CLINICAL REPORT

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Cutaneous candidiasis caused by antifungal-resistant *Candida* sp. strain in canine individual

Candidíase cutânea causada por cepa de Candida *sp. resistente a antifúngicos em indivíduo canino*

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ABSTRACT: The aim of the current report is to describe a cutaneous candidiasis case affecting a canine individual treated at the University Veterinary Hospital of State University of Maranhão (UEMA), in São Luís City. The patient had three-month history of skin diseases; it had been previously subjected to several treatments based on antibiotics, corticosteroids and antifungal drugs that have failed to show clinical improvements. Dermatological assessment has indicated generalized moist dermatitis, intense skin desquamation, alopecia, pruritus and meliceric crusts along the animal's body, mainly in its dorsal region. Complementary tests, such as skin cytology and microscopy, trichogram, qualitative PCR and serology for canine visceral leishmaniasis, as well as fungal culture and antifungigram were requested based on this scenario. Serology recorded inconclusive results for leishmaniasis, whereas PCR recorded negative results in the presence of the agent's DNA. Cytology, microscopy and trichogram results have evidenced fungal infection in the assessed samples. Moreover, mycological culture and antifungigram resulted in the growth of *Candida* sp. specimens capable of resisting antifungal agents such as amphotericin B, fluconazole, itraconazole and nystatin. The therapy adopted after candidiasis diagnosis confirmation comprised oral doses of manipulated ketoconazole, in combination to topical therapy with shampoo based on moisturizing formulas associated with Miconazole and Chlorhexidine (at 2%), for four weeks. After 30 days, when the adopted therapy was over, the aforementioned animal presented remission of the previously observed lesions and fully improved condition.

KEY-WORDS: *Candida* spp., antifungal resistance, dermatomycosis, dogs.

RESUMO: O objetivo do presente relato é descrever um caso de candidíase cutânea acometendo um indivíduo canino atendido no Hospital Veterinário Universitário da Universidade Estadual do Maranhão (UEMA), na cidade de São Luís. O paciente apresentava histórico de doenças de pele há três meses; já havia sido submetido a diversos tratamentos à base de antibióticos, corticosteroides e antifúngicos que não resultaram em melhora clínica. A avaliação dermatológica indicou dermatite úmida generalizada, descamação intensa da pele, alopecia, prurido e crostas melicéricas ao longo do corpo do animal, principalmente na região dorsal. Exames complementares, como citologia e microscopia de pele, tricograma, PCR qualitativo e sorologia para leishmaniose visceral canina, bem como cultura fúngica e antifungigrama foram solicitados com base nesse cenário. A sorologia registrou resultados inconclusivos para leishmaniose, enquanto a PCR registrou resultados negativos na presença do DNA do agente. Os resultados da citologia, microscopia e tricograma evidenciaram infecção fúngica nas amostras avaliadas. Além disso, cultura micológica e antifungigrama resultaram no crescimento de *Candida* sp. resistente a agentes antifúngicos como anfotericina B, fluconazol, itraconazol e nistatina. A terapia adotada após a confirmação do diagnóstico de candidíase consistiu em doses orais de cetoconazol manipulado, associado à terapia tópica com xampu à base de fórmulas hidratantes associado a Miconazol e Clorexidina (a 2%), por quatro semanas. Após 30 dias, encerrada a terapia adotada, o referido animal apresentou remissão das lesões observadas anteriormente e melhora completa do quadro.

PALAVRAS-CHAVE: *Candida* spp.; resistência antifúngica; dermatomicose; cães.

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INTRODUCTION

Candida spp. comprises commensal yeasts of the skin, gastrointestinal, genitourinary and respiratory tract microbiota (EGGIMANN et al., 2003; BRITO et al., 2009) of both humans and animals. Although more than 200 *Candida* species have been identified so far, only a few are capable of triggering diseases in dogs or cats (REAGAN et al., 2019), namely: *Candida albicans, Candida glabrata, Candida krusei, Candida tropicalis, Candida guilliermondii, Candida parapsilosis* and *Candida rugose* (PRESSLER et al., 2003; JIN; LIN, 2005).

Although these yeasts do not often harm their hosts, disease development is oftentimes associated with disorders in local microbiota or with the immunocompromised system of the affected animals (KASHEM; KAPLAN, 2016), a fact that gives rise to fungal infections known as candidiasis. (GARCIA et al., 2007).

Accordingly, opportunistic infections affecting animals can primarily develop through virulence mechanisms observed in the causative yeast or secondarily develop (PLAYFORD; MARRIOTT; NGUYEN, 2008) through the action of autoimmune diseases, nutritional, hormonal and metabolic imbalances, physiological factors, compromised immune system due to indiscriminate use of immunosuppressive drugs and through contamination deriving from fomites, other animals or humans (NEGRI et al., 2010; ZHONG et al., 2015).

Cutaneous candidiasis is a common condition affecting humans; however, it is less prevalent in some animal species (SHOKRI; KHOSRAVI, 2016). Canines, in their turn, can show dermatological manifestations often associated with atopy, with other immunological diseases, as well as with immunosuppressive disorders or with other changes capable of leading to immunosuppression (YURAYART et al., 2011; LEE et al., 2011). In addition, these manifestations can clinically resemble infections caused by yeast-like fungi belonging to genus *Malassezia* (SEYEDMOJTADA et al., 2018). Thus, it is necessary establishing differential diagnoses to enable identifying other dermatoses of different etiologies (HESELTINE et al., 2003).

Moreover, the role played by candidiasis as public health issue becomes increasingly evident due to the growing resistance of conventional antifungal isolates and to disease recurrence reports worldwide (SANGLARD; ODDS, 2002; COLOMBO; GUIMARÃES, 2003; POZZATTI et al., 2010).

Thus, the low incidence of clinical cases suggestive of candidiasis in small animals, and lack of regular studies focused on featuring and describing this disease in the State of Maranhão, were the very basis for the justification and description of the current case report.

CASE REPORT

A 9-year-old female mongrel dog (MD) was treated in the medical clinic sector of the University Veterinary Hospital of State University of Maranhão (UEMA) in 2020. The patient had three-month history of skin lesions; during this period, it had been subjected to several treatments based on antibiotics, corticosteroids and antifungal drugs, such as amoxicillin (50mg, BID for 15 days), prednisolone (15mg, SID, for 5 days), ampicillin (300mg, TID, for 30 days) and itraconazole (70mg, BID, for 30 days), which had failed to provide clinical improvement and to solve the clinical case.

The animal presented generalized moist dermatitis, intense skin desquamation followed by alopecia, pruritus and meliceric crusts distributed all over its body, mainly in its dorsal region, during physical examination (Figure 1). Pododermatitis was also observed, along with erythema, alopecia, edema and ulcerations.

The following complementary tests were requested due to the observed cutaneous changes: skin cytology and microscopy, trichogram, qualitative real-time PCR and serology for canine visceral leishmaniasis (RIFI and ELISA), fungal culture and antifungigram.

Serology recorded inconclusive results for leishmaniasis, whereas PCR, which was carried out through spinal puncture, recorded negative results in the presence of the agent. Skin microscopy and cytology have evidenced intense fungal infection. Trichogram has shown hair growth at resting phase, along with incidence of septate hyphae. Moreover, mycological isolation and antifungigram resulted in the growth of *Candida* sp. specimens capable of resisting drugs such as nystatin and amphotericin B, as well as triazoles such as fluconazole and itraconazole.

Thus, the treatment adopted after candidiasis diagnosis confirmation was based on antifungal therapy comprising manipulated ketoconazole (10 mg/kg, OR, SID, 30 days), in association with topical therapy with shampoo based on moisturizing formulas (Nano Hydrade 2%; Nano Coating 2%), Miconazole and Chlorhexidine at 2% (twice a week, for four weeks).

One week after the treatment had started, the animal's tutor reported gradual lesion improvement (Figure 2) and hair growth. At the end of 30 days, after the adopted therapy was over, the animal presented remission of the previously observed lesions and improved condition. The tutor did not

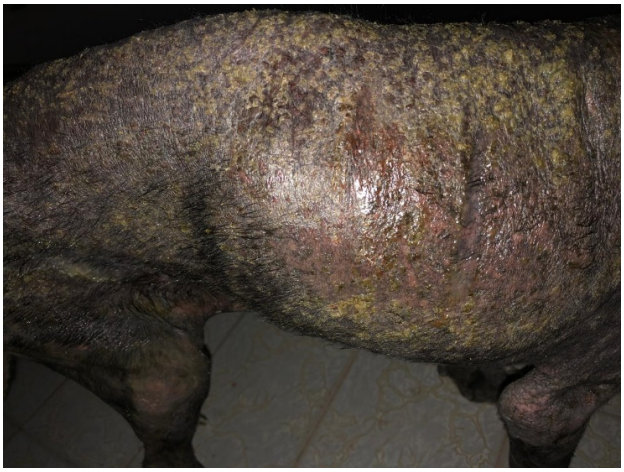

Figure 1. Generalized lesion in the dorsal region of a dog diagnosed with cutaneous candidiasis and treated at University Veterinary Hospital of UEMA.

Figure 2. Canine showing improved skin lesions after seven days of treatment for cutaneous candidiasis.

take the animal back to the clinic in order to repeat the exams and to confirm its full recovery.

DISCUSSION

To the best of our knowledge, the current report is the first to describe disseminated cutaneous candidiasis in a canine individual in the State of Maranhão. The literature has few reports of cutaneous candidiasis in dogs (MUELLER et al., 2002; MORETTI et al., 2004; MORETTI et al., 2006; CLEFF et al., 2007; LEE et al., 2011; HIRDES et al., 2016); they are mostly featured by this yeast preference to colonize humid body sites such as mucosal surfaces, mucocutaneous junctions, intertriginous areas, nail substructures, interdigital region, auditory canal and lateral surface of the ear, which favor tissue maceration (CLEFF et al., 2005).

In addition, lesions with alopecia, crusts, ulcers and edema can also happen (MORETTI et al., 2004), as observed in the animal described in the present report, who also presented intense skin desquamation and meliceric crusts after the application of antimicrobial, corticosteroid and antifungal drugs, as well as worsened dermatological condition, given the progression and expansion of the previously observed lesions.

Likely differential diagnoses, such as canine pyoderma and pemphigus foliaceus (autoimmune disease), were assumed based on the clinical aspects of the assessed animal. Both diseases are featured by dermatological clinical signs that can comprise pruritus, alopecia, purulent secretions, pustule and vesicle formations, and skin exfoliation (BARBOSA, 2012; DE SOUSA SÁ et al, 2018). However, they were ruled out based on cytopathological examination results, which evidenced intense fungal infection, as well as lack of bacteria and acantholytic cells.

Furthermore, the animal assessed in the current report has shown clinical signs compatible to canine visceral leishmaniasis (CVL), such as apathy, lymphadenomegaly, skin diseases and hematological changes, which provided evident differential diagnosis throughout the medical investigation. However, serology (ELISA) recorded inconclusive results, whereas qualitative PCR applied to the marrow bone recorded negative results for the analyzed sample.

It is worth emphasizing that the animal in the present report lived in endemic area of CVL (GARCÊS JUNIOR et al., 2016). According to Baneth (2008), negative PCR results recorded for clinical samples are not enough to rule out this infection. Thus, patients should be reassessed in these cases, in association with the application of specific tests such as real-time PCR and/or skin immunohistochemistry. Parasite load in the skin and inflammatory response are directly linked to animals' condition (GIUNCHETTI et al. 2006; VERÇOSA et al. 2008; VERÇOSA et al. 2012) and it increases the likelihood of finding this parasite in the assessed sample.

The incidence of *Leishmania* sp. and *Candida* sp. coinfection was previously reported in dogs who also presented cutaneous manifestations (MORETTI et al., 2006). Pressler et al. (2003) and Heseltine et al. (2003) have also reported the isolation of species *Candida* in animals affected by other infectious processes (feline immunodeficiency virus – FIV, bacterial infections caused by gram negative and positive agents – *Enterococcus* sp., *E. coli*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Staphylococcus* spp., and *Streptococcus faecalis*) who presented weakened immune system.

However, although fungi belonging to genus *Candida* are seen as opportunistic species, Kozak et al. (2003) have isolated some species capable of causing dermatomycoses in young animals, who did not have immunological disorders, with emphasis on species *C. albicans* and *C. krusei*. Furthermore, Brown et al. (2005) described systemic candidiasis in a dog with no apparent immune deficiency.

Accordingly, *Candida* spp. individual ability to change from commensal microorganisms to pathogenic agents, under favorable host conditions, also depends on several virulence factors (COSTA et al., 2009) that contribute to microorganism's pathogenicity (ZENG et al., 2008). Thus, yeasts belonging to this genus can abandon their commensal form and start causing infections in the most varied tissues and organs of the affected animals (KASHEM; KAPLAN, 2016).

In addition, the animal in the current report underwent several and prolonged treatments, before it was diagnosed with cutaneous candidiasis. According to Cleff et al. (2007), the indiscriminate use of drugs capable of changing animal's natural defense barriers, such as antibiotics and corticosteroids, in association with stress, can lead to fungal multiplication and favor the onset of opportunistic mycoses, such as candidiasis.

Candidiasis diagnosis was confirmed later on based on patient's clinical responses and on laboratory findings. Although skin cytology and microscopy have evidenced fungal infection of unknown genus, fungal culture was the only technique capable of identifying the etiologic agent involved in the skin disease. Genus *Candida* plays relevant role in human and animal health, although it is not always quickly and accurately identified (VAN DE GROEP et al., 2018). Mueller et al. (2002) and Lee et al. (2011) were only capable of identifying yeasts belonging to genus *Candida* after they performed fungal culture in dogs with history of chronic skin diseases, who did not present abnormalities in physical and hematological parameters. However, despite its relevance in the diagnosis and confirmation of the investigated disease, fungal culture is not always performed in the medical routine due to its high cost, mainly in emerging countries such as Brazil (DENNING; HOPE, 2010).

Candida sp. investigated in the current study has shown resistance to several antifungal drugs (amphotericin B, fluconazole, itraconazole and nystatin) that are commonly used in the clinical routine applied to dogs. The herein described causes for the development of such a resistance by *Candida* spp. strains comprised the development of mutation points in genes, reduced membrane permeability, continuous exposure to antifungal agents, among others (PEREA et al., 2001; SANGLARD; ODSS, 2002; CHONG et al., 2007). The herein reported animal had three-month history of skin lesions; it had been subjected to several treatments, which included the oral and/or topical use of antifungal agents during this period. Therefore, it is possible inferring that the isolated strain acquired resistance due to prolonged exposure to these drugs.

Thus, the number of studies proving fungal resistance to commonly used azole derivatives has increased in the literature. Brito et al. (2007) performed susceptibility tests *in vitro* with *Candida* spp. strains isolated from dogs and their results have evidenced fungal resistance to compounds such as ketoconazole, itraconazole and fluconazole. Furthermore, a study carried out with *C. tropicalis* strains isolated from different animal species in Ceará State has shown fungal resistance to both Itraconazole (38% of isolates) and Fluconazole (40% of isolates). However, Amphotericin B-resistant strains were not observed (CORDEIRO et al., 2015). Therefore, the use of such formulations should be monitored and followed-up to avoid the development of fungal resistance and, consequently, therapeutic failure (GIACOMAZZI et al., 2016).

Thus, oral ketoconazole intake and topical use of chlorhexidine and miconazole-based shampoo were prescribed after cutaneous candidiasis diagnosis and the identification of sensitivity to antifungal agents. This treatment is one of the therapies mostly indicated for superficial candidiasis cases, such as the herein reported one (MUELLER et al., 2002). In addition, the herein used formulation has broad-spectrum activity, which encompasses several *Candida* species (ROCHETTE et al., 2003; BRITO et al., 2007). Besides, it is an economically viable alternative with different presentations for veterinary use; thus, it can be used to treat chronic mycoses in several animal species (FARIAS; GIUFFRIDA, 2002).

CONCLUSION

In light of the foregoing, the current study identified a *Candida* sp. strain resistant to common antifungal drugs used in veterinary medical routine, such as nystatin, amphoterin B, as well as to triazoles such as fluconazole and itraconazole. It was possible concluding that fungal culture and antifungigram, in association with complementary exams, such as skin cytology and microscopy, played essential role in the final diagnosis of cutaneous candidiasis and in the adoption of the appropriate treatment, since the identified *Candida* sp. strain is resistant to multiple antifungal drugs.

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