Late-onset pseudoepitheliomatous hyperplasia developing within a red ink tattoo

George Badavanis[1] MD, Panayotis Constantinou[2] MD MSc, Efstathia Pasmatzi[3] MD, Alexandra Monastirli[1,3] MD, Dionysios Tsambaos[1,3] MD PhD

Affiliations: [1]Center for Dermatologic Diseases, Limassol, Cyprus, [2]Histopathology & Cytology Laboratory, Nicosia, Cyprus, [3]Department of Dermatology, School of Medicine, University of Patras, Greece

Corresponding Author: Efstathia Pasmatzi MD, Associate Professor, Department of Dermatology, School of Medicine, University of Patras, P.O. Box 1413, 26504 Rio-Patras, Greece, Tel: 30-261-0 270 577, Fax: 30-261-0 270235, Email: pasmatzi@med.upatras.gr, pasmatzi@otenet.gr

Abstract

The popularity of tattoos has increased dramatically worldwide particularly in the last three decades, giving rise to the frequent occurrence of a wide spectrum of secondary cutaneous and systemic complications. Pseudoepitheliomatous hyperplasia (PEH) is a benign irregular hyperplasia of the epidermis occurring in response to various stimuli, that clinically and histopathologically resembles cutaneous neoplasms such as squamous cell carcinoma and keratoacanthoma. In an attempt to improve the awareness of the possible occurrence of PEH in tattoos and of its diagnostic and therapeutic aspects, we present herein the case of a 30-year-old woman with histologically confirmed PEH related to a red-ink tattoo. She revealed two important features: the longest interval reported so far between tattooing and onset of PEH (two years) and the lack of the otherwise very common lichenoid tissue reaction to red ink. In view of the serious toxicological potential of tattoo inks, implementation of updated and standardized regulations worldwide regarding their use in the tattooing process is now urgently warranted and continuous efforts should be undertaken in order to enhance the awareness among tattoo artists and the public with regard to the possible serious health risks associated with the use of tattoo ink pigments.

Keywords: red ink, tattoo, pseudoepitheliomatous hyperplasia

Introduction

Tattooing is defined as the process of implantation of exogenous inerasable pigment into the dermis of the skin or other parts of the body (e.g., mucosae, lips, eyebrows, eyes) of consumers to create a design. Although tattoos in most cases are decorative, they can also serve religious or medical purposes (e.g. breast reconstruction, radiotherapy), or may occur accidentally after injuries (traumatic tattoos).

Particularly in the last three decades, the popularity of tattoos has impressively increased worldwide and has become mainstream at least for the young generation. It is estimated that more than 100 million European citizens and about 24% of the US population up to the age of 60 years have one or more permanent tattoos on their skin [1]. Already by the end of 19th century it was well known that tattoos may elicit a variety of mucocutaneous or systemic, early or delayed, acute or chronic complications. According to the type of reaction these complications can be classified as hypersensitivity or inflammatory reactions and as infectious, neoplastic, or granulomatous disorders [2].

Pseudoepitheliomatous hyperplasia (PEH) is a benign irregular hyperplasia of the epidermis that occurs in response to various stimuli and bears clinical and histopathological similarity to cutaneous neoplasms, such as squamous cell carcinoma (SCC) and keratoacanthoma [3-5]. PEH secondary to tattoo

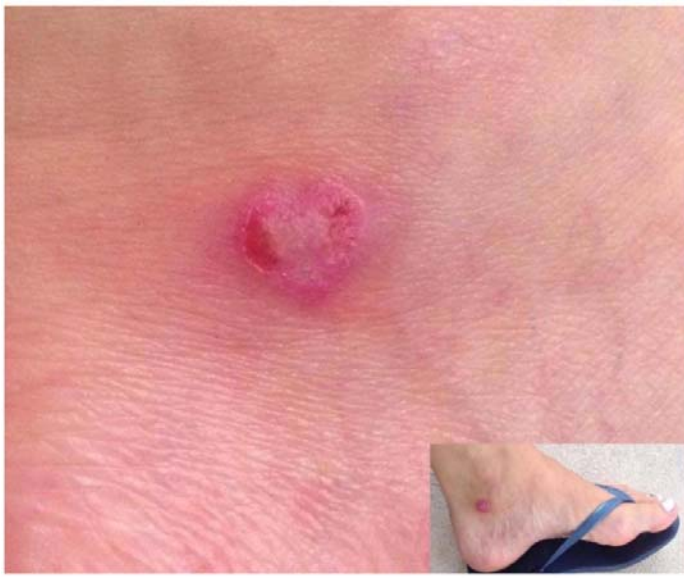

Figure 1. *Well demarcated heart-shaped firm nodule with verrucous and partly erosive surface beneath the medial malleolus of the left foot.*

is a rare complication. In an attempt to improve the awareness among physicians of the possible occurrence of PEH in tattoos and of its diagnostic and therapeutic aspects, we present herein the case of a 30-year-old woman with histologically confirmed late-onset PEH reaction to a red-ink permanent tattoo.

Case Synopsis

A 30-year-old HIV-negative and otherwise healthy woman presented to the Center for Dermatologic Diseases in Limassol, Cyprus, with a one-year history of a skin lesion progressively arising on the inner aspect of the ankle of her left foot on a red tattoo performed by a professional artist in the United States three years prior. She was not aware of the origin, the type, or the quantity of the red ink used. She had no history of malignancy or immunosuppression and received no medications on a daily basis. Clinical examination revealed a well-developed woman in no acute distress that was remarkable for a well demarcated heart-shaped firm nodule (1.3cm in diameter) with a verrucous and partly erosive surface beneath the medial malleolus of the left foot (**Figure 1**). There was no evidence of lymphadenopathy and/or hepatosplenomegaly. Routine hematological, biochemical and serological tests and X-ray examination of the leg revealed normal or negative results. The results of bacteriological and mycological examination of the skin lesion were also negative.

Histopathological examination of a deep biopsy obtained from the lesional skin revealed epidermal pseudoepitheliomatous hyperplasia, characterized by irregular acanthosis and parakeratosis. There were sharply pointed epithelial strands projecting into the underlying dermis, whereas significant cellular atypia was lacking and mitoses were rare. Prominent extracellular deposits of red exogenous pigment were found between collagen bundles in the upper and mid dermis accompanied by a mixed inflammatory cell infiltrate consisting of lymphocytes and plasma cells (**Figure 2**). Thus, the diagnosis of PEH at the site of the tattoo was established. The lesion was totally excised with excellent cosmetic results.

Case Discussion

In view of the millions of tattooed people worldwide, it is not surprising that tattoo-related complications are being increasingly encountered by dermatologists

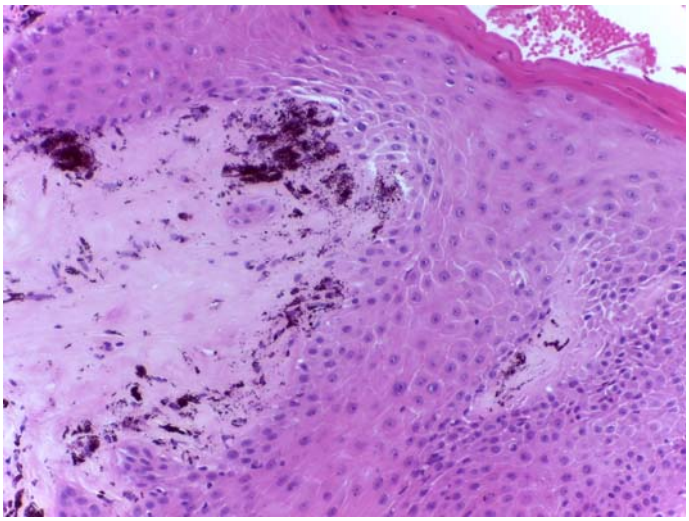

Figure 2. *Pseudoepitheliomatous hyperplasia as a reaction in a red tattoo. The epidermis reveals a distinct hyperkeratosis, parakeratosis and acanthosis with sharply-pointed epithelial strands projecting into the underlying dermis. In the papillary dermis, extracellular deposits of red pigment are seen, that are accompanied by a mixed inflammatory cell infiltrate consisting of lymphocytes and plasma cells. H&E, 100×.*

Table 1. *Mucocutaneous and systemic adverse reactions related to permanent tattoos.*

A. Systemic Reactions [1, 2, 39-41]	**B. Mucocutaneous Reactions**			
	B1. Hypersensitivity and inflammatory reactions [9, 11, 41-48]	**B2. Infections** [46, 49-54]	**B3. Neoplasms** [12, 13, 29, 46, 55-60]	**B4. Granulomatous Reactions** [1, 2, 61-64]
Abdominal compartment syndrome Bacteremia Death Endocarditis Fat necrosis Fever Gangrene Iliopsoas abscess Latex allergy Lymphadenopathy regional or generalized Lymphoedema Multiorgan failure Necrotizing pneumonia Pyelonephritis Septic shock Spinal abscesses Systemic bacterial and viral infections Systemic vasculitis Tropical pyomyositis Uveitis Xanthogranulomatous	Acute GVHD Angioneurotic oedema Bleeding / Hematoma Blister formation "Blue-foot" discoloration Burning sensation Chronic fibrosing vasculitis Contact dermatitis Contact urticaria Crusting Edematous "peau d' orange" Erythema multiforme Hypertrichosis Hypo- or hyperpigmentation Lichen planus and lichenoid lesions Light-induced urticaria Lymphoedema Morphea and scleroderma-like lesions Mucosal ulceration Necrotizing fasciitis or tissue necrosis Pain or tenderness Paradoxical skin darkening Photodermatitis Pigment diffusion Prurigo nodularis Pruritus Pseudolymphomatous lesion Psoriasis Purpura / Petechiae Pyoderma gangrenosum Scarring / Keloid Subacute or discoid lupus erythematosus Sweet syndrome Swelling Vasculitis Wells syndrome	**Bacterial** Abscesses Cellulitis Cutaneous diptheria Erysipelas Gangrene Impetigo Leprosy MRSA infections Non-tuberculous mycobacterium skin infections Staphylococcal scalded skin syndrome Syphilis Tetanus Tuberculosis **Viral** CMV Heparitis B and C HIV HPV HSV Molluscum contagiosum **Fungal** Aspergillosis Dermatophytosis Sporotrichosis Tinea cutis Zygomycoses	**Benign** Cutaneous lymphoid hyperplasia Dermatofibroma Epidermal cysts Milia Seborrhoeic keratosis **Malignant** Basal cell carcinoma Fibrosarcoma protuberans Keratoacanthoma Lymphomas Melanoma Squamous cell carcinoma	Foreign body reaction Perforating granulomatous reaction Sarcoidosis Necrobiotic reaction Tuberculoid reaction

in everyday clinical practice. The prevalence of the reported complications varies between 2% and 27% [2, 6]. Nevertheless, its accurate estimation is presently impossible because a number of cases remains unreported and controlled studies on large numbers of individuals are still lacking. Tattoo-related complications can be acute or have a protracted and chronic course [7]. **Table 1** summarizes the reported mucocutaneous and systemic complications of permanent tattoos.

Cutaneous complications of red tattoos are very common, with allergic dermatitis, photosensitivity, and granulomatous adverse reactions being the most frequent ones [8-11]. Red inks are associated with 34% of post-tattoo skin cancers, 50% of SCCs, and 73% of keratoacanthomas [12, 13]. It is believed that substances contained in red inks (e.g. 2-anisidine) function as co-carcinogens, especially in combination with sunlight exposure [14].

PEH is a benign proliferative cutaneous disorder, occurring in response to various stimuli, which is regarded as a reactive histopathological pattern rather than a distinct nosological entity [15]. Clinically PEH occurs as a nodule or plaque of various sizes with a verrucoid or vegetative surface, scaling, and possibly ulceration and crusting [16]. The main histopathological feature of PEH is the presence of follicular infundibulum-derived irregular projections of the epidermis extending deep into the reticular dermis. Orthokeratosis, parakeratosis, hypergranulosis, and keratin pearls are usual findings, whereas mitoses are sparse and not-atypical [16]. Owing to their clinical and histopathological similarities, the distinction between PEH and SCC can be very challenging. A deep biopsy including the base of the lesion and underlying dermis is usually necessary for a definitive diagnosis. Important histopathological features that favor the diagnosis of PEH are minimal cytological atypia, paucity of mitotic activity, absence of atypical mitoses, and absence of necrotic keratinocytes or vascular and perineural invasion [16, 17].

Since the original description of PEH secondary to a tattoo by Sulzberger in 1937, 20 cases have been reported (**Table 2**), [17-28]. However, owing to substantial clinical and histopathological similarity, the possibility that some cases previously reported as keratoacanthomas or lichenoid hypersensitivity reactions in tattooed patients were in fact PEH cannot be definitely excluded [10]. Interestingly, almost all tattoo-related PEH cases reported so far were associated with the use of either red or purple dye. The interval between tattooing and the onset of PEH varies between 4 days and 12 months. In our patient PEH occurred two years after tattooing, the longest interval reported so far, to our knowledge. Additionally, the lichenoid tissue reaction to red ink, that is otherwise very common among PEH patients [10], was absent in our case.

Upon transfer of the pigment into the dermis using an electric vibrating device, pigment granules are ingested by skin phagocytes and a transient inflammatory period of two-week duration is initiated that is characterized by a foreign-body reaction and fibrous tissue formation [4]. Finally, the pigment is encapsulated in dense layers of connective tissue mainly in the papillary dermis either within fibroblasts or between collagen bundles [11, 29]. Pigment can migrate, however, via lymphatics to regional lymph nodes, which in some cases are filled with pigment [12]. Recently, Sepehri et al. [30] reported the occurrence of tattoo pigments in the blood circulation and in the Kupffer cells of the mouse liver, as well. These pigments can be degraded under UV irradiation leading to the formation of toxic or carcinogenic products such as 3, 3-dichlorobenzidine [31-35].

The exact pathogenetic mechanisms of PEH secondary to tattoos still remain unknown. Since PEH is specifically related to red pigment in permanent tattoos, it has been hypothesized that early inflammation triggered by the newly introduced exogenous pigment could result in the development of PEH [4]. PEH is regarded by some authors as an autoimmune reaction and epidermal hyperplasia as the result of lymphocyte-derived chemokines inducing keratinocyte proliferation [28].

The red tattoo pigmentation was traditionally achieved by the use of cinnabar (mercuric sulfide), a well-known allergen that has been implicated in several cases of delayed hypersensitivity reactions [1]. Actually, the first described case of tattoo-related PEH by Sulzberger [18] was associated with its use. Although cinnabar has been gradually replaced by new mercury-free red pigments such as cadmium red, iron oxide, ferric sulfate, hematite, cadmium selenide, sienna, naphthol-AS pigment, azo pigments (pigment red 210, 170, 112, 122), and quinacridones (Violet 19, red 122), [1], adverse reactions in red tattoo areas still continue to occur.

Table 2. *Reported cases of PEH after tattoo.*

	Gender	Age	Tattoo pigment	Interval between tattoo and onset of PEH	Treatment	Authors
1	M	25	Red	Unknown	Unknown	Sulzberger 1937
2	M	23	Red	12 months	Surgical excision	Goldberg 1959
3	M	Unknown	Red	Unknown	Unknown	Goldstein 1967
4	M	Unknown	Red	Unknown	Unknown	Goldstein 1967
5	F	27	Purple	2 months	Surgical excision	Balfour et al 2003
6	F	59	Red, green, yellow	1 week	Surgical excision	Cui et al 2007
7	F	30	Red	1 month	Lost to follow up	Kluger et al 2008
8	F	32	Red	4 days	Topical cosrticosteroids (partial response)	Kluger et al 2008
9	F	54	Unknown	3 months	Topical cosrticosteroids (no response)	Kluger et al 2008
10	F	24	Red	12 months	Surgical excision	Then et al 2009
11	M	51	Red	1 month after tattoo recoloring	Unknown	de Freitas Ferreira Hostalácio et al 2011
12	F	50	Red	1 month	Surgical excision	De Roeck et al 2012
13	M	31	Red	2 months	Topical cosrticosteroids and surgical excision	Breza et al 2013
14	M	47	Red	7 months after tattoo recoloring	Topical 5-FU (no response)	Kazlouskaya et al 2015
15	F	44	Red	7 – 9 months	Self-resolution 6 weeks after biopsy	Kazlouskaya et al 2015
16	F	36	Red	Unknown	Unknown	Kiss et al 2016
17	F	26	Purple	6 months	Intralesional corticosteroids	Tammaro et al 2016
18	F	25	Red	2 weeks after tattoo recoloring with a new red color	Topical and systemic corticosteroids (initial clearance, relapse after 10 days)	Conti et al 2017
19	F	36	Red	Recently after injections of pigment in an 1-year tatoo	Intralesional corticosteroids	Tammaro et al 2018
20	F	52	Red	1 year	CO_2 laser treatment was programmed	Broussard-Steinberg et al 2018

Sunlight exposure of the red tattoo areas prior of the occurrence of PEH is a common denominator among the reported cases and is considered as an additional pathogenetic factor for this complication [18], possibly through the production of toxic or sensitizing substances by photodegradation or metabolic activation of the pigment molecules. The tattoo of our patient was located on the ankle of her left foot and, thus, would likely be heavily exposed to sunlight. It is possible, therefore, that UV irradiation could have contributed to the development of PEH in her tattoo.

Unfortunately, tattoo inks are not regulated by the FDA as they are considered to be cosmetics and additives, whereas in the European Union (EU) they are regarded as general consumer products and hence, are regulated under the General Product Safety Directive (92/59/EEC). It is obvious, therefore,

that the manufacturers in the US have no obligation to disclose the chemicals contained in these inks and that the ingredients of the latter have never been tested for safety when injected into the skin [35]. Guidelines in a resolution of the Council of the EU released in 2008 are:

1. The maximum permitted concentrations of carcinogenic, mutagenic and reproduction-toxic substances in tattoo inks were established, and

2. The necessary conditions for risk evaluation prior to performing tattoos and for the appropriate information of customers about the health risks of the latter were described [2, 32, 36].

However, the effectiveness of this resolution is practically limited since most inks used for tattooing are manufactured in, and can be purchased from countries outside the EU [2].

The modalities most commonly applied in the management of PEH secondary to tattoo include surgical excision, topical or intralesional corticosteroids, topical 5-FU, or CO_2 laser that reportedly reveal varying therapeutic efficacy. There are also some anecdotal reports on the treatment of PEH with photochemotherapy (PUVA), phototherapy (narrow band UVB), excimer laser, or photodynamic therapy, and topical calcineurin inhibitors based on the clinical and histological similarity of PEH with hypertrophic lichen planus [10]. Our patient was treated with excellent cosmetic results by surgical excision, which is the treatment of choice, particularly for small and well-defined lesions. Carbon dioxide laser treatment is the main alternative, especially for larger lesions, as it effectively ablates the hypertrophic tissue and leads to fragmentation of the pigment particles into smaller sizes, which can then be eliminated by physiological processes [37, 38]. However, it should be kept in mind that the latter may result in a significant alteration in the structure and chemical properties of red pigment particles associated with allergenic or toxic potential [37, 38].

Conclusion

The frequency of cutaneous and systemic complications secondary to tattoos is constantly rising as a result of the increased popularity of tattooing process. Red tattoos are associated with an increased rate of dermatological complications, including SCCs and keratoacanthomas. PEH is a rarely reported (and possibly underdiagnosed) complication of red and purple tattoos that bears considerable clinical and histopathological similarity to cutaneous neoplasms, and especially SCCs and keratoacanthomas.

We present herein the case of a 30-year-old woman with late-onset PEH (two years) to a red-ink tattoo, histologically characterized by lack of the otherwise very common lichenoid reaction. We review the relevant literature, since an extensive knowledge of PEH is mandatory for its early diagnosis and appropriate treatment. Finally, since the composition, biokinetics, metabolic activation, phototoxicity, migratory, and carcinogenic potential of tattoo inks still remains unexplored and a constant reason of serious concern, we feel obliged to emphasize the necessity for urgent implementation of updated and standardized regulations worldwide with regard to their use in tattooing. On the other hand, continuous and concerted efforts should be undertaken in order to enhance the awareness among tattoo artists and the public with regard to the possible serious health risks associated with the use in the tattooing process of ink pigments of questionable or completely unknown safety.

Potential conflicts of interest

The authors declare no conflicts of interests.

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