A gingival manifestation of histoplasmosis leading diagnosis

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Abstract

Histoplasmosis is a world-wide distributed deep mycosis caused by *Histoplasma capsulatum* which has been endemic in many countries. We present a case involving an immunocompetent man evidencing the necessity of a multidisciplinary approach and rational requisition of exams. The disease has started as a pulmonary disease mimicking tuberculosis, although the exams have been negative. Immunodiffusion test indicate histoplasmosis, not confirmed by culture of sputum. After days the patient was forwarded by a private doctor for evaluation of oral lesions at our Department of Stomatology. An incisional biopsy revealed a nonspecific granulomatous inflammation and the Grocott-Gomori methenamine silver stain identified scarce oval structures that could represent fungal yeast. Sampling oral lesions with swab, it was observed the typical growth of *H. capsulatum* on culture. This case highlights the importance of doctor's integration diagnosing histoplasmosis, while a wide spectrum of clinical manifestations should be expected. Oral lesions may be the critical manifestation leading diagnosis.

Keywords: Diagnosis, histoplasmosis, multidisciplinary communication, oral

Introduction

Histoplasmosis is a cosmopolitan mycosis with areas of particularly high endemcity, mainly in countries of the American continent. In Brazil, the contact with the fungus ranges from 2.6% to 93.2%.[1-4] The etiological agent is either *Histoplasma capsulatum* var. *capsulatum* or *H. capsulatum* var. *duboisii*, being the late restricted to African regions. The fungi are preferentially found in regions of a moderate climate with constant humidity, especially in soil enriched by bat and bird drops. After inoculation of propagules, patients usually manifest the so-called primary acute form, which is often a self-limited disease with mild or no symptoms. The progression of the infection depends on the dose of aerosol inhalation, virulence of the pathogen and the immunological status of the host.[5] In this way, more severe forms includes: (1) The chronic pulmonary form, often occurring in the presence of underlying pulmonary disease; and (2) a disseminated form, which is characterized by the progressive spread of infection to extra-pulmonary sites. The proper indication of cases depends on the experience of the clinicians, often involving a multi-disciplinary approach. The culture represents the gold standard exam confirming the diagnosis, but serology and histology usually precedes it.[5,6]

Oral manifestations have been reported as the main complaint of the disseminated forms, leading the patient to look for assistance, whereas pulmonary symptoms may be mild or even misinterpreted as flu.[3-6] The present paper was approved by de local Ethics Committee under the register 15854. Here we discuss a case of disseminated histoplasmosis and the challenges disclosing the diagnosis. In addition, we highlight the importance of a multi-disciplinary approach with a fundamental participation of the dentistry.

Case Report

A 43-year-old man was referred to the Department of Stomatology at the Heliopolis Hospital by a private dentistry complaining oral lesions. The lesions were asymptomatic and oral examination revealed ulcerative areas with granulomatous bed affecting the gingival papillae between lower central incisors, partially covered by a pseudomembranous material [Figure 1]. On physical examination, no regional and extra-regional lymphadenopathy or organomegaly was detected.

His medical history includes episodes of dry cough, costal pain, and weight loss under medical investigations. The chest radiography [Figure 2a] and computed tomography scan [Figure 2b] of the thorax have revealed a diffuse infiltrate of nodular and linear/irregular coalescent opacities, distributed throughout both lungs [Figure 2]. The hypothesis of tuberculosis has been discussed at that moment in spite of negative results for acid-fast bacilli from sputum and culture. The CD4/CD8 lymphocyte count and rate were normal. Tests for human immunodeficiency
virus (HIV) were negative. Among the requested serological exams, it has been found antibodies against *H. capsulatum* on immunodiffusion test. However, culture and histology of the specimens obtained by bronchoalveolar lavage failed to confirm the presence of fungi. Thus, the patient remained under this medical investigation without any specific treatment plain at that moment, in which the patient was evaluated by a private dentist complaining the gingival lesions described previously.

We conducted the case performing an incisional biopsy of the oral lesion. Routine sections show fragments of squamous mucosa with a marked granulomatous infiltrate composed by Langhans-type multinucleated giant cells interspersed with extensive macrophagic infiltrate with variable amounts of lymphocytes and neutrophils [Figure 3a]. Staining slides with Grocott-Gomori methenamine silver, scarce oval structures with apparent single budding, measuring 3-5 mm in diameter were found suggesting histoplasmosis [Figure 3b]. A specimen was collected with a swab from the base of lesion and sent to culture. In slide culture preparations, hyaline and septated hyphae producing numerous thick-walled and tuberculated macroconidia were also consistent with histoplasmosis [Figure 3c]. The incubation of this material on Sabouraud Dextrose Agar at room temperature by 3 weeks was sufficient to reveal the typical growth pattern of *H. capsulatum*, which consists of white to brownish filamentous colonies on the slants [Figure 3d]. The patient was treated with itraconazole 200 mg, given 6 times/day, reducing to two tablets per day after the 3rd day until the condition improves [Figure 4]. After 6 months of control the patient was referred again to his private dentist for periodontal and restorative treatment plain.

**Discussion**

The etiological agents of histoplasmosis are both *H. capsulatum* var. *capsulatum* and *H. capsulatum* var. *duboisii* (African form). The fungi are preferentially found in soil enriched with droppings of birds and bats and the infection occurs by aspiration of its mycelia. The contact has been related to excavations, activities in caves, chicken coops, and farm works. At the lung temperature the hyphae elements convert to yeasts, surviving and replicating in the host macrophages. The disease is often self-limited in individuals with appropriate cellular immune responses, with development of a T-lymphocyte-mediated immunity with fungistatic activation of macrophages. Disturbances of immune responses allow for the evolution of the disease where the HIV is the most commonly related agent. Other factors include transplantation, chronic renal disease, prolonged use of corticosteroids and extreme ages (<1 year or >65 years). On the other hand, disseminated histoplasmosis has been reported in immunocompetent patients like the present one, representing a lifelong chronic condition which can erupt in active disease if the host-pathogen balance is disrupted. We have not identified any source of immunodeficiency in our patient.

Clinically, there was a wide spectrum of disease manifestation. The pulmonary restricted forms are the most common. However, pulmonary symptoms can be identified in all forms. Usually, minor symptoms like a patchy pneumonitis, which is resolved within 1-2 weeks are related. Fever and persistent cough associated with weight loss and chest pain are seen for chronic cases, which can be easily misinterpreted as tuberculosis, as occurred with our patient. This hypothesis could not be completely discarded by microscopy and culture because cases of sputum smear negative tuberculosis have increased in the medical practice. The suspicious of pulmonary histoplasmosis also could not be confirmed by microscopy and culture. In fact, there are limitations of exams sensitivity. According to literature, for cases in immunocompetent patients, for example, serology is positive in 80-100%, immunodifusion in 71-100%, culture in 58-90% and histopathology in 40-61%. In this meaning, the diagnosis has been established by a combination of clinic, epidemiologic and an additional laboratory exam, considering the positivity in culture as the current gold standard method. In the present case, histology and culture of the sputum were negative. We received the patient at the Department of Stomatology referred by a private dentistry, and an incisional biopsy was performed. However, it is noteworthy that a cytology could have been performed by him as a reasonable sensitive and more accessible technique to non-specialists for investigation of infectious diseases.

The oral histology slides stained with Grocott-Gomori methenamine revealed scarce but non-convincing structures which could be compatible with *H. capsulatum*. Considering its previous exams, the possibility of artifacts, as well as small forms of *Cryptococcus neoformans*, *Blastomyces dermatitidis*, *Paracoccidioides brasiliensis*, *Candida glabrata* and *Pneumocystis carinii*, should not be completely discarded. We confirmed the diagnosis of histoplasmosis after positivity in culture from material of oral lesions. Herein, it is suggestive that our patient have a low fungal burden, and the experience and the integration of dentistry and the medical team was decisive to made the repetition of tests and further research, avoiding a missed diagnosis and an empiric therapy. Promissory exams involving nucleic acid amplifications have been proved to be faster and most sensitive, but the costs and accessibility of these exams are still prohibitive in most institutions of developing countries.

Oral lesions of histoplasmosis can be found in up to two-thirds of the patients with disseminated diseases and may represent the first sign of the disease. To HIV-positive patients, the lesions represents an AIDS sign. The oral lesions may be ulcerative, nodular, plaque-like, vegetative, and can resemble any granulomatous disease, mostly affecting tongue, buccal mucosa, larynx, gums, and lips. It should be included in the differential diagnosis other infectious causes such as tuberculosis, syphilis, paracoccidioidomycosis and sometimes squamous cell carcinoma. Thus, a full investigation of the patient can be necessary to the diagnosis. The final diagnosis...
**Figure 1:** Intraoral aspect showing an ulcerative lesion with a granulomatous aspect destructing the gingival papilla between the central incisors

**Figure 2a:** Radiography showing bilateral peri-hilar pulmonary involvement

**Figure 2b:** Pulmonary computed tomography scan of patient showing nodular opacities of varying sizes, with scattered areas of consolidation

**Figure 3a:** Photomicrography (Hematoxylin and Eosin) showing a granulomatous reaction with formation of Langhans-type giant cells and prominent macrophages (×20)

**Figure 3b:** Section stained with Grocott-Gomori methenamine silver showing an isolated giant cell containing elliptical structures with apparent single budding from the small end by a narrow base (×100)

**Figure 3c:** Slide culture preparation stained with lactophenol cotton blue showing hyphae and the tuberculate macroconidia
of the present case was made only after appearance of oral lesions. Akin et al.,[6] reported a case with oral lesions initially diagnosed as osteomyelitis and empirically treated. After observation of multiple ulcers involving the intestinal tract on colonoscopy, the doctor required reevaluation of the histology of oral lesions, revealing the diagnosis of histoplasmosis. In our case, it has been happened the contrary, being the dentistry the protagonist establishing the investigation leading to diagnosis. Both situations highlights that examination of oral cavity is fundamental to diagnose this systemic disease and that dentistry must be integrated and inserted in hospitals.

The treatment varies according to the host status and the clinical form of histoplasmosis. Our patient had the chronic disseminated form and any type of immunodeficiency was detected. According to a guideline summarizing the most adequate therapies, the Itraconazole represents the drug of choice for the majority of cases. For cases with relapse or severe disease, amphotericin B seems to be the best alternative.[10] The mortality rate is only high for untreated systemic disease, approaching 80%.[14]

**Conclusion**

We have observed in the present case the importance of a correct communication between all doctors diagnosing histoplasmosis, since a wide spectrum of disease presentation has been observed, and complementary exams have limitations. Our patient presented initially with an apparently restricted pulmonary histoplasmosis with discordant results between serology, microscopy and culture. Further, the appearance of oral lesions has supported the suspicious of histoplasmosis and new exams from oral lesion demystified the diagnosis.

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