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Multiloculated solitary (unicameral) bone cyst in a young dog

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Abstract

A 20-month-old female spayed Staffordshire Terrier (22.3kg) presented to the Orthopedic Surgery Service at North Carolina State University Veterinary Teaching Hospital for evaluation of a 6-week history of toe-touching to non-weight bearing lameness in the right hindlimb. Radiographs of the right stifle revealed a multiloculated lytic lesion of the distal femur, with a large open lytic zone centrally, numerous osseous septations peripherally, and focal areas of cortical thinning and loss. An aspirate of the right distal femoral lesion yielded mildly cloudy serosanguineous fluid. Cytologic examination of the fluid revealed a pleomorphic population of discrete cells that exhibited marked anisocytosis and anisokaryosis and a variable nucleus to cytoplasm (N:C) ratio, which were interpreted as probable neoplastic cells, with few macrophages, and evidence of hemorrhage. Given the clinical signs of pain, lesion size, and concern for malignant neoplasia, amputation of the right hind limb was performed. Histologically, the lesion had undulating walls 1–3mm thick with a continuous outer layer of dense fibrous tissue and an inner layer composed of reactive cancellous bone with no cortical compacta remaining. Remnants of thin fibrous or fibro-osseous septa projected from the bony wall into the cyst lumen. The final histologic diagnosis was a benign multiloculated solitary (unicameral) bone cyst of the distal right femur. Based on the histopathologic findings, it was speculated that the cells identified on cytology were a mixture of developing osteoclasts, osteoblasts, endothelial and stromal cells. This is the first report describing the cytologic examination of a solitary bone cyst in veterinary medicine.

Keywords

canine; cytology; lytic; osseous; osteoclast; skeletal

CASE PRESENTATION

A 20-month-old female spayed Staffordshire Terrier (22.3kg) presented to the Orthopedic Surgery Service at North Carolina State University Veterinary Teaching Hospital (NCSU-VTH) for evaluation of a toe-touching to non-weight bearing lameness in the right hind limb of 6 weeks duration. No known inciting injury or trauma occurred at the time the lameness was first noticed, and the lameness progressed despite strict rest. Hyporexia over the same period was also reported.

Physical exam revealed toe-touching lameness in the right hind limb with pain on manipulation of the right stifle joint. The right stifle had a positive drawer sign, negative tibial thrust, medial buttress, and joint effusion. Diffuse muscle wasting was appreciated over the entire right hind limb. No other abnormalities were identified on physical or orthopedic examination.

Radiographs of the right stifle revealed a multiloculated lytic lesion of the distal femur, with a large open lytic zone centrally and numerous curved, strand-like osseous septations towards the periphery (Figure 1). The medullary cavity was most affected; however, there were focal areas of cortical thinning and loss peripherally. The lesion extended approximately 6.5 cm proximally from the stifle joint and had a relatively short zone of transition to the normal portion of the femoral diaphysis. Radiographic findings suggested a benign lesion such as fibrous dysplasia or an aneurysmal bone cyst, but an aggressive process, such as a neoplasm, was also considered due to the extent of the lesion and cortical loss. Three-view thoracic radiographs were unremarkable.

An ultrasound-guided aspirate of the right distal femoral lesion yielded a mildly cloudy serosanguineous fluid that was submitted for cytological examination (Figure 2). Both direct and concentrated smears were of relatively low cellularity (a cell count was not performed due to insufficient submitted fluid volume) on a rich eosinophilic stippled background with minimal hemodilution and few variably sized condensed, discrete round cells. Examination of cytocentrifuged preparations revealed a population of pleomorphic discrete cells admixed with foamy macrophages that had frequent eosinophilic granular material and rare erythrophagia. The discrete cells were round to ovoid with marked anisocytosis and anisokaryosis and ranged in size from 10–45µm with variable N:C ratios. The round to ovoid and often eccentric nuclei had stippled chromatin patterns and occasional, distinct, and sometimes large nucleoli. The discrete cells exhibited scant to moderate amounts of cytoplasm that sometimes contained fine to coarse eosinophilic granulation. Cytoplasmic ruffling and blebbing were occasionally noted at the cell margins. Few bi- and multinucleated cells were seen, and a rare mitotic cell was also observed. The cytologic features of this discrete cell population, along with the absence of overt inflammation and the clinical history of a lytic lesion, led to an interpretation of probable neoplasia with evidence of hemorrhage. Suggested differentials included poorly differentiated sarcoma, poorly differentiated plasma cell neoplasia, and histiocytic sarcoma with a recommendation for biopsy and histopathology for definitive characterization.

Given the clinical signs of pain, size of the lesion, and the concern for malignant neoplasia, amputation of the right hind limb was performed by the primary veterinarian, and the limb was submitted to IDEXX Pathology Services. Grossly, the distal femur exhibited an expansile lesion with central cavitation containing serosanguinous fluid. The initial histologic review identified dense fibroplasia with multifocal extension into the surrounding bone, periosteal reaction, and bone lysis, suggestive of a bone cyst without histologic evidence of neoplasia.

Due to the uncommon nature of this lesion, histopathologic sections were submitted to the Osteopathology Service in the Department of Pathology at Texas A&M University, College of Veterinary Medicine and Biomedical Sciences for further assessment. Macroscopically, cyst walls exhibited a continuous outer layer of dense fibrous tissue (1–2 mm) and a variably thick undulating inner cyst wall (0.1–1.5mm) composed of reactive cancellous bone (Figure 3). No original cortical compacta remained. In some sites, the innermost lining of reactive bone had been mostly removed or was undergoing resorption by osteoclasts. Remnants of thin fibrous or fibro-osseous septa projected for short distances from the bony wall of the cyst into the cyst lumen. These septa were covered by fibrous tissue and had either dense fibrous or reactive bony centers. The cyst wall was lined entirely by avascular fibrous tissue or fibrovascular tissue that overlaid subjacent woven bone or recently resorbed reactive bony cyst walls. The final histologic diagnosis was a multiloculated, solitary (unicameral) bone cyst of the distal right femur.

DISCUSSION

We report the radiographic, cytologic, and histopathologic features of a multiloculated solitary (unicameral) bone cyst in a young dog, a rarely diagnosed condition of animals. To the authors' knowledge, this is the first report to document the cytologic features of a unicomeral bone cyst in the veterinary species. Given the discrepancy between the cytologic interpretation of probable malignant neoplasia and the histopathologic interpretation of a benign solitary bone cyst, this case emphasizes the value of integrating radiographic and pathologic data for diagnosis and is a reminder for clinicians and pathologists to consider uncommon processes in atypical cytologic specimens from bone lesions.

Two studies have been published that assessed the diagnostic accuracy of bone cytology in veterinary medicine. One study identified a 71% correlation between cytologic interpretation and both incisional and excisional biopsy findings, and while 92% agreement between cytology and histology occurred for the neoplastic lesions, only 27% agreement occurred for the non-neoplastic lesions. In the latter comparison, cases that received cytologic interpretations of inflammation or non-neoplastic proliferations were more likely to be diagnosed as neoplasia on histopathology.¹ A more recent study found cytology to have a diagnostic accuracy of 83% in being able to discriminate between benign and malignant bone lesions, and no benign lesions were diagnosed as being malignant by cytologic interpretation.² In both studies, the misdiagnosis was most commonly associated with low cellularity or poor quality of cytologic specimens. Neither of these studies described the inclusion of bone cysts or benign lytic lesions, further highlighting the importance of this report.

A solitary, or unicameral bone cyst (SBC) is a benign fluid-containing intraosseous lesion lined by a fibrous membrane. In humans, SBCs makeup ~3% of biopsied bone tumors, are more likely to occur in males, and primarily occur in children. They are found most commonly in the proximal humerus and proximal femur but have been documented in several other areas, including pelvic, craniofacial, and vertebral bones^{3,4}.

In comparison, SBCs are rare in veterinary medicine. The incidence is unknown, and there are only a few published case series and reports. SBCs occur in the long bones of young dogs (age 5–30 months), most commonly in the distal radius and distal ulna, with lesions also documented in the distal femur, proximal tibia, distal humerus, and patella. They occur more commonly in large breed dogs; males appear to be affected more frequently than females, and Doberman pinschers and German Shepherd dogs may be predisposed^{5–7}.

The pathogenesis of SBCs remains unclear and may be multifactorial in both humans and dogs. Several theories include venous outflow obstruction in bones leading to increased intraosseous pressure⁸; mechanical trauma at the epiphyseal line, which leads to defective endochondral bone formation⁹; a bone remodeling defect; the presence of interosseous synovial cysts¹⁰; and genetic factors.^{11–14} In the present case, based on the imaging and histopathology, it is speculated that the cystic defect arose as a remodeling disturbance in the metaphyseal spongiosa on the metaphyseal side of the growth plate during early skeletal development. The cyst fluid in SBCs has been found to contain cytokines, including prostaglandins, interleukin 1 β , and other proteolytic factors, that are known to stimulate osteoclastic resorption of bone; however, it is unclear whether this causes or perpetuates the lesion¹⁵.

In a retrospective evaluation of the cytology, in this case, we speculated that the discrete cells identified were likely a mixture of developing osteoclasts, osteoblasts, endothelial and stromal cells rounded up in the fluid, which made the cellular morphologies appear atypical¹⁶. The discrete cells were admixed with macrophages and occasional lymphocytes, which is consistent with cytologic findings reported in human SBC cases^{17,18}. Osteoclasts develop from hematopoietic stem cells of the monocyte/macrophage lineage. Receptor activator of nuclear factor kappa-B ligand (RANKL), a membrane protein found in osteoblasts and some other cell types, activates the RANK receptor on osteoclast precursors. Osteoclasts become multinucleated by fusion of RANK+ mononuclear osteoclastic precursors, which results in the production of chemokines that are chemotactic for monocytes.¹⁹ Based on the process of osteoclastogenesis, it is reasonable to suspect at least some of the discrete cells were mono-, bi-, and multinucleated osteoclastic precursors, which may account for the anisocytosis and bi- and multinucleation observed. Cytochemical staining for alkaline phosphatase activity and immunocytochemical staining for RANK and RANKL would have been useful to characterize the cells further, but, unfortunately, could not be performed due to an insufficient sample volume.^{20–22}

Two differential diagnoses for this lesion are an aneurysmal bone cyst (ABC) and fibrous dysplasia, both of which are uncommon benign lesions occurring most frequently in younger human patients. ABCs have been documented in dogs 6mo-13y that histologically are filled with central blood-filled chambers lined by fibroblasts as opposed to endothelial cells.

Vascular spaces are separated by fibro-osseous tissue that includes multinucleated cells, plump osteoblasts, and osteoid formation.²³ In human medicine, ABC cytology can be markedly hemodilute with osteoclasts, fibroblasts, hemosiderin-laden macrophages, and possible bone marrow elements.^{17,18} In one canine case of an ABC, cytology of the cyst fluid included multinucleated giant cells, spindle-shaped fibroblasts, hemosiderin-laden macrophages, and erythrocytes; however, no image was provided.²⁴

Fibrous dysplasia is also an expansile lesion, which has a cystic/radiolucent radiographic appearance that is surrounded by a narrow rim of bone. However, histologically, the cystic center is filled with a fibro-osseous tissue of uniform mesenchymal cells with thin, disorganized trabeculae of woven bone, and possible cystic regions with osteoclastic bone resorption.²³ Cytology of these lesions in humans can include osteoblasts, collagen bands, and fragments of bone¹⁸, but sampling often does not yield adequate diagnostic material for cytologic assessment.²⁵

This report describes, for the first time, the cytologic findings of a multiloculated solitary bone cyst in veterinary medicine. The cytologic appearance of the samples from this patient was highly concerning for malignant neoplasia, given the pleomorphic cell population and lack of inflammation; however, histopathology identified a benign bone cyst. While the size and instability of the bone lesion in this dog would have led to limb amputation regardless of the underlying cause, it is important to consider the therapeutic implications of a misdiagnosis of neoplasia, including unnecessary radical surgery, radiation therapy, or euthanasia. Cytology is a valuable diagnostic tool for the characterization of bone lesions in veterinary medicine, and here, we have provided a detailed cytologic description of a bone cyst to aid in the diagnosis of these uncommon lesions.

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Figure 1. Cranial-caudal (left) and lateral (right) radiographic images of the right stifle in a dog, showing a multiloculated lytic lesion of the distal femur. Size marker in the left image is 10cm.

Figure 2.

Photomicrographs of the cytology from a cytocentrifuged preparation that contained 100 μ l of fluid aspirated from a solitary bone cyst in a dog. A mix of discrete cells (arrows) displaying anisocytosis and anisokaryosis, variable N:C ratios, and occasional binucleation, with fewer vacuolated macrophages (arrowheads), are present. Wrights-Giemsa stain, 100x objective.

Figure 3.

Photomicrographs of histopathology from a multiloculated lytic bone lesion in a dog. (A) The cyst is composed of an outer layer of dense fibrous connective tissue and a central undulating layer of reactive cancellous bone of variable thickness. Multiple regions of bone exhibit active resorption by osteoclasts (inset). (B) The inner cyst wall contains variably dense fibrovascular tissue often overlying trabecula of woven bone. The cyst is entirely lined by a thin layer of flattened fibrocytes (inset). H&E, 4x Objective (A), 20x Objective (A, inset), 10x objective (B), 40x Objective (B, inset).