Paracoccidioidomycosis: epidemiological, clinical, diagnostic and treatment up-dating*

Paracoccidioidomicose: atualização epidemiológica, clínica, diagnóstica e terapêutica

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Abstract: Paracoccidioidomycosis is an acute - to chronic systemic mycosis caused by fungi of the genus Paracoccidioides. Due to its frequent tegument clinical expression, paracoccidioidomycosis is an important disease for dermatologists, who must be up-to-date about it. This article focuses on recent epidemiological data and discusses the new insights coming from molecular studies, as well as those related to clinical, diagnostic and therapeutic aspects. In the latter section, we give particular attention to the guideline on paracoccidioidomycosis organized by specialists in this subject.
Keywords: Clinical evolution; Epidemiology; Paracoccidioidomycosis; Therapeutics; Treatment outcome

Resumo: Paracoccidioidomicose é micose sistêmica de evolução aguda a crônica e causada por espécies do gênero Paracoccidioides. Pela frequente expressão clinica tegumentar da paracoccidioidomicose os dermatologistas têm que se manter atualizados em relação à enfermidade. O presente trabalho tem enfoque na atualização epidemiológica, discutindo os avanços na área propiciados pela micológica molecular, nos aspectos clínicos incluindo avanços diagnósticos e se completa com a discussão terapêutica e nesse item com foco nos dados do consenso em paracoccidioidomicose elaborado por especialistas no tema.
Palavras-chave: Epidemiologia; Evolução clínica; Paracoccidioidomicose; Resultado de tratamento; Terapêutica

INTRODUCTION

Paracoccidioidomycosis (PCM) was a recurrent theme on the Continued Medical Education in Dermatology section (EMC-D) between 1998 and 2003. A decade after the last publications, it is once more necessary to open space for a disease that is still very prevalent and of long tradition and history in the field of Dermatology. The focuses will be limited to the epidemiological, clinical and therapeutic up-dates.

EPIDEMIOLOGY

The genus *Paracoccidioides* belongs to Phylum Ascomicota, Class Euromycetes, Order Onygenales and Family Ajellomycetaceae (Onygenaceae), the same as *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immites* and *Coccidioides posadasii*, with which it shares the same thermally dimorphic character, infecting forms (arthroconidia and mycelium) and a geographically restricted habitat.[1]

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Molecular methods used to study genus *Paracoccidioides* promoted significant advances on the ecologic knowledge of this agent. For instance, *P.brasiliensis* was detected in different animal species besides the previously described *Dasypus novemcinctus* (nine-banded armadillo), such as: *D. septemcinctus* (seven-banded armadillo), *Procyon cancrivorus* (raccoon), *Cavia aperea* (Brazilian guinea pig), *Sphiggurus spinosus* (Spiny Tree Porcupine), *Gallictis vittata* (ferret) e *Eira barbara* (tayra).[2] A study was published in 2011, confirming that paracoccidioidomycosis, as a disease, is not limited to the human species. The study described the second case of canine PCM, again in a Dobermann breed dog and once more showing the prevalence of lymph node involvement, with vast histologic, mycological and molecular evidences.[3] Treatment with Itraconazole provided cure in 24 months.[3] Molecular methods were equally primordial for the detection of *P.brasiliensis* in the soil samples collected inside and around armadillos' burrows, demonstrating definitely that infecting samples exist in the soil of areas that are the habitat of these fungi.[4] The most revolutionary contribution, however, was the molecular identification of cryptic species, hidden inside genus *Paracoccidioides.* This discover showed the genetic coherence of the several phenotypes exhibited by this fungus, either in a culture medium or in experiments, demonstrating the previously known diversity expressed by: mycelium colony aspect, distinctive production of conidia, variable microscopic aspect of yeast cells, virulence and thermal tolerance and even distinct clinical behavior.[1] Following this line of thought, Matute *et al*. (2006), used genetic sequencing of samples cultivated in Brazil, Venezuela and Colombia, to propose the existence of possibly three new species, temporarily denominated PS2 (prevalent in Brazil and Venezuela), PS3 (restricted to Colombia) and S1 of an ampler distribution.[5,6] Such findings were corroborated by several authors. In 2009, Teixeira *et al*.[7] based on genetic sequencing studies of 82 fungal isolates and phylogenetic studies of 40 isolates, proposed the identification of yet another species, previously denominated Pb-01. This species exhibited a clear divergence in terms of morphology and sequencing from the aforementioned S1, Ps2 and PS3. In this opportunity they suggested to name it *Paracoccidioides lutzii* in tribute to Adolpho Lutz (1855-1940).[7] Recently, Theodoro *et al*. (2012) built a map that expresses the predominance (or even exclusiveness) of each species of genus *Paracoccidioides* in South America. The authors used the snp (*single nucleotide polymorphisms*) technique as molecular marker along with morphologic data applied to 63 isolates from patients of several countries in South America (10 of which obtained from cutaneous lesions of patients from the endemic region of Botucatu-SP), as well as isolates from armadillos from various geographic areas. This map demonstrated that (until the present): species *P.lutzii* are more prevalent in the central areas of Brazil, S1 is vastly distributed and PS3 seems to be exclusively present in Colombia (Figure 1).[8] In 2012, the species *P.lutzii* was identified as etiologic agent in 2 cases diagnosed in the south region of the State of Pará, with confirmation of the species through serologic and molecular studies.[9]

The future nomenclature, that might take effect, refers to the paracoccidioidomycosis causal agent as belonging to the "complex" *Paracoccidioides brasiliensis* or to the species *Paracoccidioides* spp. From the practical point-of-view, there is still the need to demonstrate that the different species of the *Paracoccidioides* complex produce distinct clinical profiles with regards to its severity, tropism to specific organs or systems, and varied susceptibility to different drugs (proved by diverging MIC - minimum inhibitory concentration- for the same drug or for a battery of tests with medicaments known to be effective against paracoccidioidomycosis). If these conjectures were to be proved true, we might anticipate that the therapeutic choice for the treatment of paracoccidioidomycosis may become more complex, but also more effective.

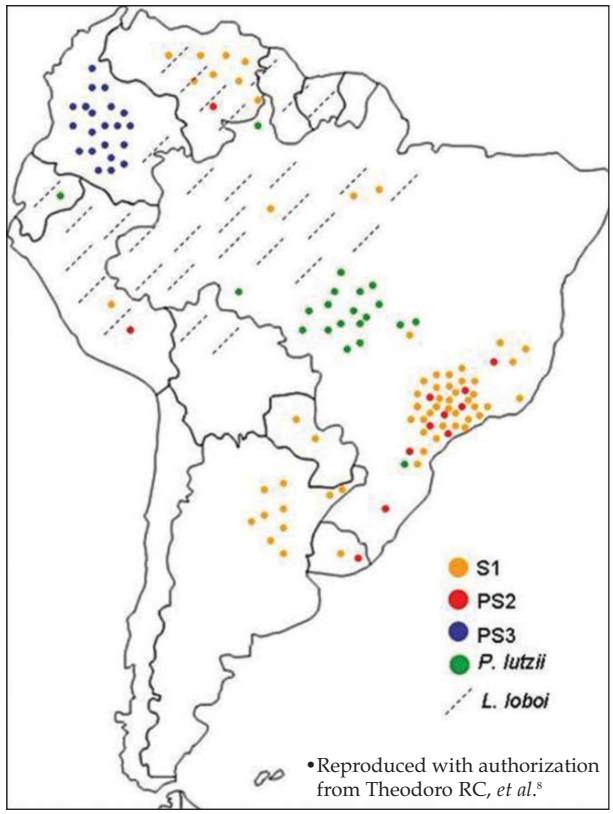

Figure 1: Geographic distribution of species of genus Paracoccidioides and species Lacazia loboi

Regarding incidence/prevalence of the disease, we highlight the report of autochthonous cases from the State of Ceará and the elevated number of cases in certain areas of the State of Maranhão (estimated as high as 10.8 cases/100,000 inhabitants in the period of 1997 to 2007), demonstrating that humid areas of the Northeast part of the country may also be considered endemic.[10,11] Of notice, also, from a clinic-epidemiologic standpoint is the situation observed at Foz do Iguaçu, in the State of Paraná (Loth *et al*., 2011), where 102 cases were diagnosed in a period of 18 months.[12] Besides the high incidence of the disease in this report, it is of special notice the elevated percentage of co-infection with tuberculosis (28,4% of all cases) and HIV (4,9%) and the 14,7% rate of death among the population studied.[12] These facts demonstrate, once more, the potential severity of paracoccidioidomycosis and the possibility of co-infections that interfere with the treatment and prognosis. A milestone as a well-conducted clinic-epidemiologic study, the publication of a series of 1,000 cases of paracoccidioidomycosis diagnosed in the region of Ribeirão Preto-SP (Belissimo-Rodrigues *et al*., 2011), presented data collected from 1960 to 1999, that showed: an estimated incidence of 1.6 to 3.7 new cases/100,000 inhabitants in the area; male/female rates of 6:1; a predominance of the adult chronic form (74.6%) and of patients with history of rural life (93.5%), high rates of smoking (64.7%) and heavy drinking (37.2%), co-infection with tuberculosis (8.3%) and HIV (4.2%).[13] These data reflect much of the knowledge already established in terms of clinic epidemiology of paracoccidioidomycosis, but this time, drawn from a single institution with a record number of cases.

Another study, from the same institution, compared data from 53 patients co-infected with paracoccidioidomycosis and HIV versus 106 cases without HIV co-infection. The results demonstrated that the co-infected were younger (33.5 years x 45.3), less likely to have rural activities either at the time of the diagnosis (27.5% x 59.4%) or previously (64.3% x 95.5%) and that they had a higher rate of associated hepatic disease, particularly infection with hepatitis C virus (15.5% x 3.8%). There was not any difference between co-infected and non co-infected regarding: rates of male-female incidence; smoking (79.2% x 84%); alcohol intake (58.5% x 64.2%) or co-infection with tuberculosis (9.4% x 5.7%).

From the clinic point-of-view, patients with HIV co-infection presented with significantly greater rates of fever (95.6% x 50.6%), lymphadenomegaly (80% x 50.6%), hepatomegaly (64.2% x 19.1%), splenomegaly (22.6% x 6.6%), cutaneous lesions (66.7% x 45.5%), but smaller rates of mucosal lesions (20.8% x 50.9%) and hoarseness (1.9% x 23.6%). It should be noticed that mucosal involvement and hoarseness, classic symptoms in the chronic form of the disease, were more frequent among patients without HIV co-infection. This fact, associated to the higher rates of the monocyte-macrophage system involvement in the co-infected patients, demonstrates the prevalence of an acute-sub acute profile of disease amongst this group. Other parameters compared between co-infected and non co-infected did not achieve statistic significance, such as: presence of lung disease (84.8% x 69.1), SNC involvement (3.8% x 5.7%), bone lesions (5.7% x 0.9%) and adrenal insufficiency (0% x 1.9%).[14] It must be highlighted that, the occurrence of paracoccidioidomycosis in patients with HIV/aids co-infection is linked to severe immunosuppression, and 83.7% of the cases studied by Marejon *et al*. had T CD4+ lymphocyte counts < 200 cells/mm^3. This same department also published data regarding the serologic anti-*P.brasiliensis* response in patients co-infected with HIV.[15] The authors used 3 methods (double-agar gel immunodiffusion -IDD; counter immunoelectrophoresis - CIEF and ELISA) to study a group of 40 co-infected patients and another of 75 patients diagnosed only with paracoccidioidomycosis. They observed a marked reduction in the detection of anti-*P.brasiliensis* in the co-infection group by all methods: IDD (65% x 89%), CIEF (79% x 99%) and ELISA (95% x 100%). Also, the titles obtained were significantly lower than those observed in the non co-infected group.[15]

These data demonstrate that in patients diagnosed with both diseases, HIV-induced immune-humoral response alterations impair the sensibility of the aforementioned tests. Therefore, eventual negative serologic results in patients co-infected with HIV must be evaluated in the likelihood of a possible false-negative result.

The first reports of co-infection between paracoccidioidomycosis and HTLV-1 infection date from 2010.[16] Four patients coming from the Peruvian Amazon were diagnosed in Lima-Peru, and in three of them the overall clinical symptoms suggested an underlying case of immunosuppression. This observation alerts for the possibility of the association of both diseases in superimposed endemic areas and also for a probable impact of the co-infection in the evolution of the cases.

Still regarding the epidemiology, we emphasize the report of PCM in patients two and three-year-old, the youngest so far, both with clinical presentation suggestive of lymphoproliferative disorders and of late diagnostic confirmation through direct exam of an abscessed lymph node secretion. However, it is important to remember that the most affected age group is that between 30 and 50 years old and that the

oldest patient recorded to date was 103 years old.[17,18] Studies on the specific mortality due to systemic mycoses began to be published in 2002. That year, the pioneer study of Coutinho *et al*. revealed that paracoccidioidomycosis was the eighth cause of death by predominantly chronic or recurrent diseases, infectious and parasitic, and the leading cause of death among the systemic mycoses in the period evaluated (1980-1995).[19] The results indicated a mean annual mortality rate of 1.45/ million inhabitants. This statement, along with data observed between 1980-1998 in Paraná State, which showed 3.48 deaths by paracoccidioidomycosis per million inhabitants are evidence that this disease is an important health problem in Brazil.[19,20] Another study to identify PCM as an associated cause of death in patients with aids in Brazil between 1998 and 2006 demonstrated: 125,633 deaths by aids; 5,898 (4.7%) associated to systemic mycoses, most frequently cryptococcosis (50.9% of all deaths), followed by candidiasis (30.2%); histoplasmosis (10.1%), aspergillosis (7.2%) and paracoccidioidomycosis (1.4%).[21] This same study, however, when evaluating the death mortality rates of patients not infected with HIV, showed diametrically opposed results, describing paracoccidioidomycosis as the major cause of death on the group of deep mycoses, corresponding to an average of 51.1% of all the deaths in the period.[21]

CLINICAL PRESENTATION

Although published in 1987, the generally used paracoccidioidomycosis clinical forms classification is little known in dermatology, therefore, it is depicted with adaptations, on chart 1.[22,23]

It is important to remember that: **1-** paracoccidioidomycosis-infection corresponds to the patient without signals and symptoms of the disease but with positive paracoccidioidin skin test reaction and differently from histoplasmosis, there is no image of pulmonary calcification. **2-** paracoccidioidomycosis-disease is divided in two groups: **2.1** acute-sub acute form that usually affects patients under 30 years old, presenting a monocyte-macrophage system (lymph nodes, liver, spleen and bone marrow) fungal tropism (Figures 2 and 3) and **2.2** adult chronic form that may be unifocal (one organ or system) or multifocal (mixed) (Figures 4,5 and 6); **3-** paracoccidioidomycosis associated to immunosuppression; **4-** Sequelae, particularly pulmonary chronic obstructive disease, stenosis and obstruction of the superior airways and adrenal insuficiency.[24]

As with other diseases caused by dimorphic fungi, the infection by *P.brasiliensis* occurs mainly by inhalation and besides experimental evidence for this, there are numerous case reports with evidence of silent primary infection or with clinical manifestations

Chart 1: Clinical classification of paracoccidioidomycosis

1.	Paracoccidioidomycosis -infection
2.	Paracoccidioidomycosis -disease
2.1.	Form acute-sub acute (juvenile form)
2.1.1.	Moderate
2.1.2.	Severe
2.2.	Chronic form (adult form)
2.2.1.	unifocal: light, moderate, and severe
2.2.2.	multifocal: light, moderate, and severe
3.	Paracoccidioidomycosis – associated to immunosuppression
4.	Paracoccidioidomycosis – sequelae

Adapted source: Franco M, *et al*.[22]

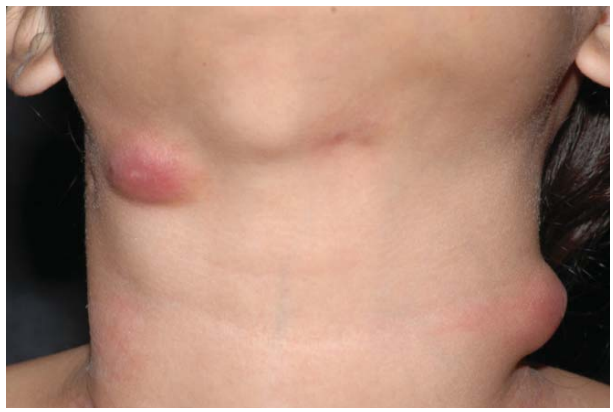

Figure 2: Paracoccidioidomycosis: acute form showing enlarged lymph nodes, with inflammatory aspect and abscess formation

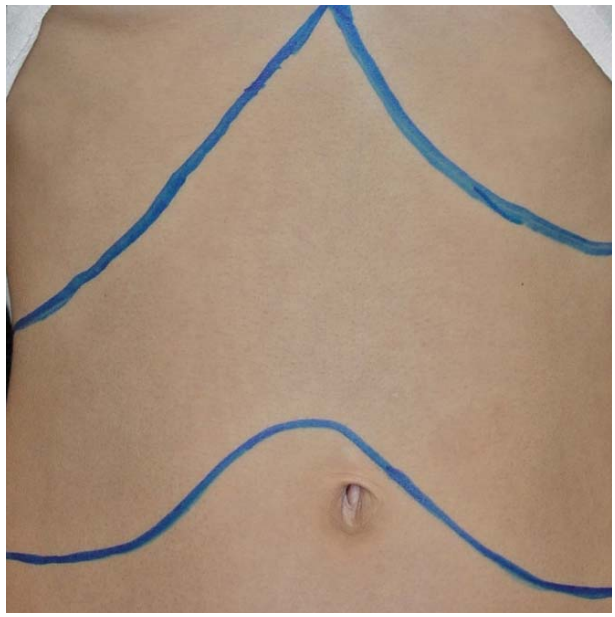

Figure 3: Paracoccidioidomycosis: acute form demonstrating marked hepatoesplenomegalia

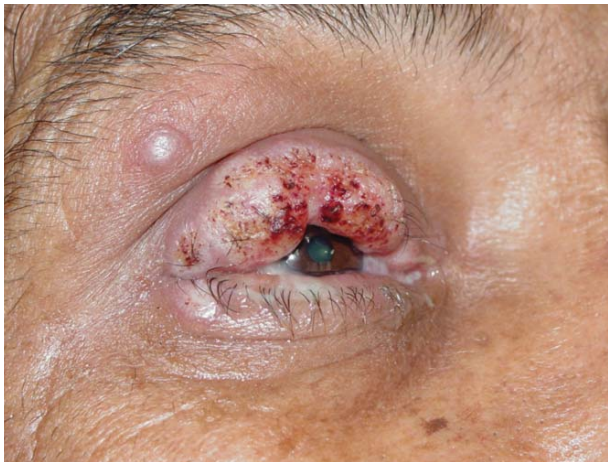

Figure 4: Paracoccidioidomycosis: eyelid and tarsus involvement depicting hemorrhagic dots on the mucosal area

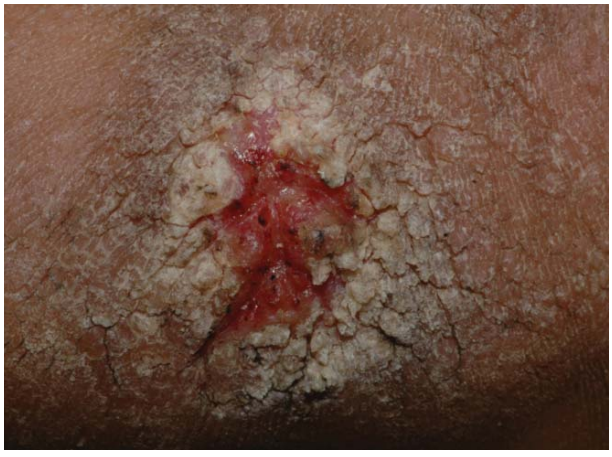

Figure 5: Paracoccidioidomycosis: plantar ulcer with hyperkeratotic edges

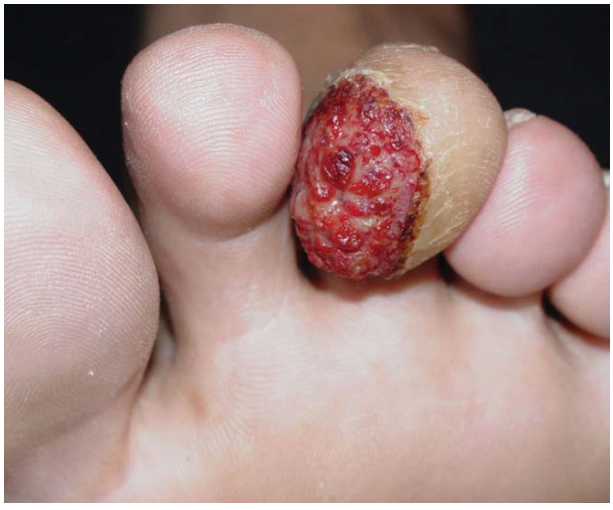

Figure 6: Paracoccidioidomycosis: vegetant and ulcerated lesion with differential diagnosis for spinocellular carcinoma

of the pulmonary primary complex. Martinez & Moya (2009) report a case of primary pulmonary infection in a young physician, otherwise healthy, non-smoker, non-drinker, eminently urban (however living in an endemic area), presenting with pulmonary symptoms associated to fever, leukocytosis with hyper eosinophilia, radiologic and tomographic signs of apical pleural-pulmonary lesions as well as hilar lymph nodes.[25] Investigations for tuberculosis, histoplasmosis and HIV infection were all negative, however the serology for PCM was positive, with an initial title of 1/16, and later 1/512. The patient was treated with Itraconazole 200 mg/day, with significant improvement after one week. He was considered cured after four months of follow-up.[25] This report demonstrates that even young individuals, with an adequate nutritional status and low exposure to infecting sources may develop infection with symptoms corresponding to primal infection and a progressive evolution to paracoccidioidomycosis-disease.

Several studies about the incidence of cancer in patients with paracoccidioidomycosis try to determine if there is a higher incidence of tumors in these patients, and if so, if it would be secondary to the immune deregulation associated to PCM or arising from habits prevalent in this population such as drinking and smoking. Shikanai-Yasuda *et al*. (2008)[26] performed a vast review on this subject and identified that most reports correspond to isolated cases or small case-series. However, the authors highlight two studies based on necropsy data, which showed discordant results: higher incidence of cancer in one study and no difference with the control group in another.[26] Severo *et al*. (2010), on the same topic, identified 25 cases of cancer in 808 consecutive patients with PCM in the same hospital (an incidence of 3.1%) and emphasized two aspects: first, that in 64% of the cases, the organ affected by the neoplasm was the same affected by PCM and second, cases of lung cancer (the most prevalent) were more frequent in patients with PCM which were also smokers.[27] Even if the cause-effect relation is not clear, it is important to be attentive to the synchronous clinical expression of paracoccidioidomycosis/carcinoma in the same anatomic region.[28] Although uncommon, paracoccidioidomycosis may occur as an opportunistic disease, following cancer treatments, therapy with corticoids or even the use of immunosuppressants, including anti-TNF α.[29-31]

The potential severity of the acute-sub acute forms of paracoccidioidomycosis (juvenile form) was expressed in the study of associated bone marrow, lymph nodes, liver and spleen involvement.

Bone marrow infiltration by PCM may present in a moderate form, as histiocitary infiltrate, with fungal cells and limited clinical repercussion or in the

other end of the spectrum, with medullar necrosis and osteonecrosis, having a major impact on the cause of death.[32,33] Acute-sub acute forms may occur in urban patients, with no history of living or staying in the rural zone, which can delay the diagnosis; also these patients must be investigated for a possible co-infection by HIV, because the have an atypical epidemiologic profile.[34,35] Monocyte-macrophage system tropism in the acute-sub acute forms includes the Payer's patches in the intestinal wall, as well as intra and extra-peritoneal lymph nodes; the latter may become abscessed and thus infect the psoas muscle on one or both sides, evolving slowly, gravely and difficult to diagnose.[36]

Genitourinary paracoccidioidomycosis is uncommon, occurring in 1.6% to 2% of chronic adult form cases, and even when present, there is wide clinic variability, with lesions often being mistaken by spinocellular carcinoma of the penis. Depending on the severity, the lesions may cause urethral obstruction and important esthetic and functional alterations.[37,38] When PCM affects the external genitalia, the main regions are the glans and scrotum, though there is no risk of sexual transmission, it is important to note that, these clinical cases are often associated to lung disease.[38]

The dissociation between clinical symptoms and pulmonary radiologic involvement was observed whilst studying patients with diffuse interstitial pulmonary PCM (85.7% of all cases) when compared to patients without radiologic evidence of involvement.[39] This demonstrates the relatively silent character of lung lesions, that when initially present are interpreted by the patient as a consequence of the smoking habit, thus delaying the search for medical attention. Anyway, it is important to point the potential severity of lung involvement, for often post-treatment fibrosis evolves to chronic obstructive disease. Bearing this in mind, studies with mice susceptible to *P.brasiliensis* lung infection showed significant reduction of the scaring sequelae in those treated with an association of itraconazole + pentoxifylline compared to isolated itraconazole or itraconazole plus corticoids.[40]

One study evaluated bone involvement secondary to paracoccidioidomycosis in 19 consecutive cases with proven bone lesions and showed that: the incidence was higher in younger patients (mean 16.1 years old, varying from 4 to 49), it affected mostly long bones (80.4% of the lesions), in the metaphysis region (46.6%), with an osteolytic pattern (62.7%), without marginal sclerosis (82.4%) or periosteal reaction (90.2%). These data reinforced the prevalence of bone involvement in association with the acute-sub acute forms of the disease.[41]

Two studies evaluated the possibility of late relapse, reporting on patients recurring 10 years (patient a) and 25 years (patient b) after the initial diagnosis and treatment.[42,43] Both were treated with the association of sulfamethoxazole plus trimethoprim (patient a) with added sulphadiazine and ketoconazole (patient b), however dosage or length of treatment were not informed, thus letting the possibility of insufficient or incomplete treatment, the main causes of relapse, unanswered. In both cases, patients moved to the urban area of large cities, outside the endemic zones, which suggests that those were real relapses instead of reinfections.[42,43] The unpublished statistics in our service show that 75% of all relapses occur up to 3 years after the initial treatment and are correlated with the sustained alcohol intake abuse, as well as irregular or incomplete treatments.

Several conference abstracts and two full publications studied paracoccidioidomycosis expressed by cutaneous lesions of a sarcoid-like pattern.[44,45] This is the typical dermatologic manifestation of PCM, with a clinical expression almost exclusively cutaneous, showing infiltrated, well-delimited and cephalic lesions that may be clinically and histologically mistaken by hanseniasis (Figure 7). Histology in these cases shows a tuberculoid, granulomatous, inflammatory pattern with a paucity of fungi. Patients are young and may present with infarcted cervical lymph nodes, but the general status is often good and the skin lesions trigger the search for medical attention. Equally atypical, but not anecdotal, is the report of carpal tunnel syndrome due to PCM.[46] The authors report a male patient with a history of serologically negative rheumatoid arthritis, in treatment with

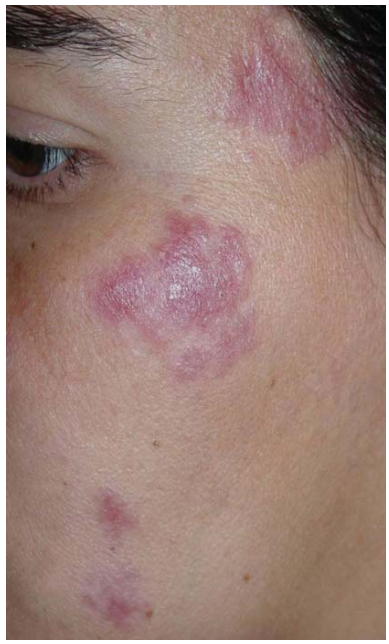

Figure 7: Paracoccidioidomycosis: infiltrated erythematous-violaceous lesion of a sarcoid pattern, with differential diagnosis for erythematous lupus and sarcoidosis

methotrexate, chloroquine and sporadic intra-articular corticoid infiltrations that evolved to tenosynovitis and carpal tunnel syndrome. Investigation revealed important demyelination of the median nerve and partial denervation of the abductor pollicis brevis muscle, consistent with carpal tunnel syndrome associated to tenosynovitis and specific paracoccidioidomycosis osteoarthritis, besides lung PCM.[46] Treatment involved surgery and combination of sulfamethoxazole plus trimethoprim, with complete cure.

A systematic review on SNC paracoccidioidomycosis comprising 257 cases and 81 studies was presented by Pedroso *et al*. (2009).[47] The authors compiled data on reports of predominantly motor symptomatology or intracranial hypertension and showed: a prevalence of the pseudotumoral form; length of complaint for a mean of 4.9 months; supratentorial (66.8%) or hemispherical (47.6%) location, particularly in frontal and parietal lobes; associated pulmonary involvement in 59.1% of all cases and an extremely high rate of mortality (44%). Neuroparacoccidioidomycosis is almost exclusively associated to the adult chronic forms of the disease (98.3%) and might be meningoencephalic (10.6%).[47] The therapeutic recommendation is at first to combine sulfamethoxazole plus trimethoprim or fluconazole, in high intravenous doses at least in the initial phase of treatment.[48] A cohort study with 213 consecutive PCM cases, with systematic search for SNC involvement, demonstrated a prevalence of 3.8% of specific lesions, with all cases presenting parenchymal location and other findings in accordance to the literature.[49]

One of the most important studies regarding the paracoccidioidomycosis diagnosis, and related to the cryptic species, was published by Batista Jr *et al*. (2010).[50] In an elegant experiment, the authors analyzed serums of several patients from São Paulo (SP) and Mato Grosso (MT), to test for antibodies by the IDD method using antigens obtained through isolates specifically from MT State or isolates used in reference laboratories in São Paulo. When the antigen obtained from the Mato Grosso isolate was used in the IDD, serologic results were positive in 92.3% of MT serums versus 41.3% of SP serums. When using the reference antigen, the results were positive in 26.2% (MT serums) versus 100% (SP serums).[50] such results demonstrate that antigenic compositions are probably related to the different species of the *Paracoccidioides* "complex" that prevail (or are exclusive), in one or the other region. From a practical standpoint, each macrogeographical region in Brazil will have to prepare antigens from isolates from their own areas to ensure the greatest possible sensibility rate of the diagnostic methods. Equally important was the study on diagnostic accuracy comprising 401 patients with proven PCM, seen in the Infectious Diseases Department, that showed the following rates of sensibility for each method: histopathology (positive in 96% of all biopsied cases) > serology (90%) > direct tissue exam (74.5%) > direct sputum exam (62.5%) > cell block sputum (55.3%).[51] These results are very important, because a patient with paracoccidioidomycosis does not always have a lesion that is easily accessible to biopsy. Unpublished data from our hospital on 29 consecutive and proven PCM cases with skin and/or mucosal lesions demonstrated the diagnostic accuracy of different methods on the following proportions: histopathology (positive in 100% of the cases) > serology (ELISA 89% and IDD 80%) > molecular (Nested PCR in biopsy fragment 56%) > biopsy fragment culture in Mycosel® 37° C (37.5%). These results reflect the extreme importance of biopsy as a diagnostic method with high sensibility, corroborating the role of the dermatologist in the process and the still discrete and secondary role of molecular methods, which steps (retrieval and transportation) need to be improved as other alternative molecular techniques must be tested.

The aforementioned highlights the clinical variability of PCM, its multidisciplinary characteristics and the important role of dermatologists in the care of patients, due to the high frequency of cutaneous and mucosal lesions and their access to diagnostic methods.[52]

TREATMENT

The main article on treatment for the period comprising this EMCD is the consensus in paracoccidioidomycosis prepared by a specialists committee including dermatologists.[53] The preparation of this consensus involved exhaustive discussions and was difficult due to the paucity of clinical trials focused on treatments with adequate scientific methodology to define the correct hierarchy of drugs, their dosage and length of treatment.

There was full agreement as to the determination of criteria that would define the light, moderate and severe forms of PCM and which treatment would be adequate to them. The recommended drugs for the light and moderate forms are still itraconazole and the combination of sulfamethoxazole plus trimethoprim, and for the severe forms amphotericin B deoxycholate (Classic amphotericin B) as seen on chart 2.

This consensus had a very instructive approach when addressing the treatments for special situations such as: paracoccidioidomycosis during pregnancy, when amphotericin B is recommended; PCM in patients with renal failure, for whom itraconazole or other azole derivatives should be used; patients with liver failure in which the drug of choice should be amphotericin B and children for whom sulfonamides

Chart 2: Treatment of paracoccidioidomycosis		
Itraconazole	Adults - 200 mg/day Once daily Children – > 30 kg or >5 years old = 5 to 10mg/kg	Light form: 6 to 9 months Moderate form: 12 to 18 months
Sulfamethoxazole + trimethoprim	Adults -1200 mg + 480 mg q 12 h Children – 50mg/Kg + 10mg/Kg q 12 h	Light form: 12 months Moderate form: 18-24 months
Amphotericin B	0,5 to 1,0 mg/Kg/day or in alternate day	Severe form: total dosage ≈30mg/Kg

Adapted source: Shikanai-Yasuda MA, *et al* [53]

or itraconazole are the more practical choices. As a rule, the treatment for severe forms is based on the use of amphotericin B, while in situations where potential drug interaction may occur or critical kidney failure is present, the choice of treatment must be carefully made, selecting always the less damaging option. In all the circumstances cited above, there must be an extremely rigorous monitoring of lab results and clinical evolution.[53] We must stress that, besides the treatment of the disease itself, it is vital to address the nutritional status of the patient, the possibility of alcohol withdraw syndrome, other co-morbidities and the patient's social situation. An interesting and practical conduct, if the patient has an evident pulmonary lesion on the radiography, is to point such lesion to him and explain that the resolution of the cutaneous-mucosal lesions is not enough; there must also be a healing on the lung lesion, which will occur much later. This initiative helps the patient realize why such a lengthy treatment is necessary and why he should not interrupt the medication when the visible lesions disappear. Cessation of smoking and drinking are likewise important to the therapeutic success in the long run. Lab controls during treatment depend on the specifications of the chosen drug. Revaluations must be performed monthly during the first three months and quarterly until the end of the first year, including biochemical, serological and radiologic tests (the latter should be repeated each three to six months in the first year).

Criteria for cure and discharge were also discussed in this consensus and they include clinical, serological and radiologic evaluation. The maintenance of a long term follow-up is advisable when the patient had a severe initial clinical presentation, or in case of relapse or lack of treatment adherence.[53]

Besides the classic drugs used to treat paracoccidioidomycosis, one must also consider the azoles of second generation. One drug of this group, voriconazole was tested in an opened clinical trial, where 53 patients were randomized in the ratio of 3:1 to receive voriconazole (400 mg on the first day, followed by 200 mg/day) versus itraconazole (200 mg/day), for six months to a year, as seen fit by the investigator.[54] Intention to treat analysis showed 88.6% of complete and partial responses for those treated with voriconazole versus 94.4% on the itraconazole group, which did not achieve statistical significance. Both drugs had a good safety profile, demonstrating that voriconazole is yet another option to treat PCM.

Gryschek *et al*. (2010) discussed the possibility of a "paradoxical reaction" when treating severe forms of paracoccidioidomycosis.[55] Paradoxical reaction was define by the authors as the clinical deterioration that may occur even if the treatment of that particular infectious disease is adequate. This reaction was previously described in cases of tuberculosis, hanseniasis and mainly in the context of immune reconstitution in patients with aids, which are treated with highly active antiretroviral therapy (HAART).[56,57] In case reports on PCM, the anti-HIV serology was repeatedly negative and in both cases an improvement in clinical conditions was observed when adding corticoids as adjuvant therapy.[55] This initiative generated an original publication about the use of corticoids as adjunct therapy in severe forms of PCM.[58] The rationale is based on the fact that severe forms launch an intense inflammatory reaction that, for a certain period, might be more damaging to the patient that the infection itself.[58]

This argument is supported by previous publications that demonstrated the high levels of circulating TNF- α in patients with severe forms of PCM and discussed its deleterious role for the patient.[59,60]

However, we must point that there are no clinical trials that support the routine use of corticoids in severe forms of paracoccidioidomycosis.

The possibility of the use of vaccines as primary prevention for PCM has been studied and tested in mice, using as antigen one peptide known as P10, that corresponds to a molecular fraction of antigen gp43, specific for genus *Paracoccidioides*. P10, used in combination to IL-12 to immunize mice susceptible to the virulent strain Pb18 of *P. brasiliensis* was efficient in reducing the rates of pulmonary infections in the animals.[61] By intramuscular injections of a combination of plasmids expressing P10 and a weekly dose of IL-12 for a month, the authors were able to eradicate the infection in a group of animals. Such results suggest that, the immunization with plasmids expressing P10 plus IL-12 is effective in preventing and treating experimental PCM and clinical trials in humans may be viable in the future.[61]

In conclusion, paracoccidioidomycosis is still a largely important disease for dermatologists, mainly due to their role in early diagnosis, the possibility of study and learning provided by the extreme variability of the clinical manifestations of this disease, new epidemiological data and the constant evolution of etiopathogenesis. Although treatment is still based on classic drugs, there are adjuvant therapies that may enhance the results in both short and long terms and it is up to each of us to gather the knowledge to achieve the goals that patients and departments yearn for. ❑

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QUESTIONS

1. The listed fungi species are temperature-dimorphic EXCEPT:
- **a)** Histoplasma capsulatum
- **b)** Coccidioides posadasii
- **c)** Cryptococcus neoformans
- **d)** Paracoccidiodes brasiliensis

2. Regarding the new species of genus Paracoccidioides, one may cite:
- **a)** Paracoccidioides loboi
- **b)** P. novemcinctus
- **c)** Lacazia loboi
- **d)** P. lutzii

3. Genus Paracoccidioides is less prevalent in the following geographic regions of Brazil;
- **a)** Center-west
- **b)** Semi arid regions of the Northeast
- **c)** Southeast
- **d)** South

4. Regardless of geographic region, the association of paracoccidioidomycosis –HIV/AIDS co-infection in expected in:
- **a)** More than 10% of the cases
- **b)** Between 4% and 6% of the cases
- **c)** Under 3% of the cases
- **d)** Over 15% of the cases

5. Regarding the association of paracoccidioidomycosis –HIV/AIDS co-infection one might expect to find:
- **a)** Absence of fever
- **b)** High rates of mucosal involvements
- **c)** High rates of lymphnodemegaly
- **d)** Absence of hoarseness

6. Regarding the association of paracoccidioidomycosis –HIV/AIDS co-infection one might expect to find all the items below EXCEPT:
- **a)** Possible false-negative serology
- **b)** An increase in sensibility for diagnosis by ELISA serology
- **c)** High serologic titles regardless of the method
- **d)** Decrease in the sensibility of immunodiffusion for diagnosis

7. Regarding the fungal diseases associated to HIV/AIDS infection one might state that:
- **a)** Cryptococcosis is the most frequent cause of death
- **b)** Paracoccidioidomycosis does not present with sever clinical symptoms
- **c)** Histoplasmosis is less important as cause of death
- **d)** Candidiasis is the least frequent cause of death

8. Regarding age groups in paracoccidioidomycosis, one may affirm that:
- **a)** Cases are more frequent in population aged 30 to 50 years-old
- **b)** The youngest case reported so far was a 3-year-old child
- **c)** Age is irrelevant regarding the clinical form of the disease
- **d)** 90 years-old is the highest limit for occurrence

9. Regarding the clinical classification of paracoccidioidomycosis, one can find:
- **a)** Infection
- **b)** Acute-sub acute form
- **c)** Adult chronic form
- **d)** All the above

10. Regarding the clinical classification of paracoccidioidomycosis the following were considered:
- **a)** Natural history of the disease
- **b)** Affected topography
- **c)** Tropism for an specific organ or system
- **d)** All the above

11. Regarding the natural history of infection in paracoccidioidomycosis, one may affirm:
- **a)** Primal infection is always via pulmonary way
- **b)** Primal infection leaves calcified sequelae in the lung
- **c)** There is not an immediate evolution from infection to disease
- **d)** Primal infection is usually asymptomatic

12. The following items interfere in the natural history of paracoccidioidomycosis:
- **a)** Abusive alcohol intake
- **b)** Mal-nourishment
- **c)** Smoking
- **d)** All the above

13- Regarding the occurrence of cancer associated to paracoccidioidomycosis, one may affirm that:
- **a)** There is a prevalence of lymphoproliferative diseases
- **b)** There are not influences from co-morbidities
- **c)** Immunologic factors do not influence it
- **d)** There is no cause-effect relation proven

14. Regarding the acute-sub acute form of paracoccidioidomycosis one may affirm:
- **a)** The main clinical expression is with lymphnodemegaly
- **b)** Liver involvement is uncommon
- **c)** As a rule, there is mucosal involvement
- **d)** There is no intestinal involvement

15. Regarding the chronic form of paracoccidioidomycosis, one may affirm that:
- **a)** There is no link to age
- **b)** Cutaneous symptoms are uncommon
- **c)** Mucosal lesions are uncommon
- **d)** The lung is the main target

16. Regarding the clinical manifestations of paracoccidioidomycosis, one may affirm that:
- **a)** Genital lesions occur only in males
- **b)** Pulmonary symptoms are early and severe
- **c)** Interstitial pulmonary infiltrates are exceptions, not the rule
- **d)** Central nervous system lesions are mainly parenchymal

17. Regarding diagnosis of paracoccidioidomycosis, one may affirm that:
- **a)** Histopathological examination is the gold standard
- **b)** Serology by ELISA has the highest sensibility
- **c)** Culture is a specific method, although with less sensibility
- **d)** All the above are correct

18. Regarding paracoccidioidomycosis treatment, one may affirm that:
- **a)** Light and moderate forms may be treated with sulfamethoxazole plus trimethoprim or itraconazole

b) For the severe forms, amphotericin B deoxycholate is recommended
c) For pregnant patients the treatment of choice is with amphotericin B
d) All the above are correct

19. Besides the choice of drug that is most appropriated to the clinical circumstances, one must be attentive to:
a) Co-morbidity investigations
b) Social circumstances
c) Nutritional circumstances
d) All the above are correct

20- Regarding post-treatment follow-up of paracoccidioidomycosis, one may affirm that:
a) Relapses are rare and if they occur, it is usually after 10 years of follow-up
b) Serologic control is not necessary
c) Radiologic control must be perform monthly
d) Criteria for cure are clinical, radiologic and serological

Answer key
Cutaneous mosaicisms: concepts, patterns and classification . An Bras Dermatol. 2013;88(4):507-17.

1) B	6) B	11) B	16) B
2) A	7) B	12) A	17) A
3) B	8) C	13) D	18) D
4) D	9) A	14) A	19) B
5) C	10) A	15) C	20) C

Papers

Information for all members: The EMC-D questionnaire is now available at the homepage of the Brazilian Annals of Dermatology: www.anaisdedermatologia.org.br. The deadline for completing the questionnaire is 30 days from the date of online publication.