Clinical Case Reports

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CASE REPORT

Imaging characteristics of disseminated *Geosmithia argillacea* causing severe diskospondylitis and meningoencephalomyelitis in a dog

Lukas T. Kawalilak, Annie V. Chen & Greg R. Roberts

Veterinary Clinical Sciences, Washington State University, 99164-7010 Pullman, Washington

Correspondence
Lukas T. Kawalilak, Veterinary Clinical Sciences, Washington State University, Pullman 99164-7010, Washington, USA.
E-mail: lkawalilak@vetmed.wsu.edu

Funding Information
No sources of funding were declared for this study.

Received: 24 March 2015; Revised: 24 June 2015; Accepted: 13 August 2015

Clinical Case Reports **2015; 3(11): 901–906**

doi: 10.1002/ccr3.372

Key Clinical Message

A 4-year-old male castrated Labrador Retriever presented for severe spinal pain. Radiographs and magnetic resonance imaging showed evidence of diskospondylitis and meningoencephalomyelitis. Blood culture revealed a *Geosmithia argillacea* fungal infection after DNA sequencing, initially misdiagnosed as *Penicillium* species. *Geosmithia argillacea* should be considered as a differential for disseminated fungal diskospondylitis.

Keywords

Fungal, MRI, *Penicillium* sp.

Case History/Examination

A 4-year-old neutered male Labrador Retriever presented to the Washington State University Veterinary Teaching Hospital Neurology service following an acute worsening of thoracolumbar pain. The dog had previously been diagnosed with diskospondylitis via radiography by a referring veterinarian and had not responded to a course of enrofloxacin, carprofen, and tramadol. There was no history of trauma or travel outside of eastern Washington State. Thoracic, abdominal, pelvic, and stifle radiographs performed by the referring veterinarian showed no obvious lesions other than diskospondylitis. DA_2PP, rabies, and *Bordetella* vaccinations were current. The dog also developed a mild right-sided head tilt 4 months prior to the presentation.

On clinical examination, the dog was anxious, but bright and alert. Neurologic examination revealed severe pain on spinal palpation in the thoracolumbar area along with severe epaxial muscle atrophy. The dog had a short, stiff-strided gait in the pelvic limbs and a root signature sign in the left pelvic limb. A right head tilt was present. Neuroanatomic localization was in two separate areas: thoracolumbar spine due to pain and right peripheral vestibular.

Investigations, Treatment, and Outcome

A complete blood count, chemistry panel, urinalysis, urine culture, and blood culture were performed. Biochemical abnormalities noted were a mildly increased total protein level (reference range) at 7.8 g/dL (5.6–7.6 g/dL) and an increased globulin level at 4.8 g/dL (2.7–3.8 g/dL). All other parameters were normal. The blood fungal culture isolated an organism that was initially identified as a *Penicillium* species, but was furthered characterized as *Geosmithia argillacea* using DNA sequencing. The urine culture was negative for infectious agents. No susceptibility testing was performed at this time due to cost concerns of the client.

Spinal digital radiography was performed using a digital radiography system (Canon CXDI-50G Digital Radiography System; Canon USA, Irvine, CA). Left lateral and ventrodorsal views of the thoracolumbar spinal region were obtained. The technique used was 85 kVp and 5.0 mAs. Destruction of the adjacent end plates along the central portions of the intervertebral disks at T6–T7, T9–T11, T12–13, L1–L2, L3–L4, and L6–L7 forming concave radiolucent defects were present with variable collapse of the intervertebral disk space and deeper sclerosis

surrounding the osteolysis, consistent with diskospondylitis (Fig. 1A). The dog was placed on a regimen of carprofen 2.5 mg/kg PO q12 h, gabapentin 9.8 mg/kg PO q8 h, codeine 2.9 mg/kg PO q8 h, fluconazole 3.26 mg/kg PO q12 h, enrofloxacin 8.9 mg/kg PO q24 h, and cephalexin 32.7 mg/kg PO q12 h. The dog was discharged following 4 days of these medications and cage rest with instructions to keep the dog cage confined for 4 weeks. Following the results of the positive fungal culture, 2 weeks after presentation, the owner was instructed to discontinue the enrofloxacin and cephalexin.

On recheck 40 days after initial presentation, the dog's pain was significantly improved, with none elicited on spinal palpation. Severe muscle atrophy of the pelvic limb and thoracolumbar epaxial muscles was still present, as was the right-sided head tilt. Recheck radiographs were recommended but declined by the client. The recommendation was made to continue fluconazole for a minimum

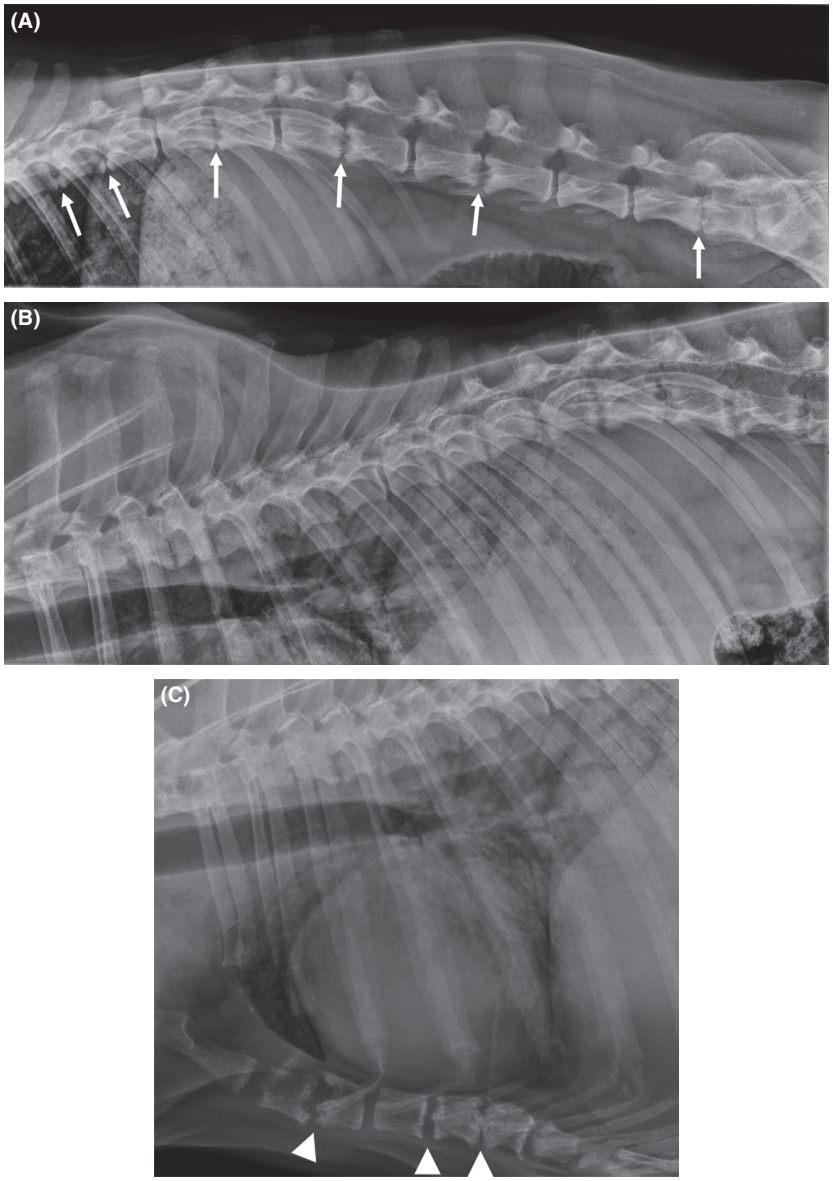

Figure 1. A left lateral thoracolumbar spine radiograph of the affected dog on presentation (A) showing typical signs of diskopondylitis including the destruction of adjacent vertebral end plates (white arrows) present at T9–T11, T12–13, L1–2, L3–L4, and L6–L7. On postmortem examination 11 months later (B), the end-plate destruction has progressed and is now present in the majority of vertebral end plates. The vertebral bodies of T5-T7 are heterogeneous and osteopenic. Lysis of the sternal end plates along with a generalized osteopenic appearance of the sternebrae is present (white arrowheads) (C).

of 12 months until the clinical signs resolved and then to use carprofen as needed for pain. The dog was discharged, and contact via email with the owner was maintained over the following months revealing no relapse of any clinical signs.

Approximately 10 months following the previous discharge (11 months from initial presentation) the dog presented with severe acute neurologic signs including circling to the left, right hemiparesis, and neck pain. A left supratentorial lesion was suspected. The dog was euthanized at the owner's request and additional imaging of the cadaver was performed. Magnetic resonance (MR) imaging of the brain and cervical spinal column was performed immediately following euthanasia using a 1.0T MR imaging system (Philips NT10 Gyroscan Intera; Philips Medical Systems, Andover, MA). T1-weighted (T1-W), T2-weighted (T2-W), and fluid attenuated inversion recovery (FLAIR) images (4 mm slices) in sagittal, coronal, and axial planes were reviewed. A marked dilation of the left lateral ventricle causing compression of the left thalamus and a midline shift of the falx to the right was noted. The fluid within the lateral ventricle was hyperintense on T2-W images and hypointense on the T1-W and FLAIR images, consistent with cerebrospinal fluid (CSF) (Fig. 2A and B). The dilated ventricle also extended caudally causing compression of the midbrain and cerebellum. A hyperintense rim surrounded the left lateral ventricle on the FLAIR images. A single 0.3 cm × 0.7 cm ill-defined, curvilinear, T2-W, and FLAIR hyperintensity was present in the left dorsorostral cerebrum, although this could not be differentiated from the edema related to the enlarged left lateral ventricle due to the lack of a contrast study. The intervertebral disk spaces of C2–C5 were narrowed with irregular contours and T2-W hyperintense end plates suggestive of diskospondyitis.

Left lateral and ventrodorsal radiographs of the spine and thorax were obtained immediately following the MR scan. The previously noted lysis and irregularity of vertebral end plates was still present, with new irregularities involving the end plates of the majority of the cervical, thoracic, and lumbar vertebrae (Fig. 1B). The vertebral bodies of T5–T7 and T11 were heterogeneous and osteopenic compared to neighboring vertebrae. Lysis of the sternal end plates along with a generalized osteopenic appearance of the sternebrae was noted (Fig. 1C).

Postmortem analysis of the body confirmed severe and diffuse diskospondylitis at C2–C5, T3–T5, T6–T8, T9–T13, and L1–L5, multifocal sternal osteomyelitis, and severe dilation of left lateral ventricle of the brain (Fig. 2C). Histopathology showed an inflammatory infiltrate containing fungal hyphae within the meninges, brain, spinal cord, liver, pancreas, spleen, kidneys, lungs, heart, adrenal glands, lymph nodes, mesentery, peritoneum, vertebrae,

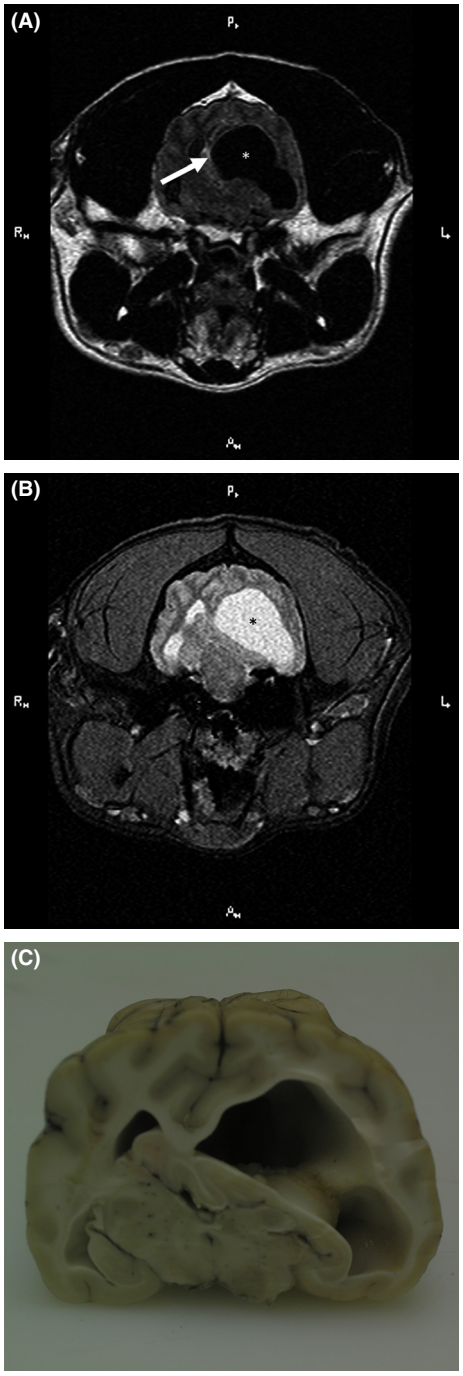

Figure 2. Fluid attenuated inversion recovery (A), T2-weighted (B) axial images and postmortem section (C) of the brain at the level of thalamus. The left lateral ventricle is enlarged (*), containing T2 hyperintense and FLAIR hypointense fluid, consistent with cerebrospinal fluid. This is causing compression on the thalamus and midline deviation of the falx to the right. The FLAIR image also shows a small rim of periventricular hyperintensity surrounding the left lateral ventricle (white arrow).

sternebrae, and bone marrow. Fungal culture and DNA sequencing confirmed the fungal organism to be the previously diagnosed *Geosmithia argillacea*. Susceptibility testing on CSF collected postmortem showed that the organism was strongly resistant to fluconazole, voriconazole, caspofungin, and amphotericin B and minimally resistant to itraconzaole and posaconzaole.

Discussion

Geosmithia argillacea is an opportunistic fungus phenotypically similar to the *Penicillium* species that has been isolated in humans suffering from genetic immunodeficiency illnesses such as cystic fibrosis and chronic granulomatous disease [1–4]. It has been assumed that these patients acquire the agent through inhalation, though the exact environmental source has not been identified [2]. There have been rare reports in humans where the fungus has become aggressive and disseminated, with involvement of the pulmonary parenchyma, chest wall, contiguous rib bones, and presumed cerebral infection [5, 6]. This is of particular concern in individuals that are or may become immunocompromised [2, 6]. The fungi involved with the human infections typically has low susceptibility to itraconazole, voriconazole, and fluconazole, variable susceptibility to amphotericin B and posaconazole, and in one study was susceptible to echinocandins, such as micafungin or caspofungin [3, 5, 6]. In contrast to previous human isolates, the isolate in this case had a high susceptibility to itraconazole and a low susceptibility to caspofungin. Due to its similar phenotypic and microscopic characteristics to both *Penicillium* and *Paecilomyces* species, a molecular approach for identification has been recommended to enable accurate identification of *Geosmithia argillacea* [4, 5]. Both organisms, however, demonstrate different susceptibility profiles to *Geosmithia*: *Penicillium marneffei*, responsible for the majority of human disseminated mycotic cases, displays little to no susceptibility to fluconazole, intermediate susceptibility to amphotericin B, and high sensitivity to itraconazole, voriconazole, ketoconazole, and miconazole; most *Paecilomyces* are typically resistant to fluconazole, moderately resistant to amphotericin B, variably resistant to itraconazole and voraconazole, and susceptible to select triazoles such as pozaconazole and ravuconazole [7, 8]. The recommended treatment in humans for both *Penicillium* and *Paecilomyces* infections is a combination of amphotericin B and itraconazole or voriconazole [8–10]. Fluconazole was chosen in this case primarily due to its ability to cross the blood brain barrier and reach concentrations in the CSF that is roughly equal to that in serum, as well as cost concerns of the client [11]. While it seemed to be initially successful at treating the fungus, based on the patient's clinical improvement, postmortem susceptibility testing showed this particular strain of *Geosmithia argillacea* ultimately became resistant to fluconazole. The use of amphotericin B and itraconazole has been reported in dogs with systemic mycosis [12, 13]. However, these treatments were prohibitively expensive for a dog of this size. Based on their limited success in humans, this organism's susceptibility to itraconazole on postmortem testing, and the near universal resistance of the most common disseminated mycotic infections to fluconazole, this combination treatment may have been more effective than the fluconazole used in this case.

Infection with the fungus *Geosmithia argillacea* has been reported only once as a case report in the veterinary literature [14]. While that case originally presented for acute onset of glaucoma in the right eye, further tests revealed osseous proliferation and a concurrent lysis of the vertebral end plates of T4–T6 and sternabrae, similar to the current case [14]. This reported case was never treated and a diagnosis of *Geosmithia argillacea* was made via necropsy. In the previous case, as with the current case, initially the fungus was incorrectly identified as a *Penicillium* species. As noted previously, the genus *Geosmithia* currently contains numerous species formerly classified as *Penicillium*. It is possible that *Geosmithia argillacea* may be isolated more commonly than has been realized up to now and overlooked given its morphological similarities to Penicillium and Paecilomyces species [2]. Differentiation using DNA PCR assays is important to correctly identify the fungus in order to start appropriate treatment.

Diskospondylititis is one of the many infections of the vertebral spinal column including vertebral physitis, spondylitis, and diskitis, and refers to a primary infection of the cartilaginous vertebral end plates with secondary involvement of the intervertebral disk [15, 16]. It is a relatively uncommon disease with nonspecific clinical signs that include malaise, neurologic deficits, and vertebral hyperesthesia or pain [15, 17]. Classic radiographic findings associated with diskospondylitis include loss of definition of end-plate margins, narrowing of the IVD space, lytic bony changes of the vertebrae adjacent to the IVD space, and sclerosis at the margins of bone lysis [18, 19]. All of these findings were demonstrated in the current case.

The primary source of infection in small animal patients with bacterial diskopondylitis alone is infrequently determined, although urogenital infections, abscesses, open wounds, and respiratory tract and oral cavity infections are frequently implicated [20]. While these areas are often responsible for inoculation of a fungal infection, the primary means of entry often remain unknown, as it the current case [21]. In one study, *Staphylococcus* species,

Streptococcus species, and *Escherichia coli* were isolated most often from cases of bacterial diskospondylitis [18]. In this case, urogenital infection and external or oral cavity wounds were ruled out based on the negative urine culture and physical examination. This leaves infection via the respiratory tract as the most likely point of infection. While thoracic and abdominal radiographs performed by the referring veterinarian were not noted to have any abnormalities, it is possible a nydus of mycotic infection was not visible radiographically.

Similarly, disseminated opportunistic mycoses are infrequently reported in dogs, with the most common etiologic agents identified as species of *Aspergillus* [22–24]. Other isolates have included *Penicillium*, *Paecilomyces*, *Sagenomella*, *Westerdykella*, as well as one case report of *Geosmithia* [14, 21, 25–27]. Clinical signs associated with these disseminated infections are often vague and can include spinal hyperesthesia, neurologic deficits, weight loss, anorexia, uveitis, head tilt, nystagmus, renal failure, and urinary incontinence [17, 23]. Interestingly, in one recent study just over half of dogs with systemic *Aspergillosis* infection showed radiographic signs of diskospondylitis [23]. Treatment in these cases is often not successful due to fungal resistance to the available medications, as well as the questionable ability of antifungal drugs to penetrate all of the affected tissues [14].

The breed most affected by disseminated mycotic infections has been the German Shepherd Dog, with this breed having an odds ratio of 43 for contracting one of the more common mycotic infections, systemic Aspergillosis, relative to a background hospital population [23]. Female German Shepherd Dogs were also overrepresented, comprising 77% of the German Shepherd Dog group [23]. Numerous reports of a wide variety of fungal infections have been reported in German Shepherd Dogs [21, 22, 27, 28]. It has been hypothesized that German Shepherd Dogs have a breed-related immunodeficiency that increases their risk of contracting mycotic infections, though a specific defect has not been identified [29]. Similarly, an immunodeficiency was suspected, but not proven, to be a contributing factor in this dog's systemic mycotic infection. In contrast, bacterial diskopondylitis has been reported to be more common in a variety of breeds, including Labrador Retrievers and Great Danes, though pure bred dogs as a group were more likely to be affected than mixed-breed dogs [17, 18, 30].

MR imaging has been used to describe diskospondylitis previously in both humans and dogs [15]. This dog displayed the typical findings previously described, with hypointense vertebral bodies and mixed signal vertebral end plates on T2-W images [15]. Due to the postmortem nature of the patient in this case report, contrast was not utilized, though contrast enhancement of vertebral bodies and paravertebral tissues has been previously reported in diskospondylitis cases [15].

MR imaging has been previously used to examine the brains of dogs infected with other intracranial mycoses including *Cryptococcus* and *Blastomyces* [31, 32]. In these cases, there were hyperintensities present throughout the internal cranial capsule on T2-W sequences. These areas were hypointense on T1-W images and enhanced minimally with gadolinium. In the present case, a similar T2-W hyperintensity was also found but instead within the dorsorostral cerebrum. This hyperintensity, in addition to multiple other sites within the brain, was confirmed on histopathology to be fungal of origin, showing the wide-spread dissemination of this organism. Periventricular changes associated with the lateral ventricles were also found in both the current and previously reported cases. The enlarged left lateral ventricle in this case is thought to have arisen from the inflammation caused by the fungus, leading to lack of CSF outflow from the ventricles. A FLAIR sequence was used to differentiate CSF within the ventricle from other inflammatory or hemorrhagic fluid, as both can appear hyperintense on T2-W images. All four of the *Blastomyces* cases had bilateral ventricular enlargement. The *Cryptococcus* case also showed gadolinium-enhanced T1-W images showing focal, contrast-enhancing areas in the frontal cortex with diffuse meningeal enhancement. These lesions were noted to have improved, but were still present after 5 months of therapy.

In conclusion, this case report is the first to demonstrate the dissemination of *Geosmithia argillacea* fungal infection in the nervous system of a dog using radiography and MR imaging. Additionally, this is the first treated case of disseminated *Geosmithia argiliacea* reported in dogs. More treated cases are needed to determine the long-term prognosis and the best form of therapy for this disseminated mycosis. Due to similar clinical, imaging, and histopathologic characteristics to disseminated *Aspergillus* and *Penicillium* species, *Geosmithia argillacea* should be considered to be a potential differential if similar lesions are encountered by practitioners in the future.

Conflict of Interest

None declared.

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