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Evaluation of Alpha-1-Glycoprotein acid and Mucoproteins in patients with Paracoccidioidomycosis treated with Sulfametoxazol-Trimetoprim

Evaluación del ácido Alfa-1-Glucoproteína y Mucoproteínas en pacientes con Paracoccidioidomicosis tratados con Sulfametoxazol-Trimetoprim

Avaliação da Alfa-1-Glicoproteína ácida e Mucoproteínas em pacientes com Paracoccidioidomicose tratados com Sulfametoxazol-Trimetoprim

ABSTRACT
Alpha-1-acid glycoprotein (AGP) and mucoprotein are proteins of the inflammatory phase that increase their plasma concentrations when they present a response to the inflammatory state, representing a defense mechanism of the organism. The aim of the study was to evaluate the profile of these proteins in patients with chronic PCM treated with sulfamethoxazole-trimethoprim (SMX-TMP) and to associate the results found with epidemiological data, risk factors, symptoms, disease progression, and treatment outcome. In the methods adopted, the medical records of 244 patients with chronic PCM from 1998 to 2014 were analyzed. Of these, 134 (54.92%) patients underwent biochemical tests for inflammatory proteins during the course of the disease. Adult patients aged 30 to 50 years predominated 73 (54.48%), smokers 123 (91.79%), alcoholics 60 (44.78%). As a result, there was a decrease in inflammatory proteins after treatment (p = 0.01803). In conclusion, AGP and mucoproteins are useful as markers of the effect of therapy and inflammatory involution.
DESCRIPTORS: Paracoccidioidomycosis; Mucoproteins; Medication Adherence.

RESUMEN
La glicoproteína ácida alfa-1 (AGP) y la mucoproteína son proteínas de la fase inflamatoria que aumentan sus concentraciones plasmáticas cuando presentan una respuesta al estado inflamatorio, representando un mecanismo de defensa del organismo. El objetivo del estudio fue evaluar el perfil de estas proteínas en pacientes con MCP crónica tratados con sulfametoxazol-trimetoprima (SMX-TMP) y asociar los resultados encontrados con datos epidemiológicos, factores de riesgo, síntomas, progresión de la enfermedad y resultado del tratamiento. En los métodos adoptados se analizaron las historias clínicas de 244 pacientes con MCP crónica de 1998 a 2014. De estos, 134 (54,92%) pacientes fueron sometidos a pruebas bioquímicas de proteínas inflamatorias durante el curso de la enfermedad. Predominaron los pacientes adultos de 30 a 50 años 73 (54,48%), fumadores 123 (91,79%), alcohólicos 60 (44,78%). Como resultado, hubo una disminución de las proteínas inflamatorias después del tratamiento (p = 0,01803). En conclusión, las AGP y las mucoproteínas son útiles como marcadores del efecto de la terapia y la involución inflamatoria.
DESCRIPTORES: Paracoccidioidomicosis; Mucoproteínas; Cumplimiento de la Medicación.

RESUMO
A alfa-1-glicoproteina ácida (AGP) e a mucoproteína são proteínas de fase inflamatória que aumentam suas concentrações plasmáticas quando apresentam um quadro de resposta ao estado inflamatório, representando um mecanismo de defesa do organismo. O objetivo do estudo foi avaliar o perfil dessas proteínas em pacientes com PCM crônica tratados com sulfametoxazol-trimetoprim (SMX-TMP) e associar os resultados encontrados com dados epidemiológicos, fatores de risco, sintomas, evolução da doença, e desfecho do tratamento. Nos métodos adotados foram analisados os prontuários de 244 pacientes com PCM crônica no período de 1998 a 2014. Destes, 134(54,92%) pacientes fizeram exames bioquímicos das proteínas inflamatórias durante o curso da doença. Predominaram pacientes adultos de 30 a 50 anos 73(54,48%), tabagistas 123(91,79%), alcoólicos 60(44,78%). Como resultado obteve-se a diminuição das proteínas inflamatórias após o tratamento (p= 0,01803). Concluindo que a AGP e a mucoproteínas são úteis como marcadores do efeito de terapia e da involução inflamatória.
DESCRITORES: Paracoccidioidomicose; Mucoproteínas; Adesão à Medicação.

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INTRODUCTION

Paracoccidioidomycosis (PCM) is known as South American blastomycosis, Lutz's disease, Almeida's disease or tropical blastomycoid granulomatosis. It is a systemic mycosis caused by a thermo-dimorphic fungus Paracoccidioides sp., Which grows in the environment in the form of mycelium, at a temperature of 25°C, and in tissues at 37°C in the form of yeast[1]. It is predominant in rural areas of Brazil and other South American countries, in areas of fertile soil, leading to a social and economic impact. [2] As it is not a disease of compulsory notification, its real incidence is unknown, as well as its latent forms. [3]

PCM is predominant in middle-aged or elderly men from rural Brazilian areas, with reactivation of a latent endogenous focus, and depends on factors related to both the infectious agent and the host. There is a lower incidence in females. [4] Most cases of PCM occur in individuals whose hygiene, nutritional and socioeconomic conditions are precarious. These individuals are usually rural workers who, due to their activity, most often remain directly in contact with land and vegetables.

It presents clinically with skin lesions on the face, perioral region, oro-pharyngolaryngeal and nasal mucosa, which are always accompanied by ganglionic reactions with a tendency to lymphatic and hematogenous spread, affecting internal organs of the digestive and respiratory system. [5, 6, 2, 7] The infection can remain localized or spread to other organs via the hematogenous route. [8] Lung, liver, lymph node, spleen, kidney, adrenals, mucous membranes and skin are the organs most frequently affected. [9]

The suspicion of the diagnosis of PCM is based on clinical and epidemiological data, but confirmation is made basically by demonstrating the etiologic agent in fresh exams, culture and histopathological preparations [10] and the treatment of PCM should include measures of clinical support and specific antifungal therapy, such as the use of amphotericin B, sulfamides and azoles. According to Shikanai-Yasuda (2006), the patient must remain under treatment and follow-up until the cure criteria are obtained, based on clinical, radiological and serological parameters. Patients should be monitored periodically until they meet the cure criteria. [2]

The cure criteria for paracoccidioidomycosis involve: clinical, radiological and mycological improvement, ESR, mucoproteins with normal results, for 3 consecutive months. [7, 11] The quantification of these markers in the serum can be useful in the detection of the acute process, as well as in its monitoring. [12]

It is worth mentioning that this study intends to identify the profile of inflammatory outbreaks in the clinical process of treating chronic PCM whose objective was to evaluate the profile of these proteins in patients with chronic PCM treated with sulfamethoxazole-trimethoprim (SMX-TMP) and to associate the results found with epidemiological data, risk factors, symptoms, disease progression, and treatment outcome.

METHODS

This is a descriptive study of retrospective exploratory analysis of data from medical records of patients with chronic PCM who demanded the Infectious Diseases Clinic of Hospital Universitário Júlio Muller, located in Cuiabá, State of Mato Grosso, in the southwest region of the Brazilian Amazon. The survey was carried out in 2016 and lasted for 10 months.

The target population of the study are patients aged 14 years or older

with paracoccidioidomycosis treated at the University Hospital Júlio Muller from 1998 to 2014, out of a total of 244 patients, only 119 (48,77%) had a record of mucoproteins and 15 (6,15%) of AGP. Only patients with laboratory confirmation of PCM and who were undergoing the first treatment of the disease were included in the analysis. Pregnant women, children and patients who did not attend more than 50% of the outpatient consultations scheduled for treatment follow-up were excluded from the analysis.

PCM was confirmed if the patient had the fungus demonstrated in at least one of the direct research exams. Data on comorbidities such as leprosy, tuberculosis, leishmaniasis and HIV/AIDS were recorded, as well as information on smoking and drinking habits, without considering the intensity of these habits.

The data collected from the medical records were entered into a microcomputer from the EpiData 3.1 statistical package (EpiData Association, Odense, Denmark) and OpenEpi. Demographic, epidemiological and clinical characteristics were tabulated and adequately described in relation to changes in alpha-1-acid glycoprotein proteins and mucoproteins in paracoccidioidomycosis.

The exams of alpha-1-acid glycoprotein and mucoproteins were considered altered, which were not between the reference values, from 41 to 121 mg/dL and from 2 to 4,7 mg/dL, respectively. The factors associated with the treatment outcome were analyzed by the odds ratio and its 95% confidence interval, when the exposure characteristic was binary. For continuous independent variables, the analysis was performed by comparing the means, using Student's t test. For all analyzes, an alpha error of 0,05 was considered.

The research was approved by the Research Ethics Committee of Hospital Universitário Júlio Müller, under number 344.877/2013. Consultation of medical records was duly authorized by the institution's clinical manager.

PCM was confirmed if the patient had the fungus demonstrated in at least one of the direct research exams. Data on comorbidities such as leprosy, tuberculosis, leishmaniasis and HIV/AIDS were recorded, as well as information on smoking and drinking habits, without considering the intensity of these habits.

RESULTS

This retrospective exploratory analysis study included data from the medical records of patients with chronic PCM treated with SMX-TMP at Hospital Universitário Júlio Muller located in Cuiabá, state of Mato Grosso - MT, in the southeastern region of the Brazilian Amazon. Of the total of 244 patients, only 119 (48,77%) had a record of mucoproteins and 15 (6,15%) of AGP.

Patients who underwent inflammatory protein tests were distributed according to demographic, epidemiological, clinical and biochemical characteristics. As for sex, there were 134 patients, 132 (98,51%) men and only 2 (1,49%) women. The group was divided into three age groups: 14-30 years; 31-50 years; > 50 years. The greatest change in inflammatory proteins occurred in the age group 31-50 years old, 36 (26,87%). As for the profession, we observed that in a universe of 106 patients, 5 (4,13%) were farmers, 8 (6,61%) bricklayers, 56 (46,28%) peasant, 2 (1,65%) miners, 50 (41,32%) others, the majority of professions related to soil management.

As for the origin, 117 (87,97 %) were from MT, 14 (10,53%) from Rondônia, and 2 (1,50%) from other states. Analyzing the aggravating factors, 123 (91,79 %) were smokers, 60 (44,78 %) were alcoholics, 32 (23,88 %) had several comorbidities and 3 (2,24 %) had PCM-HIV/AIDS co-infection. Observing the symptoms, the most frequent ones were: weight loss 93 (69,40 %), fever 35 (26,12 %), cough 91 (67,91 %), sputum 59 (44,03 %), lymphadenomegaly 66 (49,25 %), ganglia 34 (25,37 %), odynophagia 56 (41,79 %), hoarseness 34 (25,37 %), asthenia 50 (40 %), dyspnea 59 (43,70 %). Assessing adherence to treatment, 91 (73,39 %) adhered. The proportion of biochemical changes were: AGP 11 (73, 33%), and mucoproteins 54 (45,38 %) (Table 1).

In the analysis between the associated factors and the increase in inflammatory proteins, it is observed that of the 132

Table 1: Demographic, epidemiological and clinical characteristics of adults with chronic PCM in adults treated with SMX-TMP, Cuiabá - MT, 2016.

FEATURE	CATEGORY	N	%
Sex	Male	132	98,51%
	Female	2	1,49%
Age group	1 (14|-30)	2	1,49%
	2 (30|-50)	73	54,48%
	3 (≥50)		
	44,03%		
Profession	Agriculturist	5	4,13%
n=106	Bricklayer	8	6,61%
	Farmer	56	46,28%
	Gold miner	2	1,65%
	Others	50	41,32%
UF	MT	117	87,97%
n=133	RO	14	10,53%
	Outros	2	1,50%
Aggravating factors	Smoking	123	91,79%
	Alcoholism	60	44,78%
	Comorbidities	32	23,88%
	HIV/AIDS	3	2,24%
Symptoms	Slimming	93	69,40%
	Fever	35	26,12%
	Cough	91	67,91%
	Sputum	59	44,03%
	Lymphadenomegaly	66	49,25%
	Ganglia	34	25,37%
	Odynophagia	56	41,79%
	Hoarseness	34	25,37%
	Asthenia	50	40,00%
	Dyspnea	59	43,70%
Adherence related to treatment		91	73,39%
Biochemical changes	Alpha-1-acid glycoprotein	11	73,33%
	Mucoprotein	54	45,38%

SOURCE: Júlio Muller University Hospital, Cuiabá -MT, 2016. Note: the variation in n is due to the absence of information in the medical records

men analyzed, 65 (49,24%) had changes. There was no statistically significant trend when comparing age groups with changes in acute phase proteins (Table 2). Both smoking and alcoholic patients demonstrated a statistically significant increase in acute phase proteins, respectively (p = 0,03568) and (p = 0,01653) (Table 2).

When comparing the presence of symptoms with changes in inflammatory proteins, the following can be seen: weight loss 54 (58,06 %), fever 20 (57,14 %), cough 49 (53,85 %), sputum 39 (66,10 %), lymphadenomegaly 34 (51,52 %), ganglia 17 (50,00 %), odynophagia 29 (51,79 %), hoarseness 19 (55,88 %), asthenia 24 (48,00 %), dyspnoea 30 (50,85 %). An increase in acute phase proteins was observed in patients with sputum, with statistically significant relevance (p = 0,000301) (Table 3).

The analysis between changes in mucoproteins and the clinical outcome in chronic PCM in adults treated with SMX-TMP demonstrated that 36 (48%) of the patients who had changes in acute phase proteins evolved with clinical cure, 13 (68,42%) presented sequelae and 1 patient died, with no statistically significant association (Table 4).

There was a statistically significant decrease in acute phase proteins in patients with chronic PCM in the post-treatment phase when compared to the pre-treatment phase (p = 0,01803) (Table 5).

DISCUSSION

The study of the profile of AGP and mucoproteins in patients with chronic PCM contributes in an important way to the more detailed clinical follow-up

Table 2: Analysis of the association of changes in inflammatory proteins and risk factors in adults with chronic PCM in adults treated with SMX-TMP, Cuiabá - MT, 2016.

FACTOR	CATEGORY	ALTERATION OF MUCOPROTEINS AND ALPHA-1-ACID GLYCOPROTEIN				OR	CI 95%	P	P
		YES	(%)	NO	(%)	TOTAL			
Sex	Male	65	49,24%	67	50,76%	132	-	-	0,5265*
	Female	0	0,00%	2	100,00%	2	-	-	-

Age group	1 (14|-30)	1	50,00%	1	50,00%	2	-	-	-
	2 (30|-50)	36	49,32%	37	50,68%	73	-	-	-
	3 (≥50)	28	47,46%	31	52,54%	59	-	-	-
Adhesion	Yes	44	48,35%	47	51,65%	91	1,043	0,369 - 2,979	0,9293
	No	12	36,36%	21	63,64%	33			
Smoking	Yes	63	51,22%	60	48,78%	123	4,677	1,062 - 32,89**	0,03568
	No	2	18,18%	9	81,82%	11			
Alcoholism	Yes	36	60,00%	24	40,00%	60	2,313	1,097 - 4,957	0,01653
	No	29	39,19%	45	60,81%	74			
HIV	Yes	1	33,33%	2	66,67%	3	0,526	0,008738 - 10,33	>0,999*
	No	64	48,85%	67	51,15%	131			
Leprosy	Yes	0	0,00%	2	100,00%	2	0,000	0,0 - 5,641	0,5265
	No	65	49,24%	67	50,76%	132			
Tuberculosis	Yes	6	50,00%	6	50,00%	12	0,850	0,2139 - 3,373	>0,999*
	No	66	54,10%	56	45,90%	122			
Leishmaniasis	Yes	4	44,44%	5	55,56%	9	0,840	0,159 - 4,107	>0,999*
	No	61	48,80%	64	51,20%	125			
Comorbidity	Yes	21	65,63%	11	34,38%	32	1,148	0,5505 - 2,401	0,6883
	No	44	43,14%	58	56,86%	102			

SOURCE: Júlio Muller University Hospital, Cuiabá -MT, 2016. Linear chi-square * Fisher's exact test ** Exact Mid-P test

Table 3: Analysis of the association of clinical manifestations and risk factors in adults with chronic PCM in adults treated with SMX-TMP, Cuiabá - MT, 2016.

FACTOR	CATEGORY	ALTERATION OF MUCOPROTEINS AND ALPHA-1-ACID GLYCOPROTEIN				OR	CI 95%	P	P
		YES	(%)	NO	(%)	TOTAL			
Slimming	Yes	54	58,06%	39	41,94%	93	0,645	0,2703 - 1,482	0,2638
	No	28	68,29%	13	31,71%	41			
Fever	Yes	20	57,14%	15	42,86%	35	1,660	0,7142 - 3,93	0,1964
	No	44	44,44%	55	55,56%	99			
Cough	Yes	49	53,85%	42	46,15%	91	1,959	0,8817 - 4,461	0,07205
	No	16	37,21%	27	62,79%	43			
Sputum	Yes	39	66,10%	20	33,90%	59	3,637	1,69 - 8,047	0,000301
	No	26	34,67%	49	65,33%	75			
Lymphadenomegaly	Yes	34	51,52%	32	48,48%	66	1,266	0,6089 - 2,643	0,4925
	No	31	45,59%	37	54,41%	68			
Ganglia	Yes	17	50,00%	17	50,00%	34	1,083	0,4614 - 2,542	0,8402
	No	48	48,00%	52	52,00%	100			
Odynophagia	Yes	29	51,79%	27	48,21%	56	1,251	0,5953 - 2,639	0,52
	No	36	46,15%	42	53,85%	78			
Hoarseness	Yes	19	55,88%	15	44,12%	4	1,483	0,633 - 3,526	0,3192
	No	46	46,00%	54	54,00%	100			
Asthenia	Yes	24	48,00%	26	52,00%	50	1,112	0,5103 - 2,424	0,7696

	No	34	45,33%	41	54,67%	75			
Dyspnea	Yes	30	50,85%	29	49,15%	59	1,483	0,633 - 3,526	0,3192
	No	36	47,37%	40	52,63%	76			

SOURCE: Júlio Muller University Hospital, Cuiabá -MT, 2016. Chi Square Linear

Table 4: Analysis of the association of inflammatory protein changes and the clinical outcome in adults with chronic PCM, Cuiabá - MT, 2016.

FACTOR	CATEGORY	ALTERATION OF MUCOPROTEINS AND ALPHA-1-ACID GLYCOPROTEIN				OR	CI 95%	P	P
		YES	(%)	NO	(%)	TOTAL			
Clinical healing	Yes	36	48,00%	39	52,00%	75	1,608	0,6467 - 4,14	0,2632
	No	12	36,36%	21	63,64%	33			
Sequel	Yes	13	68,42%	6	31,58%	19	2,451	0,6384 - 10,33	0,1368
	No	13	46,43%	15	53,57%	28			
Death	Yes	1	33,33%	2	66,67%	3	0,348	0,005546 - 7,186	0,3749
	No	25	59,52%	17	40,48%	42			

SOURCE: Júlio Muller University Hospital, Cuiabá -MT, 2016. Chi Square Linear

Table 5: Analysis of the association of inflammatory protein changes in the pre- and post-treatment phases with SMX-TMP in chronic PCM, Cuiabá - MT, 2016.

FACTOR	CATEGORY	ALTERATION OF MUCOPROTEINS AND ALPHA-1-ACID GLYCOPROTEIN				OR	CI 95%	P	P
		YES	(%)	NO	(%)	TOTAL			
Treatment	Before	65	49%	69	51%	134	2,228	1,09 - 4,716	0,01803
	After	16	30%	38	70%	54			

SOURCE: Júlio Muller University Hospital, Cuiabá -MT, 2016. Chi Square Linear

and the evaluation of an adequate therapeutic response. There are few publications surrounding the topic and few studies addressing the follow-up of inflammatory proteins after the start of treatment. [13] Therefore, this study comes to evaluate the medical records of 134 patients who underwent inflammatory protein tests during the follow-up of the disease.

There was a predominance of patients from endemic regions, who live in rural areas or exercised agricultural activity related to soil management in the first decades of life, possibly having acquired the infection at that time, although the clinical manifestations appeared years later, having characteristics of occupational disease. Thus presenting an important factor of epidemiological correlation, and of relevance from the point of view of public health as it affects individuals in their phase of full productive activity. [14, 2,10]

The present study is in agreement with the aforementioned authors, demonstrating that after the treatment of chronic PCM with SMX-TMP

The involvement of the lymphatic system is one of the most common clinical manifestations of PCM, corresponding to 66 (49,25%) cases and presenting a frequency similar to that of other case series in the literature. Pulmonary impairment was present in up to 90% of patients, and in up to 25% of patients it is the only organ involved, with dyspnea being one of the most observed symptoms in patients with PCM. [15, 10]

The present study is in agreement with the aforementioned authors, demonstrating that after the treatment of chronic PCM with SMX-TMP, there was a substantial drop in acute phase proteins, which suggests that AGP and mucoproteins are useful as laboratory

markers of the effectiveness of therapy and of inflammatory involution.

Considering the magnitude of PCM in Brazil, and the relevance of the laboratory changes found, it is suggested the need to recommend these inflammatory markers during the treatment of chronic PCM as a useful laboratory marker of response to treatment and inflammatory regression, can be considered also as one of the criteria for curing chronic PCM.

CONCLUSION

The statistically significant decrease in acute phase proteins in a patient with chronic PCM in the post-treatment phase, when compared to the pre-treatment phase, may suggest the recommendation to request these inflammatory markers during the clinical follow-up of patients with chronic PCM, especially to indicate good response to treatment and regression of inflammatory activity.

In chronic PCM, alcoholic patients and smokers showed a significant increase in inflammatory proteins

In chronic PCM, alcoholic patients and smokers showed a significant increase in inflammatory proteins, which suggests that these serum elevations may demonstrate a tendency that this lifestyle directly influences the increase in inflammatory proteins.

The statistically significant increase in acute phase proteins in patients who had sputum as a clinical manifestation corroborates the large inflammatory component triggered by this mycosis.

Knowledge about PCM is of great medical-epidemiological interest. However, there are factors that hinder studies, such as the disease is not compulsory to report in most of the country. This study underscores the need for further research to assess the role of inflammatory proteins in neglected diseases. ■

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