

Splenomegaly in Sarcoidosis: Frequency, Treatment, Prognosis and Long-term Follow-up

Zora Pavlović-Popović^{1,2}, Bojan Zarić², Zdravko Kosjerina², Dragana Petrović³

¹University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia;

²Institute for Pulmonary Diseases of Vojvodina, Sremska Kamenica, Serbia;

³Institute of Oncology of Vojvodina, Sremska Kamenica, Serbia

SUMMARY

Introduction The splenic involvement is common in sarcoidosis, but its real frequency is still obscure, depending doubtless on the method of splenomegaly detection. Splenomegaly may be accompanied with pain or anemia, leucopenia and thrombocytopenia.

Objective The aim of this study was to investigate the frequency of splenomegaly related to clinical characteristics of sarcoidosis and to solve the dilemma – whether to introduce medicaments, and when to perform splenectomy.

Methods The method of the study is a retrospective and prospective analysis of the patients' material.

Results The study included 540 patients with sarcoidosis in a 20-year period. Of them, 26% had splenomegaly detected by computerized tomography screening. Splenomegaly was more frequently registered in the patients with a longer history of sarcoidosis (38%), as compared to those with a shorter history of the disease (23%) ($p < 0.05$). Splenomegaly was more frequently registered in the patients with other extrapulmonary lesions detected (33%) than in those who had no extrapulmonary manifestations of sarcoidosis (17%) ($p < 0.01$). Indications, possible benefits and complications of splenectomy were analysed in 11 sarcoidosis patients undergoing this intervention for various reasons, of which the follow-up period ranged from one to 20 years.

Conclusion Splenomegaly was more frequent in chronic cases or in the patients with established sarcoid lesions of other extrapulmonary organs. The primary treatment of uncomplicated symptomatic splenic sarcoidosis includes medicamentous therapy. Occasionally, splenectomy is required. Prognostically, splenomegaly indicates an unfavorable course of the disease.

Keywords: sarcoidosis; clinical characteristics; splenomegaly

INTRODUCTION

Sarcoidosis is a multisystem granulomatous disease of unknown etiology. As sarcoidosis may affect any organ, the abdominal organs may be involved as well. The spleen is frequently affected in sarcoidosis, but it is not always particularly investigated.

The normal human spleen weighs approximately 150 to 250 grams. The organ must double in size before it can be palpated beyond the costal margin. The term 'massive splenomegaly' denotes the splenic weight greater than 1,000 grams, or 4 to 6 times the normal weight, when the spleen is palpable more than 4 cm below the costal margin. Spleens involved with sarcoidosis rarely exceed two kilograms in weight, but may also be normal in size.

A slightly enlarged spleen is often asymptomatic. The patients with sarcoidosis of the spleen develop symptoms which are usually associated with a massive splenomegaly. These symptoms include early satiety, left upper-quadrant fullness, and arch, while extremely severe pain may be due to splenic infarct secondary to gastric compression, which may be the first symptom of the spleen involved with sarcoidosis [1]. Functional disorders in patients

with splenic infiltration include pancytopenia, anemia, leukopenia and thrombocytopenia, inducing fatigue and petechiae.

The splenic involvement with sarcoidosis is probable if the spleen is enlarged on the palpation or radiography in patients with established sarcoidosis. As the definite histological diagnosis may be established by splenectomy when necessary, it is important to differentiate between the splenic involvement with sarcoidosis and the sarcoid-like reaction, the latter associated with lymphoma and malignant tumors of other organs [2].

In patients with sarcoidosis, CT imaging reveals heterogeneous splenomegaly with multiple hypovascular nodules. Being hypovascular, the nodules are mostly discrete, but they may coalesce and become bigger [3, 4].

The asymptomatic, slightly enlarged spleen requires no treatment. However, massive splenomegaly associated with hematological and immunological complications may require the treatment with corticosteroids, methotrexate and/or antimalarial drugs, unless the signs of a spontaneous regression are registered. It should be kept in mind that even massive splenomegalies can have a spontaneous remission [5]. Splenectomy is indicated in the pa-

Correspondence to:

Zora PAVLOVIĆ-POPOVIĆ
Institute for Pulmonary Diseases
of Vojvodina
Department for Sarcoidosis and
Diffuse Pulmonary Diseases
Put dr Goldmana 4
21204 Sremska Kamenica
Serbia
zora.pavlovic-popovic@institut.rs

tients failing to adequately respond to the applied medicamentous treatment, in severe hypersplenism and pain, prophylaxis for splenic rupture, and neoplastic exclusion.

OBJECTIVE

The aim of this study was to investigate the frequency of splenomegaly related to clinical characteristics of sarcoidosis and to solve the dilemma – whether to introduce medicaments, and when to perform splenectomy.

METHODS

The investigated group included patients with the diagnosis of sarcoidosis established in the Institute for Pulmonary Diseases of Vojvodina, Serbia, in the period from 1992 to 2012. The patients selected for the study were submitted to control examinations and their available medical files were reviewed. With regard to a long course of the disease, the collected data were used in two methodological procedures – the retrospective and the prospective one. On the basis of the retrospective analyses of the patients' material, including the medical files (the initial diagnoses and the findings on control examinations) of a certain number of the patients with sarcoidosis, an insight into the former course of the disease was obtained. The diagnosis of sarcoidosis was based on the consistent clinical and radiological picture, the histological finding of non-caseating granulomas in one or more of the affected tissue systems, and exclusion of other granulomatous conditions mimicking sarcoidosis. The prospective analysis of the patients' material included further monitoring of their disease through control examinations of the registered patients. The comparative analysis of the former condition and the findings at control examinations have shed light on the evolution of the disease and effects of the treatment on splenomegaly in the patients with sarcoidosis.

RESULTS

There were 540 patients with sarcoidosis (212 males and 328 females) registered over the period from 1992 to 2012. These patients were submitted to the spleen size assessment by ultrasound of the abdomen. In this group, the patients with splenomegaly were additionally submitted to computerized tomography of the abdomen, which confirmed splenomegaly in 140 (26%) of them. No difference in the frequency of splenomegaly has been registered between the sexes. Severe pancytopenia was registered in two patients, who were submitted to splenectomy. In the group of sarcoidosis patients with a longer follow-up (>2 years) due to length of the disease, splenomegaly was more frequently registered (38%), compared to the patients with a shorter (≤2 years) disease history (23%) ($p<0.05$) (Table 1).

In the patients with other extrapulmonary lesions registered, the frequency of splenomegaly was 33%, as

Table 1. Computerized tomography established splenomegaly in patients with sarcoidosis

Disease history (years)	Number of patients	
	Total	With splenomegaly
≤2	440	102 (23%)
>2	100	38 (38%)
Total	540	140 (26%)

The difference between patients with the disease history of ≤2 and >2 years: $p<0.05$

Table 2. Splenomegaly and other extrapulmonary manifestations in patients with sarcoidosis

Extrapulmonary lesions	Number of patients	
	Total	With splenomegaly
Registered	310	102 (33%)
Unregistered	230	38 (17%)
Total	540	140 (26%)

The difference between the groups with and without other extrapulmonary lesions registered: $p<0.01$

compared to 17% in sarcoidosis patients with no other extrapulmonary lesions registered ($p<0.01$) (Table 2).

Hemoglobin, hematocrit and leucocyte levels were similar in sarcoid patients with either normal or enlarged spleen. Thrombocyte levels were statistically significantly lower in female sarcoid patients with splenomegaly than in those with a normal-sized spleen. This difference was not registered in male patients. A negative correlation was registered in female patients between hemoglobin, hematocrit and thrombocyte values and the spleen size, but this correlation was not found in male patients. Two of 140 patients with splenomegaly had anemia, while neutropenia and thrombocytopenia were registered in 8 and 14 of 140 patients, respectively. Pancytopenia was registered in 2 patients. Anemia accompanied with thrombocytopenia was registered in 2 female patients as well. Generally, 28 of 140 patients with splenomegaly (20%) had altered peripheral blood values suggesting hypersplenism.

In the further course of the study, 11 patients with sarcoidosis undergoing splenectomy for a variety of reasons were followed over the period of 1 to 20 years. This group included 4 males and 7 females, ranging from 20 to 54 years of age at the time of establishing the initial diagnosis. In this group of sarcoid patients with splenomegaly, the predominant symptoms were the abdominal pain, weakness and fatigue. Anemia, leukopenia and thrombocytopenia were registered in 2 patients. The immediate reasons for coming to see a doctor were skin lesions, joint pains and enlarged lymph nodes. To establish the diagnosis of sarcoidosis, biopsy samples of the skin lesions were taken, and the lungs were also sampled by transbronchial biopsy in 3 patients. This was due to the fact that 50% of these patients had a normal chest X-ray finding. In the patients with splenomegaly, splenectomy was often indicated in order to exclude lymphoma or other malignant hematological disease, or in cases of massive splenomegaly with a threatening rupture, or a severe pancytopenia responding poorly to the applied medicamentous therapy. The 1–20-year follow-ups of 11 patients with sarcoidosis submitted to splenectomy has revealed that 55% of the

patients required no further medicamentous treatment because sarcoidosis was in remission, or no medicamentous treatment was recommended either. One fatal outcome was due to neither sarcoidosis nor splenectomy, but the patient had a car accident. In other patients of this group, 45% of sarcoidosis cases were resolved by corticosteroids.

DISCUSSION

The recent data suggest the frequency of splenic involvement with sarcoidosis ranges from 10% to over 50% [6]. The palpable spleen is registered in 2–42% of the patients with sarcoidosis [7]. The study in Serbia reported a palpable spleen in 1%, and splenomegaly in 4% of the patients with sarcoidosis [8], while the study in Finland reported a palpable spleen in 6% of their examined patients with sarcoidosis [9]. Splenomegaly is more frequently registered at autopsy 54%, and granulomas in the spleen are found at autopsy in 38–77% of the patients with sarcoidosis [7, 9, 10]. Longcope and Freiman [10] reported an enlarged spleen in 65% of the autopsied subjects with sarcoidosis. In another study of 111 sarcoidosis patients, the spleen was found to be involved in 53% of the cases [11]. A review of the literature, comprising 6,074 patients from 29 studies, shows that splenomegaly is common, but a massive splenomegaly is rare (approximately 3%) in sarcoidosis patients with splenic involvement [12]. The age, sex and race of the patients with splenic sarcoidosis correlate to other sarcoidosis patients [13]. Splenomegaly due to sarcoidosis is associated with multiple organs involvement that almost always includes the lungs, and very often the liver [13, 14]. The radiological finding of the chest is rarely normal in sarcoidosis patients with splenic involvement [15]. The isolated cases of sarcoidosis of the spleen, with no extrasplenic involvement, have been reported in the literature, but rarely so [16].

The frequency of radiological abnormalities of the spleen is unknown, as all examined series are either retrospective, or they have a biased selection. The retrospective analysis of abdominal CT findings in 49 patients with the tissue-proven sarcoidosis revealed spleen abnormalities in 26 (53%) patients [17]. In their recent studies, Ebert et al. found nodules in the spleen in 15% of the patients with sarcoidosis who underwent CT scanning of the abdomen [4]. The nodular lesions correlated with the activity of the disease [4].

Comparing the contrast CT and MR imaging, the latter appears to be an equally good, or a slightly better imaging procedure to detect the nodules in the spleen and liver [18].

Ultrasound of the abdomen has also been applied in the diagnostic assessment of splenomegaly in 108 patients with sarcoidosis, detecting the sarcoid involvement of the spleen in 22 (20.3%) of them [19].

In general, the treatment of splenic sarcoidosis includes the medicamentous therapy with prednisone, methotrexate and/or antimalarial drugs, providing a good treatment response. In study of 24 patients with sarcoid splenom-

egaly, a good control of splenomegaly was achieved by corticosteroid therapy in 17 patients. Methotrexate and azathioprine are used to treat the patients with intolerance to corticosteroids, or those with a refractory disease. In some cases, splenectomy should be indicated. Baughman et al. [20] detected splenomegaly in 32 of 235 patients with sarcoidosis; in 11 of 32 patients, the enlarged spleen was palpable 4 cm below the costal margin and 9 of these patients had a good response to the applied medicamentous treatment while 2 patients required splenectomy. Patel [21] reported a patient intolerant to corticosteroids with a systemic sarcoidosis which also involved the bone marrow, who responded well to TNF antagonist adalimumab, with hemoglobin normalization and splenomegaly reduction to normal levels in a two-year period.

Sarcoidosis of the spleen may cause hypersplenism, which induces hematological disorders including anemia, leukopenia, thrombocytopenia or any of their combinations, including pancytopenia [12]. In sarcoidosis, thrombocytopenia with splenomegaly is not always the result of the splenic sequestration of thrombocytes; autoimmune thrombocytopenia may result from the development of thrombocyte-associated immunoglobulins. However, a low frequency of hypersplenism in the patients with sarcoidosis (range 0–22%) has been reported in the literature [22], despite the common splenic involvement. Pham et al. [12] reported 1 case of giant sarcoid splenomegaly treated by splenectomy in order to control the hematological abnormalities. A case with giant splenomegaly, pancytopenia and hypercalcemia has also been reported. The spleen was 15 cm below the costal margin [23].

Splenectomy is quite rarely indicated by hypersplenism or the symptoms (uneasiness) resulting from the compression in the abdomen or infarction of the spleen. It is however unavoidable in cases of the rupture of the spleen or the splenic artery, which are fortunately rare in sarcoidosis, with just one report each [24]. On the other hand, splenectomy should be indicated as a precaution against the splenic rupture, in cases of a gross enlargement, severe hypersplenism and pain, indefinite diagnosis requiring exclusion of a lymphoma or other hematological malignancies, when the medicamentous therapy failed to produce a satisfactory response, or it was contraindicated [6]. In these cases splenectomy is the last treatment option to be applied. When assessing the indications for it, long-term benefits and post-splenectomy complications should be considered. These cases are few and their long-term follow-up is often difficult [25].

The mortality rate of the patients with splenic sarcoidosis seems to be increasing, although the mortality is usually related to extrasplenic sarcoid involvement, inducing respiratory insufficiency, bleeding aspergilloma related to fibrocystic sarcoidosis, or cardiac insufficiency due to pulmonary fibrosis in terminal stage sarcoidosis. The patients with splenic sarcoidosis usually have a bad prognosis, due to persistent, chronic sarcoidosis. Their disease tends to involve multiple extrapulmonary organs, and they often have the fibrotic lung disease [26, 27].

CONCLUSION

In our study, the CT screening of the abdomen revealed the spleen involvement in one fourth of the examined patients with sarcoidosis. Splenomegaly was more frequent in chronic cases, or in the patients with established sarcoid lesions of other extrapulmonary organs. Hypersplenism

due to the peripheral blood alterations occurs exceptionally rarely. The symptoms produced by the compression of the enlarged spleen in the abdomen, as well as hypersplenism, require a medicamentous treatment. In our study, splenectomy was rarely performed for splenic sarcoidosis. Prognostically, the disease in these cases takes an unfavorable course due to its long duration.

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Учесталост, лечење, прогноза и дугогодишње клиничко праћење спленомегалије у саркоидози

Зора Павловић-Поповић^{1,2}, Бојан Зарић², Здравко Косјерина², Драгана Петровић³

¹Универзитет у Новом Саду, Медицински факултет, Нови Сад, Србија;

²Институт за плућне болести Војводине, Сремска Каменица, Србија;

³Институт за онкологију Војводине, Сремска Каменица, Србија

КРАТАК САДРЖАЈ

Увод Код особа оболелих од саркоидозе слезина је често захваћена, али стварна учесталост није позната, већ зависи од методе откривања. Спленомегалија може бити праћена болом или анемијом, леукопенијом и тромбоцитопенијом.

Циљ рада Циљ истраживања је био да се утврди учесталост спленомегалије у погледу клиничких одлика саркоидозе и разреши терапијска дилема: да ли је потребно медикаментно лечење и када треба урадити спленектомију.

Методe рада Болеснички материјал је обрађен ретроспективно и проспективно.

Резултати Током двадесетогодишњег периода испитано је 540 болесника са саркоидозом. Код 26% испитаника компјутерском томографијом установљена је спленомегалија. Она је била чешћа код испитаника који су дуго боловали и дуго клинички праћени (38%) у односу на болеснике чија је бо-

лест трајала краће (23%) ($p < 0,05$). Такође је била чешћа код болесника са другим екстраторакалним лезијама (33%) у односу на болеснике код којих се нису znale друге локације саркоидозних лезија (17%) ($p < 0,01$). Индикације, дугорочне користи и компликације анализирани су код 11 саркоидозних болесника којима је урађена спленектомија из разних разлога праћених у периоду од једне до 20 година.

Закључак Спленомегалија је била чешћа у хроничним случајевима, као и код оболелих где су саркоидозним лезијама били захваћени и други екстрапулмонални органи. Примарна терапија некомплицованих слезинских саркоидоза са симптомима састоји се од медикаментног лечења. Понекад је потребно применити спленектомију. Прогноза спленомегалије је лоша.

Кључне речи: саркоидоза; клиничке одлике; спленомегалија

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