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Clinical and morphological phenotypes in intrathoracic sarcoidosis

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ABSTRACT

Aim. To study clinical and morphological phenotypes in different variants of the course of intrathoracic sarcoidosis and isolate new phenotypes.

Materials and methods. The study included 121 patients with intrathoracic sarcoidosis aged 21–66 years (50.4% were men, 49.6% were women, the average age at the time of the disease onset was 38 years) over the period 2007–2019. During the examination, patients' complaints were studied thoroughly, and the diagnosis was histologically verified in all cases. During an extended histological examination, the quantitative and qualitative composition of biopsy specimens was investigated. The number of granulomas in the field of vision and the content of giant cells, macrophages, lymphocytes, neutrophils, and eosinophils in them were studied. Qualitative parameters were assessed for the presence of hyalinosis, Schaumann bodies, necrosis, stamping, calcification, fibrosis, and vasculitis. All patients were retrospectively divided into two clinical groups depending on the outcomes of the disease: group 1 included patients with a favorable course of sarcoidosis, proceeding without relapses and signs of progression; group 2 encompassed patients with an unfavorable course of the disease with relapses and progression, requiring long-term administration of systemic glucocorticoids.

Results. The analysis showed that among all general clinical manifestations, only the presence of dyspnea, skin manifestations, and weight loss occurred significantly more often in the patients with an unfavorable course of intrathoracic sarcoidosis ($p = 0.04$; 0.02; and 0.01, respectively). Among morphological parameters, a large number of macrophages was significantly more frequent in the biopsy specimens in this group of patients ($p < 0.01$).

Key words: sarcoidosis, morphology, phenotypes of intrathoracic sarcoidosis.

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Клинико-морфологические фенотипы при внутригрудном саркоидозе

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РЕЗЮМЕ

Цель – изучить клинические и морфологические параллели при разных вариантах течения саркоидоза органов дыхания с выделением новых фенотипов.

Материалы и методы. В исследование включен 121 пациент с саркоидозом органов дыхания в возрасте 21–66 лет (50,4% мужчин и 49,6% женщин, средний возраст обследованных на момент дебюта заболевания составил 38 лет) в период наблюдения 2007–2019 гг. В ходе обследования детально изучались жалобы пациентов, диагноз подтвержден гистологически во всех случаях. При расширенном гистологическом исследовании изучался количественный и качественный состав биоптата. Исследовалось количество гранулем в полях зрения, а также содержание в них таких показателей, как гигантские клетки, макрофаги, лимфоциты, нейтрофилы и эозинофилы. Оценивались качественные параметры на наличие гиалиноза, телец Шауманна, некроза, штампованности, кальциноза, фиброза и васкулита. Все пациенты ретроспективно были разделены на две клинические группы в зависимости от исходов заболевания. В первую группу вошли пациенты с благоприятным течением саркоидоза, протекающим без рецидивов и признаков прогрессирования; во вторую – с неблагоприятным течением заболевания, с рецидивами и прогрессированием, потребовавшие курсового и длительного назначения системных глюкокортикостероидов.

Результаты. Проведенный анализ показал, что среди всех общих клинических проявлений только наличие одышки, кожные проявления и потеря веса встречались достоверно чаще у пациентов с неблагоприятным течением внутригрудного саркоидоза ($p = 0,04$; 0,02 и 0,01 соответственно). Из морфологических параметров у этой группы пациентов в биоптатах значимо чаще встречалась бóльшая численность макрофагов $p < 0,01$).

Заключение. Предикторами неблагоприятного течения саркоидоза органов дыхания являются повышенная численность макрофагов в биоптате и более значимая потеря веса пациента.

Ключевые слова: саркоидоз, морфология, фенотипы внутригрудного саркоидоза.

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Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

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INTRODUCTION

Sarcoidosis is a granulomatous disease with characteristic granulomas in the lungs, lymph nodes, and other organs. It is known that the gold standard for making the diagnosis of sarcoidosis is biopsy taken from the affected lesion [1–3]. Granulomas are mainly composed of epithelioid cells, lymphocytes, and giant cells. Alveolar macrophages, neutrophils, and eosinophils are also involved in the formation of granulomas. In the cytoplasm of giant cells, cholesterol-containing crystalloid inclusions, asteroid bodies, and calcified Schaumann bodies are often found [3, 4].

Immunopathological processes occurring in the patient's body determine not only the clinical course, but also the prognosis of the disease. When assessing the course of sarcoidosis, an integrated approach is required, taking into account the clinical and morphological manifestations of the disease. Sarcoidosis is an extremely heterogeneous disease with an unpredictable clinical course [5].

Intensive studies on sarcoidosis in recent years have led to doubts about the correctness of criteria for assessing the course of the disease. Opinions have been increasingly expressed that, when assessing the course of sarcoidosis, it is necessary to abandon the generally accepted radiographic staging system and take into account a set of parameters [6]. In this regard, in recent years, much attention has been paid to isolating phenotypes in sarcoidosis. In the literature, there are few works on assessment of morphological parameters for predicting the course of sarcoidosis [6, 7]. Basically, the search for prognostic markers of sarcoidosis is based on laboratory and instrumental data. A number of scientists have investigated bronchoalveolar lavage and its cellular composition to determine the activity of intrathoracic sarcoidosis [8–10]. Other researchers have studied various parameters of blood serum [11–13].

Current research is focused on the study of histocompatibility complex genes. Since the accurate diagnosis of sarcoidosis is based on the results of a histological examination, it is necessary to look for reliable morphological markers that would reflect a relationship with the clinical manifestations of the disease, and, possibly, isolation of any new phenotypes. It is quite likely that for each clinical variant of the disease, there is a combination of morphological parameters which will make it possible to distinguish groups of patients with an unfavorable and recurrent course of intrathoracic sarcoidosis. In the future, it will allow to predict the course and outcome of the disease, as well as to prescribe therapy at an earlier stage with ineffective follow-up, since clinically silent pulmonary sarcoidosis can have fatal consequences. Therefore, a more detailed study of the morphometric parameters of granulomas is necessary, which will make it possible to predict the course of sarcoidosis and distinguish various clinical and morphological phenotypes of the disease.

The aim of the study was to investigate clinical and morphological characteristics in different variants of the course of intrathoracic sarcoidosis and isolate new phenotypes of the disease.

MATERIALS AND METHODS

The study included 121 patients with intrathoracic sarcoidosis aged 21–66 years (50.4% were men, 49.6% were women, the average age of the patients at the time of the disease onset was 38 years). The patients were examined at the Department of Pulmonology and Consultative and Diagnostic Clinic of Tomsk Regional Clinical Hospital in 2007–2019. A written informed consent was obtained from all patients who took part in the study. Visits to the sarcoidologist took place according to the Federal Clinical Guidelines [14]. All patients underwent a full range of examinations, including analysis of medical history and clinical and epidemiological data, as well as instrumental and laboratory methods.

During the examination, patients' complaints were studied thoroughly. In 100% of cases, we performed videothoracoscopy with targeted biopsy from the affected lesion in the lungs and from the intrathoracic lymph nodes with subsequent pathomorphological study of the specimens. The diagnosis was histologically verified in all patients. During the histological examination, the quantitative and qualitative composition of the biopsy specimens was studied. Using visual microscopy (Leica DM 3000 microscope, Leica Microsystems, Germany), the total number of cells was counted in 10 fields of view at 100-fold magnification according to the generally accepted technique. The number of granulomas in the fields of vision and the content of giant cells, macrophages, lymphocytes, neutrophils, and eosinophils in them (% from 100 in the field of vision) were studied. Such morphological signs as hyalinosis, the presence of Schaumann bodies, necrosis, stamping, calcification, fibrosis, and vasculitis were assessed qualitatively.

Calcification and vasculitis in biopsy specimens were extremely rare; they were observed only in 2 cases. No fibrosis was found in the studied material. In this regard, these parameters were not taken into account in further calculations. All patients were retrospectively divided into two clinical groups depending on the outcomes of the disease during the observation period 2007–2019 (6.4 to 11.6 years). The first group included patients with a favorable course of sarcoidosis, proceeding without relapses and signs of progression (clinical, radiologic, and functional), without the use of systemic glucocorticoids (SGC) or their accidental prescription in small doses and a short course (85 people in total, 35 men and 50 women). The second group consisted of patients with an unfavorable course of the disease, with relapses and progression,

who required a course of long-term CGS administration (a total of 36 people, 26 men and 10 women). The patient groups were matched by sex and age. The criteria for exclusion from the study were severe comorbidities in patients, such as chronic heart failure, complicated or decompensated diabetes mellitus, cancer, tuberculosis, kidney disease with kidney failure, and other lung diseases with respiratory failure determined by pulseoximetry.

Statistical processing of the data was carried out using Statistica 10.0 software (StatSoft, USA). To compare two independent samples, the nonparametric Mann – Whitney test was used, the mean values were calculated; a nonparametric cross tabulation analysis was performed with the calculation of the Pearson's $\chi 2$ contingency coefficient. If the expected phenomenon had a value from 5 to 9, the Pearson's $\chi 2$ test was performed with Yates' correction. If the expected phenomenon was less than 5, the Fisher's exact test was used for the analysis. Statistical calculations included Spearman's rank-order correlation, association analysis, and intergroup difference analysis. The strength of correlations was characterized by a weak positive relationship at values of r from 0.18 to 0.26; by a moderate positive relationship at r from 0.28 to 0.44; by a weak negative relationship at r from –0.18 to –0.26; and a moderate negative relationship at r from –0.28 to –0.44. The analysis of the confidence intervals (CI) of the compared parameters was carried out with the determination of the values of the upper and lower quantiles, and the risk ratio (RR) was calculated. The differences were considered statistically significant at $p < 0.05$.

RESULTS

The analysis of clinical symptoms in the examined patients revealed a variety of complaints: asthenic syndrome of varying severity (41.3% of cases), sweating (29.8% of cases), dyspnea (24% of cases), cough (48% of cases), chest pain (18.2% of cases), heart arrhythmia (20% of cases), pain in the joints (18.2% of cases), any skin manifestations, except for lupus pernio (21.5% of cases), altered peripheral lymph nodes (18.2% of cases), weight loss (13%), fever (29.8%). The acute course of sarcoidosis in the form of Löfgren's syndrome occurred in only 8.3% of cases (of which 6.6% of patients belonged to the group with a favorable course of the disease and 1.7% of patients were from the group with an unfavorable course of sarcoidosis without a significant difference), in most cases the disease had a chronic course.

The inter-group analysis showed that among all the general clinical manifestations, only the presence of dyspnea, skin manifestations, and weight loss occurred statistically significantly more often in patients with an unfavorable course of sarcoidosis ($p = 0.04$, 0.02, and 0.01, respectively). It should also be noted that in patients with an unfavorable course of sarcoidosis, bronchitis was also more common at the onset of the disease ($p = 0.05$, chi2 = 3.57). For the rest of the complaints in the vast majority of patients, no significant differences between the groups were detected.

The findings of our study allowed us to note that one of the most typical symptoms for sarcoidosis of any course was weight loss. It was found that in the group of patients with a favorable course of the disease, weight loss was small – on average, up to 1 kg. On the contrary, with an unfavorable course of sarcoidosis, patients had a more pronounced weight loss of 4 kg or more (up to a maximum of 40 kg). It was established that the presence of weight loss increased the risk of developing an unfavorable course of sarcoidosis by more than 3 times: RR 3.6, 95% CI 2.3–5.6. The data are presented in Table 1.

Table 1

The presence of weight loss in intrathoracic sarcoidosis in the groups, $M \pm m$

Parameter	Favorable course ($n = 85$)	Unfavorable course ($n = 36$)	p
Weight loss in kilograms	0.34 ± 0.19	3.94 ± 1.7	0,01

In accordance with the stated aim of the study, we compared the data of morphological studies in patients with different variants of the course of intrathoracic sarcoidosis. Quantitative differences between the groups in terms of the number of macrophages, lymphocytes, and neutrophils in the biopsy specimens were identified. The presence of qualitative features did not differ significantly between the groups. The data are presented in Tables 2 and 3.

It was noted that in patients with an unfavorable course of the disease, a greater number of macrophages in the biopsy specimens was significantly more frequent. In patients with a favorable course of the disease, a larger number of lymphocytes and neutrophils was more common. It was found that the predominance of macrophages in the biopsy material increased the risk of developing an unfavorable course of sarcoidosis by 1.4 times: RR 1.4, 95% CI 0.8–2.5.

Table 2

Quantitative morphological parameters of biopsy specimensin the groups throughout the course of sarcoidosis, $M \pm m$

Parameter	Favorable course (n = 85)	Unfavorable course (n = 36)	p
Granulomas, number in the field of vision	1.47 ± 0.1	1.6 ± 0.15	0.492642
Giant cells, %/100 in the field of vision	1.17 ± 0.11	1.33 ± 0.18	0.499801
Macrophages, %/100 in the field of vision	65.5 ± 1.8	78.5 ± 2.1	0.000041**
Lymphocytes, %/100 in the field of vision	30 ± 1.5	19.2 ± 1.8	0.000076**
Neutrophils, %/100 in the field of vision	3.36 ± 0.4	1.3 ± 0.4	0.001734**
Eosinophils, %/100 in the field of vision	1.0 ± 0.2	0.6 ± 0.27	0.225057

* $p < 0.05$; ** $p < 0.01$.

Table 3

Manifestations of activity according to morphological studies in the groups throughout the course of sarcoidosis

Sign	Favorable course				Unfavorable course				Statistical analysis
	present		absent		present		absent		
	абс.	%	абс.	%	абс.	%	абс.	%	
Hyalinosis	36	42.4	49	57.6	18	50	18	50	$p = 0.44$ $\chi^2 = 0.60$
Necrosis	18	21.2	67	78.8	8	22.2	28	77.7	$p = 0.89$ $\chi^2 = 0.02$* Yates' = 0.01
Schaumann bodies	14	16.5	71	83.5	10	27.8	26	72.2	$p = 0.15$ $\chi^2 = 2.03$
Stamping	44	51.8	41	48.2	20	55.6	16	44.4	$p = 0.70$ $\chi^2 = 0.15$
Total	85				36				

* $\chi 2$ (Chi-square test)

Therefore, it is obvious that the unfavorable course of intrathoracic sarcoidosis is accompanied by an increased number of macrophages in the histological examination of the biopsy specimens and greater weight loss in patients. A favorable course of the disease is associated with a relative weight loss (less than 1 kg) and a larger number of neutrophils and lymphocytes in the biopsy material.

DISCUSSION

A comprehensive analysis of clinical symptoms and morphological data between the groups different in the course of the disease showed that the cellular composition of granulomas is of great importance in assessing the prognosis of sarcoidosis. The analysis in the groups revealed that a significantly larger number of macrophages in the biopsy specimens was observed with an unfavorable and recurrent course of intrathoracic sarcoidosis. Macrophages are known to play an essential role in implementation of the immune response in sarcoidosis. These cells produce proinflammatory cytokines, such as interleukins (IL)-12, IL-6, IL-8, tumor necrosis factor alpha (TNFα), and chemokines. Chemokines, in turn, attract natural killer cells, neutrophils, and naïve T cells (Th0) to the focus of inflammation [11–13].

The above-described inflammatory mediators lead to alveolitis, granuloma formation, and tissue damage, and cytokine levels in bronchoalveolar lavage fluid and blood serum of patients can serve as markers of inflammation in sarcoidosis [14]. It was also found that in patients with an unfavorable course of sarcoidosis, weight loss (more than 3 kg) was more common. Moreover, a relationship was established according to the Spearman's rank-order correlation between the number of macrophages in the biopsy specimens and a greater weight loss in patients with an unfavorable course of the disease ($r = 0.39$, $p < 0.05$). Additionally, a relationship was identified between the number of lymphocytes and a relatively small decrease in weight in patients with a favorable course of sarcoidosis ($r = 0.32$, $p < 0.01$).

It should be noted that in modern studies, the authors not only study in detail the pathogenesis and morphogenesis of sarcoidosis, but also draw parallels between the clinical course, radiologic findings, and other data, thereby highlighting new phenotypes of the disease. M.A. Judson [15] distinguishes three groups

of patients: group 1 – patients with thoracic lymphadenopathy and silent pathological process in the lung tissue; group 2 – patients with minor lymphadenopathy and predominantly perivascular, peribronchial, and subpleural localization of granuloma complexes, as well as along the interlobar pleura, group 3 – patients with large granulomatous foci in the interstitial and peribronchial tissues, with various fibrotic changes (from moderate changes to severe cysts and bullae).

When comparing microscopic features, the author noted that in groups 1 and 2 the granulomatous inflammation was localized along the lymph-collecting vessels in the perivascular and peribronchial tissues. At the same time, in the patients of group 1, development of sclerotic changes, necrosis, and alveolitis was not detected, but in about 50% of cases, Schaumann bodies were found in giant cells, and granulomas had "stamped" appearance. In group 2, alveolitis and bronchiolitis of varying degrees were revealed, as well as zones of moderate interstitial lung disease and development of mild to moderate sclerotic changes. The patients of group 3 differed significantly: large granulomatous foci in the interstitium were observed (80% of cases), alveolitis and bronchiolitis were pronounced to varying degrees, and moderate to severe interstitial lung disease was detected. Granulomas were localized in the interstitial and peribronchial tissues, some of the granulomas affected the bronchiolo-alveolar region and led to pronounced fibrosis [15].

In another study, the author distinguished phenotypes of sarcoidosis according to the gender – age principle, determining the course of the disease in each group according to clinical symptoms [16]: 1) men from 18 to 35 years old; 2) men from 36 to 60 years old; 3) women from 18 to 35 years old; 4) women from 36 to 60 years old; 5) persons over 61 years of age. Preliminary data allow to consider histological studies with determination of the cellular composition of granulomas promising, since they can help predict a possible scenario for development of the course of intrathoracic sarcoidosis.

CONCLUSION

The data obtained indicate that the risk of developing an unfavorable course of intrathoracic sarcoidosis is associated with an increased number of macrophages in the histological examination and clinically significant weight loss in patients. The predominance of a large number of lymphocytes and neutrophils in sarcoid granulomas is typical of a favorable course of sarcoidosis. Based on the above-stated data, it is possible to distinguish two different clinical and morphological variants of the course of intrathoracic sarcoidosis: 1) macrophage-dominant sarcoidosis with severe weight loss (typical of a recurrent and unfavorable course of sarcoidosis); 2) lymphocyte-dominant sarcoidosis with minimal weight loss (typical of a favorable course of sarcoidosis).

Therefore, there is a close relationship between the clinical and morphological data of the study of the lungs and lymph nodes in pulmonary sarcoidosis. Morphological examination of biopsy specimens from the affected lesion provides significant information and complements the clinical presentation, allowing to predict the course of intrathoracic sarcoidosis. The predominance of macrophages in the biopsy material increases the risk of an unfavorable and recurrent course of sarcoidosis by 1.4 times, and the presence of significant weight loss increases the risk of an unfavorable course of the disease by more than 3 times.

With ubiquitous use of histological research methods in the diagnosis of sarcoidosis, it is necessary to search for new phenotypes of the disease course and identify new classification subtypes, taking into account morphological criteria. The presence of certain morphological markers may affect treatment and outcome of the disease. The data obtained in this study, undoubtedly, can be used to carry out morphological diagnosis in intrathoracic sarcoidosis and applied in real clinical practice.

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Authors contribution

Palchikova I.A. – conception and design; carrying out of research, formation of the database, analysis and interpretation of data; drafting of the article. Denisova O.A. – conception and design; formation of the database, analysis and interpretation of data. Chernyavskaya G.M. – conception and design; analysis and interpretation of data; final approval of the manuscript for publication. Purlik I.L. – carrying out of research; analysis and interpretation of data. Kalacheva T.P. – conception and design; drafting of the manuscript. Naumov A.O., Soloviev M.M. – analysis and interpretation of data.

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