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*Case report*

# HYPERTROPHIC OSTEOPATHY ASSOCIATED WITH LUNG ADENOCARCINOMA IN A CAT: AN OVERVIEW

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Hypertrophic osteopathy (HO) is a pathological condition characterized by progressive, bilateral and symmetrical periosteal bone hyperostosis. Hypertrophic osteopathy is considered a secondary disease that occurs as a consequence of many chronic processes, which are primarily localized in the thoracic cavity (intrathoracic lesions), and less as a result of changes in the abdominal cavity (extrathoracic lesions). We describe a case of a 3.5-year-old female unneutered short-haired cat with a history of chronic weight loss, decreased appetite, dyspnea, and wet cough. During the native X-ray examination of the thoracic cavity, a clearly limited homogeneous radiopaque shadow which covered the entire thoracic cavity was found, as well as periostitis of the front limbs, mainly on the humeri, radii and ulnae. After euthanizing the cat, a control X-ray examination and necropsy of the body was performed. The necropsy revealed a soft-tissue proliferation measuring 13 x 5 x 4 cm and weighing 228 g, and a pronounced ossified periostosis of the long bones, while the histopathological findings revealed adenocarcinoma of the lung with metastasis to the mediastinal lymph nodes. The outcome of hypertrophic osteopathy mostly depends on the primary cause. If the initial lesion had been identified and removed on time, the condition would have also receded spontaneously. The primary tool in determining hypertrophic osteopathy is X-ray diagnosis. Considering the determination of this condition is an indicator of ongoing severe disease, especially in the thoracic cavity, its early diagnosis would lead to prolongation of the animal's life.

**Keywords:** hypertrophic osteopathy, lung adenocarcinoma, periostosis, soft-tissue proliferation, X-ray

## INTRODUCTION

Hypertrophic osteopathy (HO) was first described in humans in 1800 and is known by various names: hypertrophic osteoarthropathy, osteoporotic deformities, acropachy and Pierre Marie–Bamberger syndrome [1]. It is a pathological condition characterized by progressive, bilateral and symmetrical periosteal bone hyperostosis affecting mostly

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the diaphyses and metaphyses of the long bones of the forelimbs and hindlimbs [2,3]. Although diffuse periosteal hyperostosis is not characterized by changes in the continuity of the bone compact tissue, it could still lead to varying degrees of lameness in the animal [1]. The disease occurs in both human and veterinary medicine, and is most common in dogs, and subsequently in: cats, horses, cattle, deer, elk, alpacas, chimpanzees, tigers and mink [4-13]. HO is a secondary disease that occurs as a consequence of several chronic processes, which are mainly localized in the thoracic cavity (intrathoracic lesions), and less as a result of changes in the abdominal cavity (extrathoracic lesions) [14,15].

Intrathoracic lesions in cats associated with HO are primary and metastatic neoplasms of the lung parenchyma, lung abscesses, chronic bronchopneumonia, pulmonary infarction, tuberculosis, megaesophagus, fibrosis and cardiovascular defects. Extrathoracic lesions have been identified as: renal adenoma, adrenocortical carcinoma, injection site sarcoma, as well as seven cases of idiopathic hyperostosis [4,15,16].

This report describes the clinical, radiological and histopathological findings in a cat with HO and provides a more detailed discussion on its pathogenesis, differential diagnoses and outcome using the existing literature.

## CASE PRESENTATION

This case is about a 3.5-year-old female unneutered short-haired cat, weighing 3.2 kg. The cat was admitted to the family veterinarian with a history of chronic weight loss, decreased appetite, dyspnea and wet cough. Based on the history and the clinical examination, the veterinarian suspected chronic pneumonia with indications for pleural effusion. Therefore, he treated the cat with symptomatic therapy: 1 ml/10kg of Amoxycilline (Amoxicillin 20%; Alfasan, Netherlands) and 1 ml/25kg of Dexamethasone (Colvasone; Norbrook, Northern Ireland).

Four days after beginning of the treatment, the cat showed no signs of improving its general health. Taking that into consideration, the veterinarian suggested an X-ray examination and the cat was admitted to the Cabinet for Visual Diagnostics at the Faculty of Veterinary Medicine in Skopje the same day. Native chest X-ray images were made. Regarding the thoracic cavity, X-ray images showed proximally dislocated trachea and bronchi, without radiologically visible changes in their lumina and structure. The silhouette of the heart was completely overshadowed by a homogenous radiopaque mass that occupied the entire thoracic cavity and caudally ended with a sharp edge, which could also be seen on the left side, from the 2$^{nd}$ to the 7$^{th}$ rib (Fig. 1A-B). Regarding the extremities, periostosis was observed on both extremities, on the humeri, radii and ulnae, especially expressed around the area of the distal diaphysis of the humeri (Fig. 1A-B). The determined radiographic changes in the thoracic cavity, as well as the periostosis of the extremities as an incidental finding, indicated neoplastic changes.

Considering the significantly deteriorated quality of life, two months later the cat was euthanized. This time the cat weighed only 2.3 kg. Another X-ray examination was made, and finally a necropsy was performed. Compared to the first X-ray images, the soft tissue changes in the thoracic cavity had progressed and almost the entire lung parenchyma was lost. Observing the front limbs, periostosis was found on all bones (scapula, humerus, radius, ulna, and metacarpal bones) except the phalanges, with the humeri most affected in the area of the distal diaphysis (Fig. 1C-D). Radiologically visible changes were not seen in the continuity of the spine, while in regarding to the hind limbs, HO was found on the pelvis, the femur, the tibia and the fibula, and the metatarsal bones (Fig. 2A-B). The changes were most pronounced in the femurs, the ilium and the ischium bones of the pelvis. Periostosis of the bones was symmetrical with respect to the left and right limbs, as well as the front and hind limbs.

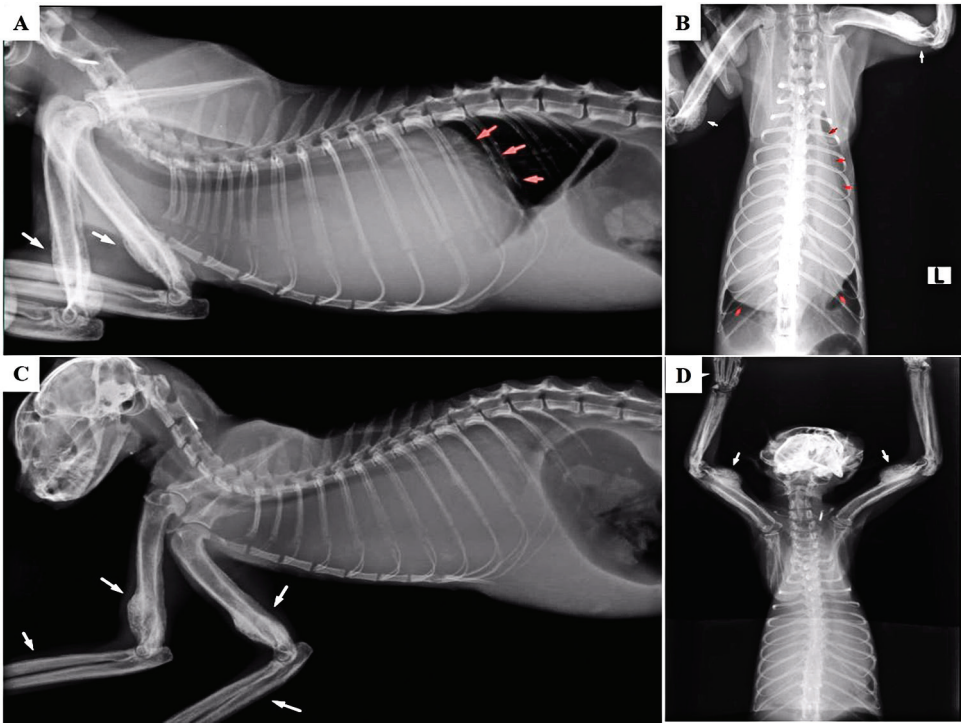


**Figure 1.** First X-ray examination – Thoracic cavity filled with a mass that gives homogeneous illumination and caudally ends with a sharp edge (red arrows). Periostosis of the forelimb bones (white arrows) (**A-B**). Second X-ray examination - Progression of the homogenous illumination with a strongly expressed periostosis of the bones (white arrows) (**C-D**).

During necropsy the following was determined: significant passive hyperemia of the lung parenchyma which is under pressure of a pronounced elliptical soft-tissue proliferation measuring 13 x 5 x 4 cm and weighing approximately 228 g (Fig. 3); the long bones which were previously described radiologically, showed a pronounced ossified periostosis, while the skeletal muscles surrounding the bones were intact; the

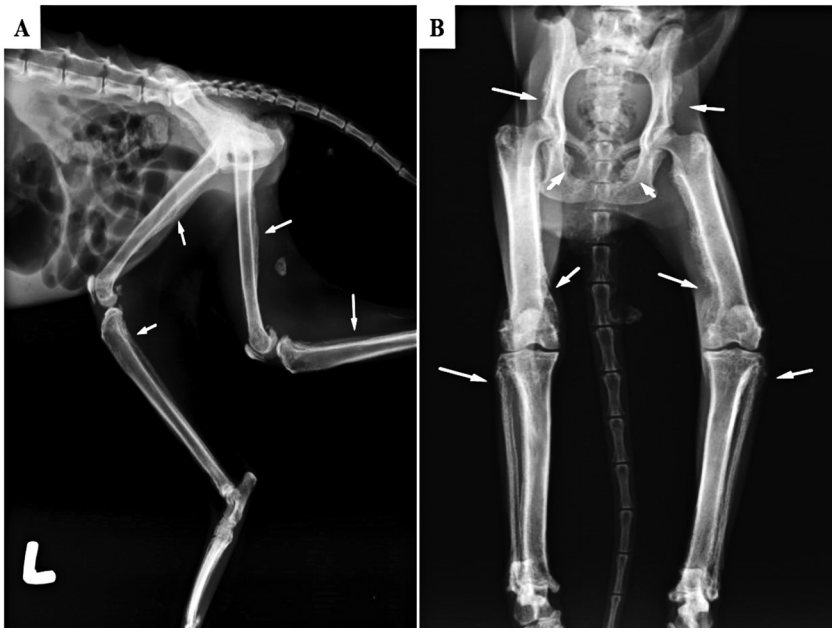


**Figure 2.** Second X-ray examination - Regarding the hind limbs, HO was found on the pelvis, the femur, the tibia, the fibula and the metatarsal bones (white arrows) (**A-B**).

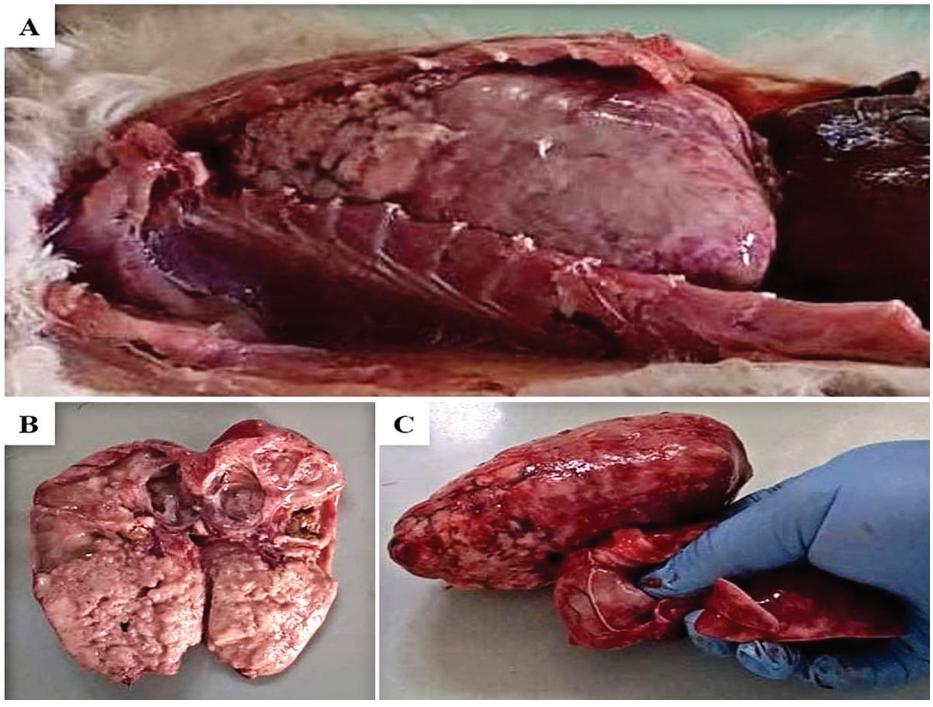


**Figure 3.** Longitudinal section of the thoracic cavity with a gross appearance of the neoplastic mass (**A**). Cross-section of the neoplastic mass (**B**). The neoplastic mass compared to the heart and the lungs (**C**).

pleura was thickened with an increased amount of pleural fluid; normal peritoneal space, as well as normal location, shape and size of the abdominal organs, with the exception of the liver which was enlarged.

Samples for histopathology examination were taken from: the soft-tissue mass, lungs, liver, kidney, and mediastinal lymph nodes. They were immersed in sterile cups in 10% formalin and submitted for histopathological examination. After fixation of the samples with paraffin embedding, 3-5 μm thick sections were made with a microtome which were then stained with Hematoxylin and eosin (H&E) stain. Sections from the tumor material showed a neoplastic proliferation consisted of large, oval-cylindrical cells, with a large nucleus with light chromatin and a prominent nucleolus. Mitoses were seen dispersedly. The cells were firmly lobular, partially acinar and focally papillary arranged. Coagulative necroses were seen as disseminated. Intense secondary inflammation with a large number of neutrophils to the formation of abscesses was present. The pleura was thickened with fibrosis. Parts of lung parenchyma had serious pulmonary edema, mild bronchitis and reactive mesothelial cells–pleural effusion. The finding is consistent with mixed, firmly acinar, poorly differentiated, mucin-nonproducing lung adenocarcinoma and severe pulmonary edema (Fig. 4). Lymphadenitis with metastatic adenocarcinoma was also observed (Fig. 5). Chronic congestion of the liver, dilated central veins with fibrosis of the adventitia, and dilated sinuses filled with erythrocytes. There were rare foci of groups of lymphocytes in the interstitium of the kidneys–focal chronic interstitial nephritis. Bone sections showed a medullary canal with hematopoietic tissue. There were islands of stroma with intense osteoblastic activity in the compact bone tissue. Externally, the skeletal muscles had a normal structure around the bone.

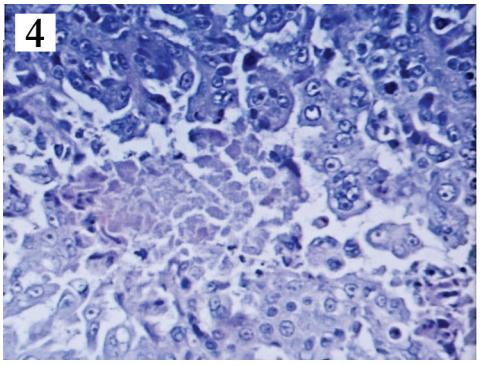


**Figure 4.** Lung adenocarcinoma with focal necrosis.

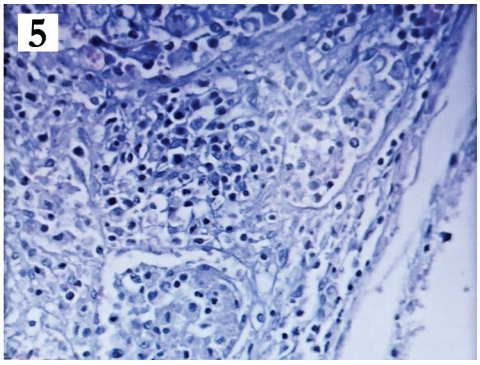


**Figure 5.** Metastatic adenocarcinoma in mediastinal lymph node.

All affected bones were further treated so that the periostosis of the affected bones could be clearly seen (Fig. 6). The first step was to remove the soft tissue from the bones, placed in boiling water until all the remaining soft tissue was removed from them. The whitening of the bones was done by adding laundry detergent 15–20 minutes before removing the bones from the water. Additionally, the bones were thoroughly coated

with a brush by applying hydrogen peroxide in order to get a white color. The purpose of the bone treatment was to confirm the radiologically determined changes of the bones providing a detailed visual representation of the HO in the affected bones.

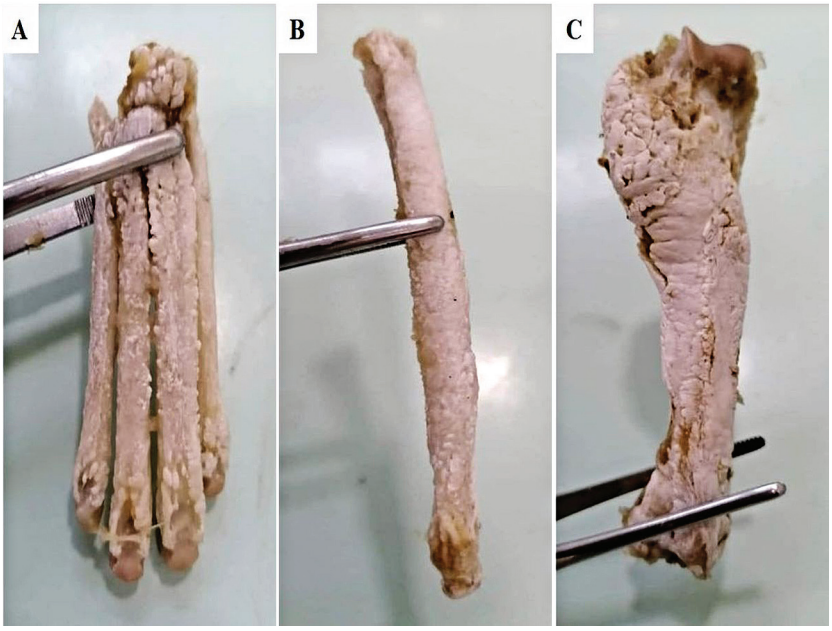


**Figure 6.** Clearly notable periostosis of the bones after boiling treatment: metatarsal bones (**A**), radius (**B**), humerus (**C**).

## DISCUSSION

Primary lung tumors are uncommon in cats, and their prevalence is 0.69–0.75% of all cats which underwent necropsy [17]. Adenocarcinoma is a type of malignant tumor defined as a neoplasm of the epithelial tissue of glandular origin and has glandular features, or both. Adenocarcinomas actually make up >50% of the primary lung neoplasms in cats [18]. Metastatic changes from the lungs to other sites range from 76-80% [19]. In cats and dogs, lung tumors most commonly metastasize to: the liver, spleen, pancreas, kidneys, heart, brain, lymph nodes and muscles [20]. In this case, metastatic changes were found only in the mediastinal lymph nodes and the literature has shown that 33.3% of primary lung tumors metastasize to the mediastinal lymph nodes [18]. Metastatic changes in cats have also been identified in the digits (lung-digit syndrome) and intraocular [20,21]. Although in this case no radiologically visible changes were detected on the digits indicating tumor metastases, one study found that as many as 21% of amputated cat digits had metastatic lung cancer [22]. In regards to HO, whenever there are clinical findings of lameness, swelling or pain in the extremities of cats, an X-ray examination of the chest cavity is inevitable.

There is no age, breed, or gender predisposition for HO in cats [15].

Hypertrophic osteopathy in our case was symmetrical, with the front and hind limbs equally affected, however the phalanges were not affected at all, which is consistent with other similar studies [2,3,23]. Hypervitaminosis A is the principle differential diagnosis of the periosteal proliferation [23]. The changes in hypervitaminosis A are typically located on the cervical spine but very little on the long bones [23]. In addition, hypervitaminosis A is associated with ankylosis of the joints, which is not the case with HO [23].

The pathogenesis of HO has not been fully defined yet and appears to be multifactorial, as suggested by several publications [24]. Several hypotheses have been mentioned however the following four are the most cited. According to the first hypothesis, increased levels of circulating toxins that are products of the primary lesion are causing irritation to the periosteum and synovial membranes [9,15]. The second hypothesis implies changes in the peripheral circulation primarily in the distal parts of the extremities due to the indirect effects of the primary lesion. The peripheral blood flow is poorly oxygenated, increased and passes through arteriovenous shunts, bypassing the capillary junction and leading to local passive congestion and poor oxygenation. This condition stimulates proliferation of connective and periosteal tissue [1,9]. The third hypothesis states that primary lung lesions fail to inactivate the growth factor that induces hyperostosis [25]. Part of the megakaryocyte fragmentation in platelets takes place in the pulmonary circulation [26]. It is believed that in primary lung lesions vascular anastomoses are formed, the fragmentation process bypasses the small blood capillaries, and fragments enter the systemic circulation and are deposited in the distal circulation [4]. The interaction between these megakaryocyte fragments with endothelial cells may result in local release of inflammatory and growth-promoting factors. Such growth factors are vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). Both factors have been shown to cause local fibrovascular proliferation, edema and eventual ossification, which are in fact characteristic signs of HO [4,27,28]. A group of scientists has found that removal of primary lung tumor lesions resulted in a drastic reduction in circulating VEGF levels [29]. The fourth and last hypothesis is the neurovascular mechanism. The autonomic neurovascular reflex originates in the thorax and is transmitted through the afferent vagus nerves. This reflex leaves the lungs near the bronchi and joins the vagus nerve from the mediastinum. Additionally, there may be an alternative afferent pathway from the parietal pleura and along the intercostal nerves [1]. These nerves are stimulated by extrapulmonary lesions, causing vasodilation of peripheral blood vessels and because of insufficient oxygenation, the periosteal proliferation is increased [15,30].

This case has shown several drawbacks due to lack of complete blood count and biochemical parameters, as well as limitations in determining the possible pathogenesis of HO.

The outcome of HO mostly depends on the primary cause. If the initial lesion had been identified and removed in a timely manner, then the HO would have also receded spontaneously. The primary tool in determining HO is X-ray diagnosis, while the determination of HO is an indicator of ongoing severe disease, especially in the thoracic cavity, where its early diagnosis will lead to prolongation of the animal's life.

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**Authors' contributions**

AJ carried out the diagnostic imaging (X-ray), interpreted the X-ray findings, conceived the study and drafted the manuscript. BD carried out the diagnostic imagining (X-ray), helped with interpretation of the X-ray findings and helped to draft the manuscript. DB treated the affected bones and explained the process. EM edited the manuscript. BN introduced the cat to the Cabinet for Cabinet for Visual Diagnostics, gave patient history and treatment. DM supervised the whole progress, reviewed and revised the manuscript, and is responsible for the integrity of the work as whole. All authors read and approved the final manuscript.

**Declaration of conflicting interests**

Hereby we disclose any financial and personal relationships with other people or organisations that could inappropriately influence our work. The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Statement of Informed Consent**

The owner understood procedure and agrees that results related to investigation or treatment of their companion animals, could be published in Scientific Journal Acta Veterinaria-Beograd.

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## HIPERTROFIČNA OSTEOPATIJA POVEZANA SA ADENOKARCINOM PLUĆA KOD MAČKE: PREGLED

Aleksandar JANEVSKI, Boris DIMITRIEVSKI, Emilija MURDZEVA, Dimitar BOZHINOVSKI, Biljana NIKOLOVA, Dine MITROV

Hipertrofična osteopatija (HO) je patološko stanje kojeg karakteriše progresivna, bilateralna i simetrična periostalna hiperostoza kostiju. Hipertrofična osteopatija se smatra sekundarnom bolešću koja nastaje kao posledica mnogih hroničnih procesa, koji su prvenstveno lokalizovani u grudnoj duplji (intratorakalne lezije), a manje kao rezultat promena u trbušnoj duplji (ekstratorakalne lezije). Opisujemo slučaj nekastrirane kratkodlake mačke stare 3,5 godine sa istorijom hroničnog gubitka težine, smanjenog apetita, dispneje i vlažnog kašlja. Prilikom nativnog rendgenskog pregleda grudnog koša utvrđeno je jasno ograničeno homogeno zasenčenje koje je prekrivalo celu grudnu duplju, kao i periostitis prednjih ekstremiteta, uglavnom do humerusa, radijusa i lakatne kosti. Nakon eutanazije mačke, urađen je kontrolni rendgenski pregled i obdukcija tela. Obdukcijom je utvrđena proliferacija mekog tkiva dimenzija 13 x 5 x 4 cm i težine 228 g i izražena okoštala periostoza dugih kostiju, dok je na histopatološkom nalazu utvrđen adenokarcinom pluća sa metastazama u medijastinalnnim limfnim čvorovima. Ishod hipertrofične osteopatije najviše zavisi od primarnog uzroka. Da je početna lezija identifikovana i uklonjena na vreme, stanje bi se takođe spontano povuklo. Primarni alat u određivanju hipertrofične osteopatije je rendgenska dijagnoza. S obzirom da je utvrđivanje ovog stanja pokazatelj tekuće teške bolesti, posebno u grudnoj duplji, njeno rano otkrivanje bi dovelo do produženja života životinje.