The histopathologic spectrum of decorative tattoo complications

Tattooing for ornamental purposes is an ancient practice that remains popular in modern times. Tattoos are encountered by the dermatopathologist either as incidental findings on skin biopsies or because of complications specific to the tattoo. A range of neoplasms and inflammatory conditions are seen in association with tattoos, many of which may be attributed to hypersensitivity to tattoo inks. The composition of tattoo inks is highly variable, and inks can contain numerous potentially allergenic or carcinogenic compounds. Infections with bacterial, viral and fungal species can occur after tattooing, sometimes after substantial delay. Atypical mycobacterial infections in particular are increasingly reported; special stains for mycobacteria should be performed and cultures recommended particularly when dense, mixed or granulomatous infiltrates are present.

**Keywords:** atypical mycobacterial infection, Mycobacterium chelonae, tattoo pigment, tattoo reaction


Placement of tattoos can be accidental or purposeful, or for decorative or medical reasons. The origin of the word tattoo is the Polynesian ‘tatau’, meaning ‘to mark’. The practice of tattoo for ornamental purposes is as ancient as the second millennium BC and has held many societal roles, including a way of communicating membership in religious or social groups and a form of punishment. In modern times, tattooing is gaining societal acceptance, although obtaining a tattoo remains associated with risk-taking behavior. The exact prevalence of decorative tattoos among the current population is unknown, but among respondents to a recent US telephone survey, 24% acknowledged having at least one tattoo.

Tattoos are encountered relatively frequently in dermatopathology practice, as incidental findings in biopsies, or as specific complications from the tattoo itself, the rate of which may be as high as 2%. We present several cases of tattoo complications and discuss the spectrum of histopathologic findings associated with tattooing.

**Case report 1**

A 35-year-old female presented complaining of ‘bumps’ within her tattoo on her back. She had the tattoo placed by a professional mobile tattoo service and noticed burning, itching and erythematous papules developing in the tattoo 3 weeks later. She had no systemic symptoms. She had several other tattoos placed by the same tattoo service in the past without any incident.

Her past medical history was unremarkable, and she did not take any medications. Physical examination showed multiple grouped papules and pustules within the tattoo, localized to the gray areas and sparing the black areas (Fig. 1). A skin biopsy was performed.

Hematoxylin and eosin (H&E) stained sections showed a dense nodular inflammatory infiltrates in the superficial dermis, comprised of lymphocytes, histiocytes and neutrophils. Admixed black tattoo pigment was noted (Fig. 2A,B). Periodic acid-Schiff stain (PAS), acid fast and Gram stains were negative for organisms. A skin biopsy was submitted for
culture, and grew 1+ *Mycobacterium chelonae* after 2 weeks. The patient was treated empirically with oral clarithromycin and levofloxacin. However, after the susceptibility test from her culture showed resistance to levofloxacin, she was maintained on clarithromycin monotherapy for 4 months, with complete resolution of the lesions.

**Case report 2**

A 38 year-old man presented for evaluation of papules that developed within a red and blue tattoo on his left forearm. He acquired the tattoo 6 years prior, and noted the onset of asymptomatic papules approximately 2 years later.

The patient’s past medical history included human immunodeficiency virus infection, with a CD4 count of 41 cells/ul (normal range 500–1500 cells/ul). Physical examination was notable for multiple tattoos on the upper extremities. Erythematous, indurated papules and small plaques were noted within the red inked areas of the left forearm tattoo (Fig. 3), as well as several of his other tattoos.

The H&E stained sections of a biopsy from the left forearm was notable for aggregates of red pigment in the superficial dermis, consistent with tattoo pigment, associated with a dense nodular perivascular lymphoid infiltrate (Fig. 4). Admixed eosinophils and plasma cells were present, and there was early germinal center formation reminiscent of a B-cell lymphomatous process. PAS and acid-fast bacillus stains were negative. A concurrent biopsy was sent for tissue culture and was also negative, and
the diagnosis of pseudolymphomatous tattoo reaction was made.

**Case report 3**

A 40-year-old woman presented complaining of diffuse pruritus. Past medical history was significant for chronic pain and substance abuse. On physical examination she was noted to have violaceous papules within a professionally placed tattoo on her forearm placed many years earlier (Fig. 5), along with two erythematous-to-violaceous plaques on non-tattooed skin on the back.

The H&E stained sections of a biopsy from the tattoo showed a perivascular and periadnexal lymphocytic infiltrate with admixed pigmented macrophages in the superficial and deep dermis (Fig. 6A, B), as well as a lichenoid infiltrate associated with dyskeratotic keratinocytes and pigment incontinence (Fig. 6C). A biopsy of a non-tattooed lesion on the flank showed a similar pattern of lichenoid dermatitis with a superficial and deep perivascular and periadnexal lymphocytic infiltrate. Dermal mucin deposition was also seen. Laboratory work-up revealed an anti-nuclear antibody titer of 1:80, normal complete blood count and normal chemistry panel including creatinine. As the patient did not have any systemic signs or symptoms consistent with systemic lupus erythematosus, the diagnosis of cutaneous lupus erythematosus-like reaction was made. The patient was treated with ultrapotent topical steroids with complete resolution of the rash in her tattoo and elsewhere on her skin.

**Discussion**

Modern, professionally placed tattoos are performed using a tattoo machine that repeatedly punctures the skin to a depth of 1–2 mm, delivering pigmented inks into the dermis.1 ‘Inks’ are suspensions of pigments, composed of metal salts and organic compounds, the majority of which are considered biologically inert. Different shades and colors are made by combining different pigments and/or diluting with water or alcohol.1 Black inks are composed primarily of iron oxides and various carbons. Traditionally, blue inks contained cobalt, chromium and copper salts; green inks primarily chromium and copper, and yellow cadmium salts. Red inks contained high levels of mercury, however contemporary red ink is derived from mixtures of cadmium and sometimes iron oxides.5 Organic azo dyes (examples include Pigment Red, Pigment Yellow) and phthalocyanines are compounds originally designed for commercial uses such as printing and car paint and are increasingly being used in tattoo inks because of their intense color.6,7

The histopathology of a banal tattoo typically shows clumps of pigment free in the dermis and within dermal macrophages (Fig. 7). The amount and distribution of pigment present depends on the several factors, including the operator, type of tattoo machine used and the age of the tattoo.6 Older tattoos show a decrease in overall pigment, with less free pigment, and the remaining pigment distributed in perivascular macrophages.6 Pigment is shed from the epidermis immediately after tattooing and still more is carried to the lymphatic system over time.8 Intracutaneous degradation because of UV irradiation may also occur.6

Tattoos can be microscopically confused with other entities with dermal pigment deposition. Blue nevi show dermal melanophages that can mimic tattoo pigment-laden macrophages. Tattoos do not contain spindled melanocytes, and
Fig. 6. A) Cutaneous lupus-like reaction with superficial and deep perivascular and perifollicular lymphocytic infiltrate with admixed tattoo pigment in the superficial dermis [hematoxylin and eosin (H&E), ×50]. B) Cutaneous lupus-like reaction; perifollicular lymphocytic infiltrate with admixed tattoo pigment (H&E, ×200). C) Cutaneous lupus-like reaction; higher power view showing vacuolar interface change with a dyskeratotic keratinocyte. H&E, ×400.

Fig. 7. Banal tattoo showing granular black pigment within perivascular macrophages and free in the dermis. Hematoxylin and eosin (H&E), ×400.

immunohistochemical stains such as S100 or Melan-A/melanin-associated antigen recognized by T cells (MART-1) may be helpful in differentiating between tattoo and blue nevus in difficult cases. Tattoos can also mimic the metal deposition disorder chrysiasis, which shows irregularly shaped black granules in macrophages in a similar perivascular distribution. Minocycline drug pigmentation also shows black granules within perivascular dermal macrophages; however, unlike tattoo pigment, the pigment deposited in minocycline hyperpigmentation is highlighted with Prussian blue and Fontana-Masson. Antimalarial (hydroxychloroquine and chloroquine) and amiodarone hyperpigmentation can also be included in the pathologic differential diagnosis of tattoo, and show yellow–brown pigment granules both inside and outside of dermal macrophages. Antimalarials and amiodarone stain with Fontana-Masson, and antimalarials may variably stain for iron. Antimalarial pigment deposition may also be deeper in the dermis than typical for tattoo.

The Federal Drug Administration considers tattoo inks to be cosmetics, although the pigments used in the inks are color additives that require premarket approval. Given the lack of regulation, the
composition of tattoo inks is erratic,\textsuperscript{14} and in many cases no list of ingredients is provided.\textsuperscript{15} Several studies have showed measurable levels of potentially allergenic or otherwise hazardous materials in tattoo inks. Using a level of 1 ppm as the standard for ‘allergologically safe’, Forte et al.\textsuperscript{5} found allergenic chromium levels in 62.5\% of 56 internationally available tattoo inks tested, and high nickel levels in 16\%. Black inks contain measurable and sometimes high levels of dibutyl phthalate, a plasticizer that has been shown to induce expression of cytokines in the skin, and benzophenone, an irritant and potential photosensitizer.\textsuperscript{15} Azo dyes, such as Pigment Yellow, release photodecomposition products upon UV exposure, the consequences of which are unknown.\textsuperscript{16} Many tattoo inks contain nanoparticles, which may be more ‘biologically active’ and thus more easily introduced into circulation.\textsuperscript{17}

Tattoos and neoplasms

Tattoos have been reported in association with various cutaneous malignancies, including basal cell carcinoma,\textsuperscript{18} squamous cell carcinoma\textsuperscript{19} and leiomyosarcoma.\textsuperscript{20} Pseudocarcinomatous, hyperplastic inflammatory reactions to tattoo pigment can mimic squamous cell carcinoma and keratoacanthoma (Fig. 8A,B). Similar microscopic findings can be seen overlying infections due to atypical mycobacteria and fungal species, and consideration should be given to special stains and/or cultures, particularly if dense inflammatory infiltrates are seen.

Whether the development of neoplasms in tattoos is coincident or in some way due to the tattoo is unknown. Local skin trauma may be a factor, as has been proposed in the case of keratoacanthoma developing in a tattoo shortly after placement.\textsuperscript{21} Similarly, epidermoid cysts and milia have been reported after tattooing.\textsuperscript{22} Trauma is probably not the only factor, however; tattoo inks have been shown to contain numerous potentially hazardous and carcinogenic compounds that hypothetically could be tumorigenic. Black inks, for example, contain carbonaceous byproducts of soot, including polycyclic aromatic hydrocarbons in amounts far above the acceptable level for drinking water.\textsuperscript{23}

The clinical and microscopic analysis of melanocytic lesions can be complicated by the presence of tattoo. Melanoma can develop within tattoos\textsuperscript{24,25} and clinical recognition can be made more difficult by the presence of surrounding tattooed areas that can mimic melanin pigment. The clinical appearance of otherwise benign nevi can be altered by tattoos, introducing scar-like areas and irregular pigment patterns reminiscent of melanoma on dermatoscopic exam.\textsuperscript{26} Histopathologically, macrophages laden with tattoo pigment can appear similar to areas of regression in melanoma.\textsuperscript{27} Tattoo pigment is taken up by dermal macrophages and delivered to draining lymph nodes, potentially misleading surgeons and pathologists in the analysis of sentinel lymph nodes.\textsuperscript{28,29}

Tattoos and inflammatory reactions

Numerous types of inflammatory reactions can develop in and around tattoos. Reactions can be because of the Koebner or ‘isomorphic’ phenomenon, as in psoriasis arising in tattooed skin,\textsuperscript{30} or may be because of the hypersensitivity to tattoo inks. Given the variability in composition of tattoo inks, even among similar appearing colors,\textsuperscript{14} it is often difficult to determine which specific ink component is responsible for a particular reaction. Nonetheless, red inks historically in general are the most frequently associated with tattoo reactions.\textsuperscript{31} Reactions to red ink continue to occur despite a transition from mercury containing inks (such as cinnabar) to other metals and dyes.\textsuperscript{32,33}

\textbf{Fig. 8.} A) Keratoacanthoma-like tattoo reaction with crateriform architecture and a mixed dermal inflammatory infiltrate. Hematoxylin and eosin (H&E), ×25. B) Keratoacanthoma-like tattoo reaction; cystic epidermal invaginations with ‘glassy’ keratinocytes, parakeratosis and a dermal inflammatory infiltrate admixed with red tattoo pigment. Hematoxylin and eosin (H&E), ×100.
Lichenoid-type reactions are a frequently reported pattern of inflammation seen in tattoo. Biopsies of lichenoid tattoo reactions show acanthosis and vacuolar alteration of basilar keratinocytes with tattoo pigment intermixed in a band-like infiltrate of lymphocytes. Cutaneous lupus erythematosus-like reactions, as in our patient, may be a variant of lichenoid tattoo reactions and, although uncommon, have been previously reported. Lichenoid tattoo reactions have been proposed to be delayed type hypersensitivity reactions and are most commonly reported with tattoos containing red dye of various compositions. Trace nickel may play a role, and other colors of ink have been implicated. Lichenoid tattoo reactions can be indistinguishable from lichen planus, and in some cases may actually represent Koebner responses of true lichen planus to the tattoo. In addition, there are reports of tattoos triggering generalized lichen-planus type eruptions.

Granulomatous reactions also frequently arise in tattoos. Sarcoideal-type reactions, particularly in the setting of interferon-alpha treatment of hepatitis C, can occur decades after a tattoo is placed and are a manifestation of ‘scar sarcoid’. All ink colors can be involved, with a clinical presentation of firm, indurated papules and plaques typically limited to the tattooed areas. Skin biopsies show dermal to subcutaneous sarcoideal granulomas with admixed tattoo pigment. Stains and/or cultures to exclude fungal or atypical mycobacterial infection are essential. Systemic manifestations of sarcoid, primarily lung disease, may occur. Patients who develop cutaneous sarcoidosis in the setting of interferon often have spontaneous remission upon discontinuation of therapy. Granuloma annulare-like reactions, although rare, also occur and show tattoo pigments and epithelioid histiocytes palisading around necrobiotic collagen. In the one reported case, blue and black pigments were implicated in a tattoo present for 7 months. Necrobiosis lipoidica (NLD) has been reported at the site of a tattoo in a non-diabetic patient, with a characteristic yellow-hued atrophic plaque developing within and around the tattoo. Biopsies showed zones of degenerated collagen without mucin deposition, typical of NLD; the authors proposed that NLD developed secondary to Koebnerization.

Pseudolymphomatous tattoo reactions are types of cutaneous lymphoid hyperplasias (CLH) that can mimic B-cell or T-cell lymphomas. Biopsies simulating B-cell lymphomas, as in our patient, show tattoo pigment and macrophages among variably dense infiltrates of lymphocytes, often with early follicle or germinal center formation. Lichenoid reactions can mimic mycosis fungoides, and T-cell rich and mixed pseudolymphomas have also been reported. Immunohistochemical stains show that infiltrates are typically mixed B and T cells, with variable populations of eosinophils and plasma cells. Immunoglobulin H and T-cell receptor rearrangement studies, when performed, show polyclonal lymphocyte populations. One case of an apparent true B-cell lymphoma has been reported in a patient after longstanding pseudolymphomatous tattoo reaction, suggesting that chronic antigenic stimulation from tattoo pigments may play a role in the development of these lesions. Red pigment is most commonly implicated in tattoo-related pseudolymphomas of all types, although CLH has been reported in green portions of tattoos as well.

In addition to cutaneous lupus, tattoo reactions can mimic other connective tissue diseases. Morphea or scleroderma-like reactions have been reported...
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Fig. 11. A) Pseudolymphomatous tattoo reaction; dense nodular infiltrate with early germinal center formation. Hematoxylin and eosin (H&E), ×50. B) Pseudolymphomatous tattoo reaction; higher power view showing a mixed infiltrate of lymphocytes and macrophages with admixed black tattoo pigment (H&E, ×400).

in tattoos, involving a multicolored tattoo in one case\(^49\) and limited to the red inked part of a tattoo in another.\(^50\) In both instances, the tattoos were pruritic, and there was no evidence of morphea or scleroderma outside of the tattoo. Kluger et al.\(^50\) hypothesize that these reactions may represent end-stage dermal sclerosis secondary to a long-standing untreated hypersensitivity reaction to the tattoo ink.

**Tattoo and infection**

Infections in tattoos can occur anywhere from a few weeks, as in the case of acute pyogenic infections, to decades, as in inoculation leprosy.\(^31\) Acute pyogenic bacterial infections occur within 1–2 weeks after a tattoo is applied, and are rarely biopsied.

Infections because of the rapidly growing mycobacterial species such as *M. chelonae*, as in our patient, and *M. abscessus*\(^51\) are increasingly reported\(^56\) and typically present within 1 month of tattooing. Many of these non-tuberculous mycobacterial infections occurred in the gray areas of the tattoo in which black pigment was diluted with contaminated tap water, implicating tap water as a source of outbreaks.\(^31\) Biopsies typically show granulomatous infiltrates in the superficial to deep dermis, with or without neutrophils. Special stains for mycobacteria may not show organisms (as in the case of our patient), and follow-up tissue culture is recommended, particularly if neutrophils or caseation necrosis are present.

Other mycobacterial infections, although less common, can occur, typically with a latency of at least several months after tattoo placement. Lupus vulgaris in a tattoo was reported in one patient who had a tattoo placed in a professional tattoo parlor in Singapore.\(^32\) Biopsy showed caseating granulomas, and acid-fast bacilli were seen with Ziehl–Nielsen staining. Similar eruptions occurred in several patients in India because of the ‘roadside’ tattooing,\(^33\) although organisms were not demonstrable in tissue sections or culture. Cases of inoculation leprosy occurring decades after tattooing have been seen in a region of India in which leprosy remains endemic.\(^34\)

Human papilloma virus (HPV) infection can be seen in tattoos and may develop years after tattooing. In one case multiple verrucae limited to one color of a tattoo developed, implicating HPV inoculation via the tattoo ink.\(^53\) Sunburn on an established tattoo was an additional inciting factor in one case.\(^56\) Whether some verrucous lesions represent true HPV infection or verrucous inflammatory reactions is not clear, as the presence of HPV virus cannot always be showed.\(^55\)

A single case of zygomycosis occurring in a tattoo has been reported. The patient was an otherwise healthy young man who developed a deep necrotic ulcer within a tattoo 7 years after the tattoo was placed. Biopsy showed mixed and granulomatous inflammation with necrosis, and thick hyphae were visible in the tissue. Cultures grew *Saksenaea vasiformis*.\(^57\)

**Summary**

A broad range of histopathology occurs in tattoos. Among neoplasms, the collision between melanocytic lesions and tattoo can be particularly challenging, leading to potential misdiagnosis. Some tattoo reactions, including pseudocarcinomatous or keratoacanthoma-like reactions, can be difficult to differentiate from true cutaneous malignancies, requiring clinicopathologic correlation. Numerous inflammatory reaction patterns can occur, particularly variants of lichenoid, pseudolymphomatous and
granulomatous patterns. Many of these probably represent hypersensitivity reactions to tattoo inks. Infections should always be kept in the pathologic differential diagnosis of tattoo reactions, even in long-standing tattoos, and work-up should include stains for fungal and mycobacterial species when appropriate.

There is an immense variability in the composition of tattoo inks, making it difficult to definitively assign causality in tattoo reactions. Increasing evidence suggests that at least some tattoo inks may contain potentially allergenic, tumorigenic or otherwise hazardous compounds. Tattoo inks can undergo further alteration or degradation in the skin, the effects of which are not presently known. As newer compounds, including organic azo dyes, phthalocyanines and fluorescent dyes are increasingly used, it is likely that the frequency and type(s) of tattoo reactions will change.

References

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