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Long-term survival in a dog with meningoencephalitis and epidural abscessation due to *Actinomyces* species

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Abstract. A 2-year-old, female spayed Golden Retriever dog was presented to The Ohio State University Veterinary Medical Center for evaluation of ataxia, cervical pain, 1 episode of acute collapse, dull mentation, and inappetence. Physical examination revealed an elevated temperature of 39.7°C and severe cervical pain. Blood work revealed a mature neutrophilia. Cerebrospinal fluid (CSF) analysis revealed nondegenerative neutrophilic pleocytosis with no infectious agents. A presumptive diagnosis of steroid-responsive meningitis–arteritis was made, and corticosteroid therapy was started. The patient improved initially but experienced a vestibular episode characterized by falling and vertical nystagmus. A magnetic resonance imaging of the brain revealed an epidural abscess in the cervical vertebral canal and diffuse meningeal enhancement in the brain and cranial cervical spine. Abscess drainage revealed degenerate neutrophils and several filamentous, branching organisms. Culture of the initial CSF using an enrichment broth revealed growth of a Gram-positive organism 5 days after fluid collection. The isolate was identified by partial 16S ribosomal DNA sequencing as *Actinomyces* spp. The patient was successfully treated with long-term antibiotics. Our study reports the long-term survival after medical treatment of bacterial meningoencephalitis and epidural abscessation due to *Actinomyces* sp. infection in a dog. Bacterial meningoencephalitis should be included as a differential diagnosis in patients with cervical pain and fever, even when a nondegenerative neutrophilic pleocytosis is found on CSF analysis. Culture of the CSF with use of an enrichment broth should be considered in all cases of neutrophilic pleocytosis to rule out infections of the central nervous system.

Key words: Actinomyces; bacteria; canine; cerebrospinal fluid; magnetic resonance imaging; steroid responsive meningitis–arteritis.

A 2-year-old, female spayed, 35-kg Golden Retriever dog was presented to The Ohio State University Veterinary Medical Center Emergency Service (Columbus, Ohio) for a primary complaint of ataxia, cervical pain, dull mentation, inappetence, and a single episode of collapse. Vaccinations were current, and there was no history of trauma or travel. The owner administered 750 mg of enteric-coated aspirin every 4–5 hr for 3 days prior to presentation for the cervical pain. Initial physical examination was unremarkable except for an elevated rectal temperature of 39.7°C. On neurologic examination, the patient was quiet, alert, and responsive. The dog had a mildly stiff gait in all 4 limbs, had a low head and neck carriage, and exhibited guarded movements of the head and neck. Moderate to severe cervical pain was elicited on palpation. No other neurological abnormalities were found. Based on signalment, history, and examination findings, differential diagnoses included immune-mediated or infectious meningitis, diskospondylitis, vertebral osteomyelitis, and spinal neoplasia.

The dog was admitted to the hospital for supportive care and additional diagnostics. A complete blood cell count revealed a mature neutrophilia of 13,600 cells/μL (reference [ref.] range: 3,000–10,400 cells/μL). All values on venous blood gas analysis were within reference range including: pH 7.457 (ref. range: 7.38–7.48), pCO2 29.6 mmHg (ref. range: 28–49 mmHg), pO$_2$ 39.8 mmHg (ref. range: 25–46 mmHg), Na$^+$ 143 mmol/L (ref. range: 143–150 mmol/L), K$^+$ 3.8 mmol/L (ref. range: 3.5–4.8 mmol/L), Ca^{2+} 5.3 mg/dL (ref. range: 4.9–5.8 mg/dL), HCT 46%, Cl$^-$ 116 mmol/L (ref. range: 111–119 mmol/L), glucose 119 mg/dL (ref. range: 78–126 mg/dL), lactate 1.9 mmol/L (ref. range: 0.5–3.5 mmol/L), and Mg^{2+} 1.14 mg/dL (ref. range: 1.11–1.53 mg/dL). A free catch urinalysis to evaluate for casts revealed a urine specific gravity of 1.019, pH 5.5, and negative findings for protein, glucose, acetone, bilirubin, blood, casts, and leukocytes. Cervical radiographs were unremarkable. Initial treatments included misoprostol[a] at 2.9 μg/kg orally every 8 hr, gabapentin[b] at 8.6 mg/kg orally every 8 hr, omeprazole[c] at 1.1 mg/kg orally every 24 hr, and 100–150 mL/hr of isotonic intravenous fluids.[d]

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A cerebellomedullary cisternal cerebrospinal fluid (CSF) collection was performed using aseptic technique to investigate the possibility of inflammatory or infectious meningoencephalitis. The results of CSF analysis revealed a severe neutrophilic pleocytosis with a total nucleated cell count of 13,725 cells/μL (ref. range: 0–5 cells/μL) and a protein level of 1,242 mg/dL (ref. range: 0–25 mg/dL). Differential count of the nucleated cells revealed 93% nondegenerate neutrophils, 6% large monocytes, and 1% lymphocytes. No infectious agents were observed. The sample was submitted for aerobic bacteriology due to the neutrophilic pleocytosis. Based on the results of the CSF tap, signalment, presence of cervical pain, and absence of neurologic deficits, a provisional diagnosis of steroid-responsive meningitis–arteritis (SRMA) was made, and treatment was instituted with an anti-inflammatory dose of prednisone[e] at 0.6 mg/kg orally every 12 hr. The patient had improvement of the cervical pain following initiation of prednisone therapy and showed no signs of aspirin toxicity. The following day, the prednisone dose was increased to an immunosuppressive dose, 1.1 mg/kg orally every 12 hr, to treat for presumptive SRMA. Culture of the CSF was negative for any growth at the time. Despite the initial clinical improvement, over the next 24 hr, the dog began to exhibit worsening cervical pain and was observed to have several severe vestibular events where it collapsed into left lateral recumbency with rapid vertical nystagmus. The episodes lasted ~30–45 sec without loss of consciousness, autonomic signs, or tonic–clonic movements of the limbs or jaw. Following each episode, the dog returned to sternal recumbency and appeared normal. The patient continued to have 2–4 vestibular episodes each day for the following 3 days.

Because of the worsening of clinical signs, magnetic resonance imaging (MRI)[f] of the brain was performed on the fourth day of hospitalization. Sequences in the sagittal, transverse, and dorsal planes included T2-weighted (T2W; repetition time [TR] 3000.0 msec, echo time [TE] 80.0 msec), T1-weighted (T1W; TR 600.0 msec, TE 10.0 msec) pre- and postcontrast, fluid attenuated inversion recovery (FLAIR; TR 11000.0 msec, TE 125.0 msec), and fast field echo (FFE; TR 966 msec, TE 16.1 msec). The MRI of the brain and cranial cervical spinal cord segment revealed a T2W hyperintense and T1W hypointense, well-defined elongated mass lesion, measuring 1.5 cm × 1.0 cm, located most likely within the dorsal epidural space extending from the foramen magnum to the level of the mid-body of the C2 vertebrae. The lesion caused severe dorsal compression of the cervical spinal cord. On T1W postcontrast images, there was moderate to strong peripheral contrast enhancement of the mass with diffuse dural and leptomeningeal contrast enhancement of the brain and cranial cervical spinal cord. On FLAIR images, the lesion was of mixed intensities. On FFE images, the area of the lesion was hyperintense with no areas of signal void. Filamentous material on T1W postcontrast image was visualized within both lateral ventricles suggesting intraventricular fibrin formation (Fig. 1).
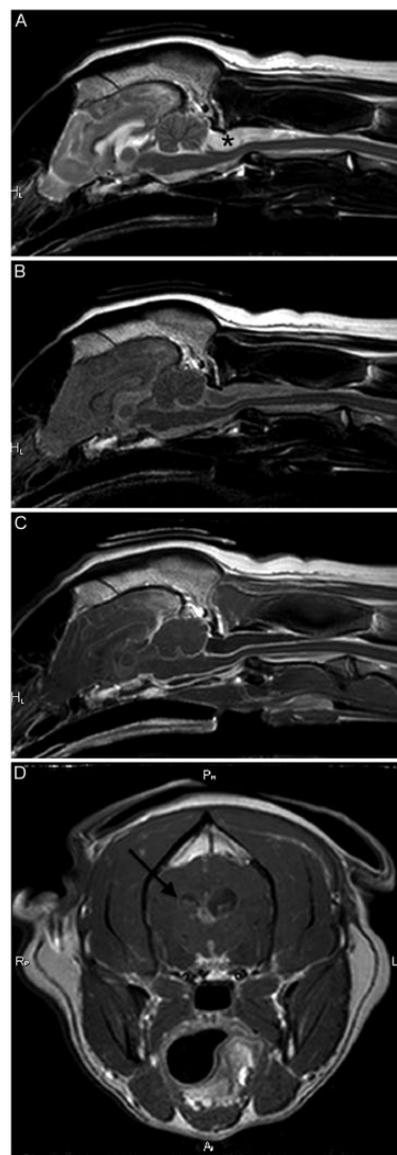

Figure 1. Magnetic resonance images of the brain and cranial cervical spinal cord of a 2-year-old, spayed female Golden Retriever dog presenting with cervical pain and vestibular episodes. Magnetic resonance imaging was performed using a 3.0-T magnet.[a] **A**, T2-weighted (T2W) sagittal image of the brain and cranial cervical spinal cord (repetition time [TR] 3000.0 msec, echo time [TE] 80.0 msec); **B**, fluid attenuated inversion recovery (FLAIR) sagittal image (TR 11000.0 msec, TE 125.0 msec); **C**, T1-weighted (T1W) postintravenous gadolinium contrast administration (TR 600.0 msec, TE 10.0 msec). T2W hyperintense (asterisk, panel A) and T1W hypointense, FLAIR heterogeneously hyperintense defined elongated lesion measuring 1.5 cm × 1.0 cm, with a strongly contrast enhancing rim, is located dorsal to the spinal cord in the epidural space from the foramen magnum to the level of the mid-body of C2 vertebra. There is diffuse leptomeningeal enhancement. **D**, T1W postintravenous contrast administration transverse image at the level of the interthalamic adhesion reveals filamentous contrast enhancing material within the lateral ventricles (arrow) suggesting intraventricular fibrin formation.
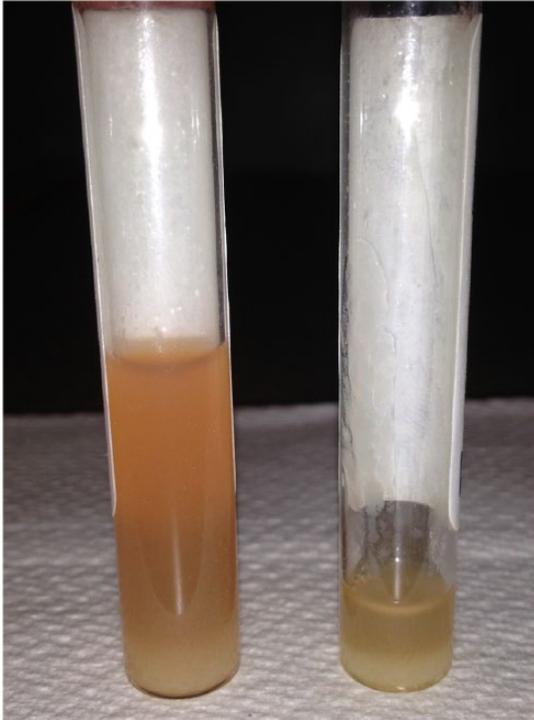
Figure 2. Fluid sample collected at the craniocervical junction from a 2-year-old, female spayed Golden Retriever dog infected with *Actinomyces* sp. The fluid was grossly yellow and cloudy.

Following the MRI, the dog was aseptically prepared at the craniocervical junction for a second CSF collection. Approximately 4 mL of orange, purulent fluid (Fig. 2) was drained using a 20-gauge spinal needle at the craniocervical junction. Because of the likely epidural location of the mass lesion dorsal to the subarachnoid space, it is probable that the sample obtained was from the mass lesion, rather than true CSF. Fluid evaluation revealed a total nucleated cell count of 126,000 cells/μL, with a protein level of 2,811 mg/dL. Cytologic examination of the nucleated cells revealed 100% degenerate neutrophils and variably sized aggregates of neutrophils with filamentous, branching organisms arranged in chains (Fig. 3). An acid-fast stain was negative. Both aerobic and anaerobic cultures were requested on the material acquired from this second sample.

Epidural abscessation and meningoencephalitis due to *Actinomyces* sp. or *Nocardia* sp. was suspected based on the filamentous morphology of the bacteria on cytologic examination. A repeat complete blood cell count on the day of the MRI (fourth day of hospitalization) revealed a leukocytosis at 22,900 cells/μL (ref. range: 4,100–15,400 cells/μL) characterized by a mature neutrophilia at 20,400 cells/μL (ref. range: 3,000–10,400 cells/μL) and a monocytosis at 2,500 cells/μL (ref. range: 0–1,200 cells/μL). Antibiotic therapy was initiated with clindamycin[g] (5 mg/kg via intravenous [IV] route every 12 hr), ampicillin[h] (40 mg/kg IV
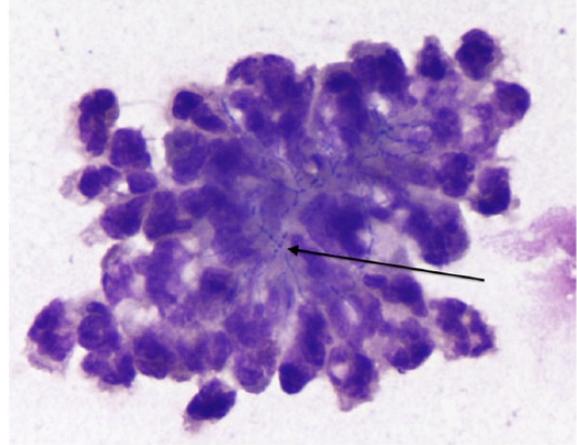

Figure 3. Cytologic evaluation of fluid obtained from the craniocervical junction of a 2-year-old, female spayed Golden Retriever dog. Variably sized aggregates of degenerate neutrophils with filamentous bacteria arranged in chains (arrow) are visible.

every 6 hr), cefotaxime[i] (50 mg/kg IV every 8 hr), and trimethoprim–sulfa[j] (22.8 mg/kg orally every 12 hr). Oral prednisone was discontinued, and anti-inflammatory doses of dexamethasone sodium phosphate[k] (0.15–0.25 mg/kg IV every 24 hr) were administered for the following 3 days then discontinued. Culture from the first CSF tap revealed visible growth in thioglycollate broth[l] only (no growth on semisolid media), 5 days after sample collection. Culture of the second tap yielded pure, luxuriant bacterial growth on Columbia agar supplemented with 5% sheep blood.[l] The bacteria from both samples were Gram-positive, branching filamentous rods, which were catalase negative and propagated under anaerobic conditions (90% N_2, 5% H_2, 5% CO_2), thus a presumptive identification of *Actinomyces* sp. was made.[26]

Further speciation of the organism was attempted via DNA extraction from pure culture followed by polymerase chain reaction (PCR) amplification of the 16S ribosomal DNA (rDNA) and direct Sanger sequencing using universal eubacterial primers 27F and 1518R.[m–p,12] Sequences were trimmed and assembled into a contig of 1,364 nucleotides and compared[q] with 2 public databases. When compared with a curated database, the maximum similarity to a named organism was 95.55% (*Actinomyces oris*; Green Genes, [cited 2015 March 8]. Available from: http://greengenes.lbl.gov/cgi-bin/nph-citation.cgi). When compared with the uncurated GenBank database, the sequence was 99% similar to a 16S rDNA amplicon described in a metagenomic study of the human skin microbiome,[2,14] and 98% similar to another GenBank accession of *Actinomyces bowdenii*, which has been implicated in infections of other body systems of the dog.[17,22] The GenBank accession number of the organism isolated in the current case is KP895554. Attempts to cultivate the organism for antimicrobial susceptibility testing were unsuccessful in Mueller–Hinton broth, both with and

without supplementation with 5% lysed horse blood in aerobic and anaerobic conditions.

Following identification of the isolate as *Actinomyces* sp. and ruling out infection by *Nocardia* sp., cefotaxime and trimethoprim–sulfa were discontinued. Further systemic workup, including thoracic radiographs, abdominal ultrasound, arthrocentesis of multiple joints, and urine culture, were unremarkable, and no apparent source of the organism was found. The dog's vestibular episodes ceased on the seventh day of hospitalization, and gradual improvement of the cervical pain was seen for the remaining duration of the patient's hospitalization. The patient was discharged on the ninth day of hospitalization with oral amoxicillin[r] (11.4 mg/kg orally every 8 hr), clindamycin[s] (8.6 mg/kg orally every 12 hr), omeprazole[c] (1.1 mg/kg orally every 24 hr), and gabapentin[b] (8.6 mg/kg orally every 8 hr). A recheck examination 1 month after discharge revealed a normal physical examination and neurological examination except for persistent mild cervical pain. The dog continued to receive clindamycin for 8 weeks and amoxicillin for 10 weeks following diagnosis. Eight months after discharge, the referring veterinarian reported the dog was normal with no signs of recurrent cervical pain or vestibular events.

Bacterial infections of the central nervous system (CNS) can spread by direct extension from the surrounding soft tissue or hematogenously from a distant site.[5,8,16,19] Diagnosis can be supported by clinical signs of fever, pain, progressive neurologic dysfunction, presence of mature neutrophilia, abnormal CSF typically characterized by neutrophilic pleocytosis, and abnormalities on advanced imaging.[5,8,16,19] The most commonly isolated bacteria in a retrospective study of dogs with bacterial meningoencephalomyelitis included *Escherichia coli*, *Streptococcus* spp., and *Klebsiella* spp.[19] Other bacterial isolates previously identified include *Staphylococcus* spp., *Pasteurella* spp., *Actinomyces* spp., *Nocardia* spp., *Peptostreptococcus* spp., *Fusobacterium* spp., and *Bacteroides* spp.[19] Myelography,[11,16] computed tomography,[13,16] and MRI[8,13] findings have been previously reported for CNS infections, but MRI is the diagnostic method of choice in humans and animals.[8,13,16] Previously reported MRI findings for epidural infections in dogs include T2W hyperintensity, T1W hypointensity, and peripheral or diffuse enhancement of the lesion on T1W postcontrast images.[8] Treatment includes appropriate antibiotics and, in some cases, surgical decompression and debridement depending on the location of the infection, degree of compression or extent of disease, and severity of signs. However, long-term prognosis is generally poor in dogs with bacterial meningoencephalomyelitis, with reported survival times of 0–42 days in a previous retrospective study.[19]

Actinomyces spp. are facultative or obligate anaerobic, Gram-positive, acid-fast–negative, filamentous bacilli.[23] *Actinomyces* spp. can cause pyogranulomatous inflammation of the cervicofacial region, thorax, abdomen, retroperitoneal space, subcutaneous tissues, distal extremities, and rarely the CNS in humans and animals.[15,23] In humans, ~20% of infections due to *Actinomyces* spp. occur in the abdomen, and 15–45% occur in the thorax.[1,10] Infection within the CNS is rare, involving <5% of all cases of human actinomycoses and may be manifested as brain abscesses, meningoencephalitis, actinomycetoma, subdural empyema, and epidural abscesses.[21] Surgery may be recommended to drain the lesion and remove the site of infection, but high doses of penicillin for a prolonged time is the treatment of choice.[9,21] Mortality rates of treated human patients can be high, up to 28% in a previous report.[10]

In dogs, *Actinomyces* spp. are among the normal flora of the gingiva, buccal, and nasopharyngeal mucous membranes.[3,7,18] Opportunistic infections may occur with disruption of the mucous membranes or penetrating wounds and are commonly associated with migrating foreign bodies such as grass awns and florets.[18,23] As in humans, infections of the CNS with *Actinomyces* spp. in dogs appear to be rare with only sporadic case reports in the veterinary literature.[3,6,20] The current study describes a spontaneous bacterial meningoencephalitis and epidural abscessation with long-term survival due to *Actinomyces* spp. in a dog.

With no evidence of trauma, differential diagnoses such as a migrating foreign body, penetrating injury through the palate or pharyngeal region, or iatrogenic introduction during CSF tap were considered in this case. Migrating foxtails have been implicated in brain, body cavity, and spinal infections, especially in California in association with *Actinomyces* spp.[4] Based on the presence of clinical signs prior to admittance and positive culture of *Actinomyces* sp. in the initial and second CSF collections, iatrogenic inoculation was considered unlikely. In our case, the fluid analysis from the second tap revealed dramatic cytological changes and positive bacterial cultures yielding much higher numbers of organisms when compared to the fluid analysis and culture from the initial CSF tap. One explanation may be that of natural disease progression. However, it is also possible that the initial administration of corticosteroids allowed proliferation of the bacteria, causing acute worsening of clinical signs. Although controversial, administration of corticosteroids concurrently with antibiotics for the first 2–4 days of diagnosis in patients with bacterial meningitis is recommended in human patients because suppression of the inflammatory response is believed to be important to decrease adverse effects such as cerebral edema, increased intracranial pressure, altered cerebral blood flow, cerebral vasculitis, and neuronal injury.[25] Currently, there are no large-scale studies to evaluate the outcome and treatment effects of corticosteroids in dogs with bacterial meningitis.[24] Therefore, current veterinary therapeutic practices are extrapolated from laboratory models and human medicine.

Bacterial meningoencephalitis should be considered in dogs presenting with cervical pain and fever, even in the absence of apparent trauma, penetrating wounds, or degenerative CSF changes without apparent infectious organisms. In our case, culture of the initial CSF remained negative on

semisolid media and was positive for growth only on evaluation of the enrichment broth 5 days following collection. This may be due to low numbers of organisms or inherent difficulties in culturing the organisms due to fastidious growth requirements.[21,23] This further underscores the fact that culturing organisms within CSF is challenging, even in known cases of bacterial meningoencephalitis.[16,23] However, the use of an enrichment broth proved critical to cultivating the agent in this case. Therefore, culture of the CSF with use of an enrichment broth in patients with neutrophilic pleocytosis and relevant clinical signs is recommended. Additionally, the clinician should be aware that it may take several days to see bacterial growth on culture as observed in the current case. The use of PCR technology is another option for investigation of infectious organisms in the CNS. Systemic workup is also recommended in patients with a high suspicion of bacterial infections of the CNS to identify possible sources of bacteria such as penetrating wounds, migrating foreign bodies, and septicemia.[16,19]

Authors' contributions

RB Song and RC daCosta contributed to conception and design of the study. All authors contributed to acquisition, analysis, and interpretation of data. RB Song and CA Vitullo drafted the manuscript. RB Song, RC daCosta, and JB Daniels critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work in ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Sources and manufacturers

a. Misoprostol, Gavis Pharmaceuticals, Somerset, NJ.
b. Gabapentin, Ascent Laboratories LLC, Montvale, NJ.
c. Prilosec, Proctor and Gamble, Cincinnati, OH.
d. Plasmalyte-148, Baxter Health Care, Deerfield, IL.
e. Prednisone, Roxane Laboratories Inc., Columbus, OH.
f. Achieva 3.0 Tesla, Philips Healthcare, Best, The Netherlands.
g. Clindamycin, Sagent Pharmaceuticals Inc., Schaumburg, IL.
h. Ampicillin, Sandoz Inc., Princeton, NJ.
i. Cefotaxime, West-Ward Pharmaceuticals Corp., Eatontown, NJ.
j. Sulfamethoxazole and trimethoprim, Amneal Pharmaceuticals LLC, Hauppauge, NY.
k. Dexamethasone SP, VetONE; Bimeda-MTC Animal Health, Cambridge, Ontario, Canada.
l. BBL, Becton Dickinson, Sparks, MD.
m. DNeasy blood and tissue kit, Qiagen Inc., Alameda, CA.
n. Platinum PCR SuperMix, Invitrogen Corp., Carlsbad, CA.
o. ExoSAP-IT, Affymetrix Inc., Santa Clara, CA.
p. ABI Prism 3730xl, Genewiz, South Plainfield, NJ.
q. Seqman Pro, DNAstar Inc., Madison, WI.
r. Amoxi-tabs, Zoetis, New York, NY.
s. Clindamycin, Ranbaxy Pharmaceuticals, Jacksonville, FL.

Declaration of conflicting interests

The author(s) declare no potential conflicts with respect to the research, authorship, and/or publication of this article.

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