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Sarcoidal granuloma presenting on tattoo: a report of a Japanese female patient and a review of Japanese published work

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Abstract. *Background:* Cases of tattoo sarcoidosis reported in English and French literature have recently been reviewed; however, only two Japanese patients were included in the review because most Japanese patients were reported in Japanese journals. *Objectives:* To determine the clinical characteristics of Japanese tattoo sarcoidosis. *Methods:* We reported a Japanese female with tattoo sarcoidosis, and reviewed the cases of tattoo sarcoidosis reported in Japanese literature. *Results:* A 27-year-old Japanese female presented with skin nodules on a tattoo. She was diagnosed as having systemic sarcoidosis by skin biopsies and systemic work-up. We identified twelve cases, including ours, with tattoo sarcoidosis reported in Japanese journals, and revealed that these cases showed clinical features closely similar to those of Japanese sarcoidosis without tattoo in terms of the onset age distributions, incidence of extracutaneous organ involvement, and laboratory abnormalities. In comparison with cases of other races, Japanese tattoo sarcoidosis was revealed to have a higher prevalence of uveitis, which might be attributable to genetic background, as incidence and organ involvement may vary from race to race. *Conclusions:* Our results suggest that a tattoo does not have significant impact on the clinical features of sarcoidosis. However, skin lesions on a tattoo can be the first sign of systemic sarcoidosis in any race; therefore, much attention should be paid to skin eruptions on a tattoo for earlier identification of patients who need work-up for systemic illness. *(Sarcoidosis Vasc Diffuse Lung Dis 2016; 33: 83-89)*

Key words: intrathoracic lymphadenopathy, Japanese, sarcoidosis, tattoo, uveitis

Introduction

Sarcoidosis is a systemic inflammatory disease that can involve multiple organs simultaneously. It forms non-caseating epithelioid granulomas at the affected organs. Although the exact pathogenesis is still unclear, it is suspected that exposure to certain extrinsic antigens, such as infectious, organic, and inorganic agents, in a genetically susceptible individual leads to the activation of inflammatory pathways that promote the formation of sarcoidal granulomas (1, 2). Skin lesions of sarcoidosis are usually classified into various subtypes, for example, papular, plaque, subcutaneous, ichthyosiform, and lupus pernio. Scar sarcoidosis is a variant of cutaneous sarcoidosis that appears in pre-existing scars caused by trauma, surgical procedures, and infections such as herpes zoster. Tattoo and permanent make-up are also known precursor conditions that often develop scar sarcoidosis. Since the first report by Madden in

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1939, many cases of sarcoidosis on tattoos have been reported. Kluger recently reviewed cases of sarcoidosis on tattoos reported in English and French-language literature (3); however, only two Japanese patients have been included in the review (4, 5), as most Japanese patients were reported in Japanese journals. We herein report a female case of tattoo sarcoidosis with a review of Japanese published cases in order to determine the clinical characteristics of Japanese tattoo sarcoidosis.

Case Report

A 27-year-old woman with no significant medical history presented with multiple, asymptomatic nodules on the back and nose. She received a multicolored tattoo on her upper back at the age of 21, and noticed eruptions on the tattooed region one year prior to visiting our department. On first examination, multiple nodules were observed on the upper back along the green-colored outlines of the tattoo (Figure 1A). Two small, non-scaly, red nodules were also seen in close proximity to each other on the right ala of her nose (Figure 1B). A biopsy of a nodule on the back showed massive, well-formed granulomatous infiltrates composed of epithelioid histiocytes with a low number of lymphocytes (Figure 2). The granulomas were non-caseating and negative for periodic acid-Schiff, Grocott, and Zeil-Neelsen stains. In the upper dermis, numerous dark-brownish, fine particles were present, which were mainly located at the periphery of the granulomas. Another biopsy taken from a nodule on the nose showed similar histological features, except for the absence of the foreign materials. These histological features suggested the diagnosis of sarcoidosis. Routine laboratory tests, including serum levels of calcium and angiotensin-converting enzyme, were normal and autoantibodies were negative. Uveitis was not observed on ophthalmologic examination. A computed tomography scan revealed mediastinal and left hilar lymphadenopathies, and miliary-sized nodules scattered in the lung. Based on these findings, we diagnosed her as having sarcoidosis. The skin nodules were treated with topical steroid, which

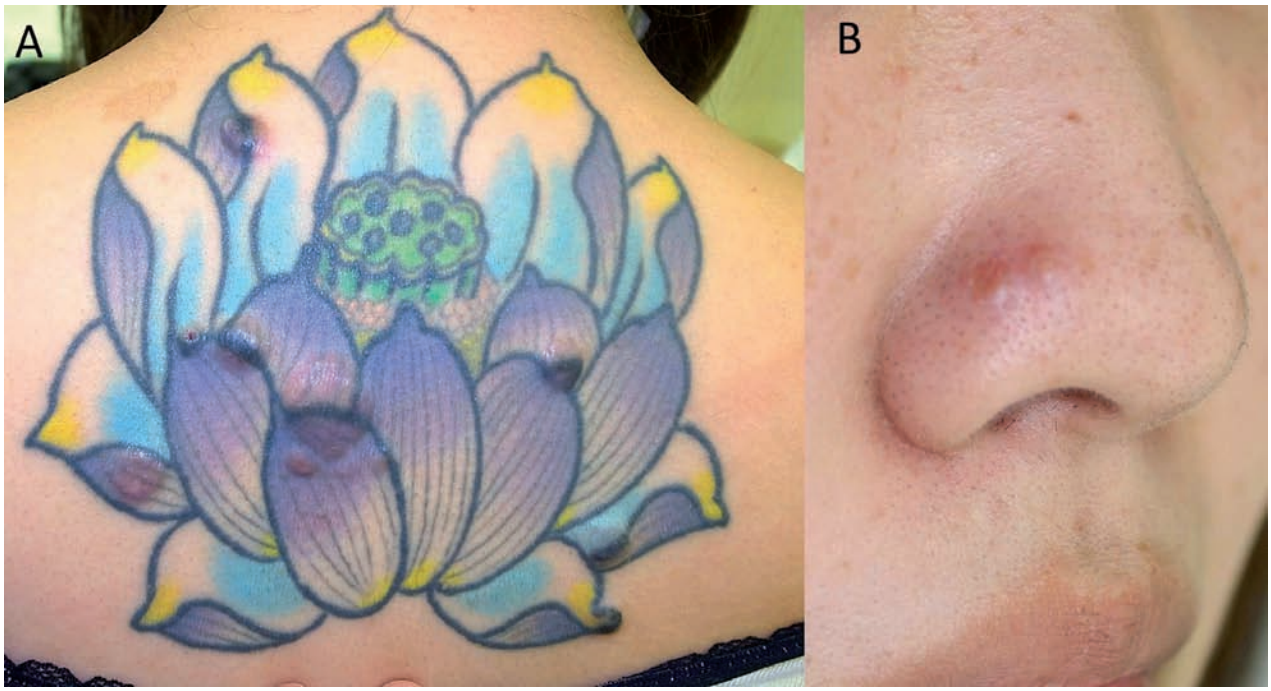

Fig. 2. Clinical manifestations of the present patient. A) Multi-colored tattoo on the upper back. Various sized, slightly red nodules presented along the green lines of tattoo. B) Two small, non-scaly, red nodules were also seen in close proximity to each other on the right ala of her nose

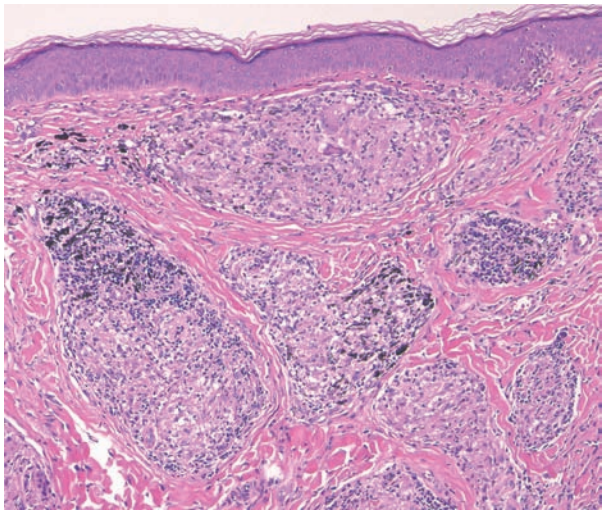

Fig. 2. Biopsy findings of the nodule on the back. Many well-formed granulomatous infiltrates composed of epithelioid histiocytes and a low number of lymphocytes were seen. The granulomas were non-caseating, and contain numerous foreign particles, which were mainly located at the periphery of the granuloma

resolved without scarring within two months. Since, she has been followed up without any treatment, and disease progression has not been observed.

Discussion

Sarcoidosis is a multiorgan disease that most frequently involves the intrathoraciclymph nodes, including the hilar and mediastinal lymph nodes, lungs and eyes. Skin lesions are also common, occurring in approximately 25% to 35% of patients (1), and may be the first presentation of the disease. Sarcoidal granuloma on a tattoo is a well-known phenomenon and regarded as a scar sarcoidosis (1, 3), but it should be differentiated from a granulomatous foreign-body reaction developed on a tattoo. In both lesions, foreign materials can be seen in the granulomatous aggregates of epithelioid cells. As there is no histological difference that reliably distinguishes tattoo sarcoidosis from a granulomatous foreign-body reaction (3), clinical information regarding the presence of either skin lesions on the site other than on tattoos or extracutaneous lesions suggestive of sarcoidosis is important to establish the diagnosis of tattoo sarcoidosis. In our case, the presence of sarcoidal granulomas on the nose and mediastinal lymphadenopathy associated with miliary opacities in the lung confirmed the diagnosis of sarcoidosis.

The incidence, clinical manifestations, and severity of sarcoidosis are known to vary by race and gender possibly under the influence of both genetic and environmental factors (1, 2, 6). For example, African Americans were reported to have a much higher incidence (35-64 cases/100,000 population) than white Americans (10-14 cases/100,000 population) (1), though female predominance is consistently noted in various racial groups (2). In the Japanese population, the incidence of sarcoidosis is estimated to be 1.01 per 100,000 population with a female to male ratio of 1.82. The age distribution was bimodal: one peak between 25 and 34 years old and the other between 60 and 64 years old (7). In addition to the lower incidence, Japanese sarcoidosis has been suggested to show lesser severity and different frequencies of organ involvement compared with Western and American populations (1, 2, 7). In order to determine the clinical characteristics of Japanese tattoo sarcoidosis, we reviewed articles using a Japanese medical-literature database provided by Japan Medical Abstract Society. The following search terms were used in Japanese: “tattoo” AND “sarcoidosis”. The articles were restricted to case reports or a case series, and meeting abstracts were excluded. Twelve cases were retrieved; however, one female with a make-up tattoo was excluded because a diagnosis of foreign-body granuloma was preferred. Eventually, we identified 12 cases, including ours, consisted of ten males and two females with the age range showing a biphasic pattern: nine cases with ages ranging between 24 and 37 years old and three cases between 61 and 69 years old (Table 1) (8-18). One female already had a symptom suspected to be of sarcoidosis prior to tattooing (case 1). After excluding this case, as well as those of two males in whom the tattooed periods prior to the appearance of skin lesions were not identified (case 5, 8), the median of such periods was 13.7 years. The cases could then be classified into two groups based on the tattooed periods prior to skin lesions: seven cases with ages in their 20s and 30s showing relatively shorter periods of 14 years or less, and two cases who were in their 60s having longer periods of 30 years or more.

In the majority of the 12 cases, the tattoo reaction was the first manifestation of sarcoidosis, and

Table 1. Summary of tattoo sarcoidosis reported in Japanese literature

Case No.	Age (yo) /sex	Tattoo prior to skin lesion	Color of tattoo*	Skin lesions on tattoo-free areas	Systemic Sar. prior to skin lesion	HL/ML	Lung involvement	Ocular symptom	ACE/ tuberculin skin test	HCV/ interferon therapy	Therapy/ clinical course	Identified foreign materials	Reference
1	61/ F	1 y	B*	+	Cardiac	Bilateral/ +	+	-	E/ -	NA/NA	PSL 30 mg/ remission	NA	(8)
2	69/ M	40 y	B*, R	+	-	Bilateral/ +	+	-	E/ -	NA/NA	PSL 20 mg/	Carbon remission	(9)
3	65/ M	30 y	B*, R*, G	-	-	Bilateral/ NA	NA	-	E/ +	+/ +	Topical St./ remission	NA	(10)
4	34/ M	10 y	B*, G*, R P, Y	-	-	Bilateral/ NA	NA	U	E/ -	NA/NA	NA/ NA	NA	(11)
5	37/ M	NA	R*, B, Y O, P	-	-	Bilateral/ NA	+	U	E/ NA	+/ +	wIFN/ remission	NA	(12)
6	25/ M	9 y	B*	-	-	-/ -	+	NA	No/ NA	NA/NA	NT/ remission	NA	(13)
7	20s†/M	10 y	G*, Br*, B R, Gr, Y, Bl	-	-	Bilateral/ +	-	Iritis	No/ -	-/ -	PSL 40 mg/ NA	NA	(14)
8	26/M	NA	G*, R* others(NA)	-	-	-/ -	NA	U	No/ +	NA/NA	Excision/ NA	Hg, Ti	(15)
9	34/M	14 y	Blue-black*	-	-	Bilateral/ NA	NA	NA	E/ -	NA/NA	PSL 20 mg remission	Cd, Ti	(16)
10	24/M	2 y	R*, G, Y Blue-green	-	-	Bilateral/ NA	NA	-	No/ -	NA/NA	Excision/ NA	Hg, Ti	(17)
11	31/M	1 y	B*, G*, R*, Y*	-	-	-/ -	+	U	E/ -	NA/ NA	PSL 30 mg remission	Hg, Ti, V	(18)
12	27/F	6 y	G*, B, Y, Yellow-green	+	-	Unilateral/ +	+	-	No/ +	-/ -	Topical St. remission	NA	Present case

ACE: angiotensin-converting enzyme; B: black; Bl: blue; Br: brown; E: elevated serum level; G: green; HCV: hepatitis C virus; HL: hilar lymphadenopathy; ML: mediastinal lymphadenopathy; NA: not available; No: normal; NT: no treatment; O: orange; P: purple; PSL: prednisolone; R: red; Sar.: sarcoidal lesion: St.: steroid; U: uveitis; wIFN: withdrawal of interferon; Y: yellow; y: year (s); yo: years old; *: affected color; †: a patient in his 20s. The exact age was not specified.

the diagnosis was established by skin biopsies. Bilateral hilar lymphadenopathy was detected in 67% (8 cases), mediastinal lymphadenopathy was found in 57% (4 of the 7 cases analyzed), and uveitis was present in 40% (4 of the 10 cases analyzed). Three cases without bilateral hilar lymphadenopathy had parenchymal lesions (case 6, 11) or mediastinal lymphadenopathy (case 12). Overall, 11 of the 12 cases (92%) had intrathoracic lymphadenopathy and/or lung involvement. Two cases with hepatitis C virus (HCV) infection received interferon- therapy, and the skin lesions newly appeared during the interferon-α therapy in one case. The clinical course was recorded in eight cases and the skin lesions were resolved in all cases.

These clinical characteristics of Japanese tattoo sarcoidosis showed a close similarity to those of Japanese sarcoidosis without tattoo except for the marked male predominance in the tattooed cases (Table 2). Furthermore, they were also similar to the characteristics of cases with tattoo sarcoidosis of other races reviewed by Kluger in some respects (3): the striking male predominance, mean age at onset, median period prior to the appearance of skin lesions after tattooing, and frequency of intrathoracic lymphadenopathy (Table 2). One remarkable difference is that uveitis was more common in the Japanese sarcoidosis with tattoo (Table 2), which might be due to a genetic difference as Japanese sarcoidosis has been noted to show higher incidence of ocular involvement compared with American and European cases (7, 19). Another difference from Kluger's subjects is higher prevalence of lung involvement in Japanese sarcoidosis with tattoo (Table 2); however, lower prevalence in Kluger's subjects might be due to the lack of description on lung disease in cases showing no abnormal findings on chest X-ray or CT scan. The striking male predominance in tattoo sarcoidosis might imply different meanings between Japanese and other races. In Western countries, the prevalence of tattooed individuals in males and females is estimated to be almost equal (3, 20, 21), suggesting the possibility that males have a greater risk of developing sarcoidosis after tattooing than females. However, the male predominance in Japanese tattoo sarcoidosis may not suggest increased risk of males but it may only result from an extremely higher ratio of tattooed males than tattooed females.

The pathogenesis of tattoo sarcoidosis remains unknown. As tattoo sarcoidosis could be the first manifestation of sarcoidosis in tattooed individuals (3, 22), some authors have suggested that an inflammatory response to tattoo pigments might trigger sarcoidosis (4), whereas Kluger speculated that foreign materials included in tattoos may be a "target" of sarcoidosis (3). In Japanese reports, various materials have been identified from biopsy samples (Table 1) (9, 15-18); red and green colored samples commonly contained Hg and Ti, respectively, and black was composed of carbon; however, many ex-

Table 2. Clinical characteristic of sarcoidosis with tattoo and without tattoo

Characteristics	Japanese without tattoo*	Japanese with tattoo	Other races with tattoo†
Number of cases (male: female)	1027 (364 : 663)	12 (10 : 2)	59 (44 : 15)
Age (mean)	0y-86 y (NA)	24y-69y (39.3y)	27y-62y (38.8y)
Tattoo prior to skin lesion (median)	————	1y-40y (13.5y)	6w-45y (14.3y)
Skin lesions on tattoo-free areas	————	3/12 (25%)	16/48 (33%)
Extracutaneous lesion prior to skin eruption	————	1/12 (8%)	2/57 (3%)
Extracutaneous involvement		12/12 (100%)	40/57 (70%)
Intrathoracicl ymphadenopathy‡	766/1011 (76%)	9/12 (75%)	27/39 (69%)
Lung involvement	463/993 (47%)	6/7 (86%)	18/39 (46%)
Uveitis	404/994 (41%)	4/10 (40%)	5/57 (8.8%)
High serum ACE level	509/981 (52%)	7/12 (58%)	————
Negative tuberculin test	449/614 (73%)	7/10 (70%)	————

ACE: angiotensin-converting enzyme; NA: not available;
*: Data quoted from reference [7]
†: Cases of sarcoidosis on permanent tattoos (Group 1 in Kluger's review [3]);
‡: Including bilateral hilar and mediastinal lymphadenopathy.

ceptions could be found among the cases. Tattoo sarcoidal reaction most frequently appeared on black and red, suggesting that certain components in these inks may have a particular potential to induce inflammatory response leading to the formation of sarcoidal granulomas. The occurrence of sarcoidal reaction to several colors could be explained by the presence of common antigens in each color (3). The frequently observed long delays of sarcoidal lesions after tattooing have been explained through several reasons: 1) slow degradation of tattoo pigments, 2) chronic exposure to ultraviolet light, 3) roles of additional factors such as HCV infection or interferon therapy (3, 23). Indeed, two Japanese cases were positive for HCV infection, which were treated with interferon- . In one case, skin lesions appeared during the interferon therapy, and they resolved spontaneously after withdrawal of interferon, indicating a promoting role of interferon- in the induction of sarcoidal reaction. The Japanese cases included in our review had their tattoos applied during their adolescence and subsequently developed skin lesions during the age ranges most susceptible for sarcoidosis in the Japanese population. This suggests that tattoo pigments may not necessarily induce the immune response leading to the occurrence of sarcoidosis in genetically predisposed individuals but act as a provocative factor that enhances the inflammatory reaction in patients who already have potential to develop sarcoidosis. In our case, the sarcoidal granulomas were mostly present on the thick green lines despite the tattoo being multi-colored. Thick lines might contain a large amount of pigments and may have been applied using large-gauge needles, which are thought to be more traumatic than tattoos using fine needles. Therefore, not only the amount of pigments but also the degree of traumatic procedure during tattooing might influence the occurrence of sarcoidal granulomas on a tattoo.

The limitation of our review is that the number of cases was small and the exact prevalence of tattooed individuals among Japanese has not been specified. However, our review may have an advantage in that the patients' race was ethnically homogeneous, which made it possible to reliably compare the clinical characteristics between cases with and without tattoos. The clinical features of Japanese sarcoidosis cases with tattoos did not differ significantly from those without tattoos in the time of onset, the incidence of intrathoracic lymph node involvement as well as uveitis, or laboratory abnormalities (Table 2), indicating that the presence of tattoos may not affect the clinical features of sarcoidosis. The difference between Japanese and other races may mainly rely on the difference of genetic background. As tattoo sarcoidal reaction may be the first manifestation of systemic sarcoidosis in any race, and the number of tattooed individuals continues to grow worldwide (24), physicians and dermatologists should be aware of skin eruptions on tattoos so as to identify patients who need work-up for systemic illness.

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