Case report

Synchronous oral paracoccidioidomycosis and oral squamous cell carcinomas with submandibular enlargement

REBECA SOUZA AZEVEDO*, ADRIELE FERREIRA GOUVÊA†, MÁRCIO AJUDARTE LOPES†, MARCELO BRUM CORRÊA‡ & JACKS JORGE†

*Oral Pathology, School of Dentistry, Fluminense Federal University, Nova Friburgo, Rio de Janeiro, †Oral Diagnosis, Piracicaba Dental School, State University of Campinas, Piracicaba, São Paulo, & ‡Oncology Center, Hospital dos Fornecedores de Cana de Piracicaba, Piracicaba, São Paulo, Brazil

Oral paracoccidioidomycosis and oral squamous cell carcinoma may occur in the same patient. As both lesions may present similar clinical and histopathological features, the diagnosis is sometimes challenging. This paper describes the case of a 54-year-old male who was a farm worker and heavy alcohol and tobacco user. He developed paracoccidioidomycosis and two lesions of squamous cell carcinoma in the oral cavity. During the follow-up, the patient presented enlargement of the submandibular lymph nodes, which was thought to be regional metastasis but was diagnosed as paracoccidioidomycosis. Therefore, the significance of this association is emphasized and discussed.

Keywords: paracoccidioidomycosis, squamous cell carcinoma, oral cavity, lymph node, differential diagnosis.

Introduction

Paracoccidioidomycosis is a granulomatous infection caused by the dimorphic fungus Paracoccidioides brasiliensis, a rare infection worldwide but endemic in Central and South America, especially in rural areas of Brazil [1,2]. The infection induces a host immune response that leads to a large spectrum of clinical presentations including skin and mucous membranes, lymph nodes and visceral organ involvement [1].

Squamous cell carcinoma accounts for more than 90% of oropharyngeal malignancies, which usually occurs in the tongue of adult males with a history of tobacco and alcohol abuse. However, the incidence in woman and young people is increasing [3,4].

The association between cancer and paracoccidioidomycosis has been recognized since 1933 [5], but its incidence has been debatable since that time [6–8]. Paracoccidioidomycosis may clinically resemble a malignancy of the oral cavity [9,10], as well as appear at other sites such as the larynx and biliary tract [11,12]. In addition, it may be histologically misdiagnosed as a squamous cell carcinoma, especially because of the characteristic pseudoepitheliomatous hyperplasia [13]. Furthermore, paracoccidioidomycosis and cancer may occur simultaneously in the same patient, affecting close anatomical areas or distant sites [8]. For example, the occurrence of oral and lung paracoccidioidomycosis with oral squamous cell carcinoma [14] or oral paracoccidioidomycosis with lung carcinoma [9]. This association may be caused by the imbalance between cell and humoral immunity observed in patients with active paracoccidioidomycosis [8]. There is an increase in Th2 type immune response with deficiencies of macrophage and natural-killer lymphocyte activity as a result of transitory impairment of host response to fungal cell antigens [15,16].
Therefore, this paper describes a case of synchronous oral paracoccidioidomycosis and oral squamous cell carcinoma in a patient who developed a submandibular lymph node enlargement and discusses their association and the diagnostic approach.

Case report

A 54-year-old man was referred to the Oral Diagnosis Clinic at Piracicaba Dental School, State University of Campinas, complaining of a burning mouth sensation lasting 4 months. He was a farm worker, with a history of tobacco smoking and alcohol abuse since the age of 10 years old. His oral mucosa showed the typical finely pinpoint granular hemorrhagic tissue proliferation with a mulberry-like appearance involving lower alveolar ridge, floor of mouth, lower labial mucosa, and right buccal mucosa (Fig. 1A & B). There was also a superficial ulcer measuring about 0.5 cm on the left hard palate. He was otherwise healthy and, as a result of the main clinical hypothesis of paracoccidioidomycosis, an incisional biopsy of the lower lip was performed under local anesthesia. Microscopic analysis revealed prominent pseudoepitheliomatous hyperplasia and dense mixed inflammatory infiltration with macrophages, lymphocytes, plasma cells, neutrophils and eosinophils dispersed in the connective tissue and migrating into the epithelium. There were also numerous epithelioid macrophages, multinucleated giant cells arranged in a granulomatous pattern, and round double-layered yeasts characteristic of Paracoccidioides brasiliensis (Fig. 2A & B), identified in Hematoxylin and Eosin, Periodic Acid Schiff, and Grocott-Gomori methenamine silver stained material, leading to the diagnosis of paracoccidioidomycosis (Fig. 2C & D). After general medical evaluation, lung involvement was detected and treatment with oral fluconazole (150 mg twice daily) was started. After two months, all oral lesions had healed except for the palatal lesion. Therapy was switched to sulfonamides with a combination of sulfamethoxazole (400 mg) and trimethoprim (80 mg) twice daily that was maintained for 4 months. The left hard palatal lesion persisted and an ulcerated exophytic polypoid nodule measuring 1.0 × 1.0 × 0.8 cm was noticed in the right soft palate and two reddish papules measuring each 0.5 × 0.5 cm on the lower labial mucosa (Fig. 1C & D). These areas were all biopsied under local anesthesia and microscopically, the labial lesions showed

Fig. 1 Clinical view of oral lesions. (A) Multiple finely granular hemorrhagic pinpoint erosions with a ‘mulberry-like appearance’ presented in the lower labial mucosa and buccal fold. (B) Left buccal mucosa, diagnosed as paracoccidioidomycosis. (C) Left hard palate ulcer with reddish edges. (D) Right soft palate polypoid granular exophytic whitish mass, both diagnosed as squamous cell carcinoma.
normal parakeratinized squamous stratified epithelium overlying a conspicuous fibrous connective tissue. However, observation of both palatal areas revealed a malignant proliferation of squamous stratified epithelium cells as sheets or islands into the connective tissue, contributing to the diagnosis of squamous cell carcinoma (Fig. 3A & B). Except for slight neutrophilia and eosinophilia, all preoperative blood tests were within normal limits and the patient was referred to an Oncology Treatment Center and submitted to surgery and radiotherapy. At 18-month follow-up, the patient presented weight loss and bilateral submandibular enlargement with two hypoechoic areas in the left submandibular gland. Fine needle aspiration biopsy (FNAB) was performed twice showing only hemorrhage

Fig. 2  Histological features of oral paracoccidioidomycosis. (A) The overlying mucosa showing pseudoepitheliomatous hyperplasia, an intense subepithelial inflammatory infiltrate (hematoxylin and eosin stain, original magnification, ×50). (B) Exocytosis, multinucleated giant cells and yeast of Paracoccidioides brasiliensis (black arrow) (hematoxylin and eosin stain, original magnification, ×400). Periodic acid Schiff stain (C) and Grocott-Gomori methenamine silver method (D) showing characteristic multiple peripheral budding of Paracoccidioides brasiliensis (original magnification, ×400).

Fig. 3  Histological features of oral squamous cell carcinoma (hematoxylin and eosin stain). (A) Parakeratinized squamous stratified epithelium showing severe dysplasia and invasive carcinoma in the left hard palate (original magnification, ×100) and (B) in the right soft palate (original magnification, ×200).

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and scarce epithelial and inflammatory cells. Because of the non-specific FNAB analysis and probably evidence of metastatic squamous cell carcinoma, the surgeon decided on a bilateral supraomohyoid neck dissection under general anesthesia. Hematoxylin and eosin stained slides showed granulomatous reaction with epithelioid and giant cells, and yeast cells characteristic of *Paracoccidioides brasiliensis* within the lymph nodes (Fig. 4). Prominent amounts of fibrous tissue interspersed the submandibular salivary glands parenchyma associated with acini atrophy and some inflammation were observed and were consistent with the diagnosis of radiation-induced fibrosis. At this time, the patient developed new mulberry-like palatal lesions and conceded that he had discontinued the paracoccidioidomycosis treatment without medical order since the initiation of cancer treatment. Salvage antifungal therapy with a combination of sulfamethoxazole (400 mg) and trimethoprim (80 mg) twice daily was restarted and oral lesions healed in three weeks. The patient is still taking antifungal medicine and is in follow-up for 18 months, without signs of any recurrences (Fig. 5).

**Discussion**

In 1933, Rabello Filho was the first to describe an association between paracoccidioidomycosis and neoplasia in a patient having systemic erythematous lupus. The patient presented paracoccidioidomycosis and upper lip basal cell carcinoma [5]. Since then, other authors have published case reports, series of cases, cohort studies and case-controlled investigations concerning the association between paracoccidioidomycosis and cancer occurring either in the same area or in different sites, simultaneously or not [8].

A number of mycotic and cancer associated sites were described, including the oral cavity that might be affected by the infection, neoplasia or both [8]. Most of the malignant tumors were squamous cell carcinoma and occurred in the same region or in adjacent tissues involved in the fungus infection [6–8]. Interestingly, these patients with cancer also had similar clinical profiles as observed in patients with paracoccidioidomycosis, such as gender, age and social behaviors [8]. Furthermore, the carcinoma was most commonly diagnosed after the concomitant infection [8]. The present case also showed both diseases in the oral cavity but in different areas with paracoccidioidomycosis being the first diagnosis, probably as a result of the disseminated and exuberant appearance of this infection.

The relative frequency of malignant tumors in paracoccidioidomycosis patients varies from 0.2–14.1% [8], whereas it had a relative frequency of 4.2% and 19.5% in general autopsied patients in the only two control groups reported in the literature [6,7]. These differences may be due to the criteria used in each study and make this relationship debatable, i.e., is the cancer incidence actually increased in cases of paracoccidioidomycosis or is cancer incidentally observed in the general population.

In general, paracoccidioidomycosis’ immunopathology is characterized by initial Th1 lymphocyte response and later Th2 lymphocyte response causing a dysfunction with increased humoral immunity and decreased cellular immunity function [1,2]. Since cell-mediated immunity is involved in identifying and killing tumor cells, the impairment of macrophages and natural killer cells activities can predispose immortalization of epithelial or lymphoid cells displaying malignant transformation as the result of continuous *Paracoccidioides brasiliensis* antigens stimulation [8].

Besides that, paracoccidioidomycosis may mimic a malignant lesion, either with respect to its appearance or microscopic features [8]. Paracoccidioidomycosis has various
forms of presentation [1,2] and may mimic a malignancy in the biliary tract [12], larynx [11], prostate [17] and oral cavity [9,10], where the typical multifocal appearance can be replaced by a single ulcer [10]. The present case showed the classical mulberry-like appearance involving multiple sites of the oral cavity not resembling an oral cancer even in the palatal lesions. It is noteworthy to note that the patients in the earlier studies had similar social histories with tobacco smoking and alcohol drinking [9,10], as those observed in the present patient. Tobacco and alcohol abuse are the major risk factors involved in oral and oropharyngeal squamous cell carcinoma pathogenesis [3,4]. Although activities associated with handling soil containing Paracoccidioides brasiliensis fungus is the most important risk factor for the infection acquisition, tobacco and alcohol use are also common social habits reported by patients with paracoccidioidomycosis [2,18]. Microscopically, paracoccidioidomycosis is characterized by a granulomatous reaction rich in multinucleated giant cells and interspersed with variable amount of double-layered yeasts [1,12]. It is common to observe pseudoepitheliomatous hyperplasia of the overlying epithelium, a reactive process that may be difficult to distinguish in small samples of oral squamous cell carcinoma [1,13,19]. In our case, histopathology of both lesions was undoubtedly different, but some authors had suggested the usage of ki-67, p53, E-cadherin and metalloproteinase-1 qualitative immunohistochemical staining as adjunct diagnostic tools [13,19].

Subsequent to inoculation, which usually involves the lung, the fungus can spread to other tissues by lymphatic or hematogenic pathway affecting especially the oral cavity and lymph nodes [1,2]. Cervical and abdominal lymph node involvement is most commonly observed in mucous membranes dissemination and it is characterized by a diffuse coalescent enlargement that frequently evolves to cutaneous fistula with purulent drainage [1,2,12,20]. In the same way, cervical lymph nodes are the most common sites to metastatic deposits from oral and oropharyngeal carcinomas and drastically reduce cure rates [21,22].

Soft palate tumors have three main lymphatic drainage routes, mainly including ipsilateral and contralateral group II, ipsilateral group III cervical lymph nodes, and in cases of clinical or medical imaging, N1 or N2 cervical metastasis, selective neck dissection seems to be the best approach [21,22]. Although in the same anatomic region, the submandibular gland is uncommonly involved in oral squamous cell carcinoma, which may occur as a result of direct invasion from the primary tumor or from adjacent or intraglandular lymph node metastasis [23]. The patient described in the present case had a submandibular enlargement with underlying diseases that may both affect submandibular lymph nodes. Since fine needle aspiration cytology is a noninvasive useful diagnostic tool for systemic infections [20,24] and malignant diseases [25], it was our first approach. However, we were not able to achieve the diagnosis, the patient continued to experience weight loss, there were multiple ultrasonographic images in the submandibular gland and the possibility of locoregional metastasis diagnosis was still present. Accordingly, a bilateral supraomohyoid neck dissection including the submandibular salivary gland was performed, the paracoccidioidomycosis diagnosis was obtained and the patient was properly treated.

The treatment of paracoccidioidomycosis is based on systemic antifungal therapy and while there is no consensus on its duration, it is known that it is necessary to obtain clinical, radiological and immunological cure [1,2,18,26]. Recurrences are common, especially if the patient discontinues the treatment [2], as occurred in our case, even 10 years after ‘an apparent cure’ was obtained [26]. In addition, it is well-recognized that patients may develop the disease decades after the infection, which is partially explained by fungus adaptation ability [1,2,7,28].

The synchronous occurrence of oral paracoccidioidomycosis and oral squamous cell carcinoma may be coincidental or may be justified by the immunopathogenesis of Paracoccidioides brasiliensis infection. The fact is that these conditions can occur in the same patient, simultaneously or not, they should both be included in the differential diagnosis of oral ulcers, even in a patient with a previous history of paracoccidioidomycosis or cancer.

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References


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