Mycobacterial neuritis in a cat

Daniel B. Paulsen, DVM, PhD, DACVP; Margaret R. Kern, DVM, DACVIM; Claire M. Weigand, DVM

- ➤ Mycobacterial neuritis should be included as a differential diagnosis for progressive peripheral neuropathy in cats.
- ➤ Diagnosis is made by detection of granulomatous or pyogranulomatous neuritis with acid-fast organisms in nerve biopsy specimens.
- ➤ Prognosis is uncertain, but long-term treatment with clofaziamine and enrofloxacin may halt progression of the disease.

A 2-year-old spayed female domestic shorthair was referred for evaluation of rapidly progressive lameness of 2 months' duration that affected the right hind limb. The cat had access to indoor and outdoor environments. The owner also had 6 other cats. The referring veterinarian had treated the cat twice with a corticosteroid during the preceding month; with each treatment, remission of clinical signs lasted only 5 to 6 days. The cat had been vaccinated against panleukopenia, viral rhinotracheitis, calicivirus infection, chlamydiosis, and rabies. Physical examination revealed paralysis of the right hind limb, mild bleeding of the right hind foot attributed to self-mutilation, and atrophy of the caudal muscles of the thigh.

Neurologic examination revealed normal findings except for abnormalities of the right hind limb. The cat stood with a dropped right tarsus and moved the limb only at the hip while walking. Conscious proprioception, hopping, placing, and righting responses were not detected in the right hind limb, whereas the patellar reflex was exaggerated. Cranial tibialis and gastrocnemius reflexes were not detected. The flexor reflex was weak at the stifle joint and not detected at the tarsus. Evidence of pain sensation was detected in the medial digit but not in the lateral digit. Some evidence of pain sensation was detected in areas innervated by the tibial nerve even though the cranial tibialis and gastrocnemius muscles were completely paralyzed, suggesting that a lesion may have been compressing the nerve and affecting the more heavily myelinated fibers. A neuropathy affecting the sciatic nerve distal to its branches to the biceps femoris, semimembranosus, and semitendinosus muscles was suspected.

A CBC and serum biochemical analyses were performed; results were within reference ranges. Results of serologic tests for feline immunodeficiency virus and FeLV were negative. Radiography did not reveal skeletal lesions in the pelvis or right hind limb. Primary differential diagnoses were trauma, nerve sheath tumor, inflammatory disease, or spinal lymphosarcoma.

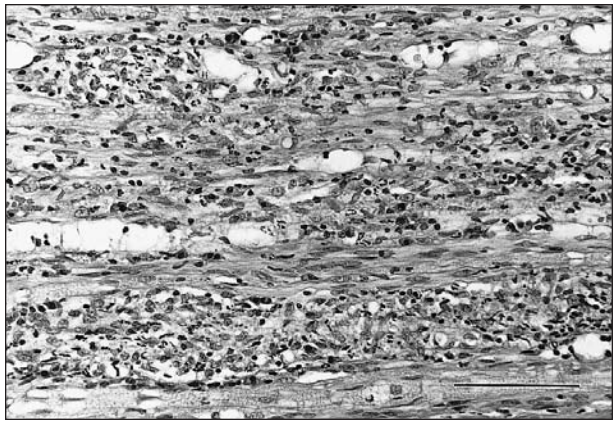

Figure 1—Photomicrograph of a section of the sciatic nerve of a cat with mycobacterial neuritis. Notice intense granulomatous to pyogranulomatous inflammatory infiltrate typical of mycobacterial infection and large, clear spaces that represent axonal digestion chambers characteristic of Wallerian degeneration. H&E stain; bar = 100 μm.

Surgery was performed to evaluate nerves in the right hind limb. The sciatic, common peroneal, and tibial nerves were enlarged. Small biopsy specimens were shaved from the proximal and distal portions of the sciatic nerve, the proximal portions of the common peroneal and tibial nerves, and the biceps femoris muscle. The cat was treated twice with cephazolin during surgery (22 mg/kg [10 mg/lb] of body weight, IV) and after surgery (22 mg/kg, IV, q 12 h) for 1 day. The cat was discharged with an Elizabethan collar; bandages on the right hind foot were changed twice weekly.

Histologic examination of biopsy specimens revealed that all nerve branches were affected by a moderate to severe inflammatory infiltrate composed of macrophages, lymphocytes, plasma cells, variable numbers of neutrophils, few mast cells, and few eosinophils (**Fig 1**). Multinucleated giant cells were not seen. The inflammatory process was contained by the nerve sheath, and moderate Wallerian degeneration was evident. Acid-fast stains revealed slender beaded bacilli within scattered macrophages, nerve fibers, and degenerate axons (**Fig 2**). The bacteria often formed chains of 2 or 3 organisms, pallisading stacks, or tangled clusters. Skeletal muscle was atrophied and had scattered perivascular lymphocytic cuffs, but acid-fast organisms were not detected. Some myocytes contained protozoal cysts with morphologic features compatible with *Sarcocystis* sp, which were considered an incidental finding. A diagnosis of mycobacterial neuritis was made on the basis of the morphologic features, arrangement, and staining characteristics of the bacteria within nerves.

Three weeks later, the cat was readmitted to the

From the Diagnostic Laboratory and Field Services Program (Paulsen) and the Animal Health Center (Kern, Weigand), College of Veterinary Medicine, Mississippi State University, Mississippi State, MS 39762. Dr. Weigand's present address is Rowley Memorial Animal Hospital, 171 Union St, Springfield, MA 01105.

The authors thank Drs. David Jennings, Todd Tobias, John Tyler, Frank Austin, and David Scollard for technical assistance.

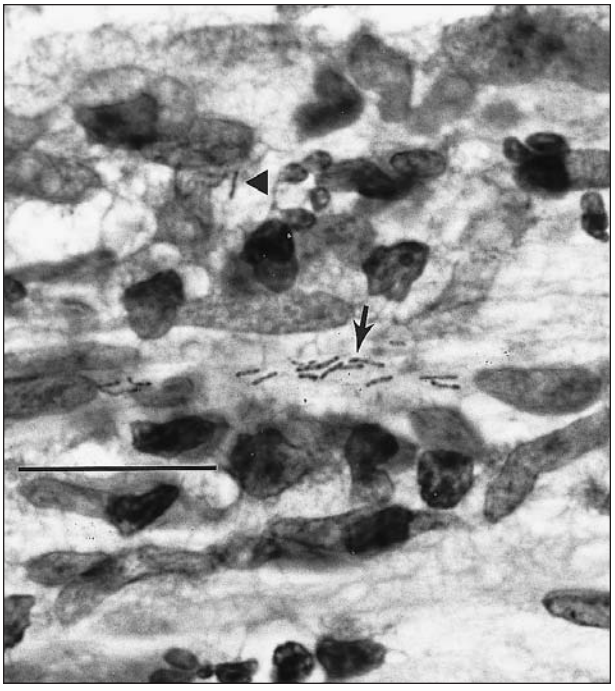

Figure 2—Photomicrograph of a section of the sciatic nerve of a cat with mycobacterial neuritis. Notice slender, beaded, bacilli (mean length, 4.7 μm) in nerve fiber (arrow) and macrophage cytoplasm (arrowhead). Ziehl-Neelsen stain; bar = 20 μm.

hospital. The withdrawal reflex (ie, hip flexion) was weak, the patellar reflex was intact, evidence of pain sensation was detected in all digits, but paralysis of muscles innervated by the sciatic nerve remained. The popliteal lymph node and further biopsy specimens from the sciatic nerve were obtained at surgery; bacteriologic cultures in Herrold's egg yolk and Lowenstein-Jensen agar, both containing malachite green with and without glycerin and with and without decontamination procedures, did not yield growth during a 3-month incubation period. Because of small specimen size, the nerve was not reevaluated histologically. Reactive hyperplasia without granulomatous inflammation or bacteria was observed microscopically in the lymph node. After receiving the negative culture results, the authors submitted remnants of the initial biopsy specimens to a mycobacteria research center[a] for genus-specific polymerase chain reaction amplification; results were negative. Treatment with clofazimine[b] (10 mg/kg [4.5 mg/lb], PO, q 24 h) was initiated. The owner had constructed a chamois boot that effectively prevented self-mutilation of the foot.

The cat was returned 2 months later for a recheck. The owner reported that diarrhea began 3 days after initiation of clofazimine treatment and gradually resolved during the first month of treatment. Attempts at self-mutilation had ceased 1 month after initiation of clofazimine treatment. Recently, the cat had been lethargic and had decreased appetite. Blood was obtained, and activities of serum **alanine aminotransferase** (**ALT**, 115 U/L; reference limit, < 100 U/L) and serum **alkaline phosphatase** (**ALK**, 36 U/L, reference limit, < 30 U/L) were slightly increased.

The cat was returned the following month and was bearing some weight on the right hind limb; however, the cat was walking plantograde and was unable to extend the tarsus. Activities of ALT and ALP had increased to 206 U/L and 49 U/L, respectively. Because of potential toxic effects on the liver, dosage of clofazimine was decreased to 10 mg/kg, administered twice weekly. One month later, activities of ALT and ALK had returned to reference ranges, but the cat had a fever (rectal temperature, 40.5 C [104.9 F]) of undetermined origin. Treatment with enrofloxacin[c] (5 mg/kg (2.3 mg/lb), PO, q 12 h) was initiated, and dosage of clofazimine was increased (10 mg/kg, 3 times/wk). Several days after these changes in the treatment regimen, normal temperature and appetite resumed. Lethargy had resolved, and the cat had regained some use of the right hind leg. Combined treatment with enrofloxacin and clofazimine was continued for 6 months, at which time administration of enrofloxacin was discontinued; administration of clofazimine was continued for another 26 months. During this period, sciatic paralysis did not resolve, and serum activities of ALT and ALK ranged from 37 to 190 U/L and 37 to 62 U/L, respectively. Additional adverse effects of treatment included temporary dark brown discoloration of urine, discoloration of skin and fur to a peach color, and bilirubinuria.

Three major clinical syndromes caused by mycobacterial infections have been identified in cats: tuberculosis, feline leprosy, and atypical mycobacteriosis or opportunistic mycobacterial granuloma.[1,2] The case reported here was a unique variant of mycobacteriosis that apparently affected only peripheral nerves (right sciatic nerve and its branches, the common peroneal and tibial nerves).

Tuberculosis in cats, caused by *Mycobacterium avium, M bovis,* or *M tuberculosis*, is a granulomatous disease that is generally localized to the respiratory or gastrointestinal tract and associated lymph nodes. In some instances, the disease disseminates and causes systemic granulomatous lesions.

Atypical mycobacteriosis is caused by saprophytic mycobacteria, such as *M fortuitum, M smegmatis, M cheloni, M phlei,* and other species. Typical lesions include chronic nonhealing wounds, multiple draining fistulae, or draining skin nodules.

Feline leprosy has been attributed to infection with *M lepraemurium*; although controversy exists concerning the causative agent, molecular determination of 16S rRNA sequences have provided strong evidence that at least some cases are caused by *M lepraemurium*.[3] Feline leprosy causes single or multiple cutaneous nodules that may or may not ulcerate.

Human leprosy causes a range of lesions, from lepromatous leprosy to tuberculoid leprosy, that presumably depend on the host's immune response. The lepromatous form has a minimal cell-mediated response; skin lesions are nodular to diffuse, commonly symmetrical, and formed by large numbers of aggregated foamy macrophages that contain large numbers of acid-fast bacilli. Peripheral nerves are often affected, usually symmetrically, and contain large numbers of acid-fast bacilli and few inflammatory cells.

In contrast, tuberculoid leprosy is characterized by

macular skin lesions that are neither numerous nor symmetrical. The lesions are focal granulomas (ie, epithelioid macrophages and giant cells surrounded by lymphocytes) that resemble tubercles and contain few acid-fast bacilli. Peripheral nerves may become enclosed within granulomatous inflammatory foci, causing muscle atrophy and anesthesia of the skin; results can be devastating and include indolent skin ulcers, muscle contracture, paralysis, and destruction of fingers or toes.[4,5]

A third syndrome, to which the case reported here bears resemblance, is primary neural leprosy, a rare disease in humans that is characterized by peripheral granulomatous neuritis without skin lesions.[6] Detection of acid-fast bacilli within nerves or infiltrating macrophages is considered diagnostic and was detected in the cat reported here, as was typical granulomatous inflammation. Negative results of bacteriologic culture and molecular techniques may have been the result of low organism numbers in the specimens, which were small and few because of the objective of returning normal function to the limb. Additionally, formalin-fixation and processing could have interfered with RNA isolation.[7] Alternatively, certain mycobacterial species such as *M lepraemurium* and *M leprae* could have been missed, because methods for culture on artificial media either have not been developed or are impractical in a diagnostic setting.[8]

The initial treatment chosen for the cat reported here was clofazimine. Later, when the cat developed a fever of unknown origin, enrofloxacin was added to the treatment regimen. Treatment was chosen on the basis of reports of the efficacy of clofazimine[9-12] and enrofloxacin[13] for various mycobacterial infections in cats. Clofazimine accumulates in macrophages and enhances respiratory burst activity.[14,15] Enrofloxacin accumulates in macrophages and neutrophils and inhibits DNA gyrase.[16] Enrofloxacin administration was continued for 6 months because subjectively, an improvement in the clinical signs was initially detected, but administration was discontinued when additional improvement was not detected. Clofazimine administration was discontinued after 3 years. Treatment was partially effective; the goal of returning normal function to the distal portion of the sciatic nerve and its branches was not achieved, but disease progression was halted, and the cat remained a viable pet. Adverse reactions were mild and similar to those reported.[12]

[a]Laboratory Research Branch, Gillis W. Long Hansen's Disease Center, Louisiana State University, Baton Rouge, La.
[b]Lamprene, Geigy Pharmaceuticals, Summit, NJ.
[c]Baytril, Bayer Corp, Shawnee, Kan.

References

1. Green CE. Bacterial diseases. In: Ettinger SJ, Feldman EC, eds. *Textbook of veterinary internal medicine*. 4th ed. Philadelphia: WB Saunders Co, 1995;367–376.
2. Scott DW, Miller WH Jr, Griffin CE. *Muller and Kirk's small animal dermatology*. 5th ed. Philadelphia: WB Saunders Co, 1995;312–319.
3. Hughes MS, Ball NW, Beck LA, et al. Determination of the etiology of presumptive feline leprosy by 16S rRNA gene analysis. *J Clin Microbiol* 1997;35:2464–2471.
4. Cockerell CJ. Leprosy. In: Conner DH, Chandler FW, Manz HJ, et al, eds. *Pathology of infectious diseases*. Stamford, Conn: Appleton & Lange, 1997;605–614.
5. Samuelson J, Von Lichtenberg F. Infectious diseases. In: Cotran RS, Kumar V, Robbins SL, eds. *Robbins pathologic basis of disease*. 5th ed. Philadelphia: WB Saunders Co, 1994;305–377.
6. Jenkins D, Papp K, Jakubovic HR, et al. Leprotic involvement of peripheral nerves in the absence of skin lesions. Case report and literature review. *J Am Acad Dermatol* 1990;23:1023–1026.
7. Fiallo P, Williams DL, Chan GP, et al. Effects of fixation on polymerase chain reaction detection of *Mycobacterium leprae*. *J Clin Microbiol* 1992;30:3095–3098.
8. Wayne LG, Kubica GP. *Mycobacteriaceae*. In: Sneath PHA, Mair NS, Sharpe ME, et al, eds. *Bergey's manual of systematic bacteriology*. Vol 2. Baltimore: The Williams & Wilkins Co, 1986;1436–1457.
9. Kaufman AC, Greene CE, Rakich PM, et al. Treatment of localized *Mycobacterium avium* complex infection with clofazimine and doxycycline in a cat. *J Am Vet Med Assoc* 1995;207:457–459.
10. Malik R, Gabor L, Martin P, et al. Subcutaneous granuloma caused by *Mycobacterium avium* complex infection in a cat. *Aust Vet J* 1998;76:604–607.
11. Michaud AJ. The use of clofazimine as treatment for *Mycobacterium fortuitum* in a cat. *Feline Pract* 1994;22:7–9.
12. Mundell AC. New therapeutic agents in veterinary dermatology. *Vet Clin North Am Small Anim Pract* 1990;20:1541–1556.
13. Studdert VP, Hughes KL. Treatment of opportunistic mycobacterial infections with enrofloxacin in cats. *J Am Vet Med Assoc* 1992;201:1388–1390.
14. Sahu A, Saha K, Banerjee NR, et al. Effect of antileprosy drugs on superoxide anion production by rat peritoneal macrophage with special reference to light exposed clofazimine. *Int J Immunopharmacol* 1991;13:419–428.
15. Wadee AA, Anderson R, Rabson AR. Clofazimine reverses the inhibitory effects of *Mycobacterium tuberculosis* derived factors on phagocyte intracellular killing mechanism. *J Antimicrob Chemother* 1988;21:65–74.
16. Hooper DC, Wolfson JS. Fluoroquinolone antimicrobial agents. *N Engl J Med* 1991;324:384–394.