

## Original Article

# Comparison of cutaneous sarcoidosis with systemic sarcoidosis: a retrospective analysis

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**Abstract:** Objective: To investigate clinical characteristics and treatment effect of sarcoidosis with cutaneous lesions in Chinese patients, and to compare them with previous works. Methods: Retrospective analysis was conducted based on clinical manifestations, systemic examinations and treatment of biopsy-proved 36 patients with sarcoidosis with cutaneous lesions in our hospital since 2000. Patients were divided into cutaneous sarcoidosis (CS) group without systemic involvement and systemic sarcoidosis (SS) group with systemic involvement according to whether extracutaneous systems were involved. Results: Male to female ratio was 1:4.1 in total 36 patients. Average age of onset was (43.6±15.8) years old in CS group and (54.4±11.5) years old in SS group. The most common cutaneous lesions were papulonodules (41.7%) and frequently found in limbs (61.1%). There were 26 patients in SS group, and lung was the most common organ with systemic involvement, followed by lymph nodes. In SS group, elevation of inflammatory parameters and evident changes of chest radiologic examination were often observed. 72.2% patients were treated with glucocorticoid and the overall therapeutic efficacy rate was 48.4%. The therapeutic efficacy in CS group (80%) was significantly higher than SS group (33.3%). Papulonodules type had better response to therapy and usually resolved after treatment. Lupus pernio type was resistant to treatment. Conclusion: Sarcoidosis occurs more frequently in females. Lung is the most commonly affected extracutaneous organ in SS patients. CS patients have better response to therapy than SS patients. Types of cutaneous lesions and existence of systemic involvement are related to prognosis of cutaneous lesions.

**Keywords:** Cutaneous sarcoidosis, systemic sarcoidosis, prognosis

## Introduction

Sarcoidosis is a multisystemic disease of unknown origin and pathologically characterized by noncaseating granulomas. It may involve multiple organs, including lung, lymph node, joints, skin and eyes. Sarcoidosis with cutaneous lesions accounts for 25-35% of sarcoidosis [1, 2]. The cutaneous lesions are diverse in sarcoidosis, and hence it is usually misdiagnosed. In addition, the relationship between variable clinical manifestations and different treatment responses has not been fully revealed.

To further explore the clinical characteristics and treatment effect of sarcoidosis with cutaneous lesions in Chinese patients, we retrospectively analyzed the clinical manifestations, systemic examinations and treatment of biopsy-proved 36 patients with sarcoidosis in our hospital since 2000.

## Materials and methods

### *Patients and materials*

From 2000 to 2012, a total of 36 patients were diagnosed as sarcoidosis with cutaneous lesions and their clinical information was collected. This study was approved by the Ethics Committee of our hospital, and informed consent was obtained before study. Diagnosis of sarcoidosis was based on clinical manifestations, radiologic examinations and pathologic data, and the other granulomatous diseases were excluded. 36 patients were subjected to skin biopsy and histopathologic examinations were performed. All of the histopathologic data showed the formation of epithelioid noncaseating granulomas, in which variable amounts of multinucleated giant cells and lymphocytes were found, and mycobacteria staining showed negative. Other examinations, including routine blood and urine test, blood biochemical exami-

## Cutaneous sarcoidosis and systemic sarcoidosis

**Table 1.** Clinical information of 36 patients in sarcoidosis with cutaneous lesions

Group	Male (n)	Female (n)	Age of onset (yrs)	Total (%)
CS	3	7	43.6±15.8	10 (27.8)
SS	4	22	54.4±11.5 <sup>#</sup>	26 (72.2)

<sup>#</sup>P<0.05 vs CS group.

**Table 2.** Characteristics of cutaneous lesions in CS group and SS group

Characteristics	CS (%)	SS (%)	Total (%)
Cutaneous manifestation			
papulonodules	4 (40)	11 (42.3)	15 (41.7)
plaques	2 (20)	5 (19.2)	7 (19.4)
erythema nodosum	2 (20)	4 (15.4)	6 (16.7)
subcutaneous nodules	1(10)	4 (15.4)	5 (13.9)
lupus pernio	1 (10)	2 (7.7)	3 (8.3)
annular	0 (0)	2 (7.7)	2 (5.6)
Scar	0 (0)	1 (3.8)	1 (2.8)
Distribution			
Face	3 (30)	7 (26.9)	10 (27.8)
limbs	6 (60)	16 (61.5)	22 (61.1)
Trunk	4 (40)	11 (42.3)	15 (41.7)
Trunk and limbs	2 (20)	8 (30.7)	10 (27.8)
Face, trunk and limbs	1 (10)	4 (15.4)	5 (13.9)

nation, detection of erythrocyte sedimentation rate (ESR), C reactive protein (CRP), antinuclear antibodies (ANA), blood calcium and serum angiotensin-converting enzyme (sACE), PPD (purified protein derivative) skin test, chest computer tomograms (CT), lung function, bronchoscopy, abdominal and thyroid ultrasonography, electrocardiography, bone and joint X-ray and ophthalmic examination, were also performed.

All patients received systemic evaluation and then were divided into cutaneous sarcoidosis (CS) group without systemic involvement and systemic sarcoidosis (SS) group with systemic involvement according to whether extracutaneous systems ( $\geq 1$ ) were affected by sarcoidosis. In this study, there were 10 patients in CS group and 26 patients in SS group.

### Treatments and follow up

Treatment modalities included topical or systemic glucocorticoids (such as prednisone, 30-50 mg/d; the dose varied with patients), immunosuppressants, hydroxychloroquine and topical tacrolimus, etc.

Patients were followed up 6 months later after treatment. The therapeutic efficacy was measured by the reduction in the number and size of the cutaneous lesions. Cure was defined as complete disappearance of cutaneous lesions; effectiveness was defined as reduction of cutaneous lesions by more than 75%; improvement as 25-75%; and ineffectiveness as less than 25%.

### Statistical analysis

Statistical analysis was carried out using SPSS version 19.0 for Windows. Data were expressed as mean  $\pm$  standard deviation ( $\bar{x} \pm s$ ) or percentage. Comparisons were done with *t* test or chi square test. A value of P<0.05 was considered statistically significant.

### Results

#### General information

Among 36 patients of sarcoidosis with cutaneous lesions (**Table 1**), there were 7 males (19.4%) and 29 females (80.6%). The ratio of male to female was 1:4.1. The age of onset ranged from 11 to 72 years old. Seven patients (19.4%) were younger than 40 years old, 10 (27.8%) were 41-50 and 19 (52.8%) were 51 or greater. The duration of disease ranged from 2 months to 11 years. There was remarkable difference in the age of onset between SS group and CS group (P<0.05).

#### Clinical manifestations

Of the 36 enrolled patients, the types of cutaneous lesions (**Table 2**) consisted of papulonodules (n=15; 41.7%), plaques (n=7; 19.4%), erythema nodosum (n=6; 16.7%), subcutaneous nodules, lupus pernio, annular (one case developed cutaneous lesions throughout the trunk and limbs; **Figure 1**) and scar. In some cases, cutaneous lesions were combined with dermatologic symptoms, such as pruritus or pain. Papulonodule was the most common type of skin manifestations, followed by plaques. There was no difference in the type of cutaneous lesions between SS group and CS group. Moreover, cutaneous lesions were most frequently found in limbs in two groups and there was no difference in the distribution of cutaneous lesions between two groups (P>0.05).



**Figure 1.** A female patient in systemic sarcoidosis group developed diffused annular cutaneous lesions on the back.

**Table 3.** Results of chest radiologic examination in SS patients

Group	Hilary or mediastinal lymphadenopathy	Pulmonary infiltration	Patients (%)
SS (lung involvement)	+	-	8 (30.8%)
	+	+	13 (50%)
SS (no lung involvement)	-	-	5 (19.2%)

**Table 4.** Therapeutic efficacy in CS group and SS group

Group	Cure	Effectiveness	Improvement	Ineffectiveness/recurrence	Efficacy rate (%)
CS	6	2	1	1	80.0
SS	3	4	12	2	33.3 <sup>#</sup>
Total	9	6	13	3	48.4

Footnotes: <sup>#</sup>*P*<0.05 vs CS group.

26 patients (72.2%) in SS group had extracutaneous organ involvement. Systemic involvement of sarcoidosis mainly affected the lung and lymph nodes. Of 26 patients, 21 patients had pulmonary impairment, and partly manifested cough, expectoration, chest congestion and fatigue. A few patients were asymptomatic in early stage of disease. Enlargement of lymph node was involved in 14 patients, and the enlargement of neck, axillary, groin and retroauricular lymph nodes was found in 9, 6, 2 and 2 patients, respectively. In addition, joint pain was noted in 5 patients, characterized by joint pain at limbs and joint swelling, but joint deformity was not seen. Ocular lesions were found in 3 patients, and presented with cataracts (n=1), retinal nodular changes (n=1), and iridocyclitis

(n=1). Thyroid lesions were diagnosed in 3 patients who manifested hypothyroidism (n=1) and nodules in neck ultrasonography (n=2). Moreover, 2 patients had concomitant vitiligo (n=1) or alopecia (n=1); 2 patients were diagnosed with gallstones by ultrasonography; 2 patients had ventricular tachycardia in electrocardiography. Furthermore, 12 patients developed non-specific systemic symptoms including fever, fatigue and weight loss.

#### Systemic examinations

In CS group, increased ESR was found in 3 patients, elevated CRP in 2 patients and weakly positive PPD in 1 patient. Other blood tests were normal. In SS group, increased ESR was noted in 12 patients, elevated CRP in 8 patients, elevated sACE in 11 patients, ANA positive in 4 patients and weakly positive PPD in 3 patients. The serum calcium levels were normal in these patients. Moreover, 17 patients underwent bronchoscopy, and bronchoalveolar lavage fluid (BALF) was collected for the detection of cell components and T lymphocyte subgroups. Results showed that in 6 patients (6/17), percentage of lymphocytes in BALF was over 10% and the ratio of CD4+/CD8+ T cell was 3 or greater.

In SS group, chest lesions in radiologic examinations were investigated (Table 3). Of 21 patients with lung involvement, 8 patients had only hilar or mediastinal lymphadenopathy and no pulmonary infiltration (8/26); 13 patients had hilar or mediastinal lymphadenopathy with pulmonary infiltration (13/26).

In SS group, chest lesions in radiologic examinations were investigated (Table 3). Of 21 patients with lung involvement, 8 patients had only hilar or mediastinal lymphadenopathy and no pulmonary infiltration (8/26); 13 patients had hilar or mediastinal lymphadenopathy with pulmonary infiltration (13/26).

#### Treatments

21 patients in SS group received treatment with oral prednisone of which 2 combined with

methotrexate, 2 with Tripterygium Wilfordii, 1 with hydroxychloroquine, 1 with topical corticosteroid and 1 with topical tacrolimus. Of the remaining five patients in SS group, 1 patient treated with Traditional Chinese Medicine, 4 with no treatment. In CS group, 5 patients were treated with oral or topical corticosteroids, 2 with hydroxychloroquine, 1 with thalidomide, 1 with Traditional Chinese Medicine, 1 with excision of cutaneous lesions. In most patients, the cutaneous lesions were improved during 1-2 months after treatment. 31 patients were followed up at 6 months after treatment. Results showed that 9 patients (29.0%) were cured, effectiveness in 6 (19.4%), improvement in 13 (41.9%), ineffectiveness in 2 and recurrence in 1. The overall therapeutic efficacy rate was 48.4% (15/31) among 31 patients. Significant difference was revealed in terms of the therapeutic efficacy rate between CS and SS groups ( $P < 0.05$ , **Table 4**). Remarkably, 3 patients with lupus pernio were non-responsive to treatment or developed recurrence. The papulonodular type was effectively responsive to treatment. Of patients with papulonodular type, cure was found in 7 patients and effectiveness in 6 patients. In SS group, the systemic symptoms and signs were also improved with the resolution of cutaneous lesions.

### Discussion

The incidence of sarcoidosis varies significantly with regions and races, and black population has the highest incidence, followed by white population and yellow population [3-5]. The onset of sarcoidosis has two peaks among populations. The first peak is noted in the third decade of life and the other in people older than 50 years. This report from Chinese patients showed that patients older than 51 years accounted for 52.8% of sarcoidosis with cutaneous lesions, and the disease is more prevalent in females (80.6%) than males. Meanwhile, patients in SS group were 10 years older than those in CS group in terms of the onset age. Similar findings have been previously reported. Chong et al [6] reported that the female patients accounted for about 40% patients with sarcoidosis in Singapore, Collin et al [7] reported that female patients accounted for about 74% patients with sarcoidosis in UK. In South Taiwan, females were as high as 84% of the total patients with sarcoidosis [8].

However, the reasons for higher incidence of sarcoidosis in females are still unclear.

The skin manifestations of sarcoidosis have a wide variety of morphologies [9]. Marcoval et al [10] reported that cutaneous lesions were mainly maculopapules (32.6%) and plaques (36%). Another study [11] also reported that nodular erythema was the most common cutaneous lesion with a high recurrence rate and was related to systemic involvement. In the present series, papulonodules and papules lesions, especially papulonodules ( $n=15$ ; 41.7%), were the most common types of cutaneous manifestations. There was no difference in the type and distribution of cutaneous lesions between SS group and CS group. 2 patients with annular lesions were entirely found in SS group. One of the patients had diffused lesions that distributed throughout the body with mild pruritus, and the lung involvement was also observed. These characteristics in this patient were rarely reported.

In the present study, cutaneous lesions were the most frequently found in limbs (61.1%), followed by the trunk (41.7%) and face (27.8%). There was no significant difference in the distribution of cutaneous lesions between SS group and CS group. On the contrary, Lee et al [8, 12] reported that facial involvement was much more frequent (59%) in Taiwanese. In India, the facial lesions accounted for as high as 65% [13]. In Western countries, about 25% of cutaneous lesions occur on the face [14]. Cutaneous sarcoidosis often occurs ahead of or simultaneously with the presence of systemic sarcoidosis. Thus, the early identification and diagnosis of cutaneous lesions in sarcoidosis is very important. The subsequent systemic examinations may diagnose or exclude the existence of systemic sarcoidosis.

In our cases, systemic involvement was detected in 72.2% of patients with sarcoidosis, and the lung was the most commonly affected organ. In the chest radiologic examinations, bilateral hilar or mediastinal lymphadenopathy with or without intrapulmonary net-like, nodule-like or patchy shadows was the main characteristic. It was reported that 90% of patients with sarcoidosis had lung involvement [15]. In our cases, patients with lung involvement accounted for 58.3% of total patients. This might be attributed to the difference in races and types

of cutaneous lesions in sarcoidosis patients. This also suggests that the skin lesion is not necessarily associated with lung involvement in sarcoidosis. The T lymphocytes and their subgroups in BALF may serve as parameters of activity of sarcoidosis. In SS group, 6 patients had abnormal proportion of T lymphocytes in BALF, which suggested the activity of lung impairment in these patients. sACE is synthesized by vascular endothelial cells, pulmonary capillary epithelial cells and macrophages. sACE can be used as an indicator for the diagnosis and activity of sarcoidosis. sACE usually increase in the acute phase of sarcoidosis [16]. In our series, both elevated sACE and ANA positive were entirely found in patients of SS group. In addition, patients with increased ESR and CRP were also mainly found in SS group. These findings indicated that the elevation of inflammatory parameters (such as ESR, CRP and sACE) may be associated with the high incidence of systemic involvement in sarcoidosis, which was consistent with the report of Collin [7]. In the present report, extrapulmonary involvement of systemic sarcoidosis was mainly found in the lymph nodes, joints and eyes, but less revealed in other organs such as thyroid, heart and kidney. Sharma et al [17] reported that about 1% of sarcoidosis patients had thyroid involvement which was characterized by hyperthyroidism, myxedema or nodular goiter. In our cases, 3 (3/26) patients had thyroid involvement. In addition, 2 patients developed vitiligo or alopecia after the diagnosis of sarcoidosis, which suggested that the pathogenesis of sarcoidosis is related to immunity. Moreover, 2 patients were diagnosed with gallstones and 2 had abnormalities in electrocardiograph. Whether gallstones and abnormal electrocardiograph are associated with sarcoidosis is still uncertain.

For sarcoidosis patients with evident symptoms or rapid progression, treatment with glucocorticoids is preferred. In the active phase, the level of sACE is helpful to monitor the therapeutic efficacy. In our cases, the level of sACE reduced in 8 patients of SS group after treatment with glucocorticoids. Hydroxychloroquine is also a standard drug used in the treatment of sarcoidosis and effective for sarcoidosis with skin or mucosa involvement [18]. For patients non-responsive to glucocorticoids or intolerant to its side effects, immunosuppressants, such

as methotrexate, azathioprine, cyclophosphamide, cyclosporin A and thalidomide, can be used. TNF- $\alpha$  plays an important role in the formation of granulomas in sarcoidosis with rapid progression [19]. Thus, TNF- $\alpha$  may become a target in the treatment of sarcoidosis. Crouser et al [20] applied TNF- $\alpha$  inhibitor (infliximab) to treat with sarcoidosis that had concomitant CD4+ cell reduction and resistance to the routine therapy. Results showed that CD4+ T cells increased significantly after therapy. Hence, they concluded that TNF- $\alpha$  inhibitor is effective for sarcoidosis patients with CD4+ cell reduction.

In our report, 72.2% (26/36) of patients were treated with topical or systemic corticosteroids. Follow up was performed 6 months later, and variable responses to treatment were observed. Results showed that the overall therapeutic efficacy rate was 48.4% (15/31). Moreover, the therapeutic efficacy rate in patients who only had cutaneous lesions (80%) was significantly higher than that in patients associated with systemic involvement (33.3%), which indicated good prognosis in CS group. Thus, our study revealed that the existence of systemic involvement was related to the prognosis of cutaneous lesions. In addition, the types of cutaneous lesions were also associated with the prognosis. Papulonodules lesions had better response to therapy and usually disappeared after therapy. By contrast, lupus pernio lesions were resistant to therapy. We may apply TNF- $\alpha$  inhibitor to these patients who are resistant to standard treatment in the future.

### Conclusion

The incidence and clinical characteristics of sarcoidosis with cutaneous lesions vary with regions and races. The incidence of sarcoidosis with cutaneous lesions has a higher proportion in females in Chinese patients. The patients with systemic sarcoidosis are usually older than those with cutaneous sarcoidosis in terms of the onset age. The cutaneous lesions are mainly papulonodules and frequently found in limbs. The lung is the most commonly affected extracutaneous organ, followed by lymph nodes. The inflammatory parameters usually increase in patients with systemic sarcoidosis. The types of cutaneous lesions and the existence of systemic involvement are related to the prognosis of cutaneous lesions. Thus, the

complete examination and evaluation on patients with sarcoidosis is helpful to predict the treatment responses and prognosis of diseases.

### Disclosure of conflict of interest

None.

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