Objective: To report clinical manifestations, diagnosis, and epidemiologic characteristics of laryngeal paracoccidioidomycosis.

Design: Case series.

Settings: Tertiary care institutional hospital.

Patients: We reviewed the hospital records of 7 patients with laryngeal paracoccidioidomycosis diagnosed by histopathological examination.

Main Outcome Measure: Clinical manifestations of laryngeal paracoccidioidomycosis.

Results: All patients were men and were middle-aged (range, 43-65 years), and most (86% [6/7]) were farm workers. All 7 patients regularly used tobacco, but only (43% [3/7]) were alcohol users. Clinical manifestations were dysphonia (86% [6/7]), dyspnea (71% [5/7]), dysphagia (43% [3/7]), and cough (29% [2/7]). Laryngeal examination revealed ulcerative lesions with a mulberry-like appearance in 3 patients and vegetative lesions in 4 patients. Many had multiple laryngeal lesions with involvement of the true and false vocal cords, the epiglottis, and the arytenoid and interarytenoid areas. The first diagnostic impression was carcinoma in all patients.

Conclusions: Laryngeal paracoccidioidomycosis may be a difficult diagnosis for the unsuspecting clinician to make. Examination of the larynx can reveal lesions similar to laryngeal cancer; therefore, diagnosis of carcinoma must be ruled out by histopathological examination or culture of a specimen.


PARACOCCIDIOIDOMYCOSIS (South American blastomycosis) is an uncommon, progressive, and systemic mycosis that is caused by Paracoccidioides brasiliensis and can be fatal if untreated.\(^1\) The disease is restricted to populations in Latin America and is distributed heterogeneously throughout the continent.\(^2\,4\) Endemicity centers in regions with relatively well-defined ecological characteristics (ie, the tropical and subtropical forests, where temperatures are mild and humidity is relatively high and constant throughout the year). Although cases have been reported in North America, Europe, and Asia, these patients had previously been residents in countries where the disease is endemic.\(^3\)

The highest number of cases have been reported in Brazil, Colombia, Argentina, and Venezuela.\(^5\,7\) The number of infected individuals in the entire area of endemicity, where 90 million people currently live, is approximately 10 million\(^8\); the disease incidence is high in areas that are contiguous to areas in which the disease incidence is very low.\(^2\) We believe, however, that the true incidence of P brasiliensis infection is underestimated and that there are more cases than have been reported. The diagnosis is frequently not made until culture or histopathological examination of a specimen is carried out, owing to the difficulty in diagnosing unsuspected paracoccidioidomycosis. Therefore, asymptomatic cases usually are not diagnosed.

Systemic mycoses are potentially serious and often lethal infections seen mainly in underdeveloped countries or in immunocompromised subjects.\(^9\) The diagnosis and treatment of laryngeal lesions is of increasing importance because of the growing numbers of persons who are immunocompromised.\(^10\,11\) However, the estimated incidence of paracoccidioidomycosis among people with the acquired immunodeficiency syndrome (AIDS) in Brazil is low (0.09%).\(^12\) The scarcity of reported cases of paracoccidioidomycosis in people with AIDS might be ex-
MATERIAL AND METHODS

We reviewed the hospital records of 7 patients with laryngeal paracoccidioidomycosis confirmed by histopathological examination. All patients were Brazilians, admitted to Department of Otorhinolaryngology of Fundação Faculdade Federal de Ciências Médicas de Porto Alegre, Complexo Hospitalar Santa Casa, Porto Alegre, Brazil, for an evaluation of their laryngeal problems between January 1994 and July 1997. The patients' records were reviewed for age, sex, race, occupation, human immunodeficiency virus (HIV) status, presenting symptoms, initial diagnostic impression, site of involvement, and evidence of concomitant pulmonary disease on chest radiograms.

RESULTS

All patients were adult men, middle-aged and older (range, 43-65 years; median, 53 years); 57% (4/7) were white, 43% (3/7) were black, and 86% (6/7) were employed in low-income occupations that involve work outdoors, often farming. All patients regularly used tobacco, but only 43% (3/7) used alcohol.

These patients had a several-month history of symptoms that resembled those of upper respiratory tract infection before seeking medical care (range, 2-22 months; median, 9 months). Laryngeal symptoms were identified in all patients; the prominent presenting symptom was hoarseness (86% [6/7]), followed by dyspnea (71% [3/7]), odynophagia (43% [3/7]), and cough (29% [2/7]). Fatigue, weight loss, and fever were minimal manifestations. All patients had alterations on chest radiograms, but only 2 patients (29%) had pulmonary involvement caused by paracoccidioidomycosis. Five patients were HIV-negative, and for 2 patients HIV status was not established.

Two patients underwent direct laryngoscopy and 5 underwent flexible fiberoptic laryngoscopy; biopsies were performed for all patients. The first diagnostic impression was laryngeal cancer in all patients. The findings of these examinations showed ulcerated lesions with a mulberrylike appearance in 3 patients and vegetative lesions in 4 patients (Figure 1). Many patients had multiple laryngeal lesions. Examination revealed lesions of the true vocal folds in 4 (57%), epiglottic involvement in 2 (29%), involvement of the false vocal folds in 3 (43%), arytenoid involvement in 3 (43%), interarytenoid area involvement in 2 (29%), and infraglottic involvement in 2 (29%).

The term blastomycosis has sometimes been taken to include a range of granulomatous systemic mycoses, including South American blastomycosis (paracoccidioidomycosis or Lutz-Splendore-Almeida disease), North American blastomycosis (Gilchrist disease), coccidiomycosis, and cryptococcosis, but it is generally restricted to the South American and North American forms of blastomycosis.

The age and sex distribution of clinical cases is peculiar. Paracoccidioidomycosis is rare in children and teenagers, and most patients are aged 30 years or older. Men are more commonly afflicted than women at a mean ratio of 15:1. This is in contrast to the infection rate as determined by a paracoccidioidin skin test, which is similar for both sexes; however, when the disease occurs in prepubertal patients, there is no correlation with sex. Studies have also indicated that the progression of paracoccidioidomycosis is less frequent in women once they reach puberty because of the protective role that estrogen plays by inhibiting the transition of conidia and mycelia to yeast form, a critical step in the pathogenesis of the disease. The occupational distribution reveals that paracoccidioidomycosis has a predilection for agricultural workers. Alcoholism has been shown to be an important predisposing factor. The scarcity of reported cases of paracoccidioidomycosis in people with AIDS may be explained by the widespread use of trimethoprim-sulfamethoxazole as prophylaxis for P carinii pneumonia; this agent is also very effective against P brasiliensis.

Paracoccidioidomycosis is a chronic mycosis; its later forms are fungus infections of viscera, lymph nodes, and mucocutaneous tissues. The disease is prevalent in South America, particularly in Brazil, as well as in portions of Mexico and Central America. The occasional reports of cases occurring within the United States are probably caused by infection in patients exposed to contami-
nated soil while traveling in endemic areas.\textsuperscript{15-17} The disease has long periods of latency, as demonstrated by cases reported outside of the endemic area; some of these patients developed overt disease symptoms 30 or more years after leaving the endemic regions.\textsuperscript{3} Primary cutaneous paracoccidioidomycosis is exceedingly rare. The more frequent primary site of infection is the lung; pulmonary disease is complicated by cavitiation in approximately one third of patients.\textsuperscript{17} Dissemination from the pulmonary focus may cause mucous membrane ulcerations and/or verrucous lesions of the skin.\textsuperscript{17}

\textit{Paracoccidioides brasiliensis} is a thermally dimorphic fungus known to exist only in its asexual state. The fungus grows as a yeast in host tissues and in the laboratory when incubated at 37°C; growth from a single mother cell becomes apparent after 10 to 15 days of incubation. In the yeast phase, the colonies are soft, wrinkled, and cream-colored and are composed of yeast cells of different sizes (4-30 µm), usually oval to elongated with multiple budding cells. The mycelial form grows after 20 to 30 days of incubation at room temperature. Colonies are white, small, and irregular and are covered by short aerial mycelia that often adhere to the agar, breaking its surface. Diagnosis by culture and histological examination relies on the most characteristic feature of the yeast form: the pilot’s-wheel appearance (ie, a mother cell surrounded by multiple peripheral daughter cells).\textsuperscript{15,18,19}

The diagnosis of laryngeal paracoccidioidomycosis may be difficult for the unsuspecting clinician. The patient may have a several-month history of symptoms that resemble those of upper respiratory tract infection, with an associated hoarse voice, productive cough, and occasional hemoptysis, as well as low-grade fever, weight loss, and general malaise. Laryngeal examination may reveal ulceration, diffuse erythema, and/or a fungating lesion very similar to carcinoma.\textsuperscript{7,16-18,22} Paracoccidioidomycosis is a polymorphic disease with a wide clinical gamut, ranging from localized disease to disseminated, acute, and chronic forms.\textsuperscript{7} Sites of dissemination include skin, bones, urogenital tract, gastrointestinal tract, brain, abdominal lymph nodes, spleen, liver, and the adrenal glands.\textsuperscript{7,9,15,21} Although laryngeal involvement with paracoccidioidomycosis is usually associated with active pulmonary disease, this is not always the case. Lesions of the larynx can be diffuse, with involvement of the whole larynx, or restricted to specific sites, such as the anterior or posterior commissure, false vocal cord, epiglottis, and infraglottis. The mode of dissemination is either hematogenous or direct exposure from infected sputum.\textsuperscript{7}

The cornerstone for the diagnosis of laryngeal paracoccidioidomycosis is the biopsy (\textbf{Figure 2} and \textbf{Figure 3}). Microscopic examination will reveal acanthosis, pseudo-epitheliomatous hyperplasia, inflammatory cells, multinucleate giant cells, and round, double-contoured single-budding organisms.\textsuperscript{7} If direct examination in potassium hydroxide preparation or hematoxylin-eosin staining does not reveal the organism, staining biopsy specimens with Grocott-Gomori methenamine-silver may be helpful.\textsuperscript{16,17} A culture of the organism can be diagnostically useful, but \textit{P brasiliensis} grows extremely slowly, even on blood agar, although in this respect Sabouraud dextrose agar is preferred.\textsuperscript{17} Serological procedures applied to paracoccidioidomycosis have allowed its early diagnosis and made it possible to treat the disease appropriately.\textsuperscript{22} However, serological tests (complement fixation and skin tests) are unreliable, since many patients with positive stains and cultures have negative complement fixation test results.\textsuperscript{6} Del Negro et al\textsuperscript{22} have reported that agar and agarose gel precipitation tests (double immunodiffusion and counterimmunoelectrophoresis) have greater sensitivity (91.3% and 95.6%, respectively), and maximum specificity (100%) compared with complement fixation (sensitivity, 71.1%; specificity, 95.4%) and indirect immunofluorescence (sensitivity, 65.2%; specificity, 90%). A polymerase chain reaction assay, a promising diagnostic tool, has been developed to detect small amounts of DNA from \textit{P brasiliensis}.\textsuperscript{2}

The differential diagnosis of paracoccidioidomycosis usually includes carcinoma, tuberculosis, lupus erythematosus, North American blastomycosis, histoplasmosis, coccidioidomycosis, sarcoidosis, syphilis, Wegener granulomatosis, granuloma inguinale, actinomycosis, leishmaniasis, and other granulomatous disorders.\textsuperscript{8} As the literature reveals, the differentiation between squa-
nous cell carcinoma and paracoccidioidomycosis may be difficult. The key to the correct diagnosis is a high index of suspicion on the part of the clinician and an unrelenting search for the fungal organisms. Despite the occurrence of cases that mimic cancer, paracoccidioidomycosis should be suspected when there are associated lung symptoms and when a patient has had previous contact with endemic areas. Repeated multiple biopsies may be necessary to obtain the organism both for histopathological confirmation and for culture growth.

A range of antimicrobial agents can be effective treatments for paracoccidioidomycosis. Intravenous amphotericin B therapy can be curative. Sulfadiazine or sulfisoxazole therapy can arrest disease progress, but relapses occur unless continuous therapy is used. Amphotericin B therapy plus a sulfanamide, such as sulfamethoxypyridazine, is even more effective. Paracoccidioidomycosis also responds well to oral ketoconazole, itraconazole, fluconazole, or intravenous miconazole therapy. When the correct diagnosis is made, successful treatment is possible; therefore, a high level of clinical suspicion is required for patients with symptoms that resemble those of upper respiratory tract infection who are from areas in which paracoccidioidomycosis is endemic.

Accepted for publication July 2, 1999.

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REFERENCES