SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2012; 29; 3-10

Results of tetanus vaccination in sarcoidosis

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Abstract. *Background and Objective:* Cellular immunity abnormalities are associated with sarcoidosis. Normal cellular immunity is required for adequate humoral immunity; therefore, a decreased humoral immune response is possible in patients with sarcoidosis. We evaluated humoral immunity by vaccinating patients with sarcoidosis against tetanus. *Patients and method:* We screened 60 patients with sarcoidosis (42 females, average age 39 ± 11 years) and 40 healthy subjects as a control (23 females, average age 38 ± 9 years). Of the 51 sarcoidosis patients and 33 controls that did not have sufficient tetanus antibody titers, 48 patients and 31 controls agreed to be vaccinated and were included in the vaccination program. Blood serum samples were collected from the subjects before and after vaccination and evaluated for tetanus toxoid IgG antibodies with an enzyme-linked immunosorbent assay (ELISA). *Results:* As a result of the vaccination, 24 of the sarcoidosis patients (50%) and 7 of the controls (23%) had insufficient antibody responses ($p = 0.019$). No relationship was found in sarcoidosis patients between the rate of having sufficient antibody levels and disease duration, activation state, and radiographic staging of the disease. Conversely, mean lymphocyte numbers were significantly lower in patients with insufficient tetanus antibody levels ($p = 0.013$). *Conclusion:* Tetanus vaccinations in sarcoidosis patients are less effective than in healthy controls, suggesting that patients with sarcoidosis have a hyporesponsive humoral immune system. *(Sarcoidosis Vasc Diffuse Lung Dis 2012; 29: 3-10)*

Key words: sarcoidosis, tetanus vaccination, humoral immunity

Introduction

Sarcoidosis is a systemic granulomatous disease of unknown cause, characterized by histological findings in affected organs, including non-caseating epithelioid cell granulomas and infiltrates of T-lymphocytes and macrophages (1). Two patterns of immune activity are evident in sarcoidosis. At the sites of disease activity, granulomatous inflammation is suggestive of exaggerated cellular immunity. However, in peripheral tissues, anergic skin test reactivity suggests a deficiency cellular immunity (2).

Although cell-mediated immunity is primarily thought to control the pathogenesis of sarcoidosis, the presence of immunoglobulins, immune complexes, and complement in sarcoid granulomas and bronchoalveolar lavage fluid (BAL) suggests that humoral mechanisms may also be involved in the pathogenesis of sarcoidosis (3). However, the action of the humoral immune system in patients with sarcoidosis is controversial. High titres of antibodies against herpes simplex, rubella, measles and para-influenza viruses, and an increased antibody response to mismatched blood have been found in patients with sarcoidosis (4- 7). However, pokeweed mito-

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gen-stimulated peripheral blood B-cells from sarcoidosis patients produces less immunoglobulin than B-cells from normal controls (8). Furthermore a recent study showed that the standard vaccination against the hepatitis B virus (HBV) does, in fact, not produce a high enough antibody titer to protect against hepatitis B (9).

Humoral immunity requires an effective cellular immune response (10, 11). In this respect, patients with sarcoidosis, a disease that involves cellular immune deficiency, can show decreased humoral immune responses.Through a literature review, it was discovered that there are only a few publications (8, 9) evaluating the antibody responce to vaccination and no reported study was found that investigated the antibody response in sarcoidosis patients when treated with the tetanus vaccination. Further research is required on this subject. Thus, the aim of this study was to evaluate humoral immunity by administering the tetanus vaccine in sarcoidosis patients to assess the production of antibodies against tetanus.

Patients and methods

This study included 60 patients with sarcoidosis. The diagnosis and extent of the disease were determined based on typical clinical, radiological, and laboratory criteria, together with the presence of non-caseating granulomas in biopsy specimens. Forty healthy subjects who requested annual physical examinations were selected randomly. All of the cases had been vaccinated either in childhood, while they were in the army, or during pregnancy. The exclusion criteria were as follows: an injury with a high risk for tetanus infection in the past 10 years; an additional immunosuppressive disease, including HIV, primary humoral immune deficiency, diabetes mellitus, chronic renal failure, malignancies, collagen vascular disorders, and solid tumors; immunosuppressive treatments; any vaccination in the past 3 months; and a bacterial infection in the past month. None of the subjects had a history of recurrent bacterial infections, which would possibly imply a primary humoral immune deficiency. Written informed consent was obtained from the sarcoidosis patients and controls. The research was conducted following the Declaration of Helsinki (1989) of the World Medical Association and was approved by the Ethics Committee at our hospital.

Patient age, sex, smoking status, body mass index (BMI), tuberculin skin test results (performed at the beginning of the study), laboratory results (lymphocyte count and percentage, and angiotensin-converting enzyme levels, gamma globulin levels), use of corticosteroids, stage of the disease, follow up time with the diagnosis, and disease activity were evaluated. The general characteristics of the patients and healthy subjects are listed in Table 1. Gamma globulin levels were within the normal range in all patients. Disease activity was suggested by two or more of the following: (1) new or progressive symptoms/signs, such as dyspnea, mononeuritis, skin lesions, sicca symptoms, fundal changes, uveitis, hepatomegaly/hepatosplenomegaly, and lymphadenopathy; (2) elevated serum calcium and angiotensin-converting enzyme (ACE) levels in a 24-h urine calcium excretion test; (3) alterations in serial chest x-rays, including new bilateral hilar lymphadenopathy or new or progressive pulmonary infiltrates; and (4) changing spirometry, such as worsening restrictive/obstructive lung function and decreasing transfer factor (12).

Blood serum samples from each subject collected before and after vaccination were preserved at -40°C. Tetanus antibody levels were evaluated with an enzyme-linked immunosorbent assay (ELISA) using the RIDASCREEN® Tetanus test (R-Biopharm AG, Germany) to test for tetanus toxoid IgG antibodies (ATT IgG). Table 2 was considered while evaluating the tetanus antibody levels (13; product information:http://www.r-biopharm.com/product_site.php?product_range=ClinicalDiagnostics&product_class_one).

Of the 51 sarcoidosis patients and 33 healthy controls with insufficient tetanus antibody titers, 48 patients and 31 controls received the tetanus vaccine between March 2008 and February 2010. (Consider revising vaccination suggestions in table 2). Ten subjects (4 healthy controls, 6 sarcoidosis patients), with no immune protection against tetanous (ATT IgG <0,1 IU/ml) were administered three doses (0, 1, and 6 months) of diphtheria- tetanus vaccines (B.NO. EU40804- B). Sixty-nine subjects (27 healthy controls, 42 sarcoidosis patients), with insufficient immune protection againts tetanus (ATT IgG <0, 6 IU/ml) were administered a single dose. Diphtheria-

Table 1. Characteristics of study subjects

Characteristics	Patients (n=60)	Controls (n=40)	P value
Age, years [a]	39 ± 11	38 ± 9	NS
Males/females	18/42	17/23	NS
BMI [a]	27 ± 4	25 ± 4	NS
Smokers	14 (23%)	15 (37%)	NS
History of tetanus vaccination [b]	7 (12%)	6 (15%)	NS
Duration of disease (months) [c]	8 (2-33)	-	-
Disease stage (I/II/III/IV)	19/27/9/5	-	-
Positive TST	0	-	-
Active disease	43 (71%)	-	-
Lymphocyte count (/mm^3) [a]	1490 ± 706	-	-
Steroid use	36 (60%)	-	-
ATT IgG: (IU/mL) [c]	0.15 (0.12-0.30)	0.16 (0.10- 0.53)	NS
No sufficient immune protection (ATT IgG < 0,6 IU/mL)	51 (85%)	33 (82%)	NS
No immune protection (ATT IgG < 0,1 IU/mL)	8 (13%)	6 (15%)	NS

[a] results were given as Mean ± SD; [b] tetanous prophylaxis applied in the last 10 years; [c] results were given as median (quarter intervals); BMI, body mass index; n, number of cases; NS, statistically nonsignificant; TST, tuberculin skin test; ATT IgG, Antitetanus Toxin IgG

Table 2. Evaluation of Antibody titer of tetanus [a]

ATT IgG (IU/mL)	Immune protection	Recommended vaccination
<0.1	none or not guaranteed	basic immunisation or booster inoculation
0.1-0.59	present but not sufficient	booster inoculation
0. 6-1	sufficient	check-up after 2 years
1.1-5	long term	check-up after 5- 10 years
>5.0	long term	check-up after 10 years

[a](product-information:http://www.r-biopharm.com/product_site.php?product_range= Clinical Diagnostics&product_class_one); ATT IgG, antitetanus Toxin IgG

tetanus vaccines were administred into the left deltoid muscle and antitoxin levels were measured after 1 month.

Statistical Evaluation

This study used SPSS Windows 11.0 to evaluate all variables, which are given as either the mean or median. A Student's *t*-test was used to compare the mean values, while a Mann-Whitney *U*-test was used for the median values. The pre- and post-treatment values of both groups were evaluated with a Wilcoxon signed-rank test. Spearman and Pearson correlation tests were used for the correlation analyses. $P < 0.05$ was accepted as statistically significant.

Results

The antibody titers of 51 sarcoidosis patients and 33 controls indicated insufficient immune protection against tetanus, *i.e.*, ATT IgG <0.6 IU/mL (Table 3).The tetanus antibody titers were 0.15 (0.12-0.30) and 0.16 (0.10-0.53) IU/mL in the sarcoidosis patients and controls, respectively (Table 3). The groups were not significantly different.

After vaccination, 24 (50%) sarcoidosis patients and 7 (23%) healthy controls did not obtain sufficient tetanus antibody titer. The ratio of subjects not reaching sufficient tetanus antibody titer after vaccination in sarcoidosis patients was lower than in healthy controls ($p = 0.019$) (Table 4). However, there was significant increase in tetanus antibody

Table 3. Levels of Antibody titers of tetanus at the begining

ATT IgG (IU/mL)	Patients (n=60)	Controls (n=40)	P value
<0.1	8 (13%)	6 (15%)	NS
0.1 -0.59	43 (72%)	27 (67%)	NS
0.6- 1	5 (8%)	4 (10%)	NS
1.1- 5	4 (7%)	3 (8%)	NS
>5	-	-	-

ATT IgG, Antitetanus Toxin IgG; n, number of cases; NS, statistically nonsignificant

Table 4. Evaluation of antibody titers of tetanus after vaccination

ATT IgG (IU/mL)	Patients (n=60)	Controls (n=40)	P value
<0.1	-	-	-
0.1 - 0.59	24 (50%)	7 (23%)	0.019
0.6- 1	1 (2%)	2 (6%)	NS
1.1-5	12 (25%)	17 (55%)	0.029
>5	11 (23%)	5 (16%)	NS

ATT IgG, antitetanus Toxin IgG; NS, statistically nonsignificant; P < 0.05; statistically significant.

titers in both the sarcoidosis ($p < 0.001$) and control groups after vaccination ($p < 0.001$).

No differences were found between the sarcoidosis patient groups that developed or did not develop a sufficient tetanus antibody titer due to disease duration, extrapulmonary organ involvement, activation state, BMI, steroid use and dose, pulmonary function parameters, and radiographic staging of the disease (Table 5). The responses were not any worse in patients lacking immune responses before the vaccination than in those with insufficient immune protection ($p = 1.0$) (Table 5). Conversely, mean lymphocyte numbers taken before, and more than 1 month after vaccination, were significantly lower in patients with insufficient tetanus antibody levels ($p = 0.013$ and $p = 0.02$, respectively). In addition, no difference was found between the control groups who did or did not develop sufficient tetanus antibody titers for the parameters evaluated.

Discussion

A variety of immunological variances have been described in patients with sarcoidosis, including cutaneous anergy and impaired mitogen induced blast transformation (14), suggesting an impairment of cellular immune function. Changes in the humoral immunity have also been reported. Hypergammaglobulinemia (15), circulating immune complexes (16), and high levels of antibodies against micro-organisms (4-7) seem to indicate an enhanced humoral immune response. However, some controversy exists concerning the humoral immune response in sarcoidosis (8, 9, 17-20). There are published studies (4-7, 14-16) that show patients with sarcoidosis exhibiting both hypo- and hyper-responsiveness of the humoral immune system.

The activation of B lymphocytes and production of antibodies, which can be used to evaluate humoral immunity, is a T cell-dependent process that is regulated by the balance between helper and suppressor mechanisms (21, 22). Patients with sarcoido-

Table 5. Evaluation of parameters between two groups of sarcoidosis patients with or without sufficient antibody titer of tetanus after vaccination

Characteristics	Group 1 (n=24)	Group 2 (n=24)	P value
Age, years [a]	39 ± 8	36 ± 9	NS
Males/females	4/20	9/15	NS
Smokers (n=9)	5 (20%)	4 (16%)	NS
*no immune protection (n=6)	3 (50%)	3 (50%)	NS
*ATT IgG: (IU/mL)[b]	0.13 (0.1-0.17)	0.15 (0.13-0.33)	NS
**ATT IgG: (IU/mL)[b]	0.28 (0.19-0.32)	4.8 (2-6.9)	<0.001
BMI[a]	27 ± 4	27 ± 5	NS
*Lymphocyte count (/mm^3) [a]	1239 ± 482	2038 ± 780	0.013
**Lymphocyte count (/mm^3) [a]	1317 ± 613	1916 ± 544	0.02
Duration of disease (mounths) [b]	36 (10-48)	36 (9-60)	NS
Active disease (n=33)	18 (75%)	15 (62%)	NS
Steroid use (n=25)	15 (62%)	10 (41%)	NS
Dose of metilprednisolone (mg) [b]	20 (12-28)	12 (11-26)	NS
Extrapulmonary organ involvement (n=11)	3 (13%)	8 (33%)	NS
Initial chest radiograph stage II or higher (n=30)	13 (54%)	17 (70%)	NS
Pulmonary functions parametersc			
DLCO, % predicted [a]	75 ± 22	79 ± 18	NS
VC, % predicted [a]	88 ± 13	80 ± 20	NS

Group 1, patients without sufficient antibody response; group 2, Patients with sufficient antibody response; [a]results were given as Mean ± SD; [b] results were given as median (quarter intervals); BMI, body mass index; n, number of cases; NS, statistically nonsignificant;* before vaccination, **after vaccinattion, P < 0.05: statistically significant; ATT IgG, Antitetanus Toxin IgG; DLCO, diffusing lung capacity for carbon monoxide; VC; vital capacity

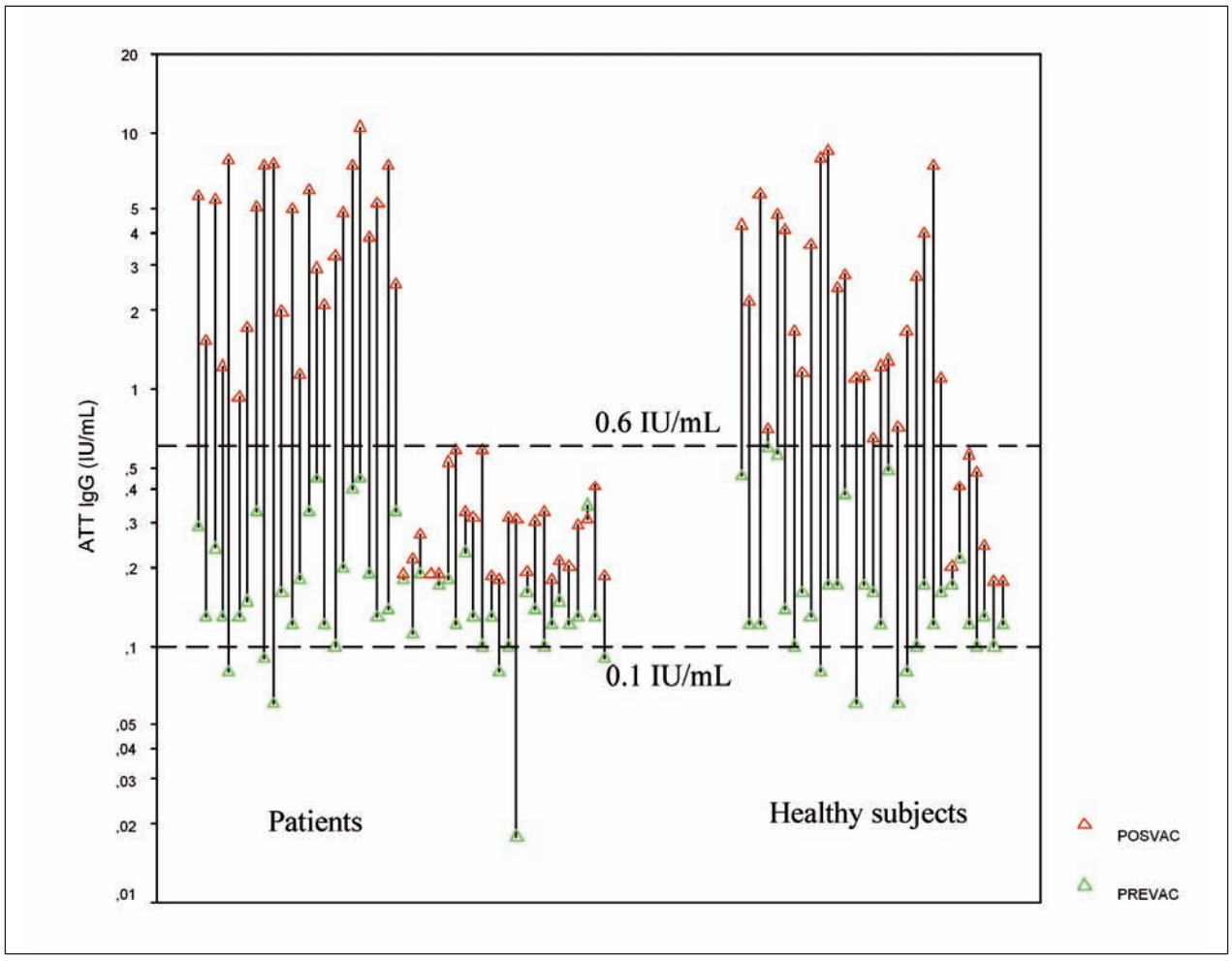

Fig. 1. Tetanus antibody levels of the subjects before and after vaccination. [PREVAC: before vaccination, POSTVAC: after vaccination, lines: thresholds for absence of immune response (<0.1 IU/mL), and insufficient immune protection (<0.6 IU/mL)]

sis have a decrease in systemic cell-mediated immunity, manifested by a reduction in the number of circulating T cells and impaired responses of B lymphocytes (22). Several studies support this hypothesis: Hunninghake et al. (17) demonstrated that antibody production was not elevated in the peripheral blood of patients with sarcoidosis; Katz et al. (8) showed that B lymphocytes from sarcoidosis patients failed to produce specific anti-sheep red blood cell (SRBC) antibodies *in vitro* after culturing with pokeweed mitogen (PWM); and Lawrence et a*l.* (18) demonstrated that patients with sarcoidosis had highly impaired *in vitro* antibody synthesis following polyclonal activation. On the other hand, Kirchner et al. (20) found that sarcoid B lymphocytes were hyporesponsive to the Epstein-Barr virus (EBV) (20). Mert et al. (9), the only reported *in vivo* study evaluating antibody response in sarcoidosis patients, demonstrated that after administration of the hepatitis B vaccine, no antibody response was detected. Consistent with the results of Mert et al., our study showed a statistically lower antibody response after tetanus vaccination in sarcoidosis patients than in healthy controls. Additionally, the reason the Mert et al. study did not identify an antibody response to the hepatitis B vaccine, but some antibody development (50%) was observed in our study may be explained by the high antigenic properties of tetanus toxoid. After analysis of these studies it is possible to conclude that lymphocytes of sarcoidosis patients

cannot produce a large enough antibody response to specific antigens, including tetanus toxoid, HBV, or PWM. These results may indicate that a lower antibody response in sarcoidosis patients is due to hyporesponsiveness in humoral immunity.

The observed decreased antibody production against the tetanus vaccine in sarcoidosis patients compared to healthy subjects could have been caused by defective immunoglobulin production, which may be explained by the lack of specific T helper cell stimulation due to cellular immune system impairment in sarcoidosis (23, 24). Alternatively, it has been suggested that the T cell and mononuclear cell-dependent induction of B cell immunoglobulin production in sarcoidosis could be defective (8). This defect in immunoglobulin secretion has been attributed to the presence of circulating "suppressor" monocytes (8, 20). As with most soluble and particulate antigens, the synthesis of antibodies to tetanus toxoid is likely regulated by T lymphocytes (25). The lack of a proliferative response by B cells in sarcoidosis patients might be caused by the presence of suppressor cells or reduced numbers of circulating T cells that inhibit tetanus-reactive B cell growth.

In a recent study, regulatory CD4+/CD25/FoxP3+ lymphocytes (T_{regs}) were raised in the periphery of the granuloma, BAL; the peripheral blood of patients with active sarcoidosis and this anti-proliferative effect of T_{regs} might explain the reported peripheral anergy (26). Regulatory T cells can inhibit diverse immunopathological phenomena by controlling the proliferation of CD4+ and CD8+ T lymphocytes *in vivo* (27), and it is possible that this mechanism is overly effective in sarcoidosis patients (28). Moreover, T_{regs} contribute to controlling immune responses against self and exogenous antigens (29). Several studies have demonstrated the role of T_{regs} in suppressing the response to self-antigens (30). In addition, the Th2-mediated immune response, which is the main mechanism of antibody production, was suppressed by the effect of T_{regs} on IL-10 production in conventional T cells (31). These data suggest that CD4+ T_{regs} contribute to the resulting ineffectiveness of tetanus vaccination in sarcoidosis patients compared to healthy controls.

Tetanus toxoid is a very safe antigen. Severe generalized reactions are extremely rare. Local minor reactions may occur in a small proportion of vaccines (32). Although the protective role of tetanus antitoxin is well documented, the establishment of protective immunity varies. Experimental human data are limited and direct observations of "protective" antibody levels are rare. In the literature, data indicating the minimum antibody titer required to provide sufficient immunity vary. Schröder et al. (13) studied human sera and assumed that immune protection could be obtained from a titer of 0.1 IU/mL, but was insufficient until 0.6 IU/mL. Conversely, Bingham et al. (33) accepted a titer of ≥ 0.2 IU/mL as positive for ATT IgG when the titer was below 0.1 IU/mL prevaccination, or a ≥ 4↔ increase of ATT IgG after the vaccination if it had been > 0.1 IU/mL prevaccination. By contrast, animal experiments suggest that a titer of 0.01 IU/mL can be classified as protective (13). Given the different protective values for the tetanus antibody, research must determine the cut-off value for tetanus antibody protection.

Advanced age (>60), obesity, history of smoking, drugs, and immune deficiency are some factors decreasing antibody production (34, 35). Byrne et al (6) was unable to identify a relationship between antibody response to viral antigens (EBV, HSV, CMV, Rubella, RSV) and radiological stage or disease activity. Furthermore Mert et al. (9) did not detect a relationship between serum antibody response against hepatitis B virus and patient BMI, lymphocyte count, disease activity, stage, duration, or treatment. In our study, the number of lymphocytes before and 1 month after vaccination was lower in patients with a low antibody response.While low lymphocyte count is a sign of cellular immunedeficiency, the result can be interpreted as acquired cellular immunedeficiency in sarcoidosis. Although a relationship between antibody response and lymphocyte number was detected, we cannot make a definite statement about the antibody response supression hypothesis, which is thought to be caused by helper T cell (CD4+) supression because we did not evaluate T lymphocyte (CD4/CD8) subgroups (Th1/Th2 cytokine profile).

In previous studies, patients were older and treated with higher doses of corticosteroids, both of which are associated with decreased antibody responses (33, 34). On the other hand, during the immunization response to tetanus vaccination in rheumatoid arthritis patients using rituximab, which induces CD20+B cell depletion, target antibody-producing B lymphocytes were unaffected (33).

Smaller, nonrandomized studies of the immunization response in patients with lymphoma and lupus treated with rituximab found decreased responses to the tetanus toxoid vaccine (36, 37). In our study, steroid use and age did not affect the antibody response to tetanus vaccination. This could be due to the small number of older patients in our population (4% of the patients were > 60 years old), the wide range, and unequal use of steroid doses, as well as differences in the populations and patients included in our and other studies.

In conclusion, the lower effectiveness of tetanus vaccination in sarcoidosis patients compared to healthy individuals could have been caused by hyporesponsiveness of the humoral immune system due to an acquired cellular immunodeficiency. We believe that sarcoidosis patients are at risk for tetanus disease and antibody levels must be measured to assess immune status. Given the less effective antibody response after vaccination, sarcoidosis patients must be evaluated more thoroughly for tetanus after injuries. Additionally, studies involving high doses or an increased number of tetanus vaccinations in sarcoidosis patients could be beneficial in evaluating the tetanus-sarcoidosis immunological relationship.

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