Hypertrophic Osteopathy Associated with Disseminated Metastases of Renal Cell Carcinoma in the Dog: A Case Report

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ABSTRACT. A 6-year-old, mixed breed, intact male dog showed signs of left carpal joint swelling and weakness of the forelimbs one month before presentation. The symptoms gradually progressed to bilateral carpal and tarsal joint swelling and tetraparesis. There were a number of radiographically identified lytic-proliferative bone lesions noted on the axial skeleton. Hypertrophic osteopathy of the metacarpals and all distal long bones was also evident. Because of the deteriorating quality of life and guarded prognosis, the patient was euthanized and a complete necropsy was performed. Renal cell carcinoma, with metastasis to the lung, thoracic vertebrae, ribs, and the right adrenal gland, was diagnosed. To our knowledge, renal cell carcinoma with bone metastases and hypertrophic osteopathy has not been reported in dogs.

KEY WORDS: canine, hypertrophic osteopathy, renal cell carcinoma.

Primary renal neoplasia occurs infrequently in dogs, with a prevalence rate of 0.3 to 2% of all canine neoplasia [4, 9, 10, 11, 13]. Of these, renal cell carcinoma (RCC) is the most common type [6, 9, 11, 17] and is believed to originate from the epithelium of the proximal convoluted tubules. RCC generally occurs in older (reported average age of 8 years old) male dogs [6, 13, 16], with no obvious breed predisposition. Here we report an unusual case of canine RCC with disseminated metastases and hypertrophic osteopathy (HO).

A 6-year-old, mixed breed, intact male dog was referred for evaluation of tetraparesis. The patient was not on a regular vaccination program, but was under routine heartworm prevention. A month before presentation, the patient started to show signs of left carpal joint swelling and weakness of the forelimbs. The symptoms gradually progressed to bilateral carpal and tarsal joint swelling and tetraparesis. An episode of hematuria had also been noted. Upon presentation the patient was anorexic and whining painfully. The patient presented with pale mucosal membranes and was cachetic, with 7% dehydration, tachycardia (150 /min), and tachypnea (60 /min). A right heart murmur was auscultated and graded as IV/VI. The patient was lying on his side, unable to stand or walk, but still with intact neurological reflexes and sensations on all four limbs. The distal parts of all limbs were swollen and firm. Multiple firm masses were palpated under the skin on both sides of the chest wall. Blood tests performed by the referring clinic showed leukocytosis (24300 cells/µl), and normocytic, normochromic anemia (packed cell volume: 27.6%, mean corpuscular volume: 65.7 fl, mean corpuscular hemoglobin: 23.3 pg). The blood total calcium concentration value was within normal limit (8.2 mg/dL). Radiographic findings of the chest showed extensive new bone formation on the bodies of the 4th, 5th, and 6th thoracic vertebrae. Lytic-proliferative bone lesions of variable size were also noted on the right 11th, 13th and the left 4th, 5th, 6th, 12th ribs (Fig. 1), and the upper margin of the right scapula. Extensive periosteal, brush-like new bone formation perpendicular to the bone axis was observed on the metacarpals and all distal long bones, with significant soft tissue swelling (Fig. 2). There was no evidence of articular involvement, and the abdominal cavity was unremarkable radiographically.

Tentative diagnoses of disseminated axial bone neoplasia and HO were made. Because of the deteriorating quality of life and guarded prognosis, euthanasia was requested by the client and a complete necropsy was performed. Necropsy revealed multifocal, firm masses distributed on

Fig. 1. Lateral radiographic view of the chest showing lytic-proliferative lesions on the ribs, bodies of the thoracic vertebrae, and right scapula (arrows).

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multiple right and left ribs (including the left 4th, 5th, 6th, and 7th ribs and all right ribs except the 5th, 9th, 12th, 13th). There was also a firm, irregular mass on the 4th, 5th, and 6th thoracic vertebrae. Multiple, white-yellowish masses measuring up to 0.5 cm in diameter were found on the right middle lobe of the lung. An irregular, white, firm mass was located on the right kidney (Fig. 3). A splenic mass was measured at $2 \times 1.5 \times 0.5$ cm in size. The liver was mottled and dark. Other organs were grossly normal.

The whole organs were immediately fixed in 10% neutral formalin, and topographically examined. For immunohistochemical (IHC) studies, the avidin biotinylated enzyme complex (ABC) method was used to demonstrate the expression of cytokeratin AE1/AE3 (cytokeratin, 1:50, Dako, Carpinteria, CA) and RCC (renal cell carcinoma, prediluted, Dako, Carpinteria, CA).

In the kidney, neoplastic cells varied from columnar, to low cuboidal, spindled and stellate. The columnar and cuboidal cells appeared to align along the basement membrane, while the spindled and stellate cells were more pleomorphic and less differentiated in appearance. The nucleus/cytoplasm ratio was 1:3. In the spindled and stellate cells, nuclei were elongate or irregularly shaped. The mitotic rate was low, at less than one per high power field. Nucleoli were variably present, generally single and small. Additional changes in the kidney included locally-extensive necrosis, osteoid metaplasia, and fibrosis. Microscopic lesions in the ribs, thoracic vertebrae, lung and adrenal gland showed similar histopathological changes and were chiefly composed of neoplastic cells arranged in lobules, sheets, nests and acini (Fig. 4). Metastasis was only detected microscopically in the right adrenal gland. IHC results were strongly positive for cytokeratin AE1/AE3 in the majority of the neoplastic cells of the affected lung tissue, and were focally positive for RCC antibody (Fig. 5).

The neoplastic epithelium, arranged in tubular and glomerular patterns, had destroyed the local bony trabeculae. Although the bodies of the 4th, 5th, and 6th thoracic vertebrae were almost totally destroyed by the metastasis, the spinal cord was intact.

There was marked periosteal bone formation on the distal long bones, metacarpal, and metatarsal. The periosteal proliferation contained multilayered trabecular bone, fibrochondroid metaplasia, and mature fibrous connective tissue (Fig. 6). No evidence of neoplastic cell invasion was noted in the lesions. The spleen and liver were also free from tumor invasion. The splenic mass is microscopically diagnosed as hematoma which consisted of a mass of lysed blood and fibrin, surrounded by degenerating leukocytes and fibrous capsule.

In dogs, the most common clinical signs of RCC are non-specific, including anorexia, depression, and weight loss.
Hematuria and fever are also common [9–11]. Due to the absence of specific clinical signs, RCC is difficult to diagnose at early stages, and has often become metastatic by the time of presentation [9, 11, 13, 17]. Metastasis of canine RCC has been reported most likely to involve the lung, regional lymph node, liver, serosal surface, and ipsilateral adrenal gland [9, 11, 13, 17].

Metastatic bone lesions from primary soft tissue neoplasia are rare, and only a few canine cases of RCC bone metastases had been reported [2, 11, 12]. The average age of dogs affected with bone metastasis is 9.5 years (ranging from 1 to 17 years) with no sex or breed predisposition [12]. The most common sites of metastases are the vertebrae, ribs, and long bones [12]. Approximately a third of affected dogs and cats with bone metastasis bear two or more lesions [12]. Since most of the lesions occur in the red hematopoietic marrow, bone metastases are generally accepted to occur via a hematogenous route [12]. This assumption is also supported by the absence of a lymphoid system in the osseous tissue and marrow cavity.

Dogs affected with primary renal neoplasia usually show normal blood examination results, especially if the neoplasm is unilateral [6, 9, 11]. Anemia, secondary to hematouria, or polycythemia may be present. The pathogenesis of polycythemia induced by excess erythropoietin production from renal neoplastic tissue remains unclear. However, polycythemia has been reported infrequently, and is now recognized as part of paraneoplastic syndromes [6, 8, 9, 11, 16]. Other paraneoplastic syndromes of canine renal neoplasia include fever, hypercalcemia, marked neutrophilia, and HO [9, 11, 14, 15].

HO is a polyostotic disease characterized by extensive periosteal new bone formation [5]. A number of species have been reported to be affected by HO, including humans, dogs, horses, cattle, and cats [1, 3, 5, 7]. The diagnosis of HO can be made with clinical and radiographic findings [1, 14]. The distal parts of affected limbs are typically swollen, sometimes warm to the touch. Lameness is often noted as well [1, 3, 5, 14]. HO is mainly associated with primary or secondary lung lesions, regardless of if the lesion is neoplastic or not. HO is also found to be secondary to other intrathoracic diseases, such as esophageal granuloma, esophageal neoplasia, and congenital or acquired heart diseases [1, 5, 7, 14]. Rarely, HO may be related to intra-abdominal neoplasms without thoracic involvement, such as urinary bladder rhabdomyosarcoma, renal neoplasia, prostate neoplasia, and adrenocortical carcinoma [1, 5, 7, 14].

The pathogenesis of HO is still largely undetermined [1, 5, 7, 14]. The three most common hypotheses are local circulation disturbances, abnormal metabolism of hormones or hormone-like substances, and neurogenic origins. The treatment for HO is to resolve the underlying primary disease and to symptomatically treat any pain and discomfort or other clinical signs [1, 5, 7, 14]. Usually, the proliferated bone change will regress in 2 to 5 weeks after elimination of the underlying cause [5, 7, 14, 15].

Hypertrophic osteopathy in the present case may be either secondary to intra- and extra-pulmonary metastases of the thorax, or as one of the paraneoplastic syndromes of canine renal neoplasia. HO mainly involves the long bones of limbs, which are not the most common sites of tumor metastasis. The characteristic radiographic sign of HO is also different from that of bone metastasis. The periosteal reaction in HO occurs without cortical destruction. The metastasis of RCC, in this case, was only found in the axial skeleton, consistent with findings in previous reports [2, 11].

In the present case, the diagnoses of HO and RCC with disseminated metastases were made based on histopathological, immunohistochemical, and radiological results. To our knowledge, canine RCC has not documented with concurrent bone metastases and HO formation. The patient was also younger than the average age of dogs with RCC and metastatic bone lesions.
REFERENCES