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Case report

Laryngeal paracoccidioidomycosis presenting as solitary true vocal fold disease

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ABSTRACT

Paracoccidioidomycosis (PCM) is a systemic granulomatous disease caused by *Paracoccidioides brasiliensis* or *P. lutzii*. It is a neglected tropical infectious disease that poses a major public health burden in endemic areas of Latin America. Mucosae of the upper digestive and respiratory tracts are commonly involved and many patients have disease at multiple mucosal sites, with or without lung involvement. Mucosal PCM presenting as solitary true vocal fold disease is relatively rare. We present the case of a 67-year-old Brazilian forest guard who presented with a 6-month history of hoarseness and *globus pharyngeus* due to a solitary left true vocal fold infiltration and vegetation diagnosed as PCM. Silent pulmonary disease was also present. A laryngoscopy video is offered as supplemental material to this report. He completely remitted after surgical removal and amphotericin B deoxycholate treatment.

Introduction

Paracoccidioidomycosis (PCM), also known as Lutz-Almeida-Splendore disease or South American blastomycosis, is a systemic granulomatous disease caused by two species of a thermodimorphic fungus, *Paracoccidioides brasiliensis* and *P. lutzii*. The disease was first described in 1908 by Adolpho Lutz [1]. It is a neglected tropical infectious disease that poses a major public health burden in endemic areas of Latin America [2]. Living in rural areas and engaging in earthmoving activities are strong predisposing factors, as well as alcoholism and smoking. The main portal of entry is the respiratory route, through inhalation of infectious spores. After environmental exposure to the organisms, most subjects develop an asymptomatic, subclinical infection. Three main patterns of clinical disease may ensue: (i) an acute/subacute disease, with no gender preference, characterized by involvement of multiple sites and observed mainly in children, young adults, and immunocompromised subjects; (ii) a chronic disease, which occurs mainly in adult, male patients and may be characterized by pulmonary infiltrates, as well as involvement of upper respiratory and digestive mucosae, skin, adrenals, among other sites; (iii) and a residual form, in which fibrotic scars lead to permanent sequelae [3].

Mucosae of the upper digestive and respiratory tracts are commonly involved in PCM, and the first such cases were described by Adolpho Lutz himself in 1908 [1]. In a large case series of 422 cases of PCM, oropharyngeal lesions were present in 21% and 66% of patients in the acute/subacute and chronic progressive forms, respectively [4]. Hoarseness was a major feature of the chronic form, being present in 31% [4]. Another large case series of 315 patients, both in acute/subacute and chronic disease, found that oropharyngeal and laryngeal lesions were present in 69.2% of the patients [5]. Mucosal lesions are located most frequently on the gingiva, palate, tongue, jugal mucosa, lips, uvula, tonsillar pillars, floor of the mouth, nose and larynx [4,6,7]. The lesions are, most commonly, a superficial ulcer with granular appearance and with hemorrhagic dots (mulberrylike stomatitis). Many

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patients have disease at multiple mucosal sites, with or without lung involvement.

Laryngeal PCM presenting as solitary true vocal fold disease is relatively rare. We wish to report on the case of a male patient in whom PCM presented as a solitary vocal fold disease, along with silent pulmonary involvement.

Case report

A 67-year-old Caucasian forest guard who was born and resided in Tanguá (22°43′48″S; 42°42′50″W), Rio de Janeiro State, Brazil, was referred to our university hospital due to a 6-month history of hoarseness and a progressive sensation of *globus pharyngeus*. There was no history of fever, dyspnea, dysphagia, night sweats or weight loss. A few months earlier he had presented at another hospital with persistent cough, which significantly improved when the antihypertensive drug losartan was substituted for captopril. He was a long-term smoker and alcohol consumer.

Clinical examination revealed a moderately overweight patient in apparently good health. Fine crackles were auscultated diffusely on pulmonary exam. Laryngoscopic examination revealed an infiltrative and vegetative lesion with an erythematous aspect at the superior part of the left true vocal fold (Fig. 1). Hemorrhagic dots were observed, mainly at the posterior portion of the vegetation. Vestibular folds and arytenoids were preserved. There were no other lesions in the upper respiratory and digestive tracts. Clinical examination was otherwise unremarkable, as were laboratory evaluations. There was no serologic evidence of syphilis, hepatitis B, hepatitis C, or HIV infection. A chest x-ray, which was normal three months earlier, disclosed bilateral, interstitial opacities in upper, middle, and basal lung zones, as well as confluent alveolar opacities mainly in basal zones (Fig. 2A). A computed tomography scan of the thorax (Fig. 1B) showed bilateral, multifocal, non-calcified pulmonary nodular opacities and focal areas of ground-glass attenuation, as well as multiple localized round and oval areas containing central ground-glass opacities and ring of consolidation, known as the reversed halo sign (RHS). These rings were seen predominantly on middle and lower lung fields. There was no evidence of central nervous system disease on cranial computed tomography. The radiographic pattern suggested a rapidly progressive pulmonary disease in a patient that was minimally symptomatic. Sputum smears were negative for acid-fast bacilli.

An excisional biopsy of the left true vocal fold vegetation, obtained via direct laryngoscopy (see Supplementary Video S1 in the online version at DOI: http://dx.doi.org/10.1016/j.idcr.2017.09.003), was performed. Histopathological analyses revealed a chronic, granulomatous inflammation with countless yeast-like elements inside multinucleated giant cells (Fig. 3). There was no histopathologic evidence of malignancy. Grocott's methenamine silver stain unveiled multiple, birefringent thick-walled yeast-like structures of variable sizes, as well as budding structures from mother cells in a pattern of "steering wheel" or "Mickey Mouse" appearance, which is pathognomonic for the agent of PCM.

Treatment was initiated with a daily regimen of amphotericin B deoxycholate, starting with escalating doses. When a cumulative dose of 1 g was reached, oral trimethoprim/sulfamethoxazole 800/160 mg bid was substituted for amphotericin B deoxycholate. The patient was discharged four weeks later, with oral trimethoprim/sulfamethoxazole maintenance. The hoarseness, dysphonia, and sensation of foreign body on the throat completely remitted. Resolution of the pulmonary opacities was also recorded.

Discussion

Laryngeal PCM usually poses a significant diagnostic challenge. The differential diagnosis is broad and includes malignant diseases, mainly squamous cell carcinoma. The larynx may be involved alone or in combination with oropharyngeal and nasal mucosa disease. In a case series from the south of Brazil, malignancy was the major diagnostic hypothesis in all seven patients [8]. In fact, both conditions may coexist [9]. The clinical picture of chronic respiratory symptoms may easily suggest tuberculosis and even chronic obstructive lung disease [10,11]. Moreover, it should be remarked that many other fungal disorders, such as histoplasmosis, aspergillosis, blastomycosis, and cryptococcosis, may also cause laryngeal disease. Histopathological examination is usually the major diagnostic procedure. Repeated multiple biopsies may occasionally be necessary. Mycological culture and serological analyses may also aid in diagnosis.

Laryngeal PCM most commonly presents with hoarseness, dyspnea, odynophagia, and cough [8]. Interestingly, fatigue, weight loss, and fever seem not to be prominent manifestations [8]. It usually presents as ulcerated lesions with a mulberry-like appearance or as vegetations, and many patients have multiple laryngeal lesions, with involvement of the true and false vocal folds, the epiglottis, and the arytenoid and interarytenoid areas [8,12]. In a case series of 17 consecutive cases with laryngeal PCM diagnosed between 1978 and 1999 in Rio de Janeiro, lesions were often present at multiple mucosal sites (laryngeal and non-laryngeal), and lung involvement was common [13]. A total of 11 patients (64.7%) had involvement of the vocal fold, most commonly as a vegetation [13]. Among these, only two had isolated vocal fold disease, one with a vegetative, the other with a scarring lesion [13].

Patients with laryngeal and/or oropharyngeal PCM may present with or without concomitant pulmonary disease. Even though a microbiological diagnosis of our patient's lung disease was not available, we strongly believe it was due to PCM. Moreover, the CT scan of the

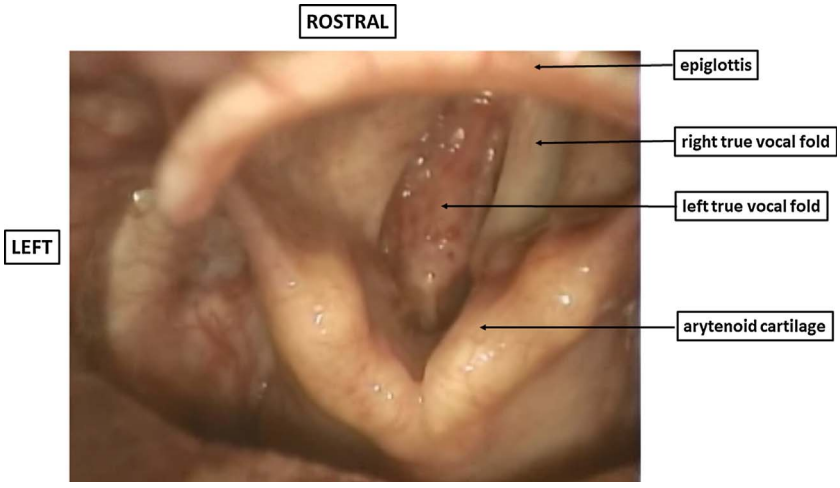

Fig. 1. Clinical image of the patient obtained via direct laryngoscopy discloses a vegetative and infiltrative lesion at the left true vocal fold. The granular surface with hemorrhagic dots resembles the classic mulberrylike aspect of PCM mucosal lesions.

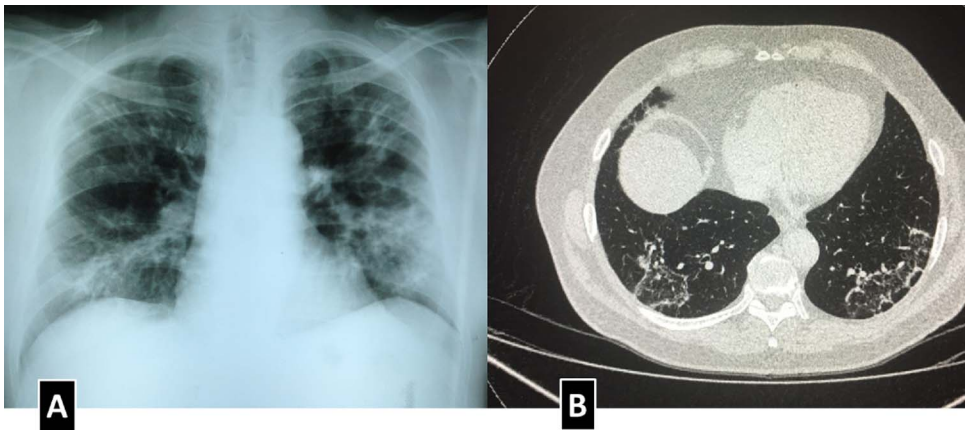

Fig. 2. (A) Chest x-ray discloses bilateral, interstitial opacities in upper, middle, and basal lung zones, as well as confluent alveolar opacities mainly in basal zones. (B) Computed tomography scan of the thorax shows bilateral, multifocal, non-calcified pulmonary nodular opacities and focal areas of ground-glass attenuation, as well as multiple localized round and oval areas containing central ground-glass opacities and ring of consolidation, known as the reversed halo sign.

chest disclosed a RHS sign, namely a central ground-glass opacity surrounded by a crescent or ring of consolidation, which is seen in approximately 10% of the patients with proven pulmonary PCM and reflects the presence of a central area of predominantly interstitial inflammation surrounded by predominantly air-space infiltration [14]. The presence of multiple RHS rings, their predominance on middle and lower lung zone fields, as well as spiculated RHS rings, have been found to be suggestive of pulmonary PCM [15]. All these features were present in the present case.

Our patient had several predisposing factors to PCM. He was an older male patient who inhabited a hyperendemic area and dealt with forest activities. Moreover, he reported long-term alcoholism and smoking. If not timely diagnosed and treated, laryngeal PCM may lead to several complications. Laryngeal stenosis [16], tracheal stenosis [17], persistent dysphonia, and voice disorders [7,18] have all been reported. Post-treatment follow-up occasionally reveals deforming scars [19]. The present case report highlights the need to consider PCM in the differential diagnosis of isolated vocal fold vegetations and infiltrative lesions, especially in patients from, or who have inhabited in, endemic areas. It also seems to underline the importance of a having a heightened awareness of the overall burden of neglected fungal diseases in Brazilian patients [20].

Conflict of interest

The authors declare that they have no conflict of interest.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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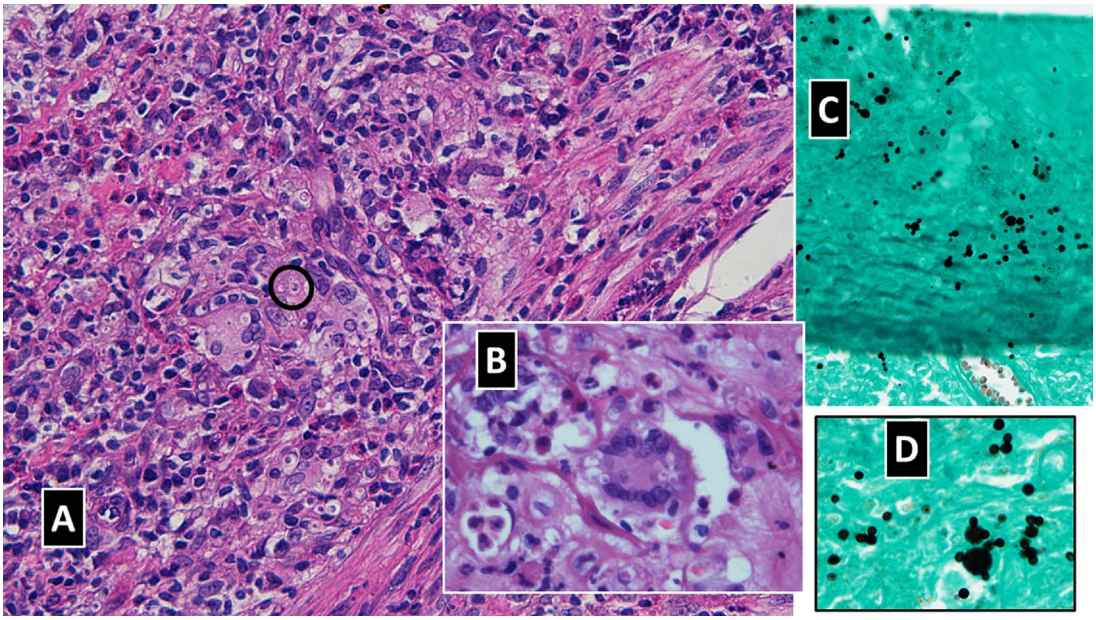

Fig. 3. Histopathological analyses of the true vocal fold vegetative and infiltrative lesion. A) Hematoxylin and eosin stain (original magnification 40×) discloses a chronic granulomatous inflammatory reaction, with the presence of Langhans giant cells, epithelioid histiocytes, plasmocytes, neutrophils, and eosinophils. Numerous yeast-like elements can be seen inside multinucleated giant cells and histiocytes. A budding element is indicated in the circle. B) Detail of a multinucleated giant cell harboring yeast-like structures (original magnification 100×). C) Grocott's methenamine silver stain (original magnification 40×) unmasks countless darkly-stained yeast-like structures of variable sizes. D) detail of budding structures from mother cells in a pattern of "steering wheel" or "Mickey Mouse" appearance (original magnification 100×).

Author's contributions

WAES and ACS proposed the publication of the case and drafted the manuscript. RPBO and LFA performed the histopathological analyses. WAES, ACS, GARS, MCVMA, JTLMSB, MAN, and IJA took part in the clinical management of the patient. NZR, FMO, CJAS, and MAS followed the patient at the Otolaryngology unit and performed the surgical procedure. All authors revised the literature and provided important contributions to conception, design, acquisition of data, analysis, interpretation, and intellectual contributions to the final version.

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