

Tattooing Granuloma: Upsurging Cases as an Early Manifestation of Sarcoidosis

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Abstract

Background: Cutaneous manifestations of sarcoidosis may occur secondarily by a precipitating factor such as scars, infections, or even tattoo ink. Tattoo pigment can precipitate many inflammatory states; however, cutaneous sarcoid granuloma is a rare reaction.

Objectives: To record all cases of tattooing granuloma and do a full evaluation regarding the clinical and histopathological pictures.

Methods: This is a case series descriptive study where all cases with tattooing granuloma were collected during the period from 2021-2023. Full demographic and clinical evaluations were done. A complete physical checkup was carried out, especially the chest and eyes examination. Biopsies for histopathological assessment were performed.

Results: Fourteen female patients were subjected to the present work, their ages ranged from 22-48 years with a mean $\pm$ SD of 32 ± 38.7 years. All gave a history of tattooing using mostly black ink and a rash appeared a few months to one year after the procedure. Almost all patients noticed swelling and itching. The sites of tattooing were located on both eyebrows except for 2(14.3%) patients, where their tattooing was located on the upper arms and trunk. Three patients had extra-eyebrows granulomatous rash involving the trunk. One (7.1%) patient was confirmed to have bilateral hilar lymphadenopathy. The consistency of the rash was almost firm rubbery plaque. The histopathology of the rash showed non-necrotizing granuloma and many of them were naked with little or no inflammatory reaction, pigmented particles were observed inside the granuloma.

Conclusion: There has been an upsurge of cases of eyebrow tattoo sarcoidosis in the last few years. The clinical and histopathological pictures of these cases have some features of cutaneous sarcoidosis. This increased frequency of tattooing sarcoidosis goes parallel with upsurge of cases of cutaneous sarcoidosis.

Keywords: Tattoo, Granuloma, Sarcoidosis, Granulomatous disease, Eyebrow, Naked granuloma.

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Introduction

Tattooing is an ancient method of physique adornment that has advanced into a general style accessory. The term tattoo is derived from the earliest Polynesian word tatau denotates "the results of tapping". They are created by the entering of exogenous dyes into the dermis, leading to a lifelong pattern.¹ The initial recognized samples were for a long time Egyptian and existed on numerous female mummies.² Nearly a quarter of

Americans as well as Europeans between 18 and 50 years of age are now identified to have at minimum 1 tattoo.³

The tattoos have 5 types: Permanent decorative, temporary, medical type, cosmetic, and traumatic. Cosmetic tattoos are considered permanent makeup and are becoming highly popular as a substitute for ordinary makeup. It frequently used as a camouflage and to enhance the appearance of the eyebrows, eyelids, or lips contour.⁴

Lack of standardized guidelines or crucial awareness of the variety of inflammatory tattoo disorders, infective conditions, and progression to systemic illnesses, might result in long-term side effects that are identified in as many as 7% of individuals getting tattoos. The most common complications are photo-dermatitis, contact dermatitis, subacute cutaneous lupus erythematosus, local or systemic infections, granulomatous, lichenoid, and pseudo-lymphomatous reactions.⁵ Moreover, tattoos have been suggested in association with the evolution of basal cell carcinoma, squamous cell carcinoma, neoplastic lymphoma, and keratoacanthoma.^{5,6}

The foreign body granulomatous reaction to tattoo pigments which is similar to other exogenous substances injected into the skin is instantly detectible as nodular and diffuse granuloma.⁴ Furthermore, as an adverse response to tattoos, many forms of granulomatous reaction might be reported like naked sarcoidal granulomas which were described by Madden for the first time in 1939. Subsequently, numerous articles have been published supporting the existence of tattoos granuloma,^{4,7} as well as tuberculoid granuloma, tattoo inoculation leprosy, suppurative granuloma, necrobiotic lipoidica/granuloma annulare, and they have a similar morphologic picture of cutaneous sarcoidosis (CS).⁸

Generally, CS favors traumatized skin sites, inside scar tissue, and around implanted foreign elements for example silica. Subsequently, these become sarcoidal granulomas after inflammation and cellular infiltration that precede systemic sarcoidosis. Hence, skin findings in scar CS or foreign body CS might be the only presentation in a case with systemic sarcoidosis. It has been reported that the granuloma was resolved after the removal of silicone gel breast implant in a patient complaining of systemic sarcoidosis.⁹

Sarcoidosis is a multisystemic disorder of indefinite cause. Skin is the main site contributed by extra-thoracic sarcoidosis. In many circumstances, CS can arise as an isolated disease or be accompanied by systemic involvement. CS shows definite cutaneous manifestations that are compatible

with noncaseating granulomas. It predominates in females and can exist as single or multiple red plaques, subcutaneous nodules or maculopapular rash.¹⁰⁻¹²

It has been documented recently that there was tremendous upsurge of CS in the last years among Iraqi population.¹³ Currently, the sarcoidosis associated with tattoos goes parallel with the CS increment. This encouraged us to plan for the present overview and provides a full assessment concerning the clinical and histopathological pictures for all cases presented with tattooing granuloma.

Methods

This is a case series descriptive study where all individuals complaining of tattooing granuloma were collected over two years, during the period from 2021-2023. They evaluated and assisted at Baghdad Teaching Hospital, Baghdad, Iraq. Full demographic and clinical evaluations were done. A complete physical examination was carried out especially chest and ophthalmological work-ups. In addition to the routine laboratory work, chest X-ray, abdominal ultrasound, and skin biopsies for histopathological assessment were performed. All cases had a positive history of tattooing. The color of exogenous pigments, the size of tattoo, and the site and duration of the appearance of skin lesions after the procedure were documented.

Furthermore, almost all cases with granuloma-forming infections such as granulomatous tuberculoid leprosy, secondary syphilis, mycobacterial and fungal infections and leishmaniasis were omitted. As well as all other granulomatous mimicking diseases like granuloma annulare, necrobiosis lipoidica, and granulomatous rosacea were fully examined, investigated and excluded. Continuous follow-up was completed to evaluate the appearance of systemic involvement. The Ethical Approval Committee revised and accepted the study. All contributing subjects gave informed consent for the publication of data and their digital photographs.

Results

This study included 14 female patients; their ages ranged from 22 – 48 years with a mean $\pm$ SD of 32 ± 38.7 years. All gave a history of tattooing using mostly black ink composed of metal and/or organic in a carrier solution followed by the appearance of rash with a duration ranging between 2-12 months with a mean of 4.1 months after the procedure. Tattoo size mostly was less than 10 cubic centimeters in 12(85.7%) patients. The character of tattoos was mainly eyebrows or body tattooing in 11(78.6%), and 3(21.4%) of subjects, respectively (Table 1).

Almost all noticed itching in 11(78.6%) of cases, while swelling presented in 4(28.6%), these were gradually increasing in severity over time. The sites of

Table 1: The frequency rate of clinical and histological presentations of tattoo sarcoidosis. (n =14).

Variables	Data
Females (n%)	14(100%)
Age, mean	32(22-48) year
Disease duration after tattooing, mean	4.1(2-12) months
Sites of cutaneous granuloma (n%)	
Bilateral eyebrows	12(85.7%)
Upper limbs	3(21.4%)
Trunk	3(21.4%)
Cutaneous sarcoidosis, tattoos-related only	14(100%)
Cutaneous sarcoidosis, non-tattoos-related in same patient	3(21.4%)
Clinical features	
Asymptomatic	3(21.4%)
Itching	11(78.6%)
Swelling	4(28.6%)
Scaly	5(45.7%)
Plaques (firm-rubbery)	10(71.4%)
Patches	4(28.6%)
The color of the rash	
Dusky red	11(78.6%)
Brown	3(21.4%)
Tattoo size	
<10 cm ²	12(85.7%)
>10 cm ²	2(14.3%)
The histopathological of naked granuloma	
Multinuclear giant cells	12(85.7%)
Exogenous pigmented particle deposition	9(64.3%)
Cellular infiltrate (epithelioid and histiocytic cells)	7(50%)
Surrounded by lymphocytes	4(28.6%)

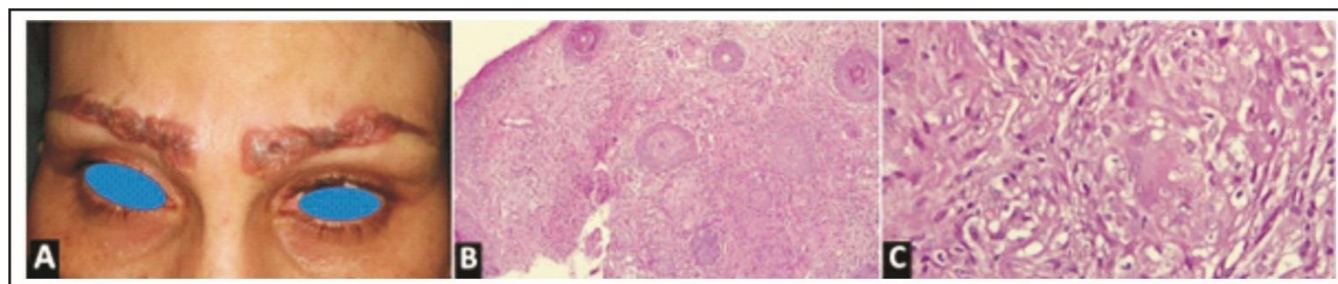


Figure 1: Forty-seven-year-old women had cosmetic tattoo, showing typical tattooing eyebrow granuloma, (A): The histopathology with HE stains of tattoo granuloma showing naked granulomatous reaction with giant cells, (B, X10) higher magnification (C, X40).

tattooing was located on both eyebrows in 12 (85.7%) of the participants (Figure 1), in addition, 6(42.8%) patients had extra-eyebrows granulomatous rash where their tattoo was located on the upper arms and trunk (Figures 2 & 3). The main distribution of rash could be localized granuloma (tattoos related rash) while 3(21.4%) cases revealed unexpected presentation of generalized site of involvement at non-tattoos-related skin rash in the

same patient (Figure 4). The consistency of plaques was firm rubbery in 10(71.4%), while 4(28.6%) of patients showed patches. The color of the rash most commonly was dusky red in 11(78.6%) cases with an apparent scaling that was noticed in 5(45.7%). No obvious eyes or other systemic involvement were detected by clinical examination or various other investigative procedures at diagnosis or afterwards, apart from one

(7.1%) patient confirmed to have tattoo sarcoidosis (TS) disorder with a bilateral hilar lymphadenopathy (Figure 5).



Figure 2: Fifty-year-old female showing extension of the eyebrow granuloma into the chest.



Figure 3: Twenty-five-year-old female of permanent character showing the tattooing granulomatous reaction of the right arm.



Figure 4: Thirty-year-old female showing eyebrow granuloma, (A); with the extension into the trunk site (B).

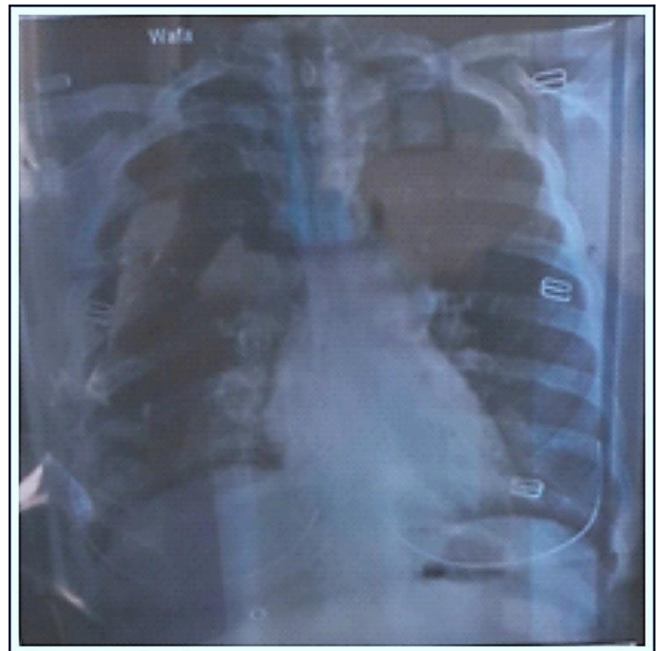


Figure 5: X-ray showing bilateral hilar lymphadenopathy in a patient with tattooing sarcoid.

The histopathological assessment of rash showed marked non-necrotizing granuloma with laden giant cells in 12(85.7%) samples that extend from the papillary dermis to the reticular dermis and many of them were naked with little or no inflammatory reaction (Figure 1A& C). Moreover, almost 9(64.3%) cases revealed that pigmented particles were observed inside the granuloma and sometimes shown free in the nearby collagenous connective tissue (Figure 6). This feature goes parallel with cutaneous sarcoidosis. Furthermore,

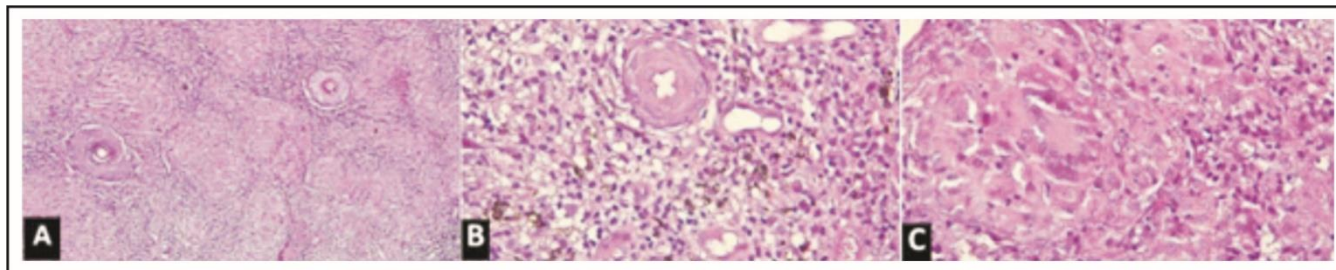


Figure 6: Showing the histopathology of tattooing showing granulomatous reaction with giant cells containing tattoo ink particles (tattoo sarcoidosis). (HE stains: A, X10; B&C, X40).

the enquiry looking at granulomatous diseases was undertaking recurrent assessment as an exclusion trial.

Discussion

Sarcoidal granuloma is a variant of cutaneous sarcoidosis which has been associated with tattooing, scars, surgery, herpes zoster infection, and vaccination.¹⁴ Sarcoidal tattoo of the skin was earlier described by Madden, without signs of systemic sarcoidosis. Subsequently, many studies and articles have been published supporting the manifestations of sarcoid granulomas triggered by tattoos of diverse colors, with or without systemic presentation of the disease.^{4,15}

The tattoo ink pigments have been considered a cosmetic substance and accepted by the US Food and Drug Administration (FDA) which did not approve them as medications. While the Council on Europe Committee on Cosmetic Products in 2008 provided guidelines for tattooing.^{3,16} At present, tattoos are a common practice globally. Approximately, between 18 and 50 years of age are now identified to have at least 1 tattoo in a quarter of Americans as well as Europeans peoples. Physicians are consequently provoked with a rising number of side effects which are largely unfamiliar or underestimated by the community.^{3,16} The Islamic religion forbade tattooing over 1,400 years ago, and this behavior is considered contrary to God's satisfaction,¹⁷ therefore, the tattoo procedure relatively uncommon in Middle East society.

Fourteen patients participated in the current study. Their mean ages were 32 ± 38.7 years. All where women gave a history of tattooing using mostly black ink for cosmetic purposes. The condi-

tion was followed by the appearance of a rash around 4.1 months after the procedure. Generally, tattoos are associated with intervals of inflammation characterized by swelling and erythema that resolves spontaneously within 2 weeks followed by complete epidermal regeneration.¹⁸ Preceding study showed that TS frequently affects young adults of both sexes with equal ratio, their ages ranged between 2 and 40 years. Granulomatous reactions often follow the black tattoos and can appear after a few months to many years after initial tattooing.¹⁹ While other authors reported an extended interval of about 10 years between the tattooing and the formation of the sarcoidal granulomas.²⁰

A recently published survey revealed that persistent skin lesions and pruritus occurring 4 weeks after the tattoo procedure. This might simply signify the development of scars or granulomas. As well as TS were significantly more common in women patients than in men and of black-colored tattoos.^{5,20} The development of sarcoidosis in cosmetic tattoos is well-recognized and can occur spontaneously.²¹ Over decades, a review from various reports by Kluger of cases presented with TS found a significant relation between sarcoidosis, male gender, the black color permanent tattoos, and the size of the tattoo (overloaded pigmentation). As well as the black TS had an association with systemic sarcoidosis.¹⁹

A new review of TS documented that extremities and trunk involvement with equal sex. However, the colored pigments more frequently lead to TS, tumors and other skin problems than black.²² Meanwhile, despite the late onset of skin lesions after tattooing, almost all noticed itching in 78.6% of cases, while swelling presented in 28.6%. These

were gradually increasing in severity over time. This should be differentiated from eczema, psoriasis, and keloid. The sites of tattooing were located on both eyebrows in 85.7% of participants, this can be explained by the most common variant representing the cosmetic tattoo which is considered as a permanent makeup enhancing the appearance of the eyebrows. In addition, 42.8% of patients had extra-eyebrows granulomatous rash, and their tattoo were located on the upper arms and trunk. Prior research approved that TS was frequently associated initially with permanent edema, itching, or skin papules.⁵

The present study showed that the main distribution of cutaneous rash could be localized granuloma (tattoos-related rash) but 21.4% of cases revealed unexpected presentation of generalized skin involvement at non-tattoos-related areas of same patient. No obvious eyes or other systemic involvement were detected by clinical examination or various other investigative procedures at diagnosis or afterwards, apart from one (7.1%) patient confirmed to have bilateral hilar lymphadenopathy. This feature goes with the same line of earlier reports where granulomas in TS occur either as a reaction in the tattooed part of the skin or as they can signify the first sign of systemic involvement. They approved that the cutaneous TS occasionally appears to provoke systemic sarcoidosis.²³

Furthermore, another study including 8 cases presented with TS without systemic sarcoidosis.^{4,15} In contrast, after a history of wide red skin tattooing, a 31-year-old man was diagnosed with a case of systemic sarcoidosis involving the skin, lung and hilar lymph nodes, with an amazing finding of fragments of red tattoo particles within lung tissue spacemen.²⁴ Currently, the tattoos, post herpes zoster, and foreign body reactions appeared to emerge sarcoidal granuloma's reaction as a type of hypersensitivity response to an extrinsic antigen in genetically liable subjects. In the meantime, TS presented as red scaly plaques, papules and small nodules limited by the tattoo area. Interestingly, the sarcoidal granulomas resolve and do not relapse after vaporization of tattoo dye by a CO₂ laser.^{5,22}

Classical cutaneous sarcoidosis could present with a red-brown or red and might be either papular, annular plaques, nodular, or mixed skin lesion.¹¹ These are comparable to the clinical features of the current study where the cutaneous manifestations of sarcoidosis revealed that plaques consistency was firm and rubbery in 71.4% of patients, while the color of the rash most commonly was dusky red in 78.6%, with an apparent scaling that was noticed in 45.7% of cases.

The naked sarcoidal granulomas were the main histopathological evidence in this work. It showed marked non-necrotizing granuloma with laden giant cells in 85.7% of samples that extend from the papillary dermis to the reticular dermis, with few or no other inflammatory cells apart from a few epithelioid and histiocytic cells. Additionally, nearly 64.3% of cases revealed that pigmented particles inside the granuloma and nearby collagenous connective tissue. These clinical and histopathological features are that of cutaneous sarcoidosis and these results of the present work are compatible with findings of several foregoing researchers who defined cutaneous TS as clinical skin lesions besides the presence of noncaseating granulomas but after exclusion of other causes of granulomatous diseases.⁷

Until now, the main cause and pathogenesis of sarcoidosis is unknown.¹⁹ But foreign body immune reaction is the commonest anticipated mechanism explaining the formation of granulomatous inflammation mediated by chronic cellular immune hypersensitivity to a foreign body antigen in genetically susceptible individuals.¹⁹ Skin injury either by trauma or vaccination will introduce foreign non-degradable product into the dermis or subcutaneous tissue, which then can initiate a typical foreign body granulomatous reaction as similarly seen in tattooing granuloma and sarcoid reaction after the entrance of exogenous black pigment to the skin in genetically liable people.²⁵ Therefore, an individual's genetic base plays a crucial role in driving toward the development of a granulomatous state direction either by an exaggerated or reduced immune response.¹⁴

During the World Trade Center disaster, the

rescue workers reported an elevated incidence of emerging systemic sarcoidosis or granulomatous pulmonary disease. Its cause has also been suggested due to exogenous airway exposure to dirty dust, supporting the hypothesis of foreign bodies autoimmunity.²⁶ Another explanation of TS has been reported is ultraviolet-light accentuated tattoos as chronic exposure of skin leads to marked variations in the dermis and eosinophilic collagen bundles, which are substituted by amorphous basophilic substance (elastotic material), that immunologically can act like a foreign element. Interestingly, neural and perineural granuloma formation is an unusual characteristic of idiopathic granulomatous progressions. The peripheral nerve damage partially clarified the development of granuloma composed of histiocytic infiltration with multinucleated giant cells in skin areas injured by trauma, tattoos, or vaccination.²⁷

Sarcoidosis has been very rare in Iraq and has not been reported by a study or case report neither systemic nor cutaneous variant. Sharquie *et al*, in 2024 had documented 24 patients of cutaneous sarcoidosis over 10 years, since 2014.¹³ Recently, TS has been observed to be increasing as documented in the present study. The reason behind this upsurging could not be explained. But the so-called epigenetic theory might find the answers as there is a reversible change in the function of genes following environmental changes, and this will influence the expression of specific genes without changing the DNA arrangement, subsequently affecting its function. So, this epigenetic modification enables quick responses to a stimulus. The new high rate of chronic stubborn courses as well as poor beneficial responses to viral infections, chronic dermatophytosis, and skin tuberculosis, support the hypothesis of epigenetics.²⁸

Similarly, this epigenetics will explain the increase of cases of CS and tattoo granuloma. As Iraq had been exposed to numerous wars since 1979-2003 where different types of chemicals exposures were used in these wars and specifically depleted uranium. These chemicals had triggered increase in the frequency of many diseases like Kaposi sarcoma, lymphoma, mycosis fungoides,

morphea and other blood diseases.²⁹ The early signal of increase in sarcoidosis and related variants in Iraq is reporting of few cases of sarcoidosis-lymphoma syndrome in 2015, followed by reporting sarcoidosis after foreign body inoculation by blast injury in 2014, that followed by sarcoid reaction which appeared after 4 years in 2018.²⁸ These early reports subsequently, followed by upsurge of cases of sarcoidosis and tattoo granuloma sarcoidosis as the pictures now.

Conclusion

To our knowledge, this is the first report supporting that tattoo sarcoidosis has evolved in the last few years in Middle Eastern countries including Iraq and mimicking cutaneous sarcoidosis such as happening in Western countries. As well as it provides insights into the continuous public alertness regarding the multiple forms of tattoos. The dramatic change in Iraqi environment following repeated wars had triggered tremendous changes in the epigenetics of related genes that followed by upsurging of many diseases including sarcoidosis and tattoos granuloma sarcoidosis. Hence, all triggering agents including tattooing must be avoided or prevented.

Ethical Approval: The Ethical Committee of University of Anbar; Ramadi, Anbar, Iraq approved this study vide Ref No. 159/2023.

Conflict of Interest: There was no conflict of interest to be declared by any author.

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Author's Contribution

KES: Conception & design, acquisition of data, critical revision of the article, drafting of article, final approval of the version to be published.

TAK: Drafting of article, final approval of the version to be published.

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