Destructive genital and oral ulcers in rural patients

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A 45-year-old man (Case 1) from a rural area in the state of Rio de Janeiro, Brazil presented with a 2-year history of dry cough and an extensive ulcerated genital lesion (Fig 1, *A*). Chest radiography showed a bilateral perihilar infiltrate. A 56-year-old man (Case 2) from the countryside of Rio de Janeiro presented with a 14-month history of an ulcerated tongue (Fig 2, *A*), dysphagia, and weight loss. In both cases, clinical samples were collected for histologic examination using hematoxylin-eosin (Figs 1, *B* and 2, *B*) and Grocott methenamine silver (Figs 1, *C* and 2, *C*) stains. Figures 1, *D* and 2, *D* depict the clinical development after treatment.

Question 1: Considering the clinical and histopathologic images, what is the most likely diagnosis for both cases presented?

A. Squamous cell carcinoma (SCC)

B. Leishmaniasis

C. Paracoccidioidomycosis (PCM)

D. Syphilis

E. Tuberculosis

Answers:

A. SCC — Incorrect. SCC is commonly seen in oral and genital areas, where it can be ulcerative and destructive. However, the histologic findings of SCC are dermal aggregations of atypical keratinocytes.

B. Leishmaniasis — Incorrect. Leishmaniasis is endemic in South America. Patients infected with *Leishmania* spp. can present ulcerations in the mouth, nose, and—rarely—genital mucosa. However, the histologic findings in patients with leishmaniasis are granulomatous dermatitis along with amastigotes parasitizing macrophages.

C. PCM — Correct. PCM is endemic in many countries in Latin America.[1] Mucocutaneous lesions are common, typically have hemorrhagic dots on their surface, and can be single or multiple, ulcerated, and infiltrated.[2] While oral involvement is common, genital lesions are rare.[3,4]

D. Syphilis — Incorrect. The chancre (primary syphilis) occurs 10-90 days after infection as a firm painless ulcer and the mouth is sometimes the primary site. However, the histological findings of syphilis are abundant plasma cells underlying the ulcer, granulation tissue, and obliterative endarteritis.

E. Tuberculosis — Incorrect. Although mucosal tuberculosis is rare, it can be destructive. The tongue is the most common site of oral lesions, and genital involvement is very rare. Histologically, complete granulomas may be observed around the ulcer, and *Mycobacterium tuberculosis* may be visible.

Question 2: Histopathologic examination, a highly sensitive method of diagnosing PCM, demonstrated the presence of a chronic, ulcerated, suppurative, granulomatous, inflammatory process, and multiple budding structures typical of *Paracoccidioides* spp., better seen in Grocott silver staining, in both cases. Which of the following is the best option for a rapid and cost-effective diagnosis of PCM in endemic countries?

A. Direct microscopy with potassium hydroxide preparations

B. Culture

C. Serology

D. Intradermal reaction

E. Polymerase chain reaction (PCR)

Answers:

A. Direct microscopy with potassium hydroxide preparations — Correct. The visualization of fungal elements typical of *Paracoccidioides* spp. is effective for PCM diagnosis, and direct microscopy allows a low-cost and rapid fungal identification.[2]

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B. Culture — Incorrect. Culture is effective, but it is often not available in rural settings. *Paracoccidioides* spp. usually takes 2 to 3 weeks to grow, and, as a dimorphic fungus, morphological conversion is necessary for diagnostic confirmation. A rapid method is important for an early diagnosis.

C. Serology — Incorrect. Serological methods for antibody detection are cost-effective and play an important role in PCM diagnosis and treatment follow-up.[2] Immunodiffusion is currently the main method employed. However, sensitivity varies from 65% to 100%, negative results can occur in 21% of acute forms and 7.3% of the chronic forms, and it is not widely available in rural settings.

D. Intradermal reaction — Incorrect. Intradermal application of paracoccidioidin antigens detects PCM infection.[1,2] It is often used in epidemiological surveys but not for diagnosis of the disease due to its low specificity.

E. PCR — Incorrect. Primers and probes have already been designed and standardized for molecular diagnosis of *Paracoccidioides* spp., and the use of PCR will be of great value for early diagnosis. However, it is currently not cost-effective and is yet to be validated for routine clinical use.

Question 3: What is the most appropriate treatment for PCM in these patients?

A. Amphotericin B

B. Surgical procedures

C. Fluconazole

D. Itraconazole

E. Ketoconazole

Answers:

A. Amphotericin B — Incorrect. Amphotericin B (deoxycholate or in lipid formulations) is effective in the treatment of PCM. However, it is indicated for severe and disseminated forms of PCM.[2]

B. Surgical procedures — Incorrect. Considering that PCM is a multifocal disease and mucocutaneous lesions are secondary to hematogenous dissemination from the lung, surgical treatment is not effective for reducing morbidity, mortality, or sequelae.

C. Fluconazole — Incorrect. Despite its *in-vitro* activity against *Paracoccidioides* spp., there is a lack of clinical experience with regard to its use for PCM treatment. Fluconazole is used in some cases, such as patients with liver disease or in combination with sulfamethoxazole/trimethoprim in neurological PCM.[2]

D. Itraconazole — Correct. Itraconazole at a dose of 200 mg daily for 9 to 18 months is the first-line treatment for mild and moderate forms of PCM due to its efficacy and safety. Sulfamethoxazole/trimethoprimat a dose of 800/160 mg twice or three times a day for 18 to 24 months is the second-line treatment. Nevertheless, it is often the first choice due to its large availability in Brazil.

E. Ketoconazole — Incorrect. Ketoconazole is effective in the treatment of PCM. However, the Food and Drug Administration warns that it should not be used as a first-line treatment for any fungal infection because there are safer options, and it can cause severe liver injury.

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Abbreviations used:

PCM: paracoccidioidomycosis
PCR: polymerase chain reaction
SCC: squamous cell carcinoma

Conflicts of interest

None disclosed.

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