DISSEMINATED ASPERGILLOSIS IN ASSOCIATION WITH *CANDIDA GLABRATA* INFECTION IN A VIZSLA DOG IN ISRAEL

Berkowitz, A[1]., Perl, S[2]., Elad, D[3]., Edery, N[2]., Kleinbard, S[1].,Shamir, M[1]. and Waner, T[4*].

[1]The Koret School of Veterinary Medicine, the Robert H. Smith Faculty of Agriculture, Food and Environment of the Hebrew University of Jerusalem, Rehovot, Israel.
[2]Kimron Veterinary Institute, Pathology Department, Bet Dagan, Israel.
[3]Kimron Veterinary Institute, Clinical Bacteriology & Mycology Department, Bet Dagan, Israel.
[4]Rehovot Veterinary Clinic, 9 Meginay Hagalil Street, Rehovot 76200, Israel
*Corresponding Author:
Dr. T. Waner, 9 Meginay Hagalil Street, Rehovot 76200, Israel.
E-mail: wanertnt@gmail.com

ABSTRACT:

A 5-year-old Vizsla female dog was presented with panuveitis and glaucoma two weeks subsequent to the left eye being enucleated due to a similar clinical manifestation. The dog was depressed, ataxic, had slow conscious proprioception in all four limbs, positional strabismus of the remaining eye and a lack of physiological nystagmus. Diffuse back pain was detected at the cranial thoracic vertebrae. Anatomic localization of the neurological signs was indicative of a multifocal lesion involving the cranial medulla, the first few segments of the spinal cord, the vertebral column and eyes. Infection of the central nervous system was suspected to be the basis of the clinical presentation. The dog was euthanized at the request of the owners. At gross pathology multifocal lesions were present in multiple organs. Histological examination revealed pyogranulomatous necrotizing changes in all of the organs with the presence of intralesional scant to moderate amount of fungal hyphae. A fungus was identified from the urine as *Aspergillus terreus*. Yeast was isolated from the stomach, esophagus and pancreas and identified as *Candida glabrata*. A diagnosis of disseminated aspergillosis in a Vizsla dog caused by *A. terreus* was made, combined with a *Candida glabrata* infection.

INTRODUCTION

Aspergillus species is a plant or soil saprophytic hyphomycete widely spread in the environment and commonly found in the soil, water and organic matter. Opportunistic pathogens with the disease in dogs include *Aspergillus fumigates, A. flavus, A. terreus, A. niger and A. deflectus* (1). In the dog the most frequently reported mycosis involving these fungi is an infection of the nasal cavities and sinuses in predominantly dolicocephalic dogs (2). *A. fumigatus* is the species most commonly involved in the nasal aspergillosis (3). The German Shepherd breed appears to be predisposed to the disseminated form of the disease caused by *A. terreus*, possibly due to a thus far undiscovered immune deficit (4).

This case report describes disseminated aspergillosis caused by *A. terreus* combined with a *Candida glabrata* infection in a Vizsla dog.

CASE HISTORY

A 5-year-old Vizsla female dog was presented to the Koret School of Veterinary Medicine Teaching Hospital (KSVMTH) with panuveitis and glaucoma of the right eye two weeks subsequent to the left eye being enucleated due to similar clinical manifestations. Histological examination of the enucleated eye revealed a severe purulent endophthalmitis however no causative agent could be identified.

Previous treatment included intravenous mannitol for therapy of suspected glaucoma. The treatment seemed to have resulted in a slight improvement which reversed once therapy was halted.

Physical examination on admission to the KSVMTH did not reveal any abnormal findings besides the ocular lesions. Blood pressure was in the normal range. Ophthalmoscopic examination of the eye revealed edema and hemorrhage of the retina. The dog was blind with a lack of both startle and papillary light reflexes. Intraocular pressure was normal. The possibility of a systemic disease was considered with resultant pathological effects on the eye. Clinical chemistry panel, blood smear examination, urinalysis and coagulation profile did not reveal any significant findings. Treatment was initiated with doxycycline (Doxylin, Dexxon, Israel) at 100mg PO SID; an immunosuppressive dose of prednisone (Rekah, Israel) (20mg PO BID) and dexamthasone - neomycin sulphate (Dexamycin, Teva, Israel) eye drops (one drop TID).

Therapy failed to improve the condition of the eye and the general condition of the dog deteriorated. The dog became depressed, ataxic, had slow conscious proprioception in all four limbs, positional strabismus of the right eye and a lack of physiological nystagmus. Diffuse back pain was detected at the cranial thoracic vertebrae. Anatomic localization of the neurological signs was indicative of a multifocal lesion involving

the cranial medulla, the first few segments of the spinal cord, the vertebral column and eyes. Infection of the central nervous system (CNS) was suspected to be the basis of the clinical presentation. Survey radiographs of the spine revealed discospondelitis of the cranial thoracic vertebrae. Cerebrospinal fluid collected from the cysterna magnum showed mixed pleocytosis with more than 3,000 white cells/µl.

Systemic fungal infection with central nervous system involvement was considered the most likely differential diagnosis at this stage. Urine and ocular anterior chamber fluid was submitted for fungal detection and culture. Following further clinical deterioration the dog was euthanized at the request of the owners.

On gross pathological examination the cornea of the eye was found to be severely edematous and opaque. An 8 cm diameter organized subcutaneous hematoma was present on right caudal aspect of the thorax. Approximately 1.5 liter of partially clotted blood was found in the pleural cavity. There was mild lung edema with moderate lung congestion. The heart showed multifocal, transmural, white, moderately soft, smooth, solid bulging masses, 1-5 mm in diameter (Figure 1). The liver also displayed multifocal masses which appeared similar to those seen on the heart. The pancreas was edematous and hyperemic containing 1-4 mm multifocal red-grey nodules. There was diffuse lymphadenomegaly of the mesenteric lymph nodes. In the spleen multifocal infarcts were in evidence with multifocal white masses similar to those seen elsewhere (Figure 2). The kidneys were swollen. On cut surface cortical multifocal infarcts were evident; the pelvis was ulcerated surrounded by white masses (Figure 3). Massive subdural hemorrhage was evident in the region of medulla oblongata. Dissection of the vertebral column revealed extensive lysis between T9-T10 and diskospondylitis of other thoracic vertebrate.

Histological examination revealed pyogranulomatous necrotizing changes in all of the organs with the presence of intralesional scant to moderate amount of fungal hyphae. The hyphae were non-pigmented, parallel sided, 4-8 micron in width, frequently septated and had dichotomous, 45 degree progressive branching and occasional conidia. Intralesional scant encapsulated, round to oval, 5-10 micron in diameter, non-pigmented, yeast like bodies mostly broad based with occasional budding were present.

A mould, having the morphological characteristics of *Aspergillus* spp. was isolated from the bladder, kidneys, liver, bone marrow, spleen, spinal cord, heart and nasal sinuses following incubation at 30°C on Sabouraud Dextrose Agar (Difco, USA). The isolate was inoculated onto Czapek Dox agar and incubated at 30°C for a week. The resulting culture was orange-brown, with columnar heads, hemispherical vesicles and biseriate sterigmata. Consequently the fungus was identified as *Aspergillus terreus* (5). *A. terreus* was also isolated from the urine. In addition yeast was isolated from the stomach, esophagus and pancreas. The yeast was identified as *Candida glabrata* by the ID32C kit (Biomerieux, France).

DISCUSSION

A. terreus has been reported as a cause of a disseminated infection principally involving the skeletal and cardiopulmonary systems in humans and in dogs. Reports are most frequent in Western Australia and North America (4, 6). Several cases of disseminated aspergillosis are diagnosed in dogs in Israel each year, some of which have been reported (13, 18) however the incidence of the disease in this region is unknown.

In dogs *A. terreus* occurs most commonly in the German Shepherd breed. It has been suggested that a hereditary immune defect might exist (4). In one survey 20/30 (67%) of affected dogs were German Shepherds (comparing to 4.5% in the examined population) and 23/30 were females (of those 18 were spayed) (10). Median age was 4.5 years (range 2-8 years) (1). Other dog breeds reported with disseminated aspergillosis include the Golden Retriever (7), Springer Spaniel (8), Dalmatian breed (6), Rhodesian ridgeback, English setter, Pug, and a Whippet (1). Five cases of aspergillosis have been reported in the Vizsla Club of America Welfare foundation 2008 health Survey (9), although it was not stated whether the cases were disseminated. Interestingly, the average age of the Vizsla dogs reported in the survey was 1.54±0.79 years which was appreciably younger than the case reported here which was 5 years old.

Common clinical signs of disseminated aspergillosis include weight loss, pyrexia, inflammatory ocular disease, neurological deficits, muscular pain, weakness, spinal column pain and lameness (10). Despite the ongoing severe pathological process, no significant clinical or clinical pathological findings were present, with the exception of the ocular and neurological signs. The reason for this is unclear but could possibly be related to the breed of dog.

Common pathological findings include diskospondylitis, osteomyelitis, pyelonephritis, other organ granulomatous infiltrate and infarction (common in the spleen) (11, 12). The lesion locations in the present case are consistent with a hematogenous dissemination. The granulomatous lesions present in the heart of the Vizsla is consistent with the previous findings from a large retrospective study where the prevalence of cardiac lesions was found to be unexpectedly high (1).

Ante mortem diagnosis is commonly reached by isolation from urine culture, but it can be obtained from many other affected tissues (13). In the present case isolation of *A. terreus* was made from both the urine and from organs. Survival time has a wide range although the prognosis is regarded as grave to poor for dogs presenting with CNS signs. A previous report described survival of more than 3 years in a dog treated with itraconazole (14).

A previous study found that affected dogs had low levels of serum IgM and IgA, and high serum IgG levels (4, 15). However, serum antibody (that was expected to be high) was not consistently demonstrated in tested cases. Lack of antibodies might suggest that much of the serum IgG may be bound in immune complexes or alternatively, may reflect non-specific polyclonal activation of IgG-secreting plasma cells (4, 15). Another report demonstrated prominent hyphal fluorescence with IgA and C3 antisera (16). The IgA reagent also marked mononuclear cells (scattered and around lesions) suggesting an abnormality of IgA production or regulation as a predisposing factor to this condition (17).

The case presented here is unusual because of the fact that

two fungal agents were isolated suggesting that the dog may have been immune compromised. According to the case history it does not appear that the dog was administered any drug that may have caused it to be immune compromised. However, a precedent for such a scenario is the proposed predisposing immune deficiency of German Shepherd dogs as a predisposing factor for the development of systemic aspergillosis (4) . There is a dearth of published reports on disseminated aspergillosis in Vizsla dogs and without added evidence no further conclusions can be made at this stage.

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LEGENDS FOR FIGURES

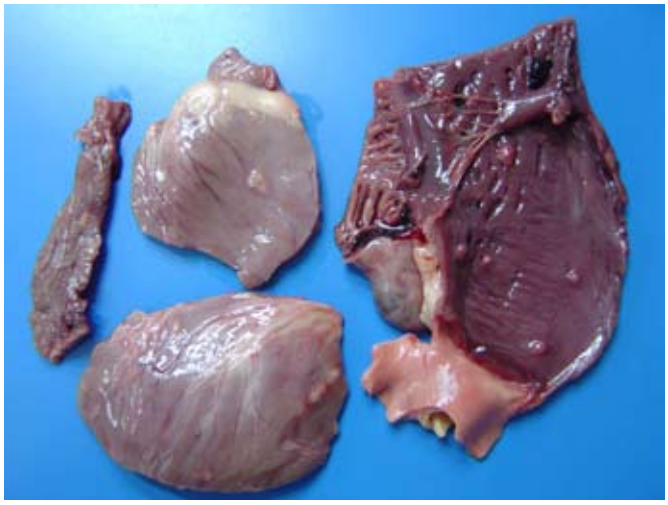

Fig. 1: Heart: Note the multifocal, transmural, white, solid bulging masses.

Fig. 2: Spleen: Note the presence of multifocal infarcts with multifocal white masses similar to those seen in other organs.

Fig. 3: Kidney: On cut surface cortical multifocal infarcts are evident and the pelvis is ulcerated surrounded by white masses.