Case Reports in Dermatology

Case Rep Dermatol 2020;13:379–383
DOI: 10.1159/000513926
Received: September 24, 2020
Accepted: December 19, 2020
Published online: July 16, 2021

Single Case

Delayed-Type Hypersensitivity Reaction to Red Tattoo Ink Triggered by Ledipasvir/Sofosbuvir for Hepatitis C: A Case Report

Meghan L. McPhie[a] Kevin Y.M. Ren[b] J. Michael Hendry[c] Sonja Molin[d] Thomas Herzinger[d]

[a]School of Medicine, Queen's University, Kingston, ON, Canada; [b]Department of Pathology and Molecular Medicine, Queen's University, Kingston, ON, Canada; [c]Division of Plastic Surgery, Department of Surgery, Queen's University, Kingston, ON, Canada; [d]Division of Dermatology, Department of Medicine, Queen's University, Kingston, ON, Canada

Keywords
Delayed hypersensitivity · Tattooing · Hepatitis C · Ledipasvir · Sofosbuvir drug combination

Abstract
Tattoos have become increasingly popular worldwide making adverse effects from tattoos a growing concern. In our report, we present a 51-year-old man who developed an unusual allergic reaction to the red ink portions of his tattoos that coincided with the initiation of ledipasvir/sofosbuvir treatment for his hepatitis C. Clinical and histological features were consistent with a delayed-type hypersensitivity reaction to red ink.

Introduction

Tattoos have become increasingly commonplace making complications from tattoos a growing concern for dermatologists. While relatively rare, delayed-type hypersensitivity reactions to red tattoo ink have been previously reported [1–3] and tend to have a variable onset ranging from weeks to months after the tattoo has been done [1], with later occurrences after years being less common. We describe an unusual reaction to red tattoo ink after initiation of direct-acting antiviral treatment for hepatitis C (HCV).

Correspondence to:
Thomas Herzinger, t.herzinger@queensu.ca

Case Rep Dermatol 2020;13:379–383
DOI: 10.1159/000513926

Case Report

A 51-year-old man presented to the dermatology outpatient clinic with a 4-month history of itchy bumps on the back of his hand that emerged 1 week after the initiation of ledipasvir/sofosbuvir (Harvoni®) for HCV. The lesions were strictly confined to the red areas of a polychromatic tattoo obtained 18 months earlier. Unfortunately, the composition of the tattoo ink was unknown. The patient had received tattoos in the past without complications. Five months after initiating antiviral treatment, a viral load showed no evidence of active HCV infection. The patient was not taking any other prescription of over-the-counter medications.

On examination, the patient had 3 dome-shaped, hyperkeratotic, erythematous nodules confined to the red portions of his tattoo on the dorsum of his right hand (Fig. 1a). Other anatomical locations with even older tattoos showed proliferative raised portions within the margins of the red ink as well (Fig. 1b). A punch biopsy of one of the nodules on the dorsum of the hand demonstrated a well-differentiated squamous proliferative lesion with abundant glassy cytoplasm and mild cytologic atypia, which may represent reactive atypia, but a well-differentiated squamous cell carcinoma could not be completely excluded. A second punch biopsy of an inflamed tattoo on the upper arm showed scattered tattoo pigment in the superficial dermis surrounded by prominent lymphocytic inflammation, in keeping with a delayed-type hypersensitivity reaction to red tattoo ink (Fig. 2a, b).

The patient was referred to plastic surgery for consideration of a wide excision of the nodules and resurfacing of the dorsal hand with a skin graft. At this time, an incisional biopsy was taken to obtain a more representative sample to resolve the differential diagnoses between delayed-type hypersensitivity reaction and squamous cell carcinoma. Histopathology showed markedly proliferative squamous epithelium, involving adnexal structures including hair follicles and eccrine ducts (Fig. 3a, b). There was associated lichenoid interface lymphocyte-predominant inflammation with admixed plasma cells, histocytes, and rare eosinophils. Civatte bodies and lymphocytic exocytosis to the basal layers were also seen. There was no definitive evidence of squamous dysplasia or invasive carcinoma. Among the dermal inflammation, there were scattered fine granular red pigment material and also chunky coarse granular brown/black pigment material.

Initial treatment with clobetasol 0.05% ointment under occlusion produced mild improvement after 7 months. The remaining nodules on the hand were managed with serial excisions; histologic features were similar to that of the previous excision and biopsy specimens at the same anatomical location.

Discussion

Delayed-type hypersensitivity reactions generally occur 48–72 h after exposure to the allergen. It involves the activation of sensitized T lymphocytes when stimulated by contact with an antigen. Historically, most hypersensitivity reactions were related to mercury-derived pigments (i.e., cinnabar); however, reactions to red ink have persisted despite replacement with alternative red pigments such a cadmium red, sienna, and organic substances such as azo, sandalwood, and brazilwood [1, 4]. Efforts to identify the specific allergen in modern red tattoo ink have been relatively unfruitful. Allergy patch testing of patients with red tattoo reactions using common allergens, textile/dyes, tattoo ink stock products, and culprit pigments has generally yielded negative or inconsistent results, calling into question the utility of patch testing in diagnosing delayed hypersensitivity reactions triggered by antigens that are deposited directly into the dermis [5, 6]. It has therefore been suggested that metabolism or haptenization with host proteins within the dermis over weeks to years is

Case Rep Dermatol 2020;13:379–383
DOI: 10.1159/000513926

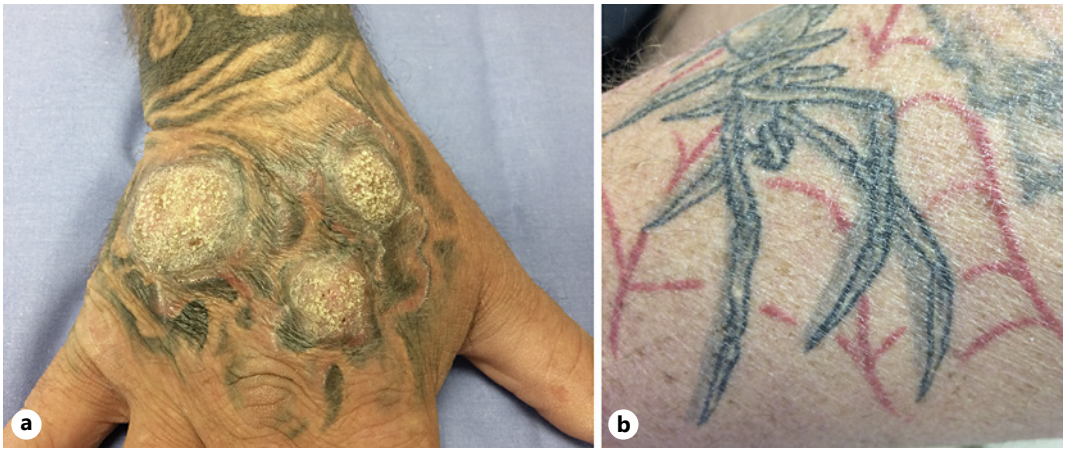

Fig. 1. Delayed-type hypersensitivity reaction to red tattoo ink. **a** Hyperkeratotic, erythematous nodules with minimal crusting and no erosions confined to the red portions of a tattoo acquired 18 months prior on the dorsum of the right hand. **b** Spiderweb tattoo on the left arm displaying a proliferative raised portion within the margins of the red areas of a tattoo acquired 6 years ago.

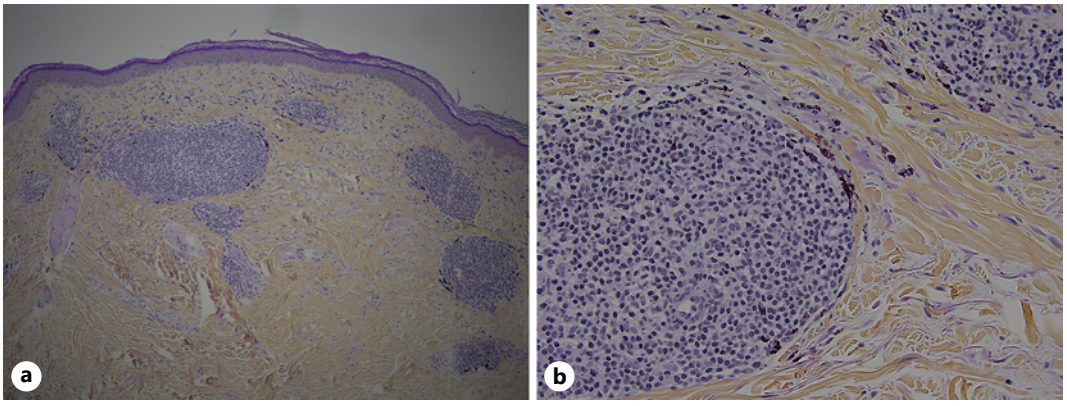

Fig. 2. Histopathology from 3 mm punch biopsy of inflamed spider tattoo on left upper arm (stained with HPS) at ×50 magnification (**a**) and ×200 magnification (**b**) shows dense dermal lymphocytic inflammation associated with red pigment material. The overlying epidermis and deep dermis appear unremarkable. HPS, hematoxylin phloxine saffron.

needed in order to trigger an allergic reaction [4, 5]. Further, external factors, such as sunlight exposure, can induce photochemical cleavage of tattoo pigments in the skin and may also play a role in allergen formation [5].

Immune reconstitution has been proposed as a possible explanation for the temporal association between antiviral treatment and cutaneous reactions. Recently, Heppt and Sticherling described 2 patients that developed plaque-type-psoriasis after initiating ledipasvir/sofosbuvir for HCV and reasoned that this might have constituted an immune restoration phenomenon [7]. Specifically, patients with chronic HCV display increased levels of FoxP3-positive regulatory T cells [8]. According to the concept of context-dependent immune cell plasticity, T cells may express the genes associated with a different helper cell subtype with respect to cytokine production and regulatory functions depending on the microenvironment [9, 10]. Thus, in accordance with this phenomenon of T-cell plasticity [9], Heppt and Sticherling [7] proposed that successful treatment of HCV may result in a conversion of

Case Rep Dermatol 2020;13:379–383
DOI: 10.1159/000513926

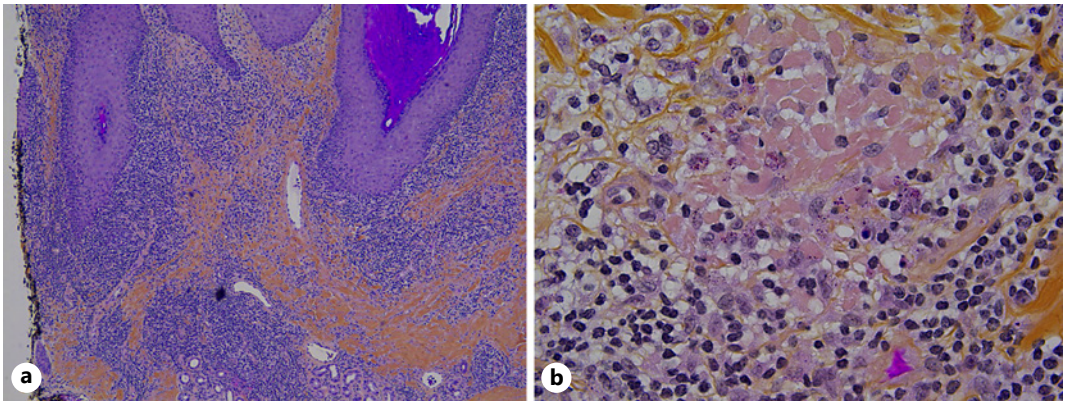

Fig. 3. Histopathology from excision of the dorsal right-hand nodule (stained with HPS) shows squamous proliferation with intense dermal inflammation at low power (×50 magnification) (**a**) and inflammatory cells and dermal fibrin surrounding red pigment material at high power (×400 magnification) (**b**). HPS, hematoxylin phloxine saffron.

FoxP3-positive regulatory T cells into interleukin 17 (IL-17) producing T cells, thereby leading to a worsening of psoriatic lesions. This concept of immune cell plasticity may also play a role in other inflammatory conditions of the skin exhibiting a T-cell component such as allergic reactions [9]. We therefore hypothesize that our patient's delayed-type hypersensitivity reaction to red tattoo ink may be related to a similar immune reconstitution phenomenon.

Similarly, a phenomenon termed immune reconstitution inflammatory syndrome has been described in several HIV patients who developed granulomatous tattoo reactions following antiretroviral therapy [4, 11]. Gamba et al. [4] noted analogous epidermal hyperplasia and dermal changes on histology in their HIV patient with an allergic tattoo reaction at baseline, which significantly worsened after antiretroviral therapy initiation. The authors also identified epidermal spongiosis; however, this finding was not seen in our case.

Unlike HIV infection, HCV infection is not classically immunosuppressive, making the presumed T-cell activation observed in the psoriasis patients [7] and our contact allergy patient less obvious. These early reports of activation of T-cell immunity after ledipasvir/sofosbuvir will hopefully prompt increased clinical awareness toward such phenomena and research of the underlying immunopathogenesis.

Statement of Ethics

Ethics approval was granted through the Health Sciences and Affiliated Hospitals Research Ethics Board. Written informed consent was obtained from the patient for publication of their case details and accompanying images.

Conflict of Interest Statement

M.L. McPhie, K.Y.M. Ren, and J.M. Hendry have no conflicts of interest to declare. S. Molin reports personal fees and nonfinancial support from Pfizer, personal fees and other from Lilly, grants, personal fees and other from Novartis, personal fees and other from Leo, personal fees from Abbvie, nonfinancial support from Galderma, and outside the submitted work. T.

Herzinger reports personal fees from Abbvie, personal fees from Pfizer, and outside the submitted work.

Funding Sources

The authors did not receive any funding.

Author Contributions

M.L. McPhie: acquisition and interpretation of data, literature review, drafting of the work. K.Y.M. Ren: acquisition of data, analysis of pathology findings, critically revising the work. J.M. Hendry: direct care of the patient, interpretation of data, critically revising the work. S. Molin: critically revising the work. T. Herzinger: direct care of the patient, conception and design, interpretation of data, critically revising the work. All the authors have read and approved the final version of the manuscript.

References

1 Gaudron S, Ferrier-Le Bouëdec MC, Franck F, D'Incan M. Azo pigments and quinacridones induce delayed hypersensitivity in red tattoos. Contact Derm. 2015;72(2):97–105.
2 Ruiz-Villaverde R, Fernandez-Crehuet P, Aguayo-Carreras P, Hernandez-Centeno JL, Cuenca-Barrales C. Inflammatory reactions to red tattoo inks: three cases highlighting an emerging problem. Sultan Qaboos Univ Med J. 2018;18(2):e215–8.
3 Joseph WJ, Roy E, Stofman GM. Delayed hypersensitivity reaction after nipple tattooing: a novel case report. Plast Reconstr Surg Glob Open. 2019;7(9):e2394.
4 Gamba CS, Lambert Smith F, Wisell J, Brown M. Tattoo reactions in an HIV patient: autoeczematization and progressive allergic reaction to red ink after antiretroviral therapy initiation. JAAD Case Rep. 2015;1(6):395–8.
5 Serup J, Hutton Carlsen K. Patch test study of 90 patients with tattoo reactions: negative outcome of allergy patch test to baseline batteries and culprit inks suggests allergen(s) are generated in the skin through haptenization. Contact Dermatitis. 2014;71(5):255–63.
6 Antony FC, Harland CC. Red ink tattoo reactions: successful treatment with the Q-switched 532 nm Nd:YAG laser. Br J Dermatol. 2003;149(1):94–8.
7 Heppt F, Sticherling M. Psoriasis as a manifestation of an immune reconstitution in two patients with hepatitis c treated with ledipasvir/sofosbuvir. Acta Derm Venereol. 2017;97(4):526–7.
8 Zhai N, Chi X, Li T, Song H, Li H, Jin X, et al. Hepatitis C virus core protein triggers expansion and activation of CD4(+) CD25(+) regulatory T cells in chronic hepatitis C patients. Cell Mol Immunol. 2015;12(6):743–9.
9 Gatzka M, Scharffetter-Kochanek K. T-cell plasticity in inflammatory skin diseases: the good, the bad, and the chameleons. J Dtsch Dermatol Ges. 2015;13(7):647–52.
10 Agrawal R, Wisniewski JA, Woodfolk JA. The role of regulatory T cells in atopic dermatitis. Curr Probl Dermatol. 2011;41:112–24.
11 Silvestre JF, Albares MP, Ramón R, Botella R. Cutaneous intolerance to tattoos in a patient with human immunodeficiency virus: a manifestation of the immune restoration syndrome. Arch Dermatol. 2001;137(5):669–70.