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# CLINICAL AND ENDOSCOPIC FINDINGS IN THE MUCOSAE OF THE UPPER RESPIRATORY AND DIGESTIVE TRACTS IN POST-TREATMENT FOLLOW-UP OF PARACOCCIDIOIDOMYCOSIS PATIENTS

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## SUMMARY

Systematic examination of the upper respiratory and digestive tracts (URDT) was performed in a group of 80 paracoccidioidomycosis (PCM) patients submitted to post-treatment follow-up ranging from 8 months to 17 years. Mucosae of the URDT had been involved prior to specific treatment in 74 patients, distributed as follows: oropharynx, 50 (41 alone, 7 in association with the larynx, and 2 with the nasal mucosa); larynx, 30 (23 alone and 7 in association); and nasal mucosa, 3(1 alone and 2 in association). Inactive lesions were observed in all the 50 patients with lesions of the oropharynx, 3 of whom with deforming scars (1 with retraction of the tongue and 2 with narrowing of the oral orifice). One case presented a destructive lesion, with perfuration of the palate. Of the other 46 cases, examination showed nacreous white striated scars which were nearly imperceptible in some cases and in others displayed partial retraction of anatomical structures without any alteration of their features. Patients presented a high rate of missing teeth.

In 3 patients with involvement of the nasal mucosa, none of whom presented active PCM lesions, 2 still had nasal voices. In 30 patients with lesions of the larynx, 1 suffered a relapse of PCM and 2 developed epidermoid carcinoma. Of the other 27 cases, none of whom had active PCM lesions, 15 presented dysphonia, 3 were tracheotomized, and 9 were asymptomatic.

**KEYWORDS:** Paracoccidioidomycosis; Treatment; Oropharyngolaryngeal lesions.

## INTRODUCTION

Reports of lesions in the mucosae of the upper respiratory and digestive tracts (URDT), one of the most frequently involved areas in PCM, date back to the description of the first two cases of the disease in 1908, by ADOLPHO LUTZ, who described lesions in the mouths of booth patients[7]. AGUIAR PUPO, in 1936[13], was the first to use the term "moriform stomatitis", - highly suggestive of the disease - and the surface of a mulberry (*Morus* sp). For many years, the mucosae of the URDT were considered the port of entry of the fungus and was the basis for the classical question in the patient's clinical history about whether he had the habit of either using twigs as toothpicks or chewing leaves. Following regression of the lesions after specific treatment, sequelae may occur such as atresia oris, dysphonia, definitive tracheostomy, and/or perfurated palate[9], causing major limitations; the literature is lacking in studies about systematic observations on the late evolution of such lesions.

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We thus felt important to report our clinical and endoscopic findings in the URDT in a large group of PCM patients in follow-up after specific treatment, systematically examined as part of an investigation concerning the activity of this mycosis.

## SAMPLE AND METHODS

I - Sample

A total of 80 patients in follow-up for PCM were evaluated at the Evandro Chagas Hospital, Oswaldo Cruz Foundation, Rio de Janeiro, for a period of 6 months to 17 years after specific treatment. The group studied consisted of 76 males and 4 females, the youngest 4 years old and the oldest 73, while most were in the 30 to 60 years age bracket. In all cases, diagnosis was confirmed by demonstrating *Paracoccidioides brasiliensis* (Pb) in direct microscopy or culture. Cases were classified according to MONTENEGRO[12]; 72 were of the adult-type chronic form and 8 of the juvenile, subacute form.

II - Methods

1. Post-treatment follow-up for an indefinite period is routine in our hospital. Patients consult every six months during the first two years following treatment and once a year from the third year on. Additional patient visits may occur because of intervening events or poor clinical progress. The following procedures are performed: clinical examination, radiography, and serology (double immunodiffusion test in agar gel). When indicated, nonspecific laboratory tests (biochemistry and hematology), mycology, and histopathology are also done.

2. Conventional examination of the URDT was performed on all of the patients. A Garcia mirror and direct or indirect beam of light was used for examining the larynx. In patients presenting exacerbated oropharyngeal reflexes, neotutocaine 1% or xilocaine 2% spray or swabbing was employed.

In the patients with laryngeal lesions, a Hopkins 90° (22X) optical instrument was used, allowing for more detailed visualization of the anatomical/clinical appearance.

Direct laryngoscopy was performed for collecting material, using an anterior commissural laryngoscope and 0° Hopkins optical laryngoscope and a straight and/or curved biopsy forceps.

1. Location:

- location of laryngeal lesions was established as proposed by LEBORGNE[2,6].

2. Characteristics of the lesions:

- edema, infiltration, destruction, fibrosis, synechia, stenosis, ulceration, vegetation.

Fig. 1: Atrophic scar in labial commissure and adjacent skin, with intense microstomia.

Six patients presenting lesions characterized by infiltration, ulceration, and/or vegetation were submitted to biopsy and histopathological examination.

The following terms were used:

- single lesion, when there was only one type of lesion in a given anatomical structure; and

- multiple lesion, when there was more than one type of lesion in a given anatomical structure.

3. Age:

For the purposes of the study, we considered the age of the patients at onset of disease.

## RESULTS

URDT mucosa was affected in 74 (out of 80) of the patients, as follows: oropharynx, 50 (41 alone, 7 in association with the larynx and 2 with the nasal mucosa); larynx, 30(23 alone and 7 in association); and nasal mucosa, 3 (1 alone and 2 in association).

With the specific treatment described in another article, similar results were obtained with the various drugs employed as long as they were properly prescribed[17], and the URDT lesions resolved in a period of up to 2 months.

Cicatricial lesions were observed in all 50 patients with involvement of the oropharynx: 1 with retraction of the tongue and 2 with narrowing of the oral orifice (Figure 1). One patient presented a destructive lesion, i.e., perfurated palate (Figure 2). The other 46 patients were asymptomatic, with nacreous white striated scars, nearly imperceptible in some and in others with partial retraction of anatomical structures, without alterations in their normal features. There was a high overall rate of missing teeth.

In 3 patients with involvement of nasal mucosa, none of whom presented active PCM lesions, 2 remained with nasal voices.

Of the 30 patients with involvement of the larynx, there was a relapse of PCM in 1 patient, 2 had epidermoid carcinoma, and 27 remained cured of PCM. Tracheotomy was necessary in 6 cases. In one patient it was performed before specific treatment, the tracheal cannula was removed after a year of treatment, and the patient has been followed up for 17 years. Tracheotomy was performed during the first 3 months of specific treatment in 2 cases: one of them was submitted to temporary tracheotomy, the cannula was removed after 6 months of treatment, and the patient has been under follow-up for 2 years. In the other, tracheotomy was maintained until the patient died from dilated miocardiopathy, occurring after three years of post-treatment follow-up; it was impossible to correct the cause of the dyspnea (total stenosis of the glottic aperture). In 3 patients, tracheotomy was per-

Fig. 2: Nacreous white striated scar and perfurated palate.

formed upon reactivation of the disease due to irregular treatment. Temporary tracheotomy was performed on 1 patient; the tracheal cannula was removed after three months of treatment, and the patient has been in follow-up for 3 years. The others remain tracheotomized, one for 9 years and the other for 15 years.

The relapse of PCM was observed after 9 years of specific post treatment follow-up. He complained of pain, had recently developed dysphonia and presented a vegetative lesion in the larynx. Histopathology of the lesion showed chronic granulomatous reaction with great number of giant cells where multibudding yeast cells of Pb were seen (Grocott).

One of the two patients with epidermoid carcinoma presented, after 15 years of post treatment follow-up, a mushroom-shaped lesion in the left aryepiglottic ligament. Histopathology of the lesion showed well differentiated epidermoid carcinoma. The other presented, after 3 years of post treatment follow-up an infiltrative lesion in the entire left hemiepiglottis and an ulcerated, infiltrative lesion in the left epiglottic fold. Histopathology of the lesion showed well differentiated epidermoid carcinoma. Both patients complained of pain and recently developed dysphonia.

Of the remaining 27 cases, all of whom were cured of PCM, 9 had no dysphonia, 3 remained tracheotomized and 15 remained dysphonic. These 15 were subdivided as follows: in 1 it was not possible to perform a laryngoscopy due to technical difficulties; 3 presented infiltrative lesions (respectively 8 months, 4 years and 17 years of post treatment follow up) and were submitted to biopsy and histopathological examination, which showed chronic nonspecific inflammatory processes without parasites. The remaining 11 patients persisted with inactive lesions.

Of the 26 cases who remained cured and in whom it was possible to perform laryngoscopy, we found isolated involvement of a laryngeal structure in 11 and multiple involvement in 15. In the same group, 16 cases presented single lesions and 10 multiple, distributed as shown in Table 1.

## DISCUSSION

With specific treatment of PCM, important sequelae may occur that can jeopardize the functionality of the affected organs. Factors such as smoking, alcoholism, poor oral hygiene, malnutrition, lengthy evolution of the disease, and irregular treatment are poor prognostic factors and facilitate the development of the other diseases.

In the sample studied, only 1 patient denied smoking; alcoholism was extremely frequent; delay in procuring medical care and technical difficulties in diagnosis contributed to the lengthy evolution of the disease; distant place of residence, length of treatment (once lesions have healed, some patients consider themselves cured and stop taking the medication), and low economic status were factors in irregular treatment; poor socio-economic conditions and difficulty in eating due to lesions in the URDT were factors in malnutrition.

The literature includes descriptions of active, predominantly moriform PCM lesions in the oropharynx[11], while reports were less frequent for ulcerative and ulcero-vegetative lesions, and such lesions are generally associated with hyperemia, edema, infiltration, sialorrhea, and painful reaction to chewing and swallowing[14]. Involvement of the lower lip can lead to macrocheilitis[5,15]. Observation of our patients yielded similar results. Lesions of the oropharynx submitted to specific treatment healed in a period of up to 2 months, and the majority of the patients (92%) progressed favorably without jeopardizing organ function. Labial edema is slow to resolve and persists for some time, even after lesions have healed. These our observations coincide with the literature[9,15].

Lack of dental care and poor oral hygiene characterized by various degrees of cavities, residual roots, presence of tartar and white matter associated with periodontal disease, dental mobility, and gengival retraction have been described by other authors[4,5] and are consistent with our findings, explaining the large number of missing teeth in these patients.

The 3 patients with oral atresia also presented lesions in the labial commissure and adjacent skin, as already described in the literature[9]. One patient had such gross microstomia that plastic surgery was needed to improve his eating. In this patient, in addition to the extensive bilateral involvement, irregular treatment leading to periodic reactivation contributed to the worsening of the sequelae. The patient with retraction of the tongue had extensive lesions on the floor of the mouth, frenulum linguae, and tongue.

Mutilating lesions with perfurated palate, already referred in the literature[9] occurred in one patient with associated tuberculosis, which can also lead this type of lesion. In this case we attributed the lesion to PCM, since the patient had mycotic lesions in the soft and hard palate, was treated for 2 months and improved, suffered a relapse later, and the perfurated palate occurred following treatment, while the tuberculosis was only detected in the lungs and treatment was performed regularly with clinical and radiological cure.

**TABLE 1**

Distribution of patients with involvement of the larynx who remained cured with dysphonia, with no dysphonia, and tracheotomized, by location and type of lesion

| Location | | N = 26 | Type of lesion | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | WD ND T | Edema | Infiltration | Destruction | Fibrosis | Synechia | Stenosis |
| | | 14 9 3 | WD-ND-T | WD-ND-T | WD-ND-T | WD-ND-T | WD-ND-T | WD-ND-T |
| | Supraglottis | | | | | | | |
| | Epiglottis | 5 7 2 | 1 | 1 | 4 1 1 | 3 6 1 | | |
| WD - 11 | Ligaments | 1 | | | | | 1 | |
| ND - 9 | Vestibular Folds | 3 2 | 2 | 1 | | 2 | | |
| T - 3 | Arytenoids | 3 2 | 1 | | | | 2 2 | |
| | Posterior commissure* | 2 1 1 | | | | 1 | 2 1 | |
| | Glottis | | | | | | | 7** |
| WD - 14 | Vocal cords | 14 3 3 | 2 | 1 | 2 | 8 1 | 4 3 | |
| ND - 3 | Anterior commissure | 4 3 | | | | | 4 3 | |
| T - 3 | | | | | | | | |
| | Subglottis | | | | | | | |
| WD - 1 | | | | | | 1 | | |
| ND | | | | | | | | |
| T | | | | | | | | |

N = number of cases
WD - with dysphonia
ND - no dysphonia
T - tracheotomized patients
* Posterior commissure (interarytenoid mucosa and mucosa of the arytenoid slope).
** Stenosis of the glottis due to synechia (e) in its structures.

About the nasal fossae involvement (3.75% in our study), other authors have referred to 6.7%[9] and 14%[3].

When lesions occur in the larynx, progressive obstruction of the glottis can occur which may lead to episodes of respiratory failure, as expressed clinically by dyspnea, stridor, and retraction of intracostal and supraclavicular fossae, leading to death if tracheotomy is not performed. When it occurs prior to specific treatment, edema of the vocal cords and, less frequently of the arytenoids and false cords poses the main risk for obstruction; stenosis is aggravated by thick, sticky pulmonary secretions[8]. Use of corticoids attenuates this complication but may not be sufficient to prevent the asphyxic attacks. With specific treatment, cicatricial stenosis leads to narrowing of the glottic lumen, and the clinical picture develops more gradually. These 2 situations were observed by AZULAY in 1952[1].

We believe that the cases in whom tracheotomy was necessary due to relapse (3 patients), prior fibrosis may have contributed to their occlusion. The tracheal cannula was removed in 3 of our patients, became definitive in 1 and 2 patients are waiting for the possibility of performing laryngoplasty in order to remove their tracheal cannula. In 394 cases studied by MACHADO & MIRANDA[9], with 11 years follow up, glottic stenosis was observed in 21. In 8, sulfa treatment was sufficient to heal the lesions. In one patient a polyp was removed, thus reestablishing airway patency. Death by asphyxia occurred in 3. Tracheotomy was imperative in 9 patients and became definitive in 6 and temporary in 1. Death by asphyxia occurred in 2 patients despite tracheotomy. Both had tracheal lesions.

Involvement of the vocal cords can lead to various degrees of dysphonia, and in our study it was permanent in

15 cases (50%). In the analysis of results from other authors[9], it occurred in 21.8% of the 96 cases studied.

Periodical examination of patients is essential to detect and occasional relapse or the appearance of another disease. Biopsy for histopathological examination was necessary in 6 of our patients. Chronic laryngitis was observed in 3, and patients were advised to stop smoking and observe periodical medical control. Relapse of the mycosis was observed in 1 patient and epidermoid carcinoma was found in 2.

Similar cases of association between PCM and neoplasms have been reported[10,16]. In our cases, it is difficult to establish a correlation, since the 2 patients were cured of PCM and both were chain smokers - it is known that smoking is a major cause of laryngeal cancer. We might merely ask whether the mycotic scars contributed to the development of the neoplasm. One of these patients already had an enlarged, firm cervical lymph node for 6 months, and that he refused to be submitted to a biopsy.

The fact that our follow-up study included tracheotomized patients and/or patients with definitive dysphonia, nasal voice, and functional alterations due to cicatricial retractions in the nasal and oral cavities, pharynx, hypopharynx, and larynx, but without active disease leads us to reflect on the high morbidity observed after traditional treatment of PCM. We propose corrective surgical techniques ranging from minor intra-oral plastic surgery to tracheolaryngoplasties.

Early diagnosis, proper treatment, proper oral hygiene, and abstinence from smoking and drinking alcohol are the most effective measures to avoid sequelae and related diseases.

## RESUMO

### Achados clínicos e endoscópicos na mucosa das vias aéreas e digestivas superiores no segmento pós-terapêutico de pacientes com Paracoccidioidomicose

Foi realizado sistematicamente o exame das vias aero-digestivas superiores (VADS) em grupo de 80 pacientes de paracoccidioidomicose (PCM) acompanhados após o tratamento específico por período que variou de 8 meses a 17 anos. A mucosa das VADS estava comprometida antes do tratamento especifico em 74 pacientes, assim distribuídos: orofaringe, 50 (41 isoladamente, 7 em associação com o laringe e 2 com a mucosa nasal); laringe, 30 (23 isoladamente e 7 em associação) e nasal, 3 (1 isoladamente e 2 em associação).

Em todos os 50 que apresentavam lesões no orofaringe observou-se lesões inativas, 3 com cicatriz viciosa (1 com retração de língua e 2 diminuição do orifício oral). Houve lesão destrutiva em 1 caso com perfuração do palato. Nos 46 casos restantes, o exame mostrou cicatriz estriada branco nacarada em alguns quase imperceptível e em outros com retração parcial de estruturas anatômicas sem alterações de suas características. Houve grande número de falhas dentárias.

Em 3 pacientes, que apresentaram comprometimento da mucosa nasal, todos sem lesões ativas de PCM, 2 permaneceram com voz anasalada. Em 30, com lesões no laringe, houve recidiva da PCM em 1 caso e 2 apresentaram carcinoma epidermóide. Nos 27 casos restantes, todos sem lesões ativas de PCM, 15 permaneceram com disfonia, 3 traqueostomizados e 9 assintomáticos.

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## REFERENCES

1. AZULAY, R.O. - Dois casos de micose de Lutz (Blastomicose brasileira) submetidos à traqueostomia. **Hospital** (Rio de J.), **42**: 135-143,1952.

2. BERTELLI, A.P. - Câncer de laringe. São Paulo, Manolo, 1980. p. 96-98.

3. COLOMBO, A.L.; CAMARGO, L.F.; FISCHMAN, O. & CASTELLO, A. - Parâmetros clínicos relevantes para o diagnóstico diferencial entre leishmaniose cutâneo-mucosa e paracoccidioidomicose. **Rev. Soc. bras. Med. trop., 25**: 171-175,1992.

4. FONSECA, J.B. - Blastomicose sul-americana. Estudo das lesões dentais e paradentais sob o ponto de vista clínico e histopatológico. **Rev. Fac. Odont. S. Paulo, 1**: 1-38, 1963.

5. LAUAND, F.; LIA, R.C.C. & PAINO, M.A.S. - Blastomicose sul-americana. Estudo clínico das lesões bucais. **Rev. Fac. Farm. Odont. Araraquara, 9**: 243-251, 1975.

6. LEBORGNE, F.E. - Classification of carcinoma of larynx. **J. Fac. Radiol. (Lond.), 4**: 264-267,1953.

7. LUTZ, A. - Uma mycose pseudococcidica localisada na boca e observada no Brasil. Contribuição ao conhecimento das hyphoblastomycoses americanas. **Bras. med, 22**: 121-124; 141-144, 1908.

8. MACHADO FILHO, J.; RÊGO, A.P.; CHAVES, A.C.F.; MIRANDA, J.L. & CASTRO E SILVA, C. - Considerações relativas à blastomicose sul-americana. Da participação laringeia e brônquica em 104 casos. Resultados endoscópicos. **Hospital** (Rio de J.), **58**: 19-34, 1960.

9. MACHADO FILHO, J. & MIRANDA, J.L. - Considerações relativas à blastomicose sul-americana. Evolução, resultados terapêuticos e moléstias associadas em 394 casos consecutivos. **Hospital** (Rio de J.), **60**: 375-412, 1961.

10. MARQUES, S.A. & SHIKANAI-YASUDA, M.A. - Paracoccidioidomycosis associated with immunosuppression, and cancer. In: FRANCO, M; LACAZ, C.S.; RESTREPRO, A.M. & DEL NEGRO, G. Paracoccidioidomycosis. Boca Raton, CRC Press, 1994. p. 394-405.

11. MENDES, R.P.; BRETAN, O.; JAVENCONE, A.C. & MARCONDES, J. - Estudos das lesões otorrinolaringológicas em doentes com paracoccidioidomicose. In: CONGRESSO DA SOCIEDADE BRASILEIRA DE MEDICINA TROPICAL, 20., Salvador, 1984. Abstracts. p.56.

12. MONTENEGRO, M.R.G. - Formas clínicas de paracoccidioidomicose. **Rev. Inst. Med. trop. S. Paulo, 28**: 203-204,1986.

13. MOTTA, L.C. & PUPO, J.A. - Granulomatose paracoccidioidica (blastomicose brasileira). **An. Fac. Med. S. Paulo, 12**: 407-426,1936.

14. PAIVA, L.J. & NOVA, R. - Lesões orofaringolaringeanas. In: DEL NEGRO, G; LACAZ, C.S. & FIORILLO, A.M., ed. Paracoccidioidomicose, blastomicose sul-americana. São Paulo, Sarvier; Edusp, 1982. p. 157-160.

15. RAMOS E SILVA, J. - Sobre as macroqueilites, especialmente as macroquelites parasitárias da blastomicose sul-americana. **J. bras. Med., 13**: 435-439, 1967.

16. RAPOPORT, A.; SANTOS, I.C.; ANDRADE SOBRINHO, J.; FACCIO, C.H. & MENUCCELLI JR., R. - Importância da blastomicose sul americana (B.S.A.) no diagnóstico diferencial com as neoplasias malignas de cabeça e pescoço. **Rev. bras. Cirurg. Cabeça e Pescoço**, 1(1): 13-33,1974.

17. VALLE, A.C.F. do - Tratamento da paracoccidioidomicose. Análise de 500 casos observados no Hospital Evandro Chagas. Fundação Oswaldo Cruz, no período de 1960 à 1986. Rio de Janeiro, 1988. (Dissertação de Mestrado - Faculdade de Medicina da Universidade Federal do Rio de Janeiro).

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