Hypertrophic Osteopathy

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Hypertrophic osteopathy is a pathologic disease process, secondary in nature, which most commonly occurs in humans and in dogs; it has also been noted to occur in the horse, cow, sheep, cat, fowl, and various other more exotic species. Initially described in humans in the late 1800s by Marie(34) and Bamberger,(4) subsequent reports of a similar disease affecting the dog were soon to be found in the European veterinary literature.(3,10,21,39) The disease did not receive notice in the English veterinary literature, however, until the 1920s in Great Britain.(26,27,55,57) Initially described in the dog as a hypertrophic osteoarthropathy related to tuberculosis, its name has changed through the years with increased understanding of the disease's basic pathophysiology and varied primary etiologies.(3,10,51) Thus, it has been referred to as osteoporosis deformans,(51) hyperplastic osteoperiostitis,(51) tuberculosis osteopathy,(39,40,51) Marie's disease of the dog,(13) achropachia,(16) hypertrophic osteoarthropathy (HOA),(5,18) pulmonary osteoarthropathy (POA),(1,35) hypertrophic pulmonary osteoarthropathy (HPOA),(13,22,41) hypertrophic pulmonary osteopathy (HPO),(53) and hypertrophic osteopathy (HO),(33,54) among other terms.(28,48,55)

In the dog the disease is characterized by bilaterally symmetrical, nonedematous soft tissue swellings affecting primarily the distal portions of all four limbs. Insidious in onset and often mistaken for early "arthritis," the initial soft tissue swellings are soon accompanied by a diffuse periosteal new-bone formation, which may ultimately affect all the bones of the limbs, resulting in severe disability. These skeletal changes are merely an outward manifestation of some underlying systemic disease, usually neoplastic in nature. Since most cases of hypertrophic osteopathy are associated with some form of pulmonary disease, the syndrome has most commonly been referred to as hypertrophic pulmonary osteoarthropathy. However, not all cases result from pulmonary lesions and in reality there is seldom an arthropathy associated with the disease, since the bony changes rarely involve articular surfaces.(7) Similarly, synovial changes are seldom observed.(23) For these reasons, some authors prefer the term hypertrophic osteopathy.(5,32,54) Regardless, a predominant number of dogs afflicted with hypertrophic osteopathy do, in fact, suffer from some kind of pulmonary disease, most commonly pulmonary neoplasia (55 of 60 dogs in one report).(5) Metastatic pulmonary lesions remain the most common cause of hypertrophic osteopathy in the dog,(5,29,31,48,50) although numerous cases of hypertrophic osteopathy occurring as a sequel to primary pulmonary neoplasia have been reported.(1,14,35,41,46,50) Dogs with primary tumors of the lung or primary tumors of bone (with lung metastases) appear to have a much higher frequency of hypertrophic osteopathy than do those with pulmonary metastasis secondary to other forms of neoplasia. Also, hypertrophic osteopathy seems unusually prevalent in those animals that have undergone primary amputation for osteosarcoma and have subsequently developed lung metastases (26% in one study).(5) In addition to occurring as a sequel to pulmonary neoplasia, hypertrophic osteopathy has also been reported in the dog as a complication of pulmonary abscess,(29,30) chronic bronchopneumonia,(15,29) infectious granuloma of the pulmonary parenchyma,(29) and as mentioned earlier, pulmonary tuberculosis.(27,29)

Spirocercosis, a disease predominant in the southeastern portions of the United States, has also been reported to not infrequently result in the development of hypertrophic osteopathy.(2,43) The disease is characterized by esophageal
granulomas, aortic aneurysms, and caudal thoracic ossifying spondylitis resulting from infection with and migration of larval and adult forms of this parasite.(2,5,37) Chronically infected animals can develop hypertrophic osteopathy as a sequela to the esophageal granuloma itself, but more commonly this disease results from the esophageal sarcomas (fibrosarcoma and osteosarcoma) that invariably seem to develop when this nematode is present in the hilar esophagus. Pulmonary metastasis need not be present for hypertrophic osteopathy to occur.(47) Although the granuloma and resultant neoplasm generally result in the demise of an infected dog, one case of a dog infected with Spirocerca lupi has been documented in which the esophageal granuloma has regressed while the clinical signs of hypertrophic osteopathy have remained static for at least 2.5 years.(2,5,29,37)

Other intrathoracic diseases, nonpulmonary in nature, that have resulted in hypertrophic osteopathy include dirofilariasis (Dirofilaria immitis), rib tumors, and bacterial endocarditis.(5,14,29,42,50,53) The disease has also been produced experimentally in dogs by anastomosis of either the pulmonary artery or the inferior vena cava to the left atrium.(7,36) The disease has been reported as a sequela to adenocarcinoma of the liver in one dog in whom there were no signs of metastasis to the lungs. It has also been described in dogs suffering from pulmonary neoplasia of the bladder (neurofibrosarcoma, botryoid rhabdomyosarcoma, transitional cell sarcoma, and undifferentiated sarcoma) both with and without pulmonary metastasis.(5,7,20,33,50)

CLINICAL PRESENTATION
Because hypertrophic osteopathy occurs secondary to a variety of disease processes, data concerning breed, sex, and age distribution have little meaning. Those figures that have been generated are readily explained in light of neoplasia being the primary cause of the underlying disease process. Boxers are an overrepresented breed, but their propensity for primary tumors of lung and bone is apparent.(5) Females tend to be more frequently affected, most likely reflecting an overall incidence of mammary cancer. The general age of afflicted animals is approximately 8.5 years, except for those animals suffering from pulmonary tuberculosis or bladder rhabdomyosarcomas, who are characteristically affected earlier in life. (5,29-35) Larger breeds of dogs have been reported to be affected more frequently,(29,35) perhaps a reflection of the incidence of primary bone tumors in these animals. Clinical laboratory findings, for similar reasons, reflect primarily the underlying disease process that is occurring and are not characteristic of hypertrophic osteopathy.(29)

The majority of affected animals are presented to the clinician with complaints of lameness and reluctance to move about. They invariably exhibit symmetric, nonedematous and firm swellings of the distal portions of all four legs (Fig. 51-1). On physical examination, the limbs are generally warm to the touch, often pulsatile and sometimes painful upon deep digital palpation.(2,35) The normally loose skin over the metacarpal and metatarsal regions feels unusually taut. Clinical signs relating to the primary disease process may or may not be evident. The diagnosis of hypertrophic osteopathy is confirmed radiologically.

FIG. 51-1 Photograph of a 6-year-old German shepherd with hypertrophic osteopathy. Note the soft tissue swelling of the limbs.

RADIOGRAPHIC FINDINGS
Radiographically, hypertrophic osteopathy usually is seen as a bilaterally symmetric and generalized periosteal proliferative reaction that affects primarily the long bones of the appendicular skeleton (Fig. 51-2). Initially only soft tissue swelling of the extremities may be seen with little to no bony abnormality. The periosteal proliferative changes have a variable spectrum from a smooth and regular (nonaggressive) to a scalloped or lacy (more aggressive) appearance. The distal portions of the limbs frequently have the earliest bony involvement, characteristically present on the abaxial aspects of the second and fifth metacarpal and/or metatarsal bones. The cortex and medullary portions of the bone are normal but may appear partially obliterated by the superimposed periosteal disease. The penosteal proliferative reaction may spread proximally to invest eventually all of the bones of the limbs (including scapula, carpal and tarsal bones) and less commonly the ribs, pelvis, and vertebrae; in one report even the penile bone was involved.(5,7,20,26,27,32,35) In very early cases, periosteal new-bone formation will not be evident initially; the increase in limb size reflects merely the severe degree of soft tissue fibrosis relating to the dramatic increase in limb peripheral blood flow characteristic of this disease (strain gauge plethysmographic
studies have revealed an increase of blood flow of two to three times normal). Not uncommonly, a dense aggregation of this fibrovascular connective tissue is most evident around the distal end of the gastrocnemius tendon. Bones, tendons, and joints are found to be equally invested by this fibrosis, and in advanced cases foci of chondroid or osteoid metaplasia may develop within its margins. As the disease becomes more chronic, however, this vascular component (i.e., hyperemia) generally diminishes somewhat and the penosteal proliferative reaction becomes more prominent. In some animals, the periosteal proliferative reaction may be so marked that articular function becomes limited. If the primary disease resolves, the bony and soft tissue radiographic abnormalities regress.

The periosteal proliferative changes of hypertrophic osteopathy can resemble and must be differentiated from early primary malignant bone tumor, osteomyelitis, hypertrophic osteodystrophy, and occasionally panosteitis. Signs of skeletal disease and hypertrophic osteopathy are generally seen months prior to any onset of dramatic symptomatology relating to the underlying disease processes. Hence, early detection and diagnosis of hypertrophic osteopathy are of considerable importance if one is concerned with diagnosis and treatment of the underlying pathologic processes. In the dog a clinical differentiation among hypertrophic osteodystrophy, early osteoarthritis, and pitting edematous changes of the limbs should be readily made on the basis of physical examination. In the cat, hypervitaminosis A and mucopolysaccharidosis must be considered also. Chest radiography in animals suspected of having hypertrophic osteopathy is essential; if abnormal, other tests such as urinalysis, fecal exams, and blood chemistry panels must be performed if one is to diagnose the underlying pathology early enough to have hope of effecting a cure.

The theory of circulating toxic products is giving way to the theory that the development of osteopathy is related to changes in the peripheral vascular supply induced indirectly by the underlying pulmonary disease. Increased peripheral blood flow is suggested by various clinical observations and also by direct physiological measurements and has been observed in both dogs and humans. Although there is an increased peripheral blood flow, the excess blood, which is poorly oxygenated, passes through arteriovenous shunts, bypassing the capillary bed. This type of blood flow tends to produce local passive congestion and poor tissue oxygenation and in this way stimulates proliferation of the various connective tissues including the periosteum and the synovial membrane. Surgical experience both in humans and in the dog shows that thoracotomy, resection of primary lung lesions, lobectomy, and rib resection all result in a prompt regression of clinical signs of hypertrophic osteopathy and regression of the bone lesions. More recent clinical studies have shown a prompt and lasting...
regression of the elevated peripheral blood flow to limbs affected by hypertrophic osteopathy after incisure of the parietal pleura, hilar and mediastinal dissection, unilateral intrathoracic vagotomy (on the side of the affected lung), and bilateral cervical vagotomy.(6,17,22,23,50,54)

Such a rapid and lasting depression in blood flow would indicate that the most likely etiology for hypertrophic osteopathy is a nervous reflex. It has been postulated that the afferent fibers of this reflex originate in the thorax and probably leave the affected lung in the neighborhood of the bronchus to join the trunk of the vagus nerve high in the mediastinum. An alternate pathway of the afferent fibers may be from the parietal pleura and along intercostal nerves. Thus, according to this theory, the prompt regression of hypertrophic osteopathy as a result of the above procedures probably relates either to the removal of the locus of afferent impulses or section of the afferent pathways themselves. Neither the nature of the stimulus generating these afferent impulses nor the efferent pathway of this reflex has as yet been determined(22,24)

Although most cases of osteopathy are associated with an underlying thoracic disorder, a significant number have been reported with primary disease in other locations, including dogs with Spirocerca lupi esophageal granulomas and dogs with botryoid rhabdomyosarcoma of the urinary bladder.(20) Such extrapulmonary lesions are thought to follow the distribution of the vasopharyngeal and vagus nerves. These cranial nerves carry fibers that innervate vascular tissues, and they have a common nucleus of termination in the gray matter that is closely associated with their efferent dorsal nuclei. It has been suggested that this might account for a common afferent arc that forms a basic part of the mechanism responsible for osteoarthropathy.(l2)

PATHOLOGY
Grossly, specimens from advanced cases have coarse osseous exostoses that may be quite nodular, covering the entire cortical surface from end to end. Vessels and tendons are located in deep grooves within the osseous proliferation. The microscopic progression of the disease is characterized primarily as a proliferation of vascular connective tissue that invests the bones and tendons of the distal limb. Spicules of new bone form perpendicularly to the underlying cortex. Chondroid or fibrochondroid metaplasia may occur in this area of new-bone formation. As the periosteum is pushed away from the original cortex by the new bone, the deeper layers of bone adjacent to the cortex may undergo lamellar reconstruction, but they never become as compact as the original cortex.

There is no endosteal bone formation. The fibrous marrow of the extracortical bone may undergo transformation into hematopoietic marrow in advanced cases. While articular enlargement and limitation in the range of motion may be observed clinically, they may not necessarily be associated with the change in the articular tissues themselves. When arthropathy is present, the synovial tissues are thickened and inflamed, and intra-articular effusion may be present. Articular surfaces are seldom affected as severely as other portions of the bone, and the epicondyles and sites of insertion of ligaments and tendons may show a moderate degree of new-bone formation. In animals, as in humans, the axial skeleton is less severely affected than are the long bones.

TREATMENT
Treatment of hypertrophic osteopathy remains predicated on removal of the underlying primary lesions. Of the above-mentioned multiple etiologies in the dog, dirofilariasis, spirocercal granulomas, and primary lung disease (including neoplasia) seem to lend themselves best to some form of treatment. Resection of primary lung neoplasms can effect dramatic relief of the signs of hypertrophic osteopathy, but long-term survival has been less than optimal (approximately 3 months postoperatively).(5) A few animals with dirofilariasis have successfully undergone pulmonary arteriotomies and enjoyed complete remission of the symptoms of hypertrophic osteopathy; however, reports of animals receiving medical therapy followed by remission of symptomatology are not available in the literature.(5,50) While a spirocercal granuloma is potentially treatable, the majority of dogs afflicted with this disease manifest signs of hypertrophic osteopathy only after transformation of the granuloma into a neoplasm; at this stage, owing to extensive local infiltration and the high frequency of lung involvement, treatment generally becomes unrewarding. In practice, then, none of the underlying disease entities has heralded good longterm survival.(5)

Multiple reports of dramatic and instantaneous remissions of signs following intrathoracic surgery have been noted, with heat and pain leaving the limbs within 1 to 2 weeks.(5,8) Within 3 to 4 months, all signs of lameness have generally disappeared and periosteal newbone formation dramatically regressed, although residual radiographic changes generally remain noticeable for much longer periods.(8,32,50,54) The rate of remission and persistence of residual bony changes may, in fact,
reflect the longevity of the pathologic changes of hypertrophic osteopathy. There appears to be no relationship between the size, site, or histologic type of thoracic lesion and the etiopathogenesis of hypertrophic osteopathy, and the deciding factor in the redevelopment of the disease postoperatively seems to be the development of well advances metastatic pulmonary lesions.

Enough similarities exist between hypertrophic osteopathy in humans and in the dog to enable the dog to serve as an excellent model for the study of hypertrophic osteopathy in humans (Table 51-1). Unfortunately, to date no consistently reliable means of recreating the disease in the dog exists, thus scientific investigation must remain limited to clinical studies alone. As a result, the etiology of the disease will probably remain obscure for many years to come.

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<th>Table 51-1. Clinicopathologic Features of Hypertrophic Osteopathy in Humans and in Dogs</th>
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