Research Article

Cutaneous Sarcoidosis as a Predictor of Cardiac Sarcoidosis

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Received: 19 April 2021; **Accepted:** 30 April 2021; **Published:** 13 May 2021

Citation: Yuta Norimatsu, Ayumi Yoshizaki, Yuki Ohno, Yuka Mizuno, Haruka Watanabe, Hirohito Kotani, Kazuki M Matsuda, Maiko Fukayama, Ai Kuzumi, Satoshi Ebata, Takemichi Fukasawa, Asako Yoshizaki-Ogawa, Shinichi Sato. Cutaneous Sarcoidosis as a Predictor of Cardiac Sarcoidosis. Archives of Clinical and Biomedical Research 5 (2021): 368-375.

Abstract

Background: Sarcoidosis is a relatively rare, systemic granulomatous disease that occurs in approximately 1–40 per 100,000 individuals but affects Japanese people disproportionately. While sarcoidosis may affect any organ, morbidity and mortality is worst for cases of cardiac sarcoidosis, which is also difficult to diagnose. In this study, we investigated whether cutaneous sarcoidosis, particularly cutaneous sarcoidosis of the face, which is visible and more easily diagnosable, can be a predictor for the development of cardiac sarcoidosis.

Method: We retrospectively examined patients with cutaneous sarcoidosis seen at the Department of Dermatology at the JR Tokyo General Hospital and the Department of Dermatology at the University of Tokyo Hospital between April 1, 2005 and March 31, 2019.

Results: Our study found that sarcoid lesions on the face increased the risk for cardiac sarcoidosis ($p = 0.0090$, odds ratio 20), whereas, sarcoid lesions on the extremities decreased the risk for cardiac sarcoidosis ($p = 0.0387$, odds ratio 0.0961).

Conclusion: Cutaneous sarcoidosis of the face is a strong predictor of cardiac sarcoidosis.

Keywords: Sarcoidosis; Cardiac sarcoidosis; Predictor

Abbreviations

FDG-PET-18F-fluorodeoxyglucose positron emission tomography; MRI - magnetic resonance imaging

1. Introduction

Sarcoidosis is a relatively rare, unexplained systemic granulomatous disease that occurs in 1-40 per 100,000 individuals [1-4]. It affects various organs, including the skin [5], and may be associated with a poor prognosis. Cardiac sarcoidosis is a serious complication that accounts for 77% of deaths in Japanese patients with sarcoidosis [6]. Moreover, two-thirds of sudden deaths in patients with sarcoidosis is attributable to undiagnosed cardiac sarcoidosis [7].

In these patients, cardiac sarcoidosis is often diagnosed only upon autopsy. As such, diagnosing cardiac sarcoidosis early is integral to decreasing disease-related morbidity and mortality. However, patients with cardiac sarcoidosis may present with normal electrocardiograms, so diagnosis through this method is often inadequate [8].

Comparatively, gadolinium-enhanced cardiovascular magnetic resonance imaging (MRI) and/or 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) can detect cardiac sarcoidosis well, but these tests are considered highly invasiveness and expensive [9].

A landmark study on Japanese patients demonstrated that four of out five patients with cardiac sarcoidosis also had cutaneous sarcoidosis that presented with lesions on the face [10].

However, no prior report has investigated whether the presence of facial skin sarcoidosis poses a risk for cardiac sarcoidosis. Cutaneous sarcoidosis occurs in approximately 25% of patients with sarcoidosis [11], and most commonly presents in the lower extremities [12, 13]. Therefore, because cutaneous sarcoidosis is less likely to occur on the face, the presence of facial lesions in cutaneous sarcoidosis may be considered a characteristic index.

If an association between cutaneous sarcoidosis on the face and cardiac sarcoidosis can be established, the dermatologist may play a greater role in diagnosing cardiac sarcoidosis through skin biopsy of similar lesions. We examined whether cutaneous sarcoidosis of the face increased the risk for cardiac sarcoidosis.

2. Method

2.1 Study design

This was a retrospective cohort study. This study was approved by the Ethics Committee of the University of Tokyo Hospital and JR Tokyo General Hospital.

2.2 Patient selection and data classification

Patients with pathologically diagnosed cutaneous sarcoidosis who visited the Department of Dermatology at JR Tokyo General Hospital or the Department of Dermatology at the University of Tokyo Hospital between April 1, 2005, and March 31, 2019, were included in our study. Sarcoidosis was diagnosed in accordance with the data in the joint statement on sarcoidosis given by the American

Thoracic Society, European Respiratory Society, and World Association of Sarcoidosis and Other Granulomatous Disorders [14]. All patients underwent electrocardiography and echocardiography. Gadolinium-enhanced cardiovascular (MRI) and/or FDG-PET was performed at least once in all patients.

The eruption site of cutaneous sarcoidosis in each patient was recorded and classified as being on the face, trunk, or extremities. Patients with multiple eruption sites were excluded from our study. The presence or absence of concomitant cardiac sarcoidosis was also collected from the medical records.

2.3 Analysis

For statistical analysis, we used the Mann-Whitney U test and Fisher's exact test. Statistical significance was set at $P < 0.05$. Prism 8 (GraphPad Software Inc.) was used for the statistical analyses.

3. Results

We identified 58 patients with cutaneous sarcoidosis. Seventeen cases were excluded from the study because the eruption spanned multiple areas. Table 1 shows the characteristics of the 41 patients included in our study.

We examined the association between lesions in the face, trunk, and extremities, and cardiac sarcoidosis. We found that facial rashes increased the risk for cardiac sarcoidosis ($p = 0.0090$, Odds ratio 20) (Table 2); there was no association between truncal rash and cardiac sarcoidosis ($p > 0.9999$) (Table 3); and the absence of lesions on the extremities slightly decreased the risk for cardiac sarcoidosis ($p = 0.0387$, Odds ratio 0.0961). (Table 4).There was no correlation between angiotensin-1-converting enzyme and the soluble interleukin-2 receptor (Table 5). The types of cutaneous sarcoidosis are summarized in Table 6.

Patient characteristics	
Male: Female	11:30
Age (mean ± SD[†])	55.27 ± 16.32
Number of years from the onset of sarcoidosis to the onset of cutaneous sarcoidosis (mean ±SD)	4.049 ± 5.196
Number of years from the onset of sarcoidosis to the onset of cardiac sarcoidosis (mean ±SD)	5.600 ± 4.561
Angiotensin-1-converting enzyme (mean ±SD)	18.65 ± 7.300
Lysozyme (mean ±SD)	7.750 ± 3.182
Soluble interleukin-2 receptor (mean ±SD)	804.3 ± 606.6

Fisher's exact test or Mann–Whitney U test was used for statistical analysis.
[†] standard deviation (SD)

Table 1: Patient characteristics.

	Cutaneous sarcoidosis + (face)	**Cutaneous sarcoidosis - (face)**	**Total**
Cardiac Sarcoidosis +	4	1	5
Cardiac Sarcoidosis -	6	30	36
Total	10	31	41

Fisher's chi-square test (for categorical variables): p-value = 0.0090
Odds ratio: 20

Table 2: Relationship between cutaneous sarcoidosis (face) and cardiac sarcoidosis.

	Cutaneous sarcoidosis + (trunk)	**Cutaneous sarcoidosis - (trunk)**	**Total**
Cardiac Sarcoidosis +	0	5	5
Cardiac Sarcoidosis -	4	32	36
Total	4	37	41

Fisher's chi-square test (for categorical variables): p-value > 0.9999
Odds ratio: not assessed

Table 3: Relationship between cutaneous sarcoidosis (trunk) and cardiac sarcoidosis.

	Cutaneous sarcoidosis + (upper or lower extremity)	**Cutaneous sarcoidosis – (upper or lower extremity)**	**Total**
Cardiac Sarcoidosis +	1	4	5
Cardiac Sarcoidosis -	26	10	36
Total	27	14	41

Fisher's chi-square test (for categorical variables): p-value = 0.0387
Odds ratio: 0.096

Table 4: Relationship between cutaneous sarcoidosis (upper or lower extremity) and cardiac sarcoidosis.

	Angiotensin-1-converting enzyme			**Soluble interleukin-2 receptor**		
	Symptom + (mean ± SD)	Symptom – (mean ± SD)	P-value	Symptom + (mean ± SD)	Symptom – (mean ± SD)	P-value
Face	22.19 ± 9.169	17.51 ± 6.374	0.2990	569	823.9 ± 629.3	-
Trunk	16.60 ± 7.979	18.83 ± 7.339	0.9335	722 ± 140	819.3 ± 661.9	0.5128
Upper or lower extremity	17.68 ± 6.475	20.43 ± 8.614	0.4746	844.3 ± 692.1	671.0 ± 132.7	0.6923
Cardiac	15.70 ± 8.938	19.11 ± 7.068	0.7101	569	823.9 ± 629.3	-

Fisher's exact test or the Mann-Whitney U test was used for statistics.
SD; standard deviation

Table 5: Patient blood test results.

	Cardiac sarcoidosis +			**Cardiac sarcoidosis -**		
	Face	Trunk	Upper or Lower Extremity	Face	Trunk	Upper or Lower Extremity
Nodule	2	0	0	1	1	4
Nail	0	0	0	0	0	1
Erythema	0	0	0	0	0	1
Plaque	0	0	0	0	0	1
Unknown	2	0	1	5	3	19

Table 6: Type of lesion in patients with cutaneous sarcoidosis.

4. Discussion

Our results suggest that cutaneous sarcoidosis of the face increases the risk for cardiac sarcoidosis, while cutaneous sarcoidosis of the extremities reduces the risk for cardiac sarcoidosis. The association between cutaneous sarcoidosis of the face and cardiac sarcoidosis was first reported by Okamoto et al. [10] in their study of five Japanese patients. Another report examined 12 Japanese patients with cutaneous sarcoidosis. Four of the twelve patients also had cardiac sarcoidosis. Among the four patients with cutaneous sarcoidosis and cardiac sarcoidosis, three patients had facial plaque-type cutaneous sarcoidosis [15]. As such, the association between cutaneous sarcoidosis of the face and cardiac sarcoidosis has been documented in existing reports, as well as in our study.

Our study showed that cutaneous sarcoidosis of the face statistically increased the risk for cardiac sarcoidosis. In our study, there were four patients with cutaneous sarcoidosis of the face and cardiac sarcoidosis. Two of these patients had nodule-type cutaneous lesions, whereas the other two patients had no available data (Table 6). Comparatively, previous reports have only suggested an association between cutaneous sarcoidosis with plaque-type facial lesions and cardiac sarcoidosis [15]. While our results are inconsistent with these reports, the combined data also suggest that cutaneous sarcoidosis of the face, regardless of the lesion type, is an important factor.

On the other hand, in a study of 13 Caucasian patients with cutaneous sarcoidosis, only one case had cardiac sarcoidosis [16]. From this report, it was unclear whether the cutaneous lesions in these patients were located on the face, trunk, or extremities. However, racial differences in sarcoidosis do exist. In Japan, the proportion of cardiac sarcoidosis and ocular sarcoidosis is higher than in other regions. Cardiomyopathy is also the most common cause of death in patients with sarcoidosis in Japan [6, 17, 18], whereas respiratory failure is the most common cause of death for patients in other regions [19, 20].

As such, in light of these known data and considering the study that examined 12 Japanese patients and ours, it may be concluded that Caucasians patients with cutaneous sarcoidosis are less likely than Japanese patients with cutaneous sarcoidosis to develop cardiac sarcoidosis [15].

It is also noteworthy that our study showed that cardiac sarcoidosis was less likely to develop when cutaneous sarcoidosis is observed in the extremities. Doherty and Rosen examined 12 cases of cutaneous sarcoidosis, of which eight, three, and one case had lesions in the face, lower extremities, and entire body, respectively. In their study, cardiac sarcoidosis was observed in 1 of the 3 cases with cutaneous sarcoidosis of the lower extremities [15]. Cutaneous sarcoidosis of the lower extremities is relatively common in Japan. In our study, 25 of the 41 cases showed involvement of the lower limbs and comprised the majority [12, 13]. It is possible that some cases of cutaneous sarcoidosis of the lower extremities have been overlooked, especially because it is difficult or time-consuming to diagnose [21]. Therefore, it is highly likely that the number of cases, particularly in the study by Doherty and Rosen, are also underestimated.

Various causes for cutaneous sarcoidosis of the face have been considered, but none have been confirmed [22, 23]. *Propionibacterium acne* and pine pollen are often cited as examples, because they easily come into contact with the face. However, *Propionibacterium acne* and pine pollen may just as easily come into contact with the palms and lower limbs. It is unknown whether any of the patients in our study had a previous history of acne vulgaris.

Cutaneous sarcoidosis has also been studied as possible sequelae of malignant tumors [24]. However, this association may have been identified due to a reporting bias, because the study that identified it was a retrospective review. This study also examined non-Japanese patients, so its findings may not be applicable to Japanese patients. In our study, there was only one patient with a malignant tumor.

In contrast, the studies by Okamoto et al. and Nakamura et al. all involved Japanese patients [10, 15]. Diffuse infiltrative erythema of the face and cardiac sarcoidosis are generally more common in Japanese patients with sarcoidosis than in other races. As such, this result may be peculiar only to Japanese patients [25, 26]. We were unable to analyze cutaneous sarcoidosis in terms of its different skin lesion types, because these data were usually not reported.

Our study followed a retrospective design. Future prospective studies may shed more light on sarcoidosis as a whole. We also recommend examining patients with cutaneous sarcoidosis with lesions in multiple parts of the body, because we excluded these patients in the current study. In conclusion, among Japanese patients with cutaneous sarcoidosis, lesions on the face and limbs may increase and reduce the risk for cardiac sarcoidosis, respectively.

Acknowledgements

No funding was received from private, public, or not-for-profit agencies.

Conflicts of Interest

The authors declare no conflicts of interest.

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