PARACOCCIDIOIDOMYCOSIS IN HEAD AND NECK: CLINICAL AND HISTOPATOLOGICAL ANALYSIS

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ABSTRACT:

INTRODUCTION: Paracoccidioidomycosis is a systemic disease with relevant head and neck manifestation. The current study is the largest case-series known and have been undertaken to establish the profile of Paracoccidioidomycosis in the upper aerodigestive tract.

METHODS: An assessment of 250 charts of patients with paracocidiodomycosis regarding age, sex, source of contagion, symptoms, smoking, alcoholism, lesion sites, involvement of cervical lymph node, type of lesion and treatment. The Fisher and Chi-square test were applied.

RESULTS: The mean age was 49,1 years, rural contagion was predominant and most affected patients were male. Smoking proved to be a significant related factor (p=0,005). A significant correlation was observed between the presence of lymph node involvement and lesions in the oral cavity (p=0,005).

CONCLUSION: Oral cavity involvement with ulcerative mulberry-like lesions and cervical lymph node involvement in a mean age of 49 years, male, and patients who smoked were characteristic traits of paracoccidioidomycosis.

INTRODUCTION

South American blastomycosis or paracoccidioidomycosis is a systemic disease that has aroused great interest in Latin America due to its relevant head and neck manifestation.[1,2,3] Although it has been reported as a predominantly Latin American disease, cases have been reported in the United States, Canada and Europe.[4-11] Since it is not a compulsory notification disease in Brazil, reliable data on its prevalence or incidence are not available. However, the estimated frequency of new cases is 1-3/100.000 inhabitants. [10,12,13] Its clinical forms are mucocutaneous, lymphatic, visceral and mixed. The first two are most common in otolaryngology as well as in the head and neck sites and present as a diagnostic obstacle due to their similarity to malignant head and neck neoplasia.[14,15] There are also reports showing a relationship between paracoccidioidomycosis and malignant neoplasia such as squamous cell carcinoma and lymphoma.[16,17] There are a few studies of blastomycosis with specific attention to involvement of head and neck structures, regarding its location in the upper aerodigestive tract, clinical forms of presentation, site of contagion, symptoms and related factors. The current study is the largest case-series known and have been undertaken with the purpose of analyzing these parameters in 250 patients, aiming to establish the profile of the South American blastomycosis in the upper aerodigestive tract related to the most frequently associated factors.

MATERIALS AND METHODS

A descriptive cross-sectional study was conducted on the charts of 250 patients at the Otolaryngology Head and Neck outpatient clinic at Hospital das Clínicas of State University of Campinas, UNICAMP, attended from January/2000 to January/2015. A protocol was applied to assess these patients regarding age, sex, source of contagion (urban or rural), smoking, alcoholism, symptoms, types of lesion, lesion sites in the upper aerodigestive tract, presence of lymph nodes and their location, performance of a biopsy, results of thorax radiology exams suggesting concomitant pulmonary disease, need for a tracheotomy and previous treatment. The lesion sites in the upper aerodigestive tract were divided into: oral cavity, larynx, oropharynx, hypopharynx, rhinopharynx and nasal cavity. A diagnosis of blastomycosis was confirmed in all the patients who underwent lesion fragment biopsy or aspirative lymph node biopsy or serologic test.

A descriptive type of statistical analysis consistent with tables measuring frequency, site, and dissemination, was utilized. The Chi-square test or Fisher test were used to verify the relationship between variables. To calculate precise estimation of proportion, 95% of confidence intervals were applied. The Memorial Sloan-Kettering Cancer Center cervical lymph node classification was used for the lymphatic chain in the neck.[18]

RESULTS

In this study, 250 patients with ages ranging from 5 to 96 years, with a mean age of 49,1 years, were observed. A higher prevalence was observed in males (90%). The source of contagion was predominantly rural (82,4%). Smoking was a significant associated factor (76,8%), but alcoholism (58%) could not be considered an

associated factor of South American blastomycosis. The reason that these patients underwent an otolaryngologic referral was: diagnosis of cervical lymph node enlargement (20,4%), an evident lesion in the head and neck region (76,4%), and the need of a specialist evaluation of patients previously diagnosed with pulmonary blastomycosis (18,4%). The clinical condition revealed a mean weight loss of 7 kg (58,8%) as the most common symptom, followed by cough (42%), hoarseness (31,8%), pain (41,2%), dysphagia (26,8%), fever (24,4%), dyspnea (22%), odynophagia (19,2%) and sialorrhea (4%). The most common lesions were the ulcerative mulberry-like and vegetative plaques. Both types were found in 65,6% of the patients. Cervical lymph node involvement was observed in 132 patients (52,8%). Of these, 80 patients (81,1%) were bilateral and 18 (18,9%) were unilateral. In all cases the cervical lymph nodes were fibro-elastic and moveable. Data regarding location in the neck was undefined in eight patients. The most common cervical lymph node level was V (28,6%). Oral cavity lesion was the most common (44,8%), followed by oropharynx (32%), larynx (28%), nose (12%), hypopharynx (3,6%) and rhinopharynx (2%). A tendency was observed to an association between rural contagion and the presence of a laryngeal lesion (p=0.06). A significant correlation was observed between the presence of lymph node involvement and lesions in the oral cavity (p=0,005). However, no correlation was observed between the presence of cervical lymph mass and other lesion sites in the upper respiratory and Paracoccidioidomycosis in head and neck digestive tracts. All diagnoses were confirmed by fragment biopsies of lesions or fine needle aspiration.

This study observed that in 53 (21,2%) patients the mucosa of the upper aerodigestive tract was affected without lung involvement. The treatment of choice in 84,8% of patients was sulfametazole-thrimetoprim (1640mg/360mg/day). Because of side effects, allergy or poor clinical response, 15,2% of patients were given ketoconazole (400 mg/day), amphotericin B (1 g/day) or sulfadimethoxine (1g/day). Only five patients required a tracheostomy due to obstruction of the upper respiratory airway. In two patients, tracheostomy was elective, while in the other three it was done as an emergency procedure and one of these procedures ended in death.

DISCUSSION

Paracoccidioidomycosis is known to be more prevalent in males (14:1). [1,2,15,19]. Alcoholism and smoking are proven risk factors for Paracoccidioides brasiliensis [1,2,15,17], but in this study, only smoking presented a statistical importance. However, when smoking associated with lesions of upper aerodigestive tract and blastomycosis is suspected, a differential diagnosis for malignant neoplasia should be performed, particularly squamous cell carcinoma.[21] Our findings regarding the age of onset of disease between 30 and 50 years is similar to findings in literature.[1,2,10,12,15] A direct micologic study of the sample or biopsy of the mucosa, with 10% potassium hydroxide (KOH), allows the fungus to be visualized and the South American blastomycosis to be diagnosed. An optical microscopic study reveals peculiar characteristics, such as the presence of a double wall and the "pilot wheel appearance" caused by multiple micro-sporulation. A histopathologic examination of lesion fragment sections immersed in 10% formalin and later in paraffin stained with Gomori-Grocott methenamine silver is also diagnostic because it provides direct visualization of the fungus with the previously cited features. [15,22,23] Several serologic tests such as complement fixation and agar gel precipitation (immunodiffusion, immunofluorescence, immunoelectrophoresis, agglutination, immunoenzymatic assays, Western blot and ELISA) are diagnostic for blastomycosis. These serologic tests have up to 100% of sensitivity and between 60 to 90% of specificity.[22,23] It is important to highlight the exclusive clinical appearance of the lymph nodal form of South American blastomycosis in children presented with adenopathy without lesions, with a fatality rate of 31% [25] Thus, otolaryngologists should also suspect South American blastomycosis when examining children with isolated cervical adenopathy. The

ulcerative, ganglionic or mixed forms are found in the upper aerodigestive tract. According to the present classification, most patients presented with acute or sub-acute forms (young individuals) and the chronic form (adults). [26] The symptomatology (loss of weight, pain, hoarseness, cough, odynophagy and adenopathy) maybe be severe and simulate the evolution of a malignant neoplasia.[14,16] Although not statistically proven, a relationship exists between South American blastomycosis and malignant neoplasia such as Hodgkin's disease, squamous cell carcinoma of head/neck and lungs, undifferentiated metastatic carcinoma and leukemia.[16-18] In this study sample, was not observed a relationship between South American blastomycosis and malignant neoplasia. At present, there is a consensus that lung compromise represents a primary disease and that lesions in the head and neck regions are secondary.[1,3,8,15] However, in our study we found 53 (21,2%) patients presented with clinical manifestations only in the upper aerodigestive tract without evidence of pre-existing or concomitant lung disease. Since those patients presented exclusive otolaryngological manifestations, they could be reclassified as a unifocal extrapulmonary disease or a unifocal otolaryngologic form, going against what is usually observed. The first characteristic lesion of paracoccidioidomycosis in the oral mucosa was described by Aguiar Pupo and confirmed by Nova in 1940.[26] This author classified the otolaryngologic form of South American blastomycosis as: typical erosive papules (mulberry like); ulcerative, hypertrophic (inflammatory infiltration of the lips and jugal mucosa); and occult tonsillitis (adenopathy and tonsillitis). The tegumentary forms may disseminate to the nasal vestibule and rhinopharynx. According to our findings, the ulcerative mulberry-like vegetative lesion is very common in paracoccidioidomycosis, but there are uncharacteristic ulcerative and infiltrative lesions as well. Differential diagnoses for these lesions are tuberculosis, syphilis, leishmaniosis and malignant neoplasia.[15,27]. We found that 52,8% of our patients had cervical adenopathy, generally bilateral (81,1%) and most commonly affecting the level V. Contrary to the literature, only lesions in the oral cavity demonstrated statistical relationship with the presence of cervical adenopathy (p=0.005). The numerical values for other sites probably were not significant due to the size of the sample. According to the literature, most frequently affected sites in paracoccidioidomycosis involves the lungs, oropharynx and cervical lymph nodes.[6,15,28] Laryngeal blastomycosis involvement may result in obstruction of the upper airways that may even require a tracheostomy. Lymph node involvement occurs via regional lymphohematogenesis or lymphatic network and could be present at any stage of the disease or even act as a reservoir for future post-treatment dissemination. [28] Fine needle aspiration biopsy of the lymph node is enough for a diagnosis of blastomycosis with lymph node involvement.[28,29] The therapy of paracoccidioidomycosis should include general measures and treatment of immunologic depression, malnutrition and infection. Specific therapy is conducted in two phases: attack with antifungal drugs such as sulfonamides derivatives (sulfadoxin 2000mg/day; sulfamethoxazole-trimethoprim (SMX-TMT) 1640mg/360mg/day), derivatives of azoles (ketoconazole 200-400md/day; itraconazole 100-400mg/day; Fluconazole 300-400 mg/day) or amphotericin B (1.5-1.75 mg/kg/day) for six months and maintenance of some of these drugs for approximately 18 months.[30-32] In Brazil, the recommended treatment is SMX-TMT and it is freely distributed by the public health system.

The recommended posology is 480-960 mg every 8-12 hours, and the combination is available for oral or parenteral administration. The main disadvantage is the need for long term treatments (more than 12 months) in moderate and severe cases. Adverse events including hypersensitivity reactions, leucopenia, megaloblastic anemia and thrombocytopenia are described. Therapeutic failure was described in 5% of patients with low sulfadiazine serum concentrations due to genetic-related factors altering the liver metabolism (acetylador phenotype). [32] Several retrospective studies concluded that itraconazole is a better option comparing to SMX-TMT, with a cure rate of 86,4 to 95% versus 51,3 to 70%, respectively and others showed no difference among the groups

regarding clinical improvement, symptoms and the time required for serology to become negative. But no double-blind randomized studies were performed until the moment to confirm these findings. [30-35] Factors most frequently related to blastomycosis in the upper aerodigestive tracts were: males; approximate age 49 years; residents in rural areas; ulcerative-vegetative lesions; smoking; bilateral cervical lymph mass; and loss of weight. It should be reminded that these factors are also often associated with malignant neoplasia of head and neck and therefore a differential diagnosis with squamous cell carcinoma should always be performed. Since there is a possibility of blastomycosis lesion and concomitant malignant neoplasia, a biopsy of a fragment of the lesion should be performed even when the serology tests demonstrates positivity for blastomycosis and the thorax radiological exams are compatible with pulmonary disease caused by paracoccidioidomycosis.

CONCLUSION

Paracoccidioidomycosis was more common in male patients, approximately 49 years old and smokers. The source of contagion was predominantly rural and the most common type of lesion was ulcerative-vegetative most frequently in oral cavity. The main symptoms were loss of weight, cough, hoarseness and pain. Bilateral cervical adenopathy was present in the majority of the patients with upper aerodigestive tract lesions caused by paracoccidioidomycosis. Diagnosis of the disease should be obtained by performance of lesion´s fragment biopsy or fine needle aspiration of lymph node enlargement. Prompt and extensive treatment should be administered for 12-24 months and may cure the patient without leaving any severe sequelae. The relationship between cervical adenopathy and oral cavity lesion was characteristic of paracoccidioidomycosis. A normal radiological thorax exam might not eliminate blastomycosis when lesions are present in the upper aerodigestive tract. A differential diagnosis for squamous cell carcinoma of the head and neck or other malignant neoplasia should always be performed when lesions are present in the upper respiratory and digestive tracts.

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