Case Report

Hypertrophic Pulmonary Osteoarthropathy Associated with Disease Progression in Renal Cell Carcinoma

Hyperfrophic osteoarthropathy (HOA), also called hypertrophic pulmonary osteoarthropathy, produces systemic or paraneoplastic manifestations of malignancies and is usually accompanied by clubbing of the digits. Many malignancies have been associated with HOA/clubbing, most being lung cancer and lung metastases from renal cell carcinoma (RCC). HOA occurs one year after the metastasis. Reviewing the literature, only five cases of RCC with HOA have been reported. If their clinical history was traceable, they consistently had disease progression. We reviewed the pathogenesis of HOA/clubbing and linked the prognosis of RCC to relevant cytokines. Therefore, HOA not only heralds a progression of disease but suggests a possible therapeutic choice by targeting some cytokines.

CASE REPORT

A 53-year-old male, who first presented with hematuria and was diagnosed to have renal cell carcinoma of the right kidney, received right nephrectomy in 1975 in another hospital. A lung tumor was noted in 1997 on a chest X-ray, which revealed a 3.5-cm mass over the right lower lung field just adjacent to the pleura. Computed tomography (CT) of the chest and ultrasonic-guided biopsy revealed an adenocarcinoma with positive vimentin and cytokeratin immunohistological stains compatible with renal cell carcinoma found previously. Further abdominal CT scan and whole body bone scan showed no other tumor recurrence. No heart disease could be de-
ected from his medical history, physical examination or image study. However, the patient refused any treatment.

He was then lost to follow-up until October 2000, when he was seen again with the complaints of bilateral knee pain and ankle discomfort for 2 years. Physical examination revealed bilateral clubbing of the fingers and toes as shown in Fig. 1. This phenomenon could also be traced back 2 years. However, no sign of clubbing could be detected by history among his relatives. Mild joint swelling with out periarticular erythema was noted over bilateral knees and ankles. No typical morning stiffness was recognizable. Serum rheumatoid factor was undetectable (< 20.0 IU/mL). Roentgenograms of the extremities disclosed the characteristic signs of hypertrophic osteoarthropathy with periosteal reaction over the tibiae, fibulae and forearms with marked thickening of the cortex (Fig. 2). Cortical irregularities and new subperiosteal bone formation were also found. The bone scan showed symmetrical enhanced periosteal uptakes along the shafts of tibiae and fibulae. Since there was no roentgenological evidence of bone metastasis and the bone scan did not favor a local metastasis of RCC, HOA was diagnosed with the typical findings of periostitis and clubbing. Mean while, serum alkaline phosphatase of this patient was mildly elevated to 116 U/L (normal, < 100). Chest film revealed a lengthened diameter in the aforementioned metastatic tumor to 8 cm accompanied by some pleural effusion. The patient was then prescribed non-steroid anti-inflammatory drugs, which relieved him a little from pain at joints and bones. Because the patient still refused any further treatment including surgery or immunochemotherapy, supportive care was given only. Unfortunately, hypercalcemia was found 10 months later (August 2001). In addition to persistent enlargement of his lung lesion, brain metastasis and multiple metastases to lymph nodes at neck were found in Jan. 2002. He eventually succumbed to metastases of RCC in May 2002. This patient exhibited disease progression in a more rapid course than before HOA was diagnosed.

**DISCUSSION**

Hypertrophic osteoarthropathy (HOA), also called hypertrophic pulmonary osteoarthropathy, is a systemic or paraneoplastic manifestation of diseases involving the lung. In 1992, International Workshop on HOA in Florence, Italy established a consensus for the diagnosis,
Clubbing fingers and periostosis are defined as the major signs and pachydermia, synovial effusion, seborrhea, folliculitis, hyperhidrosis, hypertrophic gastropathy and achorrosteolysis as the minor signs. This syn drome can be primary (hereditary) or secondary (acquired). For those secondary to malignant diseases, the origins commonly seen are neoplasms of lung, heart, liver, intestine, mediastinum, esophagus and thy mus. Non-pulmonary malignan cies can be the origins but less frequently. HOA may also come from the non-malignant diseases such as cyanotic heart dis ease, cystic fibrosis, pulmo nary fibrosis, chronic lung infection, cirrhosis and inflammatory bowel dis ease, etc. In this case, HOA sec ond ary to metastatic RCC was di ag nosed. Pri mary HOA had been ruled out by a neg a tive he red i tary his tory and the pres ence of the intrathoracic metastasis of RCC. Benign diseases, which may cause HOA, were also ruled out by his past history and systemic ex aminations. Rheumatoid arthritis was ruled out for the ab sence of rheu ma toid fac tor and lack of typ i cal radio log i cal change in rheu ma toid ar thritis such as car ti lage ero sion or juxta-articular os teo por osis, etc. As aforementioned, bone metastases were not un ly for the lack of roetgenological ev i dence and be cause dis tri bu tion of in creased up take in bone scan was sym met ri cal and along the long axis of tib iae and fib u lae.

It is un clear whether clubbing alone re pr e sents a part of the HOA syn drome or is a sep a rate entity. How ever, the constellation of clubbing, including arthralgias, synovitis and periostosis, comprising the syndrome of HOA fa vorably indi cates that clubbing is a man i festa tion of HOA. At least, clubbing shares the same etiology as HOA to a consid er able ex tent.

Reviewing the literature, Firooznia et al. first re ported the re la tion ship between HOA and RCC in 1975. He de scribed that one of 47 cases of lung metastases from extrathoracic tumors was associated with HOA. However, Wilmshurt et al. de scribed RCC with HOA clubbing in the ab sence of pulmo nary metastasis in 1979. We re viewed the liter a ture since then and found only five cases of renal cell car cinoma associated with HOA. Our case would be the sixth case re ported in the litera ture. Reviewing all cases in cluding ours, HOA/clubbing in RCC cases was al ways as so ci ated with dis ease progression and often pre dated metastasis. Once metastases were established, prognoses were usually poor un less met a static le sions could be re moved. Successful treat ment of RCC and its lung meta statics with sur gery, radio therapy or che mo therapy seemed able to ame li o rate HOA symp toms. The roentgen gra ms of HOA usu ally showed e le vated periosteum with new bone deposited beneath the perios teum while endosteal bone is resorbed, which causes ir reg u larities in the cortex. Symmetric in volve ment of the larger joints of the knees, an kles and wrist is most com mon and usually in volves bones adja cent to the aforementioned joints, in cluding the dis tal ends of the meta car pals, meta tar sals and long bones of the extremiti es. The roentgeno gram of ex trem i ties of our pa tient showed typ i cal find ings of HOA at the tib ia and fib u lae (Fig. 2).

The pathogenesis of HOA/clubbing re mains un clear. Most in ves ti gators now fa vor a role of hum oral me di a tors. In con trast, a neurogenic me chan ism, which once pre vailed, me di ated by a re flex with the vagus nerve as an af fer ent limb was rarely cited in the last de cade. The hum oral the ory pos tu lates that some tu mors pro duce hor mone-like sub stan ces capa ble of stim ulat ing new periosteal growth. These humoral sub stan ces in clude platelet derived growth fac tor (PDGF), transforming growth fac tor-β (TGF-β), and vascular endo the li al growth fac tor (VEGF), all found to be sig nifi cantly ele vated in sera of HOA patients. Earlier studies fo cused on the po ten tial role of plate lets and en do the lium in the pathogenesis of HOA. Lo cal ized ac ti va tion of en do the lial cells by ab nor mal plate lets or of platelets per se leads to the en su ing re lease of these growth fac tors. Some in vestigators hypo the sized that the ab nor mal plate lets come from pe riph eral im pa ction of me ga karyocytes and platelet clumps in the fin gers and toes, to which this par tic u late mat ter has passed in an ax ial stream. The nor mal pul mo nary vas cu lar bed re tains these large par ti cles, which then frag ment before en ter ing the sys temic cir cu la tion. Another hyp o the sis sug gests that one or more growth fac tors, which cause HOA in the sys temic cir cu la tion, are nor mally in ac ti on in the lungs. Thus, a right-to-left shunt or an arteri o venous anasto mosis in the tu mor bed may al low the growth fac tors or ab nor mal plate lets to by pass the pul mo nary vas cu lar bed. Among
the three afore mentioned growth factors, PDGF is a major mitogen for connective tissue cells and certain other cell types. Its known effects are nearly sufficient to explain the pathological changes in clubbing and HOA.\textsuperscript{12,13} VEGF and TGF-\(\beta\), however, could better explain the poor prognosis of the appearance of HOA/clubbing in RCC. RCC is one malignantancy most frequently affected by cytokine therapy.\textsuperscript{14} VEGF and TGF-\(\beta\) may exert their effects by immunosuppression and cytokine modulation. VEGF and TGF-\(\beta\) are two immunosuppressive cytokines produced in tumor growth environments that may both lead to inhibition of T-cell growth and cytotoxic T lymphocytedifferentiation.\textsuperscript{15} TGF-\(\beta\) can have additional effects of induction of T-cell energy, downregulation of cytotoxic potential, inhibition of antigen presentation, shifting of the Th1-Th2 balance to favor Th2, and downregulation of adhesion/costimulatory molecules.\textsuperscript{15} In view that patients with RCC tend to produce Th2-related cytokines in accord with stage and grade,\textsuperscript{16} it is possible that VEGF and TGF-\(\beta\) play a role in disease progression of RCC with HOA/clubbing.

In conclusion, HOA/clubbing may arise as a remote paraneoplastic effect of RCC. Since HOA/clubbing may predate metastasis, searching for early metastasis to cure the disease is important. Meanwhile, HOA/clubbing is associated with disease progression and related to some cytokines as aforementioned, tar geting as so ci ated cytokines may offer an alternative immunotherapeutic approach for metastatic RCC.

REFERENCES