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NONSPECIFIC IMMUNOLOGICAL ASPECTS RELATED TO SILICOSIS

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Abstract. The aim of the study is to analyse the profile of the non-specific systemic immune response in a group of subjects with silicosis, that have variable opacities profusion on standard chest X-ray, and to try an estimate of the immune aggression in silicosis, to find a possible association of the humoral immunological parameters with the silicosis evolution stages as a criteria for the disease progression. A group of 68 male patients with occupational exposure to crystalline silica was investigated, compared with a control group, 35 male healthy subjects, non-exposed. Humoral immunity parameters, IgA, IgG, IgM, C3 complement and circulating immune complexes (CIC) were determined using immunochemical methods. It was observed that immunoglobulin levels presented a polyclonal increase. C3 complement levels were within reference values. CIC presented elevated mean values two fold higher for the late stages of silicosis. The obtained data show a hyperreactivity of the humoral mediated immunity in silicosis, but these parameters could not be used as predictive criteria for the disease progression.
Key words: silicosis, humoral immunity

Rezumat. Studiul a urmărit să analizeze profilul răspunsului imun sistemic nespecific la un grup de pacienţi cu silicoză, cu categorii variabile de profuzie a opacităţilor pe radiografiile pulmonare standard şi să încerce o estimare a agresiunii imune în silicoză, să evidenţieze o eventuală asociere între parametrii imunităţii umorale şi stadiile de evoluţie a bolii, ca şi criterii de progresie. A fost investigat un grup de 68 pacienţi de sex masculin cu expunere profesională la siliciu liber cristalin, comparativ cu un grup de 35 subiecţi sănătoşi de sex masculin. Parametrii imunităţii umorale, IgA, IgG, IgM, fracţiunea C3 a complementului şi complexele imune circulante (CIC) au fost investigate prin metode imunochimice. A fost observată o creştere policlonală a nivelurilor serice pentru imunglobuline. Fracţiunea C3 a complementului s-a încadrat în limitele normale. CIC a prezentat valori medii, de două ori mai mari, pentru stadiile avansate de boală. Datele obţinute arată o hiperreactivitate a imunităţii mediate umoral în silicoză, dar aceşti parametrii nu au putut fi folosiţi ca şi criterii de predicţie a progresiei bolii.
Cuvinte cheie: silicoză, imunitate umorală

INTRODUCTION

Silicosis is a chronic crippling lung disease, due to inhaling for a long time of dust containing crystalline silica, either in its natural variety or an artificial allotropic variety. Airborne inhaled silica particulate, induce at the lung tissue level chronic inflammatory response subsequently accompanied by a fibrosis process with collagen deposition. The consequence of these processes is the anatomic disorganization

of the pulmonary tissue, a distinctive feature of silicosis. The pulmonary macrophages have the central role in triggering the complex row of phenomena, the vitality of which is altered by the silica particulate, thus by their destruction generating mediators with aggressive action on lung tissue, determining chronic inflammatory and fibrosis phenomena. The range of patho-phisiological processes in silicosis at the pulmonary level is complex, the participation of immunological phenomena being characterized by a local and systemic dysfunction (1). The presence of humoral and cellular immune processes in silicosis has been sustained by revealing changes in immuno-globulins, T and B lymphocytes, complement and by demonstrating the presence of auto-antibodies (2,3,4,5). A nonspecific immune stimulation action is incriminated, that would increase the production of antibodies against any antigen, determining a hyper-immunization process that in its turn may be a triggering factor for autoimmune manifestations (6).

The study analyzed the profile of the nonspecific systemic immune response in a group of subjects with silicosis that had variable opacities profusion on standard chest X-ray. The aim of the analysis was to estimate the immune aggression in silicosis and to find a possible association of the humoral immunological parameters with the silicosis evolution stages as criteria for the disease progression.

SUBJECTS AND METHODS

The study included a group of 68 male patients (group S) with occupational exposure to mineral dust containing crystaline silica and radiological chest X-ray aspect of pneumoconiosis that were declared and registered as occupational diseases. The group had a mean age of 59.65 ± 11.12 years and a mean occupational exposure duration of 15 ± 2.16 years. When selecting the group, we excluded the patients that were diagnosed with associated diseases (acute or chronic infections, malignancies, collagen or systemic diseases, other diseases or treatments that could interfere with the immune response). Regarding the smoking habit, 42 patients (61.76%) were smokers, 17 patients (25%) were nonsmokers and 9 patients (13.23%) were ex-smokers that abandoned smoking for over 3 years. In the same time we investigated a control group (group C) formed of 35 male subjects, selected from the general population of the same area, occupationally and environmentally unexposed to crystalline silica, clinically healthy, with a mean age of 57.26 ± 11.57 years. In the control group 24 subjects (68.57%) were smokers and 11 subjects (31.43%) nonsmokers.

Both groups underwent a thorough clinical examination and blood samples were drawn for immunoglobulins A, G, M, circulating immune complexes (CIC), and C3 complement fraction assays. Chest X-rays readings from the study group S were coded and interpreted according to the ILO (2000 revision) recommended methodology.

Serum IgA, IgG and IgM levels were determined by radial immunodiffusion (Mancini) assay, with monospecific antiglobulin (reference values: IgA 60-240 IU/ml; IgG 90-220 IU/ml; IgM 70-250 IU/ml). Circulating immune complexes levels were determined by the polyethylene glycol precipitation method (Haskova) (reference values <150 U). For the C3 complement fraction we used the radial immunodiffusion (reference values 60-120 mg/ml). Means were compared using *t* test.

RESULTS AND DISCUSSION

The characteristics of the studied groups are given in table 1. Mean age and smoking habit were comparable in the two groups, the differences being statistically non-significant ($p > 0.10$).

Table 1. The characteristics of the group exposed to silica compared with the control group

Variable		Group S	Group C
Number of subjects investigated		68	35
Age (years)	Average	59.65	57.26
	Standard deviation	11.12	11.57
	Median	63.5	64
Smokers no (%)		42 (61.76)	24 (68.57)
Non-smokers		24 (35.29)	11 (31.43)
Ratio, smokers/non-smokers		1.75	2.18

Regarding the profusion category of the opacities revealed on chest X-ray readings, 45% patients presented 1, 1/2 profusion, 41% had 2/2 up to 3/3 profusion and only 14% presented profusion category A, B and C (fig.1).

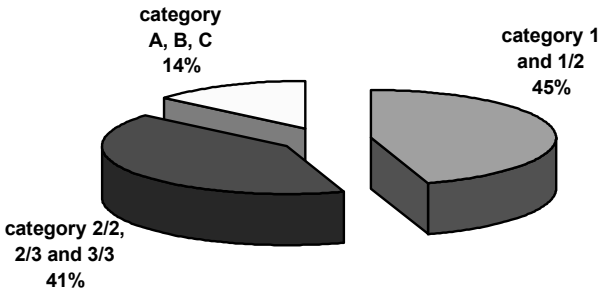

Fig. 1 Radiological findings in studied group

All tested immunoglobulins (A,G,M) were elevated in the exposed group, with higher values for Ig A and IgM. Circulating immune complexes were also elevated in this group and C3 complement fraction presented values within the reference limits, with a mean even lower than the control (table 2).

Table 2: Levels of immunological parameters in studied group S versus control C

	Ig A (IU/ml)		Ig G (IU/ml)		Ig M (IU/ml)		CIC (U)		C3 (mg/ml)	
	S	C	S	C	S	C	S	C	S	C
Mean	283.81	112	254.45	132.26	265.81	108.4	122.88	47.06	88.04	100.26
Median	256.50	64	227	122	254	91	127	91	78,5	91
Std. Dev.	±63.53	±43.16	±72.23	±49.08	±85.28	±37.67	±53.28	±31.34	±24.46	±32.69
Max.val.	498	193	476	207	496	199	237	112	132	176
Min.val.	198	49	152	68	132	68	23	0	56	61

The maximum observed values for immunoglobulins in the exposed group were at least two fold greater as in controls. The differences between the levels of the immunological parameters of the two groups were statistically significant for Ig A ($p<0.001$), Ig G ($p<0.001$), Ig M ($p<0.001$), CIC ($p<0.001$) and non significant for C3 ($p>0.05$) (fig 2).

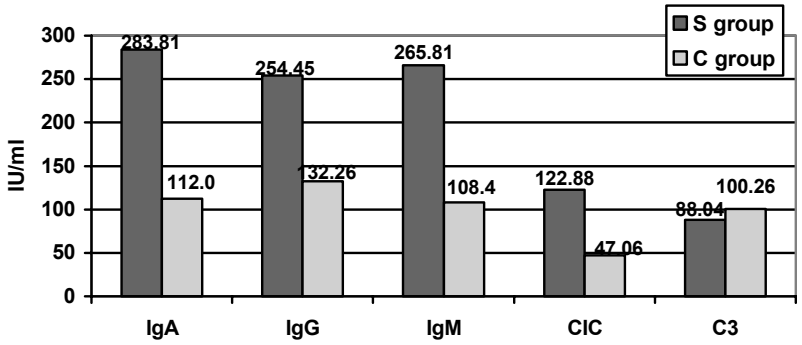

Fig. 2 Mean levels of immunological parameters in S (exposed) group compared to C (control) group

In relation to the radiological reading category of the exposed subjects, which is considered an indirect measure of the progression of silicosis, the levels of immunoglobulin were significantly elevated ($p<0.001$) for all the three categories and for all investigated immunoglobulins (fig 3, 4 and 5).

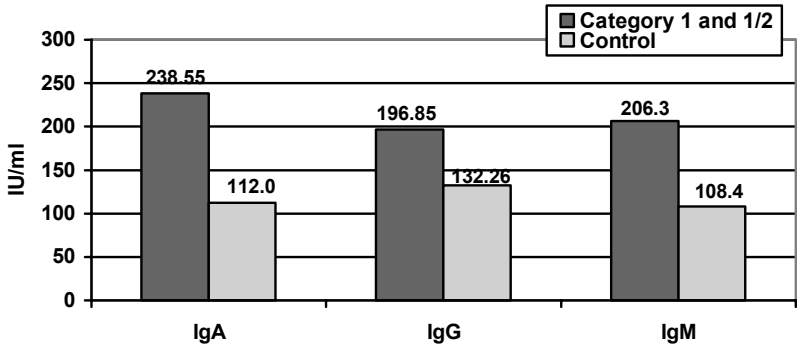

Fig. 3 Immunoglobulin levels in radiological categories 1 and 1/2, compared to controls

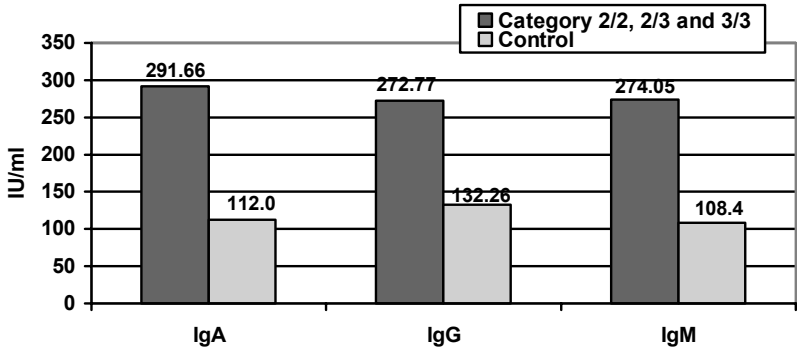

Fig. 4 Immunoglobulin levels in radiological categories 2/2, 2/3 and 3/3 compared to controls

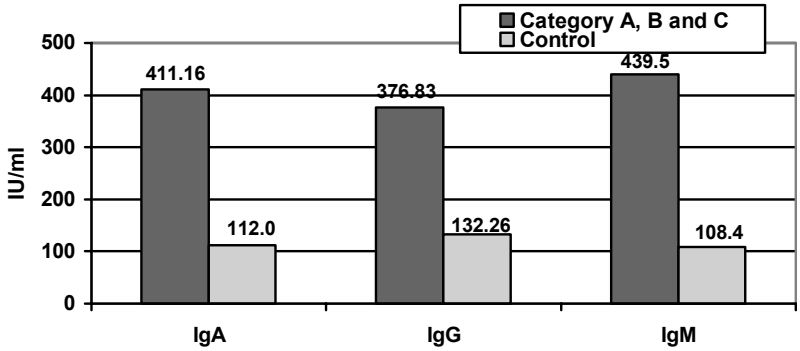

Fig. 5 Immunoglobulin levels in radiological categories A, B and C compared to controls

Circulating immune complexes were elevated in all three radiological categories, but with an obvious over two fold increases from category 1, 1/2 to category A, B, C (fig. 6).

The difference towards the control group level was significant ($p<0.001$) for categories 2/2, 2/3, 3/3 and A, B, C and with a weaker significance for category 1, 1/2.

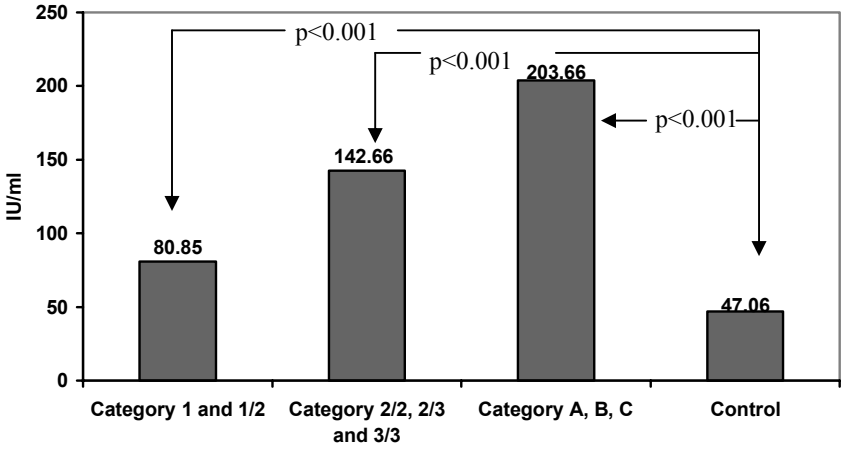

Fig. 6 Circulation immune complexes levels (by radiological category) in exposed compared to controls

C3 complement fraction levels were within the reference limits for all three radiological categories, with no significant difference compared with controls for category 2/2, 2/3, 3/3 and A, B, C (fig. 7). For category 1, 1/2 the mean level was significantly ($p<0.05$) lover than in controls, even if a bias could exist, arising from the number of control group.

Although considerable efforts have been made to reduce silica induced disease, silicosis persists as an actual problem and because it is a crippling disease it generates high medical and social costs.

The analyze of the immunoglobulin profile in the silica exposed group we observed an increase of IgA, IgG and IgM that was significant compared with levels from the non-exposed group.

Immunoglobulins elevation associated with silica exposure has been reported in experimental studies, but the increase was present for only IgG and IgM or IgA and IgG. In our study there was a policlonal immunoglobulin elevation, thus suggesting a state of general immunostimulation associated with silicosis (7,8).

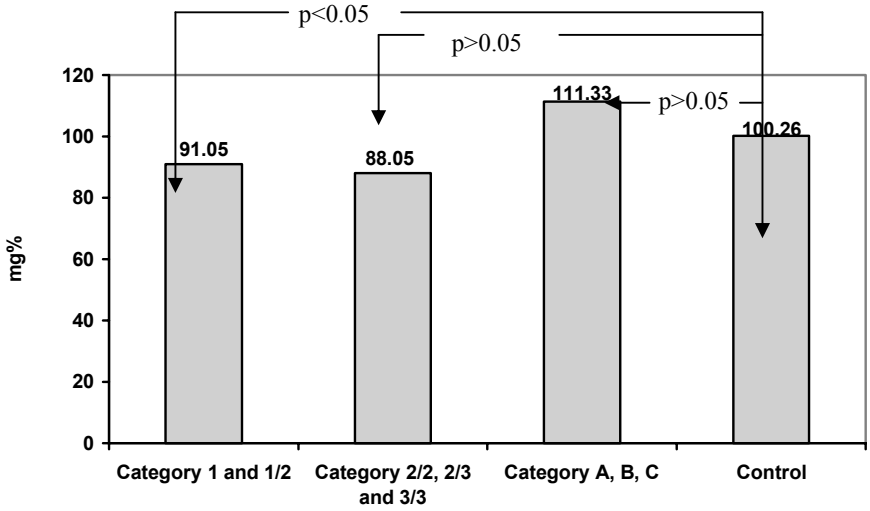

Fig. 7 C3 complement fraction levels (by radiological category) in exposed compared to controls

More human studies sustain the immunoglobulin production mainly at the lung tissue level, whereas some experimental ones indicate the pulmonary lymph node as the primary source (7).

Immunoglobulins were elevated in all stages of disease in our study. Other experimental observations sustain that the immunostimulation states only for the early stages of silicosis. Thus the progression of granulomas depends on the continually activated adaptive immune system (9,10). There are other observations that promote the detrimental effect, significant reduction of IgG, IgA, IgM, of chronic silica exposure on the immune system (11). Though the levels of immunoglobulin were raised in subjects exposed to silica, this parameter may be of limited value for determining progressive silicosis, the participation of the humoral immunity not being proven to be directly responsible for the evolution of disease. C3 complement fraction levels were not raised in our study in silica exposed subjects compared to the control group. Other studies observed decreases of this complement fraction in the early stages of silicosis (8). There are also observations that associate silicosis with a complement gene unbalance (12). Circulating immune complexes levels were significantly increased in all disease stages versus controls, with ascendant mean values from early stage to the late stage.

Other studies reported circulating immune complexes values unrelated to the stage of the disease (8).

CONCLUSIONS

Chronic silica exposure is associated with humoral immunologic changes that suggest a general immunostimulation. The immunological events in patients with silicosis are probably due to the adjuvant effect of silica dust.

Though the levels of immunoglobulin were raised in exposed subjects, this parameter is of limited value, not being associated to the progression of the disease.

Circulating immune complexes could be related to the stage of the disease, probably if autoantibodies are present. Its value as criteria for the disease progression needs further observations.

Complement levels, plead for a humoral immune component in the pathophisiology of silicosis but are not related to the disease progression.

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