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Abstract

Hypertrophic osteoarthropathy is a syndrome that includes finger clubbing, periostitis with new subperioosteal bone formation of long bones and arthritis. It is often related to an intrathoracic neoplasms or chronic infections; hence called hypertrophic pulmonary osteoarthropathy. A primary or idiopathic form, also known as Pachydermoperiostosis, also exist. It is commonly seen in children and young adults and has not been found associated with underlying disease. Platelet derived growth factors has been recently recognized to have a key role in the pathogenesis of this disorder. Hypertrophic osteoarthropathy may cause disabling symptoms. Cure of neoplasia may result in regression of the hypertrophic osteoarthropathy.

Key words

Paraneoplastic disorder; hypertrophic osteoarthropathy; Clubbing; Cancer-associated rheumatic disorder

Introduction

Rheumatic syndromes associated with cancer are generally thought to occur by one of the following mechanisms: paraneoplastic; direct invasion of bone, joint, or muscle by tumor; altered immune surveillance causing both the rheumatic and neoplastic diseases; adverse reactions to anticancer therapy (1) [Table 1]. Paraneoplastic rheumatic disorders are those cancer-associated rheumatic syndromes that occur at a distance from the primary tumor or metastases and are induced by the malignancy through hormones, peptides, autocrine and paracrine mediators, autoantibodies, and cytotoxic lymphocytes (2). The clinical course of paraneoplastic syndromes may precede, appear concomitantly with, or follow the diagnosis of cancer. In addition, the reappearance of the paraneoplastic disorder may be a result of recurrence of cancer. Cure of cancer usually results in regression of the paraneoplastic rheumatic syndrome (1). Hypertrophic osteoarthropathy (HOA) is a paraneoplastic rheumatic syndrome that has been associated with different types of neoplasms, particularly lung cancer. The clinical manifestation consists of a triad of clubbing, periostitis of long bones and arthritis or arthralgia. The physician awareness of HOA and other paraneoplastic rheumatic syndrome is essential for many considerations: these rheumatic disorders can cause a disabling manifestations; a prompt diagnosis of these cancer-associated rheumatic syndromes may facilitate earlier diagnosis of the associated cancer. In this article, the clinical features,
differential diagnosis and management of secondary HOA will be reviewed. The advances in pathogenesis and management of this syndrome are emphasized. Clinical features of hypertrophic osteoarthropathy:

1) Clubbing

Clubbing is the most consistent feature of HOA. It is often asymptomatic and is noticed by a physician on clinical examination. It gives a fluctuant sensation on palpation of proximal nail as a result of softening of the nail bed. It is recognized by Loss of the normal 15 degree angle between the proximal nail and dorsal surface of the phalanx with increased convexity in the sagittal and cross sectional planes (3). An increase in the ratio of the distal phalangeal depth to the interphalangeal depth of the index finger to 1.0 or greater was also thought useful for diagnosis of clubbing (4). At a later stage, “drumstick” appearance and hyperextensibility of the distal interphalangeal joints is seen. The toes can also be involved. Clubbing usually occurs bilaterally but unilateral involvement has been reported in association with aneurismal dilatation of large thoracic arteries, apical lung and axillary neoplasms, aortic insufficiency, hemiplegia, and brachial arteriovenous malformation (3). Clubbing is evident on clinical examination in about one third of patient with lung cancer (5).

2) Periostitis

When symptomatic, periostitis causes severe deep aching or burning pain of the involved distal upper or lower extremities, typically distal ends long bones of the forearms and legs but distal ends of metacarpals and metatarsals may also be involved. The pain, characteristically, is aggravated by dependency of the limb and can be relieved on elevation of the limb. Heat and swelling over the feet and legs may accompany the pain. Tenderness to pressure is often present in the distal end of extremities even when patient is asymptomatic. Additionally, local warmth and mild pitting edema of the affected limb may be present. In severe disease, periostitis involving the ribs, clavicles, scapulae, pelvis and malar bones can occur (6).

3) Arthritis

Arthritis affecting the knees, metacarpophalangeal joints, wrists, elbows and ankles may occur in patient with HOA. Symmetrical, fleeting or constant arthralgia has been described. This may be associated with local warmth, erythema of the overlying skin, swelling and restricted range of motion.

Flushing, blanching and profuse sweating especially of the hands and feet may occur in HOA, suggesting an autonomic dysfunction.

Secondary HOA

The differential diagnosis of secondary HOA includes many intrathoracic and extrathoracic conditions. Pulmonary malignancies and infections represent the most commonly associated etiologies. Other conditions associated with hypertrophic osteoarthropathy are listed in Table 2.

Investigation

Specific biochemistry and immunological tests are generally not required for HOA. Erythrocyte sedimentation rate and C-reactive protein are usually elevated. Rheumatoid factor and antinuclear antibody tends to be negative. When present, synovial fluid is non-inflammatory with clear, high viscosity and low total leukocytic count (< 2000/mm$^3$) with fewer than 50% polymorphonuclear leukocytes (7).

X-ray imaging may characteristically reveal periostitis with new bone formation in the subperiosteal region of distal diaphyseal of long bones (Fig. 1). This occurs mostly in the forearms and legs and less commonly in the phalanges. With prolonged disease, a multiple layers of bone may be deposited in the subperiosteal region giving an “onion skin” like appearance (8). Nuclear imaging with Tc-bisphosphonate bone scan may reveal a pericortical linear accumulation of radiotracer along the long bones (Fig.2) and sometimes along the proximal phalanges. The diffuse and symmetrical distribution of the radiotracer along the pericortical region makes it easily to separate from metastatic deposits (9).
Factors implicated in the development of HOA are generally unknown. Hormonal disturbances, cytokine dysfunction and autonomic dysfunction have been proposed \(^{(10)}\). Recent evidence suggests that vascular endothelial growth factor (VEGF) may play a key role in the pathogenesis of HOA. Normally, megakaryocytes and large platelets clumps are trapped in the pulmonary capillary bed and subsequently fragment into platelets. It is thought that in conditions such as left-to-right shunt or bronchogenic carcinoma, megakaryocytes and platelet clumps may bypass the pulmonary capillary bed and impact distally in the peripheral circulation. As a result, platelet derived growth factors are released \(^{(11)}\). VEGF, a platelet derived growth factor that is released upon hypoxic stimuli, has many vascular and bone stimulating functions such as promoting angiogenesis, increasing permeability across blood vessel wall, and promoting endothelial bone formation. In addition, it activates osteoblast function and migration \(^{(12)}\). Excessive level of VEGF has been demonstrated in the circulation of patients with HOA associated with cyanotic congenital heart disease and lung malignancy \(^{(13)}\).

Pathological features of HOA include edema of the distal digital soft tissue, hyperplasia of the blood vessel walls, fibroblastic and osteoblastic proliferation, and deposition of new collagenous...
Secondary Hypertrophic Osteoarthropathy, Nahar, et al

matrix, resulting in the uniform enlargement of terminal segments \(^{(14)}\).

**Management**

Complete resolution of HOA had been seen with cure of the primary pathology, especially removal of pulmonary tumors. Many patients with HOA have no symptoms, requiring no additional treatment. However, some patient experience disabling pain due to periostitis and arthritis that can be unresponsive to simple analgesia including non steroidal anti-inflammatory drugs. Atropine sulfate by inducing chemical vagotomy, had been tried to alleviate discomfort in resistant cases with good clinical response \(^{(15)}\). Another agent, Subcutaneous octreotide had been reported to improve discomfort associated with HOA resistant to other modalities of treatment \(^{(16)}\). High dose Colchicine was thought to be effective in improving arthralgia associated with HPO, however, it was not tolerated because of drug toxicity and it did not have an effect on finger clubbing \(^{(17)}\). Interestingly, Bisphosphonates (especially non-aminobisphosphonate) has been demonstrated to have an anti-inflammatory activity that leads to inhibition of the release of inflammatory mediators from activated macrophages, such as interleukin-6 and tumor necrosis factor –alpha and interleukin-1. Bisphosphonates have been used in the treatment of several inflammatory conditions including rheumatoid arthritis, ankylosing spondylitis and HOA \(^{(18)}\). Symptomatic relief with biphosphonates especially pamidronate has been demonstrated in many case reports \(^{(19, 20)}\).

Chemotherapy to the primary lesions has been reported to improve symptoms of HOA even when the primary lung lesion was unresectable \(^{(21)}\). In a patient with advanced lung adenocarcinoma resistant to chemotherapy \(^{(22)}\), the use of Gefitinib, a selective epidermal growth factor receptor tyrosine kinase inhibitor, resulted in disappearance of periostitis on bone scan.

In many case reports, radiotherapy to the primary tumor sites had caused partial or complete improvement of clinical or radiological abnormalities. A similar response was not seen when radiotherapy was given locally to affected site, at least from one reported case \(^{(23)}\).

HOA is a syndrome that can be associated with many pulmonary, cardiovascular, gastrointestinal and endocrine diseases. Clubbing, a prominent feature of this syndrome, can help suggest the diagnosis. Other features include periostitis and arthritis which may cause severe symptoms that are difficult to treat. Platelet derived growth factors plays an important role in the pathogenesis of this condition. Diagnosis and treatment of the underlying disease is an important therapeutic goal of HOA.

Fig. 2: nuclear scan imaging showing the uniform deposition of radiotracer along the distal ends of long bones.
References


Hypertrophic osteoarthropathy (HOA) is a syndrome characterized by abnormal proliferation of the skin and osseous tissues at the distal parts of the extremities. Digital clubbing; periostitis of the tubular bones, usually in a bilateral and symmetric way; and noninflammatory synovial effusions are the main features. Key words used in the search were hypertrophic osteoarthropathy, clubbing, periostitis, vascular prosthesis, graft, and infection. Additional case reports were identified from the reference lists of selected articles. Back to Top | Article Outline.