Review articles

Fungal colonization – an additional risk factor for diseased dogs and cats?

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ABSTRACT. The aim of the presented mini-review is to review the literature data referring to opportunistic mycoses in pet dogs and cats suffering from other concurrent diseases, comparable to human medical disorders with high risk of secondary mycoses. This review also presents the preliminary results of a project aimed at understanding the fungal colonization and occurrence of secondary mycoses in pets suffering from metabolic disorders, neoplasms and viral infections. The incidence of opportunistic mycoses is higher in such individuals, mostly because of their impaired immunity. The main risk factors are primary and secondary types of immunodeficiency connected with anti-cancer treatment or neoplastic disease itself. Moreover, literature data and the results of our investigations show that *Candida* yeasts are prevalent among diabetic animals and indicate that these fungi are the main etiological agents of secondary infections of the oral cavity, GI and urogenital tracts. Other important conditions possibly favoring the development of mycoses are concurrent infections of cats with FeLV and FIV viruses. Thus, in all cases of the mentioned underlying diseases, animals should be carefully monitored by repeated mycological examination, together with inspection of other parameters. Also, the prophylaxis of opportunistic mycoses should be carefully considered alike other factors influencing the prognosis and the outcome of primary diseases.

Key words: mycoses, dogs, cats, viral infections, diabetes, neoplasma

Introduction

One of the causes of the invasive fungal infections observed in humans are various opportunistic species. The main etiological agents are *Candida albicans*, *Aspergillus* sp. and *Cryptococcus* sp. [1,2]. Literature data indicate, that mycoses are most commonly observed in immunocompromised patients, including those suffering from AIDS [3] or neoplasms [4]. Besides these, the development of invasive fungal infection is strongly associated with the existence of such additional predisposing factors as all primary and secondary immunodeficiences, for example, those found in autoimmune diseases [1] or in anticancer therapy especially in hematological malignancies. Neutropenia and loss of defense abilities are also

noted in post-transplantation therapy, or during radiation therapy [5–7]. Moreover, an increased risk of infections is the consequence of invasive diagnostic and therapeutic methods, requiring the use of intravenous catheters or bypass feeding [2,6]. Further predisposing factors are long-term antibiotic therapy, diabetes, renal and liver failure or extensive wounds and burns [6,8].

In veterinary medicine, similar disorders and underlying diseases are observed, and some comparable medical procedures are used in small animal practice. *Per analogiam,* it is reasonable to assume that the same circumstances may elevate the risk of fungal infections in pets. A suitable example is the SCID (Severe Combined Immunodeficiency) syndrome observed in mice, Arabian horses and certain breeds of dogs: Basset Hounds, Jack Russell

Terriers and the Cardigan Welsh Corgi. The susceptibility of these animals to infections, both bacterial and fungal, increases enormously, due to disability of immune defense mechanisms [8]. However, severe fungal infections in pet dogs and cats are quite rare in clinical veterinary practice. Moreover, the cases of secondary candidiasis, aspergillosis or cryptococcosis developing as a consequence of the underlying diseases mentioned above are also infrequent. Hence, the question of whether the factors predisposing pet animals to severe mycoses are similar to those experienced by humans has yet to be answered satisfactorily.

The aim of the presented mini-review is to show the data regarding fungal infections in companion animals suffering from diseases analogous to human disorders, which predispose them to opportunistic mycoses. This review is a part of our project to investigate fungal colonization and the occurrence of secondary mycoses in various pet diseases, including metabolic disorders, neoplasms and viral infections.

Fungal infections in veterinary oncological patients

As in human oncology, one type of therapeutic agents used in the treatment of dogs and cats are cytostatic drugs such as doxyrubicin and vincristin. One of the side effects of this chemotherapy is abnormal hematopoesis, resulting in anemia, neutropenia and thrombocytopenia [9]. Antifungal immunity is known to be based on neutrophils, macrophages and dendritic cells, and the lack of these cells or any defects in their function significantly increases the susceptibility of the host [10]. Thus, post-therapy neutropenia in oncological diseases may result in secondary infections, both fungal and bacterial. Additionally, steroids employed in multi-drug anti-cancer therapy [10,11] interfere with immunity. One of the most aggravating treatments is used in acute lympho-blastic and myeloblastic leukemias. To prevent secondary infections in these cases, wide-spectrum antimicrobial and antifungal therapy should be introduced simultaneously with the first cycle of chemotherapy [11].

Colonization of the oral cavity and rectum with *Candida albicans* and/or *Malassezia pachydermatis* has been noted during mycological examinations of several dogs and cats suffering from cancer in our Mycology Lab [data not published]. Other cases of

fungal infections in neoplasmic dogs and cats can be found in the literature. Matsuda et al. [12] describe the case of disseminated systemic candidiasis in a Dachshund female with mast cell metastatic tumors. Jeroski [13] reports the case of an Alaskan Malamute with a history of coccidioidomycosis, who had been treated for coccidioidal osteomyelitis of the left tibia three years before the examination. Most frequently, coccidioidomycosis affects the respiratory system, because *Coccidioides immitis* initially infects the lungs. In most dogs, even if the infection occurs, proper cell-mediated immune (CMI) mechanisms control the disease sufficiently to resolve the disease spontaneously, but in immu-nocompromised animals with a disabled immune system, hematogenous and lymphatic spread of the fungus may lead to disseminated systemic mycosis. In this case, the immunosuppression caused by the lymphoma most probably resulted in a relapse of coccidioidomycosis. Additionally, any anti-cancer treatment used in this dog intensified the immunosuppression, worsening the prognosis and aggravating the possible therapy [13].

The consequences of neutropenia caused by anti-cancer treatment, i.e. the increased risk of secondary infections, are obvious. However, in some cases, the sequence in which the diseases occur may be reversed. Greci et al. [14] report the cases of rhino-nasal tumors in three dogs, which were diagnosed respectively 13, 22 and 30 months after successive treatment of sino-nasal aspergilosis. Antimycotic treatment with 1h infusion of clotrimazole in 1% solution was not suspected to have caused the sinus neoplasia in two of the dogs and the nasal tumor in the third. According to the FDA (Food and Drug Administration) neither this thiazole derivative nor polyethylene glycol, used as the vehiculum, have carcinogenic or mutagenic properties. The authors also excluded mycotoxins of *Aspergillus fumigatus*, because these fungal metabolites are not produced in the body temperature. The only probable reason of tumor development in these cases seems to be the chronic inflammation observed in mentioned animals prior to tumor diagnosis.

The stimulatory effects of prolonged inflam-mation on malignant cell transformation, promoting the development of tumors have been demonstrated by epidemiological and genetic studies [14]. Brunker and Hoover [15] describe another case of malignancy developed as the result of chronic inflammation in a dog first diagnosed with *Ehrlichia canis* infection, followed by systemic

Histoplasma capsulatum infection, progressive neutropenia and lymphadenopathy. Finally, immunohistochemical tests revealed neoplastic cells, positive for CD79 B-cell marker and lymphoma was confirmed. The authors suggest that *Ehrichlia* infection resulted in dysregulation or disruption of the CD4+:CD8+ ratio and influenced the immunity, what predisposed the dog to systemic histoplasmosis. Additionally, chronic inflammation inducing plasma cell proliferation and decreased B-cell surveillance followed by poor regulation of cell division allowed for lymphoma development [15]. To conclude, the risk of opportunistic fungal infections in animals should be monitored as carefully as other factors influencing the outcome of neoplasmic diseases.

Fungal colonization and infections in diabetic animals

Patients with *diabetes mellitus* are at increased risk of opportunistic infections including oral and vaginal candidiasis, periodontal and gingival diseases, dental caries and salivary dysfunction [16]. Impaired adherence of neutrophils, disturbed chemotaxis and phagocytosis lead to compromised polymorphonuclear leukocyte function [17]. Additional problems observed in sustained diabetes are abnormalities of collagen metabolism, reduced proliferation of osteoblasts and weakened mechanical properties of newly formed bone. Also, the formation of advanced glycation end-products (AGE) modifies arterial collagen and hampers normal transport in microvasculature, resulting in microvascular complications of diabetes [17,18]. Moreover, AGE fusing with monocyte and macrophage receptors increase production of IL-1 and TNF-α, what enhances tissue destruction and reduces the wound-healing capacity of fibroblasts [19].

The most frequent opportunistic mycosis observed in diabetic patients is oral candidiasis. It is a superficial fungal infection caused by various species of *Candida*. The main factor favoring the colonization of the mucous membranes is poor glucemia control, but the exact mechanism has yet to be explained. The most frequently isolated yeasts from oral cavity of humans with *diabetes mellitus* are *C. albicans*, *C. krusei* and *C. glabrata* [20]. An important reservoir for such nosocominal infection organisms as yeast-like fungi is the intestinal tract. Few studies have evidenced that in diabetes colonization of *Candida* yeasts is increased. Fungal colonization was found to be more extensive in the intestines of children with diabetes than in healthy ones. Moreover, the presence of *Candida* strains has been reported in the stools of diabetics [21,22].

Diabetes is also associated with the development of other fungal infections. About 70% of diabetic patients during the course of disease have experienced an increased frequency of *Candida* or dermathophytes infections [23,24]. Fungal colonization of skin and the development of several skin manifestations in diabetic patients with poor glycemic control and abnormal carbohydrate metabolism seems to be related to neuron degeneration and the disturbed production of collagen, impaired wound healing and micro-vascular complications mentioned above [23–26]. *Candida* yeasts are also responsible for urogenital complications: 70–75% women with *diabetes mellitus* suffer from infections caused by *C. albicans*, *C. glabrata* or *C. tropicalis* [27,28].

Additionally, diabetic individuals are prone to angio-invasive, opportunistic zygomycoses. Among the predisposing factors are ketoacidosis, phagocytic dysfunction due to neutropenia or neutrophil dysfunction and low serum pH, reducing the effectiveness of the inflammatory response against *Rhizopus*. The rhino-cerebral form of this mycosis is most common in diabetics, while the lung and cutaneous involvement are less frequent [29,30]. Other mycoses affecting diabetic patients are coccidioidomycosis and aspergillosis. To identify patients with increased risk of severe, complicated infection caused by *Coccidioides*, regular measurement of serum glucose level is recommended. In some cases, the symptoms of infection may disappear spontaneously without medical treatment [31]. Furthermore, diabetic patients demonstrating suppression of neutrophil activity are considered high-risk patients for the development of cerebral, sino-orbital and pulmonary aspergillosis [32].

In veterinary medicine, diabetic animals also at a higher risk of mycosis development. In a retrospective study on urinary tract infections in 23 dogs and 12 cats, Jin and Lin [33] report a number of medical problems in the affected animals, such as diabetes, neoplasia or renal failure, in addition to the typical clinical signs of urinary infections. Seven different fungal species were isolated from diseased animals, but *Candida albicans* was the most common [33]. Cerundolo [34] describe six cases of

generalized, chronic infections with *Microsporum canis* in Yorkshire terriers, all of whom were burdened by concurrent disease e.g. bacterial infections or diabetes. The *M. canis* dermatophytosis was resolved in diabetic dog just after stabilizing of primary disease. The author suggests that dysregulation of immune system caused by concurrent leishmaniosis, ehrlichiosis and diabetes favors the generalization of mycosis [34].

Heselitine et al. [35] describe the case of a 11-year-old Scottish terrier with systemic candidiasis and concurrent underlying *diabetes mellitus*. Additional predisposing factors were administration of corticosteroids and broad-spectrum antibiotics and the use of venous and urinary catheters. Comparable medical conditions predisposing to the development of mycosis were noted by Pressler and co-workers [36], who report 20 cases of *Candida* urinary infections in 13 dogs and 7 cats. Beside long antibiotic or steroid treatments, diabetes, non-urogenital neoplasia and non-candidal urogenital disease were concurrent medical problems, compromising the immunity of affected animals and predisposing them to urinary mycoses [36].

Our own mycological examinations of cats and dogs with diabetes have revealed the prevalence of *Candida* sp., *C. albicans*, *C. glabrata*, *C. guilliermondii*, *C. humicola* and *Malessezia pachydermatis* in oral and rectal ontocenoses. Colonization of the rectum and oral cavity with *Trichosporon* sp. was noted in one cat, while *Malessezia pachydermatis* were identified in rectal samples obtained from three other diabetic cats [37]. It was concluded, that mucosal membranes of cats and dogs with particular systemic diseases, such as diabetes or endocrine disorders, are more frequently colonized by different yeasts than healthy individuals [37]. In such cases, the risk of mycosis development in these animals is higher because of the probable immunosuppression and all other medical factors affecting them.

Fungal colonization and infections in Cushing's syndrome and hypothyroidism

Cushing's syndrome (hyperadrenocorticism) occurs in dogs, cats and horses, as well as in humans, after prolonged exposure to high levels of glucocorticoids. The overproduction of cortisol in dogs is usually caused by pituitary or adrenal tumors. Type III Cushing's syndrome occurs as a result of excessive administration of steroid

treatment of other diseases. In the course of this disease, high cortisol levels impact the immune system in a dose-dependent way, suppressing cellular immunity and increasing the risk of secondary infections, especially in patients with higher level of plasma cortisol [38–40]. In veterinary practice, increased susceptibility of animals with Cushing's syndrome is also observed. The most common complications are pyoderma and recurrent skin infections [41,42]. An altered "paper skin" lacking the shield of a proper hair coat can be easily injured or infected by the fungi colonizing the skin of the majority of dogs (e.g. *Malassezia pachydermatis*). Dermatophytoses are also observed in animals affected with hyperadrenocorticism [43]. Other fungi like *Candida* may complicate the bacterial disease or infect injured skin. Our own previous study reports the isolation of *C. albicans* from mucosae of the oral cavity and rectum of a dog with Cushing's disease [37]. The presence of this yeast in hyphal phase in a direct microscopic slide prepared from the oral cavity may suggest an ongoing candidal infection.

Another endocrine disorder increasing the susceptibility to secondary infections is hypothyroidism. In these patients, chronic mucocutaneous candidiasis of the skin, nails and/or mucosal tissues is observed [44]. Our previous study reports the identification of *C. albicans* in the oral cavity of a dog affected with hypothyroidism with no clinical signs of oral candidiasis. Additionally, the multiple colonization by *M. pachydermatis* of the skin, oral cavity and rectum was observed in another dog. Among the noted clinical signs was *dematitis interdigitalis*. However, as this skin infection is commonly observed in dogs with no other underlying endocrine disorder, we cannot conclude whether the hypothyroidism had influenced the occurrence of mycosis in this animal [37].

Mycoses accompanying viral infections

Feline Leukemia Virus (FeLV) is a retrovirus considered to account for most disease- and tumor-related deaths in cats. Moreover, it is responsible for a great number of cat FeLV-related anemia cases and secondary infections [45]. The exact mechanisms of the suppressive effects of FeLV on bone marrow and immunity destruction are poorly understood, mainly because various animals may develop different intensities of thymus and lymph nodes atrophy and present different degrees of

lymphopenia and neutropenia. Immunosuppression of viremic cats is also connected with decreased chemotactic and phagocytic abilities of neutrophils, reduced immunoglobulin production and complement depletion. Moreover, the levels of Il-2, Il-4, TNF-α and IFN-γ are changed in some cats [46–48], and the antibody response to specific antigens may be decreased or delayed in FeLV-infected cats. All of these may lead to the occurrence of secondary infectious diseases and increased risk of tumor development [49].

Candida albicans and *Cryptococcus neoformans* are the most frequent etiological agents causing opportunistic mycoses in humans and animals [5]. However, studies on cats infected with FeLV or FIV and healthy individuals carried out by Sierra and co-workers [50] did not fully support these findings. While *Candida albicans*, dermatophytes and *Cryptococcus neoformans* were rarely isolated from any cat, the diversity of fungal genera in cutaneous and mucosal biota was found to be greater in virus-infected cats than in healthy ones. The fungus prevailing in virus-positive individuals was *M. pachydermatis* [50].

The other retrovirus strongly affecting cats immunity is FIV (Feline Immunodeficiency Virus). FIV infection in cats causes acquired immuno-deficiency, predisposing them to secondary infections of the skin, urinary, gastrointestinal and respiratory tracts. Also, the risk of development of lymphoma or myeloproliferative disorders such as neoplasia and dysplasia is increased in FIV positive, FeLV negative cats [51]. During the isolation of cutaneous fungi, Reche et al. have noted a significantly lower peripheral CD4+:CD8+ T lymphocyte ratio in FIV-infected cats comparing to that found in a group of cats uninfected by FIV or FeLV [52]. Furthermore, in the group of FIV+ cats, this ratio was lower in individuals with the presence of cutaneous fungi then in those without. The authors conclude that the depletion of immunological defense abilities caused by FeLV virus can pose a risk of increased fungal colonization [52].

Multifactorial immunosuppression has been proven in cats with FeLV and FIV infections [47,48,51]. In a review of 571 cases of deep feline mycosis, Davies and Troy [53] reveal that incidence of viral FeLV infections was elevated in cases of histoplasmosis, simularity to the occurrence of FIV among animals with mucormycosis and asper-gillosis. Also, studies on cryptococcal infections carried out by Jacobs et al. [54] show that the treatment of cats infected with *C. neoformans* and seropositive for FIV or FeLV failed more frequently. However, the connection between viral infection and increased susceptibility to fungal infections sometimes remains ambiguous, especially according to statistical analysis of mycoses cases, occurring among FeLV infected or FIV positive cats. Schubach et al. [55] evaluated 347 cats naturally infected with *Sporothrix schenkii*. Among them, the co-infection with FeLV was noted only in 2 cats and co-infection with both FeLV and FIV viruses in only one [55]. Greene and Troy [56] report that 9 of 48 cats with mycoses caused by *Coccidioides immitis* were found to be infected with FeLV, but the majority of animals with coccidio-idomycosis were FeLV-negative [56].

Despite the equivocal results of the statistical analysis, immunosuppression was fonud to occur with various intensities in each case of FIV or FeLV infection. Also, the findings of these studies indicate that the fungal biota of some cats infected with viruses which influence their immunity can act as a reservoir of potentially infective species. Thus, the fungal colonization of skin and mucosal surfaces of FIV and FeLV infected animals should be carefully monitored by repeated mycological examination, simultaneously with inspection of other blood and biochemical parameters.

Conclusions

In recent years, increasing occurrence of opportunistic mycoses has been observed in humans. It is connected with the multiple factors affecting host susceptibility, such as primary and secondary immunodeficiencies, coexisting viral and bacterial infections and some metabolic or endocrine disorders (hyperadrenocorticism, diabetes). Paradoxically, the achievements of human and veterinary medicine have also contributed to higher number of fungal diseases, both in human and animals. The use of advanced surgery, modern techniques of diagnostics and treatment, intravenous catheters, transplantology, antimicrobial and immunosuppressive therapies favor opportunistic fungal pathogens and allow for mycoses development.

The aim of our mini-review was to provide an overview of the occurrence of fungal infections in pets, which are found in medical conditions resembling human diseases predisposing the patient

to opportunistic mycoses. The aim of our current research project is to investigate the fungal colonization of dogs and cats with underlying diseases known to influence the immunity of these animals: diabetes, endocrine diseases such as Cushing's syndrome or hypothyroidism, various neoplasmic diseases and virus infections. Our preliminary results have revealed increased yeast colonization of the oral cavity and rectum in cats with concurrent diabetes. Investigations on other groups of animals are ongoing, but the results obtained so far are compatible with existing literature data.

We can conclude that fungal colonization of different ontocenoses of diseased pets should be monitored carefully and simultaneously with the treatment of primary disease. All cases of neoplasms and tumors in dogs and cats present a high risk of the development of infection, both bacterial and fungal. The use of therapy with cytostatics and steroids suppresses the immune response and predisposes the host to secondary infections. Similarly to humans, diabetes of pets increases the chance of the opportunistic infections by fungal biota or environmental fungi due to debilitated immunity, microvasculature disorders, disturbed wound healing or collagen production.

Other endocrine and metabolic disorders may also predispose the host to mycoses, but further studies are needed, as the literature data referring to fungal diseases of dogs and cats with these conditions are scarce. Studies indicate that viral infections of cats with FeLV and FIV are the main cause of immunodeficiencies and neoplasmic transformations of various cells, and immuno-suppression of various intensities can be seen in these diseases. Although some statistical analysis may be confused, it is most probable that both bacterial and fungal secondary infections may occur in such cases. Thus, in each case of FeLV and/or FIV infection, cats should be also monitored for fungal colonization, and the possibility of opportunistic mycoses has to be considered.

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