Cutaneous sarcoidosis
A retrospective case series and a hospital-based case-control study in Taiwan
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Abstract
Sarcoidosis is a systemic granulomatous disorder of unknown etiology often involving skin. Studies on cutaneous sarcoidosis and comorbidities are limited. This study is aimed to describe the clinical features of cutaneous sarcoidosis diagnosed in our hospital and to determine the relationships between cutaneous sarcoidosis and comorbidities.

This retrospective study evaluates patients with cutaneous sarcoidosis in a tertiary center in Taiwan from 1996 to 2015. The records of 38 patients with cutaneous sarcoidosis were reviewed for clinical characteristics and evaluated by analysis of variance. A 1:4 case-control analysis was conducted with 152 age- and sex-matched controls who underwent biopsy for other benign skin tumors.

The male to female ratio was 1:4.4. The average age at diagnosis was 51.7 years. Female patients were on average 13.9 years older than male patients. The correlation of age with gender was statistically significant (P = .037). The most common cutaneous lesions were plaques (47.4%) and confined to the face (71.1%). Of the 38 patients, 26.3% had diabetes mellitus. Age over 40 (P = .014) and female (P = .014) were associated with facial involvement. In the case-control study, a higher percentage of patients with cutaneous sarcoidosis than of control subjects had diabetes mellitus (P = .001), hearing loss (P = .031) and eye diseases (P = .047).

The present study demonstrates a striking female predominance and high proportions of facial involvement. Diabetes mellitus, hearing loss, and eye diseases may be associated with Taiwanese patients with cutaneous sarcoidosis.

Abbreviation: CI = confidence intervals.

Keywords: case-control study, cutaneous sarcoidosis, granulomatous inflammation

1. Introduction
Sarcoidosis is a granulomatous disorder of unknown etiology, often involving multiple organ systems. The most frequently affected organs are the lung and mediastinal lymph nodes, followed by the eyes and skin.[1]

Cutaneous involvement, which usually presents at the onset of sarcoidosis, occurs in 20% to 35% of patients.[2] The recent studies reported the rate of cutaneous involvement up to 30% in Germany and about 33% in France.[3-4]

Skin lesions exhibiting a wide variety make cutaneous sarcoidosis a great masquerader. Clinical morphology of cutaneous sarcoidosis have been well described, including papules, plaques, nodules, scars, and lupus pernio.[2] Annular, angiolupoid, psoriasiform, hypopigmented, atrophic, and ulcerative lesions are relatively uncommon.[3] In histopathology, skin manifestations have been divided into specific and nonspecific lesions. Specific lesions display non-caseating granulomas, whereas nonspecific lesions represent reactive processes without granuloma formation.[6] The most common presentation of the latter is erythema nodosum, which is associated with acute disease and spontaneous resolution.[1]

The epidemiology, clinical features, and outcome of sarcoidosis vary by ethnicity.[7] There is a considerable racial difference showing a higher annual incidence and lifetime risk in African Americans than in whites.[8] Facial involvement and the angiolupoid variant appear more common in Taiwan than in western countries.[9,10] The typical apple-jelly hue, suggestive of a granulomatous process, is rarely observed in dark skin.[11]

Few studies have provided profiles of cutaneous sarcoidosis and comorbidities. The aim of the present study was to investigate the clinical features of cutaneous sarcoidosis diagnosed in a tertiary medical center in Taiwan. We examined the relationships between cutaneous sarcoidosis and comorbidities. We also compared demographic and clinical characteristics of cutaneous sarcoidosis in our study with those in the literature.

2. Methods
From January 1996 to August 2015, patients with diagnosis of cutaneous sarcoidosis were identified using the pathology database of the Department of Dermatology of Kaohsiung...
Chang Gung Memorial Hospital, a tertiary referral medical center in Taiwan. This study was approved by the Institutional Review Board of Chang Gung Medical Foundation.

Patients were included based on pathologic confirmation by skin biopsy as well as clinical and laboratory data. All patients had received skin biopsy which was examined by pathologist. Medical record, clinical photographs, and pathologic slides were all reviewed by 2 dermatologists.

Patients were excluded if their medical records were not available for review of the clinical diagnosis and laboratory data. This query generated cases with both clinically and pathologically confirmed cutaneous sarcoidosis.

The records of 38 patients with cutaneous sarcoidosis were reviewed for clinical characteristics and evaluated by analysis of variance. A 1:4 matched case-control analysis was conducted with 152 controls. As a control group, we collected patients of the same sex and similar age (± 1 year) to those in the cutaneous sarcoidosis group. The control group underwent biopsy for other benign skin tumors in our hospital during January 2014 to August 2015.

2.1. Statistical methods

Because of the small sample size in the case group, Fisher exact test and Pearson chi-square test were conducted to analyze the differences in categorical variables in 2 × 2 and r × c contingency tables, respectively. Logistic regression was performed to predict the relationships between continuous independent variables and dichotomous dependent variables. Cox regression was applied to the matched case-control data. Forward stepwise selection was used in multivariate analysis. All tests were 2 sided. A P value < .05 was considered statistically significant. The 95% confidence intervals (CI) were also calculated. All statistical analyses were performed using SPSS version 17 (SPSS, Inc, Chicago, IL).

3. Results

3.1. Clinical characteristics

Of the 39 patients with a pathologic diagnosis of cutaneous sarcoidosis over the period of 20 years, 1 patient for whom there was no clinical information was excluded. In our data set, there were 38 Taiwanese patients with both clinically and pathologically confirmed cutaneous sarcoidosis. The demographic characteristics of these patients are summarized in Table 1. The male to female ratio was approximately 1:4.4 with 7 males and 31 females. The mean age at diagnosis was 51.7 years (range, 19–76 years; median, 56 years); for males it was 41.7 years (range, 19–63 years; median, 47 years) and for females it was 55.6 years (range, 25–76 years; median, 57 years). Female patients were on average 13.9 years older than male patients at diagnosis. The correlation of age with gender was statistically significant (P = .037). The most common location of skin lesions was confined to the face (71.1%). Ten patients (26.3%) had cutaneous involvement except the face. Only 1 patient (2.6%) presented with lesions on the face and other sites. Eighteen of the 38 patients (47.4%) presented with plaques, 6 (15.8%) showed papules, 12 (31.6%) had nodules, and 2 (5.2%) were scar sarcoidosis. Thirty-four patients (89.5%) had no symptom, 3 patients (7.9%) had itching, and 1 patient (2.6%) complained of pain.

3.2. Lesion distribution and extracutaneous involvement

Age over 40 (P = .014) and female gender (P = .014) was associated with skin lesions confined to the face (Table 2). The morphology of skin lesions was not related to the distribution. There was no significant association among age, gender, lesion distribution, morphology, and extracutaneous involvement.

The common comorbidities reported by decreasing frequency were type 2 diabetes mellitus, dyslipidemia, hypertension, and malignancy (Table 3). Three patients had benign thyroid disorders; hyperthyroidism, thyroid nodules, and subacute thyroiditis. Eye diseases were found in 3 patients with 2 having glaucoma and 1 uveitis. Five patients had malignancy; comprising papillary thyroid carcinoma, gastric cancer, hepatic cell carcinoma, gallbladder carcinoma with hepatic invasion, and acute myeloid leukemia. None of the comorbidities was associated with lesion distribution or extracutaneous involvement.

3.3. Case-control study

A 1:4 case-control analysis was conducted with 152 age- and sex-matched controls, namely, 28 male and 124 female subjects. Considering comorbidities, there were significant relationships of type 2 diabetes mellitus (P < .001; 95% CI, 0.037–0.385), hearing loss (P = .013; 95% CI, 0.007–0.559), eye diseases (P = .031; 95% CI, 0.031–0.801), and dyslipidemia (P = .039; 95% CI, 0.105–0.942) with cutaneous sarcoidosis (Fig. 1). In the multivariate analysis with forward stepwise selection, a higher percentage of patients with cutaneous sarcoidosis than of control subjects had type 2 diabetes mellitus (P = .001; 95% CI, 0.038–0.409), hearing loss (P = .031; 95% CI, 0.005–0.779), and eye diseases (P = .047; 95% CI, 0.005–0.966), but not dyslipidemia (Fig. 1).

4. Discussion

In this study, we observed certain demographic characteristics and comorbidities in the diagnoses of cutaneous sarcoidosis in Taiwan. Comparisons with different races in regions other than
Taiwan, including Lebanon and Singapore, were made. We assessed the differences in comorbidities between the cases with cutaneous sarcoidosis and the controls. The main finding of the study was that cutaneous sarcoidosis was associated with type 2 diabetes mellitus, hearing loss, and eye diseases.

We compared the characteristics of our cutaneous sarcoidosis patients with several previous reported case series focused on different races (Table 4). Our data showed a marked female predominance similar to the ratio reported in Lebanese and a previous case series focused on Taiwanese, but was different from another case series in Singapore. It appears that the average age is older if female gender accounts for a higher proportion among these studies. Women with sarcoidosis were more likely to be over age 40. The trend was consistent with the significant association between older age and female gender in our study.

Over the past decades, the age at diagnosis of sarcoidosis continued to increase in both sexes.[13] In general, cutaneous sarcoidosis predominantly affects middle- and old-age persons. In Wu and Lee’s study, 5 patients (13.5%) were 40 years old or younger whereas 32 (86.4%) were over 40.[10] Those over 40 years also comprised the majority of the patients (81.6%) in the present study. Elderly patients with sarcoidosis had various extrathoracic involvements, including eye, skin, and cardiac lesions as the initial presentation.[12] It reminds clinicians to be alert to the possibility of cutaneous sarcoidosis in these age groups. Up to 71.1% of patients presented with skin lesions confined to the face in the present study. A similar trend of facial involvement and the predominance of the angiolupoid variant were found in another Taiwanese study.[12] It reminds clinicians to be alert to the possibility of cutaneous sarcoidosis in these age groups.

Figure 1. To compare with control group, there were significant relationships of type 2 diabetes mellitus, hearing loss, eye diseases, and dyslipidemia with cutaneous sarcoidosis.
presentations revealed no significant difference between those with and without systemic sarcoidosis.¹⁶

Sarcoidosis was frequently accompanied by hypertension, thyroid disorders, and diabetes mellitus, especially those with multorgan involvement.¹⁷ Sarcoi
dosis in older patients was more likely to have at least a comorbid condition.¹⁷ One meta-
alysis suggested a significant association between sarcoidosis and malignancy.¹₈ The study focused on the association between cutaneous sarcoidosis and comorbidities is limited. Our study showed that cutaneous sarcoidosis was associated with type 2 diabetes mellitus, hearing loss, and eye diseases. Type 2 diabetes mellitus should be investigated in cutaneous sarcoidosis with and without systemic involvement. Involvement of pancreas by sarcoidosis rarely occurs but was not associated with diabetes mellitus in the literature.¹⁹ One study had showed that elevated levels of serum angiotensin-converting enzyme were detected in 24% of 265 patients with diabetes mellitus.²⁰ Elevated angiotensin-converting enzyme in serum could be found in about 60% of patients with sarcoidosis and may reflect the disease activity.²¹ However, the accurate mechanism between sarcoidosis and diabetes mellitus is still unknown.

In patients with cutaneous sarcoidosis, neuropathy-related hearing loss and ophthalmic symptoms need to be kept in mind. Sudden and progressive hearing losses were both reported previously.²²,²³ Fluctuating hearing loss had also been observed.²⁴ Neurosarcoidosis with involvement of eighth nerve should be taken into consideration in patients with cutaneous sarcoidosis. Vasculitis complicated with sarcoidosis had also been considered as the possible cause of hearing loss.

Limitations of our study include retrospective design, referral bias, and a small sample size. A large retrospective study based on multicenter analysis or the Taiwan National Health Insurance Research Database is needed for further survey in Taiwanese population.

5. Conclusions

The present study demonstrates a striking female predominance and high proportions of facial involvement. Type 2 diabetes mellitus, hearing loss, and eye diseases may be associated with Taiwanese patients with cutaneous sarcoidosis.

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