REVIEW ARTICLE

# Paracoccidioidomycosis disease (Lutz-Splendore-Almeida) – clinical manifestations

## *Paracoccidioidomicose (doença de Lutz-Splendore-Almeida) – manifestações clínicas*

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### ABSTRACT

Paracoccidioidomycosis has polymorphic clinical features with lesions located in the skin and mucous membranes, as well as involvement of various organs and systems, as is potentially capable of causing death and serious sequelae. It should be included in the differential diagnosis of granulomatous diseases in endemic areas, including Brazil, so that it is recognized early, for more convenient treatment as to prevent progression with sequelae or premature death.

**Key words:** Paracoccidioidomycosis; Mycosis; Paracoccidioides.

### RESUMO

*A paracoccidioidomicose possui clínica polimórfica, com manifestações localizadas em pele e mucosas até comprometimento de vários órgãos e sistemas, potencialmente capaz de provocar sequelas graves e morte. Deve ser incluída no diagnóstico diferencial das doenças granulomatosas, em áreas endêmicas, como ocorre no Brasil, para que seja reconhecida com precocidade, tratada convenientemente e evitada sua evolução para sequelas e morte prematura.*

***Palavras-chave:*** *Paracoccidioidomicose; Micose; Paracoccidioides.*

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## INTRODUCTION

The importance of paracoccidioidomycosis (PCM) relates to social and economic costs not only derived from the active disease in individuals in the most productive phase of their lives, but from sequelae, which represent reasons for work incapacitation. The usual evolution of paracoccidioidomycosis without specific therapeutic intervention is to the death.[1,2]

This disease constitutes one of the neglected diseases by all funding agencies for its study. Despite of being endemic in Brazil, it is not always considered in the differential diagnosis of diseases that are localized with lymphadenomegaly, infiltration, and mucocutaneous vegetative-nodules, pulmonary fibrosis; or systemic with different involvement, from adrenal insufficiency to severe neurological.[3,4]

Whenever the differential diagnosis includes tuberculosis and lymphoma, the possibility of PCM must be considered, which means valuing the disease's clinical epidemiology (geography of diseases).[5-17]

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## CLINICAL MANIFESTATIONS

PCM can manifest itself in different forms: acute-sub-acute, regressive, evolutionary, or chronic and slowly progressive. Several organs and systems can be affected (Table 1). The characterization of its various forms is made as a function of the patient's age; illness form of presentation and duration; clinical manifestations; associated diseases and aggravating factors, general and nutritional state, thorax teleradiography, response to the cutaneous test with paracoccidioidin, and serum levels of antibodies anti P. brasiliensis (double immunodiffusion reaction in agar gel).[11, 14,16-27]

**Table 1** - Classification of the clinical forms of paracoccidioidomycosis

| |
|---|
| 1. Paracoccidioidomycosis infection |
| 2. Paracoccidioidomycosis disease |
| 2.1. Regressive form |
| 2.2. Progressive form |
| 2.2.1. Acute or sub-acute (youth form), with: |
| a) Superficial adenomegaly (moderate and severe) |
| b) Superficial adenomegaly (moderate and severe) |
| c) Bone involvement (severe) |
| d) Other clinical manifestations (moderate or severe) |
| 2.2.2. Chronic (adult form): light, moderate, severe |
| 2.2.3. With sequelae |

Therefore, the host-fungus interaction relates to the type and intensity of the immune response, virulence, and fungus inhalation, which determines how the initial infection may present varying courses, either for the acute-sub-acute or chronic and slowly progressive, or, more commonly, be resolved but leaving a latent focus that can reactivate (endogenous reactivation) and subsequently generate the chronic form (Table 2).[16-25]

### Regressive form

The host initial invasion by Paracoccidioidis is generally asymptomatic with possible varied clinical manifestations, from discrete to nonspecific, such as from asthenia, anorexia, evening febricula, to febrile syndrome, cough, hemoptoic, and chest pain. It resembles tuberculosis in its phase of primary complex, and constitutes a most benign form of PCM.

Its total regression can coexist with the presence of the fungus, as the quiescent form, in lymph node or lung. It can leave the skin reaction to paracoccidioidin in the memory.[11,13-16]

### Acute -Sub-acute form

From the location of the initial invasion or quiescent focus, the Paracoccidioidis may spread via bronchogenic , lymphatic, or hematogenous, and in 34% of cases, it is manifested as a disease of systemic acute sub-acute evolution with involvement of mononuclear-phagocyte system.[28-34]

It preferentially affects children, adolescents, and young adults up to 30 years old, becoming the youth age form and considered of moderate to intense gravity.[28-34]

The evolution of PCM is usually of short duration, rapidly progressive, debilitating, with the development of: asthenia, anorexia, intense weight loss capable of causing cachexia; diffuse lymphadenomegaly, with necrosis and suppuration, expressing itself as cutaneous or intra-abdominal abscesses, cutaneous fistulas with drainage of purulent material, and cutaneous areas of extensive destruction (strophulus); osteomyelitis; intestinal ulcerations; hepatosplenomegaly, and hypo or aplasia of bone marrow.

**Table 2** - Classification according to the seriousness of the acute, sub-acute, and chronic forms of paracoccidioidomycosis

| Forms | | Clinical alterations | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Lymphnodes | H-E | General state | Lungs and/ or skin | Other organs | PCD | Ac |
| Acute-sub-acute | M | Inflammatory, non-suppurative | P/A | P/A | A | A | 35 mm | B/M |
| | G | Tumoral or suppurative | P | P | P | P | 5 mm | E |
| Chronic | M | Inflammatory, non-suppurative | P/A | P/A | A/P | A | ≥10 mm | B |
| | G | Tumoral or suppurative | P | P | P | P | <5 mm | E |

M: moderate, G: severe; P: present; A: absent; E: high; B: low; M: moderate; L: lymphadenomegaly; H-E: hepatosplenomegaly; PCD: reaction to paracoccidioidin; Ac: serum levels of antibodies by immunodiffusion.

The intra-abdominal lymphadenomegaly can form bulky masses that compress different structures and determine various clinical syndromes such as biliary obstruction (cholestasis), pancreatic duct (pancreatitis), thoracic duct (chylous ascites), ureters (pyelonephritis, acute renal failure), and intestines (malabsorption syndrome, acute abdomen). Mucosal (20%) and lung (10%) alterations are infrequent. There may be increased body temperature, which represents a sign of seriousness. Pulmonary involvement, contrary to what occurs in the chronic form, is rare.

The acute or sub-acute clinical manifestations can also occur in adults, along with lymphadenomegalies that disinfect, intense eosinophilia, and serum precipitating antibodies (double immunodiffusion reaction) at higher levels than those observed in the chronic form.[5-34]

## Chronic form

It generally affects people after the fourth decade of life, slowly and progressively, from the site of Paracoccidioidis invasion or its quiescent focus (latent), which can reactivate later (endogenous reactivation), lasting more than six months.[11, 14, 16, 35-81]

Its clinical manifestations are variable, from light to even negligible to moderate and severe, with progressive impairment of the general condition with significant weight loss. The most common clinical alterations arise from the involvement of the skin, mucous membranes of the upper respiratory tract and mouth, lymph nodes, and lungs.

The main clinical manifestations are: anterior and posterior cervical lymphadenomegalies (79%), submandibular, submentovertex, supraclavicular, axillary, inguinal, and intra-abdominal (expressed through acute abdomen, tumor masses, jaundice by biliary extra-hepatic compression, chylous ascites, or intestinal malabsorption); weight loss (72%); asthenia/hipodinamia (65%); mucocutaneous paleness (62%); fever (51%); cough (50%); dysphonia, odynophagia, dysphagia, oropharyngeal ardor, nasal obstruction, epistaxis; vegetative ulcers in the mouth, throat, and nose.

The cutaneous manifestations present varied forms, with single or multiple lesions, infiltrative, vegetative verruciform, expressed primarily as papules, plaques, nodules, vegetative, or ulcers. The presence of vegetative lesions is frequent, ulcerated and painless in the oral and palate cavities (Figure 1), tongue (Figure 2), gum and lip (Figures 3 and 4), and nasal, in the pharynx, and larynx, including with satellite adenopathy (Figures 4, 5, and 6) (cervical, axillary, and inguinal). The consistency of lesions is, usually, hardened due to fibrosis in the chronic granulomatous process. The main locations are the face, upper and lower limbs, and trunk. It can evolve with secondary bacterial infections. Purely infiltrative lesions are rare with sarcoid pattern, usually with few fungi observed in microscopy, which makes the diagnosis difficult.[8-23]

**Figure 1** - Moriforme lesion in the patient's palate with multifocal chronic form. Patient assisted at the PCM Reference Center in the General Hospital from UFMG.

**Figure 2** - Ulcer and painful lesion in tongue with sialorrhea. Patient assisted at the PCM Reference Center in the General Hospital from UFMG.

Lymphadenomegaly (Figures 5 and 6) can present inflammatory non-suppurative features (less than 2 cm in diameter), tumoral (more than 2 cm in diameter), and suppurative (floating or fistulization).[11-14, 16-23]

**Figure 3** - Two oral lesions, one in the lower lip and one in the gum, with tooth loss; ulcerated, hardened, granulomatous and elevated edges. Patient assisted at the PCM Reference Center in the General Hospital from UFMG.

**Figure 4** - Skin lesions in erythematous crusted papules and nodules on the face, in the multifocal chronic form, before (A) and after (B) treatment. Patient assisted at the PCM Reference Center in the General Hospital from UFMG.

**Figure 5** - Cervical lymphadenomegalies and hardened papules in the malar region in the multifocal chronic form. Patient assisted at the PCM Reference Center in the General Hospital from UFMG.

**Figure 6** - Inguinal bilateral lymphadenomegaly in patient with the PCM multifocal chronic form. Patient assisted at the PCM Reference Center in the General Hospital from UFMG.

**Figure 7** - Skin lesions in the multifocal chronic form. Hardened nodules with elevated edges in the trunk (A) and legs (B). Erythematous papules and plaques, crusted and diffused on the face (C). Ulcerated lesion on the glands (D). Patient assisted at the PCM Reference Center in the General Hospital from UFMG.

The oropharynx (Figure 1) can present hyperemia, edema, and a moriforme aspect, infiltration or vegetating, or even ulcerated, teeth can be softened, and drilling of the hard palate can be observed.

Respiratory alterations are also of varying intensity, from mild to severe, with the physical examination of the thorax negligible in most patients, characterized by clinical-radiological semiological dissociation in which light symptoms contrasts with intense radiological alterations in the pleuropulmonary fields.

Adrenals, digestive systems, bones, and central nervous systems (CNS) alterations can still be observed.

The involvement of the adrenal occurs in 50% of cases and can determine medullar insufficiency, similar to tuberculosis lesions, as Addison's syndrome, evolving from an insidious form with asthenia, anorexia, weight loss, postural hypotension, fainting, dizziness, hyperpigmentation of the skin and mucous membranes, nausea and vomiting, reduced sexual potency and libido, and blood eosinophilia. The adrenal gland does not always retrieve its function after the specific treatment for PCM.

The CNS can be affected in its parenchyma or in the meninges in almost 25% of the cases. It can evolve as a pseudotumor or meningeal form (diffuse or localized lesions, with more frequent involvement of the base of the skull). Its evolution is dragged and resembles the tuberculous meningitis, with which it makes for a differential diagnosis.[77-81] The parenchymal form is associated with: progressive intracranial hypertension installation, signs of focal dysfunction, motor or sensory, of language, and ataxia alterations. It can be associated to focal or generalized convulsions and papilla edema. Spinal cord alterations may lead to paresthesia, anesthesia, and lower limb weakness, urinary and fecal incontinence and neurogenic bladder, with episodes of urinary retention.

Digestive alterations are varied and non-specific in most cases, presenting itself as a tumoral mass, with malabsorption and chronic diarrhea.

Bone alterations (20%) can be asymptomatic and revealed by lytic radiological lesions without perifocal reaction, with possible periosteal involvement, light and with sharp edges. Bone marrow is engaged mainly in the form of acute or sub-acute and rarely in the chronic forms, manifesting itself in the peripheral blood in combination with anemia, leukopenia, and thrombocytopenia.[11, 14, 16, 28-34, 39-76]

The least common manifestations are genitourinary (Figure 7 D), characterized by the involvement of the epididymis, testis, and prostate, in which complaints of dysuria, alguria, or hematuria dominate; in the thyroid; and eyes, which can be unilaterally altered, with lesions on the eyelids (papule, vegetation, ulcer), conjunctiva, anterior uvea, or choroid.[35-81]

The average time until death in patients who evolved spontaneously with PCM is from five to eight months, comparable to visceral leishmaniasis and aggressive malign neoplasias.[1, 2, 6, 7, 11-16]

The forms with sequelae are frequent; the lung forms standout with the predominance of fibrosis and emphysema; Addison's syndrome; neurological lesions; and disfiguring skin forms (Table 2).[35-81]

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