Pathology in Practice

In collaboration with the American College of Veterinary Pathologists

Figure 1—Postmortem images of the dissected pelvic (A) and thoracic (B) limbs of a 15-week-old cat that had intermittent, shifting-leg lameness, showing a fracture of the right femur at the distal metaphysis (arrow; A) and callus formation at the proximal aspect of the left humerus and distal aspects of the radii (arrows; B).

History

A 15-week-old 1.74-kg sexually intact male domestic shorthair cat was evaluated for an intermittent, shifting-leg lameness of 2 months' duration. Right forelimb lameness was initially observed following mild trauma and resolved without treatment. Right forelimb lameness returned 1 month later after the cat jumped off a couch. One week later, the cat was reluctant to walk and unable to bear weight in the hind limbs bilaterally. Diet history included a combination of several dry and canned commercial diets formulated for kittens.

Clinical and Gross Findings

On physical examination, the cat had a thin body condition and moderate muscle atrophy of all 4 limbs. Ocular evaluation revealed no scleral abnormalities. The oral cavity showed normal dentition for a kitten. Orthopedic examination revealed bilateral, non-weight-bearing lameness in the hind limbs, bilateral antebrachial varus deformity, and a sharp bend in the tail. Neurologic examination revealed normal reflexes in all 4 limbs. Serum biochemical analyses revealed clinically normal total calcium concentration (9.9 mg/dL; age-adjusted reference range,¹ 9.2 to 12.0 mg/dL),

phosphorus concentration (6.4 g/dL; age-adjusted reference range,² 6.0 to 10.4 mg/dL), and alkaline phosphatase activity (230 U/L; age-adjusted reference range,² 37 to 333 U/L). Urine specific gravity was concentrated at > 1.050.

A serum parathyroid hormone (PTH), calcium, and vitamin D profile revealed a mildly high concentration of PTH (33 pg/mL; age-adjusted reference range,¹ < 3 to 28 pg/mL) and clinically normal concentrations of ionized calcium (1.31 mmol/L; age-adjusted reference range,³ 1.30 to 1.34 mmol/L) and calcidiol (25-hydroxyvitamin D; 120 nmol/L; age-adjusted reference range,³ 89.6 to 126.5 nmol/L). The mildly high PTH concentration was deemed inconsequential in combination with clinically normal ionized calcium and calcidiol concentrations.

Pelvic and hind limb radiography revealed severe, diffuse osteopenia, with thin cortices, double cortical lines, and apparent widening of the medullary cavities of all visualized long bones. The epiphyses of the femur and tibia had a coarse trabecular pattern bilaterally. There were chronic folding fractures of the proximal left tibia and distal right femur at the level of the metaphyses. The seventh lumbar vertebra was shorter than adjacent vertebral bodies. There were multifocal curved caudal vertebrae with sclerotic endplates. Due to the severity of clinical signs, the owner elected euthanasia.

At necropsy, the right femur had a complete fracture at its distal metaphysis, with an area of subcutaneous hemorrhage and edema overlying the fracture site. Callus formation was observed at the proximal metaphysis of the left humerus and distal metaphyses of both radii (**Figure 1**). The left radius was moderately curved medially at the distal callus. There was no widening of the growth plates visualized. All ribs had increased pliability. The calvarium was very thin,

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Figure 2—Photomicrographs of bone from the cat described in Figure 1. **A**—There is a marked decrease or lack of cortical bone (star) with thickening of the periosteum. H&E stain; bar = 500 μ m. **B**—Abnormal alignment of cartilaginous cores within an area of microcallus, resulting from microfracture. Secondary spongiosa frequently contain reversal lines (arrow). H&E stain; bar = 50 μ m. **C**—Extension of primary spongiosa containing retained cartilage cores (arrow). H&E stain; bar = 50 μ m. **D**—Area of callus with overly abundant, disorganized cartilage (rightward) and lack of normal organized cortical bone (leftward). H&E stain; bar = 500 μ m.

with increased flexibility. The remainder of the necropsy findings, including histopathologic evaluation of the eyes, teeth, kidneys, thyroid glands, parathyroid glands, and skin, were unremarkable.

Formulate differential diagnoses, then continue reading.

Histopathologic Findings

Histologic evaluation of multiple long bones and ribs revealed marked reduction in thickness of woven bone forming the cortex, which was often lined by moderate numbers of osteoblasts and contained a thickened periosteum. Within the metaphyses, there was extension of primary spongiosa, with retention of cartilaginous cores and marked reduction in secondary spongiosa. Trabeculae of secondary spongiosa often contained reversal lines and frequent microfractures. Areas of microfracture were lined by osteoclasts. The grossly described calluses within the humerus and radii demonstrated multifocal, chronic, healing fractures with complete loss of normal cortical bone. Cortical bone was replaced by abundant and disorganized cartilage, with surrounding collagen, fibroblasts, and spicules of mineralized osteoid lined by osteoblasts and osteoclasts (**Figure 2**). No specific signs of a collagen disorder were noted; dentinogenesis and amelogenesis were normal. The periodontal ligament was widened due to bone loss, rather than abnormal formation.

Morphologic Diagnosis and Case Summary

Morphologic diagnosis: severe, diffuse osteopenia of long bones with lack of secondary spongiosa, accompanying fracture calluses and infraction lines (microfractures).

Case summary: lesions consistent with osteogenesis imperfecta (OI) in a cat.

Comments

The most common metabolic causes of diffuse osteopenia and pathologic fractures in dogs and cats are nutritional or renal secondary hyperparathyroidism.^{1,4} Nutritional or hereditary (type 1 or type 2 vitamin D-dependent rickets) vitamin D deficiency and hypophosphatemic rickets can also cause similar clinical signs.^{1,4-6} Nutritional vitamin D deficiency is uncommon in dogs and cats receiving an age-appropriate, balanced diet, and hereditary vitamin D deficiencies are rare diseases in dogs and cats.^{5,6} Measurement of serum creatinine, urea nitrogen, ionized calcium, phosphorus, vitamin D, and PTH concentrations, as was performed for the cat of the present report, screens for the aforementioned metabolic conditions. If these measurements are within the age-adjusted reference ranges, OI should be considered.

Osteogenesis imperfecta is an inherited bone disorder that is extremely rare in dogs and cats.^{1,7,8} In humans and dogs, OI most commonly results from gene mutations in type 1 collagen (*COL1A1*, *COL1A2*)^{7,9-14}; however, recent studies have shown mutations in *SERPINH1* causing OI in Dachshunds.^{11,15} Normal type I collagen forms the scaffold for bone mineralization, with abnormalities leading to lack of bone mineralization and extreme bone fragility.¹⁶ In dogs, there are no known sex predilections, but breed predispositions have been suggested in Beagles,^{11,13,17} Collies,¹⁷⁻¹⁹ Dachshunds,^{9,11,15,20} and Golden Retrievers.^{11-13,17} Although there have been individual case reports of clinically suspected OI in cats,^{8,21} the underlying gene mutations or breed predilections are unknown.

Affected dogs and cats typically develop clinical signs by 10 to 18 weeks of age.^{7,9,10,21} Common clinical signs are nonspecific and include lethargy, lameness, and signs of pain. Physical examination findings include blue-colored sclera, bone fractures without history of trauma, angular limb deformities secondary to fractures, and in severely affected dogs and cats, dyspnea and paresis or paralysis.^{1,7,10} Dentinogenesis imperfecta is a possible concurrent disorder that causes thin, roughened, discolored teeth due to thinning of the dentin layer.^{1,9,10,15,21}

Clinicopathologic analyses are unremarkable in dogs and cats with OI when reference ranges are adjusted for the animal's age. Hyperphosphatemia and high alkaline phosphatase activity, based on adult reference ranges, may be observed in puppies and kittens but are indicative of a developing animal. Most notably, age-adjusted serum concentrations of total calcium and ionized calcium are normal, and azotemia is not observed.^{4,9,10} Urine specific gravity is adequately concentrated for the age of the patient. Further hormonal testing, including assessments of concentrations of PTH, calcidiol, and calcitriol should be within age-adjusted reference ranges in dogs and cats with OI.^{3,4,8} Although calcitriol is the metabolically active form of vitamin D, serum calcidiol is routinely measured in human medicine to evaluate for vitamin D deficiency. Diagnostic imaging with radiography or CT²² demonstrates diffuse osteopenia, acute or chronic pathologic fractures, and angular limb deformities.^{1,8,10,15} Lack of wide, cupped growth plates or enlarged growth plates, which are commonly observed in dogs and cats with vitamin D deficiency,^{5,6} further supports a diagnosis of OI.

Definitive diagnosis of OI requires genetic testing for defects in type 1 collagen genes. As the genetic defect is unknown in cats, the combination of compatible clinicopathologic, diagnostic imaging, and ultimately, histopathologic features are necessary. In the case presented, absence of hypocalcemia, absence of biochemical evidence of renal disease, and normal calcidiol concentrations excluded other metabolic causes. The age of a cat is an important consideration when performing metabolic testing, as calcidiol concentrations vary in clinically normal, developing kittens. Notably, the serum calcidiol concentration was slightly low in comparison to the laboratory reference range in the cat of the present report. However, calcidiol concentration was clinically normal when adjusting for the cat's age, and in combination with a clinically normal ionized calcium and absence of radiographic changes associated with vitamin D deficiency, type 1 and type 2 rickets were considered unlikely.

Histopathology confirmed changes reported secondary to OI in the presented case, including decreased cortical bone, decreased secondary spongiosa, and callus formation at fracture sites.^{1,8–10} Accurate diagnosis is critical, as successful treatment of OI in cats is not described; clinical signs and pathologic

changes secondary to nutritional or hereditary vitamin D deficiency may improve with treatment.^{4–6} Attempts to surgically correct pathologic fractures secondary to suspect OI have not been successful due to diffuse bone fragility and lack of healing.^{8,10} Bisphosphonates are prescribed to human patients with OI¹³ and may provide palliation in dogs and cats; efficacy has not been reported. Vitamin C has been prescribed to cats with suspected OI due to effects on collagen growth; however, clinical signs did not improve in 1 report.⁸ Palliation with pain medication may improve quality of life in the short term, but prognosis for long-term survival is poor.

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References

1. Langley-Hobbs S. Musculoskeletal oddities in the cat: an overview of some curious causes of lameness. *J Feline Med Surg.* 2012;14(1):31–42. doi:10.1177/1098612X11432825.
2. von Dehn B. Pediatric clinical pathology. *Vet Clin North Am Small Anim Pract.* 2014;44(2):205–219. doi:10.1016/j.cvsm.2013.10.003.
3. Pineda C, Aguilera-Tejero E, Guerrero F, Raya AI, Rodriguez M, Lopez I. Mineral metabolism in growing cats: changes in the values of blood parameters with age. *J Feline Med Surg.* 2013;15(10):866–871. doi:10.1177/1098612X13478264.
4. Parker VJ, Gilor C, Chew DJ. Feline hyperparathyroidism: pathophysiology, diagnosis and treatment of primary and secondary disease. *J Feline Med Surg.* 2015;17(5):427–439. doi:10.1177/1098612X15581134.
5. Phillips AM, Fawcett AC, Allan GS, et al. Vitamin D-dependent non-type 1, non-type 2 rickets in a 3-month-old Cornish Rex kitten. *J Feline Med Surg.* 2011;13(7):526–531. doi:10.1016/j.jfms.2011.05.010.
6. Geisen V, Weber K, Hartmann K. Vitamin D-dependent hereditary rickets type I in a cat. *J Vet Intern Med.* 2009;23(1):196–199. doi:10.1111/j.1939-1676.2008.0220.x.
7. Campbell BG, Wootton JA, Krook L, Demarco J, Minor RR. Clinical signs and diagnosis of osteogenesis imperfecta in three dogs. *J Am Vet Med Assoc.* 1997;211(2):183–187.
8. Evason MD, Taylor SM, Bechuk TN. Suspect osteogenesis imperfecta in a male kitten. *Can Vet J.* 2007;48(3):296–298.
9. Seeliger F, Leeb T, Peters M, Brugman M, Fehr M, Hewicker-Trautwein M. Osteogenesis imperfecta in two litters of dachshunds. *Vet Pathol.* 2003;40(5):530–539. doi:10.1354/vp.40-5-530.
10. Lazar T, deHaan JJ, Peck JN, et al. Osteogenesis imperfecta in three dogs from a single litter. *Vet Comp Orthop Traumatol.* 2000;13(01):23–27. doi:10.1055/s-0038-1632625.
11. Enderli T, Burthch S, Tempel J, Carriero A. Animal models of osteogenesis imperfecta: applications in clinical research. *Dovepress Orth Res Rev.* 2016;8:41–55. doi:10.2147/orr.s85198.
12. Campbell BG, Wootton JA, MacLeod JN, Minor RR. Sequence of normal canine COL1A1 cDNA and identification of a heterozygous alpha1(I) collagen Gly208Ala mutation in a severe case of canine osteogenesis imperfecta. *Arch Biochem Biophys.* 2000;384(1):37–46. doi:10.1006/abbi.2000.2099.
13. Campbell BG, Wootton JA, MacLeod JN, Minor RR. Canine COL1A2 mutation resulting in C-terminal truncation of pro-alpha2(I) and severe osteogenesis imperfecta. *J Bone Miner Res.* 2001;16(6):1147–1153. doi:10.1359/jbmr.2001.16.6.1147.

14. Van Dijk FS, Sillence DO. Osteogenesis imperfecta: clinical diagnosis, nomenclature, and severity assessment. *Am J Med Genet.* 2014;164(6):1470–1481. doi:10.1002/ajmg.a.36545.
15. Drögemüller C, Becker D, Brunner A, et al. A missense mutation in the SERPINH1 gene in dachshunds with osteogenesis imperfecta. *PLoS Genet.* 2009;5(7):e1000579. doi:10.1371/journal.pgen.1000579.
16. Burnei G, Vlad C, Georgescu I, Gavrilu TS, Dan D. Osteogenesis imperfecta: diagnosis and treatment. *J Am Acad Orthop Surg.* 2008;16(6):356–366. doi:10.5435/00124635-200806000-00008.
17. Breur GJ, Lambrechts NE, Todhunter RJ. The genetics of canine orthopedic traits. In: Ostrander EA, Ruvinsky A, eds. *The Genetics of the Dog*. 2nd ed. CAB International; 2012: 136–160. doi:10.1079/9781845939403.0136.
18. Holmes JR, Price CHG. Multiple fractures in a collie: osteogenesis imperfecta. *Vet Rec.* 1957;69:1047–1050.
19. Schmidt V. Osteogenesis imperfecta in 2 collie litter siblings. Article in German. *Wien Tierarztl Monatsschr.* 1967; 54:92–100.
20. Eckardt J, Kluth S, Dierks C, Philipp U, Distl O. Population screening for the mutation associated with osteogenesis imperfecta in dachshunds. *Vet Rec.* 2013;172(14):364. doi:10.1136/vr.101122.
21. Cohn LA, Meuten DJ. Bone fragility in a kitten: an osteogenesis imperfect-like syndrome. *J Am Vet Med Assoc.* 1990;197(1):98–100.
22. Won S, Chung W, Yoon J. Clinical application of quantitative computed tomography in osteogenesis imperfecta-suspect cat. *J Vet Sci.* 2017;18(3):415–417. doi:10.4142/jvs.2017.18.3.415.