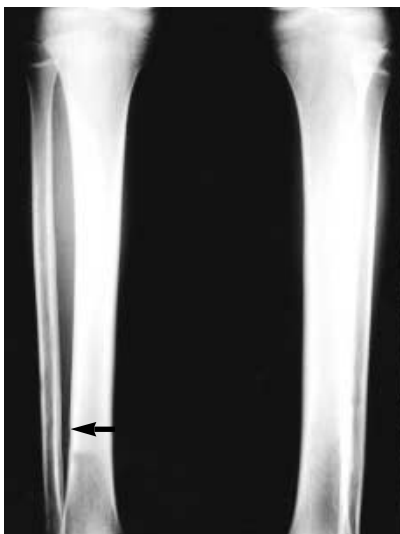


Fig. 2. Periosteal reaction. Thin opaque lines of new bone formation (arrow) are noted along the bones of both legs.

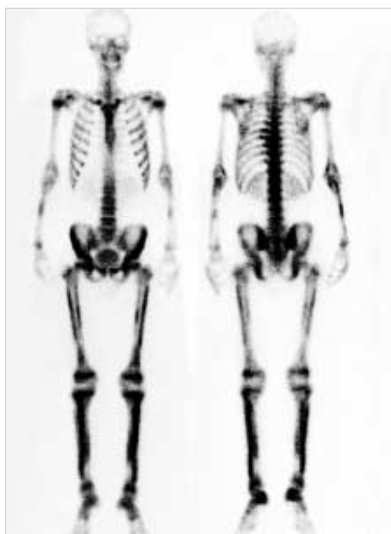


Fig. 3. Parallel tract sign. Bone scintigraphy shows intensive symmetrical uptake of radioisotope along the cortex of long bones.

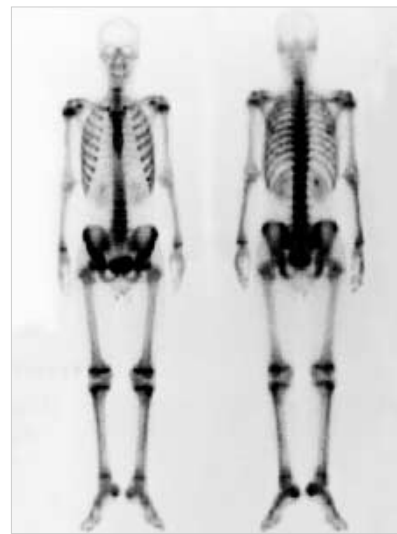


Fig. 4. Disappearance of the parallel tract sign. The increased uptake of radioisotope along the cortex of long bones disappeared on follow-up bone scintigraphy. We could verify the resolution of HOA.

mitted as an autosomal dominant trait (2). In secondary HOA, common pulmonary causes include cystic fibrosis, pulmonary fibrosis, primary or metastatic carcinoma, and mesothelioma. The most frequently associated non-pulmonary causes include congenital heart disease, liver cirrhosis, infective endocarditis, inflammatory bowel disease, gastrointestinal polyps, Grave's disease, and thalassemia (1, 2, 7). In children, 12% of those with HOA have a neoplastic disease while in adults the figure is 92% (8).

HOA associated with malignancy is very rare in children. From 1890 to 2002 only 31 children, including our case, under the age of 18 with malignancy and associated HOA have been reported (2-5). Among them, 13 cases had nasopharyngeal carcinoma. HOA may precede the discovery of recurrence or metastasis of primary malignancies by 1 to 18 months (2). In our case, HOA appeared prior to symptoms and signs associated lung metastasis by 1 month and in fact led to its discovery.

Although the pathophysiology of HOA is still unknown, significant advances in the understanding of HOA have been made in recent years. Two different theories have been forwarded to explain the pathophysiology of HOA. The neurologic theory that stimulation of the vagal neural arc as an etiologic factor is suggested by reversal of the syndrome after vagotomy (9). On the other hand, the humoral theory is to explain HOA on the basis of circulating factors in the venous circulation, which are usually removed or inactivated by the lungs (1, 10). In diffuse pulmonary fibrosis or lung cancer, a growth factor derived from abnormal tissue enters the systemic circulation and induces clubbing. The fibroblast growth factor could be the etiologic factor of the syndrome (11). In the cases of right-

to-left shunts of blood, megakaryocytes escape the normal fragmentation in the lung and reach the distal extremities, activating endothelial cells, releasing fibroblast growth factors (e.g., platelet-derived growth factors) (12). The vascular component is thought to be primarily neurogenic, while abnormalities in osteogenesis are believed to be humorally mediated (9). We believe that in our case growth factors produced by metastatic lung lesion induced abnormal proliferation of skin and osseous tissues at the distal parts of the extremities. Unfortunately, however, we did not measure the growth factors.

Differential diagnoses between HOA and coexisting bone metastasis should be made with caution. Bone scintigraphy is the most sensitive tool to distinguish between these two disease entities. Intensive symmetrical uptake of radioisotope along the cortex of long bone (so-called 'parallel tract sign') is typical of HOA (9). Plain radiographs, demonstrating prominent periosteal reaction, were also helpful for the differential diagnosis. In our patient HOA could be diagnosed by radiographic evidence of periosteal reaction and combined digital clubbing.

Many authors have reported that the treatment of HOA is elimination of the underlying condition and vagotomy. In addition, new bone formation often regresses after control of primary disease, but digital clubbing may persist (2, 9, 13). However, the prognosis of malignancies with HOA is poor and the malignancies are incurable in most cases. In our patient, HOA regresses during intensive chemotherapy but the disease status was progressive. Fourteen months after the discovery of HOA and lung metastasis, the patient died of progressed lung and pleural metastases.

In summary, we present a case of HOA associated with nasopharyngeal carcinoma with lung metastasis in a 14-yr-old boy. HOA occurring with malignancy is very rare in children. The appearance of HOA in a child with a malignancy has been reported to be a poor prognostic sign. HOA may precede the development of lung metastasis such as in our case. Therefore, we suggest that close follow-up is necessary for early detection of disease progression in malignant patients with HOA.

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