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Hypertrophic osteoarthropathy is a paraneoplastic syndrome most often found in non-small cell lung cancer. Diagnosis is confirmed by the presence of clubbing on physical examination and periostitis on bone scintigram, and the syndrome generally resolves with treatment of the underlying malignancy. This article presents a case study and describes symptom management options, including nonsteroidal anti-inflammatory agents, octreotide, and bisphosphonates.

J.C., a 69-year-old African American man with a 30-pack-year smoking history, had no significant past medical issues. In August 2010, he initially noticed bilateral lower extremity joint and bone pain. Within three months, the pain became so severe that J.C. could not get out of bed. He presented to his primary care provider with generalized weakness, marked clubbing in his fingers and toes, swelling at the ankles and knees bilaterally, bilateral tibial tenderness, a 30-pound weight loss over a six-month period, profound fatigue, depression, dyspnea on exertion, and a dry cough. Diagnostic tests included a bone scintigram showing periosteal proliferation in the shafts of the tibiae, femurs, and radii bilaterally, and a chest x-ray, confirming a 9.3 x 9 cm left upper lobe mass. A positron-emission tomography scan with a marked uptake confirmed a 9.3 x 9 cm left upper lobe mass with endobronchial extension into the left upper lobe mainstem bronchus and prominent mediastinal lymph nodes. Transbronchial biopsy of the left upper lobe revealed a poorly differentiated squamous cell carcinoma. Staging work-up with a positron-emission tomography scan and brain magnetic resonance imaging were negative for metastases.

Based on those findings, J.C. was diagnosed with T3N2M0, stage IIIA non-small cell lung cancer with the paraneoplastic syndrome of hypertrophic osteoarthropathy (HOA). His plan of care included surgical resection followed by adjuvant chemotherapy. However, because of J.C.’s poor performance status, he was not a surgical candidate and was treated with six cycles of induction chemotherapy consisting of carboplatin (area under the curve = 5, given on day 1 of a 21-day cycle) and paclitaxel (100 mg/m² given on days 1, 8, and 15 of a 21-day cycle). By the end of the first cycle, J.C.’s pain had completely resolved. He was no longer confined to bed and was able to walk a mile without difficulty. In addition, his clubbing had started to resolve.

Hypertrophic Osteoarthropathy

Paraneoplastic syndromes are rare, heterogeneous disorders that are triggered by cancer or its metastases. Although the etiology is not well understood, symptoms may result from hormones or cytokines released by the tumor, or from the body’s immune response to the tumor. Symptoms occur distant from the neoplasm and can affect almost any system of the body. HOA is one type of paraneoplastic syndrome, characterized by abnormal proliferation of the cutaneous and osseous tissues at the distal parts of the extremities (King & Nelson, 2008). The triad of clinical signs and symptoms includes clubbing, periostitis (inflammation of the connective tissue surrounding the bone), and symmetric polyarthritis (Cosa-Alas et al., 2007; Yao, Altman, & Brahn, 2009).

HOA is classified as either a primary or secondary disease. Primary HOA, also called pachydermoperiostosis, is a rare autosomal dominant disorder. Secondary HOA is more common and can be caused by pulmonary malignancy, chronic respiratory diseases, congenital cyanotic heart disease, chronic inflammation, or hepatic, gastrointestinal, and endocrine disorders (Moralidis et al., 2010). Pulmonary malignancy accounts for more than 80% of secondary HOA cases (Yao et al., 2009). Nonetheless, the incidence of HOA is rare, occurring in 0.7%–4.5% of lung cancers, most often non-small cell lung cancer (Ito et al., 2010; Izumi, Takayama, Yabunuchi, Abe, & Nakanishi, 2010; Yao et al., 2009). HOA may occur prior to the symptoms of the primary malignancy, or it may develop with disease progression (Ito et al., 2010).
Pathogenesis

Although the exact mechanism of HOA is not known, three major theories exist on the pathogenesis. First, the mechanical theory hypothesizes that arteriovenous shunting occurs within the tumor, which allows megakaryocytes to enter systemic circulation and reach distal sites. The large platelet fragments then interact with endothelial cells, leading to the release of growth factors, including platelet-derived growth factor, prostaglandin E, and vascular endothelial growth factor (VEGF). Growth factors cause fibroblast proliferation, increased vascularity, and new bone formation (Ito et al., 2010; Klippel, Stone, Crofford, & White, 2008; Nguyen & Hojjati, 2011; Yao et al., 2009). Second, the biochemical hypothesis theorizes that the tumor releases biochemical compounds, which then cause the symptoms of HOA. Potential contributing compounds may include growth factor, growth hormone-releasing hormone, VEGF, and gonadotropins (Ito et al., 2010). Finally, the neurogenic theory postulates that the tumor stimulates afferent fibers of the vagus nerve. Via the reflex arc, vagal stimuli increase the efferent nerve impulses to the distal extremities. Evidence suggests a unilateral vagotomy on the side of the malignancy, which interrupts the afferent fiber pathway, causes rapid pain relief (Ito et al., 2010).

Diagnosis

Diagnosis of HOA requires the presence of clubbing and periostitis of the tubular bones (Klippel et al., 2008). Clubbing causes a unique bulbous deformity at the distal parts of the extremities, described as a “drumstick-like appearance” (Klippel et al., 2008) (see Figure 1). The onset of clubbing is insidious, and patients often do not recognize this symptom. The periostitis is symmetrical and generally begins in the distal part of the lower extremities, then moves centrally (Klippel et al., 2008; Yao et al., 2009). Although most cases involve the tibiae and fibulae, severe cases can include all the tubular bones (e.g., ulnae, femurs, metacarpals, metatarsals, humeri, clavicles). Patients range from being asymptomatic to having debilitating bone and joint pain. HOA may be accompanied by restricted range of motion and synovial effusions, which can occur as a reaction to the adjacent periostitis (King & Nelson, 2008; Klippel et al., 2008). Bone scintigraphy is the most sensitive method for detection and evaluation of HOA-associated periostitis (Moralidis et al., 2010) (see Figure 2). Characteristic findings include symmetric, bilateral increased uptake in the long bones. Although x-ray may also be used to confirm HOA, scinti-graphy is preferred because it can detect abnormalities earlier than x-ray and is able to detect more subtle changes in disease progression or regression (Moralidis et al., 2010). No laboratory abnormalities are specific to HOA (Klippel et al., 2008).

At initial presentation, many patients with HOA are erroneously diagnosed with rheumatoid arthritis or osteoarthritis, given the similarity of symptoms. HOA differs from rheumatoid arthritis in several key ways: the synovial fluid is noninflammatory, the joints have no radiographic erosions, rheumatoid factor is negative, and the pain involves both joints and bone. Unlike osteoarthritis, HOA x-rays do not show joint space narrowing or subchondral sclerosis. In patients with known malignancies, a differential diagnosis of widespread bone metastases should be considered. However, the symmetric nature of the symptoms of HOA and the distinct pattern and location of uptake on bone scan are unique from bone metastases (Klippel et al., 2008; Yao et al., 2009).

Management

Treatment of the underlying condition often resolves HOA (Nguyen & Hojjati, 2011). When HOA is secondary to pulmonary malignancy, treatment options include tumor resection, radiotherapy, and chemotherapy. In addition, patients often require management of HOA-induced bone and joint pain. Case studies report success with nonsteroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors, indomethacin, and ketorolac (Nguyen & Hojjati, 2011). Those medications inhibit prostaglandins, which may have a role in the pathogenesis of HOA. Pain that is refractory to conventional analgesics may be managed with octreotide or bisphosphonates (Nguyen & Hojjati, 2011; Yao et al., 2009). Octreotide inhibits VEGF and endothelial proliferation and has successfully managed refractory pain in two case reports (Johnson, Spiller, & Faull, 1997; Maroto, Martinez-Quintana, Suarez-Castellano, & Perez-Arellano, 2005). A newer option is bisphosphonates, including pamidronate and zoledronic acid (King & Nelson, 2008; Nguyen & Hojjati, 2011; Yao et al., 2009). Those medications
Clinical Journal of Oncology Nursing • Volume 15, Number 5 • Advanced Practice Nursing Issues 563

influence bone metabolism and are known to decrease levels of plasma VEGF in patients with cancer (Nguyen & Hojjati, 2011). One case report found that a single dose of zoledronic acid produced rapid, long-lasting control of symptoms, despite progression of the non-small cell lung cancer (King & Nelson, 2008). However, bisphosphonates increase the risk of osteo-
necrosis of the jaw, and patients should avoid invasive dental procedures while on those medications.

Given the potential role of VEGF in the pathogenesis of HOA, the anti-VEGF agent bevacizumab also may be valuable in the management of refractory HOA (Kozak, Milne, Morrow, & Cuiffo, 2006; Nguyen & Hojjati, 2011). To date, no case studies have evaluated the use of bevacizumab in HOA, which suggests an opportunity for future research.

**Conclusion**

HOA can cause debilitating joint and bone pain, which affects emotional and physical well-being, limits mobility, creates social isolation, and prevents participation in activities of daily living. Ultimately, HOA has a negative impact on quality of life. Given that HOA frequently coincides with a cancer diagnosis or evidence of disease progression, the challenges associated with HOA often are exacerbated by cancer-related distress. Nurses play a vital role in educating patients and families about HOA, providing symptom management, and offering psychosocial support.

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**References**


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*Note. Arrows indicate increased uptake at the radii, ulnae, proximal femur, and fibulae.*

**Figure 2. Posterior View From Bone Scan Indicating Periostitis**


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