Case Report: Unusual Otolaryngologic Manifestations of Paracoccidioidomycosis: A Case Report and Review of Literature

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Abstract. Paracoccidioidomycosis is a systemic mycosis caused by *Paracoccidioides brasiliensis*. It occurs more frequently in its chronic form, which particularly affects male adults from rural areas. These patients present with pulmonary involvement and systemic symptoms. Skin and mucosal lesions are rather typical and might suggest the diagnosis. The involvement of the upper airway mucosa is common and the patients usually complain of dysphagia and dysphonia. Nonetheless, in endemic areas, physicians should maintain a high level of suspicion even when faced with some atypical symptoms. We present the case of an adult diagnosed with nasopharyngeal paracoccidioidomycosis after presenting with an unusual otolaryngologic syndrome including unilateral soft palate paralysis with velopharyngeal insufficiency and hearing loss secondary to middle ear effusion.

CASE REPORT

A 31-year-old man attended the department of otorhinolaryngology at Federal University of Paraná, in Curitiba, Brazil, in January 2015, complaining of nasal obstruction, purulent rhinorrhea, and odynophagia. Fever or any other systemic symptoms were not reported. He had been treating in our Otolaryngology clinic for chronic sialadenitis, although at that moment he denied oral discharge and parotid or submandibular enlargement.

The patient had also been diagnosed with both selective IgM deficiency and Netherton syndrome, an autosomal recessive genodermatosis and primary immunodeficiency characterized by congenital erythroderma, a specific hair-shaft abnormality known as trichorrhexis invaginata, high susceptibility to infection, and atopic manifestations.

After this first assessment, he was treated with analgesics, nasal saline irrigations, rest, and hydration. Nonetheless, 2 months later, he presented to consultation for right aural fullness, hypernasal speech, and nasal regurgitation of fluids during swallowing. He reported having been already prescribed antibiotics and oral glucocorticoids, which did not improve his condition. Physical examination revealed apathy, weakness, persistent postnasal purulent discharge, halitosis, paralysis of the right soft palate, and a retracted right tympanic membrane with the presence of air/fluid level and bubbles. Laboratory data showed only mild normochromic, normocytic anemia (hemoglobin = 13.4; mean cell volume = 90.8; mean cell hemoglobin = 30.1). The patient underwent a flexible nasolaryngoscopy which revealed diffuse irregular thickened mucosal surface of the nasopharynx, with mechanical obstruction of the right ostium of the Eustachian tube. Direct visualization did not show any mass or laryngeal abnormalities. A nasopharyngeal guided biopsy was then performed. Histopathological assessment demonstrated squamous metaplasia on nasal mucosa and intense chronic granulomatous and acute suppurative inflammation within the lamina propria, in the presence of hematoxylin and eosin (H and E)-stained and Grocott-positive spherical yeast cells

with the typical mariner's wheel pattern of multiple budding (Figures 1 and 2). Chest radiography was normal and double immunodiffusion (IDD) test for anti-*Paracoccidioides brasiliensis* antigen came back negative.

Based upon the histological diagnosis of paracoccidioidomycosis (PCM), long-term trimethoprim/sulfamethoxazole (480/2,400 mg daily) treatment was initiated. After 15 days, the patient was reevaluated. He was no longer complaining of odynophagia, nasal obstruction, or nasal regurgitation of liquids. On examination, no purulent discharge, halitosis, or velopharyngeal incompetence was observed. However, otoscopy showed the persistent presence of a retracted dull right tympanic membrane, with retrotympanic fluid and bubbles. As the patient still reported right-sided hearing loss and right ear fullness which did not ameliorate over 3 months after the first assessment, he was managed with a right tympanostomy tube insertion. Follow-up within 7 and 30 days of the procedure revealed significant improvement also of his hearing complaints.

DISCUSSION

PCM (South American blastomycosis) is a systemic mycosis originally described in 1908 by Adolf Lutz in two patients presenting with oral lesions and cervical lymphadenopathy in São Paulo, Brazil.¹ South American blastomycosis is autochthonous in Latin America and most prevalent in South America. In Brazil, the disease has been more often diagnosed in the south, southeast, and central-west regions.² The causative agent of PCM is *P. brasiliensis*, a thermodependent dimorphic fungus usually isolated from the soil of endemic areas.¹

Clinically overt cases of South American blastomycosis represent only a small proportion of the individuals infected. Subclinical disease, detected by skin tests with paracoccidioidin antigen, occurs in up to 60% of the population in endemic areas.³ Overall, it is estimated that roughly 10% of the population in endemic countries is infected, although local annual incidence of the disease reaches 1–3 per 100,000.⁴ The infection is primarily acquired within the first two decades of life. Nonetheless, clinical manifestations are uncommon in this age range (5–10% of cases).⁵ Higher prevalence of PCM is found in adults from 30 to 60 years of age and in rural communities. The adult form of the disease clearly predominates in men (male-to-female prevalence ratio of 10–15:1).² The low incidence in women is considered to

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FIGURE 1. Hematoxylin and eosin–stained histopathology (400×). Photomicrography of the nasopharyngeal mucosa of a patient infected with *Paracoccidioides brasiliensis*. Chronic granulomatous inflammation with histiocytes (arrows) and central necrosis (asterisk). (Image provided by the Department of Anatomic Pathology of the Federal University of Paraná).

be due to hormonal effects as female hormones such as estrogen inhibit in vitro transformation of *P. brasiliensis* mycelial expression to its yeast-like forms.⁶

Immune factors seem important in the immunopathology of PCM. There is a correlation of T-cell depression with its severity.¹ The immunologic control of this mycosis depends on the TH-1 cellular immune response pattern, with production of interleukins 2 and 12 and interferon gamma leading to recruitment and activation of macrophages and lymphocytes and resulting in the formation of granulomas.⁵

Inhalation of the conidium environmental form of the fungus and transformation into yeast-like expression in human

FIGURE 2. Grocott-stained section, 400×. Photomicrography of the nasopharyngeal mucosa of a patient infected with *Paracoccidioides brasiliensis*. Spherical fungal structures, observed in an inflammatory background, with narrow-necked multiple budding—some of which resemble a Mickey Mouse head or a pilot's wheel (arrows). (Image provided by the Department of Anatomic Pathology of the Federal University of Paraná).

tissues, with a primary infection of lungs and dissemination via lymphatic and blood vessels is the most frequent mechanism of infection. Up to date, there is no evidence of human-to-human transmission of *P. brasiliensis*.¹

Primary pulmonary infection usually follows a benign and often symptomless course.¹ The acute/subacute form usually occurs among children, adolescents, and young adults. Clinical features include localized or (more frequently) generalized lymph node swelling, hepatosplenomegaly, digestive manifestations as well as cutaneous-mucosal and osteoarticular involvement. The lymph nodes enlargement often progresses to confluence, leading to the formation of large masses which might also suppurate. Fever, weight loss, anorexia, and fast progressive deterioration of general condition are present in most patients. Pulmonary involvement is less common.⁵ Reactivation of quiescent lesions is considered the main mechanism of adult chronic manifestations.¹ The chronic adult form is characterized by a more insidious evolution, whose symptoms might include weakness, weight loss, fever, cough, and dyspnea. Granulomatous lesions are responsible for the typical pulmonary involvement in chronic PCM and determine the bilateral reticulonodular infiltrates frequently seen in the upper two-thirds of the lungs.² When present, cutaneous lesions might be in various stages of development and include papules, nodules, nodules with ulcerations, and ulcers.⁷

The upper aerodigestive tract is frequently affected in the chronic form of PCM. Therefore, the patient might present with a wide variety of otolaryngologic manifestations which should lead the general practitioner or the specialist to the suspicion of PCM. Oropharyngeal involvement is usual and has been reported in up to 48% patients with the disease.⁸ The oral lesions are usually multiple, involving the lip, gingiva, oral mucosa, palate, tongue, and the floor of the mouth. These lesions typically show an erythematous finely granular hyperplasia of the mucosa, speckled with pinpoint hemorrhages, and a mulberry-like surface. The gingiva and alveolar processes are usually affected, resulting in exposure of dental roots, loosening and loss of teeth.⁹ The lips might show an increase in their consistency and thickness.¹ Although uncommon, oral PCM might result in hard palatal perforation.¹⁰ Involvement of the oropharynx, epiglottis, and larynx may cause hoarseness, sialorrhea, odynophagia, dysphagia, dysphonia, and/or cervical and submandibular lymphadenopathy. Eventually, tracheostomy might be needed due to scarring of the larynx. Other mucosal surfaces can also be affected causing conjunctival, nasal, or perianal lesions.² PCM should not be based only on the macroscopic aspect of the lesions, which is frequently unspecific and similar to that of other otolaryngologic granulomatous diseases.

Unusual manifestations of oropharyngeal involvement in PCM might occur due to damages to Eustachian tube and velopharyngeal sphincter. We herein reported a case in which both structures showed functional impairment, leading to unilateral hearing loss and aural fullness secondary to middle ear effusion and hypernasal speech and nasal regurgitation as a result of velopharyngeal insufficiency.

Hematogenous dissemination of *P. brasiliensis* to abdominal lymph nodes, osteoarticular system, spleen, liver, adrenal glands, or central nervous system might result in life-threatening complications.¹ Neurological PCM usually affects those with widely disseminated disease. The granulomatous form predominates and findings include seizures, hemiparesis, cerebellar signs, and headache.¹¹

Differential diagnosis comprises various conditions including carcinoma, lymphoma, tuberculosis, sarcoidosis, syphilis, Wegener's granulomatosis, actinomycosis, histoplasmosis, cryptococcosis, blastomycosis, and leishmaniasis.¹² It must be highlighted that PCM might occasionally occur in developed countries among individuals who have traveled for a long period or lived in endemic areas. Therefore, despite its rarity, physicians must always consider this entity in the differential diagnosis.

The diagnosis of South American blastomycosis relies upon the detection of fungal elements suggestive of *P. brasiliensis* in various fresh clinical specimens prepared with potassium hydroxide 10% and/or in biopsy materials properly stained with Grocott-Gromori or periodic acid Schiff stain.⁵ Histological evaluation might reveal granulomatous lesions and birefringent yeast cells with multiple broad-based buds, characteristically with a pilot's wheel aspect.¹³ Culture can sometimes be useful in the diagnosis, although the fungus grows extremely slowly. On Sabouraud agar, colonies may appear only after 20 days.¹ Specific serologic tests are important not only as diagnostic aids but also as a parameter to monitor treatment.⁵ Agar gel IDD remains as the recommended serologic method for assessment of PCM, because of its simplicity, the fact that it does not require high cost equipment, and its relatively good sensitivity and specificity.⁵ However, several studies have shown false-negative results in IDD, supposedly attributed to technical limitations of this test such as prozone effect and antibody levels below the sensitivity of the method.^{14,15}

Treatment requires long-term antifungal therapy, and several drugs are currently available for clinical use. These include sulfonamides, amphotericin B, and imidazoles.^{1,5} The criteria for cure of PCM are based on clinical, radiological, mycological, and immunological data.^{2,5}

Received November 30, 2016. Accepted for publication January 17, 2017.

Published online March 6, 2017.

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