A 5-year-old 35.8-kg (78.8-lb) neutered male Labrador Retriever was referred to a veterinary emergency clinic and referral center because of chronic nasal discharge associated with a fungal infection. Three years prior to the referral visit, the dog was evaluated by the primary care veterinarian for unilateral (right-sided) serosanguinous nasal discharge. The dog was initially prescribed amoxicillin (13.75 mg/kg [6.25 mg/lb], PO, q 12 h) for 7 days. Treatment was then changed to enrofloxacin (3.0 mg/kg [1.36 mg/lb], PO, q 12 h) owing to a lack of response. With enrofloxacin treatment the discharge did not resolve, and the characteristics of the nasal discharge changed from serosanguinous to mucoid. Owner compliance was an issue, and the dog did not return for reexamination for 6 months. At the time of reexamination, results of aerobic culture of the nasal discharge revealed scant growth of normal flora. Rhinoscopy was then performed under general anesthesia, and abnormal accumulations of debris and destruction of the nasal bone were identified on the affected side. Biopsy results revealed purulent exudate associated with compact mats of fungal hyphae that occasionally had brown pigmentation. A biopsy sample was also submitted for fungal culture with negative results. Histologic analysis indicated infection with dematiaceous fungi, which are reportedly susceptible to itraconazole. Itraconazole (10.0 mg/kg [4.5 mg/lb], PO, q 24 h) was prescribed; however, because of poor owner compliance, treatment was not started until 6 months after diagnosis, at which time the patient had developed bilateral nasal discharge. The progression of clinical signs led to a recommendation to administer itraconazole at the prescribed dose for 6 months.

ABBREVIATION

SNA Sinonasal aspergillosis
and then return the dog for another rhinoscopic examination. Itraconazole administration was inconsistent, and 1 year later, the dog was surrendered to a local animal care and control program.

On evaluation at the referral center’s internal medicine service, physical examination revealed bilateral mucopurulent nasal discharge, mild ulceration of the left nasal commissure, and hyperkeratosis of the dorsal nasal planum. Results of a CBC and serum biochemical analysis were within the respective reference ranges. Three-view thoracic radiographs were evaluated, and no abnormalities were identified. The dog was anesthetized for a CT scan (slice thickness, 2 mm; slice interval, 2 mm; viewed with a bone algorithm). Results revealed bilateral destruction of the conchae and ethmoid turbinates. In the caudodorsal recess of the right nasal passage crossing midline was a large, complexly dense soft tissue mass with hypodense foci. The nasal passages and frontal sinuses had loss of architecture, and there was a loss of the nasal septum, the vomer bone, and a portion of the frontal sinus septum. The left palatine bone was focally lysed, and the dorsal wall of the cribriform plate had been lysed with invasion of the soft tissue mass into the olfactory region of the brain (Figure 1). The frontal bone and nasal bone lining the frontal sinuses were severely hyperostotic. Rhinoscopy performed during the same anesthetic episode revealed a large amount of turbinate destruction with a large, pale plaque evident in the caudal aspect of the right nasal passage. Biopsy samples were collected and submitted for histopathologic analysis. The tissue samples contained colonies of fungal hyphal organisms that had thin parallel walls and were often separated and branching, consistent with Aspergillus sp. The organisms were bordered by scant neutrophils, and the fungal hyphae were intermixed with small colonies of bacterial organisms. Owing to lysis of the cribriform plate and pathological invasion of the mass lesion into the olfactory region of the brain, topical treatment with clotrimazole was not recommended owing to potential adverse neurologic effects. Instead, oral terbinafine treatment and surgical debridement via rhinotomy were recommended. Representatives of the animal care and control group opted for medical management with the pursuit of rhinotomy at a later date. Terbinafine hydrochloride (20.0 mg/kg [9.1 mg/lb], PO, q 24 h) was prescribed, and the caregiver was encouraged to return the dog for surgical debridement if clinical signs did not improve.

The dog was reevaluated by the internal medicine service of the referral hospital 3 months later because of facial rubbing and pawing, and reluctance to be petted, which the caregiver interpreted as signs of increased facial pain. Amoxicillin-clavulanic acid (13.75 mg/kg, PO, q 12 h) and tramadol hydrochloride (3.0 mg/kg, PO, q 12 h) were prescribed, and rhinotomy was scheduled. The dog was returned 2 weeks later for surgical debridement via rhinotomy after incomplete resolution of the nasal discharge with antifungal and antimicrobial treatment. Routine dorsal rhinotomy was performed and revealed a large fungal plaque located within the right frontal sinus crossing midline that was removed with debridement of all grossly abnormal nasal tissue. Care was taken to prevent further

Figure 1—Sagittal (A) and coronal (B) bone density CT images of a 5-year-old male Labrador Retriever evaluated because of chronic nasal discharge. Notice the large, complexly dense soft tissue mass with hypodense foci filling the right frontal sinus (star). There is lysis of the dorsolateral wall of the cribriform plate on the left side with invasion of the soft tissue mass into the frontal cortex of the brain (arrowhead). In panel B, the left lateral aspect of the skull is to the left of the image.
disruption of the cribriform plate. The dog recovered uneventfully from anesthesia and was discharged 3 days after surgery with owner instructions to administer amoxicillin-clavulanic acid (13.75 mg/kg, PO, q 12 h), tramadol (3.0 mg/kg, PO, q 8 h), and terbinafine hydrochloride (20.0 mg/kg, PO, q 24 h).

Two weeks after surgery, the dog underwent recheck examination and was reportedly doing well. It was noted that the nasal discharge had markedly improved with only occasional clear mucoid discharge; however, the dog continued to sneeze frequently. The caregivers were recommended to continue terbinafine treatment for 3 additional months and to return the dog for collection of a blood sample every 4 to 6 weeks so that liver function could be monitored by serum biochemical analysis.

The dog was seen at the referral center’s emergency department 1 month after surgery because of acute onset of behavioral changes, including a fixed stance, gazing, and hesitation to climb stairs. On physical examination, the dog was tachycardic (heart rate, 140 beats/min) and had evidence of hyperesthesia on cervical and thoracolumbar palpation. Radiography was declined, and the dog was prescribed gabapentin (10.0 mg/kg, PO, q 12 h) and tramadol (3.0 mg/kg, PO, q 8 h). Instructions were given for strictly enforced rest. Overnight, there was no improvement, and the dog was reevaluated by the surgery department on the following day.

On physical examination, the dog was dull, appeared aware of its surroundings, and had nonpurposeful, unprovoked aggression. Low head carriage, a mildly stiff gait with all 4 limbs affected, and hyperesthesia of the cervical spine were apparent. The dog was admitted into the hospital and provided supportive care with IV fluids, fentanyl citrate (constant rate infusion; 3.0 µg/kg/h [1.36 µg/lb/h], IV), enrofloxacin (10.0 mg/kg, IV, q 24 h), and doxycycline hyclate (5.0 mg/kg [2.3 mg/lb], IV, q 12 h). Terbinafine was not administered because of inappetence. Two days later, the dog’s neurologic status had declined; mentation was dull, with an inconsistent menace response and minimal response to stimuli. There was mild proprioceptive ataxia of the pelvic limbs, and the dog would lean against walls when standing without any tendency toward a particular side. The dog was anesthetized for an MRI and collection of a CSF sample. The MRI (T2-weighted sagittal and axial images and T1-weighted pre- and postcontrast [iothalamate meglumine] axial and coronal images) revealed no further progression of fungal disease. A signal void from the nares to the olfactory bulb, consistent with the presence of air following rhinotomy, was evident. At the level of the cribriform plate, there was a hyperdense accumulation of material that was contiguous with the right olfactory bulb and the rostral extension of the right lateral ventricle into the lateral apertures of the fourth ventricle, consistent with residual, static fungal plaque infiltration. The intracerebral ventricular system from the right olfactory bulb to the cervical spinal cord contained a large amount of free air, with the right side substantially more affected. The intraventricular air caused a substantial shift of the cerebral falx to the left that caused compression of the opposite cerebral hemisphere. There was also a signal void in the right fourth ventricle at the cerebellopontine angle that tracked along the dorsal and ventral subarachnoid spaces of the cervical spine (Figure 2).

Figure 2—Sagittal T2-weighted (A) and postcontrast T1-weighted (B) MRI images of the same dog as in Figure 1, obtained approximately 1 month after dorsal rhinotomy was performed. A—Signal voids are apparent in the olfactory bulb (arrowhead), lateral ventricle (star), and fourth ventricle (arrow). B—Signal voids are evident in the ventral (thin arrow) and dorsal (thick arrow) subarachnoid spaces of the cranial part of the spinal cord at the level of C1-C2.
The dog's CSF total protein concentration was high (73.7 mg/dL; reference range, 0 to 48 mg/dL), and CSF cytology revealed moderate mixed pleocytosis (120 nucleated cells/μL, consisting of neutrophils [41%), lymphocytes [6%], and macrophages [53%]). Microbial culture of a CSF sample resulted in no growth after 48 hours. These findings were consistent with ventricular pneumocephalus, cervical subarachnoid pneumorrhachis, and meningoencephalitis. The dog recovered uneventfully from anesthesia and was placed in an oxygen cage set to deliver 65% oxygen to aid reabsorption of intracranial air. The treatment plan was modified on the basis of MRI and CSF findings. Doxycycline was discontinued, and clindamycin was administered because of its broader spectrum of activity; fluconazole (5.5 mg/kg [2.5 mg/lb], IV, q 12 h) was administered for antifungal treatment because an IV formulation was available; and enrofloxacin and fentanyl treatments were continued.

The dog had mild improvements in mental status daily while hospitalized with supplemental oxygen delivery for 4.5 days; however, unpredictable and unprovoked aggression continued, the dog began circling to the right, and physiologic nystagmus to the right was absent. At the time of discharge, the dog continued to circle to the right, had mild proprioceptive ataxia, and was aggressive. The dog’s caregiver agreed to take it home after 8 days of hospitalization with the knowledge of the neurologic deficits and risks associated with the aggressive behavior. Medications prescribed at discharge included clindamycin (11.0 mg/kg, PO, q 12 h), carprofen (2.0 mg/kg [0.91 mg/lb], PO, q 12 h), and fluconazole (5.7 mg/kg, [2.59 mg/lb] PO, q 12 h) as well as enrofloxacin and gabapentin as prescribed previously; terbinafine was discontinued because no evidence of fungal disease progression was found.

Follow-up at the referral facility 1 month after discharge from the hospital revealed the dog had markedly improved. The caregiver reported that the dog was bright, alert, and responsive and showed no aggression at home. During evaluation, the circling behavior was no longer evident, only mild proprioceptive ataxia was noted, and hyperesthesia of the cervical spine had improved. Five months after the evaluation for neurologic signs attributed to pneumocephalus and pneumorrhachis, the dog continued to do well at home. The caregiver reported that no neurologic signs were evident, and only minimal bilateral mucoid nasal discharge was present. Fluconazole was discontinued 1 month prior to this follow-up because of increased serum liver enzyme activities (aspartate aminotransferase, 96 U/L [reference range, 15 to 66 U/L]; alanine aminotransferase, 321 U/L [reference range, 12 to 118 U/L]; alkaline phosphatase, 383 U/L [reference range, 5 to 131 U/L]) and supplementation with an S-adenosylmethionine and silybin A and B product (18 mg/kg [8.2 mg/lb], PO, q 24 h) had been initiated.

Discussion

The dog of this report developed ventricular pneumocephalus, cervical subarachnoid pneumorrhachis, and meningoencephalitis following rhinotomy. These conditions could have been associated with delayed treatment for fungal infection, surgical intervention, or extension of fungal organisms intracranially. To the authors’ knowledge, ventricular pneumocephalus, cervical subarachnoid pneumorrhachis, and meningoencephalitis as complications of chronic SNA have not been reported.

Pneumocephalus is a rare phenomenon in both human and veterinary medicine. In human medicine, it most commonly occurs as a result of traumatic head injury or iatrogenic penetration of the dura during surgical procedures. Pneumocephalus can also occur with trauma, infection, or neoplasia, resulting in accumulation of air in the epidural, subdural, subarachnoid, cerebral, or intraventricular regions. The most common clinical signs in human patients include headache, lethargy, and confusion, although hemiplegia, aphasia, ataxia, and dysmetria have also been reported.

Models proposed for development of pneumocephalus include positive pressure (ball-valve) and negative pressure (hydrodynamic and inverted bottle) models. Pneumocephalus caused by these mechanisms occurs when there is a defect in the dura mater and the presence of a fistula in the brain parenchyma. The ball-valve mechanism occurs when air is actively forced into the cranial cavity due to a pressure differential, such as by coughing and sneezing, and at the completion of the cough or sneeze, the pressure differential reverts, trapping the outflow of intracranial air. The hydrodynamic theory suggests that changes in posture result in changes in pressure intracranially, allowing air to follow the pressure gradient. The inverted bottle mechanism occurs when CSF leaks through a defect in the dura creating negative pressure in the intracranial space; drawing air in along the pressure gradient. Persistent CSF rhinorrhea, appearing as a serous nasal discharge, is commonly reported clinical sign of the inverted bottle mechanism.

The cause of pneumocephalus in the dog of this report was thought to be multifactorial. Lysis of the cribriform plate permitted communication between the frontal sinus and the cranial cavity, which created the potential for intracranial pressure to be altered with postural changes. The dog had continued episodes of sneezing, allowing air to be forced into the cranial cavity and subsequently trapped, and the caregiver reported occasional clear nasal discharge that could have been the presence of CSF rhinorrhea. The clinical signs did not become apparent until a month after surgical removal of the fungal granuloma and debridement of the nasal cavity, suggesting a slow or minimal entrance of air into the cranial cavity. Pneumocephalus was not identified on the preoperative CT, and it most likely developed postoperatively. The
authors suspect that removal of the fluid, necrotic tissue, and fungal granuloma allowed communication between the atmosphere and the cranial cavity.

Pneumorrhachis can occur in the epidural or subarachnoid spaces. Air present in the subarachnoid space is almost always associated with pneumocephalus, owing to the continuous nature of the subarachnoid space from the brain to the spinal cord. Air can migrate and may give rise to increased intracranial pressure, resulting in headache and focal neurologic signs in humans. In the dog of this report, pneumorrhachis was likely secondary to the pneumocephalus, with air entering the fourth ventricle and passing through the lateral apertures of the fourth ventricle into the subarachnoid space. It was presumed that with resolution of the pneumocephalus, the pneumorrhachis would also resolve.

Treatment of pneumocephalus is determined according to the severity of clinical signs and the underlying cause. In the human literature, there is no standard treatment; however, in cases where increased intracranial pressure exists, intervention is mandatory and is typically done by identification and surgical repair of the dural defect or by temporary placement of a spinal catheter. Where tension pneumocephalus is absent, spontaneous resolution of pneumocephalus should occur. It has been shown that, in human patients, 50 mL of air can require up to 6 months to be completely reabsorbed. The rate at which the air is reabsorbed can be increased with the use of supplemental oxygen to wash nitrogen out of the alveolar spaces. This increases the diffusion rate of nitrogen from the intracranial air into the blood and elimination through the lungs owing to the creation of a pressure gradient.

The dog of the present report had mild neurologic improvement while housed in an oxygen cage. This may have been attributable to reabsorption of some air in the brain, thus decreasing the pressure within the cranium, or it may have resulted from a combination of medical treatment and spontaneous reabsorption of air. The dog had continued neurologic abnormalities at the time of hospital discharge. However, a month later, the only residual effects were mild signs of cervical pain and proprioceptive ataxia. These clinical signs were most likely caused by the resolving meningoencephalitis.

The complications that developed in this patient might have been avoided if prompt, appropriate therapy for the SNA was implemented. The dog was initially prescribed itraconazole. Systemic treatment with orally administered antifungal agents, such as itraconazole, ketoconazole, thiabendazole, or fluconazole, is not typically efficacious alone. Coupled with poor owner compliance and delayed initiation of treatment, the fungal disease spread, leading to marked nasal destruction. When the dog was evaluated at the referral hospital, CT revealed invasion of the cribriform plate, which resulted in the decision not to perform intranasal infusions with clotrimazole because of concerns over potential adverse neurologic effects. The antifungal treatment was switched to terbinafine, which has been used empirically in companion animals to treat refractory cases of SNA. While the dog was hospitalized, the terbinafine treatment was discontinued due to inappetence, and no antifungal treatment was provided until after pneumocephalus and pneumorrhachis were detected by MRI. At that time, treatment with fluconazole was initiated because an IV formulation was available and because the drug is able to penetrate the blood brain barrier. Ideally, IV fluconazole treatment would have been initiated immediately upon discontinuation of terbinafine. Orally administered fluconazole was prescribed upon discharge, although in hindsight it would have been more appropriate to prescribe both fluconazole and terbinafine. Previous studies have shown that fluconazole has decreased efficacy against Aspergillus spp when used as a sole treatment, and the combination of fluconazole and terbinafine has been shown to have a synergistic effect. Additionally, results of MRI for the dog of this report showed lack of disease progression with terbinafine treatment, further supporting that treatment with both drugs could have been advantageous. Treatment of SNA with orally administered antifungal agents requires a long drug administration period, is expensive, and can result in adverse effects such as hepatotoxicosis, anorexia, and vomiting. This dog developed liver enzyme activities suggestive of hepatotoxicosis after 4 months of treatment, and fluconazole administration was discontinued.

This report highlights the importance of early diagnosis and management of canine SNA and describes a set of unusual complications that can arise following rhinotomy as part of the treatment of chronic SNA. Care must be taken when a surgical procedure, such as trephination of the sinus or open rhinotomy, is performed on a patient with invasion of the cribriform plate. Disruption of the dura is a potential consequence of fungal invasion, and if there is communication between the nasal and intracranial cavities after surgery, pneumocephalus and pneumorrhachis may occur. Clinicians should be aware of these complications and include them in their differentials when a patient develops neurologic signs following treatment. An MRI should be performed on all dogs with a history of fungal sinus infection that are being evaluated because of neurologic abnormalities to determine the presence or absence of these conditions. Although rare, pneumocephalus and pneumorrhachis can be amenable to conservative management and can have a favorable outcome.

Footnotes

a. GlaxoSmithKline, Research Triangle Park, NC.
c. PriCara, Division of Ortho-McNeil-Janssen Pharmaceuticals Inc., Karian, NJ.
d. High Speed Advantage Helical CT, General Electric Medical Systems, Milwaukee, Wis.
e. Novartis Pharmaceutical Corporation, East Hanover, NJ.
g. Sun Pharmaceutical Ltd, Gujarat, India.
h. Amneal Pharmaceuticals of NY, Hauppauge, NY.
i. West-Ward Pharmaceutical, Eatontown, NJ.
j. Par Pharmaceutical Co Inc, Spring Valley, NY.
k. Siemens Medical Solutions USA Inc, Malvern, Penn.
l. Mallinckrodt Inc, St Louis, Mo.
m. Pharmacia and Upjohn Co, Division of Pfizer Inc, New York, NY.

References
1. Schmiedt CW, Creevy KE. Nasal planum, nasal cavity, and sinus.


From this month’s AJVR

Diagnostic accuracy of a rapid immunoassay for point-of-care detection of urinary tract infection in dogs
Megan E. Jacob et al

OBJECTIVE
To determine sensitivity and specificity of a rapid immunoassay (RIA) for point-of-care detection of urinary tract infection (UTI) of dogs, compared with criterion-referenced diagnosis with bacterial culture.

SAMPLE
200 urine samples obtained from dogs and submitted to a veterinary microbiology diagnostic laboratory for routine bacterial culture and antimicrobial susceptibility determination.

PROCEDURES
Samples were evaluated by use of quantitative bacterial culture and the RIA. Sensitivity, specificity, and positive and negative predictive values of the RIA were calculated; results of bacterial culture were the criterion-referenced outcome. A κ statistic was calculated to determine agreement between bacterial culture and RIA results.

RESULTS
56 of 200 (28%) urine samples had positive results for bacterial growth by use of culture methods; there were 18 (9%) positive results likely to be associated with bacterial UTI on the basis of sample collection method and bacterial concentration. Sensitivity and specificity of the RIA for detecting samples likely to be associated with UTI (≥1,000 CFUs/mL) were 97.4% and 98.8%, respectively. The positive and negative predictive values of the RIA for bacterial cultures with likely UTI were 0.949 and 0.994, respectively. Agreement between bacterial culture and RIA outcome for UTI was substantial (weighted κ, 0.718).

CONCLUSIONS AND CLINICAL RELEVANCE
The RIA test evaluated in this study accurately detected UTI of dogs, compared with detection with the criterion-referenced bacterial culture method. Use of this point-of-care RIA could allow clinicians to diagnose UTI at the time of a patient visit and provide information useful for immediately initiating empirical antimicrobial treatment. (Am J Vet Res 2016;77:162–166)