

Hypertrophic osteopathy in a dog associated with intra-thoracic lesions: a case report and a review

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ABSTRACT: This paper reviews hypertrophic osteopathy and describes one case report. Hypertrophic osteopathy is a rare pathologic disease process and is observed secondary to a mass in the thorax. In response to the presence of a mass(es), nonoedematous soft tissue swellings and a diffuse periosteal new bone formation develop in all four limbs. The result is mild to severe lameness. A twelve-year-old sexually intact female Cocker spaniel had undergone radical mastectomy on both sides in another veterinary hospital about two years before presentation in our hospital with lameness of both hind limbs. Pain and soft tissue swelling on the distal parts of extremities were determined in clinical examinations. Radiographs revealed periosteal new bone formation on all the long bones of all four limbs, pelvis and sternum; additionally, intrathoracic masses were observed. Euthanasia was performed five months later. Macroscopic examinations of the lungs revealed diffuse and exuberant masses with grizzled whitish cross-sectional colour and with necrotic and haemorrhagic foci. The radius-ulna, tibia, metacarpal and metatarsal bones of both limbs were examined and collected after the necropsy examination. Bone specimens were thicker and the outer surfaces seemed to be rough. At the histopathologic examination of the lung tissue, ovoid or round shaped and hyperchromatic nucleated diffuse anaplastic mammary gland epithelial cells were observed. According to these findings, these masses were diagnosed as the metastasis of malignant mixed tumours.

Keywords: hypertrophic osteopathy; hypertrophic pulmonary osteopathy; malign mixed tumor; dog

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1. Introduction

Hypertrophic osteopathy is a rare pathologic disease process, secondary in nature, which commonly occurs due to neoplastic or infectious masses in the thoracic cavity or (Caywood et al., 1985; Wylie et al., 1993; Grierson et al., 2003), less often, a mass in the abdominal cavity (Rendano and Slauson, 1982; Godber et al., 1993; van der Kolk et al., 1998; Panciera et al., 2000; Watrous and Blumenfeld, 2002; Headley et al., 2005). In response to the presence of mass(es), bilateral symmetrical,

nonoedematous soft tissue swellings affect the distal portions of all forelimbs. This appearance is characteristic for HO. These are soon accompanied by a characteristic diffuse periosteal new bone formation on the outside of the diaphysis of the long bones of the limbs, without destruction of cortical bone. These changes cause mild to severe lameness (Lenahan and Fetter, 1985; Johnson et al., 1995; Montgomery, 2003).

Hypertrophic osteopathy has also been observed in the horse, cow, sheep, cat, fowl, and various other species (Lenahan and Fetter, 1985; Godber et al.,

1993; Curtis et al., 1997; van der Kolk et al., 1998; Grierson et al., 2003). Because the masses associated with the disease generally occur in the thorax, in dogs the disease is also known as hypertrophic pulmonary osteopathy (Lenehan and Fetter, 1985; Johnson et al., 1995; Morrison, 2002; Montgomery, 2003).

This paper describes the clinical, radiological, and pathological findings of hypertrophic osteopathy and provides a more in-depth discussion about hypertrophic osteopathy with reference to the literature.

2. Case description

A twelve-year-old sexually intact female Cocker spaniel with lameness of both hind limbs was the subject of this study. The dog had undergone radical mastectomy on both sides in another veterinary hospital about two years before presentation in our hospital.

2.1. Clinical and radiographical results

Bilaterally symmetrical nonoedematous soft tissue swelling on both hind limbs and mild lameness were determined in clinical evaluations. Pain was detected on palpation. No other abnormality was detected and the patient's life conditions seemed normal. Intrathoracic radiopaque masses were determined in thorax radiographs (Figure 1); however, no abnormality was observed in abdominal radiographic and ultrasonographic assessments. Additionally, periosteal new bone formations were observed in all bones of the appendicular skeleton



Figure 1. Left side lateral recumbency; L/L Radiographic view of thorax shows intrathoracic masses

(Figure 2; white arrows), and pelvic (Figure 2; black arrows) and sternal bones.

The owner was informed about the disease and an appointment for hematologic assessments was given for the following day; however, the owner of the patient did not come to the appointment and also could not be contacted by phone. Approximately five months later, she was brought to our clinic with a euthanasia request because of impaired life condition. The dog was suffering from respiratory distress and had no strength to walk. In radiographic assessments, it was observed that the size of the intrathoracic masses had increased; however, there was no significant change in the bones. Due to poor general condition euthanasia was performed in agreement with ethical guidelines, and the body was then examined.

2.2. Post mortem evaluation

For histopathologic examinations the radius-ulna, tibia, metacarpal and metatarsal bones of both limbs were decalcified (Figure 2; cross-section of tibia, right-bottom) and subjected to a graded alcohol series and chloroform. Tissue samples taken from lungs were fixed with buffered formaldehyde, subjected to alcohol and xylol series and embedded in paraffine. From all paraffine blocks 5 μ m



Figure 2. Periosteal new bone formations in all bones of the appendicular skeleton (white arrows) and pelvis (black arrows). Cross-section of mid-shaft of tibia (right-bottom)

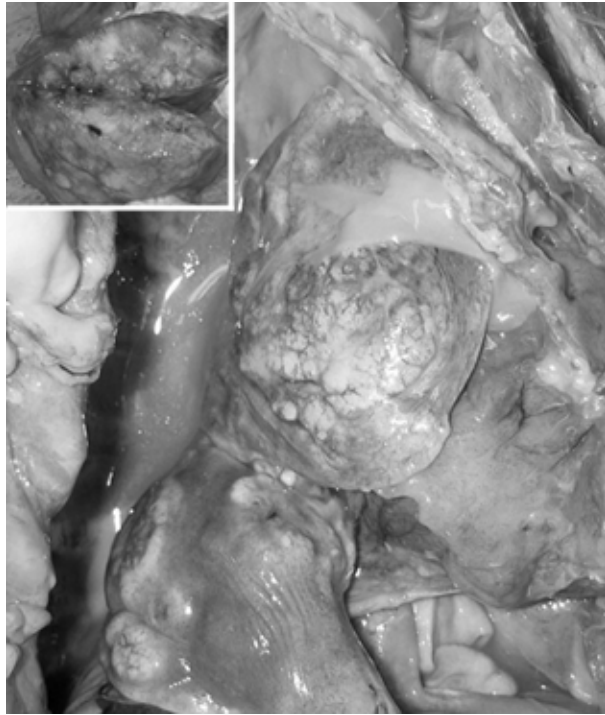


Figure 3. Macroscopic view of the lung masses. Small picture shows cross-sectional view of a mass

cross-sectional slices were taken, stained with Hematoxylin-eosine and evaluated under a light microscope.

2.2.1. Macroscopic findings

Macroscopic examination of the lungs revealed diffuse and exuberant masses of grizzled whitish cross-sectional colour and with necrotic and haemorrhagic foci (Figure 3). The collected bones were thicker and the outer surfaces were rough.

2.2.2. Histopathologic findings

At the histopathologic examination of the lung tissue, ovoid or round shaped and hyperchromatic nucleated diffuse anaplastic mammary gland epithelial cells were observed (Figure 4a). Most of these cells included mitotic figures and embryonic connective tissue cells and chondroid tissue cells were also observed between these cells (Figure 4b). Alveolar atelectasis was also observed due to the potential pressure of the tumour cells. According to these findings, these masses were diagnosed as metastasis of a malignant mixed tumour.

In the bone tissue, new bone formation originating from the periosteum was seen to form bone trabeculae perpendicular to the bone cortex and these newly formed trabeculae were seen to be compact in density (Figure 4c and 4d).

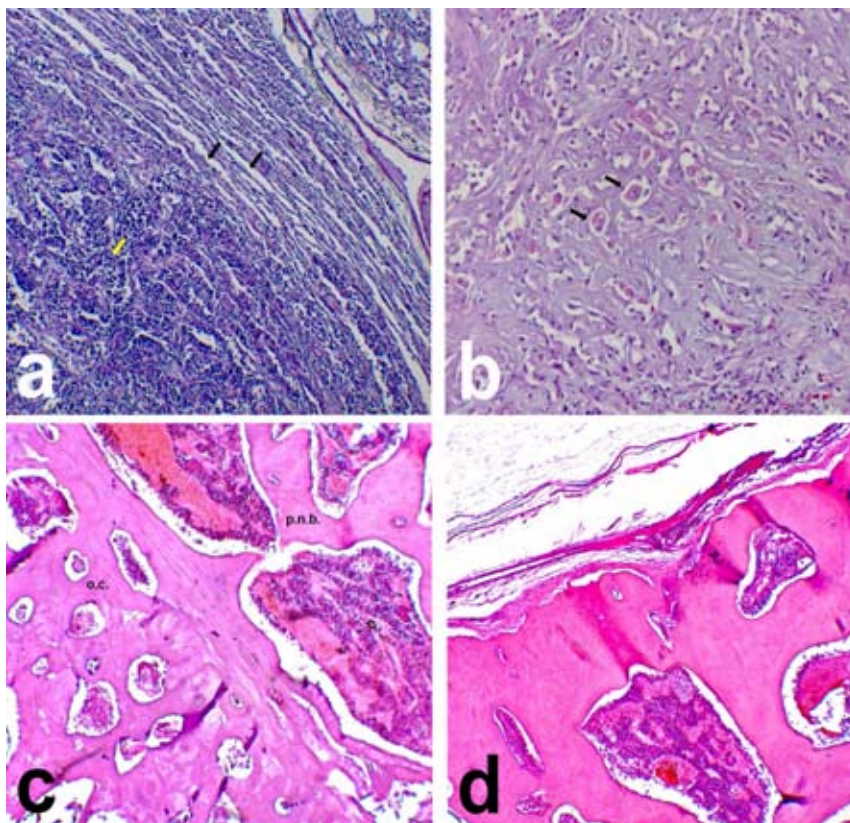


Figure 4. Atelectasis of the lung (black arrow) and tumour cells (yellow arrow); HE, 60× (a). Microscopic view of the cartilage cells in the malign mixed tumour; HE, 100× (b). Original bone cortex (o.c.) and periosteal tabecular new bone formation (p.n.b.); HE, 125× (c). Periosteal tabecular new bone formation; HE, 60× (d)

3. What is hypertrophic osteopathy (review of the literature)

Hypertrophic osteopathy, previously known as osteoperiostitis, was first described in humans in the late 1800s (Bush et al., 1974; Lenehan and Fetter, 1985; Montgomery, 2003). There is archaeological evidence of its occurrence even in the ancient world, and it was almost certainly described by Hippocrates (Martinez-Lavin et al., 1994). Hypertrophic osteopathy, generally abbreviated as HO, is also known by different names, including hypertrophic osteoarthropathy, hypertrophic pulmonary osteopathy, hypertrophic pulmonary osteoarthropathy, pulmonary osteoarthropathy, osteoporosis deformans, achropachia, Marie's disease and Pierre Marie-Bamberger syndrome (Lenehan and Fetter, 1985; Piermattei et al., 2006; Armstrong et al., 2007).

Among animals, hypertrophic osteopathy is observed in dogs most commonly (Brodey, 1971; Lenehan and Fetter, 1985; Johnson et al., 1995), but has also been reported in a variety of other domestic animals including the horse, cow, sheep, cat and in exotic species (Bush et al., 1974; Lenehan and Fetter, 1985; Godber et al., 1993; Curtis et al., 1997; van der Kolk et al., 1998; Morrison, 2002; Grierson et al., 2003; Ferguson et al., 2008). In animals, the term hypertrophic osteoarthropathy has not been used because the joints are not really involved (Montgomery, 2003; Piermattei et al., 2006); however, in human medicine, the term "osteoarthropathy" is still preferred because cases present with inflammatory arthritis (Armstrong et al., 2007; Dabir et al., 2007; Karkucak et al., 2007; Latos-Bielenska et al., 2007; Martinez-Ferrer et al., 2009; Nguyen and Hojjati, 2011).

In both humans and animals, hypertrophic osteopathy is a rare pathologic disease process, secondary in nature, and commonly occurs due to neoplastic or infectious masses in the thoracic cavity or, less often, a mass in the abdominal cavity (Lenehan and Fetter, 1985; Montgomery, 2003; Piermattei et al., 2006). In humans, primary hypertrophic osteoarthropathy was also reported as pachydermoperiostosis. This form is often familial and pachydermia is observed as an additional symptom besides the characteristic symptoms of hypertrophic osteoarthropathy (Karkucak et al., 2007; Latos-Bielenska et al., 2007; Martinez-Ferrer et al., 2009). In a recent study, evidence for both autosomal-dominant and autosomal-recessive forms of the disease was found (Castori et al., 2005). Recently, another type

of primary hypertrophic osteoarthropathy, named cranio-osteoarthropathy, was described in humans and this form presents with decreased neurocranium ossification without pachydermia (Kabra et al., 2000; Dabir et al., 2007).

In animals hypertrophic osteopathy is only reported as secondary in nature, and resulting from intrathoracic or intraabdominal masses. In response to these mass(es), bilateral symmetrical, nonoedematous soft tissue swellings affect the distal portions of all forelimbs. These are soon accompanied by characteristic diffuse periosteal new bone formation on the outside of the diaphyses of the long bones of the limbs, without destruction of the cortical bone. These changes cause mild to severe lameness. Bone changes begin distally and spread proximally to involve the humerus and scapula, femur and pelvis. Other bones such as ribs and vertebrae are also sometimes affected. These bone changes are not a primary neoplasia or metastatic bone lesions (Lenehan and Fetter, 1985; Johnson et al., 1995; Morrison, 2002; Montgomery, 2003; Piermattei et al., 2006). Although the joints are not affected, the range of joint motion may become diminished because of periarticular soft tissue swelling (Montgomery, 2003; Piermattei et al., 2006); however, inflammatory changes in the synovial membrane of swollen painful joints were reported in humans (Cooper et al., 1992).

Periosteal new bone formation has been described as "palisades" or "scalloped", resembling a city skyline, because these proliferations are either irregularly shaped perpendicular to the cortex or smooth shaped parallel to the cortex (Johnson et al., 1995; Montgomery, 2003).

Intrathoracic lesions associated with the disease are primary and include metastatic pulmonary neoplasms, pulmonary abscesses, bacterial endocarditis, *Spirocerca lupi* granulomas, and canine tuberculosis (Caywood et al., 1985; Lenehan and Fetter, 1985; Halliwell, 1993; Wylie et al., 1993; Watrous and Blumenfeld, 2002; Montgomery, 2003). Intraabdominal lesions associated with the disease include embryonal rhabdomyosarcoma of the urinary bladder, liver adenocarcinoma, prostatic adenocarcinoma, and adrenocortical carcinoma (Rendano and Slauson, 1982; van der Kolk et al., 1998; Becker et al., 1999; Panciera et al., 2000; Montgomery, 2003; Headley et al., 2005).

Because hypertrophic osteopathy is secondary in nature, information about breed, sex and age distribution have little meaning. Moreover, no breed and

gender predisposition has been reported; however, hypertrophic osteopathy occurs mostly in middle to old age dogs because of the disease's association with neoplasia. Additionally, hypertrophic osteopathy is more common in females than in males because mammary carcinomas may cause metastatic lung tumours and this may lead to hypertrophic osteopathy (Lenehan and Fetter, 1985; Johnson et al., 1995; Montgomery, 2003).

Although the exact pathogenesis of hypertrophic osteopathy has not yet been elucidated, several theories have been proposed to explain the cause of the periosteal reaction. According to one theory, circulating toxic products from the primary lesion irritate the synovial membranes and periosteum. This is supported by the observation of round cell infiltration in the fibrous layer of the periosteum before new-bone proliferation (Jaffe, 1972; Lenehan and Fetter, 1985).

Another theory implicates changes in the peripheral blood flow to the distal extremities because of indirect effects of the primary lesion. A rapid increase in peripheral blood flow, which is poorly oxygenated, passes through arteriovenous shunts, bypassing the capillary bed, and causes local passive congestion and poor tissue oxygenation. This situation stimulates connective tissue and periosteal proliferation (Lenehan and Fetter, 1985; Morrison, 2002; Piermattei et al., 2006; Ferguson et al., 2008). Increased peripheral blood flow was recorded in various clinical observations and direct physiological measurements in dogs and humans. Depression in the blood flow and regression of the bone lesions were observed after thoracotomy, lobectomy and removal of the primary lesion in both humans and dogs (Lenehan and Fetter, 1985; Ferguson et al., 2008).

A neural vascular reflex theory has also been considered. The autonomic neurovascular reflex originates in the thorax and is carried through afferent vagal fibres. This reflex leaves the lung near the bronchi and joins the nervus vagus in the mediastinum. Additionally, there may be an alternative afferent pathway from the parietal pleura and along the intercostal nerves; extrapulmonary lesions are thought to follow the distribution of these nerves. This reflex increases blood flow to the distal extremities and affects connective tissue and the periosteum. This theory was supported by the fact that there is a relief of symptoms following vagotomy or intercostal nerve resection (Lenehan and Fetter, 1985; Johnson et al., 1995; Ferguson et al., 2008).

Although the vast majority of cases of hypertrophic osteopathy are associated with pulmonary lesions, a considerable number of reports showed primary disease in other locations such as descriptions of dogs with *Spirocerca lupi* esophageal granulomas and botryoid rhabdomyosarcoma of the urinary bladder (Lenehan and Fetter, 1985). Such extrapulmonary lesions are thought to follow the distribution of the vasopharyngeal and vagus nerves which carry fibres that innervate vascular tissues (Lenehan and Fetter, 1985; Piermattei et al., 2006). Thus, this neurovascular reflex theory is fairly well accepted in veterinary medicine. Afferent impulses travelling in the vagus and intercostal nerves from the lesion to the central nervous system are probably responsible for initiating the HO. An autonomic neurovascular reflex shunts the peripheral blood supply and results in local hypoxia for the periosteum, which leads to new bone formation (Watson and Porges, 1973; Lenehan and Fetter, 1985; Montgomery, 2003; Piermattei et al., 2006).

A further theory proposes that platelet clumps and megakaryocytes, which are normally subjected to fragmentation in pulmonary circulation, have upon the development of HO, the chance to enter the systemic circulation and deposit in the distal vasculature, releasing platelet derived growth factor (PDGF). Local release of these growth factors leads to fibroblast proliferation and increased vascularity and permeability, resulting in connective tissue changes and the periosteal reaction (Dickinson and Martin, 1987). Another factor which may play a role in pathogenesis is vascular endothelial growth factor (VEGF). Like PDGF, VEGF is also derived from platelets; also, it is a potent angiogenic stimulus and osteoblastic differentiation agent that is induced in hypoxic and malignant pathologies (Martinez-Lavin, 2007). VEGF levels are reported to be elevated in both primary hypertrophic osteoarthropathy and secondary hypertrophic osteoarthropathy associated with lung cancer (Martinez-Lavin et al., 2008). Hyperestrogenism and oxygenation deficiency were also proposed as causes of hypertrophic osteoarthropathy (Ferguson et al., 2008).

Prognosis is highly dependent on the inciting cause of hypertrophic osteopathy. The treatment of hypertrophic osteoarthropathy in humans is classified as either treatment of the primary cause or symptomatic treatment. Treatment of the primary cause includes tumour resection, radiotherapy, chemotherapy, treatment of infection, replacement

of infected grafts, organ transplantation and surgical correction of cyanotic heart disease. Symptomatic treatments include vagotomy, bisphosphonates, octreotide, application of epidermal growth factor receptor (EGFR) inhibitor and adrenergic antagonists (Nguyen and Hojjati, 2011).

In the dog, the ideal treatment for hypertrophic osteopathy depends on the underlying cause. Bone changes may regress if the underlying health problem can be treated. Treatments for hypertrophic osteopathy include resection of the tumour (intrathoracic or intraabdominal), treatment of infection, surgical treatment of dirofilariasis, treatment of spirocercal granulomas, chemotherapy, and vagotomy. When hypertrophic osteopathy is caused by heartworm infestation or primary lung tumours, surgery will be a good option. Regression of clinical signs will then be observed within two weeks after surgery; however, the bone abnormalities regress gradually over several months (Lenahan and Fetter, 1985; Johnson et al., 1995; Becker et al., 1999; Morrison, 2002; Piermattei et al., 2006). Additionally, the regression of clinical signs and bone abnormalities was observed in a dog following unilateral intrathoracic vagotomy (on the affected side; Watson and Porges, 1973).

In some situations, non-steroidal anti-inflammatory drugs will be suitable for dogs to provide palliative care. Dogs suffering from hypertrophic osteopathy due to secondary lung cancer have a very poor prognosis and euthanasia is normally to be preferred above surgery.

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