A Unique Case Report of Hypertrophic Osteoarthropathy Associated With Endometrial Cancer and Literature Review

Yolanda Piña, MD1; Sowmya Nanjappa, MD2; and Ebene D. Hill, MD2

1 University of South Florida Morsani College of Medicine, Florida, United States
2 Moffitt Cancer Center. Tampa, Florida, United States

Abstract

Introduction: In this manuscript, we present an oncological case of hypertrophic osteoarthropathy (HOA) associated with endometrial cancer.

Presentation of the case: A 46 year-old woman with a history of endometrial cancer (ER+/PR+) presented with hemoptysis and severe diffuse muscle and joint pain, intractable to hydromorphone and non-steroidal-anti-inflammatories. She was diffusely tender to palpation, prominently in the bilateral lower extremities. Bone scintigraphy showed diffuse osteoblastic activity in all extremities, most prominent in the tibiae, concordant with HOA. Patient was treated with zoledronic acid (ZA) and ketorolac, achieving adequate pain control.

Conclusion: HOA has been associated with multiple primary malignancies, as well as other medical conditions. Its association with endometrial cancer has been rarely described in the literature. The pathophysiology of this disorder is poorly understood. More studies are needed to further enhance our understanding of this rare disease.

Keywords: Hypertrophic; osteoarthropathy; endometrial cancer; malignancy; pain control; zoledronic acid

Received: June 20, 2017; Accepted: July 27, 2017; Published: August 8, 2017

Competing Interests: The authors have declared that no competing interests exist.

Consent: Consent was taken from the patient for publication of this case report.

Copyright: 2017 Piña Y et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

*Correspondence to: Yolanda Piña, Univerity of South Florida Morsani College of Medicine, United States

E-mail: ypina@health.usf.edu
Introduction

Hypertrophic Osteoarthropathy (HOA; aka Marie-Bamberger’s disease or hypertrophic pulmonary osteoarthropathy [HPO]) is a rare syndrome characterized by abnormal proliferation of the skin and osseous tissue at the distal extremities, digital clubbing, periostosis of long tubular bones, and arthralgias[1, 2]. There is a primary or idiopathic form[3-5], and a secondary form associated with multiple malignancies including, most commonly, pulmonary, nasopharyngeal, esophageal, gastric, pancreatic, mesothelioma, breast phyllodes, renal cell, melanoma, thymic, and Hodgkin’s lymphoma[6-14], as well as with other noncancerous medical conditions discussed later[6, 7, 15-26]. To our knowledge, reports of HOA associated with endometrial cancer are lacking in the literature with only one case reported in 1982[27]. Here we present a case of HOA associated with endometrial cancer.

Case presentation

A 46-year-old Hispanic woman, Gravida 0 Para 0, with a history of Stage IVB endometrial cancer was transferred to our institution for evaluation of dyspnea, hemoptysis, and diffuse muscle and joint pain, eight-to-ten out of ten in intensity and not controlled with IV hydromorphone and naproxen at the previous hospital. She reported a four month history of worsening dyspnea and productive cough with whitish-yellow sputum and intermittent bright-red blood.

She was diagnosed in 2007 with Stage IVB endometrial cancer, >90% estrogen and 70% progesterone receptors positive, and was treated with total abdominal hysterectomy and bilateral salpingo-oophorectomy, followed by four cycles of taxol, doxorubicin, and cisplatin. Her cancer recurred in 2013, requiring debulking and six cycles of taxotere and paraplatin. An ultrasound-guided microwave ablation of a lesion between the diaphragm and liver was performed in 2015. Repeat biopsies of endometrium (i.e., between the liver and diaphragm), peritoneum, and multiple hilar lymph nodes were negative for malignancy. The lesions in the endometrium and peritoneum showed benign fibromuscular tissue with focal inflammation and benign fibroconnective and fibroadipose tissue, respectively.

Her family and social histories were non-contributory. Her home medications were oral daily letrozole 2.5 mg, levothyroxine 25 mcg, and cholecalciferol 10,000 units. Her physical examination was remarkable for clubbing of the hands and severe diffuse tenderness to palpation in all extremities. She was noted to have a fever of 100.5 degrees Fahrenheit on admission, otherwise remained afebrile with no signs of infection. Laboratory values were relevant for normocytic anemia (i.e., hemoglobin 10.9 g/dL) stable compared to prior values from an outside hospital, leukocytosis (i.e., white blood cell count 12.88 k/μL) with a neutrophil count 9.77 k/μL, alkaline phosphatase 145 units/L, CA 125 level 140 units/mL (increased from prior value), and erythrocyte sedimentation rate 92 MM/HR. CPK and TSH were within normal limits.

A posterior-anterior and lateral chest x-ray showed a wedge-shaped segmental right lower lobe opacity. Given this finding in the setting of worsening dyspnea and hemoptysis, a CT scan of chest and bronchoscopy were performed. CT scan showed retropharyngeal, mediastinal and right hilar lymphadenopathy, right middle lobe subpleural nodule, a 5.2 cm ill-defined liver mass, and no evidence of pulmonary embolism. The bronchoscopy did not show evidence of malignancy or source of bleeding with only inflammatory cells observed on cytology.

Given the patient’s severe diffuse pain, a bone scintigraphy was performed, which revealed
diffuse increased periosteal osteoblastic activity within the upper and lower extremity cortices, most prominent within the bilateral tibiae, concordant with HOA (Fig. 1). There was no evidence of central skeletal system foci of abnormal increased osteoblastic activity.

**Figure 1** Bone scintigraphy. Findings of diffuse increased periosteal osteoblastic activity within the upper and lower extremity cortices bilaterally, which was most noticeable within the tibiae bilaterally. These findings are consistent with hypertrophic osteoarthropathy. No evidence of central skeletal system foci of abnormal increased osteoblastic activity was identified. A. Anterior view. B. Anterior view with increased radioactive tracer technetium-99m HDP. C. Posterior view. D. Posterior view with increased radioactive tracer.

A positron emission tomography (PET) CT scan was performed and compared to prior imaging. It showed progression of metabolically active neoplastic disease within the liver, right proximal retroperitoneal, and mediastinal lymph nodes; and new metabolic activity within the right superior mediastinal lymph nodes. No hypermetabolic lytic/blastic lesions were identified in the skeleton.

Upon initial presentation, her severe pain was treated with morphine 15 mg orally every 12 hours and oxycodone 5 mg orally every 6 hours; however, the pain persisted. Once the patient was diagnosed with HOA, she was treated with a single dose of zoledronic acid (ZA) IV 4 mg and ketorolac 15 mg IV every 6 hours. Her pain significantly improved after 48 hours of treatment, with a decrease in intensity to a three out of ten. Also, given her initial fever, leukocytosis, and lung findings, she was treated with levofloxacin 750 mg orally every 24 hours for ten days. She was discharged with naproxen 500 mg orally every 12 hours and methylprednisolone 4 mg Medrol dosepak for six days.

While inpatient, she was evaluated by specialists from gynecology-oncology, gastrointestinal and thoracic surgery, who deemed her to be inoperable. She was discharged to follow up with her local oncologist for further management, including starting systemic chemotherapy.

**Discussion**

HOA is a rare syndrome characterized by digital clubbing, periostosis of long tubular bones, and mild-to-severe arthralgias that typically involve the elbow, wrist, metacarpal, knee, and ankle joints[1, 2]. It can be classified as primary (a.k.a. pachydermoperiostosis) or secondary, the latter accounting for 95% of cases. The primary form is a rare genetic condition, which typically presents with pachydermia in addition to clubbing and periostosis[3-5].
The secondary form has been associated with a wide range of medical conditions, where non-small cell lung cancers (i.e., squamous cell or adenocarcinoma) predominate accounting for 80% of HOA cases[6, 7]. Pulmonary metastasis is a rare cause of HOA, but has been reported from primary tumors such as osteosarcoma, fibrosarcoma, nasopharyngeal, and uterine cancers[2, 28]. HOA has also been linked to other primary malignancies such as nasopharyngeal, esophageal, gastric, pancreatic, mesothelioma, breast phyllodes, renal cell, melanoma, thymic, Hodgkin’s lymphoma[6-14]. To our knowledge, only one case of HOA associated with endometrial cancer has been reported[27]. In addition, HOA has been described secondary to non-malignant conditions such as inflammatory bowel disease, rheumatic diseases, cyanotic congenital heart diseases[6, 7, 15-17], liver disease[18-21], and chronic infections associated with bacterial endocarditis, tuberculosis, cystic fibrosis, syphilis, vascular prosthesis, and immune deficiency syndrome[6, 7, 22-26].

Its pathogenesis remains to be elucidated. Different hypothesis have been postulated related to circulating signals based on disease resolution after removal of the underlying causative agent (e.g., chemotherapy, tumor resection). One hypothesis is the localized activation of platelet-endothelial cells, with subsequent release of fibroblast growth factors (e.g., platelet-derived growth factor [PDGF]). Produced by different cell types (i.e., macrophages, monocytes, smooth muscle cells, vascular endothelial cells), PDGF is involved in inflammation, wound healing, and angiogenesis[29]. PDGF was demonstrated to be overexpressed in HOA[30]. It was postulated this to be due to (1) disorders with right-to-left shunt enabling megakaryocytes to bypass the lungs’ circulation and enter the systemic circulation, fostering new bone development, edema, and vascular proliferation in the extremities via production of PDGF[1, 5]; (2) tumor release of PDGF[31]; and/or (3) illnesses associated with HOA stimulating PDGF development via inflammatory cytokines[32].

Vascular-endothelial growth factor (VEGF) was also found abnormally elevated in secondary HOA associated with lung cancer[1], possibly as a consequence of its production by the tumor given that VEGF is predictably increased in a number of solid tumors[33]. Induced by hypoxia in the rapidly growing solid tumors, VEGF stimulates angiogenesis and vascular permeability[33-35]. VEGF has also been postulated to stimulate bone formation by mediating osteoclasts and osteoblasts function[36].

HOA treatment involves treating the underlying cause and/or supportive management. Nguyen et al. (2011), from a comprehensive systematic literature review of secondary HOA, reported effective treatments to incorporate primary therapies that resulted in symptom resolution, such as tumor resection, radiotherapy, chemotherapy, organ transplantation, antibiotics or other treatments for infection, and surgical correction of cyanotic heart disease. They also reported supportive therapies when the underlying cause could not be targeted, which successfully led to symptom control. These included vagotomy, adrenergic antagonist, bisphosphonates (i.e., pamidronate or zoledronic acid [ZA]), NSAID’s (e.g., ketorolac, indomethacin), octreotide, and EGFR inhibitors (i.e., gefetinib)[37].

Bisphosphonates have a high affinity for bone, where they inhibit osteoclast activity and bone resorption[38]. The effective use of pamidronate and ZA for pain control in HOA has been reported since 1997[2, 13, 24, 25, 39, 40]. ZA is a newer, more potent bisphosphonate in pre-clinical models of bone resorption, and was shown to have equal or higher efficacy to pamidronate in lytic and blastic disease[41, 42]. In a case of HOA associated with nasopharyngeal cancer, a single dose of 4 mg of ZA IV resulted in pain resolution and swelling reduction[2]. ZA is a nitrogen-containing bisphosphonate that selectively builds in areas of active bone remodeling by binding to hydroxyapatite crystals, and subsequently inhibit osteoclastic bone resorption and induce osteoclast apoptosis via inhibition of farnesyl diphosphate synthase. Its selectivity for bone and not other tissues bestows this drug with a great safety profile and limited side effects[2, 43, 44]. ZA can also have anti-tumor effects by
inducing autophagy, apoptosis, and S phase arrest[45-47], and regulating gene expression mediating inhibition of proliferation, invasion, and angiogenesis[48].

NSAID’s such as ketorolac and indomethacin were also shown to decrease pain in HOA[49, 50]. Even though the pathogenesis of HOA is unknown, the use of NSAID’s relies on aforementioned findings elucidating prostaglandin-induced periostitis in neonates with congenital heart disease[17, 51-53]. Others postulated the theory that COX2-derived PGE2 is involved in the pathogenesis of HOA given the effectiveness of COX2 inhibitors[54]. In our case, the use of ZA and ketorolac significantly improved pain control, which was intractable to high doses of opioids. The patient was discharged to initiate systemic chemotherapy to further treat her HOA.

Conclusion

Most cases of HOA have been associated with several primary malignancies. However, its association with endometrial cancer has been poorly reported in the literature[27]. Herein in the current manuscript, we report a case of a HOA linked to this primary malignancy. The pathogenesis, diagnosis, and treatment of this disease remain poorly elucidated, and more studies are needed to further enhance our understanding of it.

References