Hypertrophic osteopathy in a pregnant doe with bronchopneumonia

Elisa Heacock,[a] Anabelle Bates,[b] Kate Wulster,[c] Timothy Manzi,[c] Daniela Luethy,[b] Michelle Abraham[b]
[a]Veterinary Clinical Sciences, School of Veterinary Medicine, Philadelphia
[b]Department of Large Animal Internal Medicine, School of Veterinary Medicine, Kennett Square
[c]Department of Radiology, School of Veterinary Medicine, Kennett Square
University of Pennsylvania, PA

Abstract

An 18 month old Boer doe in late pregnancy was presented for severe distal limb swelling and lameness of all 4 limbs, hyporexia, and tachypnea. Doe was hyporexic for several days prior to presentation and was ~ 137 - 141 days pregnant. Radiography showed that the doe had bronchopneumonia, and palisading periosteal proliferation of her metacarpal bones and proximal phalanges. A diagnosis of hypertrophic osteopathy secondary to bronchopneumonia, or pregnancy, or the combined effects of bronchopneumonia and pregnancy, was made. Three months following parturition and treatment for pneumonia, doe was re-evaluated, at that time, both pneumonia and orthopedic changes were almost completely resolved. This represents the first reported case of hypertrophic osteopathy in a domestic goat. It is uncertain what role bronchopneumonia and advanced pregnancy had in the development of hypertrophic osteopathy.

Keywords: Hypertrophic osteopathy, caprine, bronchopneumonia, pregnancy

Background

Hypertrophic osteopathy (HO) is a rare skeletal disease that is characterized by palisading osteoproliferation beneath the periosteum of long bones secondary to thoracic or less commonly abdominal pathology.[1] It is most commonly reported in humans as hypertrophic osteoarthropathy that causes severe distal limb swelling and subperiosteal proliferations, but can also result in symmetrical digital clubbing of fingers and toes and arthropathy.[1] In humans, it can rarely be a primary congenital disease, but is most often a secondary disease process.[1] In animals, it has only been documented as a secondary disease, most commonly secondary to pulmonary disease; however, reports have also demonstrated intraabdominal disease, intrapelvic disease and pregnancy to have a strong association with HO,[2-4] with no sex predilection in humans.[2] Most case reports in veterinary medicine documented HO in dogs; however, it has also been described in horses, deer, cats, cows, fowl, and takin, a wild bovid species.[5,6]

There are multiple theories as to the pathophysiology of musculoskeletal changes associated with HO, including both neurogenic and vascular pathways that are suspected to result in an elevation of circulating growth factors causing limb swelling and osteoproliferation.[2] However, more recent literature has demonstrated a strong relationship between elevations in vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) with HO.[1,4] Pulmonary disease often results in pulmonary vessel shunting, thus decreased fragmentation of megakaryocytes into platelets that normally occurs in pulmonary vessels.[1] These megakaryocytes and thrombocytes then lodge in distal vasculature causing occlusion of vessels and local hypoxia.[1] This is the proposed mechanism for elevations in PDGF and VEGF in distal capillaries. These then induce mesenchymal growth and periosteal proliferation of the long bones of the distal limbs.[1] These growth factors are also elevated in systemic inflammatory conditions, hypoxia, and aberrant vascularization that can be associated with a variety of other disease processes as the primary disease causing secondary HO.[1]

Clinically, veterinary patients ultimately diagnosed with hypertrophic osteopathy typically present with a stiff gait, reluctance to rise, or lameness characterized by painful and diffusely swollen distal limbs.[7] Radiographically, HO is a palisading pattern of periosteal reaction along long bones of distal extremities, particularly the proximal phalanges, metacarpal and metatarsal bones.[2] We report the first documented case of presumptive hypertrophic osteopathy in a domestic goat. This report documents

the disease progression and resolution of suspected HO, secondary to the diagnosis of severe pneumonia and/or parturition.

Case presentation

An 18-month old, 79.1 kg Boer doe, ~ 137 - 141 days in pregnancy, was presented on an emergency basis to the University of Pennsylvania's New Bolton Center in March of 2019 for evaluation of suspected pregnancy toxemia. Owner reported that the doe had a history of pain in all 4 limbs and reluctance to stand for extended intervals that had progressed to complete recumbency and lethargy in the week prior to presentation. In the days immediately prior to presentation, the doe had become anorexic, increasingly tachypneic and dull.

On physical examination, doe appeared depressed and moderately painful with a heart rate of 112 beats per minute (normal: 70 - 90), a respiratory rate of 64 breaths per minute (normal: 15 - 40) and a rectal temperature of 38.5°C (normal: 37.8 - 39.7°). No jugular pulses were visible or palpable and cardiac auscultation was unremarkable. Harsh bronchovesicular sounds were present in all lung fields with an increased respiratory effort, but no adventitious lung sounds were noted. Doe was ambulatory but had a stiff gait and was reluctant to stand for extended intervals. Doe had diffuse swelling distal to the mid radius or mid tibia, heat, and an overt pain response on palpation of each limb. Doe had a markedly distended abdomen and an edematous vulva, consistent with her stage of pregnancy. A transabdominal ultrasonographic examination revealed 2 fetal heart beats and fetal fluids of normal echogenicity; however, no spontaneous fetal movements were noted. Reproductive department recommended supportive care until parturition to allow for full fetal development. The remainder of the physical examination was unremarkable.

Initial blood chemistry revealed hyperglycemia (142 mmol/l; reference range: 54.0 - 93.0 mmol/l), hyperlactatemia (3.3 mmol/l; reference range: 0.6 - 1.4 mmol/l), and elevated beta-hydroxybutyrate (1.7 mmol/l: reference range; < 0.9 mmol/l). The packed cell volume (PCV) (29%; reference range: 28 - 44%) and total protein (6.4 mg/dl; reference range: 6.2 - 8.0 mg/dl) were within normal limits. Doe was admitted to the hospital and a jugular catheter was placed.

Initial treatment consisted of a fluid bolus of a balanced electrolyte solution (1 liter, Isolyte®, B. Braun Medical Inc., Bethlehem, PA) followed by a continuous intravenous infusion of a balanced electrolyte solution (3 ml/kg/hour, Isolyte®, B. Braun Medical Inc.) mixed with dextrose (1.7 mg/kg/min, Dextrose 50% solution, Covetrus, Dublin, OH) and thiamine (2.4 mg/kg/hour, Thiamine HCl, Henry Schein, Dublin, OH). Intravenous fluids were continued for the first 6 days of hospitalization. Plasma fibrinogen concentrations were evaluated at admission and discharge (647 mg/dl decreased to 560 mg/dl; reference range: 200 - 400 mg/dl). Blood chemistry panel performed at admission revealed mild abnormalities including sodium of 142 mmol/l (reference range: 143 - 149 mmol/dl), total protein of 6.3 g/dl (reference range: 6.4 - 7.4 g/dl), albumin of 2.6 g/dl (reference range: 2.8 - 3.8 g/dl), CK of 136 U/L (reference range: 28- 130 U/L), and GGT of 61 U/L (reference range:10 - 60 U/L). Doe was treated with pantoprazole (Westward, Eatontown, NJ) 1 mg/kg IV, every 24 hours, florfenicol (Nuflor®, Merck, Madison, NJ) 40 mg/kg SQ, every 72 hours, and flunixin meglumine (Covetrus, Dublin, OH), 1.1 mg/kg IV every 24 hours. A rumen transfaunation was performed. During her first night in hospital, the doe became febrile with a rectal temperature of 40.6°C and was anorexic despite grain, alfalfa hay, and water being directly offered.

Treatment

Doe remained tachypneic and sternally recumbent in a straw-bedded stall during the 3 days prior to parturition. Manual assistance was necessary for the doe to stand and to change from left to right sternal recumbency every 4 hours. Despite regular flunixin meglumine treatment, the doe remained painful in all 4 limbs.

Distal forelimb radiographs were taken on second day of hospitalization to investigate swelling, heat and pain evident on palpation of these limbs that had palisading periosteal proliferations on the lateral and medial aspects of both metacarpal bones and proximal phalanges. Radiographs revealed a

moderate spiculated, palisading periosteal reaction affecting the proximal aspect of the third and fourth metacarpal bones bilaterally (left > right). The lateral aspect was more affected than the medial. A smooth periosteal reaction (Figure 1) was also evident on both left and right radius. There was diffuse moderate soft tissue swelling and thickening of the antebrachium and distal soft tissues of both thoracic limbs.

Shortly after the distal limb radiographs were obtained, percutaneous perineural blocks of the median, ulnar, tibial and peroneal nerves were performed using liposomal bupivacaine (2.0 ml per limb, Nocita®, Aratana, Leawood, KS) for extended local analgesia. However, no significant improvement in doe's comfort level was noted. A brief transcutaneous thoracic ultrasonographic examination was also performed at this time that demonstrated evidence of pulmonary disease including coalescing comet tails visible cranioventrally in both lungs. There was no evidence of pleural or pericardial effusion as well as no evidence of obvious mediastinal masses. Thoracic radiographs were acquired the following day (Day 3).

Thoracic radiographs demonstrated a multilobar, moderate interstitial to alveolar pulmonary pattern, predominantly affecting the perihilar region, but also cranioventrally and superimposed over the heart-base with prominent air bronchograms (Figure 2). A few pleural fissure lines were noted. These findings were most consistent with bronchopneumonia and parapneumonic pleural effusion. Oxytetracycline (5 mg/kg IV, every 12 hours, Liquamycin LA-200®, Zoetis, Kalamazoo, MI) therapy was initiated to provide additional antibiotic therapy targeted specifically at the most common agents causing pneumonia in goats. All other treatments were continued.

A second reproductive examination (Day 3) revealed 2 fetal heartbeats. However, there were concerns that fetal viability may be compromised if doe's health continued to deteriorate; therefore, parturition was induced with cloprostenol (1.5 ug/kg IM, Estrumate®, Merck, Madison, NJ) and dexamethasone (0.25 mg/kg IV, Phoenix, St. Joseph, MO). Doe was monitored frequently for kidding. The following night (Day 4), 3 kids were delivered via assisted vaginal delivery. The next day (Day 5), the patient appeared significantly brighter and more comfortable, however, was still mildly reluctant to stand and allow the kids to nurse. To provide additional pain relief a morphine treatment protocol was instituted (0.2 mg/kg IM, every 8 hours, Hospira Inc., Lake Forest, IL). The warmth that was previously palpable in all 4 limbs had substantially decreased; however, the diffuse limb swelling remained. Doe's appetite slowly returned over a 24 hour period. After almost 2 days of ambulating independently and allowing her kids to nurse appropriately the doe was tapered off intravenous fluid therapy and injectable flunixin meglumine was discontinued (Day 6). With the doe's continued improvement, injectable antibiotics, morphine and pantoprazole were discontinued (Day 7). Doe was treated with oral meloxicam beginning postpartum (2.8 mg/kg loading dose, then 1.0 mg/kg every 48 hours, Carlsbad Technology Inc., Carlsbad, CA) and discharged from the hospital (Day 8).

Nine weeks after discharge, the doe returned for re-evaluation of the bronchopneumonia and HO. Owner reported that the doe was doing well at home, but still had a mildly stiff gait. On presentation, the doe was bright, alert, and responsive with a physical examination within normal limits. The diffuse limb swelling had resolved in all 4 limbs and the doe was not painful on palpation.

Repeat radiographs were obtained of her distal forelimbs and thorax. Limb radiographs revealed marked improvement of the periosteal reaction of the metacarpi (Figure 3) and a persistent mild amount of irregular periosteal reaction proximally. Thoracic radiographs revealed that the previously noted pulmonary pattern had resolved (Figure 4). It was determined that the doe's bronchopneumonia and HO had resolved.

Differential diagnosis

Hypertrophic osteopathy secondary to bronchopneumonia versus hypertrophic osteopathy secondary to pregnancy versus hypertrophic osteopathy secondary to both bronchopneumonia and pregnancy

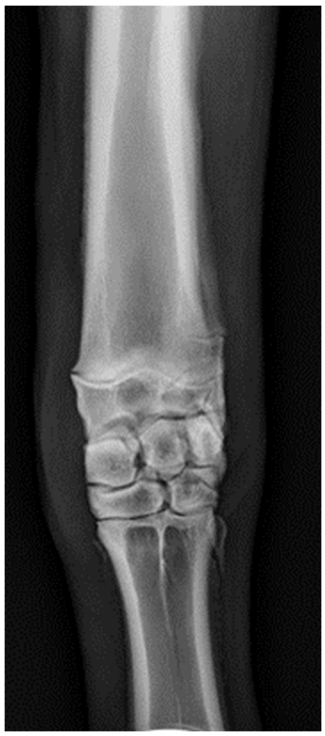

Figure 1. Radiograph of right forelimb showing periosteal reaction suggestive of hypertrophic osteopathy

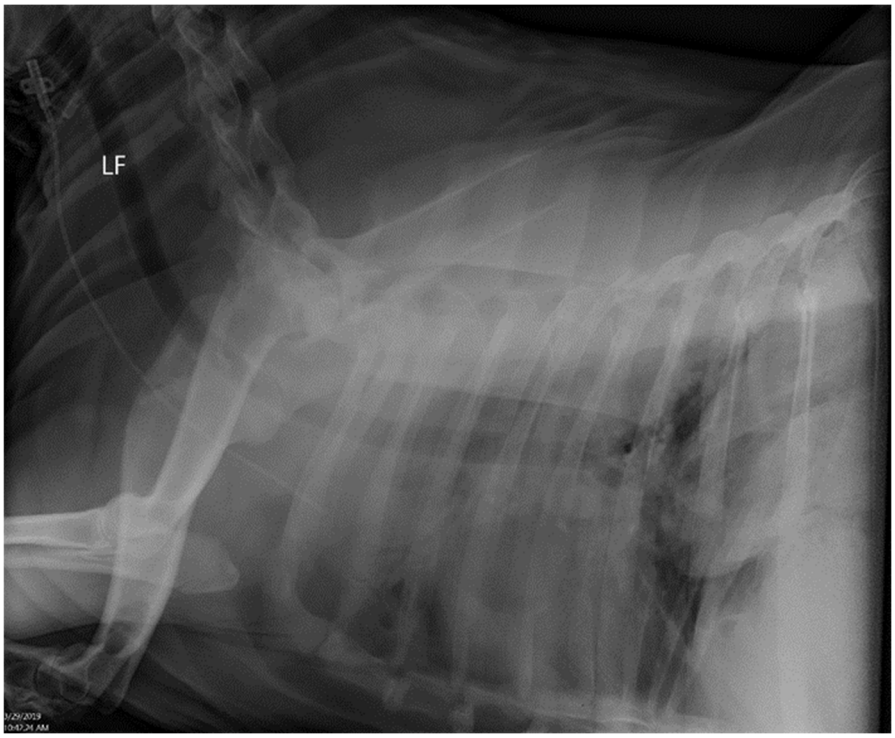

Figure 2. Thoracic radiograph showing a multilobar interstitial to alveolar pattern, most suggestive of bronchopneumonia with secondary pleural effusion.

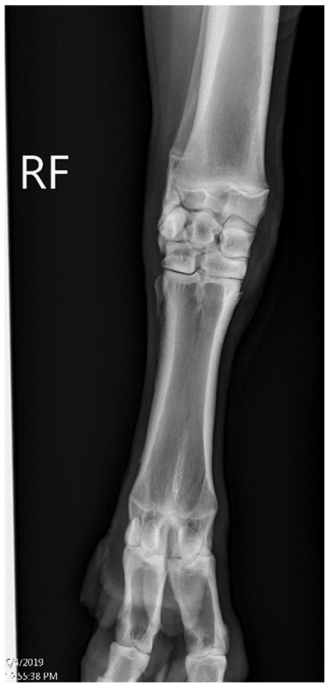

Figure 3. Repeat radiograph of right forelimb showing near complete resolution of hypertrophic osteopathy

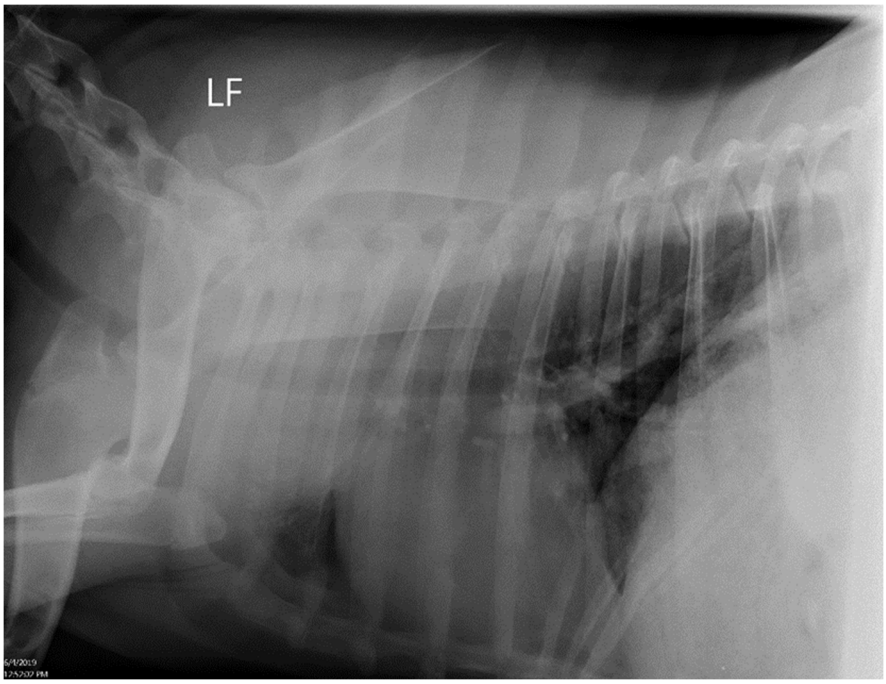

Figure 4. Repeat radiograph of thorax showing resolution of diffuse alveolar pattern, suggesting resolution of bronchopneumonia.

Discussion

This report documents a case of a periparturient Boer doe with severe pneumonia and suspected secondary hypertrophic osteopathy to either the pneumonia, pregnancy, or a combination of both.

Although the pathophysiology of HO is becoming better understood, deficits remain. It is well documented that VEGF and PDGF lead to the phenotypic changes associated with HO.[1] Both pulmonary disease and less commonly pregnancy have been implicated in causing secondary HO and this case may give further evidence to support that primary diseases can be associated with secondary HO.[4]

In most cases, HO develops secondary to severe thoracic disease such as neoplasia, granulomatous disease, or suppurative pneumonia as the primary lesion.[8] In this case, the patient was initially afebrile and the pneumonia did not cause a moderately elevated plasma fibrinogen concentration, so it is uncertain whether the severity of the thoracic changes are comparable to the severe pulmonary disease reported in cases of HO described in the literature. We cannot conclude that pneumonia was not ultimately the cause of HO in this case; however, it challenges the current theories solely implicating thoracic disease as the inciting factor in the pathogenesis of HO and whether pregnancy may exacerbate pulmonary disease. Furthermore, a recent study revealed 5 cases of presumptive HO in a takin that were associated with pregnancy.[4] The takin in that study had clinical signs similar to the doe in the present report, including shifting leg lameness, a stiff gait, and distal limb swelling that were confirmed as HO with radiographs and one CT scan.[4] Clinical signs subsided and recurred with subsequent pregnancies up to 6 times in 5 takin.[4] These investigators hypothesized that a genetic predisposition for the development of HO during pregnancy existed within the relatively small population of takin from which these animals were derived.[4] The mechanism by which HO could be secondary to pregnancy is unknown; however, it has been documented that VEGF is increased locally in the uterine environment during pregnancy associated with the proinflammatory environment that exists during the third trimester of pregnancy.[9,10] Released in response to elevations in VEGF, uterine NK cell–derived IFN-γ causes alterations in the uterine vasculature and stroma.[9] Vascular endothelial growth factor is a potent angiogenic factor that has a partially causative role in HO, and is also involved in many physiological processes during pregnancy.[9] It has been recognized as a paracrine and autocrine modulator of angiogenesis, remodeling, and vascular permeability in the endometrium, decidua, and trophoblast,[9] but in cases of HO in periparturient animals, these authors question whether it has a more systemic role as well, at least in some animals. In the human literature, increases in serum VEGF during the first trimester of pregnancy have been reported as normal and have been recognized as being positively correlated with stage of pregnancy, beta-hCG, estradiol, and progesterone concentrations.[11]

Clinical signs associated with HO in the case reported herein were most severe during the days just prior to parturition, yet much improved postpartum. Administration of nonsteroidal antiinflammatories and performing perineural blocks did not alleviate this patient's pain, consistent with cases reported in humans.[2] Following parturition, the doe would stand and was willing to eat; however, it is difficult to conclude that pregnancy was the primary cause of HO in this patient, as the improvement in clinical status could have been due to decreased weight and relief from other metabolic strains that accompanied carrying three kids in utero. Also lending support to pulmonary disease as the primary cause of HO, was that clinical improvement may have been due to an increase in pulmonary capacity achieved after delivering the kids, as well as treatment of bronchopneumonia with antibiotics. In this case, pregnancy may have exacerbated the pulmonary disease or been the primary cause of HO. However, it is uncertain whether the presence of bronchopneumonia, or pregnancy, or both led to the development of secondary HO in this doe.

Learning points

- Although very uncommon, hypertrophic osteopathy should be considered a differential in goats with painful, diffusely swollen legs, especially when thoracic disease or pregnancy is concurrent.
- Pain medications and supportive care may be helpful for mitigating the detrimental effects of hypertrophic osteopathy; however, treatment of the initiating cause often results in resolution of the disease.

- There is potentially a genetic basis in the development hypertrophic osteopathy that requires further exploration.

Conflict of interest

None to declare.

References

1. Callemeyn J, Van Haecke P, Peetermans W, et al: Clubbing and hypertrophic osteoarthropathy: insights in diagnosis, pathophysiology, and clinical significance. Acta Clin Belg 2016;71:123-130.
2. Chakraborty RK, Sharma S: Secondary Hypertrophic Osteoarthropathy. StatPearls. Treasure Island; StatPearls Publishing LLC:2020.
3. Lavoie J, Carlson G, George L: Hypertrophic osteopathy in three horses and a pony. J Am Vet Med Assoc 1992;201:1900-1904.
4. Marinkovich M, Wisner E, Brenner D: Distal limb swelling and periosteal productive reaction in periparturient Sichuan takin (*Budorcas taxicolortibetana*): five cases of presumptive hypertrophic osteopathy. J Zoo Wildl Med 2019;50:437-446.
5. Chaffin M, Ruoff W, Schmitz D, et al: Regression of hypertrophic osteopathy in a filly following successful management of an intrathoracic abscess. Equine J 1990;22:62-65.
6. Guyot H., Sandersen C., Rollin F: A case of hypertrophic osteoarthropathy in a Belgian blue cow. Can Vet J 2011;52:1308-1311.
7. Brodey RS: Hypertrophic osteoarthropathy in the dog: a clinicopathologic survey of 60 cases. J Am Vet Med Assoc 1971;159:1242-1256.
8. Mair T, Dyson S, Fraser J, et al: Hypertrophic osteopathy (Marie's disease) in Equidae: a review of twenty-four cases. Equine Vet J 1996;28:256-262.
9. Ashkar A, Di Santo J, Croy B: Interferon gamma contributes to initiation of uterine vascular modification, decidual integrity, and uterine natural killer cell maturation during normal murine pregnancy. J Exp Med 2000;192:259-270.
10. Mor G, Cardenas I, Abrahams V, et al: Inflammation and pregnancy: the role of the immune system at the implantation site. Ann N Y Acad Sci 2011;1221:80-87.
11. Daniel Y, Geva E, Lerner-Geva L, et al: Levels of vascular endothelial growth factor are elevated in patients with ectopic pregnancy: is this a novel marker? Fertil Steril 1999;72:1013-1017.