Association between paracoccidioidomycosis and cancer*, **

Associação entre paracoccidioidomicose e câncer

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Abstract

Objective: To analyze the association between paracoccidioidomycosis (Pcm) and cancer in a series of 25 cases and to review the literature on this topic. **Methods:** A retrospective review of 25 cases diagnosed with Pcm and cancer, retrieved from a series of 808 consecutive adult patients diagnosed with Pcm based on tests conducted in the Mycology Laboratory of the *Santa Casa Complexo Hospitalar*, in the city of Porto Alegre, Brazil, between 1972 and 2007. The diagnosis of Pcm was confirmed by means of direct microscopic examination, histopathological examination or immunodiffusion test. All cancer cases were confirmed by histopathological or cytopathological examination. **Results:** Respiratory symptoms were the principal complaints of the patients evaluated. Pulmonary involvement predominated, followed by skin and lymph node involvement. The most prevalent tumor was bronchial carcinoma, in 15 patients, followed by other types of carcinoma, and 1 patient had Hodgkin's lymphoma. In 16 patients (64%), the site of the Pcm was the same as that of the tumor. In most cases, Pcm treatment consisted of the isolated administration of sulfanilamide, sulfamethoxazole-trimethoprim, ketoconazole, itraconazole or amphotericin B. The most common treatment for cancer was surgery, followed by radiotherapy and chemotherapy. Of the 25 patients, 12 were cured of Pcm, and 4 died. In 9 patients, the final outcome was unknown. In the general population of the area under study, the prevalence of lung cancer was significantly higher in smokers with Pcm than in smokers without Pcm ($p < 0.001$). **Conclusions:** A diagnosis of Pcm appears to increase the risk of lung cancer.

Keywords: Paracoccidioides; Paracoccidioidomycosis; Neoplasms.

Resumo

Objetivo: Analisar a associação entre paracoccidioidomicose (Pcm) e câncer e realizar uma revisão da literatura sobre esse tópico. **Métodos:** Revisão retrospectiva de 25 casos diagnosticados com Pcm e câncer, extraídos de uma série de 808 casos consecutivos de pacientes adultos diagnosticados com Pcm com base nos testes realizados no Laboratório de Micologia da Santa Casa Complexo Hospitalar de Porto Alegre (RS), entre 1972 e 2007. O diagnóstico de Pcm foi confirmado através de exame microscópico direto, exame histopatológico ou imunodifusão. Todos os casos de câncer foram confirmados por exame histopatológico ou citopatológico. **Resultados:** Sintomas respiratórios foram as principais queixas dos pacientes. O envolvimento pulmonar foi o achado mais predominante, seguido pelo tegumentar e linfático. O tipo de tumor mais prevalente foi o carcinoma brônquico, em 15 casos, seguido de outros tipos de carcinoma, e 1 paciente apresentou linfoma de Hodgkin. Em 16 pacientes (64%), o sítio de Pcm era o mesmo do tumor. Na maioria dos casos, o tratamento de Pcm consistiu na administração isolada de sulfanilamida, sulfametoxazol-trimetoprim, cetoconazol, itraconazol ou anfotericina B. A cirurgia foi o tratamento mais comum para o câncer, seguida de radioterapia e quimioterapia. Dos 25 pacientes, 12 foram curados para Pcm, e 4 faleceram. Em 9, o desfecho final era desconhecido. A prevalência de câncer de pulmão na população geral na área em estudo foi significativamente maior em fumantes com Pcm que em fumantes sem Pcm ($p < 0,001$). **Conclusões:** .O diagnóstico de Pcm parece aumentar o risco de câncer de pulmão.

Descritores: Paracoccidioides; Paracoccidioidomicose; Neoplasias.

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Introduction

Paracoccidioidomycosis (Pcm)—caused by the dimorphic fungus *Paracoccidioides brasiliensis,* which is transmitted by the airborne route—is the leading systemic mycosis in Latin America. Depending on the immune status of the host, the primary infection can resolve or can develop into a progressive disease with an acute, subacute or chronic course.[1,2]

Only a few studies have evaluated the association between Pcm and neoplasia[3]: some have described isolated cases,[4-10] whereas others have been clinical, epidemiological investigations of hospitalized cases.[11-15] Immunological factors involved in the development of Pcm and the consequent chronic inflammatory response can play a role in this association, as has been shown in other situations.[16] The potential association between Pcm and lung cancer is of particular interest, since the lung is a common site of Pcm. Factors other than smoking can operate in the genesis of lung cancer, as has been shown in patients with COPD, who, even after having quit smoking, are at an increased risk for the development of lung cancer.[17,18]

The objective of this study was to analyze the association between Pcm and cancer in a series of 25 cases, as well as to review the literature on this topic.

Methods

This was a retrospective review of 25 patients diagnosed with Pcm and cancer, identified within a series of 808 consecutive adult patients who were diagnosed with Pcm based on tests conducted in the Mycology Laboratory of the *Santa Casa Complexo Hospitalar*, located in the city of Porto Alegre, Brazil, between 1972 and 2007.

The diagnosis of Pcm was confirmed by the identification of *P. brasiliensis* in clinical specimens by means of direct examination with 20% potassium hydroxide or in histological preparations using Gomori-Grocott staining, as well as in culture isolates or by detecting specific antibodies using double radial immunodiffusion.

In all 25 cases, the diagnosis of cancer was based on the histopathological or cytopathological examination of biopsy or surgical specimens. Demographic data and life habits, as well as the main clinical manifestations, radiological findings and laboratory findings, were reviewed, as were the treatments used for and the evolution of the two diseases.

The number of lung cancer cases identified in that group of Pcm patients was compared with that found in the general population of the area in study and was correlated with other types of exposure, especially to smoking.

The study design was approved by the research ethics committee of the institution (protocol no. 826/05).

To compare proportions, we used the chi-square test. The level of significance was set at 5%.

Results

Of the 808 patients diagnosed with Pcm, 796 (98.5%) were smokers and 25 (3.1%) presented with concomitant cancer (15 with lung cancer) during the evolution of the mycosis (Table 1). Of the 25 patients with Pcm and cancer, all were male, 24 were white, 1 was African-Brazilian (patient 11), and their ages ranged from 40 to 68 years (mean, 53.5 years). Twenty-one patients (84.0%) were below 60 years of age. Of the 4 patients over 60, 2 had lung cancer. Twelve patients (48.0%) were farmers, the remaining patients being engaged in various other occupations. All 25 patients were smokers, and 4 were also alcoholics (patients 9, 11, 18 and 25).

In the state of Rio Grande do Sul, Brazil, the population increased from 6,664,891 in 1970 to 10,582,887 in 2007. In 1990, residents of the state numbered approximately 9,500,000, 48% of whom were males and approximately 28% of whom were in the 40-70 year age bracket. The proportion of smokers in the male population over 40 years of age decreased from a mean value of 35% in the 1970s to 20% in 2004.[19,20] Therefore, assuming a mean prevalence of smoking of 24% among the male population in the 40-70 year age bracket, there were, on average, 306,000 male smokers per year during the study period, and approximately 1,600 (0.523%) of those smokers had lung cancer.[21,22] In contrast, lung cancer was seen in 15 (1.8%) of the 808 Pcm patients evaluated in our study, which is a significantly higher proportion ($p < 0.001$), the relative risk being 3.4.

All 25 of the patients with Pcm and cancer sought medical attention due to respiratory

Table 1 - Clinical characteristics of 25 patients diagnosed with paracoccidioidomycosis and cancer, Porto Alegre, Brazil, 1972-2007.

Patient	Age	Paracoccidioidomycosis		Carcinomas/lymphoma[a]			Timing of cancer diagnosis
		Site	Treatment	Organ	Histology	Treatment	
01	59	Lung, mouth	Sulfamethoxazole-trimethoprim	Lung	Squamous cell	Radiation therapy	6 years after Pcm
02	49	Lung, larynx	Sulfamethoxazole-trimethoprim	Lung	Adenocarcinoma	Surgery	Simultaneous to Pcm
03	63	Lung, larynx, lymph nodes	Sulfamethoxazole-trimethoprim	Lung	Squamous cell	No data	4 years after Pcm
04	62	Lung[b], mouth	Sulfamethoxazole-trimethoprim	Bladder	Squamous cell	Radiation therapy	12 years after Pcm
05	57	Lung	Sulfamethoxazole-trimethoprim & ketoconazole	Lung	Adenocarcinoma	Surgery	2 years after Pcm
06	56	Lung, mouth	Sulfa, ketoconazole	Kidney	Transitional cell	Surgery	Simultaneous to Pcm
07	42	Lung, larynx, mouth	Sulfanilamide	Lung	Adenocarcinoma	Surgery	2 months after Pcm
08	51	Lung, larynx, mouth	Sulfamethoxazole-trimethoprim & ketoconazole (then changed to itraconazole)	Skin	Squamous cell	Radiation therapy	3 months after Pcm
09	40	Lung, lymph nodes	Ketoconazole	Lung	Squamous cell	Radiation therapy	6 years after Pcm
10	50	Lung, lymph nodes	Itraconazole	Lung	Squamous cell	Surgery	Simultaneous to Pcm
11	54	Lung	Sulfanilamide	Lung	Squamous cell	Radiation therapy	3 years after Pcm
12	46	Lung	Amphotericin B	Lung, metastasis	Squamous cell	Chemotherapy	Simultaneous to Pcm
13	65	Lung	Sulfanilamide	Lung	Squamous cell	Radiation therapy	Simultaneous to Pcm
14	52	Lung	Itraconazole	Tongue	Squamous cell	Surgery	Simultaneous to Pcm
15	41	Lung, mouth	Ketoconazole	Larynx	Squamous cell	Surgery	Simultaneous to Pcm
16	49	Lung	Ketoconazole	Lung, metastasis	Adenocarcinoma	Radiation therapy	4 years after Pcm
17	51	Lung, larynx	Sulfanilamide	Esophagus, metastasis	Adenocarcinoma	Surgery	Simultaneous to Pcm
18	52	Lung	Sulfamethoxazole-trimethoprim	Skin	Squamous cell	Surgery	1 year after Pcm
19	56	Lung	Itraconazole	Lung	Squamous cell	Radiation therapy	10 years after Pcm
20[c]	59	Primary complex	None	Lung	Squamous cell	Surgery	Simultaneous to Pcm
21[d]	55	Lung[e,f]	None	Lung	Oat cell	Chemotherapy	6 days before Pcm
22	58	Lung, larynx	Sulfanilamide	Lung	Squamous cell	Surgery	3 months after Pcm
23	57	Lung, tongue	Sulfanilamide	Tongue	Squamous cell	Radiation therapy	Simultaneous to Pcm
24[g]	48	Lung	Sulfanilamide	Predominantly lymph nodes	Lymphoma[a]	Chemotherapy	7 years before Pcm
25	68	Lung	Amphotericin B	Pharynx, metastasis	Squamous cell	Combined[h]	2 months after Pcm

Pcm: paracoccidioidomycosis. [a]Hodgkin's lymphoma. [b]Associated with pulmonary tuberculosis. [c]Case described by Maymó Argañaraz et al.[7] [d]Case described by Gonzalez et al.[6] [e]Concomitant *Strongyloides stercoralis* infestation (larvae were found in cytologic examination and in the sputum smear). [f]Diagnosis of mycosis made by autopsy. [g]Case described by Severo et al.[8] [h]Surgery, radiation therapy and chemotherapy.

symptoms (dyspnea, productive cough or hemoptysis). Some patients also reported weight loss, dysphagia, anorexia or fever.

Among the 25 patients, the diagnosis of Pcm was confirmed by immunodiffusion in 11, by direct microscopic examination in 9 and by histopathological examination in 6. In 14 of the patients, the diagnosis was confirmed by a single method: histopathological examination in 7; direct microscopic examination in 4; and immunodiffusion in 3.

The Pcm cases were classified according to the criteria recommended by Wanke and Londero[2]: 9 (36%) as the chronic unifocal form (pulmonary involvement); 13 (52%) as the chronic multifocal form (involving two or more organs); and 3 (12%—patients 21, 24 and 25) as the acute form (behaving as an opportunistic pathogen).

Of the 25 patients, 24 (96.0%) had carcinoma. Of those 24 carcinomas, 15 (62.5%) were lung cancer. Histologically, the lung tumors were classified as follows: as squamous cell carcinoma in 10 cases, being metastatic in 1 of the 10; as adenocarcinoma in 4 cases, being metastatic in 1 of the 4; and as small cell (oat cell) carcinoma in 1 case. Epidermoid carcinomas were found on the skin (n = 2), on the tongue (n = 2), in the bladder (n = 1), in the larynx (n = 1) and in the pharynx (n = 1). In addition, esophageal adenocarcinoma and transitional cell carcinoma of the kidney were found in 1 patient each. The

Table 2 - Paracoccidioidomycosis and cancer: cases described in the literature.

Type of cancer	Site	Cases	Histological classification
		n	
Carcinoma	Lung[3,9,12,13,18,20,23,25,27,30]	25	Epidermoid (n = 8)
			Undifferentiated small cell (n = 4)
			Undifferentiated large cell (n = 1)
			Adenocarcinoma (n = 2)
			Unspecified (n = 10)
	Skin[3,21]	8	Basal cell (n = 3)
			Spinocellular (n = 3)
			Unspecified (n = 2)
	Tongue[3,8,14,21]	5	Epidermoid (n = 1)
			Spinocellular (n = 2)
			Unspecified (n = 2)
	Palate[4,21]	2	Epidermoid (n = 1)
			Spinocellular (n = 1)
	Larynx[3,8,14,15]	5	Epidermoid (n = 2)
			Unspecified (n = 3)
	Esophagus[3,4,26]	4	Epidermoid (n = 2)
			Spinocellular (n = 1)
			Unspecified (n = 1)
	Stomach[8,12]	3	Unspecified
	Bladder[3,13]	2	Unspecified
	Prostate[3,12]	3	Adenocarcinoma
	Rhinopharynx and digestive tract[3]	1 each	Undifferentiated
	Penis, adrenal, colon, kidney and parathyroid[3,7,8,13]	1 each	Unspecified
	Unspecified[3,12,19]	20	Unspecified
Subtotal		84	
Lymphoma[3,11,12,26,29]		5	Hodgkin's lymphoma (n = 2)
			Unspecified (n = 3)
Leukemia[3,14]		3	Chronic myeloid (n = 1)
			Acute myeloid (n = 1)
			Chronic lymphoid (n = 1)
Total		92	

remaining patient was diagnosed with Hodgkin's lymphoma (nodular sclerosis with lymphocyte predominance).

In 12 cases, the diagnosis of Pcm was made prior to that of cancer, whereas 3 patients were first diagnosed with cancer and 10 were simultaneously diagnosed with the two diseases. The two diseases occurred at the same site in 16 patients (64%), the lung in 15 and the tongue in 1.

In 11 patients, the treatment for cancer consisted of surgery alone, whereas radiotherapy alone was used in 9, chemotherapy alone was used in 3, the surgery/radiotherapy/chemotherapy combination was used in 1, and the details of treatment were unavailable in 1. The Pcm was treated with sulfanilamide in 7 patients, with sulfamethoxazole-trimethoprim in 5, with ketoconazole in 3, with itraconazole in 3 and with amphotericin B in 2. Two patients were treated with the sulfamethoxazole-trimethoprim-ketoconazole combination, although this had to be changed to itraconazole in 1. Another patient was treated with the combination of sulfanilamide and ketoconazole. There were 2 patients who received no treatment for the Pcm. Of the 25 patients, 12 were cured of Pcm and 4 (patients 16, 21, 23 and 25) died. In 9 cases, the final outcome was unknown.

Discussion

The combination of Pcm and cancer was first described in 1933.[23] Since then, there have been reports of only a few cases (Table 2), three of which are included in the present series (patients 20, 21 and 24). In a recent review, the clinical data for 12 patients with Pcm and carcinoma showed that the two diseases were diagnosed simultaneously in 58.3%, and that they involved the same organ or neighboring tissues in 83.3%, suggesting a possible relationship between the two conditions.[23]

Cancer is a disease with multiple risk factors.[6,7] Therefore, the simultaneous appearance of Pcm and cancer in the present study could be interpreted as a coincidence, especially in the cases in which the two conditions appeared at different sites or at the same extrapulmonary site. However, it has been suggested that there is an association between cancer and Pcm, and that the incidence of the former could be attributed to the cell immunity dysfunction seen in cases of active Pcm.[3] The acute and chronic multifocal forms of Pcm have been associated with transitory hyporeactivity to *P. brasiliensis* antigens and with a Th2 type immune response, which is characterized by the release of the cytokines IL-4 and IL-10, low secretion of IFN-γ and diminished parasite killing (by macrophages and natural killer cells).[3,23,24] The continuous stimulation of epithelial cells and of the phagocytic mononuclear system by fungal antigens might affect cell surveillance, leading to malignant transformation.

One risk factor for lung carcinogenesis is chronic inflammation with squamous metaplasia, which was reported in 33.0% of Pcm cases in a cytology study of phlegm and bronchial brush samples,[23] and in a recent population-based case-control study of 1,934 individuals with chronic bronchitis or emphysema.[18] This could be a consequence of exposure to smoking. In addition, chromosome aberrations have been reported in cultures of lymphocytes from patients with Pcm, suggesting that aneuploidy plays a role in the development of at least some types of cancer.[25]

All 25 of the patients diagnosed with Pcm and cancer were male smokers over 40 years of age, as were 98.5% of the whole series of 808 patients with Pcm. Carcinomas accounted for 96.0% of the cases (Table 1), and lung cancer was the predominant tumor (60.0%), which is in agreement with previous reports, among which this combination was seen in 90.3% of the cases (Table 2). The annual mean number of patients with lung cancer in this male population was calculated to be approximately 1,600.[17] Since almost all of the 25 patients evaluated in the present study were smokers and smokers make up over 90% of the male population with lung cancer in the area under study, it would be reasonable to assume that the higher proportion of cases of lung cancer among the 808 patients with Pcm is attributable to the accompanying mycosis. A common factor, such as reduced immunological surveillance, might contribute to both conditions, or one condition could favor the other, such as when there is chronic inflammation and scarring in Pcm lesions, thereby increasing the risk for carcinogenesis.[26]

In the medical literature, it has been reported that lung cancer can develop in fibrotic foci (scars) from previous infections, such as those caused

by *Mycobacterium tuberculosis* or *Histoplasma capsulatum*.[27] In most cases, the scar is a desmoplastic response to the tumor. However, it can also precede the neoplastic state.[27,28] This could explain the occurrence of Pcm and cancer at the same site or in neighboring tissues, as seen in our study, as well as in similar documented cases.[3] The Pcm-related damage found in the lungs of such patients is due to the active disease, rather than to scarring. However, they could represent the reactivation of quiescent processes, dating back to the beginning of the infection (16 years or more).[29]

The correlation between the severity of the clinical presentation of Pcm and the degree of depression of the immune system is also known.[16] Cancer itself appears not to interfere with the clinical natural history of Pcm.[9] Therefore, patients with solid tumors present the chronic form of the disease, and the mortality rates among such patients are similar to those reported for immunocompetent patients, excluding those submitted to cytotoxic therapy or with metastasis. When the infection is concomitant with cancer of hematological origin, such as lymphoma or leukemia, it tends to follow a more severe clinical course, with higher mortality. Immunosuppressants, such as corticosteroids, together with the immunosuppressive effect of the lymphoma or leukemia, lead to reinfection or reactivation of quiescent Pcm foci, commonly located in the lungs.[10]

This opportunistic behavior of *P. brasiliensis* is revealed by a clinical presentation that tends to be similar to that of the disseminated acute and subacute forms,[2] as found in patients 21, 24 and 25. In patients with cancer, unlike in patients with lymphoma or leukemia, severe fungal infections are rare. In this population, the main risk factors for the development of the mycosis are the use of immunosuppressants and the dissemination of the neoplastic disease. In the present study, however, the diagnosis of Pcm preceded that of cancer in 12 patients, and the diagnosis was simultaneous in 10, prior to any kind of antineoplastic treatment.

Chronic diseases, such as granulomatous inflammation and pseudoepitheliomatous hyperplasia, have been found to mimic well-differentiated malignancy, predisposing to an incorrect diagnosis of cancer rather than Pcm. Misdiagnoses of cancer have often had severe consequences for the lives of patients, and clinicians should be aware of the importance of the differential diagnosis in such cases.[23] Since cancer and Pcm can occur concomitantly, biopsies should be requested in order to establish the correct diagnosis as soon as possible. Aside from microbiological and histological methods, immunodiffusion is an important tool for the diagnosis of Pcm, with a sensitivity of 84.3% and a specificity of 98.9%. However, it can produce false-negative results in immunosuppressed patients.[28] In our study, 3 patients (11, 14 and 19) were diagnosed with Pcm based on the clinical manifestations, positive immunodiffusion results for by *P. brasiliensis* and the exclusion of cross-reactions with other agents.

In conclusion, a diagnosis of Pcm appears to increase the risk of cancer in general, and of lung cancer in particular.

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