Paracoccidioidomycosis

By

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Description:

- Paracoccidioidomycosis is a fungal infection endemic to South and Central America, most notably Brazil, Argentina, Colombia, and Venezuela (see the image below). It is caused by the thermally dimorphic fungi *Paracoccidioides brasiliensis* and *Paracoccidioides lutzii*.[1] Although the infection is usually subclinical, the fungus can also cause chronic and severe disease.

- History
- *Paracoccidioides brasiliensis* was first discovered by Adolfo Lutz in 1908 in Brazil.[5] Although Lutz did not suggest a name for the disease caused by this fungus, he made note of structures he called “pseudococcidica” together with mycelium in cultures grown at 25 °C.[5] In 1912, Alfonse Splendore[6]
- Finally in 1930, Floriano de Almeida created the genus *Paracoccidioides* to accommodate the species, noting its distinction from *Coccidioides immitis*.[5]

Etiology

Risk factors for paracoccidioidomycosis include the following [8] :

- Agricultural work (especially coffee growers in Brazil) - The fungi are believed to reside in soil
- Malnutrition
- Smoking
- Alcoholism
- Immunodeficiency - Eg, from HIV/AIDS

Dimorphism

- The mycelial form of *P. brasiliensis* can be converted to the yeast form *in vitro* by growth on brain heart infusion agar or blood-glucose-cysteine agar when incubated for 10–20 days at 37 °C.[9] Under these conditions, hyphal cells either die or convert to transitional forms measuring 6–30 μm in diameter, which ultimately detach or remain on the hyphal cells, yielding buds.[9]
- New buds develop mesosomes and become multinucleated.[9]
- In contrast, yeast-like cultures can be converted to the mycelial form by reducing the incubation temperature from 37 to 25 °C.[12]

Epidemiology

- *P. brasiliensis* causes a disease known as paracoccidioidomycosis characterized by slow, progressive granulomatous changes in the head mucosa, notably the nose and sinuses or the skin.
- Uncommonly, the disease affects the lymphatic system, the central nervous system, the gastrointestinal tract, or the skeletal system.[9]
- Due to the high proportion of cases affecting the oral mucosa, these tissues were originally thought to be the primary route of entry of fungus.[2] However, strong evidence now indicates the respiratory tract is the chief point of entry[9] and *P. brasiliensis* lung lesions occur in nearly a third of progressive cases

Clinical manifestations

- *P. brasiliensis* causes mucous membrane ulceration of the mouth and nose with spreading through the lymphatic system.
- A hypothesis for entry of the fungus to the body is through periodontal membrane.[28][29]
- The route of infection is assumed to be inhalation following which the infective propagule gives rise to the distinctive multipolar budding yeast forms in the lung resembling a "ship's wheel" seen in histological sections.[8][30]
- Both immunologically normal and compromised people are at risk for infection.[8]
- The lungs, lymph nodes, and mucous membrane of the mouth are the most frequently infected tissues.[9] The pathological features of paracoccidioidomycosis are similar to those seen in coccidioidomycosis and blastomycosis.[31] However, in the former, the lesions first appear in the lymphoid tissue and then extend to mucous membranes,[31] producing localized to diffusive tissue necrosis of the lymph nodes.[31]

- The 2 general clinical categories of paracoccidioidomycosis are (1) an acute/subacute form (juvenile paracoccidioidomycosis) and (2) a chronic form (adult paracoccidioidomycosis).
- Signs and symptoms
- *Juvenile form*
- Lymphadenopathy and hepatosplenomegaly
- Systemic symptoms - Include fever, weight loss, and malaise; present in most patients.
- Symptoms related to lymph node enlargement, suppuration, and sinus tract formation
- Multiple skin lesions
- Mucous membrane and respiratory symptoms - These are unusual

- *Adult form*
- Primary lung infection - Cough (productive or nonproductive), dyspnea, malaise, fever, and weight loss are common symptoms
- Chronic pulmonary sequelae - Develop in one third of patients; can include pulmonary fibrosis, bullae, and emphysematous changes that can contribute to pulmonary hypertension and cor pulmonale in 5% of cases.
- Mucous membrane involvement - Occurs in 50% of patients with acute pulmonary infection; includes laryngeal and pharyngeal lesions
- Oral lesions - May be associated with nasal and pharyngeal ulcers (Aguiar-Pupo stomatitis) and with mandibular or cervical lymph node enlargement
- Cutaneous lesions - Caused by hematologic dissemination from the lungs; occur in 25% of patients; crusted papules, ulcers, nodules, plaques, and verrucous lesions are typical
- Lymphadenopathy - Most common in the cervical region

Differential diagnosis

- The cutaneous lesions of paracoccidioidomycosis may be mis-diagnosed as histoplasmosis, sporotrichosis, leishmaniasis, syphilis or psoriasis.
- Mucocutaneous leishmaniasis is endemic in the same regions as paracoccidioidomycosis and can cause similar lesions. However, nasal lesions are seldom seen in paracoccidioidomycosis.
- Patients with histoplasmosis may also present with oropharyngeal and laryngeal ulcers that can bedifferentiated from paracoccidioidomycosis by their elevated borders and the absence of the typical fine granulation surface.
- Laryngeal tuberculosis is difficult to distinguish from paracoccidioidomycosis.
- The differential diagnosis of oropharyngeal and laryngeal lesions also includes squamous cell carcinoma and lymphoma.

Diagnosis

- **Microscopy**
- Microscopic examination of potassium hydroxide preparations of sputum, bronchoalveolar lavage (BAL) fluid, exudates, pus from draining lymph nodes and other clinical material can permit the diagnosis of paracoccidioidomycosis if the characteristic large, oval to round yeast cells with translucent walls and multiple peripheral buds are seen.
- Sometimes, however, yeast cells with single buds or small yeast cells may be seen that cannot be differentiated from other fungal pathogens, such as *Histoplasma capsulatum*, *Blastomyces dermatitidis*, or *Sporothrix schenckii*, or capsule-deficient *Cryptococcus* species. Histopathological examination of stained biopsy sections is usually diagnostic: *P. brasiliensis* cells will often be found enclosed within granulomas.

Culture

- The definitive diagnosis of paracoccidioidomycosis depends on isolation of the fungus in culture. Mould colonies can be obtained after incubation at 25–30◦C for 3–4 weeks on glucose peptone (Sabouraud's dextrose) agar supplemented with cycloheximide (actidione). The organism grows slowly and cultures should be retained for 4–6 weeks

Serological tests

- Serological tests are useful for the rapid presumptive diagnosis of paracoccidioidomycosis, particularly in cases of untreated disease. These tests may also be used to monitor the response to treatment.
- The immunodiffusion test is performed with mycelial-phase culture filtrate antigen. It is highly specific and is positive in 65–100% of patients with paracoccidioidomycosis. Although cross-reactions can occur in patients with histoplasmosis, these are uncommon.
- The complement fixation (CF) test, performed with yeast-phase culture-filtrate antigen, is positive in 70–100% of patients, higher titres being obtained in those with more severe disease.
- A CF titre of at least 1:8 is considered presumptive evidence of paracoccidioidomycosis.

Colonial Appearance

at 30°C on glucose peptone agar

Diameter	5–10 mm in one week
Topography	domed, folded or tufted
Texture	glabrous to floccose, becoming felt-like or velvety
Colour	white to buff
Reverse	yellow-brown

at 37°C

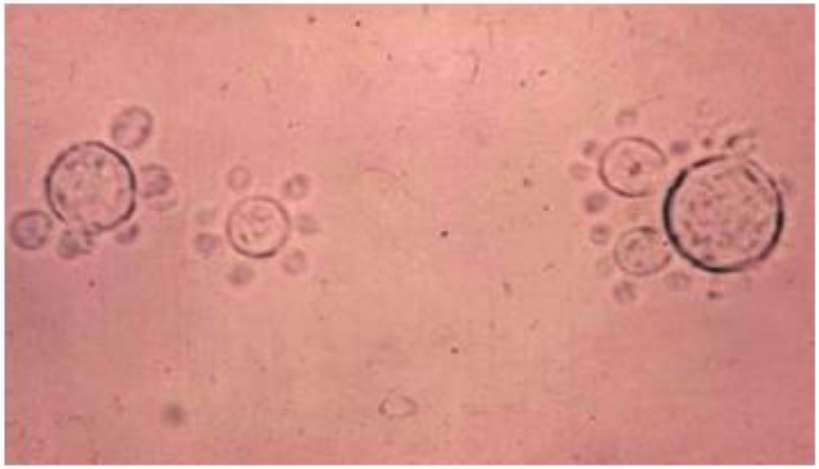
Topography	much-folded, heaped yeast-like colonies
Texture	rough
Colour	white to cream
Reverse	non-pigmented

Microscopic Appearance

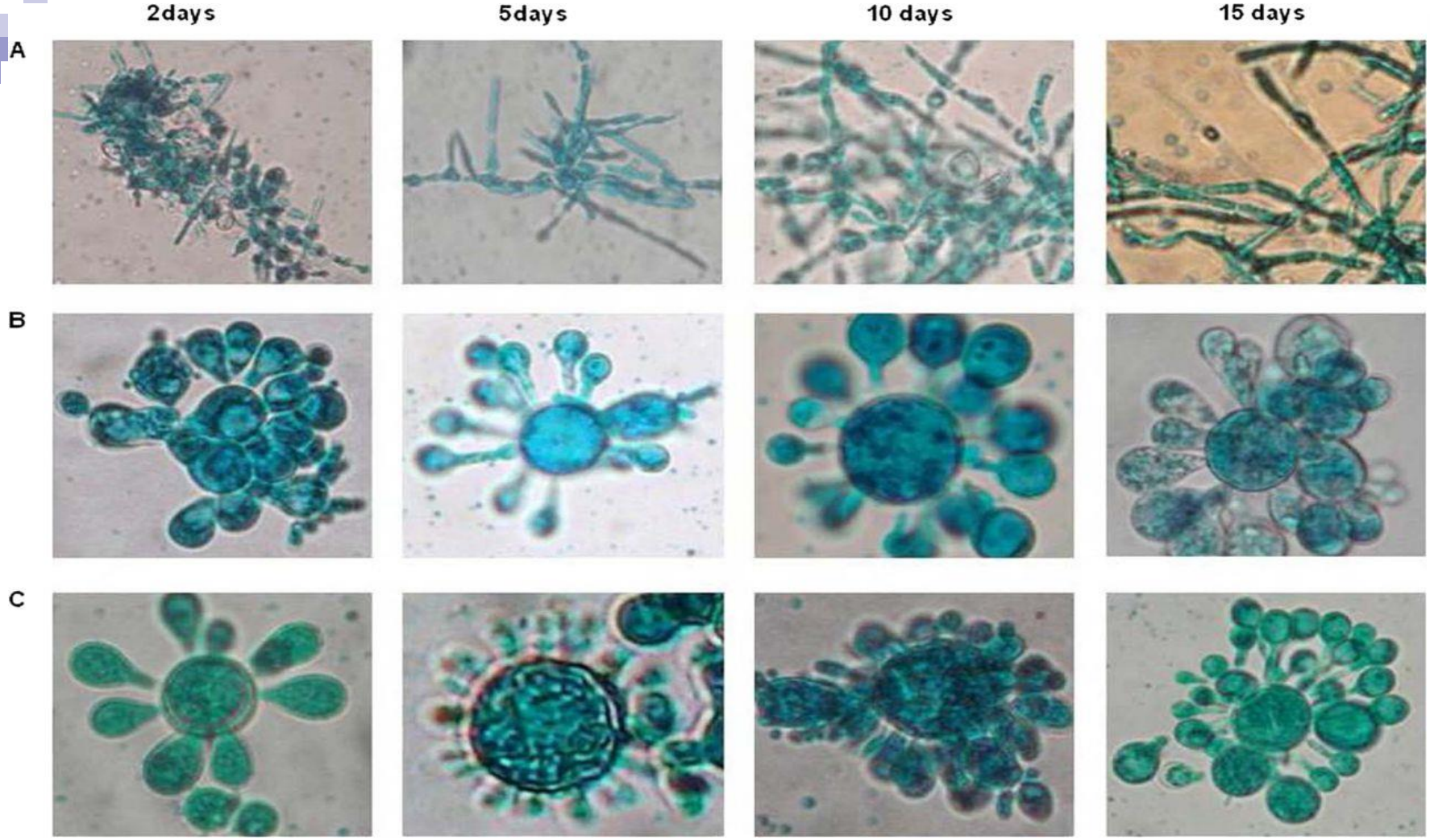
at 30°C

Predominant features	hyphae only, with occasional chlamydospores;
Conidia	sporulation poor on glucose peptone agar; on yeast extract agar pear-shaped to oval aleuriospores are produced directly on the sides of the hyphae or on short conidiophores; thick-walled, square to rectangular arthrospores may also be produced

Culture of *Paracoccidioides brasiliensis* mycelial phase (front).



Microscopy of *P. brasiliensis* yeast phase showing multiple budding.



P. brasiliensis morphology at 37°C after 2, 5, 10, and 15 days of incubation. Cultures were prepared with 0.01 ml of the fungus and 0.001 ml of lactophenol solution and observed by optical microscopy at ×400. (A) Yeast–mycelium transition of the Penguin *P. brasiliensis* isolate cultivated in RPMI 1640 medium supplemented with 2% glucose; (B) yeast morphology of the Pb10 *P. brasiliensis* isolate cultivated in MMH medium; (C) morphology of the Pb9 *P. brasiliensis* isolate cultivated in YPD medium (yeast positive control).

Antigen detection tests

- Tests for the detection of *P. brasiliensis* antigen in serum, urine, cerebrospinal fluid and BAL fluid appear to be useful, particularly in immunocompromised patients.
- They may also be helpful in evaluating the response to treatment. No validated commercial tests are currently available.
- Antigen tests for diagnosis of blastomycosis and histoplasmosis have been reported to give false-positive reactions with urine and other body fluid samples from patients with paracoccidioidomycosis.

Treatments

- Sulfonamides are the traditional remedies to paracoccidiodomycosis. They were introduced by Oliveira Ribeiro and used for more than 50 years with good results. The most-used sulfa drugs in this infection are sulfadimethoxime, sulfadiazine, and co-trimoxazole. This treatment is generally safe, but several adverse effects can appear, the most severe of which are the Stevens-Johnson syndrome and agranulocytosis. Similarly to tuberculosis treatment, it must be continued for up to three years to eradicate the fungus, and relapse and treatment failures are not unusual.
- Antifungal drugs such as amphotericin B or itraconazole and ketoconazole are more effective in clearing the infection, but are limited by their cost when compared with sulfonamides.

Thank you