

Sarcoid-like lesions in Paracoccidioidomycosis: immunological factors*

Paracoccidioidomicose sarcoidiose símile: aspectos imunológicos

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Abstract: The clinical presentation of paracoccidioidomycosis is spectral. Spontaneous cure, state of latency or active disease with different levels of severity can occur after the hematogenous dissemination. The morphology and number of skin lesions will depend on the interaction of host immunity, which is specific and individual, and fungus virulence. Some individuals have natural good immunity, which added to the low virulence of the fungus maintain the presence of well-marked granulomas with no microorganism and negative serology for a long time, making the diagnosis a challenge. Factors inherent to the fungus, however, may modulate the immune response and modify the clinical picture over the time. We present a sarcoidosis-like clinical presentation and discuss the immunological factors involved.

Keywords: Adaptive immunity; Bacterial infections; Immunity, innate; Mycoses; Paracoccidioidomycosis; T-Lymphocytes

Resumo: A apresentação clínica da paracoccidioidomicose é espectral. Podem ocorrer cura espontânea, estado de latência ou doença ativa após disseminação hematogênica com vários graus de gravidade. A morfologia e o número de lesões cutâneas irão depender da interação entre fatores próprios da imunidade do hospedeiro, que é específica e individual, e da virulência do fungo. Alguns indivíduos com boa imunidade natural somada a baixa virulência do fungo mantêm por tempo prolongado granulomas bem formados sem microorganismos e sorologia negativa, tornando o diagnóstico um desafio. Entretanto fatores inerentes ao fungo podem modular a resposta imune e modificar o quadro clínico ao longo do tempo. Os autores apresentam um caso sarcoidose símile e discutem os aspectos imunológicos envolvidos.

Palavras-chave: Imunidade adaptativa; Imunidade inata; Infecções bacterianas; Linfócitos T; Micoses; Paracoccidioidomicose

INTRODUCTION

The *Paracoccidioides brasiliensis* (PB) is a dimorphic fungus, present as yeast in tissues and filamentous form in cultures.¹ Ulcers and their variants, infiltrative lesions, papular-nodular lesions, vegetating and verrucous forms, abscesses or other rare forms could be observed in decreasing order of frequency.^{1,2}

The sarcoidosis-like clinical presentation is an unusual type of infiltrative form, differing from the others by the presence of tuberculoid granulomas in the histological exam 3. The fact that fungi are not found in skin samples make the diagnosis a challenge. There are immunological reasons for this presentation, and for the fact that lesions remain or are modified over time.²

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CASE REPORT

A 30-year-old woman complained of redness and pimples on the nose for 6 months. She had an infiltrated erythematous plaque with papules, pustules and telangiectasia all over the nasal area (Figure 1). Histopathology showed superficial and deep tuberculoid inflammatory infiltrate without caseous necrosis, consistent with granulomatous rosacea. Fungi and acid fast-bacilli resistant staining negative.

The disease progressed despite the rosacea treatment. The plaque became less defined and larger (Figure 2A). There were four new infiltrated erythematous-brownish sarcoidosis-like plaques on the left and right eyebrows, on the right temporal region and on the left jaw (Figure 2B and 2 C)

The investigation was extended to possible granulomatous infectious diseases. Chest X-ray was normal, PB serology, syphilis serology, Montenegro reaction and tuberculin test (PPD) were non-reactive. The histology report was sustained after new biopsies (Figure 3).

After 1 year of follow-up, the patient complained of throat pain. In the oral cavity there was a slightly verrucous lesion with fine granulation tissue and bleeding points similar to strawberry-like stomatitis (Figure 4). In the middle of mixed inflammatory infiltrate there were some thick-walled spores with double contour and multiple budding, compatible with PB (Figures 5 and 6). After treatment, the patient achieved clinical cure.

DISCUSSION

Primary skin infection by PB occurs rarely by direct inoculation. The most common way is by inhaling the agent with lymphatic spread to the nearest lymph node, forming the primary complex as in tuberculosis. Hematogenous dissemination occurs after this phase and leads the agent to the skin.^{1,2} The clinical presentation will be spectral. Spontaneous healing, state of latency or active disease at different levels of severity could happen. The morphology, number



FIGURE 1: An infiltrated erythematous plaque with papules, pustules and telangiectasia in the nasal dorsum, extending bilaterally into the maxillary region with defined borders

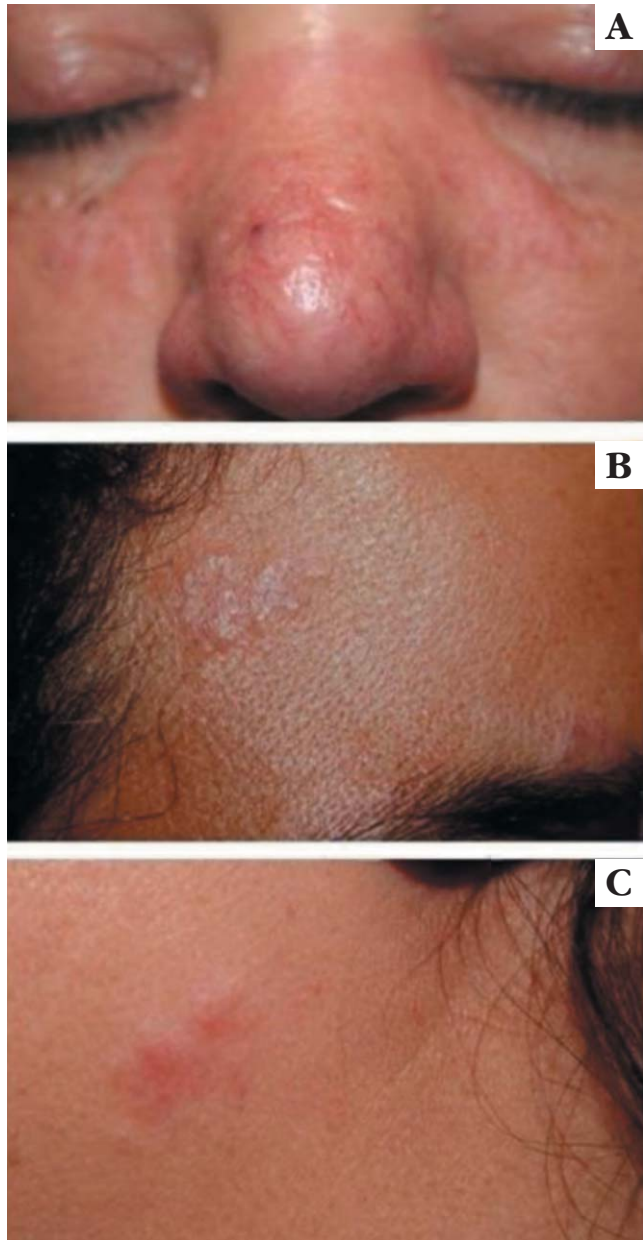


FIGURE 2 A, B AND C: A. The nasal plaque extended to the glabella and defined borders were lost. New sarcoid-like plaques. B. On the right temporal region and right eyebrow. C. On the left jaw

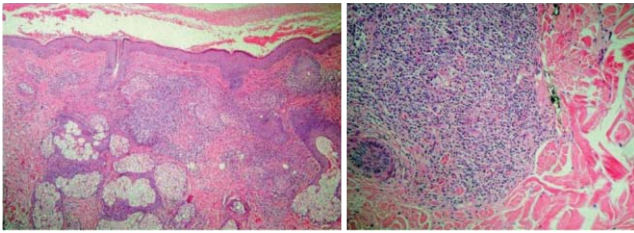


FIGURE 3: Superficial and deep well-defined tuberculoid granulomas without caseous necrosis



FIGURE 4: Strawberry-like stomatitis on palate

and frequency of skin lesions will depend on many factors related to the fungus' pathogenicity and the hosts' immune capacity.^{3,4}

The intensity and quality of the innate immune response will determine the ability to contain the agent.^{4,5} The number of phagocytes in the first site of contact is responsible for this initial inflammatory response to infection. The spread of the fungus is easier in sites with a low number of phagocytes. In addition, not only the number, but the cell function is crucial in containing the infectious process. Neutrophils of individuals with natural resistance have increased phagocytic activity, increased production of hydrogen peroxide and reactive oxygen species featuring high fungus destruction capacity.^{4,5} Women appear to have more efficient polymorphonuclear cells than men.⁶

Resistant individuals will stimulate the response of T helper 1 lymphocytes (Th1) leading to the typical organized tuberculoid granuloma, with rare fungi.^{4,7} The serology may be negative or in low titers. Well-defined types like infiltrative forms, sarcoid-like plaques or spontaneous healing are more commonly found.⁴ This event has been proven in animal models through improving the Th1 lymphocytes after infection with the aim to formulate a vaccine that promotes healing or at least stimulates the immune system to contain the agent's spread.⁷

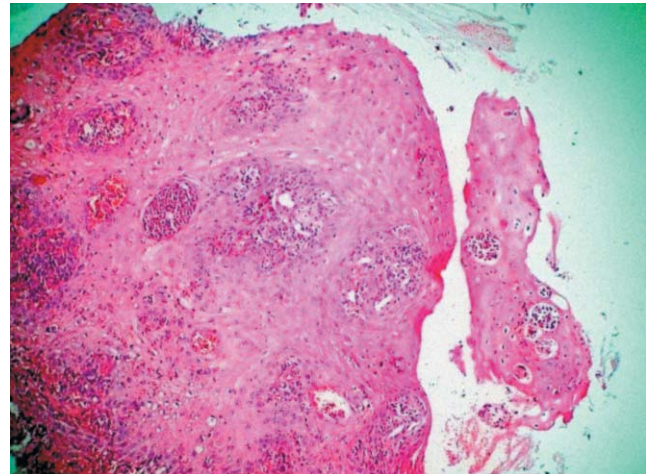


FIGURE 5: Multiple microabscesses in the mucosal biopsy

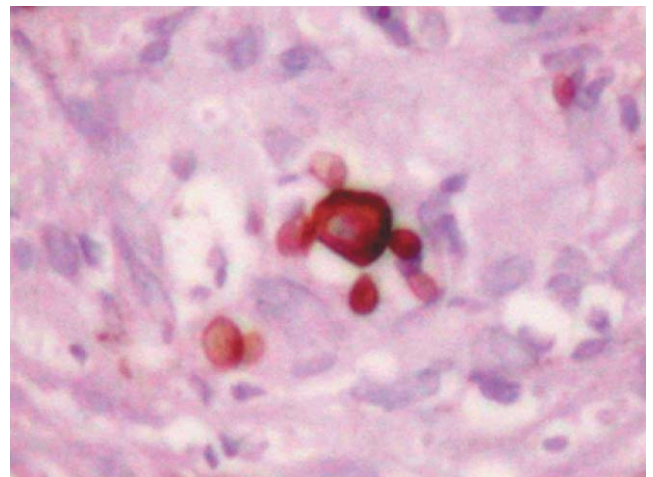


FIGURE 6: *Paracoccidioides brasiliensis* found in the middle of infiltrate

The response pattern can be gradually changed by the occurrence of adverse events, natural or acquired, in the individual or production of virulence factors by the fungus, which can influence in the invasion capacity and growth. The first one of these virulence factors is the antigen, which is given by the alpha 1 and 3-glucan capsule components.⁴ They are responsible for fungi adherence to host cells. Their greater expression in the cell membrane increases the power of infectivity of this particular fungi strain.⁴

The second one is the influence of the type and number of exoantigens produced by PB. They progressively inactivate CD4 + T cells, natural killer cells and gradually decreases the IL-2 lymphokine-dependent's (IFN-gamma and TNF) produced by Th1 lymphocytes. This changes the cytokine's pattern production, with the increase in suppressive action of interleukin (IL) 10, IL-5 and transforming β growth factor (TGF β).^{4,8} The polymorphonuclear cells do not show

the same phagocytic capacity as in the early disease. They phagocyte but fail to efficiently destroy the fungus, causing higher tissue injury.⁵ This process slowly leads to the failure of cellular immunity, the shift to Th2 response, multiplication of the fungus, dissolution of the granulomas and spread of the disease. The humoral immunity expression improves, finally leading to antibody production, especially in the anti-gp70 and anti-gp 43, increasing the chance of positive serological tests.^{4,8}

Variations in the immunity degree could lead to a predominantly Th2 response early in the infection process. The macrophages may have low innate protective effect, failing to destroy the fungus, a fact expressed clinically with ill-defined ulcers and absces-

ses.⁸ Male rats have naturally higher Th2 response and increased production of suppressive cytokines, compared with females exposed to the PB. It is one of the possible explanations for the presence of more severe disease in men.⁶

Therefore, individuals with good specific immunity against PB, like the present case, can be confounded clinical and histologically with the other granulomatous diseases. Leprosy can fit perfectly in the clinical aspect, but the negative Mitsuda test was essential to avoid a therapeutic prove. The negative PPD reaction, the absence of caseous necrosis plus the unusual lesion ruled out tuberculosis. The great challenge in granulomatous infectious diseases without an obvious etiology is to be patient and persist in the investigation until the agent is found. □

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