The Irony of the Cat in the Name

Equine Paranasal Cryptococcosis

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Introduction

Cryptococcus spp. is an environmental fungal organism that can be a rare cause of fatal encephalitis and pneumonia in horses. The causative agents are *Cryptococcus neoformans* and *Cryptococcus gatti*.[8] These organisms are mostly found in bird droppings and soils of tropical and subtropical regions, even though its distribution has been reported worldwide.[7] Pigeons are the natural reservoir. This fungi is capable of surviving in bird feces for over a year and humidity can enhance its proliferation in soil.[4] It is an encapsulated basidiomycete that produces melanin and can affect a wide range of mammalian organisms including dogs, cows, birds, sheep, goats, alpacas, ferrets, horses, humans and wildlife, but it is by far more common in cats.[7,8] It is very rare in the South East of the United States. In horses, young animals, and breeds such as Thoroughbred and Standardbred seem to be predisposed.[7]

In general, Cryptococcus spp. are opportunistic pathogens of immunocompromised animals and people.[4] The way of transmission is by inhalation of the spores or direct contact with cutaneous lesions, and once in tissues, it lives in the form of a yeast. Direct transmission between animals has not been reported, for which it is not considered a contagious or zoonotic pathogen.[7] Cryptococcal granulomatous pneumonia seems to be the primary form of disease in horses, contrary to cats were a deforming rhinitis is more common.[7] Regardless, in all species the potential of hematogenous spread to the central nervous system causing neurological signs is possible.

A tentative diagnosis can be made by cytology examination of the nasal discharge or any of the lesions with Gram stain.[8] Definitive diagnosis is achieved by collecting a biopsy sample surgically or through endoscopy and submitting it for culture and histopathology. The presence of encapsulated spherical yeasts (2-10 μm in diameter) with narrow neck budding surrounded by

a thick mucoid capsule (1-30 μm in diameter) confirms diagnosis.[4, 9] This capsule does not stain with hematoxylin and eosin.[4] Special stains like periodic acid-Schiff (PAS) and Gomori's methenamine silver (GMS) can be used for the yeast, and mucicarmine and alcian blue can be used to stain the capsule, allowing for appropriate identification of this organism.[4]

Treatment for cryptococcosis in horses typically include a multimodal approach of antifungal medications. Fluconazole, itraconazole, nystatin, ketoconazole and amphotericin B are some of the drugs used.[10] The potential for critical complications due to hematogenous spread, such as encephalitis, osteomyelitis and fungal pneumonia, decrease the prognosis even more. The rest of the treatment is aimed to alleviate clinical signs and complications such as pneumonia and neurological signs. Treatment is long term, it requires intensive patient care, and can easily become cost-prohibited for the owner resulting in euthanasia in most cases.

Since this is an opportunistic saprophytic pathogen, prevention of exposure in endemic areas can be challenging and not feasible. Nevertheless, there are some measures that can be taken to decrease exposure such as controlling the pigeon population and keeping the facilities clear of nests and bird droppings.[4] Also, special precautions should be taken with animals in long term corticosteroid therapy as the immune system is decreased; long term steroid usage should be avoided when possible, especially in endemic areas.[4]

History and Presentation

Hannah Lena Cat is a 9-year-old quarter horse mare, who first presented on 10/16/19 to the MSU- CVM Equine Surgery Service with a history of intermittent bilateral epistaxis. She was referred by her RDVM for surgical removal of a suspected ethmoid hematoma detected under endoscopy. She worked as a cutting horse and was up to date on vaccinations. She was

negative and up to date in Coggins test and had recently traveled to Texas. On presentation, Hannah Lena Cat was bright, alert and responsive, and mild unilateral serosanguinous discharge was appreciated coming from the left nostril with no other visible abnormalities associated with it. She had a body condition score of 6/9 and a weight of 1020 lb. Her heart rate was 40 beats per minute, with a respiratory rate of 16 breaths per minute, a temperature of 98.8 ˚F, and normal digital pulses. On thoracic auscultation no cardiac abnormalities were detected and the lung fields sounded clear of crackles or wheezes. In abdominal auscultation there were normal motility sounds in all four quadrants.

Diagnostic approach

Skull radiographs were taken for surgical planning in which a smoothly marginated ovoid soft tissue mass of approximately 5.2cm by 3.3cm was appreciated invading the caudal aspect of the left nasal cavity and involving the ethmoid turbinates. Other differentials considered at this time that may resemble an ethmoid hematoma grossly are: nasal polyp, granuloma of fungal origin, neoplastic tumor.[6] On 10/17/19, a left-sided frontal sinus flap was performed in right lateral recumbency in order to surgically remove the mass. During surgery a mass of approximately 6cm by 6cm with no attachment to the periosteal bone and gross appearance consistent with a hematoma was removed and a biopsy was submitted for histopathology. Her sinus was packed with *Kerlix* soaked in epinephrine and sterile saline, and the incision was closed leaving an opening in the cranial aspect of the incision to maintain access to the sinus to remove the packing and allow the sinus to be lavaged post-operatively. Hannah Lena Cat was kept in the hospital for the next 3 days. A bandage was placed to protect her surgical site and potassium penicillin, gentamicin and flunixin meglumine were administered for antibiotic and

anti-inflammatory therapy. She was discharged on 10/20/19 on Uniprim and Firocoxib to continue at home until recheck in two weeks for staples removal.

Histopathology results came back revealing a severe granulomatous to pyogranulomatous rhinitis with intralesional yeast organisms consistent with *Cryptococcus spp*. This confirmed a diagnosis of sinusoidal cryptococcosis.

Pathophysiology

Cryptococcus spp. is a saprophytic air-borne pathogen. Immunocompromised animals in endemic regions inhale the *Cryptococcus spp*. spores.[4] Less commonly, direct inoculation with the spores in open wounds may occur.[7] The spores will then embed in the tissues as a yeast and form encapsulated masses that can vary from gelatinous to granulomatous in formation.[8] Neutrophils, eosinophils, macrophages, giant cells, plasma cells and lymphocytes are the main cells found in these lesions, while epithelioid cells appear in less frequency in comparison to other mycotic responses.[4,8] Even though cryptococcosis is as a common systemic disease in a diverse range of animals, disease in horses is very rare. Lesions in horses are typically seen in the nasal cavity, paranasal sinuses, lungs, bones, eyes, mesenteric lymph nodes, intestines and meninges.[3, 4, 9] Placentitis, uterine infections, abortion and neonatal pneumonia are other uncommon presentations of this disease in equids.[4, 9]

Presentation of the granulomatous nasal or sinusoidal form usually involves unilateral or bilateral sanguineous, serosanguineous or purulent nasal discharge. In these cases, it is not uncommon for this organism to penetrate the cribriform plate into the central nervous system directly or by leucocyte trafficking and hematogenous spread.[3, 4] When this occurs, it typically remains superficial causing a meningoencephalitis with gelatinous thickening of the

leptomeninges.[3] In most species, multiple small cyst-like cavitations in the leptomeninges can be appreciated in necropsy, but these have not been reported to form in horses.[3] At microscopic level, some of the changes observed in the central nervous system include presence of fibrin, edema, vascular congestion, and mononuclear inflammatory infiltrate.[4] Neurologic signs seen in the patient may include depression, ataxia, seizures, paresis and blindness, but they will vary depending on the depth and location of the lesions.[4]

Treatment

Before starting treatment, it is important to consider any corticosteroid therapy or immunodeficiency diseases as this can predispose the patient or make treatment more challenging if not addressed. When it comes to equine medicine, there are a limited amount of products that are approved by FDA to manage fungal diseases.[10] For this reason, extra label use is often needed. The preferred sole treatments are fluconazole with a loading dose of 14 mg/kg followed by 5mg/kg/day orally or itraconazole at 5/mg/kg/day orally due to its bioavailability in the horse and good susceptibility of the organism to it, but fluconazole is more stable than itraconazole in compounded formulations.[8,10] Both of these drugs belong to the azoles family which work by interfering with the cytochrome P-450 enzyme system inhibiting ergosterol synthesis in the fungal cell membrane, but they have a high potential of interaction with several drugs. For example, it can increase the metabolism and lower the plasma concentration of drugs such as rifampin and phenobarbital, or increase the accumulation of drugs cleared by the kidneys such as beta-lactams.[10] Long term use of these may increase the chances of liver toxicity, but compared to other drugs, side effects in general are minimal.[5] Amphotericin B, even though is one of the most effective antifungal therapies available, it is very nephrotoxic and intravenous administration with DMSO is recommended over oral for appropriate absorption which can be

challenging for client administration.[10] Other products such as potassium iodide had demonstrated to enhance the trans-epidermal elimination of some fungi, which may justify its use as an adjunctive therapy.[5]

Regardless of the medication used, treatment is for several months depending on the extent and severity of the condition. It is preferred to do a multimodal approach between a systemic and a topical antifungal. Debulking removal of the granulomas through surgery or endoscopy is also recommended to reduce the number of organisms present and enhance the antifungal penetration to the lesions. Treatment for *Cryptococcus spp*. infections in horses can quickly become expensive, becoming cost prohibited for most owners. The length of treatment, intensive patient care and the potential side effects of therapy are also factors that decrease owner compliance. The sum of these can be very challenging and the lack of treatment can have devastating consequences which is why euthanasia is commonly elected, resulting in high mortality rate for this disease.

Case Outcome

On 10/22/19 Hannah Lena Cat presented once again. Owner reported that Hannah Lena was uncomfortable at home and that she injured her left eye while rubbing her face due to the bandage. On physical exam she was mildly depressed, sweating and shaking. There was mild epistaxis still present, and blepharospasm of her left eye could be appreciated. Her heart rate was 48 bpm, her respiration rate was 12 brpm, her temperature was 100.1 ˚F, and her mucous membranes were pink and moist with a capillary refill time of less than 2 seconds. No abnormalities were detected on thoracic and abdominal auscultations. Her incision site looked dry and without any signs of inflammation. A liver large animal profile was taken showing mild hyperglycemia with no other remarkable findings. A consultation with the ophthalmology

service revealed a superficial corneal ulcer of her left eye. Topical atropine was applied to the affected eye for comfort and topical ophthalmic antibiotic therapy was started every 4 hours.

Due to the diagnosis of sinusoidal cryptococcosis, owner agreed to start antifungal therapy at this time. On 10/23/19 Hannah Lena Cat was started on 2.5g of oral fluconazole every 12 hours in combination with a daily local flush of the frontal sinus with 15ml of clotrimazole. For this last procedure she was sedated alternating between a combination of 2 mg of detomidine and 2 mg of butorphanol, and 150 mg of xylazine intravenously. Clotrimazole (15 ml) was then injected through the opening left on the cranial aspect of the incision site to reach the frontal sinus for topical antifungal therapy. By two days of starting treatment, her nasal discharge changed from serosanguinous to mucopurulent.

As the day progressed Hannah Lena Cat developed colic signs. An ultrasound and a rectal palpation exam suggested a cecal impaction. She was initially managed medically. A nasogastric tube was placed, and she was managed with oral fluids, balanced crystalloids with added calcium gluconate and magnesium sulfate for intravenous fluid therapy, metoclopramide and a lidocaine CRI. On 10/29/19 she underwent a laparotomy were several fecaliths were collected from her large colon. Enrofloxacin, misoprostol and DMSO where added to her treatment protocol. Ice bracelets in all four limbs were also started at this time.

On 11/1/19 Hannah Lena Cat was taken out to graze and experienced a suspected seizure characterized by teeth grinding, curled lips outward, ears pinched back, abnormal gait (criss-crossing), increased respiratory rate of 50 breaths per minute, and unresponsiveness to her environment. This episode lasted an approximate of 10 minutes and no medications were given. On 11/3/19 she had a grand mal seizure for which she received 10 mg of Diazepam IV. At this time, an intravenous catheter was placed, and a blood sample was collected. An ISTAT revealed

mild hyperglycemia, but no electrolyte abnormalities. Later in the day, an ultrasound guided CFS tap through the atlantooccipital joint was attempted as a secondary fungal encephalitis was highly suspected at this point, but no sample could be collected. During the following days, Hannah Lena Cat developed some other seizure episodes that included muscle fasciculations, ear twitching, nystagmus, limb hyperextension and pupillary dilation. Depending on the severity of these, she was administered diazepam, and sedation with butorphanol and detomidine were added as needed. Her nasal discharge decreased significantly until it became absent. She also developed laminitis and an infection of her colic surgical incision line. On 11/8/19 she got started in 5 mg/kg of phenobarbital every 8 hours. The next day the phenobarbital frequency got reduced to every 12 hours and on 11/13/20 the dose got reduced to 3 mg/kg. On 11/22/19 phenobarbital administration got changed to 2 mg/kg orally every 12 hours. On 11/23/19, 40 mg/kg of organic iodides orally every 24 hours got added. The organic iodides dose got decreased to 17 g once a day in 11/26/19.

Hannah Lena stayed in hospital a total of 46 days after her second presentation and finally got discharged on 12/6/19. She went home with instructions of continuing the 2.5 grams of fluconazole orally twice daily for the next 30 days and the17 grams of organic iodide once daily for the next 60 days as antifungal therapy. To control her seizures, phenobarbital at 2mg/kg twice daily was to be continued for the next 3 days and then decreased to half the dose (1mg/kg) twice daily. Flunixin at 1.1 mg/kg orally every 24 hours was also to be continued for another 10 days and recommendations to keep her in probiotics during treatment were given. Also, instructions for proper care of her incision and hernia belt, feeding, stall confinement, foot care, monitoring for water consumption and monitoring for signs indicative of complications were sent home with the owner. Hannah Lena Cat was scheduled to have a recheck to re-evaluate her

nasal passages and sinus around 30 days prior to discontinuing her organic iodide, but she did not return to the hospital.

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