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Legg-Calvé-Perthes Disease in a Rhesus Macaque (*Macaca mulatta*)

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A juvenile rhesus macaque presented with atrophy of the musculature of its left leg. Physical examination localized the problem to the coxofemoral joint. Radiography revealed changes consistent with Legg-Calvé-Perthes (LCP) disease. Femoral head ostectomy was performed, and the femoral head was submitted for histologic examination, results of which confirmed a diagnosis of LCP.

Osteonecrosis of the femoral head and neck of young, growing animals, commonly referred to as Legg-Calvé-Perthes (LCP) disease, was first described in veterinary literature in dogs by Tutt in 1935 (24). At that time, he described the disease as tuberculosis of the hip. Drs. Legg, Calvé, and Perthes (16, 5, and 23, respectively) independently described the condition in children in 1910. At that time, Legg stated the currently accepted pathogenesis: impairment of the blood supply to the femoral epiphysis, or vascular/circulatory deprivation. The disease has been described in spontaneously hypertensive rats (11), a red panda (6), and a lowland gorilla (7); a similar condition, capital femoral epiphyseal infarction in chickens (8), also has been described. Common synonyms for LCP are avascular necrosis of the femoral neck, aseptic necrosis, osteonecrosis, coxa plana, and osteochondritis deformans juvenilis. Here, we present a case of LCP in a juvenile female rhesus macaque (*Macaca mulatta*). To the authors' knowledge, this is the first published report of LCP in a macaque.

Case Report

A 27-month-old female rhesus macaque was evaluated for a size discrepancy between the musculature of the left and right legs (Fig. 1). At the time of presentation, it was singly housed in a 4.3-ft^2 squeeze-back cage, with a height of 30 in., at an AAALAC-accredited facility. The affected animal was a native-born (NIRC, New Iberia, La.), Indian-origin rhesus macaque that was seroneg-ative for herpes B virus, simian T-cell lymphotropic virus, simian immunodeficiency virus, and simian retrovirus, and had negative results of the intradermal mammalian tuberculin test for TB. The animal weighed 3.2 kg, had no previously reported clinical problems, and had no prior experimental use. It had been maternally reared, and was peer group housed in a corncrib until approximately eight months prior to presentation, at which time it was housed singly for acclimation, conditioning, and testing in preparation for an IACUC-approved experimental protocol. The diet consisted of approximately 150 g of Teklad NIB modified 8733 primate diet (Harlan Teklad, Madison, Wis.) in two daily feedings, and drinking water was provided ad libitum via an automatic watering system. Room temperature (24.4 to 26.6°C), and photoperiod (12:12-h light:dark cycle) were controlled. This animal was participating in an IACUC-approved environmental enrichment program.

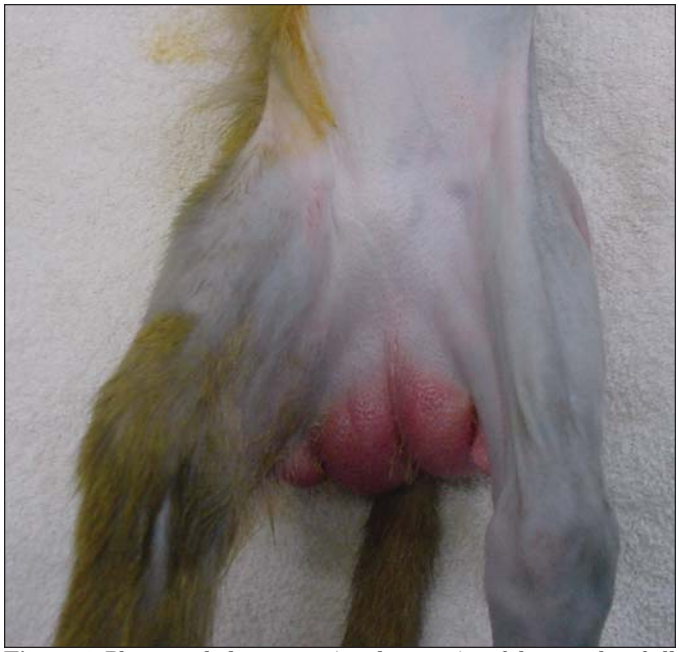

Figure 1. Photograph demonstrating the severity of the atrophy of all of the major muscle groups of the left leg in the affected rhesus macaque. Notice also the prominent sex skin in the perineal area.

The animal in question had 50 to 75% atrophy of the muscles of its left leg. A subtle gait abnormality also was present. The animal would leap back and forth across the cage, but it put little weight on its left leg as it jumped and when it landed. The animal had a substantial amount of sex skin present and was displaying sexual behavior. The animal was sedated with ketamine (KetaVed VEDCO, St. Joesph, Mo.; 10 mg/kg of body weight, i.m.), and was examined. Skin defects or other external lesions

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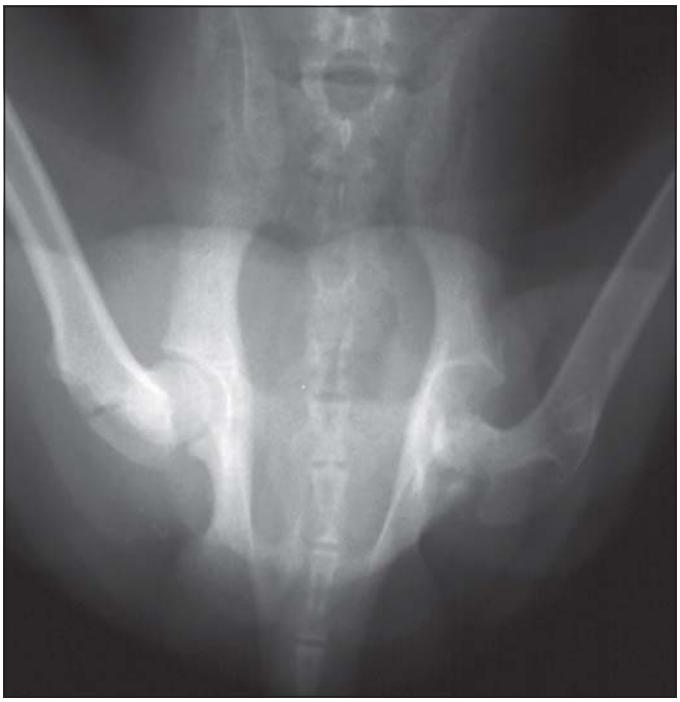

Figure 2. Radiographic view using frog-leg positioning of the pelvis of the affected animal. Notice widening of the left acetabulum, and loss of the sclerotic margin of the cranial acetabular rim. The left femoral head is small and irregular.

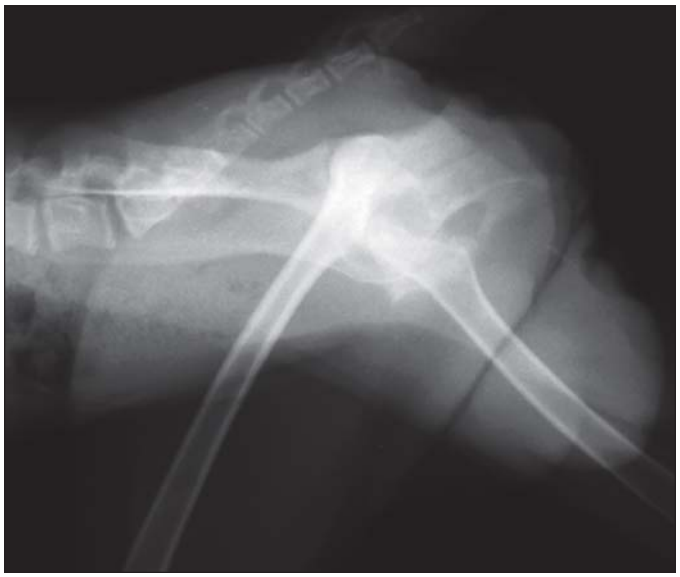

Figure 3. Lateral radiographic view of the pelvis of the affected animal. Notice thinning of the cortex of the femur of the affected leg.

were not present on the leg. Palpation of the bones of the left leg and the stifle and tarsal joints yielded normal results, and the limb had good pulse quality. The patellar, sciatic, cranial tibial, and gastrocnemius reflexes were present, though determination of hyper- or hyporeflexia could not be made because the animal was sedated. The coxofemoral joint had appreciable crepitus on palpation and reduced range of motion.

Radiography revealed widening of the left acetabulum and loss of the sclerotic margin of the cranial acetabular rim (Fig. 2 and 3). The left femoral head was misshaped and appeared small. There was a summation opacity superimposed over the proximal portion of the femoral head, and a physeal fracture could not be completely ruled out. These findings were considered to be consistent with a diagnosis of LCP disease by a board certified veterinary radiologist, though trauma could not be ruled out.

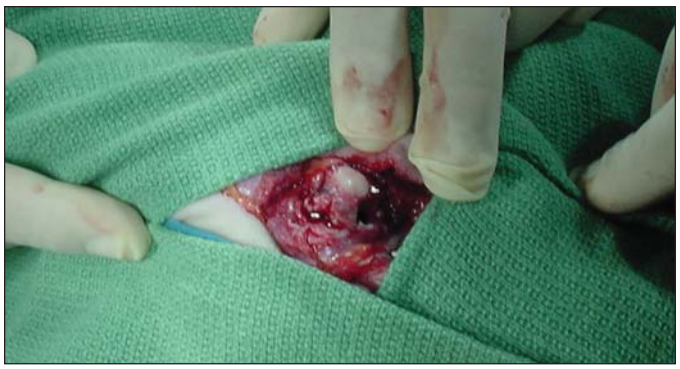

Figure 4. Photograph taken after exposure of the femoral head during the ostectomy procedure. Notice the small, misshapen femoral head. Cartilage is absent, and irregular bone is present over most of its surface.

The animal was treated orally twice daily with 20 mg of ibuprofen/kg of body weight (Ibuprofen oral suspension, Alpharma USPD Inc., Baltimore, Md.), and was observed for improvement in its gait. When improvement was not seen after 7 days, 0.03 mg of buprenorphine/kg (Buprenex Reckitt Benckiser Healthcare (UK) Ltd., Hull, England) was given intramuscularly twice daily for additional analgesia. The animal was observed for an additional 2 weeks, with little to no improvement.

At that point, the animal was sedated with tiletamine/zolazepam (Telazol, Fort Dodge Animal Health, Fort Dodge, Iowa; 5 mg/kg, i.m.) and intubated, then isoflurane (Forane Baxter Healthcare Corporation, Deerfield, Ill.) was administered. Femoral head ostectomy (FHO) was performed. At surgery, the left femoral head appeared to be about half its normal size, with cartilage present only on its most proximal portion and irregular bone present over most of its surface (Fig. 4). The acetabulum appeared wide. Fractures were not observed. Buprenorphine and ibuprofen for analgesia were continued at the preoperative doses. After surgery, the animal had immediate but slight improvement in its gait. As of four months after surgery, it continues to have improved use of the affected leg, and is slowly regaining the lost muscle mass.

The femoral head and neck were fixed in neutral-buffered 10% formalin, decalcified, and processed in routine manner. Slides were stained with hematoxylin and eosin (H&E).

Microscopic changes consisted of marked architectural alteration of the left femoral head (Fig. 5). Epiphyseal cartilage was absent, as was much of the trabecular bone that arose from the secondary ossification center in epiphyseal cartilage. Some remaining fragments of trabecular bone had undergone necrosis and were surrounded by dense sheets of fibrous connective tissue that contained moderate infiltrates of macrophages (Fig. 6). Viable trabecular bone in the epiphysis had a flat, eburnated surface that was in contact with the coxofemoral joint space. The epiphyseal growth plate was irregular, and lateral margins were replaced by fibrous connective tissue. Endochondral ossification in the central region of the epiphyseal growth plate appeared normal. Venous thrombi were observed in the histologic sections

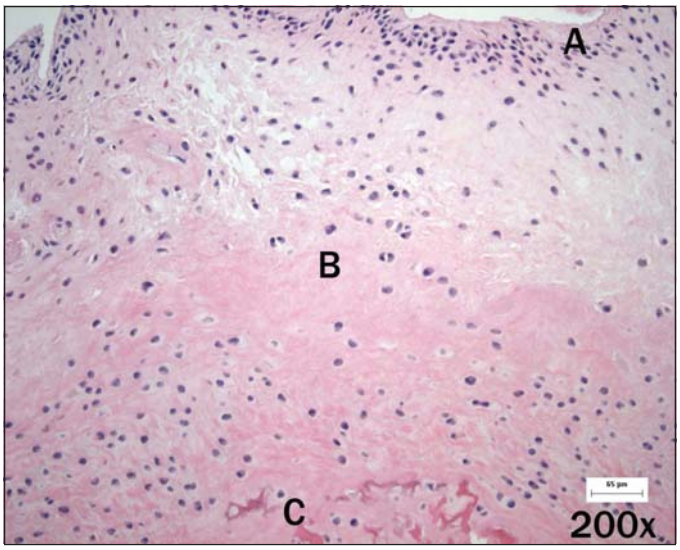

Figure 5. Photomicrograph of a section of the left femoral head showing loss of articular cartilage (A), dense sheets of fibrous connective tissue with macrophage infiltrates (B), and fragments of necrotic bone (C). H&E stain; magnification, 200×.

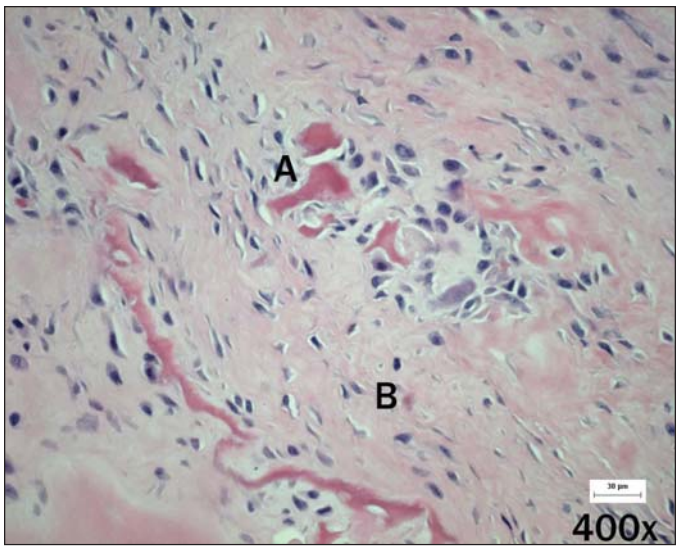

Figure 6. Higher magnification image of the aforementioned necrotic bone fragments (A) surrounded by macrophages and fibrous connective tissue (B). H&E stain; magnification, 400×.

examined (Fig. 7), confirming a diagnosis of avascular osteonecrosis of the femoral head or LCP disease (3, 15, 20, 27).

Discussion

The cause of LCP disease is currently unknown. The pathologic features are typical of avascular necrosis of bone. Blood supply to the femoral head is interrupted, resulting in the death of bone cells. Avascular necrosis develops predominately in young animals because the blood supply to the femoral head in animals with open physes is derived solely from epiphyseal vessels, which run extraosseously along the surface of the femoral neck (1, 2). Increased intraarticular pressure may collapse the vessels and result in reduced blood flow to the epiphysis (9, 26, 27). Vascular compromise may occur in the absence of increased intraarticular pressure, due to clotting, emboli, and/or traumatic disruption (12, 13, 19). Potential causes of LCP include abnormal limb position, trauma, synovitis, corticosteroid administration, endotoxin, immune reactions, and endocrine abnormalities (3, 10, 17, 18, 21, 22, 28, 29, 31). There appears to be an autosomal recessive genetic predisposition to this condition in dogs (25). Ljunggren suggested a possible endocrinologic cause for LCP in the dog, and reported that osteonecrosis develops in association with high doses of steroids (estrogens and/or testosterone) (17, 18). In the case presented here, the animal had early onset of sexual characteristics and behavior, suggesting that hormones may have predisposed this animal to develop LCP.

Ischemic necrosis is usually followed by a period of revascularization, where the femoral head is subject to remodeling and/or collapse, creating an irregular fit into the acetabulum (20). This incongruency of the femoral head and acetabulum will result in degenerative joint disease (DJD). The condition may be asymptomatic, or the animal may present with lameness, crepitus on palpation, reduced range of motion, limb shortening, and/or disuse muscle atrophy of the affected leg. This condition may follow a chronic, progressive course as it did in this case, or it may result in an acute non-weight bearing lameness, due to fracture of the femoral head.

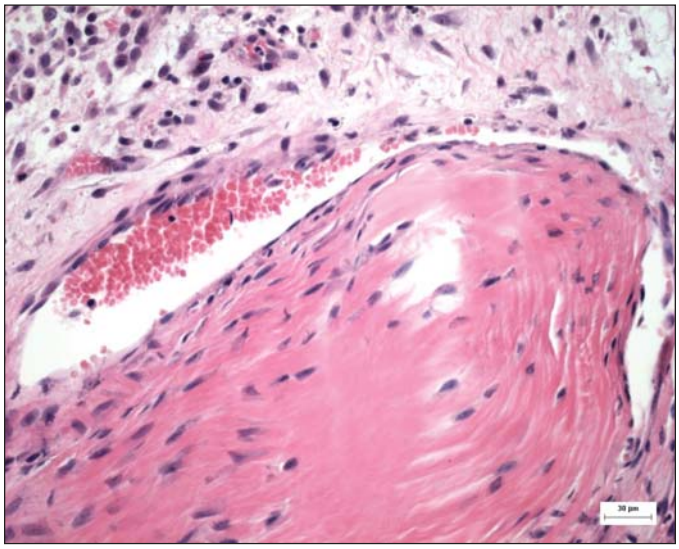

Figure 7. Photomicrograph of a section of recanalized thrombus surrounded by granulation tissue. H&E stain; magnification, 400×.

Radiographically, the disease is characterized by increased joint space, foci of decreased bone opacity in the femoral head and neck, irregularity of the femoral head and neck, and resultant widening of the acetabulum (4, 15). Osteophytes and subluxation and fracture of the femoral head and neck may also be seen.

There is still discussion about the indications for and modalities of treatment for LCP in human and veterinary medicine. If the condition is diagnosed early, the main objective of treatment is prevention of deformation and malalignment of the hip joint. The use of splints or bandages may be justified if there is improvement of the containment and reduction of the femoral head; otherwise, surgical treatment should be considered (30). In this instance, the animal had appreciable DJD at the time of diagnosis. Conservative treatment with anti-inflammatory and analgesic drugs was tried, but resulted in minimal to no improvement. In dogs that are manifesting clinical signs of disease,

FHO is currently the favored treatment (14). To our knowledge, use of this procedure has not been reported in primates. Our initial concern, that the locomotory differences between the primate and the canine could make the procedure less suitable for nonhuman primates, turned out to be unfounded. The animal has regained good range of motion, and its gait continues to improve. Long-term prognosis in the canine is good, but it can take in excess of 6 months for full recovery after FHO in dogs with severe muscle atrophy. It appears likely that a similar time course for recovery may be necessary for the animal reported here.

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