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Review Article

Coccidioidomycosis and Histoplasmosis in Equines: An Overview to Support the Accurate Diagnosis

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ABSTRACT

Fungal infections of the respiratory tract of horses are not as frequent as those of bacterial and viral origin, often leading to worsening of clinical conditions due to misdiagnosis and incorrect treatment. Coccidioidomycosis and histoplasmosis are systemic mycoses caused by the dimorphic fungi *Coccidioides* spp. and *Histoplasma capsulatum*, respectively, which affect humans and a variety of other animals, including equines. These systemic mycoses of chronic and progressive nature can exhibit clinical manifestations similar to other microbial infections. Thus, this article broadly discusses the epidemiology, etiology, virulence, pathogenesis, clinical presentation, treatment, and diagnostic strategies of coccidioidomycosis and histoplasmosis, to support accurate diagnosis.

1. Introduction

Coccidioidomycosis and histoplasmosis, respectively caused by *Coccidioides* spp. and *Histoplasma capsulatum*, share some similarities: both etiologic agents are saprophytic dimorphic fungi that can infect humans and several other mammal species, including horses, mainly through the inhalation of fungal propagules that are present in the environment, and both diseases have diverse clinical presentations [1–3]. Throughout the last decades, several researches focusing on novel diagnostic strategies for human coccidioidomycosis and histoplasmosis have been published, which have contributed for better understanding these diseases in human hosts. However, literature on equine coccidioidomycosis and histoplasmosis is still scarce, as it is mainly limited to a few case reports. Curiously, in some regions where these mycoses seem to be endemic, according to the notification of human cases, the diagnostic resources in veterinary practice are still insufficient. In fact, the broad spectrum of clinical presentations of coccidioidomycosis and histoplasmosis in horses can lead to misdiagnosis. Besides the difficulty of establishing the clinical diagnosis of systemic mycoses, these diseases are not of compulsory notification [4], which contributes for the little epidemiologic data on coccidioidomycosis and histoplasmosis in horses. Furthermore, it is important to highlight the technical limitations associated with the manipulation of the culture of these fungal pathogens, which are restricted to biosafety level 3 laboratories [5]. All these issues justify the development of this work that

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makes a parallel approach of these mycoses in humans and horses, mainly considering the great number of scientific papers on human medical literature addressing this theme, but at the same time highlighting peculiar aspects of these mycoses in horses. Initially, taxonomic, morphologic, and eco-epidemiologic aspects of *Coccidioides* spp. and *H. capsulatum* var. *capsulatum* were quickly presented, followed by the discussion of the virulence and pathogenesis of these fungal pathogens and a description of the clinical presentations and treatment of coccidioidomycosis and histoplasmosis. Finally, different strategies for the diagnosis of these mycoses are thoroughly discussed and presented in this article.

2. Taxonomy, Morphology, and Eco-epidemiologic Aspects of *Coccidioides* spp. and *Histoplasma* spp.

The genera *Coccidioides* and *Histoplasma* are classified in the Onygenales order, which is contained in the Eurotiomycetes class, in turn included in the Ascomycota phylum, belonging to the Fungi kingdom [6]. *Coccidioides immitis* and *Coccidioides posadasii* are the only species in the genus *Coccidioides*. The first species is native and restricted to San Joaquin Valley, California, United States, whereas the second presents larger geographic distribution, occurring in other states in the United States, and other countries, such as Mexico and Central and South America [7,8]. This genus belongs to the Onygenacea family [9].

In turn, the *Histoplasma* genus is part of the Ajellomycetaceae family and presents the species *Histoplasma capsulatum*, whose teleomorph is named *Ajellomyces capsulatus* [6]. This species has three varieties: *H. capsulatum* var. *capsulatum*, which is pathogenic to humans and a variety of mammals, including equines causing classic histoplasmosis [10–13]; *H. capsulatum* var. *duboisii*, restricted to Central Africa, which causes African histoplasmosis, mainly in humans; and *H. capsulatum* var. *farciminosum*, endemic to western, northern, and northeastern countries in Africa and Asia, including India, Pakistan, and Japan, causing epizootic lymphangitis in horses [2,14].

Coccidioides spp. have a mycelium formed by hyaline and septate hyphae that originate arthroconidia, which are asexual reproduction structures, measuring 2–4 μm by 3–6 μm, intercalated with sterile cells devoid of cytoplasmic material known as disjunctor cells (Fig. 1A). When reaching maturity, the infective arthroconidia are released, and the remnants of the disjunctor cells are seen at the end of individual arthroconidia. This characteristic is responsible for their easy aerial propagation. The yeast form is named spherule, which are large rounded structures with thick walls that measure 20–200 μm in diameter. Each spherule produces a large number of small endospores inside, measuring 2–4 μm in diameter (Fig. 1B) [15].

The filamentous form of *H. capsulatum* shows a mycelium composed of hyaline, septate, and ramified hyphae, with two types of conidia. The first, microconidia, are oval structures with smooth walls and a diameter of about 2–4 μm, which are easily dispersed in the air due to their small size and are considered the main infective propagules of this fungus [16]. The second type, macroconidia, also called tuberculate macroconidia, are round large structures, measuring 8–15 μm, with a rough wall covered with distinctive projections (Fig. 1C) [16–18]. The yeast form presents small oval uninucleate cells, measuring about 3–5 μm in diameter (Fig. 1D) [17,18].

Coccidioides spp. are geophilic fungi that develop in soils with high salinity and alkaline pH, usually found at a depth of 10–50 cm [7]. They are associated with arid and semiarid regions, which have an average temperature above 30°C, recurrent droughts, and poor and sparse xerophytic vegetation [19]. The survival of *Coccidioides* species is substantially reduced by competition with other microorganisms in the soil [15]. Several studies have confirmed the importance of armadillo burrows in the ecology of *Coccidioides* spp. especially in Northeastern Brazil [20,21]. There are also reported cases of coccidioidomycosis associated with contact with rodent burrows [22].

The saprophytic phase of *H. capsulatum* is also geophilic, but it has been associated with soils rich in nitrogen compounds, with acidic pH and high moisture, which are characteristics found in soils enriched with the feces of birds and bats [23,24]. Thus, places like caves, hollow trees, chicken pens, and abandoned houses and parks are likely sites of colonization by this fungus [25]. Bats are susceptible to infection caused by *Histoplasma capsulatum* var. *capsulatum* and actively participate in the epidemiology of histoplasmosis. By their migration, these animals can disseminate the pathogen from one location to another, through the elimination of viable forms of the fungus in

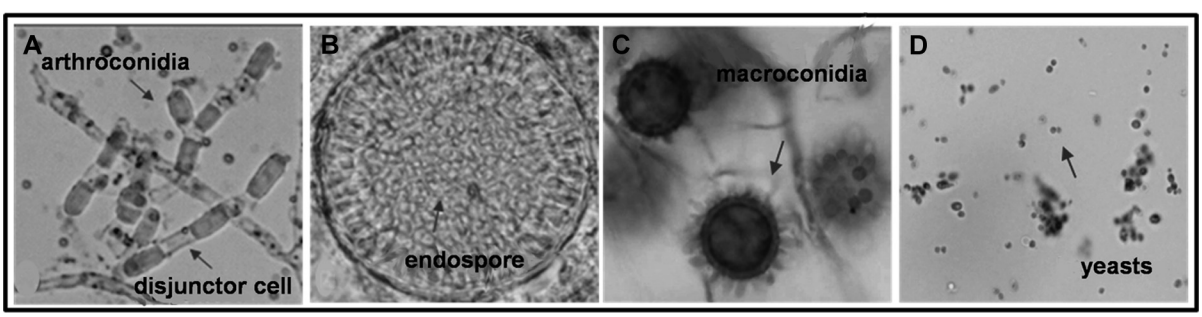

Fig. 1. Micromorphologic aspect of *Coccidioides spp.* (A and B) and *H. capsulatum* (C and D). (A) Filamentous phase, showing arthroconidia and disjunctor cells; (B) Yeast phase, demonstrating a mature spherule with numerous endospores; (C) Filamentous phase, showing tuberculate macroconidia; (D) Yeast phase, showing oval and rounded yeasts.