Research in Veterinary Science 114 (2017) 186–193

Contents lists available at ScienceDirect

Research in Veterinary Science

journal homepage: www.elsevier.com/locate/rvsc

Cartilage lesions in feline stifle joints – Associations with articular mineralizations and implications for osteoarthritis

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ARTICLE INFO

Keywords:
Cartilage
Cat
Computed tomography
Joint
Meniscus

ABSTRACT

Feline stifle osteoarthritis (OA) is common, however little is known about the early stages of the disease. Furthermore, the importance of small articular mineralizations (AMs) in feline stifle OA is controversial. This study aimed to describe microscopic articular cartilage lesions and to investigate associations between cartilage lesions and AMs, synovitis, osteochondral junction findings and subchondral bone sclerosis. Stifles of 29 cats, aged 1–23 years and euthanized for reasons other than stifle disease, were examined. Osteochondral tissue and synovial membrane changes were histologically evaluated. Computed tomography and radiography were used for evaluation of AMs. Global cartilage scores (GCS, $n = 28$) were summarized and joints assigned a histologic OA grade. Minimal to mild histologic OA was seen in 24/28 joints. In 27/29 joints tibial cartilage lesions were seen, whereas femoral lesions were only seen in two joints. Articular mineralizations were detected in 13/29 joints, 11 were small and 12 were located entirely within the medial meniscus. There was no association between GCS and presence or volumes of AMs. However, higher GCS was associated with synovitis ($P = 0.001$) and age ($P < 0.0005$). Presence of subchondral bone sclerosis ($P < 0.0005$) and disruption of the calcified cartilage or tidemark ($P < 0.0005$) were associated with cartilage lesions. We conclude that the tibial articular cartilage is a common location for histologic OA lesions in cats. Synovitis and changes in the subchondral bone and calcified cartilage may be important in the pathogenesis of feline stifle OA, whereas small AMs likely represent incidental findings.

1. Introduction

Osteoarthritis (OA), a disease of synovial joints, can be regarded as a whole-organ failure (Loeser et al., 2012). The condition is characterized by progressive degradation and loss of articular cartilage, related to altered intrinsic mechanisms of the cartilage, influenced by changes in other intra-articular tissues such as the synovium, the subchondral bone and menisci (Wei and Bai, 2016). Osteoarthritis is common in cats, and the prevalence of appendicular OA has been estimated to range between 61% and 91% based upon radiographic detection of joint changes (Clarke et al., 2005; Hardie et al., 2002; Lascelles et al., 2010; Slingerland et al., 2011). Despite this high prevalence little is known about the etiology and pathogenesis of the disease in cats (Bennett et al., 2012). Age is an important predisposing factor for OA in humans (Musumeci et al., 2015) and an age-associated increase in OA has also been demonstrated in cats (Freire et al., 2014; Ryan et al., 2013; Slingerland et al., 2011). Few studies have focused on describing microscopic joint changes in naturally occurring OA in domestic cats (Freire et al., 2010, 2014; Ryan et al., 2013; Voss et al., 2017) and histologic descriptions of cartilage and synovial membrane changes in feline stifle OA are so far limited to results found in 500–600 μm thick whole-stifle specimens (Voss et al., 2017).

Articular mineralizations (AMs) are commonly detected in radiographs of feline stifle joints (Freire et al., 2010, 2011) and the prevalence of AMs has been reported to increase with age (Freire et al., 2010). Articular mineralizations are highly variable in size, distinct in location from osteophytes, and often located in the cranial horn of the medial meniscus (Freire et al., 2010; Voss et al., 2017). Histologically, AMs are characterized by deposits of mineralized fibrocartilage or formation of bone that may include a marrow centre (Freire et al., 2010; Voss et al., 2017). According to some authors AMs constitute incidental findings without clinical consequences for the cat (Allan, 2000; Mahoney, 2012; Whiting and Pool, 1985). However, a recent study concludes that larger AMs should be considered pathological and that these are associated with increased degenerative joint changes (Voss et al., 2017). There is considerable speculation regarding the clinical implication of small stifle AMs and the possible role these play in development of stifle OA in cats, and a consensus is currently lacking (Freire et al., 2010; Voss et al., 2017).

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http://dx.doi.org/10.1016/j.rvsc.2017.04.008
Received 23 November 2016; Received in revised form 21 March 2017; Accepted 15 April 2017

The purpose of this study was to describe histologic features of naturally occurring feline stifle OA in cats euthanized for reasons other than stifle disease. To further elucidate processes involved in early feline stifle OA the study investigated whether cartilage lesions were associated with AMs, synovitis, osteochondral junction lesions and subchondral bone sclerosis. The study was performed as part of a larger study aimed at characterizing feline OA from morphologic and diagnostic perspectives using a whole-animal approach in determining prevalence of affected joints by computed tomography (CT). The hypotheses were that histological evidence of OA, as determined by presence of cartilage lesions, would be a common finding, and that presence of AMs, morphological signs of inflammation (i.e. synovitis), osteochondral junction lesions and subchondral bone sclerosis would be associated with the presence of cartilage lesions.

2. Materials and methods

2.1. Study population

A total of 29 cats submitted to the Section of Pathology at the Swedish University of Agricultural Sciences in Uppsala, Sweden for post-mortem examination or specifically donated by the owner for participation in the study were included. Cats over 12 months of age presented for reasons other than stifle disease and without a clinical suspicion of immune-mediated joint disease were included in the study. Due to its chondrodysplastic predisposition, no individual of the Scottish Fold breed was included (Malik et al., 1999). Owner consent for using the animal in research was given for all cats. Twenty eight animals were fully examined and sampled either the same day or the day after euthanasia, and one animal was examined and sampled 2 days after euthanasia.

The ages of the cats ranged from 1 to 23 years, with a median of 9 years (mean 9.8 years). Sixteen cats (55.2%) were neutered males, 10 cats (34.5%) were neutered females and the remaining 3 cats (10.3%) were intact females. Twenty cats (69.0%) were Domestic Shorthaired cats and 9 cats (31.0%) were pure-bred (two Persian cats, and one individual each of Norwegian Forest Cat, British Shorthair, British Longhair, Birman, Burmese, Cornish Rex and European Shorthair).

2.2. Diagnostic imaging

Whole-body CT was performed on each individual. The CT images were obtained using a 64 slice multidetector CT scanner (Definition, Siemens Medical Systems, Erlangen, Germany). Transverse images were acquired using; 250 kV, 160 mAs, slice thickness 0.6 mm, slice increment 0.3 mm, focal spot 1.2 mm, high-resolution kernel (B70s) and field of view 156–249 mm. The cats were placed in ventral recumbency with extremities extended. Mediolateral projection radiographs (Adora RF CPI, Canon, Tokyo, Japan) were taken of the right stifles in neutral position using a computed radiography system (Fujifilm FCR XG-1, Tokyo, Japan) with exposure settings 50 kVp and 2.5 mAs.

2.3. Sampling for histology

Following diagnostic imaging the right stifle joint was opened by incision of the joint capsule. The integrity of menisci and ligaments, the articular cartilage of the tibial plateaux, the femoral trochleae and condyles, the patella, and the synovial membrane were assessed. To more accurately visualize cartilage defects the articular cartilage was painted with India ink (Lefranc & Bourgeois, Le Mans Cedex, France) diluted 1:5 in 0.9% sodium chloride solution. The ink was removed by gently blotting the cartilage surface with gauze moistened with 0.9% sodium chloride solution. After visual examination, the joints were fixed in 10% neutral buffered formalin. Synovial membrane was sampled for histologic assessment from the lateral, medial and cranial aspects of the joint approximately 48 h after fixation, and pooled for light microscopic evaluation. In one joint the synovial membrane adjacent to meniscal tissue and decalcified osteochondral tissues was the main tissue available for histologic evaluation due to absence of a lining layer in the standard sections. Osteochondral tissue was fixed in formalin for 7 to 18 days before being decalcified in formic acid (20% v/v, Kristensens lösning, Solveco AB, Rosersberg, Sweden). Osteochondral tissue, including the full thickness of the articular cartilage and adjacent subchondral bone, was obtained from the femoral condyles and the tibial plateaux in the coronal plane, approximately halfway between the most cranial and caudal borders of the articular cartilage. In two cats however, the lateral and medial femoral condyles were sampled in a parasagittal plane. Osteochondral samples from the patella were obtained parasagittally. If articular cartilage lesions were detected on macroscopic inspection of the joint these were included in sampled areas. All samples were processed routinely for histology, cut into approximately 4 μm thick sections and stained with hematoxylin and eosin. In addition, osteochondral sections were stained using toluidine blue for detection of proteoglycans. Due to poor reproducibility of staining intensity in toluidine blue stained sections these sections were only used as a complement to hematoxylin and eosin stained section to highlight osteochondral tissue changes but not relied upon for assessment of cartilage lesion grades.

2.4. Histological assessment of osteochondral tissue and synovial membrane

Histological changes in the articular cartilage, subchondral bone and synovial membrane were individually assessed and graded in coded sections by two veterinary pathologists (AL, CL). If there was disagreement between grade values, the final grade was decided by consensus. Lesions in the articular cartilage were graded from 0 to 6.5 using the Osteoarthritis Research Society International (OARSI) histopathology grading system for human OA (Suppl. Table S1) (Pritzker et al., 2006). Due to the uncertain nature of grade 1 (Pritzker et al., 2006), this grade was not used as a definite criterion for OA cartilage lesions. Individual cartilage lesions between grade 1.5 and 2.5 were considered mild, 3–4.5 moderate and lesions ≥ 5 severe. Five articular cartilage regions; the articular cartilage of the lateral and medial tibial plateau, the lateral and medial femoral condyle and the patella were individually assessed for surface integrity, matrix loss, cellular change (chondrocyte hypertrophy, clustering and necrosis) and depth of lesions (fibrillation, fissures, erosion and ulceration). Since the axial part of the feline medial tibial plateau contains large amounts of fibrocartilage and lacks the ordinal zonal chondrocyte arrangement of hyaline cartilage (Suppl. Fig. S1A and B), the grading protocol was modified for this region to exclude the zonal chondrocyte arrangement criteria. Instead, the depth of cartilage involvement was subjectively assessed as superficial, middle and deep fibrocartilage regions, and grades thereafter used as for the OARSI histopathology system. A global cartilage score (GCS) was assigned to each joint by adding the scores for the five evaluated regions, creating a maximum total score of 32.5 points. Based upon the highest grade of cartilage lesion in each individual joint region and the GCS, each joint was designated a histologic OA grade (Table 1). Additionally, in each assessed region the presence of tidemark redupli-

Table 1
Classification of overall histologic osteoarthritis (OA) severity in feline stifle joints.

OA severity	Criteria[a]
Normal	GCS ≤ 5, no lesion > 1
Minimal OA	GCS ≤ 7.5, worst lesion 1.5–2.5
Mild OA	GCS ≤ 7.5, focal lesion ≥ 3; or GCS 8–12.5
Moderate OA	GCS 13–22.5
Severe OA	GCS 23–32.5

[a] Based upon the global cartilage score (GCS) and the individual lesion grades in each of the five assessed cartilage regions (lateral and medial tibial plateaux, lateral and medial femoral condyles and patella).