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Scar Sarcoidosis: A Retrospective Investigation into Its Peculiar Clinicopathologic Presentation

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Background: Scar sarcoidosis (SS), a rare form of cutaneous sarcoidosis, develops from preexisting scars. Owing to its rarity, the clinicopathologic features and its significance in clinical prognosis have been obscure.
Objective: This study aimed to investigate clinical, laboratory and histopathologic findings and to clarify characteristics associated with the development of SS and systemic involvement.
Methods: We retrospectively assessed clinical, laboratory and histopathologic findings of SS. Clinical factors including demographics, anatomic area, number of lesion (single, multiple), presence of symptoms, latent period, injury types related to scar and the proportion of systemic involvement were investigated.
Results: Of the 21 patients with SS, skin lesions appeared predominantly in females (85.7%) and in the head and neck (57.1%). The mean latent period was 163.5 months and 13 patients (61.9%) had multiple lesions. Injury types were varied, with no specific type identified as associated with SS. Histologically, discrete sarcoidal granulomas surrounded by densely packed collagen bundles with a thickening of numerous fibers were observed. Ten patients (47.6%) had systemic involvement and showed significantly more of the multiple lesions, longer latent period and higher level of mean serum angiotensin-converting enzyme than those without systemic involvement.
Conclusion: Various causes of scar were related to SS, but no specific injury type was identified as leading to SS. Although the exact pathomechanism remains unclear, the possibility of systemic involvement could be considered when the patients have multiple lesions, longstanding scars, and elevated serum angiotensin-converting enzyme.

Keywords: Granuloma, Sarcoidosis, Scar

INTRODUCTION

Cutaneous sarcoidosis (CS) accounts for nearly 25% of sarcoidosis[1]. It can manifest as an isolated feature of the sarcoidosis or as one of a constellation of features of systemic sarcoidosis[2]. Of note, scar tissue could be one of the vulnerable sites for CS. Scar sarcoidosis (SS) is defined as CS arising from preexisting scars and could be clinically recognized by color change (dusky red or purple), induration and increased size of the scar[3]. SS has been mentioned in several case reports and briefly in a few research of CS[4,5]. A wide range of physical injuries, including venipuncture, burn, laser ablation and procedures associated with cosmetic surgery have been suggested as possible triggers of SS[6-9]. In CS, the estimated proportion of SS has ranged from 3.0% to 12.0%[4,5].

Until now, reporting on SS has been limited regarding comprehensive clinical features, prognosis regarding systemic progression. Therefore, we performed a retrospective analysis of 21 patients with SS who visited our institution over a 10-year period.

MATERIALS AND METHODS

Study population and design

This study was approved by the institutional review board of our hospital (IRB no. H-1903-023-077). We retrospectively identified the subjects diagnosed with SS through our patient record database from July 2009 to October 2018. The diagnosis of SS was made based on the medical history and histopathological features. All patients had a previous history of extrinsic injury and subsequent scar formation before the onset of SS. We assessed their clinical, laboratory and histopathologic information. The clinical findings included demographics, anatomic area, number of lesion (single, multiple), presence of symptoms, latent period, the injury types related to the scar, and the proportion of systemic sarcoidosis. We divided the involved anatomic areas into head and neck, trunk, upper extremities, and lower extremities. "Multiple" was designated when SS occurred as 2 or more lesions regardless of anatomic area. The latent period of SS was defined as the period from initial scar formation to the occurrence of SS. The injury types related to the scar were categorized into 4 domains as follows: (i) surgical procedure, (ii) injection-related injury, (iii) accidental trauma, and (iv) unknown cause.

We also performed a laboratory investigation including routine complete blood count, liver function test, ionized calcium, and serum angiotensin-converting enzymes (ACE). Histopathologic findings were categorized as follows: (i) the predominant location of granuloma. Because the extent of infiltrating area was mostly overlapped, we separated the location as superficial to deep dermis /deep dermis to subcutaneous tissue/superficial dermis to subcutaneous tissue. (ii) The degree of inflammatory cells (lymphocyte, plasma cells, and giant cells) infiltrating the granulomas. Due to the absence of standardized degree stratification, it was classified into '+/–' to '++' by partially modifying the method used in the previous literature[10-12]. If the inflammatory cells scarcely observed, it was marked as '+/–', when remarkable and easily observed, it was marked as '++', and '+' for the intermediate level. (iii) The degree of stromal fibroplasia, characterized by the prominent dermal fibrosis (like scar tissue) around the granulomas and the overall interstitial area. We stratified the degree of fibrosis according to the above criteria in (ii). (iv) The presence of necrotic change and foreign materials.

Additionally, all patients were divided according to whether there was systemic involvement or not, and this was evaluated in detail by ophthalmology, pulmonology, and other departments that require specialized evaluation. Furthermore, the relevant factors were evaluated for association with systemic involvement. Finally, we assessed the clinical, laboratory, and histopathologic differences between SS with and without systemic sarcoidosis.

Statistical analysis

All statistical analyses were performed using IBM SPSS (ver. 21; IBM Corp., Armonk, NY, USA). Categorical variables and continuous variables were described using absolute and relative frequencies, means and standard deviations, respectively. For comparison of the investigated data between the groups with and without extracutaneous involvement, Fisher's exact test was used to compare categorical variables (e.g., the presence of multiple lesions), whereas two-independent samples t-test was used with continuous variables (e.g., mean latent period). A *p*-value of less than 0.05 was considered statistically significant.

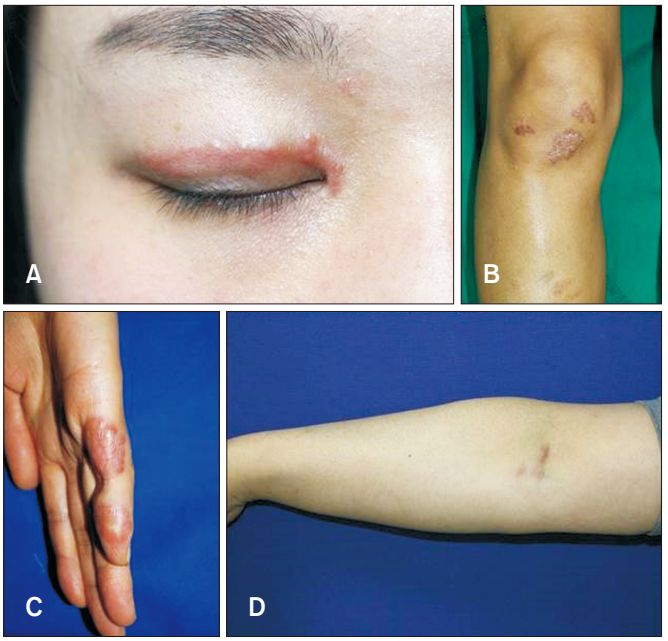

Fig. 1. Representative cases of scar sarcoidosis related with various injury types. (A) Blepharoplasty. (B) Fall down injury. (C) Repair of laceration. (D) Venipuncture.

RESULTS

Clinicolaboratory characteristics

A total of 21 patients with SS were enrolled in the study. The mean age was 50.0 years and the female predominance was observed (85.7%). Regional predilection was found in the head and neck (57.1%) followed by upper extremities, lower extremities, and trunk. About two-thirds (61.9%) had multiple lesions. With regard to symptoms, 11 patients (52.4%) were asymptomatic and 10 patients (47.6%) had mild itching or pain. The latent period was variable from 3.0 to 420.0 months with the mean period of 163.5 months. The injury types were varied as follows (Fig. 1): i) surgical procedure (e.g., mass excision, repair of laceration, blepharoplasty, caesarean section), ii) injection-related injury (e.g., venipuncture, filler, botulinum toxin, unknown material), iii) accidental trauma (e.g., fall, penetrating injury, burn), iv) unknown. The most frequent type was surgical procedure with eight patients (38.1%). Ten patients (47.6%) showed systemic involvement and lung involvement was the most frequent with nine patients, followed by the eye with two patients. Only one patient had both lung and eye involvement. In laboratory profile, only the mean serum ACE was abnormally increased to 64.5 IU/L while other laboratory findings remained within the normal range (Table 1, 2).

Table 1. Clinical findings of scar sarcoidosis (n=21)

Parameter	Value
Age (yr)	50.0±7.7 (25.0~62.0)
Sex	
Male	3 (14.3)
Female	18 (85.7)
Anatomical distribution	
Head & neck	12 (57.1)
Trunk	7 (33.3)
Upper extremities	9 (42.9)
Lower extremities	8 (38.1)
Latent period (mo)	163.5±126.0 (3.0~420.0)
Presence of symptoms	10 (47.6)
Occurrence pattern	
Multiple	13 (61.9)
Single	8 (38.1)
Extracutaneous manifestation*	
Pulmonary	9 (42.9)
Opthalmic	2 (9.5)

Values are presented as mean±standard deviation (range) or number (%). *One patient showed coexistence of ophthalmic and pulmonary involvement.

Histopathologic findings

All specimens showed typical sarcoid granulomas, most of which were distributed in the superficial to deep dermis (57.1%) and the others were distributed in the deep dermis to subcutaneous tissue (33.3%), superficial dermis to subcutaneous tissue (9.5%), respectively. The degree of infiltration of lymphocytes and plasma cells around the granulomas was scarce in most patients (57.1%, 66.7%). Giant cells were present in all specimens and the majority showed moderate infiltration (52.4%). All specimens showed abnormal fibrous stromal change of the dermis, such as densely packed collagen bundles with a thickening of numerous fibers, which mostly revealed moderate severity (47.6%). Necrotizing change was found in only one patient (4.8%) and the presence of a foreign body reaction was noticed in two patients (9.5%) (Table 3, Fig. 2).

Comparison according to the presence or absence of systemic involvement

The mean latent period was 236.8 months in the group with systemic involvement and 84.9 months in the group without it (p=0.002). Also, the occurrence of multiple lesions was found in nine patients (90.0%) with systemic involvement and four

Table 2. Injury types associated with scar sarcoidosis (n=21)

Injury type	Value
Surgery	8 (38.1)
Mass excision	3 (37.5)
Repair of laceration	2 (25.0)
Blepharoplasty	2 (25.0)
Caesarean section	1 (12.5)
Injection-related injury	6 (28.6)
Filler injection	2 (33.3)
Venipuncture	2 (33.3)
Botulinum injection	1 (16.7)
Unknown	1 (16.7)
Accidental trauma	4 (19.0)
Fall down	2 (50.0)
Penetrating injury	1 (25.0)
Burn	1 (25.0)
Unknown	3 (14.3)

Values are presented as number (%) and the proportions within each category of injury are presented.

patients (36.4%) without it (p=0.024). In the laboratory testing, only the mean ACE showed a distinctively higher level to 75.4 IU/L in patients with systemic involvement than in patients without it which showed 45.4 IU/L (p=0.003) (Table 4).

DISCUSSION

Among the various specific forms of the CS, only SS is associated with preexisting cutaneous lesions as could be deduced from its name. SS can be limited solely to the skin, but it sometimes precede or accompany the systemic involvement.

Table 3. Histopathologic findings of scar sarcoidosis (n=21)

Parameter	Value
Location of granuloma	
Papillary to reticular dermis	12 (57.1)
Reticular dermis to subcutaneous tissue	7 (33.3)
Entire dermis to subcutaneous tissue	2 (9.5)
Lymphocyte	
±/+	12 (57.1)
++	6 (28.6)
+++	3 (14.3)
Plasma cell	
±/+	14 (66.7)
++	6 (28.6)
+++	1 (4.7)
Giant cell	
±/+	6 (28.6)
++	11 (52.4)
+++	4 (19.0)
Stromal fibroplasia	
±/+	6 (28.6)
++	10 (47.6)
+++	5 (23.8)
Necrotic change	1 (4.8)
Foreign body	2 (9.5)

Values are presented as number (%).

Although SS might have intriguing characteristic findings, the reporting of the clinical data has been very limited and we found only one article in dermatologic field[13].

With regard to demographics, SS showed middle-age and female dominance, which was similar findings of CS[4]. But the proportion of female dominance (85.7%) was particularly higher compared to CS and this finding was also demonstrat-

Table 4. Comparison of clinicolaboratory features according to the presence or absence of systemic involvement

Parameter	Without systemic involvement (n=11)	With systemic involvement (n=10)	p-value
Demographic			
Mean age (yr)	52.3±4.4	47.2±9.8	0.137
Sex (male:female)	1:4.5	1:9.0	1.000
Clinical finding			
Mean latent period (mo)	84.9±76.5	236.8±110.5	0.002
Presence of symptoms (%)	6 (54.5)	4 (40.0)	0.395
Multiple lesions (%)	4 (36.4)	9 (90.0)	0.024
Anatomical distribution (%)			
Head & neck	6 (54.5)	6 (60.0)	1.000
Trunk	4 (36.4)	3 (30.0)	1.000
Upper extremities	3 (27.3)	6 (60.0)	0.198
Lower extremities	6 (54.5)	2 (20.0)	0.183
Injury types (%)			
Surgery	5 (45.4)	3 (30.0)	0.659
Accidental trauma	2 (18.2)	2 (20.0)	1.000
Injection-related injury	3 (27.3)	3 (30.0)	1.000
Unknown	1 (9.1)	2 (20.0)	0.586
Laboratory profiles			
Serum ACE (IU/L)	45.4±14.8	75.4±24.0	0.003
Serum ionized calcium (mmol/L)	1.22±0.06	1.25±0.04	0.137

Values are presented as mean±standard deviation or number (%). Two-independent samples t-test and Fisher's exact test were used to compare the variables between two groups. ACE: angiotensin-converting enzymes.

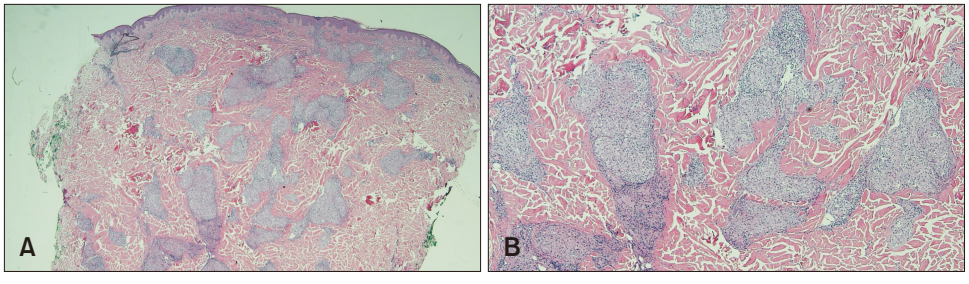

Fig. 2. Representative histologic figures of scar sarcoidosis. (A) Various sized sarcoidal granulomas infiltrating from superficial to deep dermis (H&E, ×20). (B) Thick and densely packed collagen fibers diffusely located between granulomas and stroma (H&E, ×40).

ed in recent study of SS (90.9%)[14,15]. Although we suspected that a specific injury type could be more related to SS, the injury types were quite varied. One of the intriguing injuries related to SS was blepharoplasty reported to present on the both eyelids or a single eyelid[9,16]. Some authors stated that the difference in surgical technique or postoperative care had resulted in an asymmetry of lesion development[17]. However, there is no identified mechanism for why SS occurs in only one eyelid, even though the patients were treated bilaterally.

Presence of symptoms could be related to increased disease activity, but nearly half of the patients in our series were asymptomatic and did not show any significant correlation with systemic involvement[3,18]. The latent period of SS has been variably reported from months to decades and our findings were within this range[19]. One of the longest latent periods of SS was 50.0 years, which emanated from scars by fall injury[20]. Kim et al.[21] suggested that external stimuli could be associated as a triggering factor for the reactivation of the stabilized scar. However, we could not identified any causative external stimuli before the onset of SS.

Histologically, our findings were similar to previous studies of CS in that proportion of infiltrating cell type[10,12,15]. Yet, compared to CS, we found distinct stromal fibroplasia around naked granuloma and hypertrophic scar-like changes, more frequently up to 71.4%. In CS, the fibrotic change was noted mainly on the granulomatous portions at a rate of 1.0%~14.0%[12,15,16]. Rarely, a foreign body reaction is also reported in CS ranged from 10.0% to 50.0%[22,23]. Sarcoidosis and foreign body granuloma are not mutually exclusive. One of the proposed mechanism is that the formation of sarcoid granuloma could be initiated by prolonged antigen (a so-called nidus of sarcoid granuloma) presentation[10].

The proportion of systemic involvement in CS was reported in 62.0% to 85.7%[4,6,18]. The relevant factors associated with this include race (African-American and South Asian[4]), specific lesions (ulcer[2], lupus pernio[5], and angiolupoid[16]), and high titer of ACE[24]. Although there were reports that SS itself may be a predictor, up to 78% in a large scale study, this assertion seems to have some discrepancy with our data[5]. Moreover, this proportion has been reported in a rather various range (20.0%~60.0%) in other studies[10,15]. We found that the relevant factors were the multiple lesions, long latent period, and elevated ACE. Contrary to these findings, one previous study of CS showed there was no relationship between extent of lesions and systemic progression[5]. But our study included only SS, and this relationship could be different among the clinical subtypes of CS. Long latent period could be associated with systemic involvement, because the greater exposure to the pathogenic antigen, the higher possibility that chronic inflammatory process could get systemically worsen. ACE is produced by epithelioid cells of sarcoidal granulomas, which are helpful for the diagnosis of sarcoidosis[3]. This increase was frequently found associated with a specific form of CS and disease progression in a recent research[24]. We found that this association also coincided with SS for systemic involvement.

Our study was limited by its retrospective design and small sample size. There could be the potential for recall bias of some clinical factors such as onset of injury, latent period and exact injury type. Especially in terms of latent period, most SS developed from scars with more than one year duration, and this can be limitation of this study. Furthermore, since the number of patients with systemic organ involvement may increase with continuous follow-up, this can be another limitation of present study. Further large-scale clinical research is necessary to better clarify our results.

In conclusion, we investigated the clinicopathologic features including injury types and the factors associated with systemic involvement in SS. There was no substantiated specific injury type identified as leading to SS. As well, the propensity toward systemic involvement could be more pronounced when SS patients have multiple lesions, longstanding scars, and elevated serum ACE. Although the pathomechanism and clinical significance have been limitedly explored, our findings could help understanding the nature of SS and dealing with it.

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The patients in this manuscript have given written informed consent to publication of their case details including photography.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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