International Journal of
Clinical Images and Medical Reviews

Research Article

Clinicopathological analysis of 20 cases of subcutaneous sarcoidosis in South Korea

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Abstract

Aim: To evaluate the clinicopathological features of subcutaneous sarcoidosis and their relationship with systemic involvement of the disease.

Methods: All patients performed skin biopsy and diagnosed with subcutaneous sarcoidosis from 2003 to 2013 were reviewed. Demographics, laboratory and histological finding, and clinical characteristics were analyzed.

Results: Mean age is 48.2 years and female : male ratio is 5:1. Twelve (66.7%) patients had a single cutaneous lesion, and 6 (33.3%) had lesions with two or more site. Sixteen (94.5%) patients demonstrated subcutaneous nodules at the time of diagnosis. The cutaneous lesions were located on the lower extremities in 12 (66.7%) patients, upper extremities in 7 (38.9%), head in 4 (22.2%) and 2 (11.1%) in trunk. Eight (44.4%) patients demonstrated cutaneous lesions in two or more locations. In chest radiographic stage, stage 0 was 16 (94.5%)patients, stage I was 2 (11.1%) patients. There is no patient stage II, III and IV. Nine (50.0 %) of 18 patients demonstrated only specific cutaneous involvement during the follow-up period and the remaining patients presented systemic involvement. Serum angiotensin-converting enzyme (ACE) level and erythrocyte sedimentation rate (ESR) in patients with systemic involvement tended to be higher than those without, although there was no statistical significance. Six (33.3%) patients presented remission and 9 (50%) patients presented partial remission. Four (22.2%) patients presented with relapse with lung involvement and were treated with oral steroid with azathioprine, which resulted in partial remission.

Conclusions: In this study, half of patients with subcutaneous sarcoidosis had systemic involvement. This is lower than other studies, so it is not clear whether subcutaneous sarcoidosis is associated with systemic involvement. ACE and ESR levels may be helpful in predicting systemic involvement.

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Received: April 28, 2022 Accepted: May 05, 2022 Published: May 09, 2022

Key Words: subcutaneous sarcoidosis, systemic involvement

INTRODUCTION

Sarcoidosis is a multisystem granulomatous disorder of unclear origin.1 The diagnosis of sarcoidosisis well established when clinical and radiological findings are supported by histological evidence of non-caseating granulomas in one or more tissues.2 It involves mainly the lungs, mediastinal and peripheral lymph nodes, skin, liver, spleen, eyes and parotid glands.3

Cutaneous lesions of sarcoidosis are the second most common location of sarcoidosis after pulmonary lesions and are seen in 25% of cases typically at disease outset.1 Skin lesions are heterogeneous and classified as specific and nonspecific.4 Specific lesions contain noncaseating granulomas and non-specific lesions represent a reactive process and do not contain the classic granulomas. 5-7 Subcutaneous sarcoidosis is the least frequent specific subset of cutaneous sarcoidosis and its prognostic significance has not been clearly estabilished.8 It is limited to the subcutaneous tissue and it is clinically characterized by multiple, firm, asymptomatic to slightly tender, mobile, round to oval, skin-colored nodules commonly located on the extremities (forearms and legs), commonly in a bilateral and asymmetric fashion.9 Due to the limited number of case reports, the characteristics of subcutaneous sarcoidosis in the evolution of systemic disease have not been elucidated. Recently, some studies have been shown an association between subcutaneous sarcoidosis and mild systemic involvement.4,10 Subcutaneous sarcoidosis is rarely reported in Asia. The purpose of this study is to evaluate the clinicopathological features of 18 patients with subcutaneous sarcoidosis and their relationship with systemic involvement of the disease according to subtype.

MATERIALS AND METHODS

Study design and patient selection

We enrolled patients diagnosed with subcutaneous sarcoidosis who visited our center, Jeju National University Hospital from 2003 to 2013. The diagnosis of subcutaneous sarcoidosis was based on skin biopsy.

Clinical evaluation

The patients' clinical records were retrospectively reviewed to obtain

Citation: WooSeong Jeong, Eun-Jung Park, Jinsoek Kim. Clinicopathological analysis of 20 cases of subcutaneous sarcoidosis in South Korea . Int Clin Img and Med Rew. 2022; 2(2): 1065.

***DOI:** 10.55920/IJCIMR.2022.02.001066*

the following data: age, gender, types, and sites of cutaneous lesions, extracutaneous lesions, chest x-ray stage, laboratory findings and histopathologic results.

Skin lesions are categorized by specific and non-specific. Specific lesions contain noncaseating granulomas and non-specific lesions represent a reactive process and do not contain the classic granulomas. Specific lesions are subdivided into nodulopapules, papules, maculopapular eruption, scar sarcoidosis, lupus pernio. Angiotensin converting enzyme, calcium, Erythrocyte sedimentation rate and gammaglobulin level were measured and plain chest radiograph was performed. Initial chest radiographic stage was classified as usual: stage 0 when normal; stage I if bilateral hiliar and/or paratracheal adenopathy; stage II when adenopathy with pulmonary infiltrate; stage III only pulmonary infiltrates and stage IV if pulmonary fibrosis.

Treatment

We used glucocorticoid, hydrocychloroquine, Cholchicine for primary treatment. If patient had no reponse, we used azathioprine or azathioprine combination with primary drug or combination of primary drugs.

Statistical analysis

The significance of differences among groups was determined by the Mann-Whitney U test and the chi-squared test. All statistical analysis was carried out using SPSS software program (version for Windows: SPSS Inc., Chicago, IL, USA). A value of $p < 0.05$ was considered to be significant.

RESULTS

Baseline characteristics of patients

Ten years of studying from 2003, 18 patients are diagnosed with subcutaneous sarcoidosis. The mean age was 48.2 years. Fifteen (83.3 %) were women and 3 were man, with female: male ratio of 5:1. The mean follow up period was 1.7 years. The clinical characteristics of the patients are summarized in Table1.

Seventeen (94.0 %) patients demonstrated specific subcutaneous sarcoidosis. The most common morphology of cutaneous lesion was nodulopapules in 15 (88.9%) patients, followed by maculopapular eruption in 1 (5.5%) and papules in 1 (5.5%). Scar sarcoidosis and Lupus pernio were not seen in our patients. Ten patients had a single cutaneous lesion, and 8 (44.4%) had lesions with two or more site. In most of the patients, subcutaneous nodules appeared at the beginning of the disease. One case presented pulmonary and neck lymphadenopathy with cutaneous lesion on extremity at the time of diagnosis. Only 2 cases had an extrapulmonary lesion first (pulmonary lymphademopathy). These 2 cases presented skin nodules within 6 months after diagnosis. There were no patients appeared at beginning of the disease in articular, lymph nodes, eye, parotid gland, muscular lesion. The cutaneous lesions were located on the lower extremities in 12(60%) patients, upper extremities in 7 (35%), head in 4 (20%) and 2 (10%) in trunk. Eight (40%) patients demonstrated cutaneous lesions in two or more locations. In chest radiographic stage, stage 0 was 16 (94.5%)patients, stage I was 2 (11.1%) patients. There is no patient stage II, III and IV.

Systemic involvement during the follow up period

Nine (50.0 %) of 18 patients demonstrated only specific cutaneous

Table1: *Baseline characteristics of patients*

Variables	Number (%)
Sex	
Male	3 (16.7)
Female	15 (83.3)
Age (yr, median ± SD)	48.2 ± 14.1
Follow-up duration (yr, median ± SD)	1.7 ± 0.7
Specific subcutaneous sarcoidosis	17 (94.5)
Non-specific subcutaneous sardoicosis (patch)	1 (5.5)
Specific cutaneous lesion	
Nodulopapules	15 (83.3)
Papules	1 (5.5)
Maculopapular eruption	1 (5.5)
Scar sarcoidosis	0 (0)
Lupus pernio	0 (0)
First manifesation	
Cutaneous and Extracutaneous lesion	1 (5.5)
Cutaneous lesion	15 (83.3)
Extracutaneous lesion	2 (11.1)
Lung and hilar lymphadeopathy	2
Distribution of skin lesion	
Lower extremities	7 (38.9) 12
Upper extremities	1 (5.5) 8
Trunk	0 (0.0) 2
Head	2 (11.1) 4
Neck	0 (0.0) 1
More than one site	8 (44.4) 8
Initial chest radiographic stage	
Stage 0	16 (94.5.0)
Stage I	2 (11.1)
Stage II	0 (0.0)
Stage III	0 (0)
Stage IV	0 (0)

SD: standard deviation

Table 2: *Systemic disease identified during the follow-up periods in patients with subcutaneous sarcoidosis*

Systemic disease	Number (%)
Pulmonary	9 (50%)
Arthritis	3 (16.7)
Spleen	1 (5.5)
Renal, dactylitis, parotitis or mucositis, peripheral neuropathy, Uveitis	0 (0)
More than one site	6 (33.3)

involvement during the follow-up period and the remaining patients presented systemic involvement which included 9 (50.0 %) lymphadenopathy with 4 (22.2 %) lung parenchymal lesion, 3 (16.7%) arthritis, 1 (5.5%) splenic involvement. (Table 2) Subtype of subcutaneous sarcoidosis was not related to systemic involvement.

Association between abnormal laboratory test and abnormal chest radiographs

Serum angiotensin-converting enzyme (ACE) level and erythrocyte sedimentation rate (ESR) in patients with systemic involvement tended to be higher than those without, although there was no statistical significance. (Table 3)

Treatment and response

Fifteen (83.3%) patients were treated with glucocorticoid with or without hydroxychloroquine. Two (11.1%) patients were treated with combination with hydroxychloroquine and colchicine. Six (33.3%) patients presented remission and 9 (50%) patients presented partial remission. Four patients presented with relapse with lung involvement and were treated with oral steroid with azathioprine, which resulted in partial remission. (Table 4)

Table 3: *Association between abnormal laboratory test results and systemic involvement in patients with subcutaneous sarcoidosis*

Laboratory test	No. of pateints with abnormal (elevated) result/ total no. of patients tested (%)	No. of abnormal chest radiograph
Angiotensin-convertingenzyme	6/18 (33.3)	4
Calcium	2/18 (11.1))	2
Erythrocyte sedimentation rate	7/18 (38.9)	4
Gammaglobulin	3/5 (60.0)	1

Table 4:*Treatment and the response of patients with subcutaneous sarcoidosis*

	Number (%)
Primary treatment	
Glucocorticoid	15 (83.3)
Hydroxychloroquine	8 (44.4)
NSAIDs	0 (0.0)
Colchicine	2 (11.1)
Treatment response	
Remission	6 (33.3)
Partial remission	9 (50.0)
Relapse	4 (22.2)

Discussion

Sarcoidosis is a systemic granulomatous disease of unknown origin that can affect any organ in the body. The lung, mediastinal and peripheral lymph nodes, skin, liver, spleen, eyes and parotid glands are commonly involved. Cutaneous involvement is seen in 25% of cases typically at disease outset of sarcoidosis.1 The most frequent specific cutaneous lesions of sarcoidosis are lupus pernio, infiltrated palques, maculopapular eruptions, infiltration of old scars, and subcutaneous sarcoidosis.3,7,11 Subcutaneous sarcoidosis has been reported to occur in 1.4~6% of patients with systemic sarcoidosis10,12 and occur in 11.8~14.4% of patients with cutaneous sarcoidosis. 10,13

In this study, mean age of onset of subcutaneous sarcoidosis was 48.2 years old. This is similar to what has been reported previously3,4,10, but is higher than the first peak average age of onset of sarcoidosis.6,14 Previous studies showed female : male ratio of 1.9:1 ~ 9:1 in subcutaneous sarcoidosis patients.3,4,10 Female : male ratio of this study is 5:1. Most of the skin lesions were seen in the upper limbs in previous studies but our study showed in lower limbs predominantly.

In this study, cutaneous lesions of subcutaneous sarcoidosis were the first manifestation in 15(83.3%) of total patients, similar with other studies.3,8,10 In 66.7% of patients showed systemic involvement which is lower than previous studies (72.2%~80%).4,14 Skin lesions are classified as specific and nonspecific on the basis of the presence or absence of sarcoidal granulomas. Specific skin lesion of sarcoidosis had been considered that have no prognostic significance and is not correlated with the presence of systemic disease.10,15 Subcutaneous sarcoidosis is specific subset of cutaneous sarcoidosis frequently associated with systemic disease.4,10,16 In this study, at the time of diagnosis, 15 (83.3%) of total patients had only subcutaneous sarcoidosis, and 6 (33.3%) patients had additional systemic involvement during follow up. Systemic involvement was present in 50% of patients, which is lower than other studies (64%~100%). In previous studies, 76% to 100% of patients with subcutaneous sarcoidosis had pulmonary involvement4,10, whereas one study in China reported 58.3% with pulmonary involvement.17 In this study, 50.0% of patients had pulmonary involvement, similar to china study. Based on this, Asian patients with subcutaneous sarcoidosis may be relatively less likely to have pulmonary and systemic involvement.

Spontaneous resolution of sarcoidosis is seen in up to 60% of patients. 18 Sarcoidosis is chronic and progressive in only 10–30% of patients, and mortality is observed in 1–5% of cases.19 There are few guidelines for the initiation of therapy for sarcoidosis. An observation of 3–12 months is usually recommended to determine the general course of the disease.6 In treatment of sarcoidosis, there is no standardized indications but drug of choice is corticosteroids when treatment is required. 20 Current regimen for treatment is use of 20–40 mg/day of prednisone for 8–12 weeks, followed by gradual tapering of the dose to 10–20 mg every other day for the 6–12 months until an optimal minimal dose is established.1,10 J. Marcoval et al. showed that 6 of 10 (60%) patients were spontaneously remitted in less than 2 years' time. However, the patients in this study started treatment immediately after diagnosis. So spontaneous remission rate was unknown. In this study, most of the patients had remission or partial remission to steroid therapy, and 4 patients who relapsed showed partial remission to steroid and azathioprine combination therapy.

ACE is produced in epithelioid cells of sarcoid granuloma and clinically it is increasing in 40% of active sarcoidosis patients.6 Although measuring serum ACE could have limitation to diagnose sarcoidosis, patients of specific cutaneous lesions treating with immunosuppression showed decreasing in serum ACE levels which helps to monitor the treatment.4,6,20 In this study, the patients with systemic involve-

ment related more prominence in ACE level and ESR but statistical significance is not shown.

Despite the first case control study of subcutaneous sarcoidosis with clinical characteristics in Korea, it is limited to analyze within a small size. Therefore, studies have to be done with more patients.

Conclusion

Other baseline characteristics were similar to those of previous studies. However, this study showed more lesions in the lower extremities. Serum ACE and ESR level were higher in patients with systemic involvement but not statistically significant. In this study, patients with subcutaneous sarcoidosis showed lower pulmonary and systemic involvement compared to the previous studies. Other studies have reported that subcutaneous sarcoidosis is related to systemic involvement, but it may be different in Asians.

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