

# Case Report

## Hypertrophic osteopathy secondary to gastric squamous cell carcinoma in a horse

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### Introduction

Hypertrophic osteopathy (Marie's disease) is a syndrome characterised by periosteal proliferation along the metaphyses and diaphyses proximal and distal to the joints of long bones classically associated with space-occupying lesions of the thorax (Butler *et al.* 1993). The syndrome is most frequently documented in human and canine patients (Brown *et al.* 1980), but has also been diagnosed infrequently in the cat (Nafe *et al.* 1981), cattle, sheep (Smith *et al.* 1972), deer (Brown *et al.* 1980), alpaca (Curtis *et al.* 1997) and horse (Mair *et al.* 1996). Only recently has hypertrophic osteopathy been documented secondary to extrathoracic lesions in the horse (Sweeney *et al.* 1989; Lavoie *et al.* 1992; Mair *et al.* 1996; van der Kolk *et al.* 1998).

**This is the first known published record of hypertrophic osteopathy secondary to gastric squamous cell carcinoma in the horse.**

### Case details

#### History

A 15-year-old 420 kg American Quarter Horse gelding was referred for evaluation of intermittent pyrexia of 5 months' duration. A 6 week history of increased respiratory effort, apparent joint enlargement, inappetance and loss of condition were also reported. Haematology and blood biochemistry obtained 6 days prior to presentation revealed hypoalbuminaemia (18 g/l; reference range [rr] 32–39 g/l), hyperglobulinaemia (49 g/l; rr 23–43 g/l) and hypocalcaemia (2.5 mmol/l; rr 2.6–3.2 mmol/l). Creatinine, BUN and fibrinogen concentrations were within normal limits. There was a normocytic, normochromic anaemia attributed to chronic disease with a mature neutrophilia and lymphopenia consistent with a stress leucogram.

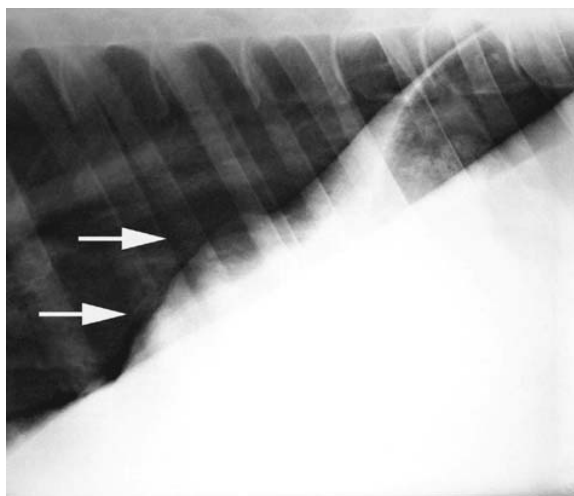
### Clinical examination and diagnostic procedures

Upon presentation the horse was dull and afebrile, with rectal temperature 36.9°C (98.5°F), pulse 40 beats/min, respiration 24 breaths/min, capillary refill time 2.5 secs and pink mucous membranes. The body condition score was grade 3/9 (Anon 1998) and the horse exhibited a dull hair coat. There was moderate expiratory effort and adventitious lung sounds were auscultated bilaterally. The left lung field exhibited decreased bronchointerstitial sounds with friction rubs caudodorsally. Wheezes were evident over the right lung field, loudest caudodorsally. There was no mucus auscultated in the trachea and a cough could not be elicited via tracheal manipulation. Nasal discharge and submandibular lymph node enlargement were absent. There was marked enlargement of the metacarpo- and metatarsophalangeal regions with a decreased range of motion in the affected joints. The carpi and tarsi were also moderately enlarged; the swellings were firm but not palpably painful, and the horse did not exhibit overt lameness.

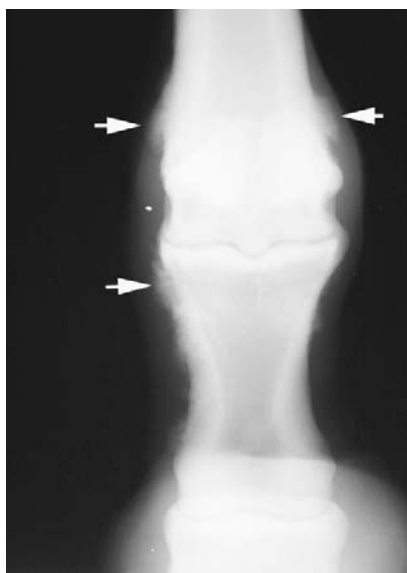
Thoracic radiographs demonstrated a 16 cm irregular border of the left diaphragm approximately 20 cm distal to the dorsal recess of the left diaphragmatic crus. The border was displaced cranially with anterior thin linear radiodensities consistent with soft tissue mineralisation (**Fig 1**). The lungs exhibited a bronchointerstitial pattern and fluid obscured the definition of the cranioventral cardiac silhouette. Radiographs of the metacarpo- and metatarsophalangeal joints showed marked periosteal reaction proximal and distal to the joints (**Fig 2**). The articular surfaces did not appear to be affected. The carpi had similar nonarticular periosteal proliferation proximally and distally.

Ultrasonography of the thorax revealed an abnormal soft tissue density in close proximity to the pericardium at the apex of the heart. This density extended caudally to involve the diaphragm and abdominal cavity where it became modestly hypochoic, causing the diaphragmatic and liver borders to be indiscernible. These findings were consistent with a mass disrupting the left crus of the diaphragm, as seen radiographically. A mild amount of thoracic fluid was also noted. There were no other significant ultrasonographic findings.

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**Fig 1:** Thoracic radiograph depicting deviation of left diaphragmatic crus with arrows indicating associated soft tissue mineralisation.



**Fig 2:** Radiograph of left metacarpophalangeal joint indicating periosteal reaction consistent with hypertrophic osteopathy. Periosteal proliferation is indicated by arrows.

### Differential diagnosis

The horse was hospitalised for observation. A tentative diagnosis of hypertrophic osteopathy was made and an initial list of differential diagnoses was compiled to include thoracic or abdominal neoplasia, thoracic or abdominal abscessation, maldigestive/malabsorptive disorders (i.e. granulomatous diseases) and chronic gastric ulceration. The horse became febrile that evening 40.5°C (104.9°F) and phenylbutazone was administered (4.5 mg/kg bwt *per os*, once).

**Course of condition:** Results of follow-up serum biochemistry revealed hyperproteinaemia (78 g/l; rr 57–70 g/l), hyperglobulinaemia (58 g/l; rr 23–43 g/l), hypoalbuminaemia



**Fig 3:** Gastric endoscopy photograph depicting squamous cell carcinoma of the lesser curvature (yellow arrows). The margo plicatus is indicated by the red arrow.

(20 g/l; rr 32–39 g/l) and hypercalcemia (3.3 mmol/l; rr 2.6–3.2 mmol/l). Fibrinogen registered 6 g/l (rr 1–4 g/l), compatible with chronic inflammatory disease. Haematology revealed a low normal red blood cell count ( $7.82 \times 10^9/l$ ; rr  $6.5\text{--}12.5 \times 10^9/l$ ) and a white blood cell count within normal limits.

Abdominal fluid obtained by paracentesis was yellow and turbid with a protein of 38 g/l and specific gravity of 1.021 (rr 1.000–1.065). Cytology revealed a suppurative inflammatory effusion with an increased white blood cell count of  $28.8 \times 10^9$  cells/l characterised by primarily nondegenerate neutrophils with infrequent macrophages and lymphocytes. No neoplastic cells or bacteria were observed.

Due to the proximity of the mass to the diaphragmatic left crus and stomach, gastric endoscopy was performed. A large, friable, necrotic, nodular, tan mass in the nonglandular squamous portion of the stomach encompassing approximately 95% of the lesser curvature was observed (**Fig 3**). Four deep pinch biopsies of the mass were obtained with endoscopic biopsy forceps, placed in formalin and submitted for histopathology, which revealed widely necrotic debris with suppurative inflammation and adherent mixed bacteria. A definitive histopathological diagnosis could not be made given the superficial nature of the biopsy specimens obtained.

Due to the chronicity, progression of clinical signs and severity of the gastric mass with the likelihood of gastric squamous cell carcinoma and associated grave prognosis, the horse was subjected to euthanasia.

### Post mortem examination and definitive diagnosis

**Post mortem** examination revealed changes that predominantly affected the abdominal viscera. The stomach was bloated and firm with multifocal coalescing small, yellow, firm nodules

approximately 0.5 cm diameter dispersed across the serosal surface of the greater curvature. The nodules became more frequent at the lesser curvature, which was very firm and adhered to the diaphragm by an extremely firm adhesion. The adhesion measured approximately 30 cm diameter with a beige, granular cut surface that displayed thin veins of pink colouration. It involved the diaphragm and extended into the thoracic cavity, including the pleura at the tip of the left caudal lung lobe. This adhesion was continuous with a large mass affecting approximately 65–70% of the nonglandular stomach. It extended approximately 20 cm into the gastric lumen of the lesser curvature and was nodular, tan and necrotic. On cut surface the centre of the mass was extremely firm, granular and white with areas of brown and red whorls and streaks. The glandular portion of the stomach at the greater curvature and the pylorus appeared largely unaffected. The small and large intestine appeared grossly normal, with the exception of approximately 0.6 m of hyperaemic jejunum. The small and large intestinal mesentery, however, had infrequent 0.5 cm, spherical, firm, yellow nodules. Similar-appearing nodules also diffusely affected the omentum. The peripheries of the spleen and liver were also dotted with very few variably sized nodules. The peritoneal and pleural surfaces of the diaphragm contained diffuse clusters of flat nodules approximately 0.5 cm diameter. In the thoracic cavity, the pericardium appeared to be diffusely thickened, purple, nodular and firm. On the mediastinum and caudal pulmonary pleura, there were rare very small nodules. The pulmonary parenchyma did not appear to be affected. Sections of glandular and nonglandular stomach, jejunum, ileum, kidney, spleen, liver, omentum, diaphragm, pleura, lung, heart, pericardium and thymus were submitted for pathological evaluation. The resulting histopathological diagnosis was primary gastric squamous cell carcinoma with dissemination to the intestinal serosa, spleen, liver, omentum, mesentery, diaphragm, pleura, pericardium and thymus. The resultant hypertrophic osteopathy in this horse was thought to be secondary to the invading gastric squamous cell carcinoma.

## Discussion

Hypertrophic osteopathy (Marie's disease) has long been recognised as a syndrome associated with space-occupying lesions of the thorax (Ogilvie 1998). The disease was first recognised in man in the late 19th century and, in human medicine, is divided into 2 categories, primary and secondary, dependent upon aetiology. The primary form is idiopathic, inherited and characterised by finger clubbing. The secondary form is a sequel to a neoplastic or infectious aetiology (Leach and Pool 1992). In human medicine, the disease is termed hypertrophic osteoarthropathy because the articular surfaces of the joints are frequently involved (Lavoie *et al.* 1992). Historically, the disease in animals was termed hypertrophic pulmonary osteopathy or hypertrophic osteoarthropathy, but these terms are now considered inaccurate, as hypertrophic osteopathy has been described secondary to extrathoracic pathology and typically does not involve the articular joint surfaces in animals.

Hypertrophic osteopathy has been documented most frequently in man and dogs (Brown *et al.* 1980), but has been observed in cats (Nafe *et al.* 1981), cattle, sheep (Smith *et al.* 1972), deer (Brown *et al.* 1980), alpacas (Curtis *et al.* 1997) and horses (Mair *et al.* 1996). Until recently, reports of secondary hypertrophic osteopathy in horses were associated with intrathoracic lesions including tuberculosis (Cotchin 1944), primary and metastatic pulmonary squamous cell carcinoma (Lavoie *et al.* 1992), pulmonary abscesses (Chaffin *et al.* 1990), pulmonary granulomatous and fibrosing pneumonia (Wright *et al.* 1979), granular cell myoblastoma (Alexander *et al.* 1965; Godber *et al.* 1993), rib fracture with pleural adhesions (McClintock and Hutchins 1981) and pulmonary infarctions (Messer *et al.* 1983). There are very few reports in the literature documenting hypertrophic osteopathy as a sequelae to extrathoracic disease. Included in the limited list of extrathoracic causes are ovarian dysgerminoma (Mair *et al.* 1996), ovarian granulosa cell tumour (Lavoie *et al.* 1992), ovarian carcinoma (van der Kolk *et al.* 1998), pituitary adenoma (Sweeney *et al.* 1989) and pregnancy (Lavoie *et al.* 1992).

Animals suffering from secondary hypertrophic osteopathy may present with weight loss despite dental and nutritional modification, lethargy, asymmetrical limb swelling, stiff gait, reluctance to move and decreased range of motion of affected joints (Mair *et al.* 1996). Radiographically, the characteristics of hypertrophic osteopathy are diagnostic and include active periosteal proliferation with subsequent subperiosteal new bone deposition and soft tissue swelling along the metaphyses and diaphyses proximal and distal to the joints of long bones (Butler *et al.* 1993). The disease manifests itself in multiple sites and is often found in all 4 limbs. Most commonly, growth of new bone is seen on the cranial, lateral and medial aspects (Orsini 2002) of the metacarpal and metatarsal bones and phalanges (Shneerson 1990). It has also been documented on the radius, carpal bones, tibia and tarsal bones (Mair *et al.* 1996).

The pathogenesis of hypertrophic osteopathy is unknown. Several aetiological theories have been proposed, including pulmonary vascular shunting, hormonal disturbances, chronic periosteal hypoxia and afferent parasympathetic stimulation (Lavoie *et al.* 1992). It is known that initially there is an increase in blood flow to the distal extremities, followed by an overgrowth of vascular connective tissue. This proliferative vascularity leads to osteoid deposition perpendicular to the long axis of the bone separating the periosteum from the cortical surface (Orsini 2002). Suggestion of a neuronal aetiology is supported by the hypothesis that afferent impulses from a focus of intrathoracic disease may be responsible for activation of vasodilation via parasympathetic stimulation (Mair *et al.* 1996). Additionally, vagotomy has been shown to decrease blood flow to the limbs and reverse the periosteal changes associated with hypertrophic osteopathy (Orsini 2002). Parasympathetic stimulation via the vagus nerve is a possible aetiology for the hypertrophic osteopathy presented in this report. It is possible that stimulation of the parasympathetic pathway occurred through the disturbance of vagal innervation to the stomach. The vagus nerve, composed of afferent and efferent parasympathetic fibres, innervates the stomach at the lesser

curvature and pylorus, while gastric branches of the dorsal vagal trunk pass over the lesser curvature to innervate the visceral surface (Budras *et al.* 1994; Evans and Christensen 1979). The normal anatomical and physiological properties of the stomach may have been altered by the tumour, allowing parasympathetic activation from abnormal impulse foci, although no clinical gastrointestinal disturbances were reported. This stimulation could elicit vasodilatory effects at the extremities and consequent osteoid deposition. Furthermore, it can be hypothesised that the hypercalcaemia seen in this case may have contributed to osteoid deposition. It has been shown that certain tumour types, including carcinomas, in horses may secrete a parathyroid hormone-related peptide that has similar physiological properties to endogenous parathyroid hormone (Ogilvie 1998). Parathyroid hormone activates osteoclasts to release calcium deposits from bone, increasing the concentration of calcium in the blood and potentially favouring dystrophic calcification.

The prognosis for regression of secondary hypertrophic osteopathy is directly related to the primary cause. Some cases of hypertrophic osteopathy have been shown to resolve with the removal of the primary cause (Orsini 2002), i.e. pregnancy (Lavoie *et al.* 1992) or intrathoracic abscess (Chaffin *et al.* 1990). However, the presence of hypertrophic osteopathy suggests a chronic pathological process that often carries a guarded prognosis. In one study, 71% of horses with secondary hypertrophic osteopathy were subjected to euthanasia due to progression of clinical signs and poor response to treatment (Mair *et al.* 1996).

In summary, secondary hypertrophic osteopathy is a syndrome that is associated classically with intrathoracic pathology. To the authors' knowledge, this is the first described case of hypertrophic osteopathy secondary to a primary gastric squamous cell carcinoma with metastases. When diagnosing gastric squamous cell carcinoma, it is important to realise that deep pinch biopsies of squamous cell carcinomas, even those which are large and necrotic, may not be diagnostic. When presented with a case of secondary hypertrophic osteopathy, it is important to recognise it as a sequelae to a primary disease process. The aetiological process should be diagnosed to allow an accurate treatment protocol and prognosis.

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