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Case Report

Paracoccidioidomycosis with sarcoid-like lesions: a diagnostic challenge

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Abstract

Clinical presentation of paracoccidioidomycosis (PCM) can be diverse. Morphology and quantity of skin lesions depends on interactions between host immunity and fungus virulence. Diagnosis can be a challenge considering that this fungus has low virulence and some individuals have immunity to microorganism, which results in well-marked granulomas without visible microorganisms. We report herein a clinical presentation of sarcoid-like PCM, initially diagnosed as tuberculoid leprosy. This rare type of PCM is often mistaken for other types of chronic granulomatous diseases. Diagnosis was confirmed after 4 years when a special stain analysis helped in the identification of the specific etiologic agent.

Keywords: Diagnostic errors. Leprosy. Paracoccidioidomycosis.

INTRODUCTION

Paracoccidioidomycosis (PCM) is a systemic mycosis endemic in Brazil caused by the dimorphic fungus *Paracoccidioides brasiliensis*, which can present as yeast in tissues and as a filamentous form in cultures. PCM primarily affects the lungs after inhaling the fungus and can either be spontaneously resolved or persist in a latent form and then spread through the blood to various organs 1.

The acute-subacute form usually affects young patients of both sexes; it especially affects the reticuloendothelial system, while the chronic form is more prevalent in men and may be unifocal (one organ or system) or multifocal (mixed)[1]. The unifocal form presents with chronic progression, accompanied by weakness, weight loss, cough, dyspnea, and lung infiltrate; the multifocal form presents with extrapulmonary involvement, such as the skin, mucous membranes, lymph nodes, adrenal glands, central nervous system, intestines, osteoarticular system, epididymis, liver, and spleen[1,2].

In the skin, lesion morphology is variable and may occur as ulcers, papules, nodules, and abscesses or as vegetative, verrucous, or infiltrative plaques. The infiltrative plaques comprises up to 26.6% of skin lesions, including sarcoid-like plaques. The sarcoid-like plaques has few lesions that are indolent lesions, and the general status is often good, probably as a consequence of equilibrium between the agent pathogenicity and host defense. The clinical expression is almost exclusively cutaneous, showing well-delimited and cephalic lesions. Histology shows a tuberculoid granuloma with a paucity of fungi. This makes diagnosis of PCM challenging and may lead to misdiagnosis, often misinterpreted as other granulomatous conditions such as tuberculoid leprosy, leishmaniasis, and sarcoidosis[3-6].

This report describes a case of PCM with sarcoid-like skin lesions; this case is noteworthy owing to the difficulty of diagnosis and confusing clinical presentation.

CASE REPORT

A 35-year-old female patient, a homemaker from Monte Castelo (São Paulo State, Brazil), complained of a facial lesion over the past five years (**Figure 1**). Three years ago, after her husband was diagnosed with lepromatous leprosy, she was visited by her family physician for a routine examination of household contacts. The lesion was biopsied, and the sample exhibited chronic inflammation compatible with tuberculoid leprosy. She was treated with multidrug therapy (MDT) using the paucibacillary (PB) scheme for 6 months.

As the lesion did not disappear after completing treatment, a new biopsy was performed; the new biopsy showed slightly thinned epidermis with epithelioid cell granulomas of different sizes; some multinucleated, giant Langerhans cells; eosinophilic

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and amorphous material (necrosis) in the cytoplasm; and a few acid-fast bacilli covering and destroying nerves. These findings seemed to be compatible with tuberculoid leprosy. Bacilloscopy results of five areas were negative as usual in tuberculoid leprosy. She restarted the same treatment regimen, but lesions continued to increase and became edematous and pruritic.

Based on the clinical outcome, we assumed that the case was more compatible with dimorphic leprosy, and the sudden worsening of the lesion could be interpreted a type I reaction. Thus, treatment was possibly insufficient due to a classification error. In addition, we suggested using a multibacillary scheme (MB-MDT) and prednisone 1mg/kg/day as an alternative treatment for this case. We also solicited a smear of five areas but the patient returned one year later complaining of swelling and a painful wound on her face that had lasted for 20 days.

She reported having completed the second round of PB-MDT, but the lesion only improved after using higher doses of prednisone. She was examined in a different dermatology clinic and, after a third biopsy, a diagnosis of leprosy type 1 reaction was made, and she was directed to continue with 40mg/day of prednisone. Physical examination revealed an ulcerated lesion on the face (**Figure 2**) and painful discrete submandibular and cervical lymphadenopathy, with no other changes, associated with low-grade fever. The following diagnostic possibilities were considered: dimorphic leprosy with necrotic type 1 reaction, co-infection (leprosy and PMC), opportunistic infection due to immunosuppression by prolonged corticosteroid therapy, or another chronic granulomatous disease that had been misdiagnosed as leprosy since the beginning.

The patient was hospitalized and treated with ciprofloxacin, ceftriaxone, and acyclovir; the prednisone dose was decreased to 20mg/day, and a new skin biopsy was performed. Testing showed that bilirubin, serum glutamic oxalocetic transaminase (SGOT), serum glutamic pyruvate transaminase (SGPT), alkaline phosphatase, glucose, urea, creatinine, blood count, and total protein and fractions were normal; serology for human immunodeficiency virus (HIV), hepatitis B and hepatitis C were negative; and simple chest radiograph and abdominal ultrasound were normal. However, the erythrocyte sedimentation rate was elevated (58mm/h). Microscopy of a Gram-stained direct smear of the discharge revealed polymorphonuclear cells, and Gram-positive cocci and culture for bacteria showed the growth of coagulase-negative *Staphylococcus epidermidis*. Based on the findings of the histopathology and Gömöri methenamine silver stain, a final diagnosis of PCM was made (**Figure 3A, B** and **C**). We decided to study the previous biopsies and noticed that the initial sample was superficial, with specific staining negative for acid-fast bacilli and fungi (**Figure 3D** and **E**), but in the other two subsequent biopsy samples, special stains revealed the presence of *P. brasiliensis* (**Figure 3F** and **G**) and absence of acid-fast bacilli.

The prescribed treatment was oral itraconazole, 200mg daily for 12 months, with progressive improvement and complete healing of the lesions after 120 days of treatment. Follow-up with an immunodiffusion test at 6-month intervals up to two years was negative.

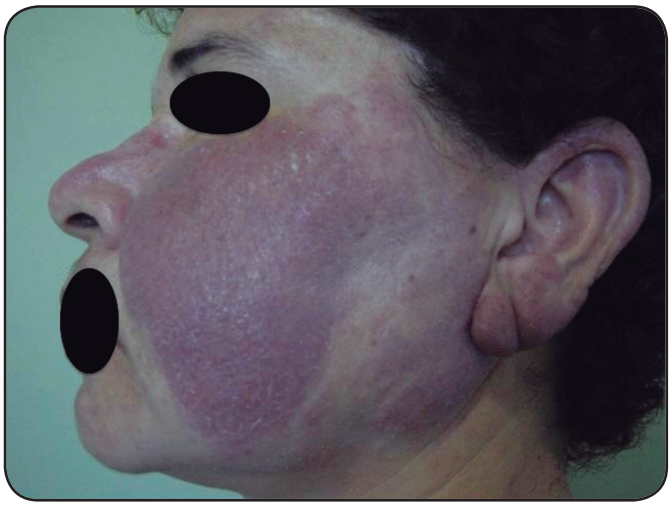

FIGURE 1 - Infiltrated erythematous poorly defined plaques showing slightly scaly, and affecting left hemiface, ear, and nasal dorsum.

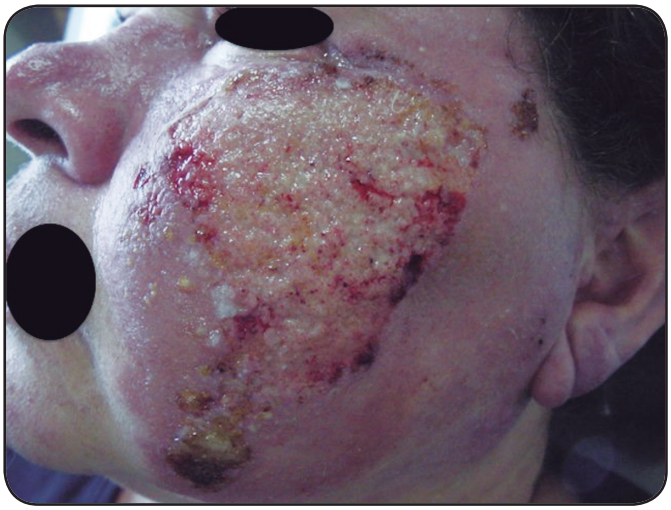

FIGURE 2 - Erythema and edema throughout the left hemiface, ear, and nose, with extensive ulceration, covered with purulent exudate and crusting, bleeding points, and adjacent fistulous orifices. Local heat and intense pain were present upon touch.

DISCUSSION

The clinical presentation of PCM is diverse: spontaneous healing may occur, or it may remain in a latent state and then progress to active disease with varying severity. Morphology, number, and frequency of skin lesions depend on factors related to pathogenicity of the fungus and the host immune response[1]. Infiltrative sarcoid-like lesions are a variant of multifocal chronic PCM. This type is rare, and its morphological substrate is tuberculoid granulomas, similar to tuberculoid leprosy, sarcoidosis, leishmaniasis, or tuberculosis. Thus, differentiation among these diseases can be a challenge due to clinical and histopathological similarities[1,4-6].

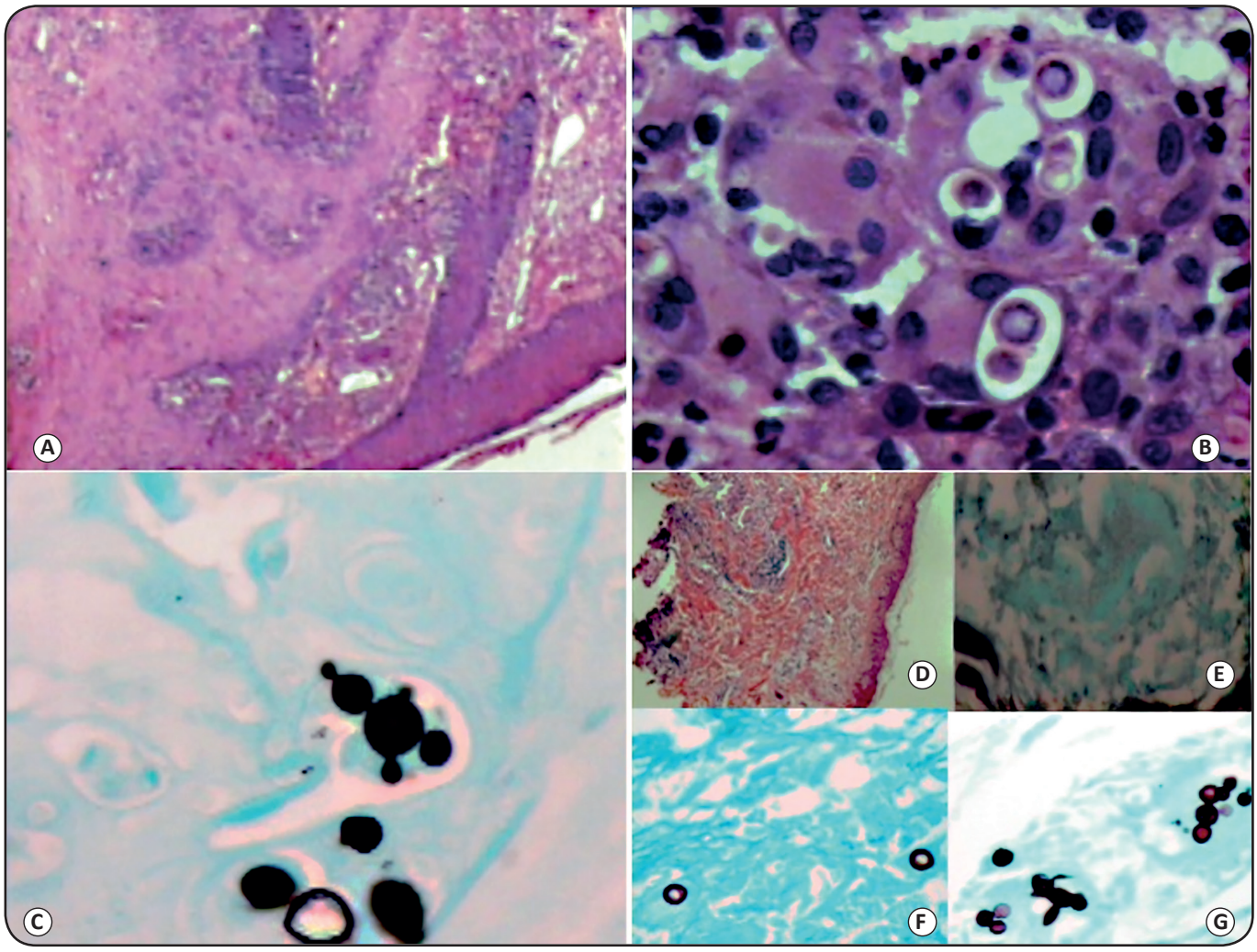

FIGURE 3. (A): pseudoepitheliomatous hyperplasia (4×; HE); (B): Granulomas with *Paracoccidioides brasiliensis* (40x; HE); (C): Bi-refringent corpuscles, stained black with Gömöri methenamine-silver, exhibiting exosporulation, identified as *P. brasiliensis* (40×; Gömöri); (D): First biopsy revision: epidermis, papillary, and superficial reticular dermis (4×; HE); (E): First biopsy revision: Absence of fungus (40×; Gömöri), (F): Second biopsy revision: *P. brasiliensis* (40×; Gömöri); (G): Third biopsy revision: *P. brasiliensis* (40×; Gömöri).

Immunological reasons account for this presentation. Individuals with sarcoid-like lesions within the so-called hyperergic pole exhibit good specific immunity against *P. brasiliensis* and stimulate the response of T helper 1 lymphocytes. This event leads to the typical organized tuberculoid granuloma arrangement. Usually, patients have few lesions, and these lesions show a paucity of fungi. However, at any time, failure of cellular immunity may lead to changes in the T helper response 2 with increased suppressive action of interleukin-10, interleukin-5, and transforming growth factor-β; these cytokines are responsible for fungal multiplication, dissolution of granulomas, and spread of disease. This contributes to the emergence of the typical clinical picture, as occurred in the present case, where the onset of ulceration led to the diagnosis; the final diagnosis was possibly favored by immunosuppression due to prolonged use of high doses of corticosteroid[6-9].

Histological diagnosis of tuberculoid granuloma is possible when there are characteristic features of a specific disease or sufficient quantity of infectious agents to be detected using special staining techniques. It is noteworthy that perineural inflammation may occur not only as a clinical neurological symptom in leprosy, but also in other diseases such as syphilis, herpes virus infections, and PMC[10]. If available, more sensitive methods, such as immunohistochemistry and polymerase chain reaction, can establish an accurate diagnosis[4,11,12].

The major failure detected in the conduct of the current case was the lack of communication between the clinician and the pathologist. This contributed to the delay in diagnosis, since the use of special stains for fungi could have identified the etiologic agent at the very beginning. Additionally, the positive epidemiology for leprosy and the clinicohistopathological aspects common to endemic diseases in Brazil contributed to the misdiagnosis. However, the persistence of the lesion after two cycles of MDT should have alerted the need for another diagnosis. Instead, there was rapid improvement with itraconazole.

Marques et al.[4] reported a similar case, but with important systemic involvement. According to the authors, dapsone, a sulfonamide derivative present in MDT, could have delayed the clinical evolution of their patient; this may have also occurred in our case, since sulfonamide is an alternative option for the treatment of PCM[4].

The diagnosis of sarcoid-like lesions is challenging when there is no obvious cause for the granuloma. The history and the clinicohistopathological correlation, with cooperation between the clinician and the pathologist, is essential to confirm the diagnosis. It is necessary to persist in such investigations until identifying the causative agent.

Conflicts of interest

The authors declare that there is no conflict of interest.

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