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<Case Report>

Fulminant multicentric osteosarcoma with systemic metastasis in a dog

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Abstract: A 15-year-old castrated mixed breed dog presented due to a 5-month history of cough and difficulty in ambulation. Necropsy showed multiple periosteal and intramedullary infiltrative masses in the appendicular skeleton. In addition, single and multiple neoplastic nodules were observed in several organs, including the lungs, liver, kidney, and heart. Microscopically, several skeletal neoplastic masses and nodules in the parenchymal organs revealed similar changes. The neoplastic cells were spindle- to polygonal-shaped with prominent osteoid production and occasional cartilaginous and bone formation. Based on the gross findings and histopathology results, the case was diagnosed as multicentric osteosarcoma with systemic metastases.

Keywords: dogs, metastasis, neoplasm, osteosarcoma

Osteosarcoma is a neoplasm originating from the skeleton, although it can also derive from organs other than the skeletal system. Osteosarcoma is the most common primary bone tumor in dogs, accounting for about 80% of all reported malignant bone tumors in these animals [13]. Hematogenous metastasis to the lungs commonly occurs early in the disease process, and pulmonary metastases are detected radiographically at the time of initial diagnosis in approximately 10% of dogs with osteosarcomas originating from bones [13]. Although much less common, metastasis to other parts of the skeleton also occurs [13].

Multicentric osteosarcoma was originally defined as an osteosarcoma arising from two or more skeletal sites [3, 4, 6, 7]. In humans, it has been considered a distinct clinical entity, with poor prognosis, presenting as multiple primary tumors in bones [3, 4, 6, 7]. More recently, however, multicentric osteosarcoma has been regarded as multiple bone metastases from one primary tumor [4, 6]. Also in veterinary medicine, a few cases of multicentric osteosarcoma have been described [2, 11]. This report describes a dog with multicentric osteosarcoma accompanied by multi-organ metastases. The origin of the tumor, its possible pathways of dissemination and the significance of bone metastasis are discussed.

A 15-year-old castrated mixed breed dog was presented to the Veterinary Medical Teaching Hospital of Seoul National University, Korea, with a 5-month history of consistent coughing and difficulty in ambulation. Serum chemistry panel and hematology values were unremarkable except for a marked increase in alkaline phosphatase concentration (373 U/L; reference range, 8–100 U/L). Routine physical examination revealed multiple firm swollen areas throughout the left hindlimb, the left distal forelimb, and the right proximal and distal forelimbs. Radiography revealed both aggressive and nonaggressive periosteal reactions and osteolysis in the left and right radii and ulnae as well as in the left tibia and fibula. Radiography detected round nodular masses in the left median lung lobe. Abdominal ultrasound showed round nodular masses in the lateral lobe of the liver, as well as multiple hyperechoic regions in the cortex and medulla of both kidneys and a hypoechoic cyst in the left kidney. Multiple fine needle aspiration cytology of the periosteal bone lesion showed that the cells were highly pleomorphic, ranging from oval to spindle to polygonal in shape, with moderate amounts of basophilic cytoplasm and round to oval nuclei containing two to three prominent nucleoli. Extracellular accumulation of an eosinophilic substance and bone material was also noted. Based on these cytologic features, the animal was tentatively diagnosed with osteosarcoma. The condition of the dog continued to deteriorate and it died 5 days after referral. A necropsy was performed immediately after death.

At necropsy, multiple firm ill-defined masses were observed in the appendicular skeleton, resulting in deterioration of the normal bone architecture. One $9 \times 7 \times 5$ cm^3 sized mass involved the left tibia and fibula, a $4 \times 4 \times 3$ cm^3 sized mass

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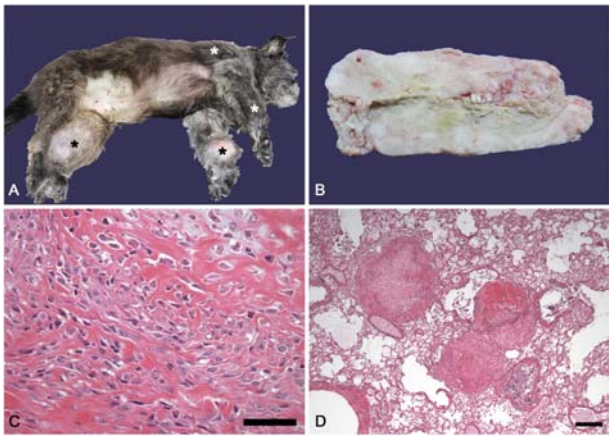

Fig. 1. (A) Dog. Note multiple firm masses (asterisk) in both forelimbs and the left hind limb. (B) Radius and ulna. On cut section, severe diffuse irregular periosteal bone formation with adhesion of the radius and ulna was noted. The medulla was partially occupied by a mass with multifocal necrotic foci. (C) Radius and ulna. Neoplastic spindle cells forming streams separated by eosinophilic fibrillar substance (osteoid). (D) Lung. Note multiple metastatic nodules consisted of neoplastic spindle cells with bone differentiation. H & E stain (C and D). Scale bars = 50 μm (C), 400 μm (D).

was present in the left radius and ulna, a 3 × 3 × 2 cm^3 sized mass was observed in the right radius and ulna, and a 3 × 4 × 3 cm^3 sized mass was found in the right scapula (Fig. 1A). On cut sections, severe diffuse irregular periosteal bone formation was noted and the medulla was partially occupied by a mass with multifocal necrotic foci (Fig. 1B). A round, firm, tan, elevated nodule about 6 cm in diameter was present in the left lung lobe, with similar looking nodules, 2 cm and 3 cm in diameter, observed in the left ventricle of the heart and left lobe of the liver, respectively. Cross sections of these nodules showed firm yellowish to tan areas with necrosis, hemorrhage, and mineralization. Numerous similar well-circumscribed firm, tan, round neoplastic nodules, about 2 to 6 mm in diameter, were also present throughout both kidneys and all pulmonary lung lobes. Similar looking nodules about 1 cm in diameter were observed in the diaphragm and in the fourth rib.

For histopathology, after decalcification, tissue samples were fixed in 10% neutral phosphate-buffered formalin, processed in a routine manner, embedded in paraffin wax, and stained with hematoxylin and eosin. Microscopic examination of sections taken from multiple bone sites and neoplastic nodules revealed almost identical changes. The neoplasms consisted of highly pleomorphic infiltrative neoplastic cells, round to spindle to polygonal in shape, forming short streams and whorls. These neoplastic cells had indistinct cell borders, a small to moderate amount of eosinophilic cytoplasm, and round to ovoid, hyperchromatic nuclei with one to two prominent nucleoli (Fig. 1C). Occasional multinucleated cells and one to three mitotic figures per high power field (400×) were observed. Foci of an eosinophilic fibrillar substance (osteoid) were present between the neoplastic cells (Fig. 1C). Multiple foci of interconnected mineralized trabeculae rimmed by osteoblasts and chondrification were also noted. Tumor emboli were present in the blood vessels. Areas of massive necrosis and hemorrhage were also present. Based on the gross and histologic features of the neoplasm, the tumor was diagnosed as multicentric osteosarcoma with systemic metastases (Fig. 1D).

Osteosarcoma involving two or more skeletal bones is called multicentric osteosarcoma (MOSA) [3, 4, 6, 7]. MOSA is an uncommon condition in humans and is rarely reported in animals [2-4, 6, 7, 11]. MOSA is classified either as synchronous, when two or more lesions are present at the time of initial diagnosis, or as metasynchronous, when only one lesion is present at the time of initial diagnosis and additional bone lesions are found later [4, 11]. It is unclear whether MOSA is a multiple primary bone tumor or a single primary bone tumor with metastases to other skeletal sites [3, 4, 6, 7, 11]. MOSA was originally coined to denote multiple primary bone tumors in the absence of pulmonary metastasis [3]. However, according to recent publications, MOSA has regarded as multiple metastases from one primary bone tumor [4, 6]. The hypothesis, that multiple bone lesions are metastatic lesions from a single primary tumor, is supported by findings of a large, dominant lesion which is considered as the primary mass and a correlation between the responses to chemotherapy of the dominant lesion and the other lesions [4, 6]. Bone-to bone metastasis via Batson's plexus or lymphatic spread has also been suggested [1, 7].

The dog described here had a dominant mass involving the left tibia and fibula, with other masses at three other sites of the appendicular skeleton. In addition, the animal had disseminated metastasis to the lungs, heart, liver, kidneys, and diaphragm. It is impossible to determine whether the multiple bone lesions were primary or metastatic. However, the findings of a dominant lesion, similar histological appearances of the multiple bone lesions, and systemic metastases to the lungs at the time of initial diagnosis, suggest that the bone lesions are more likely metastases than multiple primary tumors. The metastases to the lungs and the presence of tumor emboli in blood vessels suggest a hematogenous route of dissemination. Although the origin of the tumor is difficult to determine, the largest mass involving the left tibia and fibula is likely the primary mass accepting the prevailing view considering the largest mass as the primary tumor.

Osteosarcoma often metastasizes to the lungs via a hematogenous route [13]. Bone metastasis from osteosarcoma is unusual and normally appears late in the disease, with or without pulmonary metastasis [5, 10, 12]. Reports in both humans and dogs, however, have suggested that bone metastases are more frequent than previously thought [2, 7, 9]. The actual frequency of bone metastasis may be underestimated because of the infrequency of thorough examination of the skeleton at necropsy [13]. Thus, the possibility of bone metastasis should be assessed carefully in osteosarcoma

patients at initial presentation. Nuclear scintigraphy has been found to be more sensitive than radiography and is being used to detect possible early bone metastasis in dogs with osteosarcoma [8, 11].

The current report described an unusual fulminant MOSA accompanied by systemic metastasis in a dog. The tumor showed rapid growth and dissemination, but the patient was not clinically examined until the terminal stage of disease progression so the full spectrum of progression from the initial stage could not be determined. The frequency of metastasis to other skeletal sites from primary site might be underestimated in osteosarcoma and a thorough radio-imaging to detect possible early bone metastasis should be considered clinically. Full postmortem examination has been performed on only a limited number of MOSA in dogs. Further reciprocal clinical as well as pathological investigation is warranted to obtain a better understanding of the biology and metastatic mechanism of MOSA in dogs. The possibility of bone metastasis should be always considered in dogs with osteosarcoma.

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