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Neoplasia and paracoccidioidomycosis

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Abstract Published studies on the association between cancer and paracoccidioidomycosis consist either isolated cases or clinical data based on hospital cohorts of paracoccidioidomycosis. The frequency of neoplasia in series of ≥ 80 patients with paracoccidioidomycosis ranges from 0.16 to 14.1%, mean of 3.96%. There are only two retrospective controlled studies, one of them showing greater incidence of carcinoma in biopsy and necropsy samples of paracoccidioidomycosis (12 cases in 147 patients with the mycosis: 8.2%) than in the necropsies of the control group (320 cases in 7,302 necropsies: 4.9%). In the other, 22,409 autopsies were reviewed and 4,372 cases of cancer were found; of the 85 patients with paracoccidioidomycosis, 12 were diagnosed with cancer. No differences were observed in the frequency of malignancies between the group of patients with paracoccidioidomycosis (14.1%) and the control group (19.5%). Considering all the reported cases, carcinoma was more frequent than hematological malignancies, and was more often found at the same site or in a neighboring site affected by the mycosis, usually occurring after the diagnosis of the mycosis. Commonly, the basic cause of death was related to secondary infections or neoplasia. Lymphoma was associated with poorly organized rich in fungi granuloma. The clinical course and mortality were related to the cancer evolution or secondary infections and was worse in lymphoid series, metastatic carcinoma or in patients under cytotoxic chemotherapy. Additionally, as in several cases the clinical and histopathological data

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may mimick neoplasia, the correct diagnosis of both diseases is essential to guarantee an early and safe intervention.

Keywords Paracoccidioidomycosis · Cancer · Neoplasia · Lymphoma · Leukemia · Carcinoma

Introduction

The association between cancer and paracoccidioidomycosis has been established since 1933 [1]. In fact, the incidence of the malignancy may be attributed to the dysfunction of cell immunity in the active paracoccidioidomycosis. The acute and multifocal chronic presentation of this mycosis have been associated to transitory hypo-reactivity to *P. brasiliensis* antigens and to TH2 type immune response, characterized by IL4, IL10 cytokines secretion, low IFγ secretion [2], deficiency in the killing activity of macrophages and natural killer cells [3]. Continuous stimulation of epithelial cells and phagocytic mononuclear system by fungal antigens might predispose these cells to malignant transformation and surveillance against malignancy might be affected. In parallel, granulomatous inflammation and pseudo-epitheliomatous hyperplasia observed in this chronic disease mimic well-differentiated malignancy [4], predisposing to incorrect diagnosis of cancer instead of paracoccidioidomycosis.

Cancer or paracoccidioidomycosis?

Many reports have focused on the similarities between malignancy and paracoccidioidomycosis based on clinical manifestations like lymphoma or leukemia or primary malignancy of the biliary tract [5] in the acute/subacute form of this mycosis. Other carcinoma diagnoses—instead of this mycotic lesions—were reported, such as colon cancer in case of intestinal involvement [6], laryngeal or intra-oral carcinoma, in the oral and laryngeal involvement by this mycosis [7, 8] and posterior fossa tumor in cases of cerebral paracoccidioidomycosis [9, 10]. Misdiagnosis of cancer have often caused severe consequences in patientś life and their relationship with their families and community, so clinicians need to be aware of the differential diagnosis of such diseases. Both diseases may occur concomitantly and biopsies should be requested to establish the correct diagnosis as soon as possible.

Citology has also been useful in the diagnosis of squamous cell cancer, presenting sensitivity of 86.5%, accuracy of 89.6%, predictive positive value of 95.7%, and specificity of 94.3% [11].

More recently, immunohistochemical expression of some tumor markers was analyzed in the granulomatous inflammation and pseudo-epitheliomatous hyperplasia. P53 was absent in normal cells and paracoccidioidomycosis inflammatory granuloma, in contrast to neoplastic lesions [12].

Moreover, cytokeratins expression was analyzed during inflammatory processes, with the objective of describing differences between cancer and mycotic lesions, concerning these filament of epithelial cells expression during the processes [4]. In oral lesions of 28 paracoccidioidomycosis patients and in the mucosa of healthy control individuals, CK1, CK10, CK14, CK6 and CK16 were not found. In contrast, the latter three cytokeratins were expressed in the basal layer of the epithelium of cancer lesions.

Cancer and paracoccidioidomycosis

Most published studies consisted either of single case reports or clinical and epidemiological data collected from hospital-based cohorts of patients with paracoccidioidomycosis [13–38]. Only two studies analyzed the relationship between cancer and paracoccidiodomycosis [13–14].

Retrospective controlled studies

In the first study, published in 1980, Leão & Mendes included necropsies and biopsies from Faculdade de Medicina da Universidade de São Paulo and found 12 patients with cancer (8.2%) among 147 paracoccidioidomycosis patients, as well as 360 carcinomas in 7302 necropsies (4.2%) in the control group [13]. The authors considered this difference significant (Yule coefficient) and suggested higher incidence of cancer in paracoccidiodomycosis patients than in the control group. A total of 11 out of such 12 malignancy lesions were carcinoma, 6 of them were located in the

same area of the mycosis: one lymphoma, one stomach carcinoma, two lung metastases of carcinoma and two prostate adenocarcinoma. The authors did not comment on the inclusion criteria of cases and controls, the period of study, the absence of biopsy control group, the description of malignancy in the same area of mycosis, clinical forms of mycosis, temporal relationship between both diseases, and activity of mycosis at the time of the cancer diagnosis.

In the second controlled study, Conceição, 1996, analyzed the incidence of cancer cases during an 18-year period (1974–1991) in a retrospective study of autopsy records in Faculdade de Medicina da Universidade de São Paulo, both in the group of patients with paracoccidioidomycosis and in the general autopsy record group [14]. The mycosis was diagnosed based on mycological and/or serologic and/or histopathologic exams. The following variables were observed: sex, clinical manifestations, age, anatomic location, and histopathology of malignancies, time interval between the diagnosis of both diseases, and cause of death. Children under 14 years and HIV-infected patients were excluded. A total of 12 cases of cancer were registered among 85 paracoccidioidomycosis patients (14.1%) and 4,372 cancer cases among 22,409 cases of necropsies (19.5%). No statistically significant difference was found in the frequency of malignancies between paracoccidioidomycosis and control group of necropsies (chi square test, $P = 0.26$). Malignancies associated with the mycosis presented a gender distribution similar to that observed in control group. Most malignancies occurred in patients over 44 years in both groups. Lung cancer and hematological malignancies were predominant both in the control group of necropsies (11% and 21.3%, respectively) and in the paracoccidioidomycosis group (41.7% and 25%, respectively).

Considering only lung cancer, it was more frequent in the mycosis group than in the control group ($P < 0.05$), two out of five of paracoccidioidomycosis patients with lung carcinoma were smokers. Given that it was a retrospective study, information about smoking and other variables were not reliable, final analysis was not conclusive and its result needs to be considered in a prospective study. In the control group, lung cancer was the second more frequent for men and the fourth for women; the most frequent cancer for both sexes was leukemia/lymphomas.

Histology showed three patients with hematological malignancies: Acute myeloid leukemia, chronic lymphoid leukemia and Hodgkin lymphoma, and nine patients with carcinoma: Digestive tract carcinoma, oat cells lung carcinoma—two cases, esophagus epidermoid carcinoma, lung carcinoma, bronchus carcinoma, adenocarcinoma, of the lung and adenocarcinoma of the prostate, rhinopharyngeal carcinoma.

A total of 7 out of these 12 cancer associated paracoccidioidomycosis cases presented the mycosis 6–96 months before the diagnosis of cancer. In four of them, cancer diagnosis was made from 1 to 60 months before the diagnosis of mycosis. Active mycosis was found in 10 out of 12 cases.

Considering the presence of cancer at the same anatomic site of mycosis, five patients presented both carcinoma and paracoccidiodomycosis in the lungs and one also presented chronic lymphoid leukemia and lymph node and epiglottis involvement. One unexpected result was the low frequency of severity or dissemination of the mycosis only in two cases: one with acute myeloid leukemia under chemotherapy and one with lung carcinoma. In most cases of this study, paracoccidiodomycosis was not regarded as a determinant factor leading to mortality. Death was more frequently related to infections as immediate causes and malignancy as the basic cause.

Hematological and solid organ malignancies

Regarding case reports, Rabello Filho first described the association of paracoccidioidomycosis and superior lip epithelioma in 1933 [1].

The first association with a hematological malignancy was registered by Lacaz et al, 1948, in a 34-year-old patient with adenomegaly, oral and laryngeal mucosa lesions, anemia, hypoproteinemia, lung condensation, whose sputum and mycologic exam of oral mucosal lesion identified *Paracoccidioides brasiliensis* [15]. Although treatment with sulfadiazine was introduced, the patient died 11 months after the diagnosis, and disseminated exsudative lesions containing fungal forms were described in the amygdales, larynx, and liver. Hodgkin lymphoma was found in the lung, spleen and lymph nodes. A second case of this association was

registered in 1960 in a chronic-form patient with 49 years, referring oral lesions 16 years before. The patient presented Thorax R-X abnormalities and the hypothesis of tuberculosis was not confirmed 8 and 15 years later, when the diagnosis of paracoccidioidomycosis was made. Biopsy of axilar lymph-node was performed, because the patient did not improve after having received amphotericin B (800 mg) and sulfamides, and revealed the presence of lymphoma.

Two more cases of Hodgkin lymphoma association were described by Alterio & Del Negro, 1960, and Severo, 1980 in 49-and 44-year-old patients with lung involvement and chronic form of the mycosis [16, 17]. The diagnosis of malignancy was made in the first case after axilar lymph node biopsy because no improvement was observed after receiving amphotericin B (800 mg) and sulfamides, presenting fever, anemia, adenomegaly and splenomegaly.

In Argentine, 1957, Gonzalez described the first association of carcinoma (lung) and paracoccidioidomycosis of hand and thorax skin [18]. Although skin lesions improved after sulfa treatment, a biopsy was indicated considering the persistence of pulmonary signals and symptoms (blood, sputum), revealing the presence of carcinoma without fungal lesions in the site of biopsies.

Nine non-controlled studies reported a series of cases collected on hospital-based cohorts of patients with paracoccidioidomycosis (Table 1).

Machado Filho & Miranda, 1961, Brazil, described six cases of carcinoma (1.52%) among 394 patients with paracoccidioidomycosis: three lung, one bladder, one penis and one adrenal carcinoma, two of them diagnosed at the same time of the mycosis, three after the mycosis and one before the mycosis [19]. The immediate case of death was malignancy in five out of six patients.

In 1971, Padilha-Gonçalves, Brazil described one patient with basocelular epithelioma and chronic form of the mycosis with oral, lymph node, and lung involvement among 130 patients with paracoccidioidomycosis [20].

In a series of 471 paracoccidioidomycosis cases, Rapopport et al. 1974, Brazil, reported 10 cancer patients (2.12%): eight of spinocelular and two of basocelular carcinoma [21]. Most of them were diagnosed simultaneously and only in one case, the anatomic site was the same for the cancer and the mycosis.

Rizzon et al. described in Brazil, 1980, two cases of lung malignancies in 82 patients of paracoccidioidomycosis: one in a patient with disseminated form and another in a patient with primary complex of paracoccidioidomycosis [22].

In Ecuador, 1983, Ronquillo et al. registered two cases of cancer among 133 patients with paracoccidioidomycosis: one with esophagus epidermoid carcinoma and the other with oral epidermoid carcinoma, associated with tuberculosis and histoplasmosis [23].

Gonçalves et al. 1984, Brazil, reported seven carcinoma cases among 81 patients with paracoccidioidomycosis: two in the larynx, two in the stomach, one in the tongue, one in the intestine, one in the parathyroid [24].

In 1992, Valle et al. Brazil, observed two lung carcinoma among 159 patients initially examined by Thorax R-X [25] and Tiraboshi et al. Argentine, described three cancers among 20 patients with paracoccidioidomycosis: two lung carcinoma and one larynx carcinoma [26].

Table 1 Frequency of neoplasia associated with paracoccidioidomycosis in cohorts based on hospital collections

Number of patients with Paracoccidioidomycosis	Number of Patients with		%, Reference
	Carcinoma	Hematological cancer	
0343	06	0	1.75 [19]
0130	01	0	0.16 [20]
0471	10	0	2.12 [21]
0147	12	01	8.16 [13][a]
0133	02	0	1.50 [23]
0081	07	0	8.75 [24]
0084	09	03	14.1 [14][b]
0405	18	03	5.18 [27]
1794	64	07	3.96

[a] Necropsy and biopsy samples for paracoccidioidomycosis and necropsy for control group;

[b] Necropsy series for both groups

More recently, Campos et al. 2007 reported 21 cases of neoplasia among 405 paracoccidioidomycosis patients from Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo in the period of 1966–2000 [27]. Eight were diagnosed at the first visit to the hospital (8/405 = 0.02%). In thirteen (62%), neoplasia was diagnosed 9–408 months after the diagnosis of the mycosis (median = 92 months). In nine patients (42.8%), the diagnosis of cancer was coincident with the reactivation of the mycosis in the same site of first fungal infection. A total of 11 (52.4%) presented the neoplasia in the same organ of mycotic lesion. Leukemia, lymphoma and lymph node adenoma were observed in 19-20-and 41-years old patients, two males and one female with acute/subacute presentation of paracoccidioidomycosis. Carcinoma were observed in 18 patients, 17 males and one female, from 31 to 71 years of age, with chronic presentation of the mycosis, five in the lungs, three in the esophagus, two in each one of these sites: tongue, lymph node and skin, and one in each one of these sites: stomach, appendix, bladder and cornea. Death was registered in four cases and was caused by malignancy.

Other 23 single reports or series reports, one from Mexico, one from Argentina, and the others from Brazil, only described cases presenting malignancy and mycosis without references to the total number of patients observed in these cohorts of paracoccidioidomycosis [28–38]. One case of lung carcinoma, one of them in a patient receiving chemotherapy (oat cell carcinoma) and presenting *Strongyloides stercoralis* in the sputum, whose pulmonary biopsy showed oat cell carcinoma and the necropsy, large necrotic areas and bizarre forms of the fungi [28]. Association of esophagus carcinoma and chagasic megaesophagus and megaduodenum and mycosis was registered in a patient with 57 years of age [31]. Lung carcinoma and paracoccidioidomycosis were described in a male patient whose diagnosis was made by cytological examination of sputum [11]. Two patients with chronic paracoccidioidomycosis (63 and 56 years of age), the first with lung carcinoma and tuberculosis and the other with tongue and amigdala carcinoma presenting malignancies and mycotic lesions in the same organ were cured after sulfamide treatment. In the latter, late skin hypersensitivity tests to ubiquitous antigens and lymphoblastic transformation to phytohemaglutinin were negative [33]. Seven cases of lung paracoccidiodomycosis and seven cases of disseminated form were reported as associated to malignancies, 64% were represented by bronchus carcinoma, followed by skin, kidney, bladder, esophagus and lymph—node carcinoma. In 50% of the cases, the first diagnosed disease was the mycosis and tuberculosis was present in 4 of them; favorable evolution was registered in 43% of them. Three more cancer cases presenting malignancy and mycotic lesions in the same organ (oral mucosa and in larynx) were described [36, 38]. Squamous cell carcinoma of the lung was described in a patient with oral mycotic lesions, whose diagnosis was made lately after lack of improvement with antifungal treatment [37].

Hematological malignancies and paracoccidioidomycosis

Hematological malignancies were registered in only six publications, five cases of Hodgkin lymphoma, two of leukemia (one acute myeloid, other chronic lymphoid), and two non specified malignancies.

Six out of eight patients were male, one female, and for one the gender was not mentioned, age ranges from 23 to 70 years. Hodgkin lymphoma and acute leukemia occurred more commonly in acute form patients than in chronic form in contrast with distribution of paracoccidioidomycosis in immunocompetent cases.

Mycosis was known before malignancy in three cases and independently of chemotherapy, four cases presented the acute form and three cases the chronic form of the mycosis. Histopathology showed in six cases poorly organized granulomata with a high number of fungal cells and affected either the same or different organs than that of the malignancies. More severe disease, higher mortality and 40% of therapeutic failure were observed in lymphoma and acute leukemia in comparison with the evolution of the disease in patients without immunosupression.

Carcinoma and paracoccidioidomycosis

Considering the total of 97 malignancies associated with 95 patients with paracoccidioidomycosis, carcinoma represented the great majority (84.5%) as seen in Table 2. The primary site of carcinoma was respiratory or the digestive tract (Table 2).

In 48 cases with available information, gender distribution showed large predominancy of male, age ranged from 37 to 75 years and the neoplasia affected either the same or neighboring tissues in 64.7% of the

Table 2 Type of malignancy in 95 patients with paracoccidioidomycosis and anatomic site

Hematological malignancies	14
Hodgkin lymphoma	07
Leukemia	05
Acute myeloid	02
Chronic lymphoid	02
No reported	02
Pleomorfic adenoma of lymph node	01
Carcinoma	
Lung carcinoma	27
Epidermoid	07
Undifferentiated	06
Adenocarcinoma	02
No reported	12
Skin Carcinoma	11
Basocelular	04*
Spinocelular	04*
Mycoses fungoides	01**
No informed	02
Oral Carcinoma	10
Tongue epidermoid	04
Tongue	04
Palate epidermoid	01
Palate	01
Esophagus	06
Epidermoid	03
Spinocelular	02
No informed	01
Larynx	05
Epidermoid	01
No informed	04
Stomach	04
Epidermoid	03
No informed	01
Bronchus carcinoma	04
Epidermoid	02
Squamous cell	01
No informed	01
Bladder carcinoma	03
Prostate carcinoma	03
Kidney, parathyroid, penis, adrenal, colon, cornea, appendix, Undifferentiated digestive tract Carcinoma	01 each type
Metastatic cancer (primary site unknown)	02

*One patient presenting skin spinocellular and basocellular carcinoma and other patient presenting oat cell esophagus Ca and mycosis fungoides of the skin

cases (Table 3). Considering 51 cases, paracoccidioidomycosis was diagnosed before the malignancy in 56.9%, after the malignancy in 17.6% and in 21.6% both were diagnosed simultaneously. Treatment was made predominantly with sulfamides, and mortality was not attributed to paracoccidioidomycosis in the majority of cases but to infection or malignancy complications. In a patient with oat cell carcinoma

Table 3 Paracoccidioidomycosis and neoplasia in 51 patients: clinical, epidemiological, and histopathological data

Age, gender (years old)	Mycosis site	Cancer site	1st diagnosis	Reference number
47 male	Respiratory tract	Lung carcinoma	Not mentioned	[11]
34 male	Oropharynx, larynx lung, liver	Hodgkin lymphoma	Lymphoma	[15]
49 male	Lung	Hodgkin lymphoma	Mycosis	[16]
48 male	Lung	Hodgkin lymphoma	Lymphoma	[17]
29 male*	Lymph node	Hodgkin lymphoma	Simultaneous	[32]
50 male	Skin	Lung Ca	Mycosis	[18]
55 male	Lung	Lung Ca	Carcinoma	[28]
59 male	Lung	Lung Ca	Carcinoma	[29]
52 male	Lung	Parathyroid Ca	Simultaneous	[30]
65 male	Lung, palate	Palate Ca	Simultaneous	[21]
57 male	Lung, adrenal	Esophagus Ca	Carcinoma	[31]
56 male	Oral, LN, lung	Tongue Ca	Simultaneous	[33]
63 male	Oral, LN, lung	Lung Ca	Mycosis	[33]
54 male	Oral, LN, lung	Tongue Ca	Mycosis	[26]
52 male	Oral, larynx, lung	Larynx Ca	Mycosis	[26]
51 male	LN	Undifferentiated digestive Ca	Mycosis	[14]
70 male	Pharynx larynx, LN	Chronic lymphoid leukemia	Leukemia	[14]
55 male	Mucosa, lung	Undifferentiated lung Ca	Not mentioned	[14]
55 male	Oral mucosa, LN	Esophagus epidermoid Ca	Mycosis	[14]
58 male	Suprarenal	Prostate adenoCa	Carcinoma	[14]
64 male	Liver, lungs	Bronchus: epidermoid Ca	Mycosis	[14]
23 male	Kidney, prostate	Hodgkin lymphoma	Mycosis	[14]
69 male	Lung	Undifferentiated lung Ca	Mycosis	[14]
30 female	LN	Myeloid acute leukemia	Simultaneous	[14]
56 male	Mucosa, lung	Lung epidermoid Ca	Carcinoma	[14]
49 male	Lung	Lung adenoCa	Mycosis	[14]
70 male	Oral mucosa, lung LN	Rhino pharyngeal Ca	Mycosis	[14]
62 male	Mucosa, LN, lung	Bronchus squamous cell Ca	Mycosis	[37]
71 male	Prostate	Chronic lymphocytic leukemia	Leukemia	[35]
66 male	Larynx	Larynx epidermoid carcinoma	Simultaneous	[38]
52 male	Lung, LN	Tongue: epidermoid Grade II Ca	Mycosis	[27]
48 male	Larynx, lung	Ca epidermoid: LN metastasis	Mycosis	[27]
53 male	Oral mucosa, lung	Esophagus oat cell Ca Skin mycosis fungoides	Mycosis	[27]
43 male	Skin, digestive, larynx	Appendix adenoCa	Mycosis	[27]
43 male	Skin, mucosa LN, adrenal	Skin spinocelular and basocelular grade II Ca	Mycosis	[27]
43 male	LN	LN metastasis: Ca	Simultaneous	[27]
41 male	LN	LN: pleomorfic adenoma	Simultaneous	[27]
68 male	Lung	Cornea: epidermoid intraepithelial Ca	Mycosis	[27]
41 female	Digestive, LN	Stomach Ca	Mycosis	[27]
54 male	Skin, oropharynx	Esophagus epidermoid grade II Ca	Mycosis	[27]
46 male	Oropharynx	Skin spinocelular Ca	Mycosis	[27]
56 male	Oropharynx, lung	Bronchus epidermoid Ca	Mycosis	[27]

Table 3 continued

Age, gender (years old)	Mycosis site	Cancer site	1st diagnosis	Reference number
68 male	Lung, adrenal	Lung Ca	Simultaneous	[27]
20 female	Oropharynx	Amigdala: invasive lymphoma	Simultaneous	[27]
53 male	Lung	Lung epidermoid invasive Ca	Mycosis	[27]
69 male	Lung	Lung undifferentiated oat cell Ca	Mycosis	[27]
19 male	LN, liver	Myeloid acute leukemia	Mycosis	[27]
31 male	Oropharynx, lung	Lung oat cell Ca	Mycosis	[27]
71 male	Oropharynx	Tongue epidermoid Ca	Simultaneous	[27]
59 male	Oropharynx	Lympho-histiocitic lymphoma	Mycosis	[27]
60 male	Oropharynx, lung	Bladder Ca	Mycosis	[27]

*HIV infection

under chemotherapy without diagnosis of this mycosis [29], necropsy showed suppurative focci in the lungs with a large number of bizarre, multibudding forms of *P. brasiliensis*.

Carcinoma has been associated with chronic form of the mycosis, gender distribution is similar to that seen in chronic form of the disease and age ranges showed predominancy of 50 years or older patients (75.7%, Table 3).

Carcinoma and mycosis are located in the same anatomic site or neighboring tissue in 64.7% of patients and more frequently, the mycosis was diagnosed before the malignancy.

Mortality is not attributed to the mycosis except for patients under cytotoxic therapy or dissemination of malignancy.

Comments

In patients with paracoccidioidomycosis and hematological malignancies, clinical manifestations of the mycosis are more frequently disseminated than localized; appearing before malignancy and independently of chemotherapy. Histopathological findings showed a high number of fungi and poorly organized granulomata. Therapeutic failure was observed in about 40% of the cases, indicating that an early diagnosis as well as early and efficient intervention is necessary for better therapeutic results.

In contrast, carcinoma might affect immune response depending on its invasive ability and dissemination. Attention to the diseases with similar clinical manifestations is important to avoid misdiagnoses and to indicate as soon as possible the best therapeutic procedure. Cytological and histopathologic examination followed by direct mycological and culture tests are indicated in cases without proven diagnosis of mycosis or malignancy.

In paracoccidioidomycosis, several risk factors predisposing to a malignant transformation of cells could be observed, such as the deficiency of T cell immunity and of the surveillance against malignancies, chronic antigenic stimulation of the lymphoreticular system and associated factors such as smoking and poor oral hygienic habits.

Higher frequency of carcinoma in chronic form presentation and its localization in the same organs simultaneously or recently invaded by the fungus might be taken in consideration, suggesting that antigenic continuous stimulus and surveillance deficiency against cancer, as seen in malignant transformation of scars, could contribute to malignant transformation of the epithelial or other cells in the inflammatory tissue.

In contrast, the type of malignancies preferentially observed in acute/subacute form patients of this mycosis involves lymphoid tissue and phagocytic mononuclear system. In parallel, in acute/subacute form of the mycosis occurs the strongest disfunction of T cell immunity, and consequently, cytokines dependent macrophage activation and natural killer surveillance against microorganisms and tumors may be affected.

Although controlled studies were not conclusive about the relationship between paracoccidioidomycosis

and malignancies, the incidence of cancer in both controlled studies in mycosis population needed to be better examined in prospective studies. In parallel, the major incidence of some malignancies according to the clinical presentation of the disease or by patientś age could be further studied. In effect, carcinoma has not been observed in young patients with acute form disease and was largely observed in chronic multifocal presentation.

Finally, the knowledge of host-parasite interaction at the systemic and tissular levels in patients with cancer and paracoccidioidomycosis remains as a challenge to understand mechanisms involved in malignant transformation aiming to avoid and control such undesirable event.

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