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Original Article

Extrapulmonary Sarcoidosis with Multiple-Organ Involvement

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ABSTRACT

Objective: In cases of pulmonary sarcoidosis, extrapulmonary involvement is not uncommon. The skin, eyes, and lymph nodes are the most common sites of extrapulmonary involvement, and multiple organs may be involved at the same time. In this study, patients with extrapulmonary sarcoidosis were investigated in terms of the localization of involvement.

Methods: Patients diagnosed with sarcoidosis between 1994 and 2015 were evaluated retrospectively. Demographic characteristics, symptoms, organ involvement, diagnostic methods, and the length of time between the diagnosis of sarcoidosis and additional organ involvement were recorded. The patients were consulted to the departments of dermatology, ophthalmology, and cardiology, and a chest X-ray, high-resolution computed tomography, and abdominal ultrasound examinations were performed.

Results: Extrapulmonary involvement was detected in 144 of a total of 337 sarcoidosis patients. In 92% of those patients with extrapulmonary involvement, there was accompanying pulmonary involvement. Women made up 75% of the group, and the mean age was 43 years. The most commonly detected extrapulmonary involvement was of the skin (n=41), followed by erythema nodosum (n=37), and involvement of the liver (n=24), lymph nodes (n=20), spleen (n=18), and salivary/parotid gland (n=15). The most frequent diagnostic method used was mediastinoscopy (n=41), followed by a skin biopsy (n=23), and a transbronchial lung biopsy (n=19). Of the 26 (18%) patients who had multiple-organ involvement, 2 were diagnosed as stage 0, 14 were stage 1, 9 were stage 2, and 1 was stage 3. The mean length of time before a diagnosis of extrapulmonary involvement was 24 days.

Conclusion: If there is extrapulmonary involvement in a case of sarcoidosis, it should be kept in mind that more than 1 organ system may be involved and the relevant additional tests may be required.

INTRODUCTION

Sarcoidosis is a chronic granulomatous disease with multisystemic involvement of unknown etiology. The lungs are the most commonly involved organ.[1] The incidence of extrapulmonary sarcoidosis, which frequently accompanies pulmonary sarcoidosis, has been reported at 36% to 50%.[2,3] Isolated extrapulmonary involvement is rare (5–9%).[3–5] Different phenotypes of organ involvement have been described in sarcoidosis.[6] The liver, spleen, skin, eyes, and peripheral lymph nodes are the most common sites of involvement after the lungs. There may be involvement in more than 1 organ system. Clinical and laboratory findings vary according to the organ involvement.[1] Extrapulmonary findings may also differ according to age, gender, and race.[4] Data on the number of involvement sites in patients with extrapulmonary sarcoidosis have been reported.[5,7,8] Extrapulmonary sarcoidosis can be life-threatening, especially in patients with neurological and cardiac involvement,[9,10] and treatment changes may be required. This may be a result of a different immunopathogenesis and/or phenotype in extrapulmonary sarcoidosis.[5] The

aim of this study was to describe the experience of a clinic in Turkey's biggest pulmonary hospital with extrapulmonary sarcoidosis in order to make a contribution to the literature on the subject.

MATERIAL AND METHODS

The medical files of patients who were diagnosed with sarcoidosis between January 1994 and December 2015 and followed-up in a single tertiary teaching hospital for chest diseases and thoracic surgery center were reviewed retrospectively. The study was approved by the University of Health Sciences Sureyyapaşa Chest Diseases and Thoracic Surgery Education and Research Hospital ethics committee (12.03.2018/023) and was conducted in accordance with the Declaration of Helsinki. Informed consent of the patients to review their medical records was not obtained; patient data were de-identified.

For the diagnosis of sarcoidosis, a histopathological examination should reveal non-caseous granuloma and/or clinical-radiological compliance. Clinical and radiological compliance were pursued after the exclusion of other diagnoses when the patient did not consent to a biopsy and/or had Löfgren's syndrome. Bronchoscopic procedures for a histopathological diagnosis (bronchoalveolar lavage, transbronchial biopsy, endobronchial forceps biopsy, transbronchial needle aspiration biopsy, endobronchial ultrasonography), peripheral or scalene lymph node biopsy, mediastinoscopy and/or mediastinotomy, open lung biopsy, skin or salivary gland biopsy, or a breast biopsy was performed. Gallium scintigraphy was performed for patients who declined a biopsy procedure and who were followed up clinically and radiologically.

The criteria specified in the ACCESS (A Case Control Etiologic Study of Sarcoidosis) trial were used for the definition of organ involvement.[3] All of the patients were asked about extrapulmonary complaints, physical examination findings were evaluated, and the symptoms and findings were investigated in order to determine extrapulmonary organ involvement. In addition, electrocardiography, echocardiography, whole abdominal ultrasonography, dermatological, and ophthalmological examinations were requested from all patients regardless of complaints or physical examination findings.

Study protocol

Demographic characteristics, symptoms and physical examination findings; complete blood count, serum angiotensin-converting enzyme (ACE), calcium, and other biochemical parameter levels; tuberculosis skin test (PPD); pulmonary function test and diffusing capacity of carbon monoxide measurements; chest X-ray findings; radiological grade, number, and kind of organs involved; diagnostic tools used; and the mean length of time until diagnosis were recorded in patients diagnosed with pulmonary sarcoidosis with and without extrapulmonary sarcoidosis and those with isolated extrapulmonary sarcoidosis. Patient chest X-rays were evaluated and radiological staging was performed according to the Siltzbach classification:[1]

Stage 0: Normal chest X-ray.

Stage 1: Bilateral hilar lymphadenopathy.

Stage 2: Parenchymal infiltration together with bilateral hilar lymphadenopathy.

Stage 3: Parenchymal infiltration without lymph node involvement.

Stage 4: Diffuse parenchymal fibrosis and honeycomb lung.

Statistical analysis

IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA) was used to perform the data analysis. The mean±SD of parametric continuous variables was calculated, and counts and percentages were used as applicable.

RESULTS

Extrapulmonary involvement was detected in 144 (43%) of 337 sarcoidosis cases in the study period. Of the study group, 75% of the patients were women and the mean age was 43±11 years (min-max: 20–70 years). In cases of extrapulmonary involvement, 92% had accompanying pulmonary involvement. The staging results in patients with extrapulmonary sarcoidosis according to posteroanterior (PA) chest X-ray images are shown in Table 1.

The most common extrapulmonary involvement was skin involvement other than erythematous nodosum (n=41). This was followed by erythema nodosum (n=37), liver (n=24), peripheral lymph nodes (n=20), spleen (n=18), and salivary/parotid gland (n=15) involvement. The symptoms of the patients are provided in Table 2 and the findings in Table 3.

While hypercalcemia was detected in 8 patients, the serum

Table 1. Stages of extrapulmonary sarcoidosis according to posteroanterior chest X-ray

Stage	n	%
0	11	7.6
1	93	64.5
2	33	22.9
3	7	4.8

Table 2. Chief complaints in patients with extrapulmonary sarcoidosis

Symptom	n	%
Dyspnea	45	31.2
Fatigue	18	12.5
Erythema nodosum	17	11.8
Back pain	16	11.1
Chest pain	13	9
Joint swelling	13	9
Weight loss	13	9
Joint pain	11	7.6
Sweating	11	7.6
Sputum		
Skin involvement other than erythema nodosum	9	6.2
Anorexia	10	6.9
Ocular involvement	8	5.5
Fever	8	5.5
Hemoptysis	4	2.7
Headache	3	2
Bone pain	3	2

Table 3. Findings in patients with extrapulmonary sarcoidosis

Involvement	n	%
Skin findings other than erythema nodosum	41	28.4
Erythema nodosum	37	25.6
Liver	24	16.6
Peripheral lymph node	20	13.8
Spleen	18	12.5
Salivary/parotid gland	15	10.4
Ocular	11	7.6
Joint	7	4.8
Cardiac	4	2.7
Neurological	2	1.3
Renal	2	1.3
Breast	1	0.6

ACE level was elevated in 75 of the 138 patients whose serum ACE level was measured. The PPD was negative in 82 of the 112 patients tested.

The most commonly used methods for diagnosis were mediastinoscopy in 41 patients, skin biopsy in 23 patients, and a transbronchial lung biopsy in 19 patients (Table 4). Ten patients who declined to have a biopsy for tissue diagnosis underwent a number of noninvasive tests to exclude other diagnoses and were diagnosed with extrapulmonary sarcoidosis during clinical and radiological follow-ups.

Table 4. Diagnostic methods used in patients with extrapulmonary sarcoidosis

Procedure	n	%
Mediastinoscopy	41	28.4
Skin biopsy	23	15.9
Transbronchial biopsy	19	13.1
Bronchoalveolar lavage	13	9
Peripheral lymph node biopsy	11	7.6
Clinical-radiological	10	6.9
Gallium scintigraphy	8	5.5
Scalen lymph node biopsy	7	4.8
Bronchial mucosa biopsy	3	2
Mediastinotomy	2	1.3
Minor salivary gland biopsy	1	0.6
Parotid salivary gland biopsy	1	0.6
Transbronchial needle aspiration biopsy	1	0.6
Breast biopsy	1	0.6
Uveitis	1	0.6
Endobronchial ultrasonography	1	0.6
Open lung biopsy	1	0.6

In all, 26 (18%) patients had multiple-organ involvement, including 4-organ involvement in 2 patients and 3-organ involvement in 3 patients. Of the 26 patients with multiple-organ involvement, 20 (77%) were female. The mean age of this population was 44 years (min-max: 26–69 years). According to PA chest X-rays, 2 of the patients were at stage 0, 14 were stage 1, 9 were stage 2, and 1 was classified as stage 3.

Cases with isolated extrapulmonary sarcoidosis without pulmonary involvement represented 8% of the group. In this group, the female/male gender ratio was 7/4 and the median age was 40 years. Skin involvement other than erythematous nodosum (n=8), and involvement of a joint (n=2), peripheral lymph nodes (n=1), and the liver (n=1) were detected.

The disease stage and the location of involvement in extrapulmonary sarcoidosis patients with multiple-organ involvement are shown in Table 5. The mean length of time until diagnosis was 24 days (min-max: 1–111 days). Patients with erythema nodosum or other skin findings were diagnosed earlier. In patients with multiple-organ involvement, the mean duration until diagnosis was longer (mean: 34 days; min-max: 6–111 days).

Table 5. Disease stage and involvement sites in extrapulmonary sarcoidosis patients with multiple-organ involvement

Sarcoidosis Stage	Number of patients	Median age	Sex (F/M)	Number of organs involved	Involvement site
0	2	40	1/1	2	Skin other than EN, liver, joint
1	14	46	10/4	2.1	Skin other than EN, liver, spleen, cardiac, ocular, neurological, salivary gland, PLN
2	9	42	7/2	2.4	Skin other than EN, liver, spleen, cardiac, joint, salivary gland, PLN, EN
3	1	32	1/0	3	Neurological, ocular, joint
4	0	–	–	–	–

F: Female; M: Male; EN: Erythema nodosum; PLN: Peripheral lymph nodes.

DISCUSSION

In our study, extrapulmonary involvement was detected in 144 (43%) of sarcoidosis patients examined retrospectively from a 21-year period. Of the patients with extrapulmonary involvement, 92% had accompanying pulmonary involvement. Sarcoidosis may have varied clinical findings and extrapulmonary manifestations, which must be considered in the differential diagnosis. This study of patients from our clinic adds valuable data about extrapulmonary sarcoidosis patients in Turkey to the literature. The incidence of isolated extrapulmonary involvement was 8%. In the ACCESS study, the incidence of extrapulmonary involvement was 50% (368 in 736 patients), while isolated extrapulmonary involvement was reported as 2%.[4] In the study performed by Rizzato et al.,[2] the percentage of extrapulmonary involvement in sarcoidosis patients was 36%. As for data published in our country, in a multi-center, prospective study conducted between 2004 and 2006 by the Turkish Thoracic Society Clinical Issues Study Group,[7] the extrapulmonary involvement rate was 40.6%, while Aykan et al.[8] reported a rate of 43%.

Extrapulmonary sarcoidosis is more common in women.[5] In the ACCESS study, 64% of the patients were female.[4] Ocular involvement, erythema nodosum, and neurosarcoidosis were also more common in women than in men.[4] James et al.[5] found that isolated extrapulmonary involvement was more common in women and that skin involvement was also seen more frequently among women. Zurkova et al.[11] reported that the female/male ratio was similar; however, there were fewer affected organs found in women. The results of our study were consistent with those of the ACCESS study: 75% of the patients with extrapulmonary sarcoidosis were female. However, contrary to the results of Zurkova et al.,[11] in our study multiple-organ involvement was found more frequently in women (75%).

In general, sarcoidosis disease is typically seen at the age of 25 to 40 years and has a second peak at 50 to 65 years of age in about 30% of cases.[12] According to the ACCESS study, organ involvement in extrapulmonary sarcoidosis varies according to age: peripheral lymph node involvement is more frequently in patients below 40 years of age, while calcium metabolism disorder is more commonly observed in those over age 40.[4] Although the mean age of the patient population in our study was similar to that seen in the literature, multiple-organ involvement was found to be more frequent in patients over 40 years of age (15/26). Similarly, Aykan et al.[8] also found that extrapulmonary organ involvement was more frequent in patients over 40 years of age (56%).

In sarcoidosis, the most commonly involved organs other than the lungs are the skin, including erythema nodosum, followed by the liver and the peripheral lymph nodes.[4] In the present study, the rates of skin involvement (28/16), erythema nodosum (26/8) and liver involvement (17/12) were higher than those of the ACCESS study, while the involvement of peripheral lymph nodes (14/15) was similar.[4] In a study conducted in Spain, the 35% rate of erythema nodosum found was higher than that seen in our study, while skin (9%) and peripheral lymph node involvement (3%) were less frequent, compared with our results.[13] Li et al.[14] reported extrathoracic lymph node involvement of 23% and skin involvement of 14%.

Extrapulmonary involvement may be the first sign of sarcoidosis in some patients, or it may be observed simultaneously during the initial diagnosis or at a later stage in follow-up. In addition, there may be a single extrapulmonary finding, or multiple-organ involvement detected. Although extrapulmonary findings are generally known as having a benign course, life-threatening neurological and/or cardiac involvement may occur and early detection of these conditions is important for the prognosis of the patient. Likewise, chronic hypercalcemia and nephrocalcinosis, chronic uveitis, cystic bone lesions, lupus pernio, and nasal mucosa involvement are other extrapulmonary involvements with a poor prognosis. In our study, the rate

of multiple extrapulmonary organ involvement was 18% at the time of initial diagnosis. Life-threatening organ involvement was detected in 2 of 3 patients with simultaneous 3-organ involvement (patients 4 and 116) and 1 of 2 patients with 4-organ involvement (patient 193). None of these cases returned for follow-up. In a study reported by James et al.,[5] skin involvement was most common, with a rate of 49%, 2-organ involvement was seen in 29%, 3-organ involvement in 14.3%, and more than 3 organs in 10% of cases of isolated extrapulmonary sarcoidosis.

A limitation of our study was the retrospective, descriptive, single-centered design. Nonetheless, it provides useful clinical information due to the large sample size and specific patient group.

In conclusion, we found extrapulmonary sarcoidosis in 43% and multiple-organ involvement in 18% of the sarcoidosis patients in our study population. Extrapulmonary findings should be investigated, regardless of the presence of symptoms, when a patient is diagnosed with sarcoidosis and it should be kept in mind that there may be one or more other organs involved, and particular care should be given to investigate vital organ involvement.

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Ethics Committee Approval

Ethics committee approved.

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Authorship Contributions

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Conflict of Interest

None declared.

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Ekstrapulmoner Sarkoidozda Birden Fazla Organ Tutulumu

Amaç: Sarkoidozda pulmoner tutulumla beraber ekstrapulmoner tutulum sık görülür. Deri, göz ve periferik lenf nodları akciğerler dışında en sık tutulum yeridir ve birden fazla organ aynı zamanda tutulabilir. Bu çalışmada ekstrapulmoner sarkoidozlu olgular tutulum yerleri açısından incelendi.

Gereç ve Yöntem: 1994–2015 arasında sarkoidoz tanısı ile takip edilen hastalar geriye dönük olarak değerlendirildi. Çalışmada sarkoidoz ekstrapulmoner tutulum tanısı olan olguların demografik özellikleri; semptomları, organ tutulum yer ve sayılar, tanı yöntemleri ve süreleri kaydedildi. Hastaların cildiye, göz ve kardiyoloji konsültasyonları yapıldı ve akciğer grafisi, yüksek rezolüsyonlu bilgisayarlı tomografi (YRBT) ve batın ultrasonografi (USG) istendi.

Bulgular: Üç yüz otuz yedi hastanın 144'ünde ekstrapulmoner tutulum saptandı, olguların %92'sinde pulmoner tutulum ile birlikteydi. Ortalama yaşı 43, %75 kadındı. En sık tutulum şekli eritema nodozum dışı cilt tutulumu (n=41), eritema nodozum (n=37), karaciğer (n=24), lenf nodu (n=20), dalak (n=18) ve tükrük bezi-parotis (n=15) idi. En sık tanı yöntemleri 41 hastada mediastinoskopi, 23 hastada cilt biyopsisi ve 19 hastada transbronşial akciğer biyopsisiydi. İki hastada dört, üç hastada üç ayrı bölgede olmak üzere 26 (%18) hastada birden fazla tutulum saptandı. Birden fazla tutulum olan hastaların ikisi evre 0, 14'ü evre 1, dokuzu evre 2 ve biri evre 3 idi. Hastalarda saptanan ortalama tanı süresi 24 gündü.

Sonuç: Sarkoidoz tanısı konulan olguda ekstrapulmoner tutulum varlığında birden fazla organda tutulum olabileceği akılda tutulmalı ve gerekli inceleme ve değerlendirmeler bu yönde yapılmalıdır.

Anahtar Sözcükler: Ekstrapulmoner tutulum; sarkoidoz; tanı.