

SARCOIDOSIS ON TATTOOS: A REVIEW OF THE LITERATURE FROM 1939 TO 2011

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ABSTRACT. Sarcoidosis is an autoimmune disease of unknown etiology characterized by the presence of non-caseating epithelioid cell granulomas in multiple organs. Cutaneous sarcoidosis occurs in approximately 25% of the cases. Sarcoid reactions on old scars, traumatized skin sites and around embedded foreign material have long been observed. For the past 70 years, sarcoidal granulomas on tattoos and permanent make-up have also been documented. Granulomatous and sarcoidal tattoo reactions may be the first and sometimes only cutaneous manifestation of systemic sarcoidosis. This review summarizes the currently available data on this topic and discusses the issues related to the diagnosis, management and physiopathogeny of sarcoidal reactions on tattoos. (*Sarcoidosis Vasc Diffuse Lung Dis* 2013; 30: 86-102)

KEY WORDS: sarcoidosis; granuloma; tattooing; permanent make-up; uveitis; ink; Koebner phenomenon; scar

INTRODUCTION

Sarcoidosis is an autoimmune disease of unknown etiology characterized by the presence of non-caseating epithelioid cell granulomas in multiple organs (1). Skin is involved in 25% of all cases and displays various clinical presentations (1,2). Sarcoid reactions on old scars, traumatized skin sites and around embedded foreign material have long been reported (3), and they affect 3% (4) to 30% (5,6) of the patients. Tattooing consists of the introduction of exogenous pigments and dyes into the dermis to obtain a permanent design (7). The first case of sarcoidal reaction in a tattoo (without systemic sarcoidosis) was described by Madden in 1939 (8). Since then, cases of sarcoidal reactions/sarcoidosis on tattoos have been regularly reported.

Approximately 10% to 25% of the general population in Western countries are tattooed (9,10), and sarcoidosis is estimated to affect approximately 10 to 20 per 100,000 inhabitants (1,2). Therefore, it is expected that 1 to 2 per 10,000 tattooed individuals have sarcoidosis. The clinical presentation of tattoo sarcoidosis thus deserves further recognition by physicians as it may be the first or sole presentation of the disease. We present here a comprehensive review of the published literature on this topic and discuss the issues related to sarcoidal reactions restricted to tattoos.

METHODS

References for this review were found through a search on PubMed and Scopus using the terms "tattoo or tattoos or tattooing" AND "sarcoidosis" from 1952 to 2011 with no restriction. Articles in English and French were systematically selected. If easily available, articles in German and Spanish were also selected. We excluded cases in other languages, as well as cases with missing data (11). Last, one article

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prior to 1952 was included (8). No conference abstracts were selected.

RESULTS

We selected 61 publications, for a total of 75 patients from 1939 to 2011. We considered three distinct groups separately: (1) sarcoidosis on permanent tattoos, which can be performed on any part of the body, depicting symbols, text or pictures; (2) sarcoidosis on permanent make-up tattoos (PMU, "cosmetic" tattoos), which are performed mainly on the eyebrows or lips of women for aesthetic reasons (12); and (3) the rare association of a granulomatous tattoo reaction and uveitis, with no other sign suggesting sarcoidosis.

Sarcoidosis on permanent tattoos

Forty-seven articles were included, for a total of 59 cases of tattoo sarcoidosis (8,13-57). Only three series of patients were reported: four cases out of a series of 15 patients from military personnel stationed in Hawaii (19), four cases of ethnic tattoos from Tunisia (30), and seven cases of ethnic tattoos from India (41). All the other articles were case reports of one or two patients. The data are summarized in Table 1.

The patients were between 27-62 years old (mean age: 38.8), with 44 males (27-62, mean age: 37.6) and 15 females (23-60, mean age: 44) and a male-to-female sex ratio of 2.9. Ethnic tattoos were mainly worn by women (Maghreb, India) (30,41). The ink composition of these "traditional" tattoos are most likely different from that of the "modern" tattoos performed in Western countries and are usually made of a single dark color. When traditional tattoos were excluded, the sex ratio was even more in favor of males, with only four female patients (sex ratio of 11), and the age was lower: 31.5 years. The reaction occurred from 6 weeks to 45 years after tattoo completion, with a median delay of 14.3 years. Patients usually sought medical advice within several weeks to two years after development of lesions on the tattoos. Red and black were clearly most often affected, but other colors were also involved (blue, green and brown). In cases of multicolored tattoos (25 cases of tattoo reactions), several colors were af-

ected in 40% of the cases (10/25). Thirty-one patients had other tattoos on their body and 84% (26/31) had other tattoos affected. Interestingly, not all tattoos nor all colors were affected, despite multiple color involvement (21,22). Two patients had a history of sarcoidosis before presentation, but none had tattoos performed after sarcoidosis was diagnosed (26,45).

Lesions were mainly made up of asymptomatic, itchy or sometimes tender – but rarely painful – papules, nodules, plaques or infiltrations on the tattoos, with scaling sometimes observed (Figures 1-6). Subcutaneous, ulcerative or blistering lesions were unusual. Thirty-three patients were free of any other lesions, while 16 (33%) were not. In those cases, lesions were located in the vicinity of the tattoos but in "non-tattooed" areas or on other scars. In other cases, the patient had only a very few nodules elsewhere on the skin (35). Whether biopsies were performed on the tattoo or another lesion, microscopic analysis always disclosed a granulomatous pattern compatible with sarcoidosis, but which was sometimes difficult to distinguish from foreign-body granuloma. In some cases, biopsies of inner organs (lung, lymph nodes) confirmed sarcoidosis. Systemic involvement, defined as symptomatic or asymptomatic extracutaneous manifestations of sarcoidosis, was found in 40 cases (70%, 40/57, absent in 17 cases, and unknown in 2): 69% (27/39) had involvement of mediastinal lymph nodes and 46% (18/39) had parenchymal sarcoidosis. Lung involvement was sometimes present, without hilar lymph nodes. Other manifestations included uveitis (5 cases, including one isolated bilateral chronic granulomatous panuveitis during immune syndrome restoration (38)) and arthritis (7 cases), and more rarely peripheral palpable lymph nodes, erythema nodosum (2 cases), fever, asthenia, hypercalcemia, hypercalciuria with calcium lithiasis (57), parotidomegaly, and lacrymal gland infiltration. Angiotensin-converting enzyme levels were not consistently elevated in patients with tattoo sarcoidosis (36,45,50).

Seven patients had hepatitis C. In six cases, sarcoidosis occurred under interferon (IFN)-ribavirine therapy (39,42,47,48,50) or IFN alone (37), but one patient had hepatitis C-related sarcoidosis (44). One patient developed sarcoidosis during HAART for HIV infection, as a consequence of immune restoration syndrome (38).

Table 1. Sarcoidosis on tattoos

Age, Sex	Tattoo prior to skin reaction	Delay of reaction prior to admission	Affected color	Multicolored tattoo (Yes, No)/one color affected (Yes, No)/color(s) spared (Yes, No)	Other tattoos (Y, N)/affected (Y, N)	Past history of BBS	Clinical presentation	Other BBS lesion	Systemic involvement	Treatment	Evolution	Other	References
27, M*	7 yo	NA	NA	NA	No	No	Nod	NA	No	NA	NA	NA	[7]
52, M	20 yo	< 2 mo	Red, blue, green	Y, No, No	Y, Y	No	Inf, Sca	No	hLN, Rh, Fe, U	sCS	Eff		[13]
30, M	10 yo	5 mo	Red	Y, Y, blue and the red not overlying the plate	Y, No	No	Nod, Sca	No	hLN	Plate withdrawal	SR	Occurred 4 y ears after radius fracture and placement of a plate; Only the red part on the plate affected	[14]
29, M	10 yo	8 mo	Red, blue	No	No	No	Pap, Inf,	No	hLN, pLN, L	iCS	Eff	Afro-american	[15]
41, M	20 yo	1 mo	Green, Red	Y, No, No	Y, Y	No	Itch	Y**	No	iCS	Eff	Foreign body reaction or sarcoidosis ?***	[16]
35, M	20 yo	6 mo	Green	Y, Y, blue	No	No	Itch	Eczematous dermatitis	NA	Excision	Eff	PT + potassium dichromate	[17]
48, M	5 yo	2 y	Black	NA	Y, Y	No	Inf	NA	NA	sCS	Eff		[18]****
60, M	45 yo	Recent	Blue, red	Y, No	No	No	Nod	No	L	No	SR		[19]
4 patients, M*	NA	NA	Red	NA	NA	NA	Nod, Itch	NA	No (3/4)	NA	NA		[20]*****
29, M	9 yo	1 y	Red, blue, green	Y, No	Y, Y (3 out of 4)	No	Nod	No	pLN, hLN, L	NA	NA	NA	[21]

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Age, Sex	Tattoo prior to skin reaction	Delay of reaction prior to admission	Affected color	Multicolored tattoo (Yes, No) / one color affected (Yes, No) / color(s) spared (Yes, No)	Other tattoos (Y, N) / affected (Y, N)	Past history of BBS	Clinical presentation	Other BBS lesion	Systemic involvement	Treatment	Evolution	Other	References
29, M	11 yo	2 mo	Red	Y, Y, NA	Y, No	No	Nod, itch	No	hLN	NA	NA		[21]
30, M	6 wk	6wk	Red, blue	Y, No	Y, Y (red and blue), but green and black spared	No	Inf, Crusts	Y	pLN	NA	NA		[22]
32, M	13 yo	18 mo	Red, brown, green	Y, No	Y, Y	No	Nod	No	hLN, Rh	NA	NA		[23]
29, M	11 yo	6 mo	Red, blue, green, black	Y, No	Y, Y	No	Inf, Scal	No	hLN	No	SR		[24]
40, M	22 yo	3 mo	Green	Y, Y, NA	Y, Y	No	Nod, Scal	No	Fa, Fe, hLN, Rh, EN	NA	NA	Skin and systemic manifestation are simultaneous	[25]
40, M	25 and 26 yo (2 tattoos)	Recent	Red, blue	NA	Y, Y	Lung, 2 yo prior to skin symptoms	Inf, Scal	No	hLN, L	No	Flare with lung symptoms	Patient refused treatment	[26]
31, M	1 yo	NA	Red	Yes, No, yellow, black, green	Y, Y	No	Nod, Itch	No	Fa, Fe, pLN, L, U	sCS	Eff	Similar pigments particles found in the lung	[27]
27, M	10 yo	Recent	Blue	NA	Y, Y	No	Inf, depigmentation	No	hLN	NA	NA	Elevated liver enzymes, Mother with a history of sarcoidosis	[28]

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Age, Sex	Tattoo prior to skin reaction	Delay of reaction prior to admission	Affected color	Multicolored tattoo (Yes, No)/one color affected (Yes, No)/color(s) spared (Yes, No)	Other tattoos (Y, N)/affected (Y, N)	Past history of BBS	Clinical presentation	Other BBS lesion	Systemic involvement	Treatment	Evolution	Other	References
M, 32	15 yo	3 mo	Red	Y, Y, black, orange, yellow, green, blue	Yes, Yes (only red)	No	Nod, Itch	No	hLN, hyperCau, Rh, EN	sCS	Eff		[29]
60, F	54 yo	3 mo	NA°	NA°	Y, Y	No	Nod	No	L, Rh	sCS	No Eff		[30]
55, F	"Child-hood"	3 mo	Black	NA°	No	No	Pap, Nod	No	L	sCS	Stability		[30]
60, F	"Child-hood"	2 mo	NA°	NA°	Y, Y	No	Subcutaneous nod	No	Rh	Nitrogen	Slight regression		[30]
48, F	41 yo	3 mo	NA°	NA°	No	No	Nod	No	L	Nitrogen	Improvement		[30]
29, M	10 yo	18 mo	Blue	Y, No, red, yellow, black	Y, N	No	Nod, Seal	No	L	sCS	Improvement		[31]
33, M	15 yo	6 mo	Black	Y, No, NA	Y, Y	No	Pap, Inf, Itch	Y, one papule	hLN	NA	NA		[32]
40, M	15 yo	several weeks	green, blue-black	Y, No	Y, Y	No	Nod	Y, Scars, knees, elbows	hLN	NA	NA		[33]
33, M	14 mo	3 mo	Red	Y, Y, black, yellow, green		No	Nod	NA	pLN, Fa, Fe, L, U	NA	NA		[34]
29, M	6 to 10 yo	2 y	Black, red	Y, No	Y, Y	No	Nod	Y, one nodule of the canthus	hLN, L	NA	NA	Skin and systemic manifestation are silent	[35]
34, M	15 yo	2 mo after IFN initiation	Red, green, brown, blue	Y, No	Y, No	No	Nod	No	hLN	NA	NA	Neodymium:YAG laser treatment by accident	[36]

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Age, Sex	Tattoo prior to skin reaction	Delay of reaction prior to admission	Affected color	Multicolored tattoo (Yes, No)/one color affected (Yes, No)/color(s) spared (Yes, No)	Other tattoos (Y, N)/affected (Y, N)	Past history of BBS	Clinical presentation	Other BBS lesion	Systemic involvement	Treatment	Evolution	Other	References
42, F	NA	5 mo after HAAART	NA	NA	No	No	Inf, pain	Y, "subcutaneous nodules around the tattoos"	hLN, L	sCS, discontinuation of IFN after 1 mo of treatment	Eff	HCV, IFN	[37]
41, M	20 yo	1 yo	Black	No	Y, Y	No	Pap	Y, scar	U	ICS, discontinuation of HAAART	Eff	HIV HAAART Immune restoration syndrome	[38]
51, M	> 30 yo	Several months after IFN-Riba	NA, ("multiple") ^{oo}	NA	Y, Y	No	Inf, Scal	No	hLN	None	SR	HCV, IFN-Riba	[39]
32, M	7 yo	NA	Black ^{ooo}	No	No	No	Pap	No	hLN	None	SR		[40]
42-52, F (7 cases)	11-20 yo	2-4 mo	Blue-black	NA	NA	No	Inf, Pap, Nod	Y, 3/7 cases	No, 7/7	sCS	Eff	Roadside tattoo artist going in villages, no systemic relapse after 1 to 4 y of follow-up, Chhattisgarh, India)	[41]
54, M	> 20 yo	4 mo after IFN-Riba	Red, black, green, blue, yellow	Y, No	Y, Y	No	Nod, ulceration	No	L, hLN	ICS, discontinuation IFN-Riba	Eff	HCV, IFN-Riba	[42]
23, F	1 yo	2 mo	Black	Y, Y, Turquoise	No	No	Inf, Itch	No	No	ICS, sCS	Improvement and stability	Pt nickel and cobalt	[43]

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Age, Sex	Tattoo prior to skin reaction	Delay of reaction prior to admission	Affected color	Multicolored tattoo (Yes, No)/one color affected (Yes, No)/color(s) spared (Yes, No)	Other tattoos (Y, N)/affected (Y, N)	Past history of BBS	Clinical presentation	Other BBS lesion	Systemic involvement	Treatment	Evolution	Other	References
37, M	NA	4 y	Black	No	Y, Y	No	Pap	Scar	hLN	ICS	Improvement	HCV	[44]
31, F	13 yo	3 y	Brown	Y, Y, green, purple, blue	No	Y, hLN	Inf, blistering, pain	No	No	NA	NA	NA	[45]
NA, M	NA	NA	Dark ^{ooo}	NA	No	No	Inf	Y, Scar, pap	hLN, L	ICS	NA	NA	[46]
29, M	< 10 yo	6 wk	Black	No	Y, Y	No	Pap, Inf, Itch	No	hLN	ICS, IFN-Riba discontinued 1 mo before symptoms	Eff	HCV, IFN-Riba	[47]
44, M	NA	10 mo after initiation INF-Riba	black ^{ooo}		No	No	Inf, Itch, Pain	Y, Scar	N	ICS	Improvement with withdrawal of treatment	HCV, IFN-Riba	[48]
53, M	6 mo	3 wk	Blue	Y, Y, red	No	No	Inf, Itch	No	No	ICS	Eff	Eff	[49]
45, M	NA	NA	Red ^{ooo}	NA	NA	NA	Inf	NA	No	sCS	Improvement and relapse when sCS disrupted	HCV, IFN-Riba	[50]
30, F	15 yo	NA	Black	No	No	No	Pap	Y	F, hLN, aLN, L, HMG, Rh, SMG	ICS	Eff	Eff	[51]
41, M	NA	6 mo	Black	No	Y, Y	No	Pap	Y, perifollicular cutaneous sarcoidosis	U, Lacrymal glands infiltration	NA	NA	Afroamerican patient	[52]

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Age, Sex	Tattoo prior to skin reaction	Delay of reaction prior to admission	Affected color	Multicolored tattoo (Yes, No)/one color affected (Yes, No)/color(s) spared (Yes, No)	Other tattoos (Y, N)/affected (Y, N)	Past history of BBS	Clinical presentation	Other BBS lesion	Systemic involvement	Treatment	Evolution	Other	References
36, M	10 yo	4 mo	Black	Y, Y	Y,	No	Nod	No	hLN	No	SR		[53]
32, M	6 yo	6 mo	Blue	NA	No	No	Pap	No	hLN, L	ICS, HCQ	Eff		[54]
36, M	NA	3 mo	Red ^{ooo} and dark ^{ooo}	No	Y, Y	No	Pap, Scal	No	hLN, Rh,	sCS, HCCQ	Eff		[55]
					Y, Y			No					
34, M	NA	5 mo	Black		No	No	Inf, Scal, Pain		L, U, hyperCa	NA	NA		[56]
62, M	NA	6 mo	Blue, brown	Y, No	Y, Y, but not all, only 2 colors	No	Pap		hLN, L, HyperCau	HCCQ	Eff		[57]

BBS: sarcoidosis; Eff: Efficacy of the treatment and regression of the lesions; EN: Erythema nodosum; F: Female; Fe: Fatigue; HCV: Hepatitis C Virus infection; HCQ: hydroxychloroquine; hLN: hilar, mediastinal and/or paratracheal lymph nodes; IFN: Interferon; IFN-Riba: Association of IFN and Ribavirin; iCS: intratestal corticosteroid therapy; Inf: Infiltration, thickening or induration; L: parenchymal lung sarcoidosis; ICS: local corticosteroid therapy; M: Male; mo: month(s); NA: Not Available; No Eff: No efficacy; Nod: Nodule(s); Pap: papule(s); pLN: peripheral lymph node; PT: Patch testing; Rb: rheumatic involvement; Scal: Scales, Scaling lesions; sCS: systemic corticosteroid therapy; SR: spontaneous resolution or remission; U: urticaria; Y: Yes, y: year(s); yo: years old

* case reported in 1939, but seen in 1924

** Two lesions of untattooed skin enclosed by black tattoo lines, histology was considered as resembling sarcoidosis but diagnosis was not considered

*** Bricklayer, chronic dermatitis, improvement of dermatitis with tattoo excision; one biopsy specimen showed sarcoïdal granuloma and the other foreign-body granuloma

**** haemophysis mentioned in the observation

***** Goldstein reported 4 cases of photo-induced sarcoïdal-like tattoo reaction with no systemic involvement on red tattoos out of a series of 15 patients.

° most likely monochromic black or dark ethnic tattoos from Maghreb

°° Dark blue or green according to the figure in the article

°°° As stated on the picture of the articles

When mentioned, management included local or systemic corticosteroid therapies or antimalarial therapy. Abstention alone was associated with regression of the lesions in the following months (39,40).

Sarcoidosis on permanent make-up tattoos

Sarcoidosis on PMU was reported in eight female patients, all between 38 and 70 years old (mean age: 48.9 years) and tattooed 2 to 25 years prior to re-



Fig. 1. Scattered papules of granulomatous reaction on a black tattoo without any evidence of systemic sarcoidosis disclosing a granulomatous reaction on a tattoo. The reaction spontaneously resolved during follow-up. (From the collection of Dr Hervé Garat, Tournefeuille, France).



Fig. 2. Papules in a blue turtle disclosing sarcoidosis (From the collection of Pr Luc Thomas, Lyon)



Fig. 3. Sarcoidal reaction within the purple of a dragon tattoo. The check-up failed to find any systemic sarcoidosis. 3b. Close-up view (From the collection of Pr Marie Thérèse Leccia, Grenoble, France)

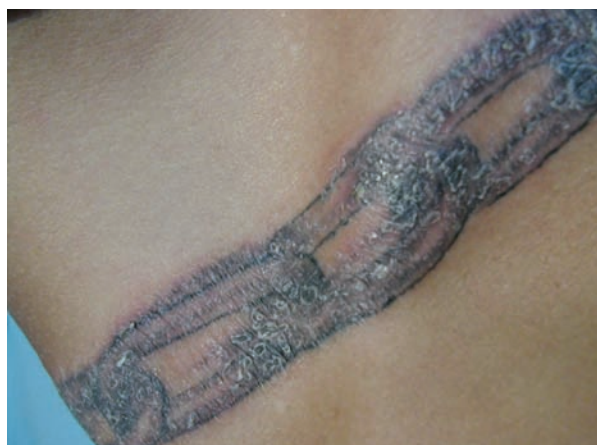


Fig. 4. Sarcoidosis. Infiltrated squamous lesions in a patient with systemic sarcoidosis (From the collection of Pr Marie Thérèse Leccia, Grenoble, France)



Fig. 5. Sarcoidosis. Infiltrated papules in a tattooed geisha (From the collection of Pr Marie-Aleth Richard, Marseille, France)



Fig. 6. Sarcoidosis. Hypopigmented sarcoidal lesions on a panther (From the collection of Dr Philippe Guilpain, Montpellier, France)

ferral (Table 2) (58-65). Tattoos were located on the lips ($n = 5$), the eyebrows ($n = 4$), and the eyelids ($n = 1$). Four out of five of the patients had both lips affected, two out of four had both eyebrows affected, and two had involvement of different sites (eyebrows and eyelids, eyebrows and lips). Three of them had multiple PMU, but only two had lesions at different locations. Two patients had a history of lung sarcoidosis, documented 12 to 15 years earlier. Clinical presentation was not specific, with asymptomatic infiltration, papules or nodules. Lesions were sometimes scaly or itchy. Four patients had skin lesions elsewhere (59,62,65), again restricted to a few nodules and sometimes in the vicinity of the tattoo (62,63). Two patients showed involvement of other scars (58,59), including one at the site of a previous filler injection of the lip (58). Punch skin biopsy of the lesions disclosed features of sarcoidal granuloma or non-caseating granuloma. Six patients had systemic involvement (6/8, 75%) with either mediastinal lymph nodes or lung involvement. In one case, organ involvement was not specified (63). One patient developed sarcoidosis two years after presentation, while systemic involvement was found concomitant to skin involvement in the others. Management varied: local or oral corticosteroids, tacrolimus 0.1% ointment twice daily, cyclines, mepacrine, allopurinol, or abstention. Reported responses ranged from slight improvement to efficacy. In one case, sarcoidosis occurred under IFN therapy for malignant melanoma. The therapy was conducted until its end and the sarcoidosis then resolved spontaneously (58).

Isolated uveitis

Uveitis is one of the most common ophthalmological manifestations of sarcoidosis (1) and may be its initial manifestation (66). As noted earlier, several patients with tattoo sarcoidosis showed eye involvement with uveitis in association with other systemic manifestations (13,27,34,38,52,56). However, several intriguing cases of isolated uveitis associated with tattoos reactions have been reported in the literature since 1969 (67) (Table 3). This "subgroup" was analyzed separately because these cases were reported mainly in eye journals, and the ophthalmological perspective made it a different group.

To date, eight male patients between 21 and 53 years old have developed bilateral uveitis after tat-

Table 2. Sarcoidosis on permanent make-up tattoo

Age (yo), Sex	Tattoo prior to skin reaction	Delay of reaction prior to admission	Affected color	Other tattoos (Y,No)/affected (Y,No)	Past history of BBS	Clinical presentation	Other BBS lesion	Systemic involvement	Treatment	Evolution	Other	References
54, F	Lips – 3 yo	no delay	Red/purple*	No	No	Nod	No	L	No	SR in 1 mo	IFN for melanoma 15 mo after initiation	[58]
50, F	Lips – 2 yo	1 y	Pink* (iron oxide and glycine)	No	Lung (12 y before)	Inf	Scar	L	ICS, mepacrine	Eff		[59]
70, F	Eyebrows 25 yo	3 y	Brown-black	No	No	Inf, Scal	No	hLN, L	ICS, sCs, tacrolimus	Eff		[60]
31, F	Eyebrow – 2 yo	3 mo	Red	Y (lips), No	No	Pap, Itch	No	hLN	NA	NA		[61]
41, F	Eyebrows, Lips – 3 yo	2 mo	Pink*	No	No	Pap	One nodule on the forearm	hLN	ICS, cyclines	Eff		[62]
59, F	Lips – 6 yo	2 y 2 mo 4-5 mo	Red/purple*	No	No	Nod	2nd nodule nearby the tattoo	No**	ICS, allopurinol	Eff	Developed systemic sarcoidosis within the next 2 following years** and relapse on the lips	[63]
48, F	Lips – 9 yo, repeated 2 yo prior to referral		Blond-brown Brown	No	Lung (15 years before)	Inf	No	No	ICS, cyclines	Slight improvement	Laser IPL for facial rejuvenation session 3 weeks prior to reaction	[64]
38, F	eyebrows, eyelids – 7 yo, repeated 2 yo			Y,Y	No	Pap, Inf	Lips (collagen injection)	No	sCS	Improvement		[65]

BBS: sarcoidosis; Eff: Efficacy of the treatment and regression of the lesions; F: Female; Fa: Fatigue; Fe: Fever; hLN: hilar, mediastinal and/or paratracheal lymph nodes; IFN: interferon; Inf: Infiltration, thickening or induration; L: parenchymal lung sarcoidosis; ICS: local corticosteroid therapy; M: Male; mo: month(s); NA: Not Available; Nod: nodules; pLN: peripheral lymph node; PT: Patch testing; Scal: Scales, Scaling lesions; sCs: systemic corticosteroid therapy; SR: spontaneous resolution or remission; U: uveitis; y: year(s); yo: years old

*As stated on the picture of the articles

tooing (67-72). The uveitis was either anterior or posterior. In 87% of the cases (7/8), infiltration, swelling and the itchiness of the tattoos preceded the ocular episodes by six months to five years (67-69) or occurred almost simultaneously (71,72). In three patients, the tattoo never healed (67,68). Moreover, microscopic analysis of skin samples disclosed non-necrotizing granulomas surrounding pigments granules in the dermis. In most of the cases, the description does not allow a definite pathological distinction between foreign-body reaction and sarcoidal reaction. Although no patient displayed other cutaneous or systemic involvement, Rorsman *et al.* mentioned that one patient presented infiltrates “resembling erythema nodosum” on the shins (67). They found positive patch testing for cobalt chloride 2% in two patients who reacted to blue tattoos, which were known to contain cobalt in those days. Management included local corticosteroids (67,71) and systemic treatment (systemic corticosteroids, azathioprine, cyclosporine A) (70,71,72). Mansour and Chan reported that a skin rash appeared one week before the uveitis episodes (68). A similar chronological link between skin and eye episodes was noted by Rorsman *et al.* (67). Last, notable improvement and remission of uveitis were reported within the first year after excision *in toto* of the culprit tattoo(s) (69,67,71).

DISCUSSION

To date, the prevalence of cutaneous complications on tattoos has not been fully assessed. Kazandjewa *et al.* estimated 2% in their series of patients (75). According to a self-reported survey in Germany, Klügl *et al.* found that 6% of the tattooed individuals had “persistent skin problems” in the tattooed area: 0.7% complained of “elevated skin” and 0.4% of “skin papules” (10). Høgsberg *et al.* reported that 27% of Danish tattooed individuals presented complaints about their tattoos, albeit minor (itching, elevated skin), persisting for more than three months after completion (76). However, without a biopsy of the lesions (10,76), their true nature is impossible to determine. It is statistically expected that 1 to 2 out of every 10,000 tattooed Caucasians have sarcoidosis. Naturally, this does not mean that all will develop a tattoo reaction, but it stresses the possibility

that some of them may have sarcoidosis that will be revealed by a tattoo reaction. Sarcoidosis may be underestimated for several reasons: (I) tattooed individuals usually see their tattooist first, believing that healthcare providers know less about tattoos and fearing a judgmental approach. They therefore seek medical advice only when symptoms become unbearable or worrisome; (II) physicians do not always perform a skin biopsy and patients may be misdiagnosed with an “allergy to the ink” without further exploration; and (III) a clear-cut distinction between foreign-body granulomas and sarcoidal granulomas on biopsies is not always possible. The presence of foreign bodies does not exclude sarcoidosis (77), and these granulomas may thus often be misdiagnosed. Yet, what diagnosis should we give to a patient with only a sarcoidal tattoo reaction on one color? In the case of no systemic involvement, only mid- to long-term follow-up will confirm whether the reaction is a sarcoidal foreign-body granuloma or the first manifestation of sarcoidosis; (IV) scar sarcoidosis may resolve slowly and spontaneously (3); and (V) there is currently little interest in reporting cases of sarcoidosis on tattoos.

The mean age of presentation of tattoo sarcoidosis was similar to that reported in the literature (1,2), but we observed a striking male predominance with a sex ratio of 2.9. Females have been consistently found to be at greater risk than males (1). Currently, women account for half the tattoos (9,10) and almost all the PMU tattoos. Therefore, the discrepancy is not fully explained by a sex ratio difference between tattooed males and females. Only two cases of Afro-American individuals were reported. Dark-skinned individuals may be more reluctant to be tattooed, as they need to use dark colors exclusively to ensure tattoo visibility.

Patients with tattoo sarcoidosis do not present with lesions on all their tattoos. Papules or nodules are scattered along the tattooed area with no precise distribution, but sarcoidosis never seems to present as a diffuse infiltration of all the tattoos. Additional lesions may present in the vicinity of the tattoo or on tattoo-free areas within the design. These lesions may provide a valuable site for biopsy if the patient refuses to allow a biopsy *on* the tattoo (33,44). The involvement of several colors is evocative of sarcoidosis (23), but granulomatous restriction to one color in multicolored tattoos should never rule out the diagnosis of sarcoidosis (29).

Table 3. Isolated uveitis after tattooing

Age, Sex	Delay of uveitis after tattooing	Tattoo color	Skin rash before uveitis	Uveitis	Treatment	Evolution	Other	References
25, M	6 mo	Light blue + yellow	Infiltration since completion, no real healing	bilateral uveitis with keratotic precipitates	ICS, sCS, tattoo excision	Corticosteroid sensitivity, remission 11 mo after excision	Positive PT for cobalt chloride	[67]
28, M	18 mo	Light blue	Infiltration since completion, no real healing	bilateral uveitis	ICS, sCS, tattoo excision	Slight improvement, improvement 9 mo after excision	Positive PT for cobalt chloride	[67]
22, M	6 mo	Light blue	No, concomitant	bilateral uveitis, retinal edema, pseudoholes in the macula	ICS, sCS, tattoo excision	Mild improvement of the eye, No remission one mo after excision	Episode of EN	[67]
35, M	12 y	NA	5 years before, recurrent swelling	bilateral anterior non granulomatous uveitis	NA	Relapse for 7 years, between 1982-1989	Extensive tattoos performed between 1960 and 1970 Swelling preceded uveitis of one week	[68]
53, M	NA	NA	2 months before, swelling eruption	bilateral anterior uveitis	ICS, tattoo excision	Recurrence of uveitis, remission after excision		[69]
21, M	6 y	NA	No	Posterior uveitis with macular cystoid edema and retinal vasculitis	sCS, AZA, CyA	Improvement	No skin rash	[70]*
24, M	3 y	Red	No, concomitant	panuveitis of the right eye, iridocyclitis of the left eye	ICS, sCS, CyA, tattoo excision	Remission after excision and immunosuppressive treatment		[71]
49, M	NA	Extensive tattoos	No, concomitant	bilateral panuveitis and macular edema	sCS, AZA	Improvement		[72]

AZA: Azathioprine; CyA: cyclosporine A; EN: Erythema nodosum; F: Female; ICS: local corticosteroid therapy; mo: month(s); NA: Not available; PT: Patch testing; sCS: systemic corticosteroid therapy; y: year(s)

* The authors reported here a case of uveitis and retinal vasculitis in a tattooed patient with out any skin reaction on the tattoo or elsewhere. This article has been included in this review in a concern of sufficiency. However, we do not share the position of the authors as link between the tattoo and the eye inflammation

Patients with tattoo sarcoidosis very rarely displayed other specific skin lesions elsewhere on the body. In some cases, old scars (33,38,44,46,59,63) or previous sites of filler injections (65) were affected. In a few cases, patients showed one or a few papules or nodules in various part of the body (35,62). A thorough examination of the skin is mandatory, with attention paid to isolated papules or nodules (35); a normal skin examination should be expected in most cases. Erythema nodosum was mentioned rarely (25, 29). Overall, the clinical presentation of tattoo sarcoidosis is as follows: asymptomatic and nonspecific, with lesions restricted to tattoos, few cutaneous lesions elsewhere, and a striking male predominance. The multiple clinical facets of tattoo sarcoidosis are illustrated here by the cases of granulomatous foreign-body (figure 1) and sarcoidal tattoo reactions revealing (or not) systemic sarcoidosis (figures 2 to 6).

The histopathology of specific lesions of cutaneous sarcoidosis is characterized by the presence of non-caseating granulomas. However, exogenous foreign bodies are always seen on a biopsy of a tattoo reaction. In our experience, there is no histological sign that can allow to draw a definite diagnosis of sarcoidosis compared to foreign body reactions. Even though sarcoidal granuloma does have some peculiar features such as a paucity of lymphocytes within the infiltrate or a good circumscription of the granuloma, those features are not consistent. Therefore, it is not always possible for the pathologist to draw a definitive conclusion, especially when there are no other extracutaneous symptoms. In practice, the dermatopathologist will rely on the ratio between the epithelioid histiocytes and giant cell infiltration and the number of foreign bodies.

It has been estimated that 70% of the patients with specific cutaneous lesions have concomitant systemic manifestations or that 30% will develop systemic involvement within months to years (1,2). We found a very similar result in this review. Because sarcoidosis is a systemic disease, technically granulomatous inflammation needs to be established in two organs for the diagnosis to be established (3). In our review, we found that 30% of patients with tattoo sarcoidosis did not have extracutaneous manifestations at the time of diagnosis. However, as there was no follow-up in most of the published cases, it is unknown whether some of the patients later developed the systemic disease. This situation is not uncommon in dermatology practice, and thus we did not exclude these cases from this re-

view. Also, it is difficult to determine whether the older reports underestimated systemic involvement. In our experience, chest X-ray may be falsely negative and miss mediastinal involvement (28,35,44). We thus recommend long-term follow-up of patients with tattoo sarcoidosis. We further suggest that patients with foreign-body granuloma reaction or sarcoidal reaction undergo a thoracic CT scan at least during the initial check-up instead of a chest X-ray. A work-up algorithm is presented in Figure 7.

The immunopathogenesis of sarcoidosis has not yet been fully elucidated (1). It has been suggested that environmental factors, such as infectious, organic, and inorganic agents, are possible antigens in a predisposing genetic background (1). Unfortunately, since the first reports from Madden (7), case reports of tattoo sarcoidosis have unanimously focused on the clinical presentation of the sarcoidosis, and discussion on the physiopathology has usually been "conventional." To our knowledge, only Hanada and Hashimoto showed the increased lesional expression of metallothionein in a patient with tattoo sarcoidosis (34).

Some authors have suggested that the tattoo might be the trigger of sarcoidosis (27). However, such conclusions are based only on the chronological link of "tattoo first-sarcoidosis after." From our point of view, the tattoo is most likely the target of sarcoidosis, rather than its cause. The possibility of a seemingly disease-free individual having a tattoo done and then developing lesions on that very tattoo – thereby revealing asymptomatic lung sarcoidosis, for example – cannot be ruled out. Indeed, this hypothesis is supported by numerous cases of patients with only tattoo sarcoidosis and mediastinal involvement (14, 21, 24, 28, 32, 36, 39). It should be stressed that, according to the Boyd-Nelder classification of the Koebner phenomenon, sarcoidosis belongs to category IV (poor or questionable trauma-induced processes) (78). The observations that support this categorization are the following: (I) sarcoidosis sometimes develops 45 years after the trauma, (II) not all pigmented areas are affected, and (III) not all the tattoos are always affected (45).

Sarcoidosis is an exaggerated immune response to exogenous or autoantigenic stimuli. A specific antigen in the tattoo may drive a cell-mediated immune response characteristic of granuloma formation in predisposed individuals. Tattoo inks may share common components despite being different colors and, conversely, inks of similar colors may not have the same

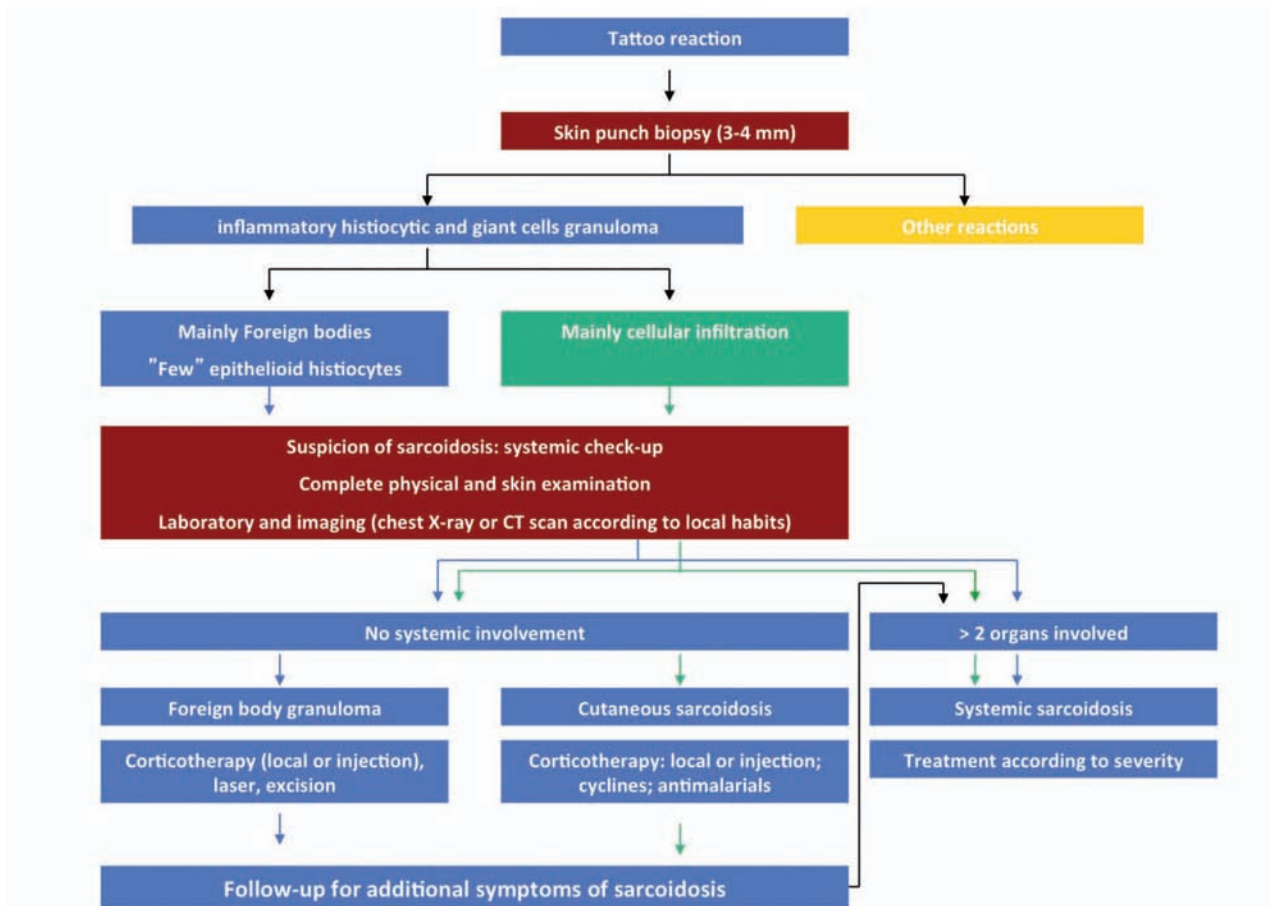


Fig. 7. Work-up algorithm on what to do when a patient is found to have a granulomatous tattoo reaction upon histology

components (7). Therefore, sarcoidal reactions to one or several colors could be explained by the presence of a common antigen in each involved color. The long delay of reaction implies an additional precipitating factor, such as hepatitis C, or interferon or IFN-ribavirine therapy. Moreover, tattoo components are slowly degraded over time and in response to chronic sun exposure. Goldstein clearly showed sarcoidal reactions obtained on red tattoos in mice after sun exposure (20). We suspect that the culprit reaction-trigger may be a reactive ink by-product that appears during the patient's life, rather than a component that is introduced *during* the actual tattooing. This process may be similar to the formation of a *pencil-core granuloma*, during which the graphite of the pencil is degraded until a critical size under which a granulomatous reaction may occur, sometimes 20 years after the trauma (79).

The precise physiopathology of isolated uveitis and tattoo granulomas remains unknown. Rorsman *et*

al. speculated that an allergen was slowly absorbed from the inflamed tattoo, accumulating in the uvea to induce and maintain eye inflammation (67). But, even today, the potential diffusion of tattoo particles or by-products beyond the lymph nodes is unknown. Mansour *et al.* suggested that the pattern of lymphocytes infiltrating the tattoo was in favor of a delayed-type hypersensitivity rather than a sarcoidal-type infiltration (68). It is still not known whether a component in itself or a component by-product can lead to a hypersensitivity reaction (69). Such granulomatous skin reactions associated with uveitis are reminiscent of the granuloma annulare associated with uveitis without sarcoidosis (73). Moschos *et al.* made a parallel between tattooing and uveitis mouse model, where hypodermal injections are used to trigger uveitis (70). We think that these cases of uveitis-tattoo granuloma are instead a variant of sarcoidosis rather than a distinct entity. Therefore, in cases of granulomatous tattoo re-

action associated with uveitis, we suggest a complete check-up for sarcoidosis before considering the potential role of an antigen contained in the tattooed skin (74). In addition, skin biopsy is mandatory to determine as precisely as possible whether the granulomatous reaction is suggestive of a foreign-body reaction or sarcoidosis. Last, long-term monitoring would help to predict whether these patients will develop sarcoidosis later in life. We found the assumption that tattoos are a triggering factor of uveitis and retinal vasculitis to be highly debatable in the absence of any other lesion, especially if the tattooed skin is free of any lesion (70).

CONCLUSION

Sarcoidal tattoo reaction is a type of scar sarcoidosis. With the increasing popularity of tattoos, such reactions will become more frequent and may be of help in diagnosing sarcoidosis. A full check-up should be performed in cases of granulomatous tattoo reaction, even if the reaction is restricted to one color and there is a foreign-body reaction. Patients should be followed over the long term in cases of granulomatous reaction or at least be warned to consult again in the event of new symptoms. Unfortunately, since its description 70 years ago, nothing much has been done to determine (1) the risk of patients developing more severe systemic disease, (2) the optimal management and treatment strategies, or (3) the origin of this phenomenon. It is clear that antigens are involved, which are either introduced in the ink during tattooing or as by-products that appear only later in the dermis. Sun exposure may also play a role, as well as factors like hepatitis C, IFN therapy, and immune restoration syndrome. All these cases strongly point toward an immunological reaction directed against an antigen in the tattoo. The role of an additional factor that can precipitate the reaction is more than likely.

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