Primary synovial osteochondromatosis of the stifle in an English Mastiff

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Summary
A two-year-old, 97 kg, male neutered English Mastiff was evaluated for left pelvic limb lameness of five months duration localized to the stifle joint. Following radiographic, computed tomographic and arthroscopic examination, the lameness was subsequently diagnosed as being caused by primary synovial osteochondromatosis. In total, 194 osteochondral bodies were removed using arthroscopy in combination with a mini-arthrotomy. Histology and immunohistochemistry of the loose osteochondral fragments confirmed the diagnosis with a moderately high degree of differentiation and low cellularity. Nuclear staining for Ki-67 revealed decreasing differentiation and increasing cellularity in the fragments. At the 13 months telephone follow-up the owner reported that the dog was free from lameness and had a vastly improved function compared with preoperative levels, although mild lameness did occasionally occur. This is the first report of computed tomography, arthroscopy and immunohistochemistry confirming a case of primary synovial osteochondromatosis in a dog.

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Introduction
Synovial osteochondromatosis (SOC), synovial chondromatosis, synovial chondrometasplasia and synovial chondrometaplasia are terms used to describe a well recognized but uncommon and poorly understood condition affecting synovial joints, and less commonly, bursa and tendon sheaths of humans and animals. Synovial osteochondromatosis is characterized by the production of multiple intra-articular osseous and cartilaginous bodies often referred to as ‘joint mice’ (1–6).

Synovial osteochondromatosis is most commonly considered to be a benign disorder of the joint characterized by chondrometaplasia of the synovial membrane and formation of cartilaginous nodules. These cartilaginous nodules may become pedunculated and detach from the synovial membrane, becoming free within the joint space (7). An alternative hypothesis is that, in some cases, the nodules are derived from fragments of cartilage eroded from a damaged articular cartilage surface as part of a pre-existing joint disease (8).

In humans, despite reports of clonal karyotypic abnormalities and rare malignant changes, SOC is still considered to be a metaphasic and not a neoplastic disease of synovial cells (8). Although SOC has been characterized in humans the precise pathobiology has not been elucidated; in dogs less information is available (1–3, 9–11).

Treatment in humans may be conservative, particularly for non-weight bearing joints, consisting of non-steroidal anti-inflammatory drugs, analgesic medications and physical therapy (12). Surgical removal of intra-articular bodies either via arthrotomy, arthroscopy or arthroscopy with miniarthroscopy is often recommended to ameliorate clinical signs and to slow degeneration of the joint secondary to mechanical trauma from the intra-articular osteochondral fragments (12). Surgical removal in humans is combined with synovial stripping and symptomatic medical management (1, 2, 4, 12). Treatment principles in dogs, though rarely reported, appear to have been extrapolated from the human literature and have included surgical fragment removal with synovial stripping (1).

The Ki-67 protein, a cellular marker for proliferation, has been used in human patients to assess whether significant cartilage proliferation is associated with primary SOC, however, results have been variable with only some individuals with SOC expressing detectable quantities of the protein (13, 14).

The purpose of this report is to describe the clinical, radiographic, computed tomographic, arthroscopic and histological findings in a dog with primary stifle SOC. Additionally, we compare the results of Ki-67 staining of the osteochondral bodies removed from the dog to samples of secondary SOC, cardiac chondrosarcoma and osteochondrosarcoma. To the best of the authors’ knowledge this is the first docu-
mented case of SOC utilizing computed tomography with three-dimensional reconstruction and arthroscopy to aid diagnosis and treatment.

Case report

A two-year-old, 97 kg, male neutered English Mastiff was referred for evaluation of intermittent left pelvic limb lameness of five months duration. The lameness had been unresponsive to symptomatic treatment prescribed by the referring veterinarian. The dog had been in the owner’s possession since a puppy, had no known history of trauma, and had been fed commercially available maintenance dog food according to manufacturer’s instruction. Other than lameness in the left pelvic limb, the dog was clinically normal with no other history or physical findings suggestive of musculoskeletal disease. At a walk the dog had a grade 3/5 lameness (15). Physical examination revealed generalized swelling of the left stifle joint. Signs of pain of moderate severity were evident on flexion and extension of the stifle joint and there was a reduced range-of-motion but no ligament instability was detected. Digital palpation of the joint was striking in that the joint had the consistency of a ‘bag of pebbles’ in addition to generalized effusion and moderate crepitus when placed through range-of-motion; the right stifle joint and the remaining joints were considered to be unremarkable.

The results of a complete blood count values were within normal limits. Serum biochemical analyses revealed hypercholesterolemia (365 mg/dl; reference range 150 to 275 mg/dl) and mild hyperglycemia (150 mg/dl; reference range 65 to 130 mg/dl). Radiographic examination of the left stifle joint revealed signs of multiple, smooth bone densities of variable size present along the lateral and dorsal side of the distal femur diaphysis, stifle and proximal tibial diaphysis and multiple bone densities in the cranial and caudal stifle joint space; the largest bone density was approximately 2.4 x 1.6 x 2.1 cm in diameter (Fig. 1 A and B). A mild increased soft tissue density was present in the cranial and caudal stifle joint space, and radiographic evidence of osteophytosis was present at the base and apex of the patella and the medial and lateral border of the proximal tibia. Radiographic signs consistent with very mild osteoarthritis were visible in the right stifle joint. Three-view radiographic examination of the thorax was unremarkable. Computed tomography examination of both stifle joints under general anaesthesia revealed similar findings as were seen on radiographic examination although the extent of the disease was considered more evident, particularly following three-dimensional reconstruction (Fig. 1 C-F). The left stifle joint capsule was severely distended caudally, proximally and distally and contained multiple variably sized and shaped bone-dense structures.

Six millilitres of synovial fluid were aspirated from the left stifle joint using an aseptic technique and the fluid sample was grossly pink, with a nucleated cell count of 2000 cells/μl and a total protein of 3.0 g/dl. Cytology of the synovial fluid revealed a moderate number of mononuclear cells with <10% non-degenerative neutrophils among red blood cells and proteinaceous material; rare erythrophagia was seen. This result was considered to be consistent with a diagnosis of osteoarthritis with evidence of mild haemorrhage. Subsequent aerobic and anaerobic culture of synovial fluid for bacteria was negative.

Arthroscopy of the left stifle joint was performed using a 4.0 mm arthroscope, and three access ports; cranio-lateral (arthroscope), proximal-medial (egress), and cranio-medial (instrument). Exploration and inspection of the joint was prevented by a striking barricade consisting of multiple intra-articular smooth white bodies (Fig. 1G). Multiple grasp biopsies were taken from representative areas of inflamed synovium adjacent to the viewing window cranial to the inter-condylar notch and submitted for routine histological examination and bacterial culture. Following sample collection, the administration of cefazolinb (22 mg/kg IV q 90 minutes until extubation) was commenced and then cephalixin (20 mg/kg BID PO) was administered for 14 days. To expedite fragment removal, the cranio-medial portal was enlarged to a mini-arthrotonomy of approximately 2 cm length. Osteochondral bodies were found in all regions of the joint and removed with grasping forceps. In total, 194 individual bodies were removed and a selection was submitted for histological and immunohistochemical examination. Following removal of all visible and palpable free osteochondral bodies complete arthroscopic examination of the joint was performed. The patellar and trochlear groove cartilage had multiple localized cartilage lesions, graded as modified Outerbridge Grade 3 and there was generalized moderate synovial hyperplasia and inflammation (16). The cruciate ligaments were considered unremarkable based on visual and probe examination. Complete examination of the medial and lateral menisci was limited by the integrity of the cruciate ligaments but was considered unremarkable. Following examination one litre of sterile lactated Ringer’s solution was flushed through while the joint was moved through a full range-of-motion. Closure of the portals and arthroscopy was routine.

Postoperative care included the administration of hydromorphone (0.05–0.1 mg/kg SC, IV q4–6 hours as required to provide sufficient analgesia) for two days and thereafter tramadol (2 mg/kg q8–12 hours PO) for 10 days and carprofen (2.2 mg/kg q 12 hours SC or PO) for 10 days. A modified Robert-Jones bandage was applied for 48 hours together with topical cryotherapy using an icepack placed on the surface of the bandage or on the skin during bandage changes (10 minutes q 4 hours) for three days.

Approximately two days following surgery the bandage was removed and mild generalized soft tissue swelling of the stifle

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a Toshiba America Medical Systems, Inc., Tustin, CA, USA
b Cefazolin: Sargent Pharmaceuticals, Schaumburg, IL, USA
c Hydromorphone: Baxter Health Corporation, Deerfield, IL, USA
d Tramadol: Amneal Pharmaceutical of New York, Hauppauge, NY, USA
e Carprofen: Pfizer Animal Health, New York, NY, USA
A joint extending distally was observed. Upon manipulation of the stifle there was a smooth range-of-motion with signs of mild discomfort, consistent with recent surgery. The dog was weight bearing on the affected limb with a grade 3/5 lameness.

The dog was discharged with instructions for leash restricted exercise for four weeks. Follow-up was available at 13 months postoperatively by telephone. No medications were being administered to the dog and it was typically normal with only occasional periods of mild weight-bearing lameness. The owner assessed function to be vastly improved compared with preoperative levels and the dog was allowed unlimited exercise.

### Histological and immunohistochemical examination

Tissue samples were fixed in 10% formalin solution, paraffin embedded and routinely processed and stained using haematoxylin and eosin. Sections of tissue were examined by light microscopy from the dog reported here and compared to control samples from four other dogs: normal cartilage, secondary SOC, cardiac chondrosarcoma and osteochondrosarcoma (Table 1). Tissues were assessed for the following parameters: organization of chondrocytes (individual or organized into rows or clumps), cellularity of cartilage (1 = poorly cellular; 2 = mildly cellular; 3 = moderately cellular; 4 = highly cellular), degree of nuclear pleomorphism (1 = within normal variation of maturing cartilage; 2 = moderate increased pleomorphism; 3 = markedly increased pleomorphism), extent of calcification, ossification or both combined (1 = less than 10%; 2 = 10–50%; 3 = more than 50%), and mitotic figures (rare or frequent). Immunohistochemistry was performed using an antibody to the cell cycle-associated protein, Ki-67\(^\text{a}\) (dilution 1:50). Staining was performed on an autostainer utilizing Envision\(^\text{b}\) + anti-rabbit HRP\(^\text{b}\) followed by Vector Nova Red\(^\text{b}\) and a haematoxylin counter staining. Evaluation was performed using point scales to grade abundance of positive cells (0 = absent, 1 = up to 5%, 2 = 5–25%, 3 = more than 25%) and intensity (1 = weak; 2 = moderate, 3 = high).

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**Table 1** Histopathological features and proliferation index (Ki-67) of cartilaginous proliferative lesions and normal cartilage.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Diagnosis</th>
<th>Signalment</th>
<th>Organization</th>
<th>Cellularity score (2-4)</th>
<th>Nuclear pleomorphism score (1-3)</th>
<th>Calcification score (1-3)</th>
<th>Ki-67 Abundance</th>
<th>Ki-67 Intensity score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reported case</td>
<td>Primary synovial osteochondromatosis</td>
<td>English Mastiff 2 years Male entire</td>
<td>1 0 2 2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>Normal cartilage</td>
<td>German Shepherd 6 years Male neutered</td>
<td>0 1 2 1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0-2 2-3</td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>synovial osteochondromatosis</td>
<td>Mastiff 2 years Male neutered</td>
<td>1 2 1 1-2</td>
<td>1-2</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td>chondrosarcoma</td>
<td>Labrador Retriever 12 years Female neutered</td>
<td>3 0 0 3-4</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>2-3</td>
<td></td>
</tr>
<tr>
<td>Osteochondrosarcoma</td>
<td>Golden Retriever 4 years Male neutered</td>
<td>2 0 1 2-4</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2-3</td>
<td></td>
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</tbody>
</table>

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\(^{a}\) Ki-67, AB833: Abcam, Cambridge, MA, USA

\(^{b}\) Dako Autostainer Universal Staining System: Dako North America, Carpinteria, CA, USA

\(^{1}\) Dako EnVision: Dako North America, Carpinteria, CA, USA

\(^{2}\) Anti-rabbit HRP: Dako North America, Carpinteria, CA, USA

\(^{3}\) Vector Nova Red: Vector Laboratories, Burlingame, CA, USA
strong nuclear staining). Cells with only cytoplasmic staining were counted as absent.

Tissue sections from the tissue of primary SOC (dog reported here) comprised a hyperplastic synovial membrane with thick long folds expanded by lobules or replaced by nodules of unorganized cartilage with individual chondrocytes or chondrocytes in small dense clusters of two to six cells (Fig. 2A); mitotic figures were rare, organizing haemorrhage with lakes of haematoxin were present. No microorgan-

isms were seen. The matrix was largely cartilaginous with small areas with collagen deposition and occasional ossification in the centre of larger nodules. In comparison, the cartilage tissue from a dog with secondary synovial osteochondromatosis (Fig. 2B) lacked ossification, was less cellular, and overall better organized with approximately half of the cells loosely arranged in rows with rare mitotic figures. Histopathological features of tissue from dogs with osteochondrosarcoma and chondrosarcoma were typical for neoplastic lesions. The results of semi-quantitative histopathological and immunohistochemical (Fig. 2C, 2D) analysis are detailed in Table 1.

**Discussion**

This case was classified as SOC based on the findings of radiographic and histological examination. This distinction between synovial chondromatosis and SOC is somewhat arbitrary as these conditions are considered a continuation of the same pathological disease and are believed to represent metaplastic nodules of hyaline cartilage that may undergo calcification. If lesions are cartilaginous nodules, the lesion is called synovial chondromatosis, whereas if more than a few nodules have undergone ossification, it is called SOC (17). This case was classified as osteochondromatosis due to the presence of distinct bone in sections of the nodules examined histologically.

Synovial osteochondromatosis is termed primary when occurring as an idiopathic or spontaneous disease process or secondary as a metaplastic response to chronic irritation, following trauma or detachment of cartilage or subchondral bone (1, 18). This classification may be an oversimplification and criteria based on histological examination have been reported in the human literature to allow sub-classification of SOC. In one case series, these criteria were considered difficult to apply to dogs (1).

This case was considered to be primary SOC based on negative joint culture for bacteria and our inability to identify any underlying disease stimulating formation of bone fragments. There was no known
history of trauma to the left stifle joint and no evidence of gross pathology such as osteochondrosis dissecans, cruciate disease or meniscal injury. Based on synovial biopsy and fluid analysis, a diagnosis of inflammatory arthropathy was excluded. The presence of gross cartilage lesions and histological findings of chronic haemorrhage of the synovium were consistent with abrasions from multiple osteochondral lesions 'rubbing' against the cartilage and synovial membrane. Blood sampling did reveal hypercholesterolemia that could potentially be related to hypothyroidism; we did not investigate this further due to a lack of clinical and physical signs, and lack of pathology in the contralateral stifle joint.

The term 'snow storm knee' has been proposed to describe the arthroscopic appearance of severely affected knee joints with SOC in humans, and this term could also be used to describe the appearance of the stifle joint reported in this case. Because the large bone fragments limited the radiographic evaluation of the stifle joint, a computed tomographic examination was performed to rule out underlying lesions causing these bone fragments. In our opinion, computed tomography with three-dimensional reconstruction may be a more sensitive method to diagnose SOC, and it may be useful to differentiate primary from secondary cases.

Synovial osteochondromatosis has been categorized into three phases: early (active intra-synovial disease but no loose bodies), transitional disease (active disease and loose bodies), and late (multiple loose bodies but no intra-synovial disease). This case was most consistent with late phase classification due to the absence of disease within the synovial membrane, beyond synovitis that might be expected in an inflamed joint.

In humans, SOC appears more frequent in men than women and usually affects young and middle-aged adults (30 to 50 years) with knee involvement in 50–66% of cases followed by the hip, elbow, wrist and shoulder (12–14, 21). The condition is typically mono-articular, as was the case with this dog, although multiple joint involvement has been reported (11). The majority of the intra-articular disease is reported in the knee (50–66% of cases) followed by the hip, elbow, wrist and shoulder (21). In contrast to the frequency of SOC affecting the knee in humans, SOC affecting the stifle joint has been rarely reported in the dog.

In humans, both spontaneous regression of SOC as well as malignant transformation (chondrosarcoma) has been reported but is considered rare (13). One report in the veterinary literature describes a five-year-old male shepherd dog with intra- and extra-articular SOC affecting the stifle that underwent transformation to chondrosarcoma, however to the best of the authors’ knowledge, no other reports of malignant transformation of primary SOC exist (11).

Treatment of SOC has been rarely reported within the veterinary literature. One case series documented SOC of the scapulohumeral joint in four medium to large breed dogs and the talocrural joint in one dog (1). In those dogs, treatment involved surgical exploration of the joint, nodule debridement, and the synovium was also partially stripped from some of the joints. In four out of five dogs, a dramatic improvement in lameness was observed that was maintained for at least 10–39 months of follow-up (1).

The value of synovectomy in humans is controversial and debate continues as to whether removal of chondral bodies alone is sufficient or if synovectomy should be performed in all cases (22–24). To the authors’ knowledge, synovial stripping in the stifle using arthroscopy has not been reported in the dog.

Limitations of this case report are the lack of objective outcomes such as force-plate evaluation, as well as the lack of clinical, and radiographic or computed tomographic examination.

As expected, the typical layered organization of cartilage on microscopic examination was absent in all examined cases. The samples of primary and secondary SOC had retained a moderately high degree of differentiation and low cellularity, whereas the sample with osteochondrosarcoma that was examined for comparison was moderately differentiated and cellular. The example of chondrosarcoma tissue was poorly differentiated and highly cellular in comparison with the other samples. In samples taken from the dog reported here, decreasing differentiation and increasing cellularity were reflected by the percentage of chondrocytes in the proliferation cycle as determined by nuclear staining for Ki-67 (Table 1).

Proliferative activity in primary SOC has been reported as either nil or low in humans (13, 14, 21). In the secondary SOC, only rare cells stained positive for Ki67, whereas the primary SOC had less than five percent positive cells within the cartilaginous portion and 15–20% within the synovia. In normal cartilage, the percentage varied depending on the cell layer examined and ranged from zero percent (mature) to 25% (zone of proliferation). The osteosarcoma showed five to 25% positive cells per fragment, averaging 15%, whereas the chondrosarcoma had 30–60% positive cells per fragment averaging 50%. Whilst these assessments are crude, this data supports the notion that primary SOC is a proliferative process in this dog whereas secondary SOC is a metaplastic process which is consistent with descriptions of these conditions in humans (14, 15, 25). However, whether these conclusion are true for other dogs with SOC requires further investigation. The proliferation index of the two malignant neoplasms with cartilaginous differentiation examined for comparison in this report was moderate to high as expected and is of prognostic value in chondrosarcomas of people (14, 25).

In this case of primary SOC, computed tomography examination was considered useful to allow full appreciation of extent of joint involvement. Arthroscopy was easy to perform and aided removal of the osteochondral bodies via a small arthroscopy incision. However further understanding of the disease process involved in primary SOC in humans and dogs is needed before the best treatment method can be recommended.

References