Hypertrophic osteoarthropathy (HOA) is a syndrome characterized by digital clubbing and periosteal proliferation of the tubular bones. Digital clubbing is the oldest clinical sign in medicine, and remains one of most definitive physical findings in clinical practice. Its recognition in a patient usually signifies the presence of a severe internal illness.

Recent evidence suggests that vascular endothelial growth factor (VEGF) may play a key role in the pathogenesis of HOA. Overexpression of this cytokine may explain the histologic alterations underlying HOA, and the mechanisms whereby disparate hypoxic and neoplastic diseases may induce this unique syndrome. We describe a case of pulmonary HOA with abnormal VEGF expression. Removal of the tumor led to disappearance of HOA and to reduction of circulating concentrations of VEGF.

CASE REPORT

A 44-year-old woman had a 4 year history of progressive diffuse bone pain that became unresponsive to different antiinflammatory and narcotic medications. In the 6 months prior to admission, she noted digital clubbing and generalized malaise. In this period, she lost 12 kg of weight. She had smoked one package of cigarettes per day for the last 20 years.

Examination showed a pale, chronically ill looking woman with normal vital signs. Examination of her chest and abdomen was unremarkable. She had marked clubbing of her 20 digits with a digital index of 11.1 (normal < 10). There was prominent tenderness at palpation of the long bones, particularly on tibias and radii, with no synovial effusions.

Chest radiographs showed a poorly defined left apical mass. Bone radiographs revealed periosteal proliferation on tibias and fibulae (Figure 1) as well as acroosteolysis. Additional imaging studies showed no evidence of metastatic seeding. ELISA revealed serum VEGF levels of 1061 pg/ml (normal range in our laboratory 8.9–250 pg/ml); plasma VEGF levels were 390 pg/ml (normal 0–26 pg/ml).

Histochemical studies of the excised tumor confirmed abnormal VEGF production.

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A wide surgical excision of the lung mass was performed. Histology confirmed large cell adenocarcinoma. Immediately after surgery, there was a dramatic disappearance of bone pain. The clubbing deformity of her fingers regressed from 11.2 to 10.2. Serum VEGF levels fell to 524 pg/ml and plasma levels to 25 pg/ml. Immunohistochemistry study of the lung mass showed positive signals for both VEGF and VEGF receptor on the surface of large cells (Figure 2). Semiquantitative reverse transcription-polymerase chain reaction (RT-PCR) of the resected lung tumor showed increased VEGF mRNA expression in a proportion 45% greater than normal control lung tissue (Figure 3).

At followup one year after surgery, the patient was asymptomatic, with no digital clubbing.

**DISCUSSION**

HOA is characterized histologically by vascular hyperplasia, edema, and excessive fibroblast and osteoblast proliferation. These abnormalities are located preferentially at the most distal parts of the extremities.

HOA is induced by a variety of severe internal illnesses, particularly by hypoxic diseases with right-to-left shunts of blood such as cyanotic heart diseases or the hepatopulmonary syndrome of advanced liver cirrhosis. Diverse types of lung cancers also induce this acropathy. Additionally, HOA may develop with no underlying illness; such cases are classified as having primary HOA.

Substantial advances in understanding the mechanisms that lead to HOA have been made in recent years. An iconoclastic mathematical theory proposed that in normal circumstances all platelets are formed in the lung as a consequence of progressive megakaryocyte fragmentation in the highly subdivided pulmonary circulation. It was proposed that in pathologies with right-to-left shunts of blood, a large proportion of megakaryocytes would not break up in the lung vasculature; instead they may gain direct access to the systemic circulation, affecting the most distal sites, there activating endothelial cells and inducing clubbing through the release of tissue growth factor(s). For lung cancer, it was postulated that a tumor-derived growth factor could gain direct access to the systemic circulation and thus inducing clubbing. This hypothesis is supported by the finding that patients with HOA associated with cyanotic heart diseases have giant platelets with bizarre volumedistribution curves as well as megakaryocytes trapped inside the glomeruli. Further, such patients have signs of enhanced platelet/endothelial cell activation, indicated by elevated circulating concentrations of von Willebrand factor antigen.

VEGF has several characteristics that fit well into the pathogenesis of HOA: it is one of the platelet-derived growth factors; its action is induced by hypoxia. Diverse types of cancer growths produce VEGF as a mechanism of tumor dissemination. These features can theoretically explain how different hypoxic or neoplastic pathologies can induce excessive circulating VEGF levels. On the other hand, it has been determined that VEGF is a potent angiogenic and permeability-enhancing factor as well as a bone-

![Figure 2. VEGF and VEGF receptor immunolocalization in adenocarcinoma.](https://www.jrheum.org/615-615)
forming agent. VEGF receptors are expressed by bone-forming cells, promoting endochondral bone formation as well as stimulation and migration of osteoblasts. These features may explain the histologic alterations underlying HOA such as vascular hyperplasia, edema, and fibroblast/osteoblast proliferation.

Abnormal VEGF expression is known to occur in different highly vascularized diseases frequently associated with HOA, such as mesothelioma, Graves' disease, inflammatory bowel diseases, and nasopharyngeal carcinoma.

These theoretical considerations are now supported by experimental data. Patients with lung cancer-related HOA and with primary HOA have increased circulating VEGF concentrations compared to healthy controls. Patients with cardiogenic HOA also display elevated values, although the differences with controls did not reach statistical significance.

Studies of VEGF expression in the case reported here suggest that the cytokine may play a major role in the pathogenesis of HOA. Our case had the defining HOA features of digital clubbing and periosteal proliferation of the tubular bones. Her severe symptoms occurred simultaneously with high circulating VEGF levels. Removal of the lung tumor was followed by immediate relief of her bone pain, regression of the clubbing, and marked decrease in circulating VEGF concentrations. Immunohistochemistry and reverse transcription-polymerase chain reaction studies of the excised tumor confirmed intrinsic VEGF production. Investigation of local VEGF expression in the clubbed digits of this patient would have added important information. However, we felt it was inappropriate to ask her to undergo biopsies of her fingers at this time.

Abe et al recently described a case similar to ours, with lung adenocarcinoma, elevated serum VEGF levels, and VEGF production from the tumor cells. We did not measure other types of growth factors, and we note that Hirakata and Kitamura report elevated levels of transforming growth factor-β1 in a group of patients with finger clubbing due to lung cancer.

There are theoretical and experimental data to suggest that the oldest clinical sign in medicine, digital clubbing, and its full expression in HOA may be caused by excessive circulating VEGF, and findings from our case support this view.

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