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Innovation of the Parasitic Cycle of *Coccidioides* spp.

Bertha Muñoz-Hernández¹, Ma. De los Angeles Martínez- Rivera²,
Gabriel Palma-Cortés¹ and Ma. Eugenia Manjarrez¹

¹Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas

²Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional
Mexico

1. Introduction

Coccidioides immitis and *C. posadasii* are etiologic agents of coccidioidomycosis. Major endemic zones are arid and semi-arid climates in North America, such as the northern Mexican states and the southwestern United States. *Coccidioides* spp. is a dimorphic fungus that forms arthroconidia during its mycelial phase while growing in soil. *Coccidioides* spp. enters the lungs through airways and causes an infection and the inhalation of arthroconidia by a susceptible host, initiates the parasitic phase. The infection is usually benign, however, the infection is sometimes severe and lethal, particularly in immunocompromised patients. Elderly persons are at greater risk of developing severe pulmonary disease, while disseminated infection is more frequent in black patients and pregnant women. Transplant patients on immunosuppressive therapy or with human immunodeficiency virus infection have a higher risk of developing severe and progressive coccidioidomycosis. In the host the arthroconidia is transformed into endospore-containing spherules, which are classically found in *Coccidioides* spp. infected tissue. Although parasitic mycelial structures have been identified in some cases, these non classic mycelial structures of *Coccidioides* spp. have not been observed in human tissue or fluid, but when fungal structures are examined, hyphae can be found in up to 50% of specimens. Parasitic mycelial forms have been observed mainly in specimens from lung tissue, sputum, cerebrospinal fluid, and nervous tissue. Parasitic mycelial forms of *Coccidioides* spp. are less frequently observed in pleural fluid, and gastric lavage product. Pulmonary coccidioidomycosis shares clinical manifestations with other pulmonary pathologies, including other mycoses, neoplasia, and tuberculosis. Diagnosis of pulmonary coccidioidomycosis is a multidisciplinary effort.

2. Epidemiology and geotyping

Coccidioidomycosis was described for the first time in 1892 by Alejandro Posadas, a medical student, who reported the case of Domingo Ecurra, a soldier whose death is attributed to this disease. The etiological agent was considered to be a protozoan of the genus *Coccidia*. Gilchrist and Rixford studied the first case in the U.S. Later, Stiles denominated the etiological agent: *Coccidioides immitis* (coccidia-like). It was in 1896 that Opulus and Moffitt discovered the fungal origin of the pathogen. In Mexico in 1932, Cicero and Perrín presented

the first case and they later described diverse cases in patients residing in northern Mexico and the southern U.S., the main endemic zones of coccidioidomycosis. Also, in Argentina (1967), 27 cases of the disease had been described. *Coccidioides immitis*, the etiological agent of this mycosis represented the unique species recognized of this genus. Baptista et al., utilizing U.S. environmental variables and geospatial reference points of the U.S. and Mexico, reported that the main ecological niche for *Coccidioides* is found in the arid deserts of North America (Hirschmann 2007; Baptista-Rosas et al., 2007).

2.1 Epidemiology

Coccidioidomycosis is the most frequent and serious respiratory mycosis in endemic areas inhabited by the fungus. The infection is acquired via the respiratory pathway by exposure to the infectious propagules (arthroconidia) of the fungus. Person-to-person transmission has not been described; however, intrauterine transmission has been (Charlton et al., 1999). *Coccidioides* spp. is the causal agent of coccidioidomycosis or "Valley fever,". The fungus infects at least 150,000 people annually, whom develop a pulmonary infection. Sixty to seventy percent of individuals who have been in contact with the fungus present the infection asymptotically, while only 1% develops the disseminated infection. The male/female ratio is 4:1; the disease affects persons of any age, from children (newborns) to elderly individuals aged ≥ 80 years. It is an occupational disease: archeologists, agricultural workers, soldiers, and construction workers, as well as specialists in microbiological diagnosis, can acquire the infection. Animal species inhabiting endemic areas, such as horses, field mice, armadillos, donkeys, foxes, dogs, and cats acquire the infection and disseminate it to surrounding zones (Negroni 2008; Sharpton et al., 2009).

Discovery of the teleomorphic state of *Coccidioides* complicated the classification of this ascomycete until the similarity was discovered between the asexual spores of *C. immitis* and aleuroconidia of the mitosporic genus *Malbranchea*. Phylogenetic studies suggest a close relationship of this pathogen with *Uncinocarpus reesii*; in its anamorphous state, both produce barrel-shaped arthroconidia, generally placing them in *Coccidioides* genus, Onygenaceae order. Sharpton and coworkers consider *Coccidioides* species are not soil saprophytes, but that they have evolved to remain associated with their dead animal hosts in soil, and that *Coccidioides* metabolism genes, membrane-related proteins, and putatively antigenic compounds have evolved in response to interaction with an animal host (Sharpton et al., 2009).

2.2 Geotyping

Coccidioides spp. is found in the Western Hemisphere at latitudes between 40°N and 40°S from California to Argentina. Distribution of these organisms is patchy. It is endemic in Southwestern U.S., including Arizona (where the incidence in humans is particularly high), parts of New Mexico, Texas (west of El Paso), and in Central and Southern portions of California, especially the San Joaquin Valley. The endemic area extends into Mexico, and foci of infection have been detected in Central and South American countries including Argentina, Colombia, Guatemala, Honduras, Venezuela, Paraguay, and Brazil (Sharpton et al., 2009).

On investigating the intraspecific relations of this fungus, the authors compared the Restriction fragment length polymorphism (RFLP) of the total genomic DNA of the different

isolates of patients, of the environment, and of a sea lion, observing different profiles (Zimmermann et al., 1994). The separation of *C. immitis* into two main groups, Group I and Group II, was reported for the first time by Zimmerman and colleagues in 1994. The two groups are referred by Koufopanou and cols and other investigators: *C. immitis* CA (Concentrated in California) clade, and *C. posadasii* non-CA (represented by clinical isolates from Arizona, Texas, Mexico, and Argentina) clade. Biogeographic distribution of *Coccidioides* has been reported by Fisher and Taylor in populations from endemic zones in the U.S., (Central and Southern California, Arizona, and Texas), North, Central, and Southern Mexico, and South America (Venezuela, Brazil, and Argentina). *C. immitis* seems to be restricted to California, but it might exist in some adjacent areas of Baja California (Mexico) and Arizona. *C. posadasii* is found in the remaining regions (Koufopanou et al., 1997; Fisher et al., 2002; Taylor & Fisher 2003; Sharpton et al., 2009).

3. Parasitic polymorphism of *Coccidioides* spp.

Taylor and Fisher in 2002, using molecular biology technologies, separated two *Coccidioides* species. Data on biological cycle or pathology prior to this date are referred as the *Coccidioides immitis* species; after this date, information appears as *Coccidioides immitis* or *Coccidioides posadasii*. However, no knowledge is available on whether both species are similar or whether they share the same characteristics. All information refers to *C. immitis* or *C. posadasii*, but not to both species; thus, from this point on, we will refer both species as *Coccidioides* spp. for events described for either of the two species (Taylor & Fisher, 2002).

Coccidioides spp. is a dimorphic fungus. The saprobic phase grows as mycelia in desert and semi-arid soils, and disturbances in the soil facilitate the dispersal of arthroconidia, which are the infectious propagules. These become airborne as the result of the action of the wind or some other disturbance of the soil. Susceptible humans acquire the infection by inhalation of arthroconidia, which differentiate into large, endosporulating spherules that are found in the typical parasitic-phase form. Observation of these structures in pathological specimens is considered as diagnosis of the disease. In addition, we describe different mycelial forms and chronic pulmonary coccidioidomycosis in patients with diabetes (Figure 1a). Also, these mycelial forms were described in chronic and cavitary pulmonary, ventriculoperitoneal shunt, and different cases of Central nervous system (CNS) infections by other researchers (Dolan et al., 1992; Hagman et al., 2000; Heidi et al., 2000; Klenschmidt-DeMasters et al., 2000; Meyer et al., 1982; Muñoz et al., 2004; Muñoz-Hernández et al. 2008; Nosanchuk et al., 1998; Wages et al., 1995; Zepeda et al., 1998).

In addition, mycelial parasitic forms have been described in coccidioidoma, and fungal ball as a spheroid mass of hyphae. *Coccidioides* is established in pulmonary cavities and the fungus is in direct contact with the air, modifying O₂/CO₂ relation, favoring mycelial grow. This fungal mass is similar to a macrocolony of highly branched hyphal elements with no host cells inside the fungal ball (Figure 1b).

4. Host risk factors for arthroconidia and parasitic mycelial forms development

Coccidioides spp. can infect immunologically competent individuals. The disease exhibits protean manifestations, ranging from an inapparent or benign pulmonary infection to a

progressive and often lethal disseminated form that most commonly involves the CNS, skin, and bones. This spectrum includes the following: i) an inapparent infection; ii) primary respiratory disease (usually with uncomplicated resolution), but one half of these patients develop an atypical pneumonia, iii) cutaneous infection; iv) valley fever; v) stabilized or progressive chronic pulmonary disease, and vi) extrapulmonary dissemination that is acute, chronic, or progressive. The degree of severity varies considerably within each syndrome and depends on the dose of inhaled arthroconidia, fungus virulence factors, the genetic predisposition of the host, and the host's immune response. In this chapter, we analyze the relationship between clinical spectrum, fungus virulence factors, mycelial parasitic forms, and host immune response in chronic pulmonary coccidioidomycosis, due to that we found these arthroconidia and parasitic mycelial structures in specimens from patients with diabetes with chronic and cavitary pulmonary coccidioidomycosis (Muñoz-Hernández et al., 2008).

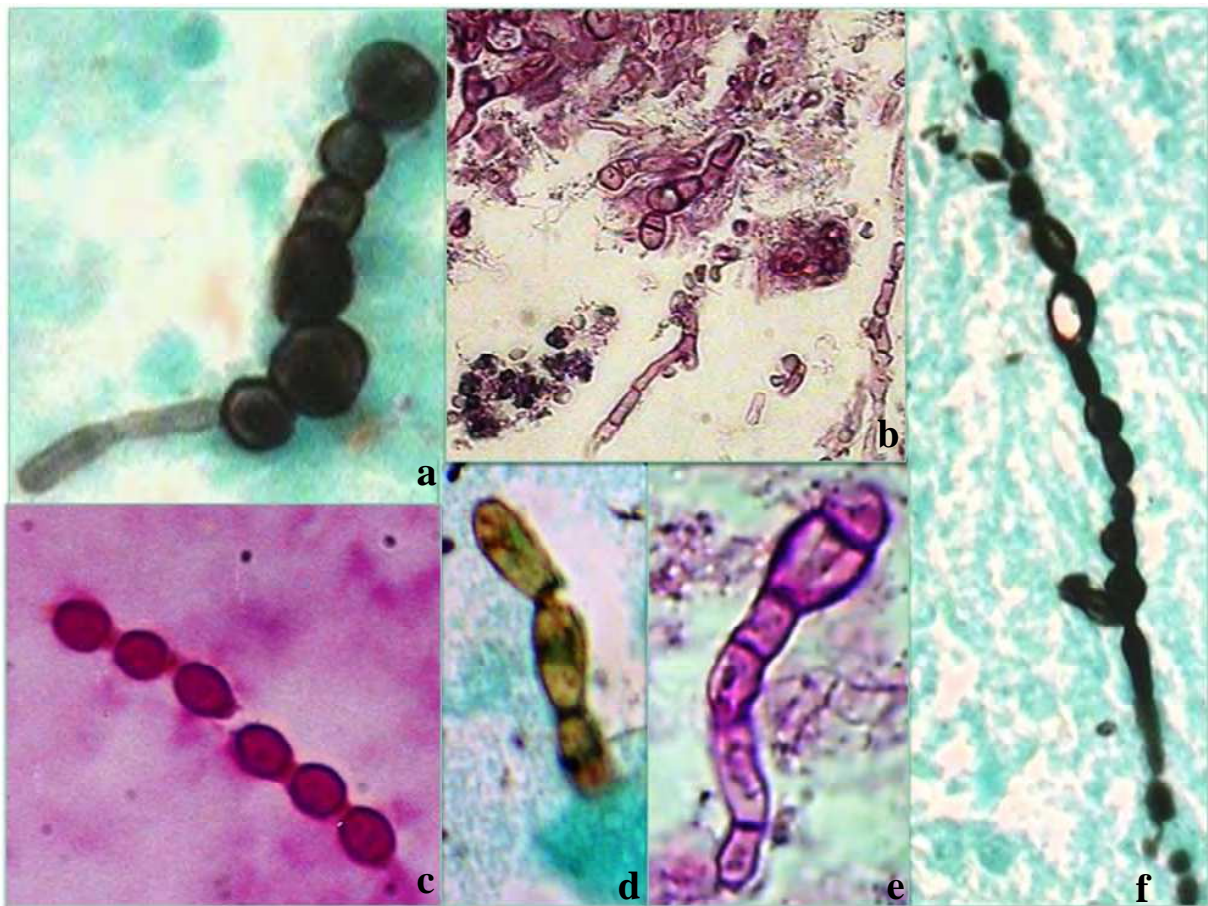


Fig. 1a. *Coccidioides* spp. parasitic hyphal phenotypic diversity. a) and f) Hyphae forming ovoid and spherical cells. b) Pleomorphic cells producing septate hyphae. c) Chain of ovoid cells. d) Separation of arthroconidia. e) Septate hyphae forming a barrel-shaped cells. a), d) and f) Grocott stain of sputum. b), c) and e) Lung tissue stained with periodic acid-Schiff.

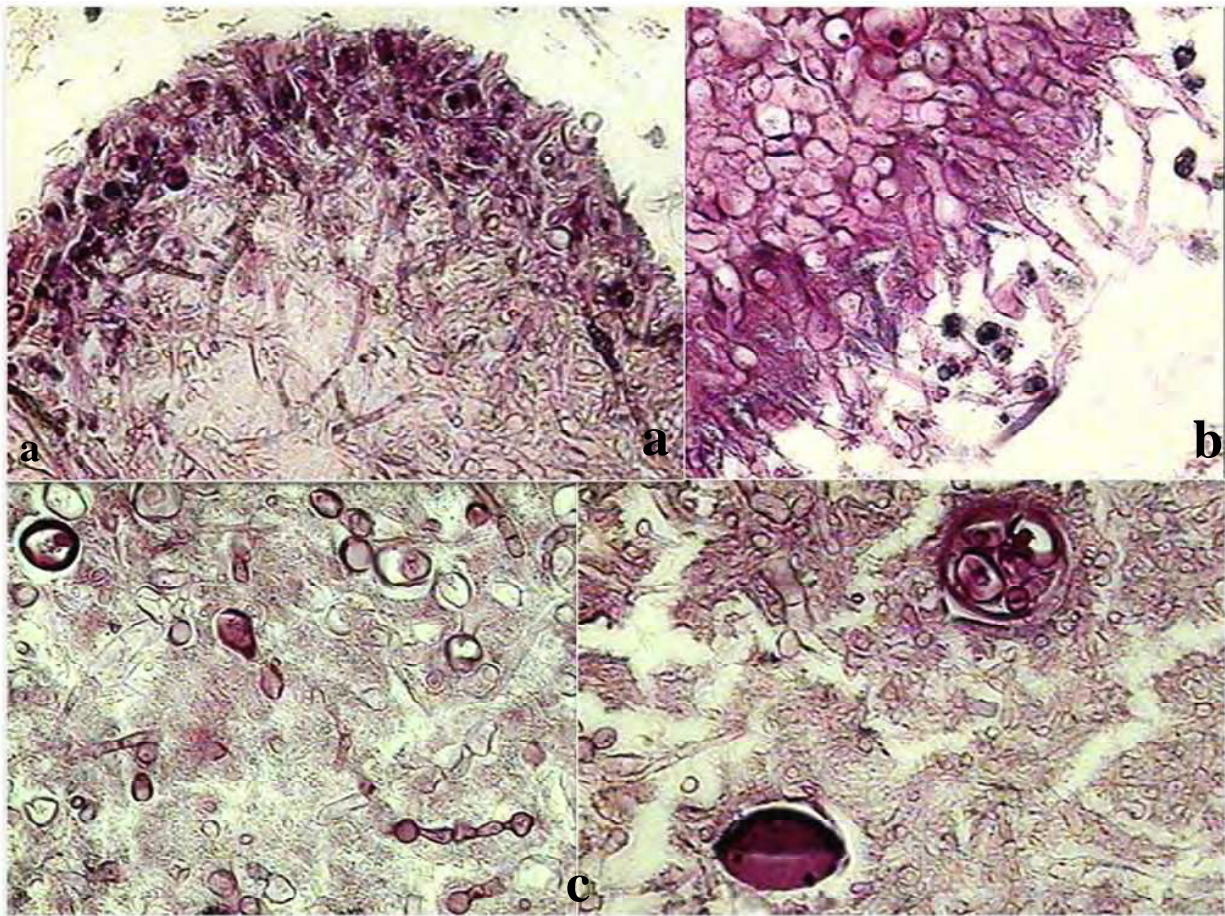


Fig. 1b. *Coccidioides* spp. a) Mycelium fungal ball with septate hyphae and spherules b) Arthroconidia fungal ball forming barrel-shaped and globose cells, both predecessors of spherules. c) presence of septate hyphae in the fungus ball forming arthroconidia, endospore filament, immature spherules, and endospores. Lung tissue stained with periodic acid schiff.

4.1 Pulmonary coccidioidomycosis

Individuals with primary coccidioidomycosis develop persistent pulmonary coccidioidomycosis in 5% of cases, manifested by chronic progressive pneumonia, miliary disease, pulmonary nodules, or pulmonary cavitation. Pulmonary nodules are usually benign but can become cavitory. A classic radiologic finding is the presence of a thin-walled cavity, which typically fails to exhibit a surrounding-tissue reaction; it is strongly suggestive of coccidioidomycosis. The majority of patients have cavities, multiple or multilocular; one half of cavities eventually close spontaneously. Possible complications of cavitation include hemorrhage, secondary infection, progressive increase in size, and, if located peripherally, bronchopleural fistulae. Cavities are formed during acute pneumonia and tend to grow intensively. Infection with this fungus may be asymptomatic, but approximately 50% of immunologically competent persons develop an atypical pneumonia characterized by a cough, fever, and pleuritic chest pain that is often accompanied by rashes, sore throat, cephalgia, arthralgia, myalgia, or anorexia (Cole et al., 2006; Cox & Magee 2004).

A few patients develop chronic progressive pulmonary involvement, with symptoms of cough, weight loss, fever, hemoptysis, dyspnea, and chest pain that may persist for years. Radiographic results include inflammatory infiltrates, biapical fibronodular lesions, and multiple cavities. Chronicity is an essential factor in the development of mycelial forms in lung coccidioidomycosis. In our study, all patients with mycelial parasitic forms presented cavitory lesions (Figure 2). Another risk factor is the concomitant diseases that alter the patient's immune response; these forms have also been observed in patients with CNS and chronic pulmonary coccidioidomycosis. We do not know whether Mexican population possesses the Human leukocyte antigen system (HLA), which is related with the control of or which favors the development of arthroconidia and parasitic mycelial forms of *Coccidioides*. In our studies, all patients were born in Mexico. We found a close association between evolution time of coccidioidomycosis and presence of parasitic mycelial forms, suggesting that chronicity is an essential factor in the development of arthroconidia and mycelial forms. We formulated a comprehensive definition based on the results as follows: patients with pulmonary coccidioidomycosis with an evolution >8 months, cough, hemoptysis, radiological evidence of cavitory lesion, and type 2 diabetes mellitus develop arthroconidia and mycelial forms of *Coccidioides* spp. Based on microscopic images of patient's specimens and descriptions of chronic pulmonary or CNS coccidioidomycosis, we propose incorporating mycelial forms into the parasitic phase of *Coccidioides* spp. (Figure 3) (Muñoz-Hernández et al., 2008).

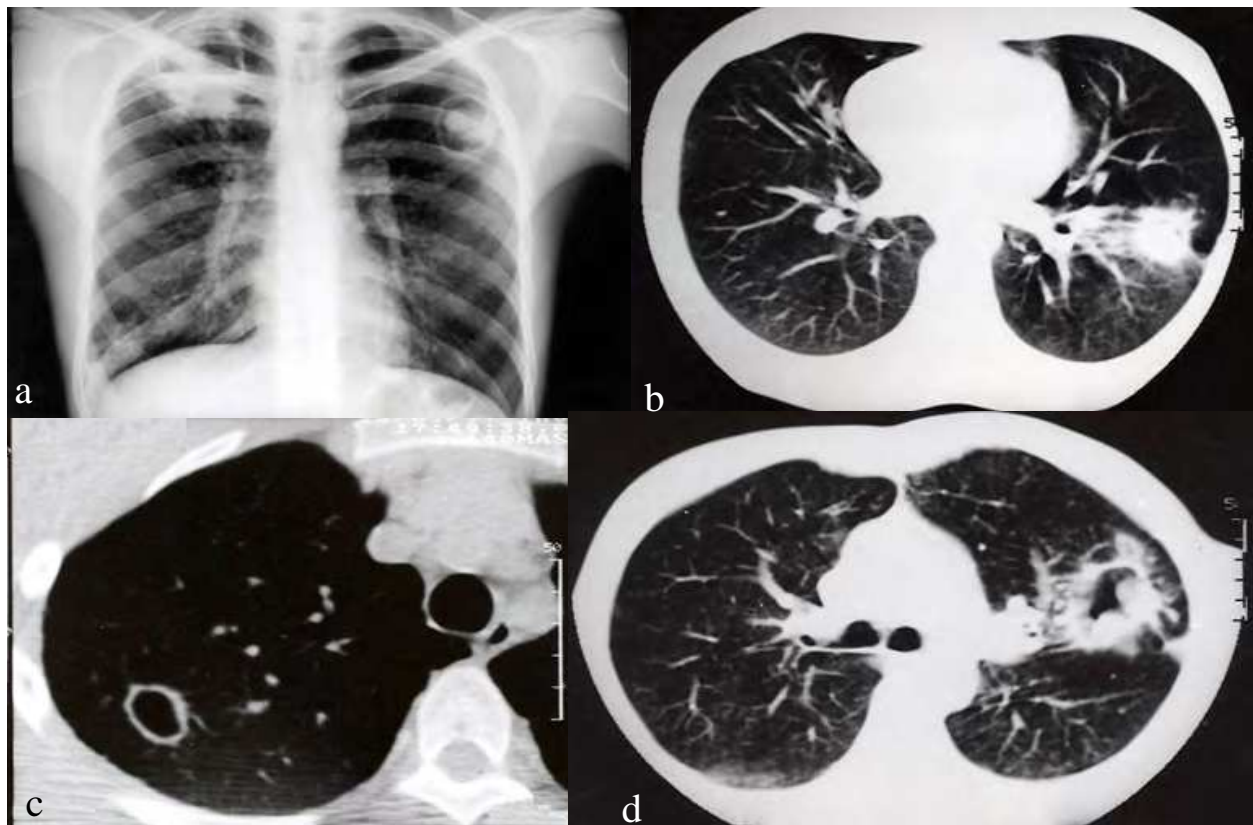


Fig. 2. Radiological evidence of pulmonary coccidioidomycosis. a) Right apical pulmonary cavity with abscess and fluid levels. Left apical cavity occupied. b) Left lobe region coccidioidoma peripheral calcifications and fibrosis, bilateral micronodules. c) Coin shaped lesion with fibrous reaction and scattered micronodules. d) Left lobe cavitory lesion occupied with fibrous reaction.

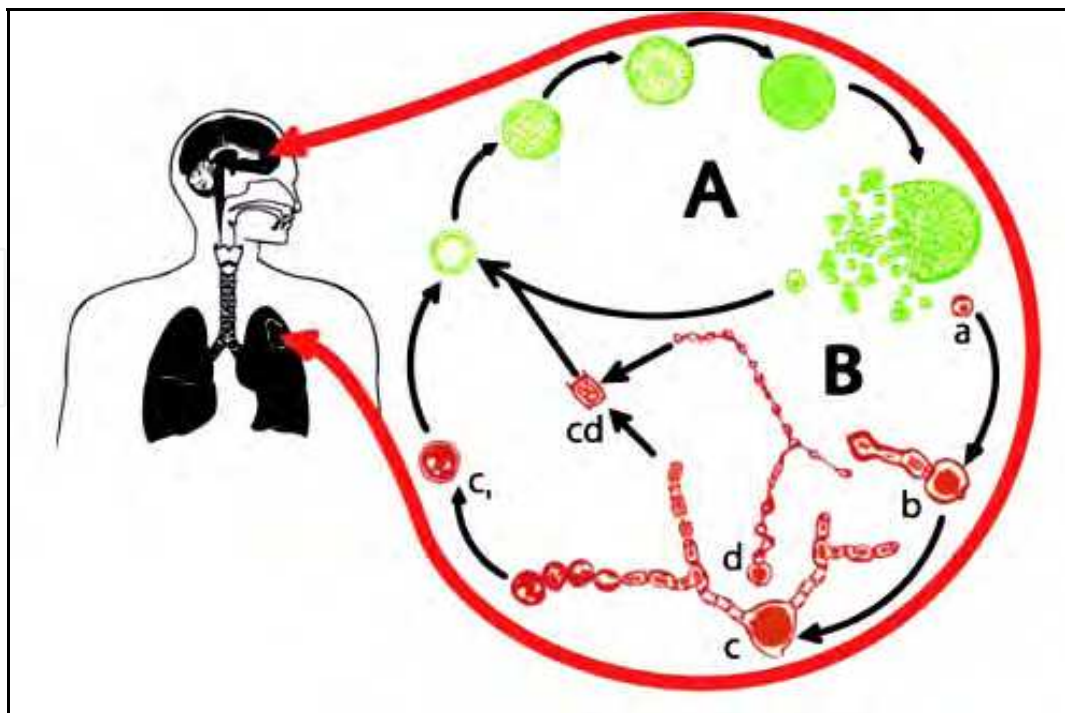


Fig. 3. Mycelial forms and spherules during the parasitic phase of *Coccidioides* spp. in diabetic patients with chronic cavitary pulmonary coccidioidomycosis. Also observed in patients with CNS infection. With permission.

4.2 Virulence factors, immune response, and microenvironment

We think that interactions between virulence factor traits associated with *Coccidioides* spp. and the host immune response determine the clinical form of infection, which in our studies comprises chronic pulmonary coccidioidomycosis and integrates the microenvironment that will permit the development of diverse parasitic fungal forms, including spherules, endospores, arthroconidia, and different mycelial forms. Indeed, the microenvironment will favor the predominance of some of these parasitic forms, or their co-existence.

4.2.1 *Coccidioides* spp. virulence factors

Adhesins

Coccidioides spp. is a dimorphic fungus that has a saprobic phase characterized by mycelia that produce enterothallic arthroconidia; the latter are typically barrel-shaped, measuring 2.5 a 4 μm in width and 3 a 6 μm in length. Thus, they are sufficiently small to reach the alveoli of the lungs when inhaled. Adhesion to laminin and collagen type IV, which act as interlinking molecules. Adhesins are present on spherules and endospores. During isotropic growth, there is intense synthesis of a Spherule outer wall glycoprotein (SOWgp), a specific component of the parasitic phase, which has shown to be important in *Coccidioides* pathogenicity. SOWgp is located in the wall of the endospores and is transported by exocytic vacuole to the spherule's extracellular outer wall. Expression of SOWgp during pathogen growth appears to be restricted to spherule-endospore formation stages, but it is present only in the spherule. SOWgp in the *Coccidioides* spp. spherule form binds to host ECM proteins. In addition, this glycoprotein is an immunodominant antigen that is capable

of eliciting both humoral and cellular responses in infected patients. Thus, SOWgp acts as an adhesin and modulates the host immune response (Hung et al., 2002; 2005; 2007; Klein & Tebbets 2007; Mendes-Giannini et al., 2005).

Dimorphism

Within the mammalian host, *Coccidioides* spp. effects arthroconidia differentiation into spherule-phase cells. This process is unique to *Coccidioides* spp. Dimorphism is an adaptive response of the fungus to a hostile host, modifying its parasitic structures as well as its microenvironment.

Protein kinases

Dimorphism is triggered by exposure to host conditions, particularly temperature, and the fungus leads to the programs required for adaptation to the host environment, including expression of genes for survival and associated virulence factors. Potential signals for histidine kinase sensing in dimorphic fungi include temperature, osmotic or oxidative stress, nutrient deprivation, redox potential, and host-derived factors such as hormones like 17- β -estradiol, which induces germ tubes in *Candida albicans* and blocks the mold-to-yeast transition of *Paracoccidioides brasiliensis*. The histidine kinase system senses host signals and triggers the mold-to-yeast transition and also regulates cell-wall integrity, sporulation, drug resistance, and the expression of virulence genes *in vivo*. Histidine kinase regulates sensing of environmental changes required for morphogenesis in *C. albicans*, *Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Coccidioides* spp., and *Aspergillus fumigatus*. System signaling pathway components are often similar in fungi, but system structures and mechanisms of activation may differ from species to species. These pathways have recently been implicated in environmental sensing and cell development in eukaryotes; phosphorylation/dephosphorylation cycles represent a major mechanism for switching cellular pathways in response to changing microenvironmental factors, both internal developmental cues and external environmental stimuli. Histidine kinase functions as a global regulator of dimorphism and virulence in pathogenic fungi. Protein phosphorylation is generally accepted as playing a key role in transducing the signals involved in several processes such as cell adhesion, internalization, and killing of pathogens (Johannesson et al., 2006; Mendes-Giannini et al., 2005; Nemecek et al., 2006, 2007). We suggest that histidine kinases sense environmental signals such as temperature, CO₂ concentration, and pH and that they play key roles regulating *Coccidioides* spp. phase transition and dimorphism, allowing for the following in parasitic polymorphism: arthroconidia; mycelial forms, and spherules or spherules/endospores in lung tissue as a result of the balance generated by histidine kinases.

CO₂, trehalose, and nitrate reductase

Dimorphism is an adaptive response of the fungus to a hostile host. Temperature (between 34 and 41°C), CO₂ (20%), and a partial pressure of 20 a 80 mm of Hg are essential for development of the parasitic phase of *Coccidioides* spp. The aforementioned conditions are present in pulmonary tissue. Dimorphism initiates with isotropic growth characterized by spherical-cell enlargement and the rounding and swelling of the cells followed by synchronous nuclear divisions and segmentation (Lones & Peacock 1960).

The central portion of the young spherule is occupied by a vacuole. Progressive compartmentalization of the cytoplasm surrounding the vacuole gives rise to uninucleate

compartments reproducing by mitosis and differentiating into endospores. The mature spherule measures 30-100 μm in diameter and can contain 200-400 endospores. At maturity, the spherule ruptures, releasing the endospores (Figure 4), which measure 2-4 μm in diameter. The high fecundity of *C. immitis* is a feature that contributes to the aggressive nature of this primary human fungal pathogen (Mendes-Giannini et al., 2005). Thus, at any given point, the infected host is exposed to immature, mature, and rupturing spherules, newly released endospores, arthroconidia, and mycelial forms (Figure 5). These parasitic forms can disseminate from the lungs to multiple other body organs. We think that, in pulmonary cavities, O_2/CO_2 exchange is inefficient; CO_2 partial pressure will be near 0 mm Hg and there additionally, there is tissue damage. Both CO_2 concentration and tissue damage could permit the co-existence of these polymorphic parasitic forms. When Coccidioidoma is developed, fungus can colonize the pulmonary cavity; in these microhabitats, alterations are increased, favoring the growth of hyphae; thus, there is plentiful mycelial growth.

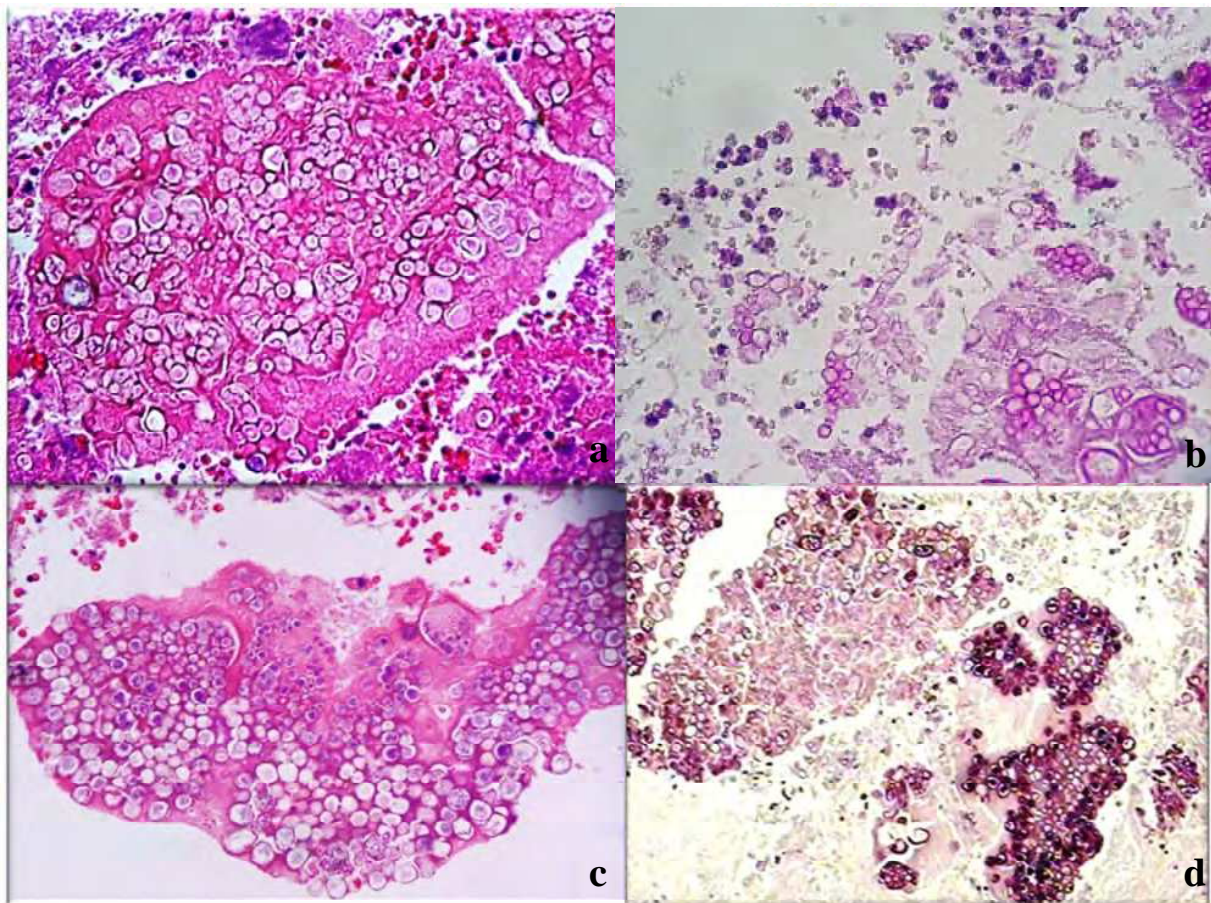


Fig. 4. *Coccidioides* spp. lung tissue: a) Young spherules differentiated, b) Hyphae, spherules with endospores and presence of inflammatory infiltrate; c) Immature spherules and spherules rupture expelling endospores, d) Dissemination of spherules in lung tissue. a, b, c) Staining with hematoxylin-eosin, d) Stained with periodic acid-Schiff.

In addition, the nitrate reductase (*nir*) gene is expressed during the parasitic phase growth in *Coccidioides* infection. This gene is likely to be an important virulence factor in *Coccidioides* because it allows fungi to grow under anoxic conditions. Several fungi that are considered

as obligate aerobes could be facultative anaerobes, due to their presence in the host's microhabitat, inside of an abscess or in a granuloma, if they possess and express the *nir* gene (Moran et al., 2011).

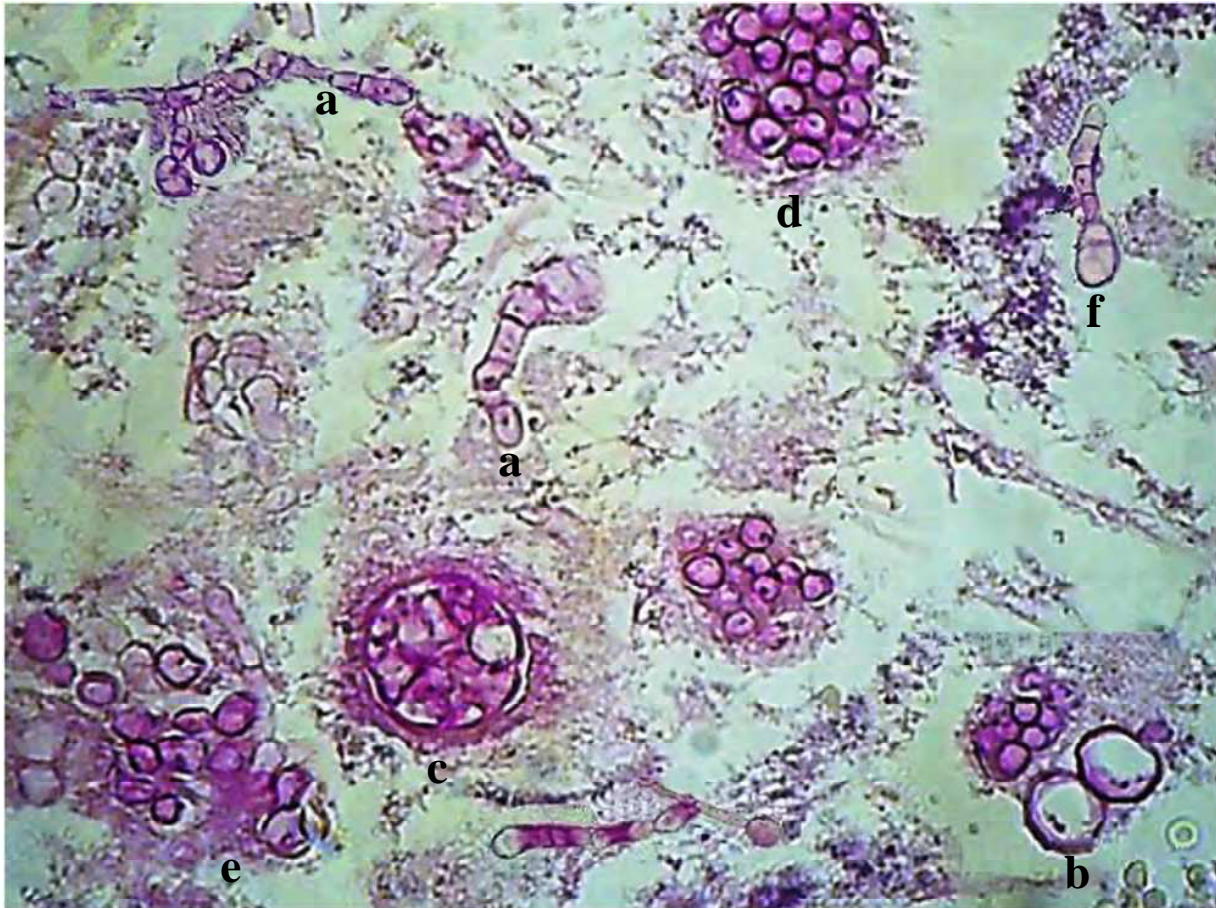


Fig. 5. Parasitic forms of *Coccidioides* spp. observed in patients with chronic cavitary pulmonary coccidioidomycosis. a) Hyphae forming arthroconidia, b) Immature spherules, c) spherules with endospores, d) Morulae forms, e) Alone endospores. f) Endospores filament. Lung tissue stained with periodic acid-Schiff.

Also, in the *Coccidioides* spp. parasitic phase, genes involved in trehalose synthesis are increased. Trehalose can protect fungi against thermal stress (heat, cold), desiccation, and oxidation (Johannesson et al., 2006; Moran et al., 2011).

Melanin

Melanins are multifunctional polymers that are negatively charged, hydrophobic pigments with a high molecular weight. Melanin is considered a virulence factor for human pathogenic fungi such as *Cryptococcus neoformans*, *Aspergillus* species, *Exophiala dermatitidis*, *Sporothrix schenckii*, *P. brasiliensis*, *H. capsulatum*, *B. dermatitidis*, *C. albicans* and *Coccidioides* spp. Melanin or melanin-like compounds are present in *Coccidioides* arthroconidia, spherules, and endospores *in vitro* and *in vivo*, but not in hyphae. Melanin is deposited in the cell wall and cytoplasm. Melanin protects fungi against diverse insults, including extremes temperatures, Ultraviolet (UV) light, solar or gamma radiation, oxidants, hydrolytic enzymes, antifungal drugs, microbicidal peptides, enzymatic degradation, and

killing by macrophages (preventing the respiratory burst). Melanins are immunologically active; they affect macrophages, reduce proinflammatory cytokines, and can downregulate the afferent immune response. Melanin production may promote fungal survival in different environments, increasing their resistance to immune effector responses in the infected host and reducing their susceptibility to antifungal drugs (Nosanchuk et al., 2007; Tabora et al., 2008).

Enzymatic activities

Enzymatic activities from host and fungus, together with the host immune response, play the following key roles in the fate of the infection: death of the pathogenic infection; establishment of chronic infection, or dissemination of the fungus. It is not possible to separate fungal virulence factors from the host immune response, due to that there is a close interaction between these.

Metalloproteinase

Metalloproteinase (*MEP1* gene) activity has been found from the crude Spherule outer wall (SOW) fraction isolated from first-generation, parasitic-phase cultures during the endospore-differentiation phase. SOWgp disappears from the endospore surface under the control of a specific metalloproteinase. SOWgp is present only in the spherule wall's outer membranous and amorphous layers. Endospores (diameter size, 2 a 4 μm) that emerge from ruptured spherules do not possess glycoprotein; thus, they are not recognized by SOWgp antibodies and evade immune response when they are most vulnerable to killing by host phagocytes, whereas the surfaces of mature spherules are coated with the immunodominant antigen and demonstrate high affinity for the anti-SOWgp antibody. However, Polymorphonuclear neutrophils (PMN), macrophages, or Dendritic cells (DC) cannot kill spherules due to that they are too large (40 a 100 μm in diameter) to be rendered phagocytic by these cells. It is possible, therefore, that the SOW complex provides protection to the pathogen against the host innate immune system's phagocytic and fungicidal activities. This evasive mechanism contributes significantly to the survival of the pathogen within lung tissue and potentially to the establishment of a persistent coccidioidal infection in the host (Hung et al., 2005, 2007).

Arginase

L-arginine is generated by both host and fungus. Macrophages express two arginase isoforms: arginase I, and arginase II. Arginase I is located in the cytosol of macrophages, while arginase II is a mitochondrial enzyme. Arginase activity from pathogens interferes with and competes in host L-arginine pathways. In *Coccidioides* infection, arginase can play multiple roles related to fungus metabolism and evasion of the immune response. Some of these are described as follows.

Urease

Urease activity has been reported in *Coccidioides*; it hydrolyzes the urea molecule to release $[\text{NH}_4/\text{NH}_3]$, pH 8. The urease protein has been localized to the spherule cytoplasm and vesicles and to the large central vacuole. L-arginine is the arginase substrate and catalyzes the break of arginine in ornithine + urea. Urease hydrolyzes the urea molecule to release $[\text{NH}_4/\text{NH}_3]$; therefore, *Coccidioides* generates its own alkaline environment due to the release of ammonia (Figure 6). Enzymatically active urease is released from the contents of mature

spherules during the parasitic cycle's endosporulation stage. The enzyme subsequently associates with the surface of intact endospores (Klein & Tebbets 2007). Urease activity of *Coccidioides in vivo* may contribute to the generation of an alkaline microenvironment near the fungal pathogen's surface, as well as stimulation of the host inflammatory response to the extracellular protein and exacerbation of the severity of coccidioidal infection by contributing to a compromised immune response and damage at infection foci of the host tissue. In *Helicobacter pylori* infection, the persistent inflammatory response causes damage to mucosal tissue and exacerbates the ulcerated condition. Some studies have suggested that engulfment of urease-producing bacteria by macrophages in the presence of exogenous urea results in intraphagocytosis of ammonia, which has an inhibitory effect on the macrophage surface expression of major histocompatibility complex class II molecules. In *Coccidioides* infection, there could be similar consequences: both an alkaline microenvironment, and an intense inflammatory response with the production of proinflammatory cytokines; if these are generated at high levels and in a persistent manner, they cause an intense inflammatory

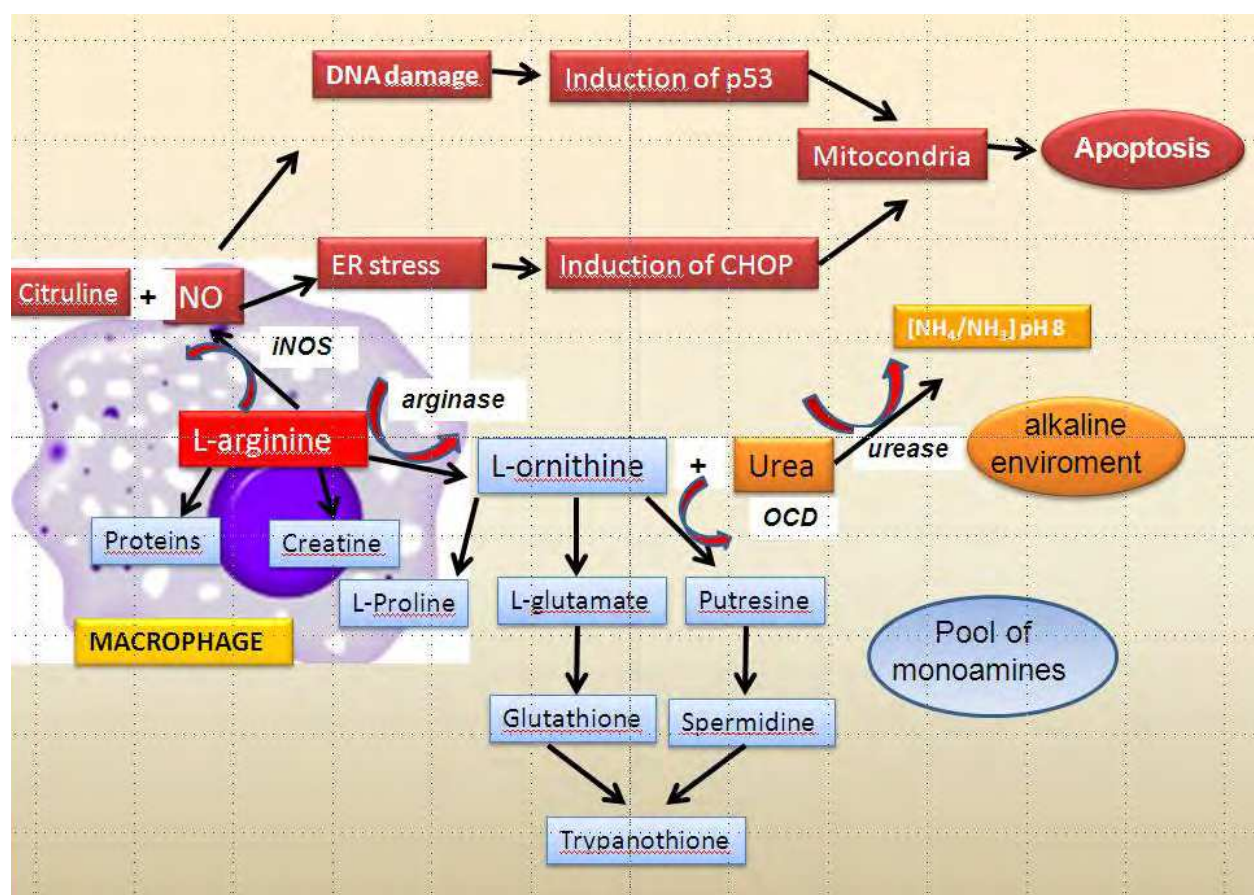


Fig. 6. Enzymatic activity in *Coccidioides* spp. Induction of elevated production of host arginase I and coccidioidal urease, which contribute to tissue damage at focus infection. Arginase I compete with iNOS in macrophages for the common substrate, L-arginine, and thereby reduces nitric oxide (NO) production and increases the synthesis of host ornithine and urea. Excess of NO induce apoptosis mediated by ER involving CHOP. Abbreviations: NO, nitric oxide; ODC, ornithine decarboxylase; CHOP, C/EBP homologous protein; inducible nitric oxide synthase, iNOS); ER endoplasmic reticulum. Modified from Vincendeau, et al., 2003.

response localized at the infection site. Urease released from spherules during the *Coccidioides* spp. parasitic cycle contributes to host-tissue damage, which further exacerbates the severity of coccidioidal infection. This damage may be mediated both by the pathogen and the host. PMN are the dominant cells in this response, although macrophages are also present. However, these cells only partially disable *Coccidioides* growth and are unable to kill it (Vincendeau et al., 2003; Mirbod-Donovan 2006; Hung et al., 2007).

Polyamines

L-ornithine is generated by arginase activity and is the substrate for Ornithine decarboxylase (ODC), which is a key enzyme in polyamine biosynthesis (Figure 6). Host-derived L-ornithine may promote pathogen growth and proliferation by providing a monoamine pool, which could be taken up and used for polyamine synthesis via the parasitic cells' metabolic pathways. Polyamines possess the following multiple roles: stabilizing nucleic acid and membranes; regulating cell growth and the cell differentiation pathway, and regulating *Coccidioides* parasitic-cell differentiation. Polyamines can also regulate the cellular death process, known as apoptosis. In extreme cases, high exogenous polyamine concentrations can lead to cell death. Effects of the polyamines comprise both induction and inhibition of biosynthetic and catabolic enzyme activities, which are associated with the increase and decrease of apoptosis (Figures 6 and 7) (Vincendeau et al., 2003; Wallace et al., 2003).

Nitric oxide (NO) synthesis

Arginase I competes with inducible Nitric oxide synthase (iNOS) in macrophages in order for the common substrate, L-arginine, to produce NO following macrophage activation by microbial products and antigen-specific, T-cell-derived cytokines. Therefore, the Th1/Th2 balance could also be considered as a mechanism whereby the immune system regulates and limits NO production (Figure 6) Dendritic cells (DC) have also been shown to upregulate arginase I expression and arginase activity on Th2 stimulation. This leads to the depletion of L-arginine, a substrate of NOS, resulting in lower levels of cytotoxic NO and increased production of polyamines. Expression of NOS creates a cytotoxic environment, promoting microbiostasis and favoring vasodilatation, which might be important in the early wound-healing phase, and arginase activity produces an environment favorable to fibroblast replication and collagen production and is therefore required for tissue repair (Vincendeau et al., 2003; Wallace et al., 2003). The concentration of L-arginine is crucial in determining the effect of NO-dependent parasite killing by macrophages. NO is a messenger molecule functioning in vascular regulation, host immunity, defense, neurotransmission, and other systems. ODC and polyamine uptake are negatively regulated by NO, given that host-arginase activation may result in decreased levels of NO production in macrophages and may permit intracellular survival of the fungal pathogen. In macrophages, a Th1 response, mainly Interferon (IFN)- γ , induces NO synthesis and parasite killing, whereas Th2 cytokines, Interleukin (IL)-4 and IL-10 inhibit NO synthesis and favor parasite growth. Th1 and Th2 cytokines regulate iNOS/arginase equilibrium in macrophages. Parasite survival appears to be related with the host's ability to mount an effective granulomatous response to the pathogen, which leads to clearance of fungal cells from infected lung tissue (Figure 6) (Wallace et al., 2003).

Apoptosis

High production of arginase I results in increased polyamine synthesis, decreased NO production, and alkalinization of the microenvironment as a consequence of the increased

urea concentration and microbial urease activity at infection sites. These metabolic events contribute to the survival of *Coccidioides* in the hostile environment of the host. Low concentrations of NO protect cells from apoptosis. NO-induced apoptosis is mediated by the Endoplasmic reticulum (ER) stress pathway involving C/EBP homologous protein (CHOP) induction. ER stress has been implicated in a variety of common diseases such as diabetes, ischemia, and neurodegenerative disorders (Figure 7). Excess NO induces programmed cell death (apoptosis) in several cell types. ER stress and induction of the p53 pathway-mediated apoptosis have been described in *Coccidioides* spp. (Figures 6 and 7) (Hung et al., 2007; Vincendeau et al., 2003).

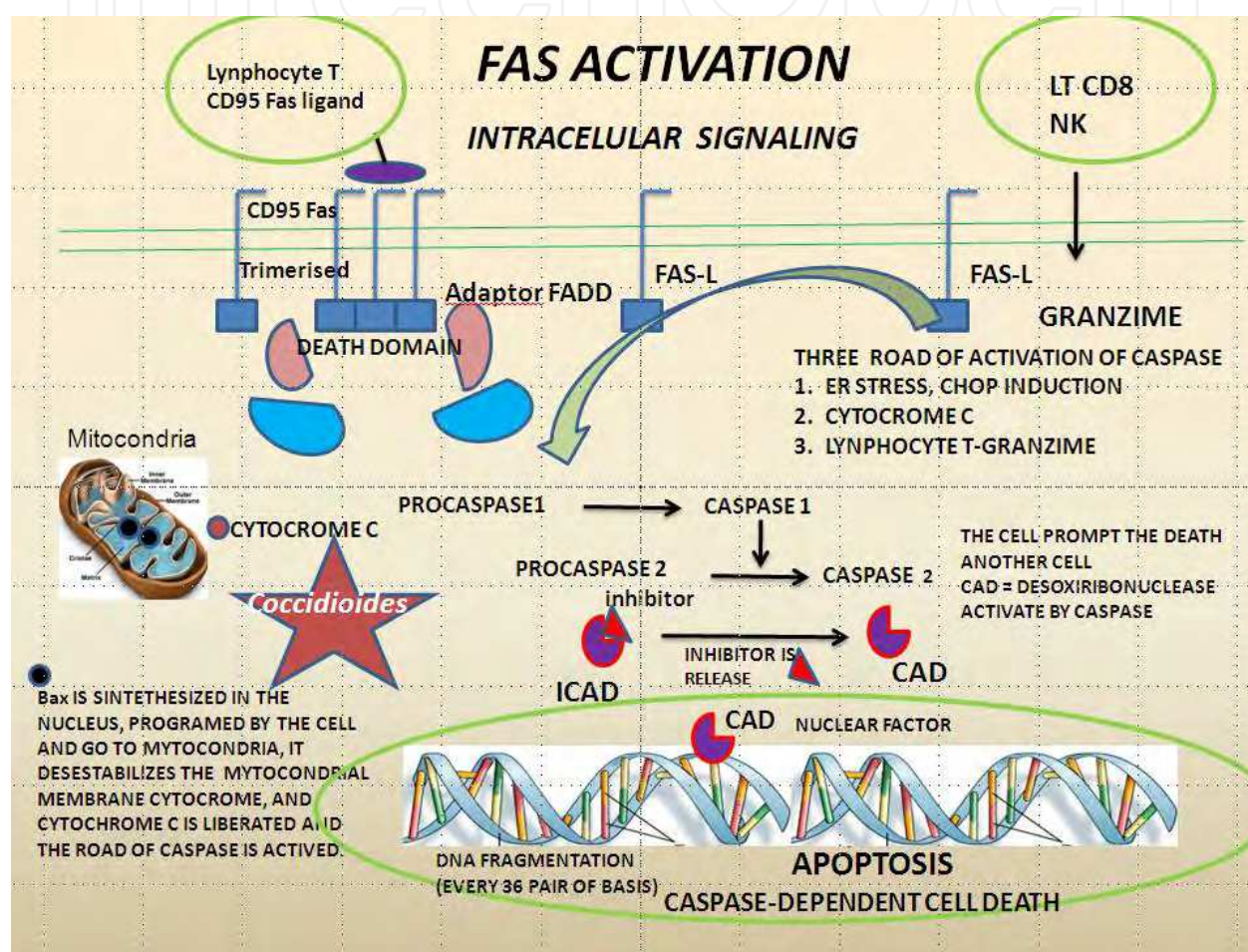


Fig. 7. Apoptosis via Fas activación. *Coccidioides* spp. induce apoptosis by ER stress or mitochondria (cytochrome C) pathway activate by caspase. Abreviations: APO-1/CD95, encodes a transmembrane type I receptor.

5. Immune response

The immune system comprises the innate immune response (constitutive) and the adaptative immune response (induced and specific). Both immune-response types share cells and cytokines (inductors and effectors), but they also possess specific components of every type of immune response. In chronic progressive pulmonary coccidioidomycosis, the integral result of the immune response (innate and adaptative) can be observed in tissue imaging. In coccidioidal infection, there are microabscesses with abundant

Polymorphonuclear neutrophils (PMN) and mononuclear cells. In addition, there is an increase in the size of endothelial cells, with intense perivascular infiltrators. Spherules and spherules/endospores are significantly increased in patients with poor prognosis for recovery (Figure 4). Granulomas are also present, with abundant Langhans cells, lymphocytes, and monocytes, and scant eosinophils, plasmacytes, and epithelioid cells surrounding the spherules and spherules/endospores. When *Coccidioides* infection has progressed, there are plentiful fungal structures. Granuloma a fibrous wall with a necrotic center, in which are found spherules (Figure 8) (Winn et al., 1994).

5.1 Innate immunity

Innate immunity in *Coccidioides* spp. protects healthy individuals from coccidioidal infection in 70% of cases; thus, it is highly efficient in healthy subjects. However, this response is not sufficiently efficient to kill arthroconidia-infectant propagules. The major members responsible for the innate immune response in *Coccidioides* infection are PMNL, monocytes/macrophages, Natural killer (NK) cells, DC, and Surfactant protein A (SP-A).

PMNL

These comprise the first cellular influx into the arthroconidia. This response may be attributable to chemotactic components released by the arthroconidia. Arthroconidium phagocytosis is enhanced in the presence of immune serum. Ingestion of arthroconidia is followed by a respiratory burst, but <20% of arthroconidia are killed by the encounter. Transformation of arthroconidia into spherules prevents phagocytosis and the killing of these by PMNL, owing in part to the increased spherule size (60-80 μm) relative to that of the PMNL (12 μm). Rupture of spherules and release of endospores newly trigger a PMNL influx. The host mounts an intense inflammatory response to the released products. Neutrophils are the dominant innate cells found associated with endosporulating spherules, although macrophages are also present (Figure 8).

Monocytes/macrophages

Both *Coccidioides* spp. arthroconidia and endospores are phagocytized by monocytes/macrophages, but <1% of phagocytized cells are killed. *Coccidioides* appears to inhibit the fusion of arthroconidia- or endospore-containing phagosomes with lysosomes. However, a significant increase in phagosome-lysosome fusion was observed in macrophages when adaptive immunity was specifically activated with fungus antigens. This increase in fusion correlated with the ability of the macrophages to kill *Coccidioides* spp.

Natural killer cells

NK cells comprise a major component of innate immunity. They can migrate to inflammation sites in response to chemokines. NK cells secrete cytokines, IFN- γ , and chemokines, which induce inflammatory responses and control monocyte and granulocyte growth.

Dendritic cells

These are potent Antigen-presenting cells (APC) and play a pivotal role in innate and adaptive immunity. On initial infection, precursor DC are recruited from the blood to inflammatory sites, where they transform into immature DC. In the initial interaction, the pathogen binds to pattern-recognition receptors, notably Toll-like receptors (TLR), which

recognize structurally conserved pathogen-associated microbial products. This initial recognition leads to induction of proinflammatory cytokines, which include Tumor necrosis factor alpha (TNF- α) and Interleukin (IL) -1, IL-6, and IL-8. The spherule-phase antigen induces maturation of peripheral blood-derived DC from healthy, nonimmune subjects. When immature DC are exposed to the coccidioidal antigen, this encounter can generate anergy in patients with systemic infection.

Surfactant protein A

The pulmonary surfactant is a complex mixture of lipids and proteins that reduces surface tension at the air-liquid interface within alveoli. The most abundant protein component of alveolar surfactant is Surfactant protein A (SP-A). This protein binds to macrophages, generating diverse phenotypical and functional alterations into macrophage biology-increased phagocytosis through complement receptors (FcR); there is altered production of proinflammatory cytokines such as TNF- α and IL-1 and decreased production of NO in response to stimuli. Thus, in the lung, macrophages produce Reactive oxygen intermediates (ROI) promote host defense and avoid host damage. Therefore, SP-A inhibits ROI production through NADPH oxidase by human macrophages in response to stimuli by reducing NADPH oxidase activity. In addition, SP-A contributes to the alternate activation phenotype of alveolar macrophages and to the maintenance of an anti-inflammatory environment in the healthy lung (Crowther et al., 2004).

5.2 Adaptive immunity

Adaptive Cell-mediated immune response directly correlates with specific resistance to *Coccidioides* spp. infection, whereas susceptibility correlates with expression of Th2-associated cytokines, which potentiate the production of IgE and IgG1 antibodies and suppress macrophages and T-cell responses. Disseminated coccidioidomycosis is associated with T-cell anergy and the production of exaggerated levels of anti-*Coccidioides* immunoglobulin (Ig)G and IgE antibodies. The mechanisms that induce CMI responses in coccidioidomycosis are probably under genetic control. Persons with Asian, Afro-american, or Hispanic ancestry are at higher risk for developing disseminated coccidioidomycosis than those with Caucasian ancestry.

5.2.1 Cell-Mediated Immunity (CMI)

Cell-mediated immunity has been related with induction of Th1-associated immune responses (IL-2, IL-12, TNF- α , and IFN- γ). The cumulative response includes processing and presentation of critical antigens by macrophages and/or DC, leading to the induction of T-cells to produce IFN- α and other Th1-associated cytokines. These cytokines provide the signals for recruiting and activating immune effector cells. One example is that activation of immature DC leads to their secretion of chemokines and maturation of DC into highly efficient APC, which function in T- and B-cell response regulation. APC interact with T- and B-cells. Mature DC induces and triggers multiple events to develop the cellular and humoral adaptive immune response. The Cell-mediated immunity response comprises the following: i) cutaneous delayed-type hypersensitivity; ii) cytokine production, and (iii) cytokine activation of monocytes (Cox & Magee, 2004; Xue et al., 2005)

Cutaneous delayed-type hypersensitivity

The classic antigen preparation, a soluble broth-culture filtrate of mycelial cells (coccidioidin) or the culture of the spherule-endospore phase *in vitro* (spherulin), both are employed as a coccidioidin skin-sensitivity test. Persons with primary, asymptomatic, or benign disease characteristically have strong skin-test reactivity to coccidioidin and low or nondemonstrable levels of anti-*Coccidioides* complement fixation (CF) antibody. Skin-test reactivity persists in the majority of persons who recover from primary infection, and these persons are endowed with immunity to exogenous reinfection. Patients who develop progressive or chronic pulmonary coccidioidomycosis manifest a reaction to the coccidioidin skin-sensitivity test. Low or nonresponse to the latter test denotes poor prognosis for recovery. Anergy occur in patients who have severely disseminated disease involving multiple infection foci.

Cytokine production

Cytokines and chemokines are host factors that guide Th1- and Th2-cell differentiation. Th1/Th2 cytokine profiles correlate with resistance and susceptibility to *Coccidioides* infection, respectively.

TNF- α

This is a cytokine produced by a large variety of cells, including macrophages, DC, and T- and B- lymphocytes. In patients with active coccidioidomycosis, TNF- α is responsible for many of the biological and physiological consequences of acute infection, immunological reactions, and tissue injury. Additionally, TNF- α is required for control of acute infection and formation and maintenance of granulomas, but, on the other hand, it has been implicated as a major component in host-mediated destruction of lung tissue (Figure 8).

IFN- γ

Is another cytokine that is produced in coccidioidal infection. Lymphocytes from patients with pulmonary disease secreted IFN- γ levels comparable to those of healthy persons. In contrast, in patients with disseminated disease, IFN- γ was significantly lower than in healthy persons with the coccidioidin skin-sensitivity test. The mechanism by which IFN- γ and TNF- α can activate macrophages is generating NO and related reactive nitrogen intermediates via nitric oxide synthase, using L-arginine as substrate (IoVelle 1987; Hung et al., 2002; Magee & Cox 1995).

Production of these cytokines was at the infection site and generally revealed quantitative rather than qualitative differences. Although IFN- γ production is assigned to Th1 T-cells, natural killer cells also produce abundant levels of this cytokine. One mechanism by which IFN- γ might mediate resistance to *C. immitis* is by activating macrophages to inhibit or kill the fungus (Magee & Cox 1995).

SOW (without glycoprotein)

Is rich in lipid complexes with high amounts of phospholipids; this fraction is highly immunogenic and induces high amounts of IFN- γ . The principal functions of IFN- γ *in vivo* are activation of macrophages and increased expression of the Major histocompatibility complex (MHC), which can result in stimulation of a host immune-response Th1 pathway.

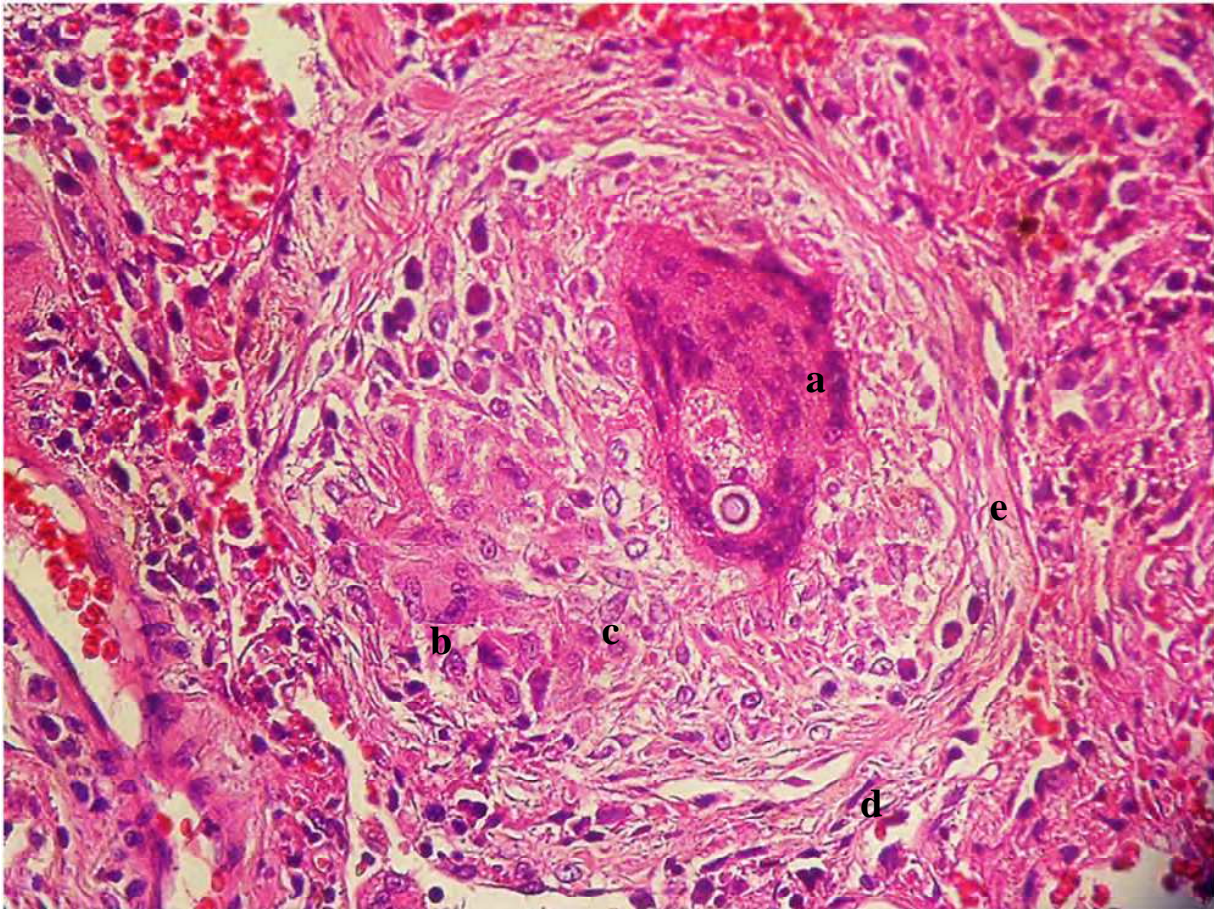


Fig. 8. *Coccidioides* granuloma in inflammatory infiltrate. a) Spherule embedded in a cell of Langhans; b) Langhans cell with nuclei arranged in a horseshoe shape; c) epithelioid cells; d) fibroblasts; e) fibrin. Hematoxylin-eosin staining in lung tissue.

IL-2

This has been shown to modulate early development of Th1 vs. Th2 responses. IL-12 plays a role as an important control mechanism for developing protective host defenses against coccidioidal infection. IL-12 possesses multiple functions, such as stimulation of T-lymphocyte and NK cell proliferation, promotion of cytolytic activity of macrophages, and induction of the secretion of other cytokines, including IL-2, TNF- γ , and IFN- α . It has also been correlated with the induction of a protective TH1 immune-response pathway against systemic fungal infections (Magee & Cox 1995).

Cytokine activation of monocytes

Phagocytized, non-activated (innate immunity) monocytes do not kill *Coccidioides* arthroconidia or endospores. Fungi might survive intracellularly by employing inhibition of phagosome-lysosome fusion. In contrast, monocytes specifically activated by IFN- γ or TNF- α (adaptive immunity) augmented the fungicidal capabilities for killing *Coccidioides* spp. structures.

5.2.2 Humoral immunity

The Th2 immune response compromises host protection against coccidioidomycosis and exacerbates the disease course, while Th2-type immune response produces high levels of IL-4, IL-5, IL-6, and IL-10, which in turn stimulate the B-cells to produce antibodies; this type of response exacerbates the disease course. In addition, there is no evidence that this response protects the host from coccidioidal infection. High amounts of IL-6 correlate with intense inflammatory response to *Coccidioides* infection, which may contribute to host-tissue damage and exacerbation of disease too (Hung et al., 2005, 2007).

Antibodies

High antibody titers to *Coccidioides* in patients with this respiratory disease typically correlate with poor clinical outcome. Chronic or progressive coccidioidomycosis is associated with polyclonal B-lymphocyte activation, and Th2 response, as evidenced by elevated levels of IgG, IgA, and IgE in serum. Serum IgG levels directly correlate with disease progression; highest titers are present in patients with multifocal involvement. The serum IgA level is elevated in patients with chronic pulmonary disease. In addition, there is IgE hyperproduction, with highest incidence occurring in patients with disseminated disease. SOWgp is the major cell-surface antigen of *Coccidioides* that elicits both antibody-mediated and cellular immune responses in patients with coccidioidal infections. SOWgp may contribute to a bias in Th1 vs. Th2 pathways during the course of *C. immitis* infection. The SOWgp antigen exerts an influence on the host to react to *Coccidioides*-associated respiratory diseases by activation of a T-helper 2 (Th2) pathway (Hung et al., 2002, 2007).

Immune complexes

Circulating C1q-binding immune complexes have been detected in sera from patients with coccidioidomycosis and were shown to correlate with disease severity (7). Whereas 33% of sera from patients with the disease involving a single-organ system had elevated immune complex levels, 67% of sera from patients with disseminated multifocal disease demonstrated circulating immune complexes. Analyses of immune complexes in serum from a patient with severe disseminated disease revealed *Coccidioides* antigen, C1q, and anti-*Coccidioides* IgG antibody (Hung et al., 2002, 2007).

6. Diagnosis

Coccidioidomycosis can be clinically and radiologically confused with other respiratory apparatus pathologies such as neoplasms, fungal and bacterial infections, and mainly with tuberculosis; in tissue slices, histopathological images are found that are similar to those of other mycotic or bacterial infections. Laboratory diagnosis is complicated if no typical spherules/endospores are observed in the pathological specimens. Therefore, in order to arrive at the correct analysis of this disease, the collaboration is necessary of a multidisciplinary group of health professionals in which Clinicians, Epidemiologists, Radiologists, Mycologists, and currently Molecular Biologists, who have contributed considerably to the identification of the etiological agent and in the diagnosis of this mycosis.

Coccidioides is a dimorphic fungus; it grows in its saprobic or vegetative phase as a mycelium, forming a large amount of arthroconidia, and in its parasitic phase, it is differentiated in structures denominated spherules, which generate in its interior hundreds of endospores. They are considered diagnosis for active infection. However, a parasitic phenotypic diversity has been observed in the transition of arthroconidia to spherules/endospores; in this variation are included the parasitic mycelial forms of *Coccidioides*, which have been observed in >50% of patients with chronic pulmonary coccidioidomycosis (Figures 1, 2, 4, and 5) (Muñoz-Hernández et al., 2004, 2008). Notwithstanding microscopic observation of hyphae and arthroconidia of *Coccidioides*, these are not diagnosed; it is necessary to have knowledge of their presence in this mycosis and to recognize them in biological samples. This morphological diversity can generate errors in fungal identification due to the morphological similarity that these can possess with other fungi, or parasites, and even with artifices present in pathological specimens. All of these characteristics of the pathogen considerably complicate the final diagnosis of this disease. In addition, it is considered the most infectious and virulent of the mycoses, and difficult to treat. Therefore, the laboratory diagnosis is relevant.

In order to perform a specific diagnosis, it is important to work with an adequate sample, which should derive from the lesion site, to have a sufficient amount, and to transport it immediately to the laboratory for its processing. It is suggested to analyze a minimum of three pathological specimens. Muñoz-Hernández and colleagues report that the most frequently analyzed biological product was sputum, achieving a good result without the need of using invasive methods during specimen-taking, followed by bronchial lavage and brushing (Muñoz-Hernández et al., 2004, 2008).

The most customary methods for laboratory diagnosis comprise microscopic analysis, whether by observing the product in its fresh state with KOH or in histopathological preparations with different stains, in which diverse parasite forms can be observed: from arthroconidia and septate hyphae with multiple morphologies, to conidia transition, spores to mature spherules and endospore-releasing spherules (Figures 1, 2, 4, and 5). This technique is the most rapid and the result can be given on the same day that the sample is received in the laboratory. Isolation of the etiological agent is the best test for identification of this infectious agent. Identification of the fungus is performed by recognizing the macro- and microscopic phenotypic characteristics of the fungus. For management of cultures and all material containing *Coccidioides* spp. arthroconidia, the use of level 3 biosafety hoods is recommended (Ampel, 2010; Soubolle, 2007). Genus confirmation from the culture is detected by means of exoantigens and through the use of a genetic probe (Accuprobe, GenProbe, San Diego, CA, USA). Characterization of *C. immitis* and *C. posadasii* species is carried out employing molecular methods. Serology is a useful auxiliary method for diagnosis and prognosis of the disease; however, the sensitivity of this test is not ideal. Determination of coccidioidal galactomannan is commercially available for detecting the antigen in urine, this tool is highly sensitive and it is recommended in patients with more severe forms of coccidioidomycosis (Durkin, et al., 2008). Molecular methods had been proved useful to *Coccidioides* identification. Darko Vucicevic considered PCR successful when culture is negative. However, few laboratories can provide these techniques (Darko, 2010; De Aguilar et al., 2007; Galgiani et al., 2011).

7. Conclusions

Coccidioides is a fungal pathogen that causes diseases ranging from mild to severe infection, the knowledge of their parasitic cycle, virulence factors and host immune response are important for understanding its pathogenesis and effect the accurate diagnosis. The subregistry of this mycosis is closely linked to clinical and laboratory diagnosis. Laboratory diagnosis is very important, since coccidioidomycosis may be confused with pulmonary tuberculosis or other lung diseases.

Typical parasitic forms of *coccidioides* *ssp* are spherules and spherules/endospores, however, other parasitic structures have been reported. It is important identify the diverse parasitic morphological forms of *Coccidioides* spp., they are spherules, spherules/endospores and mycelial forms. Mycelial forms are pleomorphic cells and can present as: hyphae forming ovoid and spherical cells, pleomorphic cells producing septate hyphae, chain of ovoid cells, arthroconidia, and septate hyphae forming a barrel-shaped cells. We think different parasitic forms of *Coccidioides* spp. are present in function of:

- Virulence factors
 - Quorum- sensing.- protein kinases sensing host conditions and dimorphism is triggered by exposure to temperature, pH, and CO₂ concentration, so the fungus leads differentiation and dimorphism: Parasitic forms, Spherules and spherules/endospores
 - Tissue damage with inflammatory infiltrate.- urease activity of *Coccidioides in vivo* can contribute to the generation of an alkaline microenvironment near the fungal pathogen's surface, as well as stimulation of the host inflammatory and exacerbation of the severity of coccidioidal infection, lead to generate apoptosis, cavity lesion with relation O₂/CO₂ exchange inefficient: Parasitic forms, spherules/endospores and mycelial forms
- Clinical form
 - Chronic pulmonary coccidioidomycosis, central nervous system coccidioidomycosis, chronic and cavitary pulmonary coccidioidomycosis (>8 months), ventriculoperitoneal shunt and fungal ball: Parasitic forms, spherules, spherules/endospores and mycelial forms.
- Comorbidity
 - Diabetes mellitus type 2 and chronic pulmonary infection: Parasitic forms spherules, spherules/endospores and mycelial forms
- Cellular immune response
 - CMI responses in coccidioidomycosis are probably under genetic control. Persons with Asian, Afro-american, or Hispanic (possibly HLA) ancestry are at higher risk for developing disseminated coccidioidomycosis than those with Caucasian ancestry: Parasitic forms, spherules and spherules/endospores and mycelial forms.
 - Granulomas are present, with abundant Langhans cells, lymphocytes, and monocytes, and scant eosinophils, plasmocytes, and epithelioid cells surrounding the parasitic fungal: Parasitic forms, spherules and spherules/endospores.

Based on microscopic images of patient specimens and on observations of mycelial structures in our studies, as well as those reported by various authors in coccidioidal infection in the lung and central nervous system, we propose that mycelial forms should be incorporated into the parasitic phase of the *Coccidioides* spp.

8. Acknowledgements

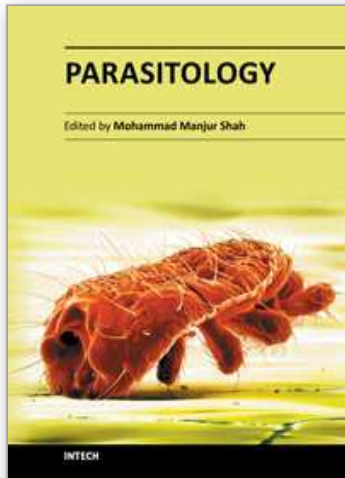
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Parasitology is an established discipline that covers a wide area of subjects, ranging from the basics (study of life cycle, ecology, epidemiology, taxonomy, biodiversity, etc) to the advanced and applied aspects (human and animal related, although control aspect remains the most important task). There is a great scarcity in the amount of available literature that is freely accessible to anyone interested in the subject. This book was conceptualized with this in mind. The entire book is based on the findings of various studies performed by different authors, comprising reviews and original scientific papers. I hope this book will be helpful to diverse audiences like biologists, zoologists, nematologists, parasitologists, microbiologists, medical doctors, pathologists as well as the molecular biologists, by providing them with a better understanding of the subject.

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University Campus STeP Ri
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InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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