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Diagnosis of primary bone tumors

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INTRODUCTION
Primary bone tumors include a large number of different histotypes (almost all malignant) such as osteosarcoma (OSA), chondrosarcoma (CDS), fibrosarcoma (FSA), hemangiosarcoma (HSA), giant cell tumor of bone (GCT), multilobular osteochondrosarcoma (MLO), liposarcoma, multiple myeloma, lymphoma, histiocytic sarcoma, etc. The most frequent is OSA that accounts for up to 85% of all primary bone tumors and represents 3-4% of all canine tumors. OSA may be appendicular (75%), axial (24%), and extraskeletal (mammary, spleen, eye, esophagus - from granuloma of Spirocerca lupi, etc; 1%)1,2. In case of appendicular OSA, forelimbs are more often involved (twice as much as hindlimbs). OSA is more often “far away from the elbow and close to the stifle”: based on this simple rule, it develops more frequently at the level of the distal metaphysis of the radius and proximal humerus than of distal tibia and femur and proximal tibia. Other less common localizations are proximal femur, distal humerus and proximal radius8, ulna, scapula, etc. Appendicular OSA affects mainly 5-7 year old male large-giant dogs (usually of more than 30 kg of weight); however another peak of age is observed at 18-24 months (OSA of the ribs affect often dogs of 4-5 years of age). Males are prevalent; affected females belong mainly to breeds such as Great Dane, Saint Bernard and Rottweiler. OSA may affect dogs of less than 15 kg in about 5% of cases. The other histotypes are usually observed in adult medium to large dogs at different preferential locations. Multiple myeloma affects elderly dogs of any breed. OSA is both a local and systemic disease. Appendicular OSA is locally aggressive, with early bone lysis, variable tumoral bone growth and periosteal reaction, and swelling of the surrounding soft tissues. It is highly metastatic but, at presentation, more than 90% of dogs fail to show lung metastasis at radiographs. The spread to regional lymph node(s) is rare (<5%) but, if present, it represents a negative prognostic factor4,14. Metastatic localization other than lungs is rare but possible (e.g. bone may be secondarily affected more often after chemotherapy). Lung metastasis represents the cause of death within 5-12 months in approximately 90 per cent of dogs with OSA treated solely with amputation, probably as a result of micrometastasis already present at the time of surgery. The metastatic rate of canine mandibular OSA appears more limited: CDS is prevalent at the level of flat bones such as scapula, ribs, pelvis, nasal bones but it may also develop in the appendicular skeleton; it is usually considered less malignant than OSA. FBS, that is characterized by a low metastatic rate, may be localized both in the axial (70%, mostly skull) and in the appendicular skeleton (30%). GCT is often epiphysial and may metastasize. Feline primary bone tumors (including OSA) affect more likely the hindlimbs and are characterized by a low metastatic rate (<10%); en bloc resection alone may be curative in many cases or followed by a long survival.

CLINICAL PRESENTATION
When the tumor involves primarily the appendicular skeleton, clinical signs include swelling and/or angular deformity (because of a pathological fracture), limping of variable severity because of pain (caused mainly by periosteal activation or fracture), and muscular atrophy of that limb. Pathological (spontaneous) fracture is more likely in HSA, lymphoproliferative disorders (including myeloma) and bone metastasis than in OSA dogs. The tumoral growth of bone HSA is mainly intracortical into the diaphysis, actually with minimal pain until the fracture is established. In HSA dogs, bone may be the primary and sole site or other structures may be concurrently involved (spleen, liver, right heart, lungs, etc). Pelvic bone tumors, that may be palpated either externally or transrectally, may cause limping (functional or neurological), fecal constipation and, more rarely, urethral compression. In case of rib localization, an external hard and firm swelling at the level of the costo-chondral junction is usually palpated, even though the tumor tends to occupy the intrathoracic space rather than growing externally; as a consequence, compression and pleural effusion may be present. Vertebral tumors are associated with both pain and neurological signs; MLO (that is prevalent in bones grown through an intramembranous ossification process) may develop, for example, from the occipital bone into the foramen magnum. Skull bone tumors, depending on their localization, may cause external deformation, compression, neurological signs, exophtalmos (retrobulbar), epistaxis (endonasal), inability to open the mouth, swallowing disorders, sialorrhea and altosus (oral tumors), etc. In case of lymphoproliferative and histiocytic disorders clinical signs, apart from fractures, are often systemic.

DIAGNOSIS
After a complete collection of all the historical data available (trauma, previous orthopaedic surgery mainly if in the same area, other tumors, etc) and clinical examination, the work up includes:
• RADIOGRAPHIC examination of the suspected lesion in at least two projections. In case of an appendicular lesion, it is often advisable, especially in case of early lesions, to compare the affected limb with the controlateral one. Changes depend on the histotype, bone involved, malignancy grade, and tumor age. Elements that should be evaluated are: cortical bone (erosion or evidence of new bone - reactive vs. neoplastic), spongy bone (prevalence of lysis or bone thickening, mot eaten, etc), margins of the lesion, periosteal reaction, distribution of lesion(s), and soft tissue and joint involvement. Almost all primary bone tumors, including OSA, do not usually cross the articular cartilage (in case of synovial cell sarcoma the bone segments composing the joint are often all involved); in contrast, after the cortex has been destroyed, soft tissue is variably invaded (also calcified in case of osteogenetic OSA). Periosteal reaction may be limited to simple thickening or thin external proliferations perpendicular to the cortex (remember that the Codman’s triangle is not specific for tumor) or, in more advanced cases, there are very thick growths (“sun-burst”) that are associated with the swelling (and pain) seen clinically. X-ray evaluation of the primary tumor should be also addressed to define the neoplastic extension if a limb sparing has been programmed. Primary bone tumors are usually monostotic and, in case of OSA, the lesion is typically metaphyscal (multicentric OSA is unusual); multiple lesions may be found more frequently in HSA (that grows into the diaphysis), lymphoproliferative disorders (such as myeloma that may also be “solitary” and lymphoma), histiocytic disorders, and as a result of metastatic spread (also from OSA)6,9. Radiographically, OSA may be osteoproducive or osteolytic, central (from the medullar cavity), periosteal (from the periosteal/cortical surface), and parosteal (or juxtacortical). In terms of biological aggressiveness, there is no difference between central and periosteal OSA; in contrast, parosteal OSA is a slow-growing tumor that is apposed on the surface of the bone from which it arises (en bloc surgery may be curative). Telangiectatic OSA and FBS are lytic, CDS may not be differentiated radiographically from OSA and fibroblast OSA is recognized only histologically. HSA is lytic and growing into the diaphysis, with or minimal periosteal reaction (no pain and pathological fracture at presentation). GCT of bone is lytic and epiphyseal, with minimal periosteal reaction. Indeed, MLO is typically calcified and grows externally. Lytic lesions are also seen in case of lymphoproliferative and histiocytic disorders, with or minimal periosteal reaction. Feline primary bone tumors are prevalently lytic with no or minimal periosteal reaction6.

There are many differentials when a primary bone tumor is suspected radiographically even though a tumor is more likely in almost all occasions6. These tumor-like lesions, some of which are also predisposing diseases for primary bone tumors, include bone cysts (monostotic, polyostotic, aneurysmatic), bone infarction, fibrous dysplasia, osteomyelitis (bacterial or fungal), periosteal reaction (including the subperiosteal calcified hematoma), calcinosi, multiple osteochondromatosis, ossifying myositis, synovial osteochondromatosis, craniomandibular osteopathy, hyperthrophic osteopathy, etc. Erosive arthropathies (sep-tic, autoimmune, etc) should be considered as a differential for synovial cell sarcoma. Radiographic diagnosis should always be confirmed histologically;

• RADIOGRAPHIC evaluation of the thorax (right/left lateral and dorso-ventral views) to exclude the presence of lung metastasis (from 0.5 mm of diameter). It is a general rule that only a few patients are positive for lung metastasis at presentation (< 5-10%). CT scanning of the thorax is superior in detecting lung lesions (from 2 mm of diameter);

• BONE BIOPSY: may be “incisional” (with scalp) or taken with the Jamshidi needle; the biopsy taken with the Jamshidi is characterized by a high rate of accuracy6, both the incisional technique and the Michelle trephine (for its size) are preferentially avoided for the risk of complications (haematoma, swelling, pathological fracture), especially when a limb sparing has to be performed (if so, it is imperative to remove all the area of biopsy during surgery). The radiographic centre of the lesion should be sampled (at the periphery it is more likely to get reactive bone) but necrosis or blood may complicate the diagnosis (make multiple samplings from the original hole just changing direction and perform a cytology of your sample to assure that a good specimen of tissue has been taken for histology); in contrast, too superficial samplings may give as a result only normal or reactive bone. Recently, CT or US-guided biopsy has been reported11,12. Several diagnostic tests may be initiated from the biopitic specimen such as cytology, histology, bacteriology/mycology, etc, as indicated. Cytology may be also performed by fine needle biopsy of the bone lesion using a normal 22 G needle, even in presence of a thick periosteal reaction. Apart from non diagnostic samples (necrosis, blood, normotyptic osteoblasts), the cytological examination may just indicate the nature of the lesion (sarcoma) but in many cases the cytologist may also recognize the histotype (OSA, lymphoproliferative and histiocytic disorders); more recently it has been described that the staining of malignant mesenchymal cells for the presence of alkaline phosphatase is suggestive of OSA12,13. In general, regarding the evaluation of the histological result of the biopsy, it is the author’s experience that when the diagnosis is sarcoma the result is correct, but the contrary may not be the case since reactive or necrotic tissue could have been sampled. In myeloma cases, cells are sometimes so undifferentiated that it is im-

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possible to recognize their plasmacellular nature. The examination of the synovial fluid in case of synovial cell sarcoma is usually non diagnostic.

Histologically OSA may produce tumoral osteoid (osteoblastic or osteogenetic OSA), cartilage (chondroblastic OSA) and/or fibrous tissue (fibroblastic OSA); it can also be telangiectatic (or malignant bone aneurysm that should be differentiated from HSA) or formed by giant cells or be poorly differentiated or undifferentiated. Fibrosarcoma may be confused with the fibroblastic OSA. Grading of OSA is significant on a prognostic point of view and it is likely it will also become important for other histotypes, including CDS;

- **BONE MARROW BIOPSY** is performed when a lymphoproliferative or histiocytic disorder is suspected;
- **FINE NEEDLE BIOPSY** of any enlarged lymph node, especially if regional;
- **CT or MRI SCANNING** of the primary site: useful in case a limb sparing has been programmed or in more complex cases (e.g. pelvic localization);
- **BONE SCINTIGRAPHY**; if available, it is useful to find skeletal metastasis (very atypical for OSA at presentation and more likely after failure of chemotherapy) and multiple tumors; lesions appear as unspecific “hot spots” that should be biopsied to confirm the diagnosis. If not available, a radiographic evaluation of all the skeleton is warranted;
- **ULTRASOUND EXAMINATION OF THE ABDOMEN**: it is rarely useful in case of OSA since regional metastatic lymphadenopathy (e.g. sublumbar from a hindlimb or pelvic OSA) is rare. However, it should be performed to complete the staging work up. Indeed, it is very important in case of multiple myeloma, lymphoma and histiocytic disorder as organs such as spleen, liver, kidneys and abdominal lymph nodes may be involved;
- **ULTRASOUND EXAMINATION OF THE HEART**: this is done to prepare the dog for surgery and chemotherapy (mainly if doxorubicin is used). It is part of the staging scheme in case of HSA;
- **LABORATORY TESTS**, including a coagulation profile. Many unspecific changes may be found such as leukocytosis, leukopenia and increase of #alpha#-2- and/or #beta#-globulins, regenerative anaemia (especially in case of HSA), and increase of both total and bone fraction of alkaline phosphatase. Hypercalcemia is rare in case of OSA. Indeed it may be present in case of multiple myeloma, actually together with monoclonal hyperglobulinemia (immunoglobulins, with consequent hyperviscosity), erythrocytosis (dehydration), altered renal parameters, Bence-Jones proteinuria, leukopenia, anaemia and thrombocytopenia (due to massive bone marrow involvement), and altered coagulation. In cats serology for Feline Immunodeficiency Virus and Feline Leukemia Virus is indicated.
- **CLINICAL STAGING** (see below). Most OSAs are IIB at presentation.

### STAGING OF PRIMARY BONE TUMORS

- **T (primary lesion)**
  - T0 - no evidence of tumor
  - T1 - tumor confined to medulla and cortex
  - T2 - tumor over the periosteum
- **N (unusual, less than 5%)**
- **M (distant metastasis)**
  - M0 - no evidence
  - M1 - present (specify)

### SURGICAL STAGING OF PRIMARY BONE TUMORS

- **Histological grade**
  - G1: low grade
  - G2: high grade
- **Anatomical evaluation**
  - T1 or A: intracompartimental
  - T2 or B: extracompartimental
- **Regional or distant metastasis** (M - M0 no evidence, M1 metastasis)
- **STAGE**
  - Stage I: G1 / M0 (T1 o T2)
  - Stage II: G1 / M1 (T1 o T2)
  - Stage III: G1 / G2 / M1 (T1 o T2)

### PRINCIPAL PROGNOSTIC FACTORS FOR CANINE OSA

- **NEGATIVE**: size of the tumor (possible correlation with metastatic disease); localization at the level of the proximal part of humerus and scapula; less than 4 years of age; high histological grade; soft tissue
and vascular invasion (metastasis more likely); metastatic regional lymphadenopathy\textsuperscript{14,11}; increase of both total and bone fraction of alkaline phosphatase\textsuperscript{14,20}; p53 mutations and multiple drug resistance gene (MDR1); COX-2 expression\textsuperscript{22};

- **POSITIVE:** less than 40 kg of weight; localization at the level of mandible (1 year survival in 71\% of dogs if resection is “clean”); dogs with OSA distal to carpus and tarsus have longer survival; histology (parosteal OSA is less aggressive).

**REFERENCES**


