A canine case of appendicular osteosarcoma with hemangiosarcoma developing during treatment

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Abstract
An 11-year-old castrated male dog of mixed breed was referred to the hospital for treatment of suspected osteosarcoma of the left distal radius (Day 1). Limb amputation was performed on Day 4. A diagnosis of osteosarcoma was made histopathologically. The dog was treated with an adjuvant chemotherapy series with carboplatin. On Day 427, abdominal ultrasonography revealed a mass in the medial right hepatic lobe. A partial liver lobectomy was performed, and the lesion was diagnosed as hyperplastic nodules by histopathology. On Day 849, abdominal ultrasonography revealed a mass surrounding the sublumbar arteriovenous area. A Tru-cut biopsy was performed, and histopathology confirmed the diagnosis of hemangiosarcoma. Complete remission of the osteosarcoma was achieved. The patient enjoyed an excellent quality of life for 956 days until death resulting from hemangiosarcoma.

Key word: dog, hemangiosarcoma, osteosarcoma

In large breed dogs, osteosarcoma typically manifests as a primary bone tumor and accounts for 85% of malignant bone tumors [4, 7]. Limb involvement is observed in 75% of osteosarcoma cases, with a high likelihood of metastasis at the time of diagnosis [4]. The median survival time following surgery alone ranges from 102–168 days [1, 10, 12-14]. In a study of small breed dogs, osteosarcomas represented less than 50% of all skeletal neoplasms, frequently affected the axial skeleton, and had no apparent predilection for the distal radius [3]. However, the skeletal neoplasms of small breed dogs are poorly characterized [3]. This report describes a case of appendicular osteosarcoma in a small breed dog that suffered from liver hyperplasia and hemangiosarcoma after limb amputation.

The patient was an 11-year-old castrated male dog of mixed breed with a body weight of 8.7 kg. One month prior to presentation at this hospital, the dog's left distal radius became swollen without lameness, and bone radiography of the affected limb revealed osteolysis. Bone biopsy revealed a possibility of osteosarcoma. The dog was referred to the Takahira Animal Hospital for diagnosis and further treatment.

The dog was in a good physical condition and showed no lameness. A complete blood count (CBC) analysis revealed no abnormality. Serum chemical analysis revealed an increase in the level of alkaline phosphatase (ALP) (510 U/L; reference range, 68-300 U/L). Bone radiography of the left distal radius revealed osteolysis and a spiculated periosteal reaction (Fig. 1). Thoracic, abdominal, and other bone radiographic and abdominal ultrasonographic examinations revealed no abnormalities (Day 1).

Limb amputation was performed on Day 4. A histopathological examination of the tissue sample obtained during amputation led to a diagnosis of osteoblastic osteosarcoma with invasion of the cortical bone; tumor cell atypia was strong, the mitotic figures were moderate in number, the surgical margin was reportedly clean, and infiltration into blood vessels was not observed. Carboplatin (carboplatin injection 150; Nichi Iko Co., Ltd., Toyama, Japan) (100–120 mg/m², every 3-4
weeks) was selected for chemotherapy from Day 14 to Day 451. Piroxicam (Palpasin; Towa Pharmaceutical Co., Ltd., Osaka, Japan) (0.3 mg/kg, e.o.d.) was administered orally from Day 1 to Day 914.

Thoracic radiography was performed once a month from Day 14 to Day 426 and revealed no abnormalities. On Days 119 and 355, abdominal ultrasonography was performed because a serum chemical analysis revealed increased levels of alanine aminotransferase (ALT) (150 and 101 U/L; reference range, 23–89 U/L) and ALP (604 and 869 U/L); however, no abnormality was revealed. Bone marrow suppression (neutropenia; grade 1: VCOG classification [15]) was observed 3 weeks after each chemotherapy session from Day 115; gastrointestinal toxicity tests showed no abnormality during chemotherapy from Day 14 to Day 426. On Day 426, CBC revealed no abnormality. Serum chemical analysis revealed increased levels of ALT (228 U/L) and ALP (2140 U/L). Abdominal ultrasonography revealed a mass in the medial right hepatic lobe (3.9×3.4 cm). Thoracic and bone radiography revealed no abnormalities. A partial liver lobectomy was performed on Day 433. Hyperplastic nodules and hepatitis were diagnosed on the basis of the histopathological findings. Neither ALT nor ALP levels showed any abnormality 2 months after surgery. Carboplatin administration was stopped on Day 451 because of concerns regarding the accumulation of toxicity (the total number of carboplatin doses was 16, and the cumulative dose was 1660 mg/m²).

Thoracic radiography and abdominal ultrasonography were performed once a month from Day 451 to Day 849 and revealed no abnormalities. On Day 849, CBC analysis revealed no abnormality. Serum chemistry revealed an increase in ALT (205 U/L) and ALP (>3500 U/L) levels. Abdominal ultrasonography revealed a mass surrounding the sublumbar arteriovenous area (4.1×2.4 cm) (Fig. 2a), but revealed no abnormalities in the liver. Thoracic and bone radiography revealed no abnormalities. A Tru-cut biopsy of the abdominal mass led to the diagnosis of hemangiosarcoma. Dalteparin (Dalteparin sodium injection 5000 IU; Teba Pharmaceutical Co., Ltd., Nagoya, Japan) (100 IU/kg, SC, once a week) was used to prevent disseminated intravascular coagulation (DIC) caused by hemangiosarcoma from Day 882 to Day 956.

On Day 879, the patient exhibited left hind-limb edema. Abdominal radiography and ultrasonography showed that the mass was enlarged (8.0×5.0 cm), and lymphostasis was suspected (Fig. 2b). Thoracic and bone radiography revealed no abnormalities. Only carboplatin (80 mg/m², because of the accumulation of toxicity) was administered once (because of neutropenia) on Day 882. The hind-limb edema subsequently resolved, but the size of the mass did not change.

Thoracic radiography was performed once a month and revealed no abnormalities from Day 882 to Day 952. Abdominal radiography and ultrasonography were also performed once a month, and the mass showed signs of progressive disease.

Fig. 1. Bone radiography of the left distal radius.
Osteolysis and a spiculated periosteal reaction are shown.
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From Day 882 to Day 952. Because the patient exhibited anorexia and loose stools, only supportive care was performed. On Day 952, the patient presented with hind-limb edema and difficulty in urinating. A CBC indicated thrombocytopenia (111 $\times 10^3$ cells/µL), and a serum chemical analysis revealed an increase in the levels of blood urea nitrogen (BUN) (39.0 mg/dL; reference range, 9.1–30 mg/dL). The patient died on Day 956. DIC was suspected as the cause of death; however a necropsy was not performed.

This report describes a rare case of osteosarcoma followed by a development of hemangiosarcoma during treatment. The hemangiosarcoma was suspected of possibly being a secondary cancer resulting from the administration of a chemotherapeutic agent.

In large breed dogs with osteosarcoma, the median survival period following limb amputation and adjuvant chemotherapy with carboplatin is 308–322 days [2, 9]. Shida et al. reported that a low-dose carboplatin chemotherapy may improve outcomes in cases of canine osteosarcoma with limb amputation [11]. This small dog’s case of osteosarcoma was treated with piroxicam [6] and a low-dose carboplatin as adjuvant chemotherapy, and survived for 956 days from the date of first presentation. Although it is possible that the transfer rates of small dogs are lower than those of large dogs, the skeletal neoplasms of small dogs are poorly characterized [3]; therefore, further studies with a greater number of cases are needed.

When a hemangiosarcoma was discovered surrounding the sublumbar arteriovenous area, only the piroxicam treatment was continued [5]. In this case, a regimen of doxorubicin and cyclophosphamide was another possibility, but was decided against because the agents are metabolized hepatically. Therefore, carboplatin was selected [8] when the patient showed left hind-limb edema. This regimen successfully alleviated the dog’s edema. These findings suggest that the mass had blocked the dog’s lymphatic circulation.

The patient exhibited no distant metastasis until 952 days after surgery; therefore, there are three potential etiologies: an absence of microscopic metastasis when the limb was amputated, the possibility of long-term stochastic survival (in large breed dogs, osteosarcoma cases have about a 20% 2-year survival rate, and about 10% survival for more than 3 years), or the disappearance of microscopic metastasis resulting from adjuvant chemotherapy.

It was suspected that the biological behavior of this small breed dog’s osteosarcoma was different from that of large dogs, and it is possible that the difference in treatment (standard chemotherapy versus low-dose chemotherapy) had an influence on the prognosis, but the influence was likely weak. To more accurately clarify the characteristics of this disease, further studies with greater numbers of cases are necessary.
References


和文要約

雑種犬、去勢雄、11歳齢が骨生検による骨肉腫疑いとの事で来院した。左前肢体幹部断脚術を行い、病理検査にて骨肉腫と診断した。術後の補助的化学療法として、カルボプラチンにて治療を行った。初診より1年2ヵ月目に超音波にて肝臓内側右葉に腫瘤を発見した。肝葉切除術を行い、病理検査にて過形成性結節と診断した。その後、一般状態は良好であったが、初診より2年4ヵ月目に超音波検査にて腰椎下動静脈周囲に腫瘤を発見した。Tru-cut 生検にて血管肉腫と診断した。本症例は、骨肉腫の治療中に肝臓腫瘤・血管肉腫に罹患したが、亡くなるまでの2年7ヵ月間、骨肉腫の再発もなく、非常に良好な QOL を維持することができた。

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