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The autoimmune/inflammatory syndrome induced by adjuvants and sarcoidosis

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Аутоиммунный/провоспалительный синдром, индуцированный адъювантами, и саркоидоз

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Summary

The autoimmune/inflammatory syndrome induced by adjuvants (ASIA) is an entity that includes various autoimmune conditions observed after an exposure to an adjuvant. The possible reason for the development of sarcoidosis (SC) is the influence of various exogenous and endogenous trigger factors. The aim of this study was to evaluate the relationship between ASIA and SC. **Materials and methods.** A prospective comparative study was conducted. The first group consisted of patients with histologically verified lung SC (n=58), while the control group consisted of healthy donors (n=22). All the patients underwent a standard examination and were interviewed according to the standardized "ASIA Research Questionnaire". Statistical analysis was carried out with Statistica 10.0, $p<0.05$ was considered statistically significant. **Results.** Patients with ASIA-triggers, n=52 (89.6%) significantly more often demonstrated autoimmune symptoms in comparison with patients without ASIA triggers, n=6 (10.3%). 79.3% of the patients with SC met two major ASIA diagnostic criteria, which were significantly more frequent (p=0.000) than in the control group (22.7%) and had an average, statistically significant correlation between the number of ASIA-triggers and the number of symptoms typical for ASIA syndrome (r_s=0.46). **Conclusion.** In patients with SC ASIA — triggers and clinical signs of autoimmune pathology were observed, that met ASIA diagnostic criteria.

Keywords: sarcoidosis, autoimmune syndrome induced by adjuvants, adjuvants, autoimmunity, interstitial lung diseases

Резюме

Аутоиммунный / провоспалительный синдром, индуцированный адъювантами (АСИА), включает в себя различные аутоиммунные состояния, возникшие под воздействием адъюванта у генетически предрасположенных лиц. Согласно одной из теорий причиной развития саркоидоза (СЗ) является влияние различных экзогенных и эндогенных триггерных факторов. Изучение связи между синдромом АСИА и СЗ послужило целью настоящего исследования. **Материалы и методы.** Проведено проспективное сравнительное исследование. В первую группу входили пациенты

с гистологически верифицированным саркоидозом легких и внутригрудных лимфатических узлов (n=58), а группу контроля составили здоровые лица (n=22). Все участники исследования прошли стандартный комплекс обследования и были анкетированы по стандартному опроснику «ASIA Research Questionnaire». Статистическая обработка проводилась с применением Statistica 10.0. Значения p<0,05 считались статистически значимыми. **Результаты.** Пациенты с наличием АСИА-триггеров, n=52 (89,6%) достоверно чаще демонстрировали наличие аутоиммунных симптомов в сравнении с пациентами без АСИА-триггеров, n=6 (10,3%). При этом соответствие двум большим диагностическим критериям АСИА было получено у 79,3% больных СЗ, что достоверно чаще (p=0,000), чем в контрольной группе (22,7%). Также была получена средняя статистически достоверная корреляция между количеством АСИА-триггеров и количеством симптомов, типичных для синдрома АСИА (r_s=0,46). **Выводы.** Заболевание у пациентов с СЗ при наличии АСИА-триггеров протекает с клиническими признаками аутоиммунной патологии и укладывается в диагностические критерии синдрома АСИА.

Ключевые слова: саркоидоз, аутоиммунный синдром, индуцированный адъювантами, адъюванты, аутоиммунитет, интерстициальные заболевания легких

Introduction

In 2011 Shoenfeld and co-authors identified autoimmune / proinflammatory syndrome induced by adjuvants (ASIA), which combined immunopathological conditions in genetically predisposed individuals after the effect of the adjuvants [1]. An adjuvant is defined as a substance that can induce, maintain, and enhance an antigen-specific immune response [2]. Among the trigger factors that cause the development of ASIA a silicone, vaccines, dermal fillers (compounds of hyaluronic acid, acrylamide and methacrylate), dental amalgam and a number of foreign materials, such as metal implants, prostheses, and other has been described [3–6].

Nowadays the following conditions are associated with the occurrence of the ASIA syndrome: postvaccinal phenomenon, macrophage myofascial syndrome, Persian Gulf syndrome, siliconosis and sick building syndrome [7]. According to Scanzi F. et al [8] patients with undifferentiated connective tissue diseases exposed to adjuvants could meet the criteria of ASIA. The main clinical manifestations of ASIA include myalgia, arthralgia, chronic fatigue syndrome with sleep disorders. The diagnostic criteria suggested by Shoenfeld et al are presented in Table 1. According to the recommendations for diagnosis we need the presence of 2 major or 1 major and 2 minor criteria [1].

Sarcoidosis (SC) is a systemic inflammatory disease with an unknown etiology, it is characterized by the formation of epithelioid cell non-caseifying granulomas in various organs and tissues. Numerous studies indicate the multifactorial nature of the disease, the influence of various environmental factors, including the occupational hazards plays a leading role [9, 10].

In 2004, the Case Control Etiologic Study of Sarcoidosis (ACCESS) demonstrated the relationship between the effects of certain external factors and the HLA genotype on the development of SC, as well as their influence on the development of a certain clinical form of the disease. It was found that a variant of the gene HLA DRB1*1101 is

Table 1

Diagnostic criteria for the ASIA syndrome [1]

Major criteria	Exposure to an external stimuli (infection, vaccine, silicone, other adjuvant) prior to clinical manifestations (from months to years) Appearance of at least one of the following "typical" clinical manifestations: – myalgia, myositis, muscle weakness – arthralgia and / or arthritis – chronic fatigue, not-restful sleep, sleep disturbances – neurological manifestations (especially those associated with demyelization) – cognitive alterations, memory loss – fever, dry mouth Improvement after removal of the initiation agent Typical biopsy of the involved organs
Minor criteria	Appearance of autoantibodies or detection of antibodies against the suspected adjuvant Other clinical manifestations (i.e, irritable bowel syndrome or other) Specific HLA (i.e, HLA DRB1, HLA DQB1) Initiation of autoimmune disease (i.e., multiple sclerosis, systemic sclerosis and other)

associated with a professional contact with insecticides and extrapulmonary sarcoidosis, and in patients with HLA DRB1*1101 with influence of mold and musty odor pulmonary sarcoidosis often developed [11, 12]. One of the hypotheses of the SC development is its relationship with autoimmunity. A genetic predisposition to SC, the systemic nature of the disease with a possible generalization of the process, the overlap of clinical manifestations with symptoms of autoimmune process (arthralgia, erythema nodosum, fatigue and other) may allude to this theory. Antivimentin antibodies which high titers were found in patients with SC is currently considered as one of the potential autoimmune target in SC [13, 14].

The search for literature data showed no studies examining a clear relationship between the ASIA syndrome and SC. The reason for this study was to determine the spectrum of ASIA — triggers and their effects on the course and the development of SC.

Materials

A prospective case-control study was performed from January to December 2017 in St. Petersburg Research Institute of Phthisiopulmonology and Municipal Hospital No 2. The study included 58 patients with histologically verified sarcoidosis of the lungs and intrathoracic lymph nodes (group I, main group): men, n=33 (57.2%), women, n=25 (42.8%), the average age at the time of inclusion in the study was 37.2 (±1.5) years and at the time of onset of the disease 36.1 (±1.5) years. The control group (group II) consisted of healthy individuals (n=22). The groups were matched for sex and age. The exclusion criteria for the main group were: the period of more than 2 years from the initial detection of changes at the chest X-ray, the use of immunosuppressive therapy at the time of inclusion (except for inhaled glucocorticosteroids), treatment with anti-tuberculosis drugs, a course of plasmapheresis for less than 2 months from the date of inclusion in the study, the presence of HIV infection and syphilis, decompensated diabetes, other granulomatous lung diseases. The control group was selected according to the following inclusion criteria: healthy subjects without malignant neoplasms or chronic infectious diseases, systemic or organ-specific autoimmune disease in both the subject and first-line relatives, negative results of immunological examination for tuberculosis and without contact with tuberculosis patients.

The examination results of I and II group were compared with the determination of compliance with the ASIA syndrome diagnostic criteria, as well as comparison of patients with SC with and without ASIA triggers.

All the participants signed an informed consent. The study was approved by the Local Ethics Committee of the Saint-Petersburg State University (Protocol No. 01-126

Table 2

Features evaluated in the "ASIA Research Questionnaire"

1. Medical history	Autoimmune systemic or organ-specific diseases in the patient and his first-line relatives. Smoking. Allergy to metals, medications, vaccines and others (according to the patient's history, without special allergological testing). Chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome, history of cancer. Number of pregnancies, duration of breastfeeding. Reception of biological additives, other drugs
2. Foreign materials	Piercing (including earrings), tattoos, skin fillers (collagen, hyaluronic acid, silicone, etc), silicone implants of any localization, dental amalgam, intrauterine device, contact lenses, heart valves, pacemakers, artificial joints, metal structures, metal implants, dental crowns, veneers — with an assessment of local complications after installation (suppuration, inflammation, necrotic changes, local redness, pruritus), as well as reducing the manifestations of the disease after the removal of foreign materials
3. Vaccinations received over the past ten years before the onset of the disease	Vaccination (against hepatitis B and A, seasonal influenza, H1N1 influenza, human papillomavirus, DPT vaccine, pneumococcal infection, tetanus vaccine and others); complications from vaccination (within 7 days after vaccination)
4. Clinical manifestations	Fever, general weakness, chronic fatigue, weight loss or weight gain, myalgia, myositis, arthralgia, arthritis, pruritus, chronic rash, peripheral lymphadenopathy, chronic pain, sleep disorders, cognitive impairment, memory disturbances, postural hypotension and tachycardia, recurrent non-infectious cystitis
5. Biopsy of the involved organ	
6. Accepted therapy	Analgesics, antihypertensive drugs, sleeping medications, oral contraceptives, aspirin, nonsteroidal anti-inflammatory drugs, hydroxychloroquine, azathioprine, methotrexate, intravenous immunoglobulins, rituximab, tumor necrosis factor inhibitors, corticosteroids and etc.

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Authors declare no conflicts of interest.

Methods of the study

All patients underwent a standard examination, including clinical assessment of the disease, multispiral chest computed tomography (MSCT), ultrasound examination of the abdominal cavity, laboratory blood tests, including the level of angiotensin-converting enzyme activity (ACE); immunological, molecular genetic and bacteriological examination for tuberculosis, histological verification of changes in the lungs and / or lymph nodes. The diagnosis of sarcoidosis was established on the basis of standard criteria of American Thoracic Society (ATS), European Respiratory Society (ERS) and World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG): typical X-ray changes (mediastinal lymphadenopathy, dissemination in lungs); histological verification of changes in the lung or intra-thoracic lymph nodes (detection of epithelioid cell granulomas without caseous necrosis and acid-resistant mycobacteria); exclusion of other causes of granulomatous changes, primarily tuberculosis [15].

To assess the impact of trigger factors, as well as to determine the compliance of existing clinical manifestations with the ASIA syndrome diagnostic criteria, all participants of the study were surveyed according to the standardized "ASIA Research Questionnaire" (Table 2). In addition, the history of professional contact with trigger factors (long-term contact with printer toner, dust, metals, chemicals, cars etc.), as well as the impact of stressful situations preceding the appearance of clinical and radiological manifestations of the disease was studied.

Statistical analysis was performed using the program Statistica 10.0. Socio-demographic indicators and clinical characteristics are presented using descriptive statistics (n, % or Mean ±SD). P<0.05 was statistically significant. To identify the relationship between the features, the rank correlation coefficient was calculated.

Results

Table 3 presents a comparison of the most statistically significant trigger factors in the groups.

According to the presented data, the most significant factors were: the impact of stress in patients with SC within 2 years before the development of the disease (84.4% vs. 9.1%, p=0.000) and professional contact with trigger factors (65.5% vs. 27.2%, p=0.003), especially contact with dyes in the printer toner (25.8% vs. 0, p=0.008).

Accordance with the ASIA — diagnostic criteria in the study groups is presented in Table 4.

The required two major diagnostic criteria of ASIA was significantly more frequently obtained in patients with SC compared with the control group (79.3% vs. 22.7%, p=0.000) in assessing the combination of ASIA trigger and the development of typical clinical manifestations.

Table 5 presents the results of clinical manifestations comparison in SC patients exposed to ASIA triggers (n=52) with SC patients without ASIA triggers.

When comparing the groups of patients with SC with and without ASIA triggers, we found that patients with ASIA triggers significantly more frequently had key symptoms of ASIA (88.5% vs. 50.0%, p=0.042). A significant difference was obtained for the following diagnostic symptoms: general weakness (71.1% vs. 16.7%, p=0.011), sleep disturbances (67.3% vs. 16.7%, p=0.025) and memory disturbances (48.1% vs. 0, p=0.032).

Correlation analysis between the number of ASIA triggers and the number of symptoms typical for ASIA syndrome demonstrates that in patients with SC had an average, statistically significant correlation (r_s=0.46).

Table 3

Trigger factors in the study groups

	I group Pulmonary sarcoidosis, n (%) n=58	II group Healthy subjects, n (%) n=22	χ^2	P-level
Medical factors				
Stressful situations	49 (84.4)	2 (9.1)	39.230	0.000
More than 3 pregnancies	11 (18.9)	0	4.838	0.029
Trigger factors				
Professional factors	38 (65.5)	6 (27.2)	9.426	0.003
Long-term contact with the printer toner	15 (25.8)	0	7.003	0.008

Table 4

ASIA-criteria in the comparison groups

Ammount of "major" criteria	Pulmonary sarcoidosis, n (%) n=58	Control group, n (%) n=22	χ^2	P-level
One criterion: presence of ASIA — trigger* and/or professional factor	52 (89.6)	21 (95.4)	0.672	0.67
Two criteria: presence of ASIA trigger* and / or professional factor + 1 and more clinical manifestation of ASIA**	46 (79.3)	5 (22.7)	22.098	0.00

* Vaccines, foreign materials; ** general weakness, chronic fatigue, sleep disorders, memory impairment, postural hypotension, myalgia, myositis, muscle weakness, arthralgia and/or arthritis.

Table 5

Influence of ASIA — triggers on clinical manifestations of sarcoidosis

Patients with lung sarcoidosis (I group)	ASIA triggers (+), (n/%) n=52	ASIA triggers (–), (n/%) n=6	χ^2	P-level
Symptoms typical of ASIA	46 (88.5)	3/6	6.070	0.042
General weakness, n (%)	37 (71.1)	1/6	8.074	0.011
Sleep disorders, n (%)	35 (67.3)	1/6	5.860	0.025
Memory impairment, n (%)	25 (48.1)	0	5.070	0.032

In the control group the correlation between the indicators was low, statistically insignificant (r_s=0.30).

Discussion

We did not reveal a statistically significant difference in the presence of ASIA triggers in patients with SC and the control group (89.6% vs. 95.4%, p=0.67). But patients with SC more frequently matched the diagnostic criteria for ASIA syndrome (79.3% vs. 22.7%, p=0.000). We also determined that the presence of ASIA triggers in patients with SC was significantly associated with the ASIA syndrome criteria and the development of autoimmune features, which is confirmed by the results of the correlation analysis.

In assessing the impact of various trigger factors on the development of pulmonary SC, we found significant difference in the frequency of stress impact for 2 years before the development of the disease (84.4% vs. 9.1%, p=0.000). The influence of psychological stress has been demonstrated as a factor affecting the development of SC as well as autoimmune pathology, including by reducing testosterone and estrogen levels, which leads to a decrease in the number of T-regulatory cells responsible for controlling auto-reactivity of T and B cells [16, 17]. In an additional survey, we revealed a relationship of professional contact with the trigger factors in patients with SC (65.5% vs. 27.2%, p=0.003), especially a long-term contact with dyes in the printer toner, copier or when working in print industries (25.8% vs. 0, p=0.008). Taking into account the probable multifactorial nature of SC and the role of the different triggers of the disease, the impact of such multi-component substances as paint in the toner of printers or copiers, especially during a prolonged direct use, it could be considered as one of the adjuvants for the development of SC. This assumption may be supported by the characteristics of the toners, as shown in the work of Ewers U. and Nowak [18–20].

Thus, according to our data, the similarity of the course of SC and ASIA is that the impact of ASIA triggers may induce the autoimmune features of the disease. One of the criteria of ASIA syndrome is improvement or reduction of symptoms after the elimination of the trigger factor. The sarcoid reaction meets this definition, it is characterized by limited process, due to a causal phenomenon (as a paraneoplastic process, the impact of antitumor therapy, various environmental factors, such as metals, implants) and regress after the removal of this factor. It is necessary to solve the question of the relationship of chronic pulmonary sarcoidosis and the sarcoid reaction to the not always known trigger, which cannot be eliminated (for example, due to the inhalation pathway of the adjuvant).

Conclusion

Our results may indicate that SC and ASIA are related to each other. SC in patients with the presence of ASIA triggers occurs with clinical signs and symptoms of autoimmune pathology and meets the diagnostic criteria of ASIA.

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