Granulomatous ulceration of the palate

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CLINICAL PRESENTATION

A 55-year-old white man, a rural worker who did not smoke or consume alcohol, was referred to the oral medicine outpatient clinic of the School of Dentistry, São Paulo State University (UNESP), (Araçatuba, Brazil), for an extensive lesion in the palate; the lesion had evolved over a period of 3 years. In anamnesis, the patient reported that 9 years before he presented to our clinic, the ulcerated and painful facial skin lesions with fast evolution had been diagnosed as pyoderma gangrenosum, which was treated with 30 sessions of hyperbaric oxygen therapy. All of the infectious wounds healed, except for 1 on the left ear (Figure 1A).

Three years ago, the oral lesion appeared on the soft palate, and a nystatin mouthwash (twice a day for 1 month) was prescribed by a physician. There was no response to the treatment; 2 biopsies were performed at that time, but the analysis was inconclusive. The patient did not seek professional care for 2 years, but because of progression of the lesion, he finally came to the outpatient clinic of this center.

Intraoral examination revealed an extensive, painless, exophytic, bilateral ulcer, with a granulomatous surface on the hard palate extending to the soft palate, palatine tonsil, and posterior wall of the oropharynx (Figure 1B).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of granulomatous ulcers is quite wide. In the case described here, the differential diagnosis, which was made difficult by the previous inconclusive histologic analysis, included bacterial, fungal, and viral infections; malignancies; and chronic granulomatous diseases.

Bacterial infections, including tuberculosis (TB), syphilis, and leprosy, were considered in the differential diagnosis. TB is an infectious granulomatous disease caused by *Mycobacterium tuberculosis*, an acid-fast bacillus that is transmitted primarily via the respiratory route.[1,2] According to the World Health Organization, TB is responsible for approximately 2 million deaths each year. The primary disease generally affects the lungs and the disease subsequently spreads to other organs and systems, including the oral mucosa, through self-inoculation via infected sputum, blood, or the lymphatic system, characterizing the secondary stage of TB.[2] Although the clinical presentation is variable, oral lesions typically consist of ulcers with irregular borders and granulomatous surfaces, as seen in the present case, and the ulcers may be painful or asymptomatic.[1-3]

Syphilis is a sexually transmitted infection caused by *Treponema pallidum*[4,5] but may spread through vertical transmission or contaminated objects, as in hospital accidents with sharp instruments or needles.[4] Syphilis is called the "great imitator" because of its widely variable clinical presentation.[4] Syphilis has 4 stages: primary, secondary, latent, and tertiary.[4,5] The first sign of primary syphilis in the oral mucosa is a hard chancre, and the lips are the most affected of the extragenital sites.[5] Secondary syphilis mostly appears as white plaques, papules, or nodules.[5] However, at this stage, syphilis shows variable clinical presentations when affecting the oral mucosa. Oral granulomatous ulcers or erosions are commonly observed in secondary syphilis. The manifestations of the disease on the palms and soles are characteristic of this stage,[4] but these were not observed in our patient. After the secondary stage, the infection may undergo long periods of latency. Oral manifestation of the tertiary stage of syphilis is characterized by gumma formation, with severe tissue destruction.[4,5]

Leprosy is caused by *Mycobacterium leprae*.[6] It is considered a major public health problem, especially in the tropical countries, including Brazil, which ranks second with regard to the global number of cases (World Health Organization, 2016).[7] Oral lesions are usually asymptomatic; they may present as papules or nodules of reddish-yellow color, sessile, and firm on palpation and may evolve to ulceration and necrosis, affecting mainly the hard and soft palates.[6]

Paracoccidioidomycosis (PCM) is caused by the dimorphic fungus *Paracoccidioides brasiliensis*.[8-14]

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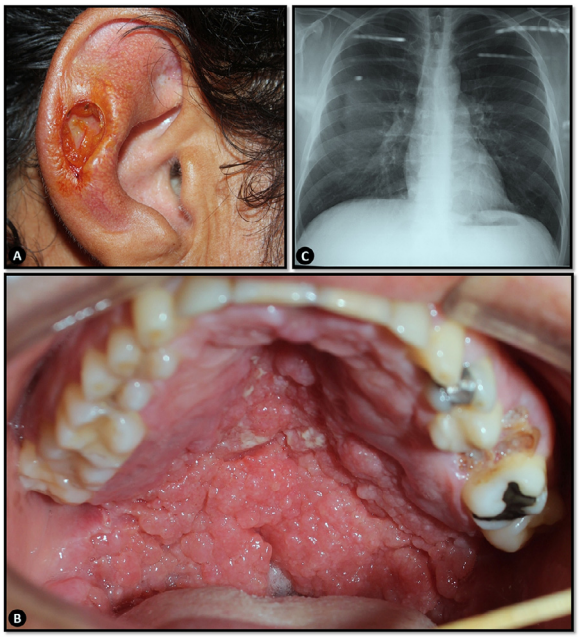

Fig. 1. **A,** Ear with sequelae of pyoderma gangrenosum. **B,** Extensive granulomatous ulcer on the palate extending to oropharynx. **C,** Chest radiograph imaging with no changes.

PCM is an systemic fungal infection that is endemic in Latin America.[8-14] In Brazil, it is the 18th highest cause of mortality among chronic or recurrent infections.[8,10] The primary disease generally affects the lungs, but oral mucosal lesions may be the first visible manifestation of the disease.[8,12,13] The most frequently observed oral manifestation is the presence of ulcers with hemorrhagic strawberry-like spots, and the most commonly affected sites are the lips and the oropharynx,[8-14] as observed in the present case.

Squamous cell carcinoma (SCC) represents greater than 90% of all oral cancers. It mainly affects males, between the sixth and seventh decades of life.[15] The lateral border of the tongue, the floor of the mouth, and the retromolar region are the most frequently affected sites, although SCC may occur at any oral mucosa surface.[15] Chronic tobacco smoking and alcohol drinking are the major risk factors for oral squamous cell carcinoma (OSCC).[15] The clinical appearance of an ulcer that develops within a few months suggests OSCC, but biopsy is mandatory to confirm the diagnosis.[11,12]

We also considered another malignant neoplasm, although it is unusual and very aggressive, was extranodal natural killer-/T-cell lymphoma, nasal type (NKTCL). Palatal ulcers have been observed in other cases.[16,17] Less frequently, anterior maxillary gingival ulcers with diffuse erythema have been reported.[16,17] NKTCL is characterized by fast destruction of the soft tissues of the upper respiratory tract.[18] Although it presents nonspecific symptoms, such as nasal obstruction, rhinorrhea, and epistaxis, NKTCL is a progressive disease. It is more frequent in males, and it has no age predilection.[18]

Polyangiitis (PA) is an idiopathic, systemic inflammatory disease characterized by chronic granulomatous inflammation.[19,20] Oral involvement of PA occurs in approximately 6% to 13% of the cases. The mouth can be the initial site of clinical presentation in a small fraction of the cases (5%−6%).[19] Oral manifestations of PA include oral ulceration of the buccal and/or lingual mucosa and of the floor of the mouth and hyperplastic gingivitis. The lesions may vary from red to purple in color, with many petechiae ("strawberry gingivitis").[19,20] Other features include delayed healing of extraction wounds and desquamation of the lips.[19]

Sarcoidosis is multisystemic granulomatous inflammation.[21] Clinical features of sarcoidosis in the head and neck are highly variable. Oral cavity lesions are commonly asymptomatic nodules or granulomatous ulcers that may affect the lips, tongue, hard/soft palate, buccal mucosa, or gingivae. Diagnosis of sarcoidosis is made by exclusion of other infectious, neoplastic, and granulomatous diseases.[22] Noncaseating granulomas with epithelioid cells, which are the histologic hallmark feature, generally enable the pathologist to distinguish it from other systemic granulomatosis.[22] Corticosteroids are the first choice in sarcoidosis therapy and may be used alone or in combination with a steroid-sparing agent, depending on the severity of disease.[22] Furthermore, although rare, this condition may be associated with pyoderma gangrenosum, either because of its natural course or as a result of the immunologic dysregulation caused by long-term corticoid therapy.[22]

DIAGNOSIS AND MANAGEMENT

In the case presented here, initially, blood tests were performed. Neither scoring nor morphology parameters were altered for red blood cells and white blood cells, thus ruling out an infectious process. Microbiologic culture of the sputum excluded TB and leprosy. Negative VDRL (Venereal Disease Research Laboratory) and FTA-ABS (fluorescent treponemal antibody absorption) tests excluded syphilis. Chest radiography did not demonstrate any alteration (Figure 1C). Human immunodeficiency virus type 1 (HIV-1) and HIV-2 test results were negative.

Biopsy and histopathologic analysis revealed granulomatous inflammation, with the presence of lymphocytes, epithelioid cells, and multinucleated giant cells (Figures 2A and 2B). Silver methenamine staining was negative for fungal infection (Figure 2C). Given the absence of malignancy and the presence of granulomatous inflammation suggestive of chronic infection, we decided to repeat the microbiologic culture experiments. At the time of collection of biologic material

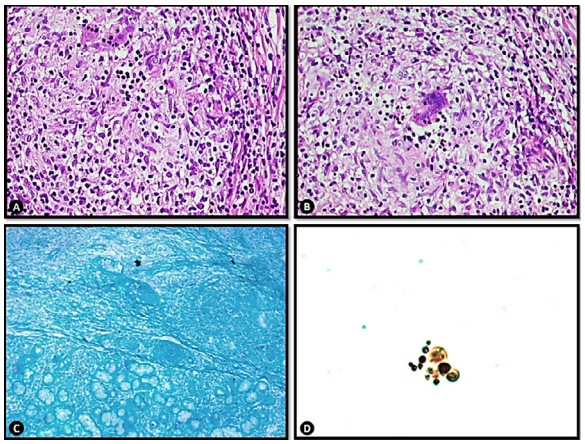

Fig. 2. **A,** Photomicrography showing lymphocytes, epithelioid cells (hematoxylin and eosin [H&E; original magnification × 400). **B,** Multinucleated giant cells forming a typical granulomatous inflammatory response (H&E; original magnification × 400). **C,** Grocott silver staining showing no presence of the fungus (H&E; original magnification × 100). **D,** Fungal cells of *Paracoccidioides brasiliensis* showing multiple budding of the fungal spores with a birefringent membrane (Gram stain; original magnification × 400). *A high-resolution version of the images A and B and of image C are available as Virtual Microscope eSlide: VM05814 and eSlide: VM05815.*

from the lesion, we set up a slide for cytologic analysis, in which we observed the presence of multiple budding of the fungal spores (Figure 2D), and the diagnosis of PCM was confirmed.

Immunodeficiency or other systemic diseases were ruled out, suggesting primary inoculation of the fungus in the oral mucosa.

DISCUSSION

PCM, also known as *South American blastomycosis*, is an endemic fungal infection in southern and southeastern Brazil and is caused by the dimorphic fungus *P. brasiliensis*.[8-14] The disease develops after inhalation of the conidiospores of the fungus, which reach the lower airways. Via lymphatic and hematogenous vessels, the infection may spread to other organs and systems, and to the oral and oropharyngeal mucosae through breathing and via sputum.[9,11-14] The primary inoculation of the fungus in the oral mucosa is rare, but as seen in the present case and as previously reported,[8,9] it may occur. Therefore, clinicians must be aware that the absence of symptoms in other organs and systems, including the lungs, does not rule out PCM. The manifestation of the disease depends on several factors, such as the virulence of the microorganism and the hormonal, genetic, nutritional, and immunologic status of the patient.[13]

PCM affects mainly adults between the third and fifth decades of life. Men involved in rural activities are generally more affected compared with women, at a ratio of 15:1.[8-14] This may be explained by the protective effect of the female hormones.[8] Beta-estradiol seems to inhibit the transformation of the PCM mycelium into yeast.[8,12-14]

The most frequently observed oral manifestations of PCM are superficial, poorly delimited ulcers characterized by hemorrhagic spots (strawberry-like ulcers) that may affect any part of the oral and oropharyngeal mucosae.[13] In the present case, the ulcer did not have the typical strawberry-like appearance, but its granulomatous appearance was still suggestive of PCM. In cases of PCM, the differential diagnosis usually includes conditions with a similar clinical appearance, such as OSCC, syphilis, TB, leprosy, and PA.[9,12,13] The atypical manifestation of the disease as a single oral ulcer that does not heal within 2 weeks may lead to suspicion of OSCC.[11,12] Given the inclusion of this malignant disease in the differential diagnosis, biopsy is mandatory for differentiation. Usually, the diagnosis of PCM on the basis of the presence of oral lesions is confirmed with histomorphologic analysis; silver methenamine staining may be helpful to detect the fungus if hematoxylin and eosin (H&E) staining does not reveal the spores.

In the present case, both the H&E and silver methenamine stainings were inconclusive, although the granulomatous inflammation observed in the H&E analysis was highly suggestive of a deep fungal infection. A direct smear was necessary for the final diagnosis. Although most clinicians make use of biopsy to diagnose PCM, Cardoso et al.[23] recommended direct smear examination as the primary diagnostic tool because it is fast and inexpensive, does not cause physical or psychological damage to patients, and has sensitivity of 67.9% and specificity of 91.7%. The cytologic smear, stained with either the silver methenamine stain or the periodic acid−Schiff stain is reliable for the diagnosis of PCM, on the basis of detection of round fungal structures with birefringent walls.[24] In the present case, direct smear examination was not only feasible, it was also essential for the diagnosis of PCM because the gold standard method was not conclusive. Given the experience with the present case and the evidence found in the literature, we recommend that the clinician individualize the management for each case and that exfoliative cytology be performed when suspicion of PCM is stronger than that of OSCC.

Among the main risk factors for the development of the chronic form of PCM is tobacco smoking. In greater than 90% of cases, the patients are smokers and their risk for developing mycosis is 14 times higher than in nonsmokers.[9] Alcohol intake may acts as a co−risk factor associated with smoking,[8] besides predisposing the organism to evolve to deep mycoses in

the presence of malnutrition and immunosuppression,[9,10] which contribute to an impaired immune response that favors fungal proliferation and dissemination.[11,12] However, in the present case, the patient did not have a history of such habits.

Coinfection by HIV is investigated in PCM cases as a routine because the infection is more common in immunocompromised patients and/or in older adults. HIV infection may exacerbate and mask the clinical characteristics of the lesions. Other immunosuppressive conditions, such as Hodgkin disease, leukemia, lymphoma, and carcinoma, especially lung, oropharyngeal, and laryngeal carcinomas, are also reported as comorbidities with PCM.[10]

Radiographic findings in posteroanterior thoracic lesions consist of nonspecific alterations, such as linear reticular opacities; nodules of various sizes; patchy, ill−defined opacities; airspace consolidation; and cavitation.[9] However, these changes were not found in our case.

Early diagnosis and appropriate clinical management are fundamental to preventing PCM and its complications. The most common diagnostic tools are direct smear examination and histopathologic analysis. In the present case, biopsy was performed because of its high sensitivity and specificity.[23,25] Furthermore, because OSCC is considered in the differential diagnosis, histomorphologic analysis is mandatory. In this case, the histopathologic analysis showed granulomatous inflammation with lymphocytes, epithelioid cells, and multinucleated giant cells. Silver impregnation and periodic acid−Schiff staining did not reveal the presence of fungi and yeasts.

Treatment of PCM is individualized, and rigorous follow-up is crucial. The choice of medications depends on the severity of the condition. Amphotericin B has been the treatment of choice for patients with PCM.[11] Ketoconazole, fluconazole, and itraconazole have been increasingly used as therapies for PCM and other systemic mycoses.[11,13] Treatment duration varies and requires patient compliance to avoid subclinical persistence of the infection or even death.[8,9] Cure is difficult because of the risk of relapse. Treatment success must be established through clinical and radiographic follow-up. Recurrence is common, but only among immunosuppressed patients.

CONCLUSIONS

PCM is a common infection in South America regions, but extremely rare in other regions. There is, however, a dearth of information in the literature regarding the ideal methods for diagnosing oral lesions. Although many authors have considered histologic analysis as the gold standard, exfoliative cytology seems to be more useful in specific cases. In this case, diagnosis was made more difficult because of the history of pyoderma gangrenosum and negative results on H&E and silver methenamine analyses. Thus, this case demonstrates that exfoliative cytology is not only advisable in the presence of clinical suspicion of PCM because of its easy applicability, low cost, and fast results but is also accurate, even when gold standard methods fail to yield an accurate diagnosis. However, because the differential diagnosis includes OSCC, clinical expertise is extremely relevant to the decision regarding the diagnosis method, to avoid pitfalls. The reason for the fungus not being detectable on biopsy, as shown in the present case, requires deeper investigation. Therefore, more accurate and individualized diagnostic guidelines must be developed to avoid delays in treatment.

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