

## CASE REPORT

## Rapid postoperative recurrence of a cranial multilobular tumor of bone in a young dog

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### Case Report

A 2-year and 11-month-old male neutered Jack Russell Terrier presented to the Queen Mother Hospital for Animals, the Royal Veterinary College, University of London for further evaluation of focal seizures and cervical hyperesthesia of 7-day duration. General physical examination was within normal limits. Neurological examination revealed obtundation, bilaterally absent menace responses, and cervical hyperesthesia. No other abnormalities were noted during the neurological examination. A multifocal neuroanatomical localization with forebrain and cervical spinal cord involvement was considered most likely. Results of a complete blood count and a biochemistry profile were within normal limits. The dog was premedicated with methadone 0.1 mg/kg IV. Diazepam (0.3 mg/kg IV) was administered prior to induction of anesthesia with propofol (4–6 mg/kg IV dosed to effect). Anesthesia was maintained with sevoflurane vaporized in oxygen. Magnetic resonance imaging (MRI; 1.5T Intera, Philips Medical Systems, Eindhoven, the Netherlands) of the head included sagittal and transverse plane T2-weighted

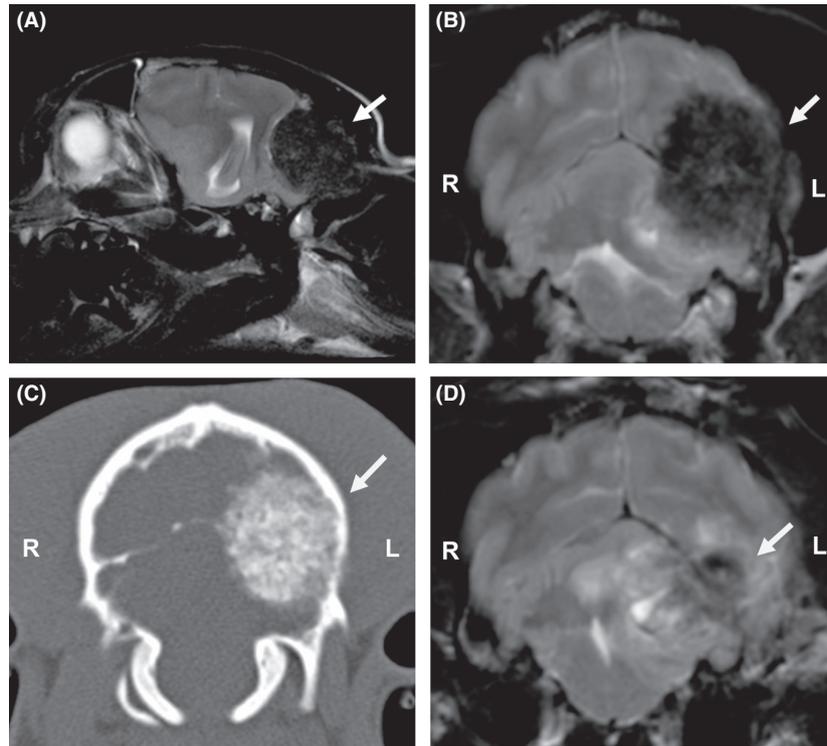
### Key Clinical Message

Although resection of multilobular tumors of bone can be associated with a good prognosis and long disease-free intervals in dogs, osteosarcomatous transformation should be considered a cause for rapid recurrence of clinical signs.

### Keywords

Craniotomy, neurology, osteosarcom, veterinary

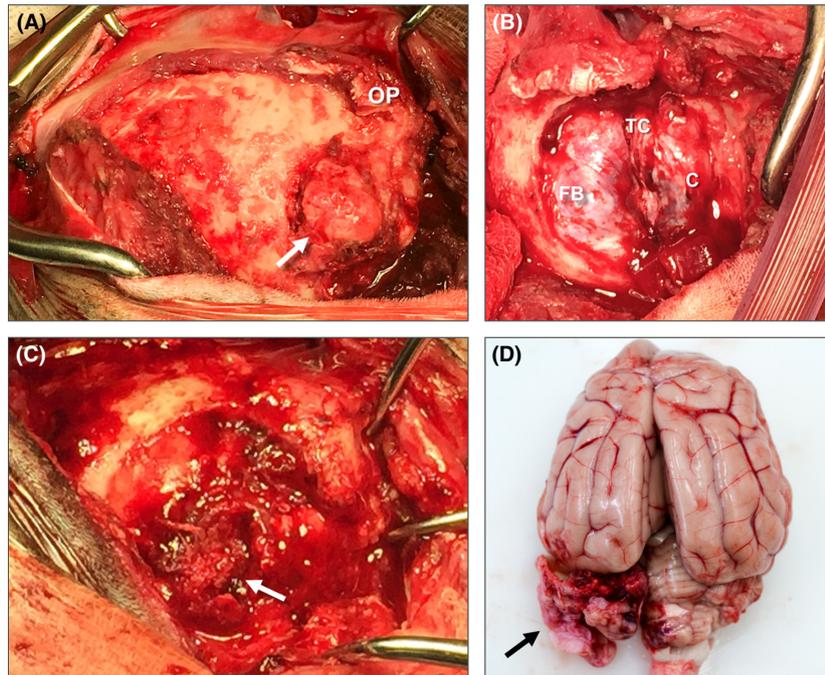
fast spin echo (repetition time [ms] [TR], echo time [ms] [TE], 2882/110 in sagittal, and 5099/110 in transversal plane), transverse plane T2-weighted fluid-attenuated inversion recovery (FLAIR) (TR/TE, 6000/120), and transverse T2\*-weighted gradient echo sequences (TR/TE, 753/23, 18° flip-angle). Sagittal and transverse plane T1-weighted turbo-spin echo (T1W TSE) (TR/TE, 450/15) images were acquired before and after IV injection with gadolinium contrast (0.1 mmol/kg gadobutrol, Bayer plc, Strawberry Hill, UK). MRI examination demonstrated a large (20 mm × 21 mm × 18 mm), well-demarcated, irregularly margined, left-sided, extra-axial mass, arising with a broad base from the left occipital bone, compressing the left occipital lobe and left cerebellar hemisphere (Fig. 1A and B). The mass was hypointense on T2-weighted, T1-weighted, FLAIR, and T2\*-weighted gradient echo sequences compared to surrounding brain parenchyma. Peripheral contrast enhancement was present, and raised intracranial pressure was suggested by the presence of a midline shift and foramen magnum herniation. MRI of the cervical spinal cord demonstrated syringomyelia. A subsequent computed tomography (CT;



**Figure 1.** T2-weighted sagittal (A) and T2-weighted transverse (B) MR images and a CT image (C) of a 2-year and 11-month-old male Jack Russell Terrier presented for further evaluation of focal seizures and cervical hyperesthesia. Transverse T2-weighted MR image at the time of recurrence of clinical signs (D). (A and B) A large, extra-axial, left-sided, hypointense mass associated with the skull (arrow) causes compression of the occipital lobe and left cerebellar hemisphere. (C) The mass is isodense to bone and contains stippled mineralized densities (arrow). (D) A poorly demarcated hypointense mass lesion is visible at the same site of previous tumor resection (arrow). The mass is surrounded by a large amount of perilesional edema, which is possibly caused by the previous surgery.

MX8000 IDT, Philips Medical Systems) study of the thorax and abdomen was within normal limits, while CT of the head demonstrated the mass to have a similar attenuation to bone (Fig. 1C). Although the largest portion of the mass was within the cranial vault, an extracranial portion was evident, with distortion of the lateral aspect of the occipital and parietal bones. Multilobular tumor of bone, osteosarcoma, and chondroma was considered the most likely differential diagnoses at this time. The dog was anesthetized the next day with the aforementioned protocol and positioned in sternal recumbency. A combined left-sided rostral tentorial and caudal fossa craniotomy were performed, which allowed removal of the well-defined bony mass *en bloc* (Fig. 2). The wound was closed routinely without performing a cranioplasty. The dog recovered uneventfully from anesthesia. Intraoperative analgesia consisted of an IV constant rate infusion of remifentanyl (0.15–0.4 µg/kg/min), while early postoperative analgesia consisted of a combination of paracetamol (10 mg/kg IV q12 h), methadone (0.1–0.2 mg/kg IV q4 h), and dexamethasone (0.2 mg/kg IV q24 h). The dog demonstrated ambulatory cerebellar ataxia and

bilaterally absent menace responses the day after surgery. He gradually improved, was discharged from hospitalization 5 days after surgery and was, according to the owners, neurologically normal 7 days after surgery. Histopathological examination of cruciate sections representative of the mass and surgical margins revealed a neoplasm composed of multiple islands and anastomosing trabeculae of well-differentiated woven bone and occasional cartilage surrounded by few polygonal to spindle cells, separated by thin, irregular fibrovascular septa. There was mild anisocytosis and anisokaryosis, and five mitoses were observed in 10 high-power fields (Fig. 3). Neoplastic cells extended to the surgical margins. These findings were consistent with a multilobular tumor of bone (grade II) [1]. Eight days after surgery, the dog developed hypermetria of the left thoracic limb, which rapidly progressed to nonambulatory ataxia and a right-sided head tilt. Neurological examination revealed nonambulatory vestibular ataxia, with a right-sided head tilt and a tendency for rolling and falling to the right side, a miotic right pupil, and disconjugate nystagmus, which changed directions with changes in position of the head.



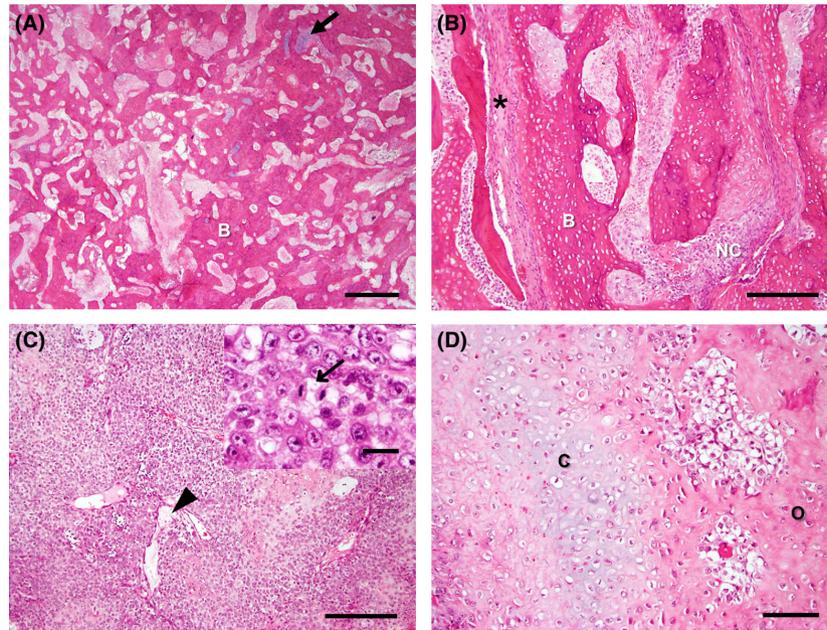
**Figure 2.** Intraoperative pictures of initial tumor removal (A and B), second surgery after recurrence of clinical signs (C) and post mortem evaluation (D). (A) A mass associated with the skull is clearly visible (arrow). Rostral to the left and occipital protuberance indicated by OP. (B) Tumor removed *en bloc* after craniotomy. Rostral to the left. Forebrain (FB), tentorium cerebelli (TC), and cerebellum (C) indicated. (C) Second surgery 11 days after the first surgery indicates tumor regrowth (arrow) at the same site as the previous surgery. Rostral is to the left. (D) Large extra-axial mass visible at the same site as previous tumor removal.

These findings were suggestive for a central vestibular syndrome. General anesthesia was induced and maintained with the aforementioned protocol. Repeat MRI examination of the head revealed a large, poorly demarcated, extra-axial mass lesion at the site of the previous surgery. The lesion had a heterogeneous, predominantly hypointense intensity on all sequences compared to surrounding brain parenchyma (Fig. 1D). No IV contrast medium was administered during this study. Hematoma formation at the site of surgery and/or tumor regrowth was considered the most likely causes for this postoperative neurological deterioration. The next day, the dog was anesthetized again as described above and underwent surgical exploration of the previous surgery site. Surgery revealed a large firm mass lesion at the same site of previous tumor resection (Fig. 2C), suggesting tumor regrowth. At this time, the owners of the dog elected euthanasia during surgery. Postmortem examination revealed a roughly spherical,  $20 \times 15 \times 15$  mm bony mass that compressed the left occipital lobe and left cerebellar hemisphere (Fig. 2D). Gross postmortem examination of the thoracic cavity, abdominal cavity, appendicular, and axial skeleton did not reveal any evidence of tumor metastasis. Histopathological examination of the mass revealed disorganized sheets of polygonal

spindloid cells, with occasional fibrous septa and blood vessels. There were disorganized islands and trabeculae of osteoid, woven bone, chondroid matrix and cartilage, and extensive necrosis. Anisocytosis and anisokaryosis were marked, and 12 mitoses were counted per 10 high-power fields (Fig. 3). The underlying compressed cerebellum was partially malacic (necrotic). These findings were consistent with a multilobular tumor of bone with osteosarcomatous differentiation (grade III) [1].

## Discussion

Multilobular tumors of bone (MTBs) (synonyms; multilobular osteochondrosarcoma, chondroma rodens, cartilage analogue of fibromatosis, calcifying aponeurotic fibroma, juvenile aponeurotic fibroma and multilobular chondroma or osteoma) are uncommon, but not rare, neoplasms in dogs, which most often affect the flat bones of the skull [2]. Multiple additional sites including the axilla, hard palate, os penis, ribs and pelvis have also been reported [2–8]. Although the most common clinical presentation is that of a solid and firm mass of the skull, neurological signs can result if compression of the brain occurs. The nature of neurological signs is then reflected by the specific location of the neoplasm. MTB is typically



**Figure 3.** H&E stained sections of a multilobular tumor of bone removed during the first surgery (A and B) and during postmortem examination after tumor regrowth was observed (C and D). (A) Anastomosing trabeculae of mature bone (B) and occasional cartilage (block arrow) separated by fine fibrovascular septa ( $\times 20$ , bar = 1 mm). (B) Fibrovascular septa (asterisk) and low numbers of neoplastic cells (NC) surrounding the bony trabeculae (B) ( $\times 100$ , bar =  $250\ \mu\text{m}$ ). (C) There is loss of trabecular architecture with neoplastic cells arranged in sheets with occasional blood vessels (arrowhead). Inset – marked cellular and nuclear pleomorphism, prominent nucleoli, and a mitotic figure (line arrow) ( $\times 100$ , bar =  $250\ \mu\text{m}$ , inset bar =  $10\ \mu\text{m}$ ). (D) Neoplastic cells undergo multifocal chondroid (C) and osseous (O) differentiation ( $\times 200$ , bar =  $100\ \mu\text{m}$ ).

a slow-growing and locally invasive neoplasm with moderate potential for metastasis [2]. The relatively slow growth rate of this tumor allows it to grow to a relatively large size prior to causing clinical signs [2].

Multilobular tumors of bone are locally invasive, and recurrence after surgical resection is therefore common. Recurrence occurs typically only after a prolonged period of time and affected dogs therefore have a long disease-free interval and long survival times after surgery [1, 2]. In dogs undergoing surgical excision, with or without adjunctive radio- and/or chemotherapy, median time to recurrence was 14 months, while the median survival time was 22 months [1]. Even longer survival times were reported in another study, indicating median survival times and times to recurrence of 797 days after surgery [2]. In dogs receiving chemotherapy alone a median survival of 144 days is reported [9]. Surgery therefore remains the treatment of choice and predictably, time to local recurrence has been reported to be shorter in dogs with a higher tumor grade (grade I to III, in which grade III represents the most malignant grade) and incomplete surgical margins (disease-free interval 330 days vs. 1332 days with complete surgical margins) [2]. Despite the presence of incomplete surgical margins in the dog described in this report, local recurrence in 8 days was still considered an unusually short disease-free interval.

Histopathological examination of both the originally excised tumor and the recurrent tumor revealed substantial morphological differences. The tissue obtained during the first surgery demonstrated relatively benign characteristics including a well-organized lobular or trabecular structure, low cellularity and mild cellular pleomorphism, typical of MTB. The tumor regrowth, on the other hand, displayed a markedly disorganized structure, high cellularity, extensive necrosis, marked cellular pleomorphism, and a higher mitotic count. These histopathological findings were considered consistent with osteosarcomatous transformation [10].

Although MTB with more malignant characteristics has occasionally been reported, the authors of this report are unaware of previous cases that experienced such rapid tumor regrowth [1, 2, 7]. Little information is therefore available on the frequency and risk factors for malignant transformation of MTB in dogs. It is possible that the combination of pre-existing hypoxia within malignant tissue, tumor-derived immunosuppression, a local inflammatory environment, and borderline immunosuppressive doses of dexamethasone postprocedurally, all created an environment conducive for malignant transformation [11–13]. Although the tumor was resected *en bloc*, microscopic examination indicated that tumor-free surgical margins had not been achieved. It can therefore also not be excluded that the most

peripheral parts of the tumor already demonstrated more malignant characteristics and that examination of the incompletely resected tumor therefore underestimated its malignant potential. It should also be noted that other clinical indications of malignancy, including presence of metastases, were not observed during the initial diagnostic investigations or postmortem examination.

p53 index, as assessed by immunohistochemical labeling, has been reported to show a strong correlation with typical features of malignancy including histologic grade and mitotic index [14]. Given the high grade and mitotic index of the second sample, a high p53 index would be expected. Although MTBs typically occur in middle to old-aged (median 8 years), medium to large-breed dogs, the dog in this report was less than 3 years old and considered a small-breed dog as is rarely reported [2, 7, 10]. The dog in this report also experienced a short duration of observed clinical signs before he was admitted for initial diagnostic investigations. It is, however, unclear if the atypical breed, the young age of the dog, and the short duration of clinical signs presented here could indeed be associated with a more malignant character of the diagnosed MTB. Further studies are therefore necessary to evaluate if signalment and clinical presentation can be used as prognostic indicators for dogs with MTB.

This case report indicates that although resection of MTBs is typically associated with a good prognosis, long disease-free intervals, and prolonged survival, malignant transformation of residual tumor should be considered a potential cause for rapid recurrence of clinical signs. Further studies are necessary to evaluate risk factors for transformation for this type of neoplasia.

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None.

## Conflicts of Interest

None declared.

## Authorship

SC: involved in case management, manuscript construction, submission, and response to reviewers. AC: carried out histopathology, manuscript drafting, figure preparation, and response to reviewers. RL: performed imaging interpretation, figure preparation, manuscript drafting, and revision. JF: involved in case management, revision surgery, manuscript drafting and revision. DN: involved in case anesthesia, manuscript drafting, and revision. SP:

carried out histopathology, manuscript drafting, figure preparation, and response to reviewers. SDD: involved in concept, case management, surgical intervention, manuscript construction and revisions, figure preparation, and response to reviewers.

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