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Clinical Presentation of Adverse Tattoo Reactions

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ABBREVIATIONS

ACD – allergic contact dermatitis

BCC – basal cell carcinoma

BfR – Bundesinstitut für Risikobewertung

CD154/CD40L – cluster of differentiation154 / CD40 ligand

CO2 – carbon dioxide

CRABAT – Cancer Risk Attributable to the Body Art of Tattooing

DAMPs – damage-associated molecular patterns

HBV – hepatitis B virus

HCV – hepatitis C virus

HIV – human immunodeficiency virus

HPLC – high-performance liquid chromatography

HPV – human papillomavirus

HSV – herpes simplex virus

KA – keratoacanthoma

MALDI-MS – matrix-assisted laser desorption/ionization mass spectrometry

MM – melanoma

PAHs – polycyclic aromatic hydrocarbons

QS – quality-switched

QS Nd: YAG – quality-switched neodymium-doped yttrium aluminum garnet

RMC – Reflectance confocal microscopy

SCC – squamous cell carcinoma

UV – ultraviolet

1 SUMMARY

Tattoos have been practiced across cultures for thousands of years and are now present in approximately 30% of adults in Western countries. Despite being generally considered safe when performed under hygienic conditions, tattooing is associated with a broad spectrum of adverse reactions.

Tattoo inks consist of pigments, binders, solvents, and additives. Their chemical composition raises toxicological concerns, as inks may contain polycyclic aromatic hydrocarbons, aromatic amines, and heavy metals. Once deposited into the dermis, pigment particles are taken up by macrophages and may migrate to regional lymph nodes, initiating both local and systemic immune responses.

Adverse reactions are classified into allergic, inflammatory, infectious, granulomatous, pseudolymphomatous, neoplastic, and miscellaneous complications. Allergic reactions, especially to red pigments, represent the most frequently reported and clinically challenging category, often presenting as lichenoid or granulomatous patterns with a delayed onset of months to years. Infections range from common bacterial pathogens such as Staphylococcus aureus to atypical mycobacteria and viral agents. Neoplastic associations, while documented in case reports, remain unproven as causal relationships.

Diagnosis requires a structured, sometimes multidisciplinary approach combining clinical examination, patient history, histopathological evaluation, and laboratory investigations. Patch testing has limited sensitivity in tattoo reactions, as the causative allergen frequently remains unidentified. Skin biopsy remains the diagnostic gold standard.

Treatment is guided by the underlying pathological mechanism. First-line management includes topical and systemic corticosteroids and antihistamines for allergic and inflammatory reactions, while infectious complications require pathogen-specific therapy. Laser tattoo removal is contraindicated in active allergic reactions, as pigment fragmentation may trigger systemic hypersensitivity. In severe, refractory cases, complete surgical excision remains the only definitive treatment, as demonstrated by the included case report of a patient with systemic delayed-type hypersensitivity to red tattoo pigment.

The European REACH regulation has restricted over 4,000 hazardous substances in tattoo inks since 2022, yet red pigment allergy persists, as the causative hapten likely forms within the skin over time and cannot be identified or banned as a specific substance. Ongoing challenges include inaccurate ink labeling, persistent heavy metal exceedances, and insufficient surveillance of adverse reactions.

In conclusion, adverse tattoo reactions represent a complex clinical issue spanning dermatology, immunology, toxicology, and surgery. Greater interdisciplinary awareness improved diagnostic strategies, and continued research into ink composition and long-term safety is essential to enhance patient counseling, prevention, and treatment outcomes.

1.1 LITHUANIAN SUMMARY

Tatuiruotės praktikuojamos įvairiose kultūrose tūkstančius metų, o šiandien apie 30 % suaugusiųjų Vakarų šalyse turi bent vieną tatuiruotę. Nors tatuiravimas paprastai laikomas saugiu, kai tinkamai laikomasi higienos reikalavimų, su juo siejamas platus nepageidaujamų reakcijų spektras.

Tatuiruočių dažai sudaryti iš pigmentų, rišiklių, tirpiklių ir priedų. Jų cheminė sudėtis kelia toksikologinių susirūpinimų, nes dažuose gali būti policiklinių aromatinių angliavandenilių, aromatinių aminų ir sunkiųjų metalų. Pigmento dalelės, patekusios į odą, yra fagocituojamos makrofagų ir gali migruoti į regioninius limfmazgius, sukeldamos vietines ir sistemines imuninės sistemos reakcijas.

Nepageidaujamos reakcijos skirstomos į alergines, uždegimines, infekcines, granulomatozines, pseudolimfomatozines, neoplazines ir kitas komplikacijas. Alerginės reakcijos, ypač į raudonus pigmentus, yra dažniausiai aprašomos ir kliniškai sudėtingiausios, jos dažnai pasireiškia lichenoidiniais ar granulomatoziniais židiniais ir gali išsivystyti praėjus mėnesiams ar net metams po tatuiravimo. Infekcijas sukelia įprastos bakterijos, pvz., Staphylococcus aureus, tiek atipiniai mikobakterijų štamai ir virusai, atvejai Aprašyti su tatuiruotėmis susijusios neoplazijos , tačiau priežastinis ryšys dar nėra įrodytas.

Diagnozė reikalauja struktūrizuoto, kartais tarpdisciplininio požiūrio, apimančio klinikinį įvertinimą, paciento anamnezę, histopatologinį tyrimą ir laboratorinius tyrimus. Odos lopo testų jautrumas nedidelis, todėl alergenas dažnai lieka neidentifikuotas. Odos biopsija išlieka diagnostikos auksinis standartas.

Gydymas parenkamas atsižvelgiant į patofiziologinį mechanizmą. Pirmoji gydymo linija apima vietinių ir sisteminių kortikosteroidų bei antihistamininių vaistų skyrimą esant alerginėms ir uždegiminėms reakcijoms, o infekcinės komplikacijos reikalauja sukėlėją atitinkančio specifinio gydymo. Lazeriniai tatuiruočių šalinimo metodai yra kontraindikuotini, esant aktyvioms alerginėms reakcijoms, nes pigmento dalelių suskaidymas gali sukelti sisteminę padidėjusio jautrumo reakciją. Sunkiais, atspariais gydymui atvejais visiškas chirurginis išpjovimas išlieka vienintelis galutinis gydymo metodas.

Europos REACH reglamentas nuo 2022 metų apribojo daugiau nei 4 000 pavojingų medžiagų tatuiruočių dažuose, tačiau alerginės reakcijos į raudonus pigmentus išlieka problema, neshaptenas greičiausiai susidaro odoje laikui bėgant ir negali būti identifikuotas ar uždraustas kaip konkreti cheminė medžiaga. Nuolatiniai diagnostinia iššūkiai apima netikslias dažų etiketes, viršijamas sunkiųjų metalų ribines vertes ir nepakankamą nepageidaujamų reakcijų stebėseną.

Apibendrinant, nepageidaujamos tatuiruočių reakcijos yra sudėtinga klinikinė problema, apimanti dermatologiją, imunologiją, toksikologiją ir chirurgiją. Didesnis tarpdisciplininė informuotumas, patobulinti diagnostikos metodai ir tolimesni tyrimai dėl dažų sudėties ir ilgalaikio saugumo yra būtini siekiant pagerinti pacientų konsultavimą, prevenciją ir gydymo rezultatus.

1.2 KEY WORDS

Tattoo, tattoo complications, tattoo ink, allergy, hypersensitivity reaction, skin, infections, granulomas, pseudolymphomas, neoplasms, reactions, tattoo removal, laser

2 INTRODUCTION

In Western countries, tattoos are present in approximately 30% of the population (1), reflecting the growing popularity of body art across diverse demographic groups. However, tattooing can lead to a variety of reactions. While it is generally considered safe when performed with proper hygiene, numerous complications have been reported. These include acute inflammatory responses, bacterial and viral infections, delayed hypersensitivity, granulomatous or lichenoid reactions, and, in rare cases, benign or malignant skin lesions within tattoos (2). Allergies, especially to red ink, are among the most significant adverse effects because they can occur months or even years after tattooing, making them difficult to diagnose and treat. Beyond cutaneous diseases, tattoo pigments can contain potentially harmful substances, and pigment particles may migrate past the skin to regional lymph nodes and other tissues. For these reasons, tattoo complications represent a relevant and evolving topic in medicine. A clear understanding of their clinical presentation, pathogenesis, and risk factors is crucial for accurate diagnosis, appropriate treatment, and improved patient counseling (2).

2.1 AIMS AND OBJECTIVES

This thesis aims to summarize the key aspects of clinical presentations of adverse tattoo reactions through a narrative literature review, supported by an illustrative clinical case study. The objectives are, first, to gather information on the history of tattoos, their chemical components, and the harmful substances associated with them. Second, to understand the pathophysiological mechanisms behind adverse tattoo responses, including mechanical and immunological factors. Third, to categorize adverse complications such as allergic, infectious, inflammatory, miscellaneous, and neoplastic manifestations. Fourth, to evaluate diagnostic methods ranging from detailed examinations and patient history to biopsy, visualized through a diagnostic algorithm. Fifth, to discuss management and treatment options, including conservative, surgical, and laser techniques, along with insights into complications and prognosis.

The report features a case of a patient with widespread skin inflammation linked to a red-pigmented tattoo, underscoring the significance of allergic reactions. This is followed by a critical discussion of the quality of current research, potential future challenges, and public health strategies to ensure patient safety. Additionally, clinical images from various scientific articles are included to demonstrate different tattoo-associated skin complications.

2.2 METHODOLOGY

This thesis presents a narrative literature review of adverse tattoo reactions, focusing on various pathologies and the clinical procedures. The aim of this review is to summarize the available research on inflammatory, allergic, infectious, granulomatous, neoplastic, and miscellaneous complications linked to tattoos, along with their diagnostic and management strategies. Electronic literature searches were primarily conducted between October 2024 and April 2026 using PubMed and Scopus, which are significant databases for publications on adverse tattoo reactions. Additionally, the bibliographies of relevant articles and review papers were examined to identify further publications not captured by the initial database search. Literature was cited if it was primarily published between 2010 and 2025, with inclusion of older seminal publications where relevant. The search strategy combined general terms about tattoo complications with more specific words related to pathology, diagnosis, treatment, and outcomes. Key search concepts were “tattoo”, “adverse tattoo reaction”, “tattoo reactions”, “tattoo complications”, and “tattoo inks”, along with specific complications such as “tattoo allergy”, “tattoo hypersensitivity reactions”, “infections”, “granulomas”, “pseudolymphoma”, and “neoplasms”. The literature search was performed iteratively, with additional keywords and relevant MeSH terms related to the topic. Management-related phrases such as “diagnostic,” “treatment,” “management,” “removal,” “laser,” and “prognosis” were also included. The search used Boolean operators, specifically AND and OR, to combine these terms. To ensure the research's relevance and reliability, inclusion and exclusion criteria were established. Studies addressing adverse tattoo reactions or complications, as well as those examining pathological or immunological mechanisms, were included. Studies also needed to contain diagnostic algorithms, therapeutic strategies, and outcomes. The main sources consisted of case reports, case series, retrospective cohort studies, review articles, or relevant therapeutic guidelines, as long as they were available as full-text, peer-reviewed articles. Exclusion criteria featured reports lacking clinical relevance, concerning permanent make-up, procedures without clear links to tattoo responses, animal studies, abstracts without full peer-reviewed articles, and publications in languages other than English or German. As this thesis is a narrative review, the literature search and study selection were not performed according to PRISMA guidelines. Consequently, the process may not be fully reproducible. Study selection was performed in several stages. Firstly, records were identified through the database, resulting in a total of [n = 4,278] articles. After that, entries were screened for title and abstract. Articles considered as potentially relevant were then assessed in full text. Following full-text evaluation, [n = 63] studies were included in the final review.

A formal standardized quality assessment tool was not applied. Instead, studies were appraised qualitatively based on relevance, methodological transparency, and clarity of findings. Greater emphasis was placed on sources with well-documented clinical work-up.

3 BACKGROUND

For centuries, tattoos have held a special significance for humanity. They have a long-standing tradition and are practiced across all continents and in nearly every human society (2). Tattooing can be defined as an intentional or accidental insertion of colored pigment into the skin. It refers to the creation of symbols or motifs on the integument as a body modification. The pigment is introduced into the dermis using needles of varying strength and shape (3,4). In 2004, the American Academy of Dermatology described five main categories of tattoos in a patient brochure. Traumatic tattoos result from accidental insertion of dirt, debris, or graphite into the skin after injury. Amateur tattoos are usually self-applied or done by friends and tend to look simple and less detailed. Professional tattoos include traditional cultural styles and modern designs created by trained artists using tattoo machines. Medical tattoos are used in healthcare to mark areas for radiation therapy. Cosmetic tattoos are applied as permanent makeup for reconstructive and camouflage purposes (4). Compared with architecture, painting, and sculpture, tattooing is difficult to date precisely due to the lack of archaeological remains. The oldest archaeological evidence of tattooing dates to 12,000 years ago. Those appear as tattoo-like markings on sculptures. The first undisputed proof is the Iceman “Ötzi”, who was discovered in 1991 in the Austrian Alps. This 5,400-year-old mummy decorated himself with 61 marks, in the form of dots and lines (5,6). Further examples include tattooed mummies from the American Arctic, Siberia, Western China, Africa, the Philippines, and the Andes, as well as detailed sources from Greek and Roman studies (6). In ancient Greece, tattooing was called Stigma, originating from the Latin word meaning “sign” or “brand” (7). The modern term “tattoo” is derived from the Polynesian word “Tatau,” meaning “skin decoration” or “mark” (8,9).

3.1 GROWING POPULARITY OF TATTOOS

There are many key factors contributing to the growing popularity of tattoos over the past few decades. The cultural shift toward internet use, including social media platforms such as Instagram, TikTok, and Facebook, play a crucial role in expanding the visibility and acceptance of tattoos. Celebrities, movies, and everyday interactions present bodies to millions, thereby contributing to the normalization and popularization of body art (2,10). The prevalence of tattooing has increased consistently over the past decades and continues to grow. Current estimates indicate that roughly one quarter of the U.S. population has at least one tattoo, while reported figures for European countries range from approximately “9% - 12%” to slightly more. Tattoos appear to be equally common among men and women. The highest rates are reported among young adults, particularly those aged 20-29, with nearly half of individuals reporting tattoos (11).

3.2 CULTURAL SIGNIFICANCE AND DEMOGRAPHIC TRENDS

The motivations for getting ink on the skin are highly diverse. For many, tattooing serves as a form of body art, fashion, and personal aesthetic. Through this medium, individuals can express their identity and present their distinctiveness. It allows people to differentiate themselves from others and control their own appearance. Moreover, skin art can signify group affiliations and commitments, particularly within subcultures, tight-knit communities, or for organizations, such as gangs. Thus, tattoos can function as a form of resistance, whether against mainstream societal structures or expectations (2). In other contexts, tattoos are rooted in spirituality and cultural traditions, carrying ancestral or religious meanings (2). The Māori of New Zealand have used symbolic tattoos for generations. Tattooing is used to indicate their connection to a specific tribe, region, or family, as well as to symbolize power, strength, and skill. Furthermore, their skin is marked during important life events and social rituals, such as weddings or the transition from childhood to adulthood (12). In addition, the act of skin pigmentation can become an addiction. Endorphins are released during the painful experience, while the psychological aspect of collecting more and more tattoos can also contribute to this addictive effect. Apart from these motivations, tattooing can also occur without deeper reflection. It is rather an impulsive decision or a result of spontaneous actions under the influence of drugs or alcohol (2).

3.3 RISING DERMATOLOGICAL CONCERNS ASSOCIATED WITH TATTOOS

The dermis, also known as the corium, is a collagen-fibre-rich connective tissue layer of the skin located beneath the epidermis. Anatomically, the dermis can be divided into two distinct layers: the stratum papillare (“papillary layer”), which consists of loose connective tissue, and the stratum reticulare (“reticulate layer”), the deeper region composed of dense irregular connective tissue, containing various immune cells, including macrophages, mast cells, and dermal dendritic cells, which play important roles in immune responses (13). Tattoo inks are introduced into the dermis, where they are taken up and encapsulated by macrophages (14,15). These immune cells play a crucial role in contributing to the visibility of tattoos. Macrophages absorb and store the ink pigments. When these cells undergo apoptosis, the previously stored pigment particles are released into the extracellular matrix and are taken up by newly recruited macrophages. This process ensures the long-lasting appearance of tattoos (15). Nevertheless, tattooing may be associated with various adverse outcomes, including improper injection depth, which can lead to inadequate pigment deposition, blurring, or discoloration. Additionally, adverse effects such as infections, hypersensitivity reactions,

chronic inflammation, granuloma formation, impaired wound healing, and numerous other clinical complications have been documented (10,16).

4 LITERATURE REVIEW

4.1 TATTOO INKS AND THEIR COMPOSITIONS

Tattoo inks are composed of four principal components: pigments, binders, solvents, and additives (fig. 1) (2). Pigments provide color and are insoluble in the liquid phase. The binders play an important role in keeping the pigment particles together, thereby facilitating long-lasting deposition in the skin. Binders are generally considered less reactive, although their toxicological profile remains incompletely characterized (2). A solvent adjusts viscosity, drying behavior, and dispersibility. It primarily consists of water and small amounts of alcohols or polyols.

However, excessive alcohol concentrations may irritate the skin. Additives constitute about 5% of the formulation. They are present in small concentrations to optimize the ink. These comprise surfactants, also called Tensides, for stabilizing pigment dispersion; thickening and thixotropic agents to prevent sedimentation during storage; and preservatives to inhibit microbial growth (2).

4.1.1 CHEMICAL COMPONENTS OF TATTOO INKS

Pigments can further be categorized into organic and inorganic pigments, carbon black, and fillers. Each category has specific attributes, such as durability or color intensity. Inorganic compounds like titanium oxide, iron oxide, and chromium oxide are valued for their opacity and stability. Titanium oxide is widely used as a white colorant and as a modifier to lighten colors, due to its strong light-scattering capacity and high refractive index. Iron oxide variants are available in yellow, red, and brown. However, their color intensity is relatively low, resulting in muted tones, making them more suitable for permanent make-up (2).

Chromium oxide compounds are exclusively used for green coloration. They share similarities with iron oxides, for example, high chemical stability but limited chromatic brilliance. Therefore, they are mainly used in permanent make-up. Inorganic pigments naturally contain traces of metals, including nickel, cobalt, copper, and chromium. Although metals are often bound within pigment matrices, sensitization may still occur, particularly in predisposed individuals (2).

Organic pigments are insoluble, carbon-based substances used in tattoos to produce bright and highly saturated colors. Their chemical structures enable efficient light absorption and high color intensity, allowing almost every color to be created. Compared to inorganic pigments, they often have lower dispersibility and require additives to improve even spreading. The main groups are azo and polycyclic pigments. Phthalocyanines are commonly used for green and blue shades. While generally

low in heavy metals, the synthetic processes used in their manufacture may introduce other undesirable by-products, such as aromatic amines, which are of toxicological relevance (2). Carbon black is one of the most used pigments in tattoo inks due to its deep black coloration and long-lasting stability. While carbon black itself is not strongly associated with allergic reactions, its safety profile depends heavily on the manufacturing method. Certain production processes can introduce polycyclic aromatic hydrocarbons (PAHs), which are toxic and potentially carcinogenic. Therefore, strict quality control is essential to minimize PAH contamination. In addition, polycyclic aromatic hydrocarbons can take up ultraviolet light and promote the formation of reactive oxygen species (particularly singlet oxygen), thereby inducing cytotoxic effects that may compromise cutaneous tissue integrity (10). Fillers are inorganic substances in tattoo inks to improve storage stability and pigment distribution. Most frequently used fillers include silica and barium sulfate. These materials provide structural support within the ink formulation, easier pigment mixing after storage, and good pigment spreading, without directly contributing to coloration. Dyes are unsuitable for inks because their solubility allows them to diffuse easily within the tissue. As a result, dyes used in tattoos would fade quickly, leading to a lack of long-term stability. Pigments, on the other hand, are insoluble, therefore enabling them to remain in the integument without dissolving over time (2).

Popular but temporary henna tattoos, on the other hand, color only the outermost layer (the stratum corneum) of the skin, not involving the deposition of pigment into the dermis. Their coloration results from surface staining rather than intradermal pigment implantation. For color intensity and prolonged visibility, various additives, including beet, lemon juice, sugars, and plant-derived components like walnut shells or paraphenylene diamine, are used to promote faster fixation. Allowing the design to remain visible for approximately 1 to 3 weeks before fading naturally (8).

Previously cited, black is the most frequently used tattoo color, yet its chemical composition has only been investigated in a limited number of studies. Available data show that black tattoo inks are chemically complex and highly variable, often containing between a few and more than 50 organic substances. The main pigment is carbon black, whose composition depends strongly on the manufacturing process. As a result, the content of polycyclic aromatic hydrocarbons (PAHs) (a group of well-known carcinogens) can vary greatly across products, ranging from very low to very high levels (2).

4.1.2 KNOWN ALLERGENS AND HARMFUL SUBSTANCES

Several compounds in tattoo inks have raised concerns about their potential impact on human health. Certain compounds have been associated with carcinogenic properties, the induction of immune-mediated responses, and the development of allergic reactions. Some studies of tattoo inks available

on the European market have detected chemicals of toxicological relevance, most notably polycyclic aromatic hydrocarbons, aromatic amines, heavy metals, and specific preservative agents. Tattoo pigments are manufactured industrially and consist of solid particles with dimensions ranging from the micrometer to the nanoscale. Because of their extremely small size, these materials may interact biologically, thereby increasing health risks, although their toxicological significance remains uncertain, particularly given the long-term presence of pigments in the skin and their possible transport to lymph nodes and internal organs (2,17).

4.1.3 THE EQUIPMENT

The devices used for tattooing have undergone technological changes over the past decades. It advanced from handmade and improvised devices to highly standardized, industrially manufactured systems. Consequently, precision, ergonomics, and most importantly, hygiene and infection control have been significantly enhanced in modern professional tattoo practice (2).

The introduction of electrically powered tattoo machines in the late nineteenth century marked a major turning point for tattooing. Aspects such as reduced weight, lower vibration, quicker performance, and improved both artist comfort and procedural control. In parallel with machine development, grips and tattoo needles have also evolved. Historically, needles were often reused under suboptimal hygienic conditions. Nowadays, needles are manufactured from stainless steel and are predominantly single-use and pre-sterilized. Disposable needles, tubes, and grips reduce the risk of contamination and infection. Moreover, modern studios cover their equipment and surfaces with plastic coverings to provide additional barrier protection (2).

4.2 PATHOPHYSIOLOGY OF REACTIONS

Tattooing introduces exogenous pigments into the skin, causing extensive mechanical injury by creating numerous microscopic punctures that pass through the epidermis and extend into the mid-dermis (8,17). This mechanism disrupts the dermo-epidermal junction, and tattoo pigments are deposited in the papillary to upper reticular dermis approximately 1–2 mm beneath the surface (depending on the anatomical site)(18). Once the skin barrier is disrupted, physiological wound-healing responses are initiated immediately to restore tissue health. During this phase, small capillaries are ruptured by the puncture, resulting in minimal bleeding that merges with the ink. Due to their poor solubility and needle penetration to enzymatic breakdown, these particles remain in the dermis over the long term. Following the procedure, damage to the basal membrane and local cell necrosis of dermal and epidermal cells trigger an acute inflammatory cascade (8,17).

4.2.1 IMMUNE RESPONSE MECHANISMS

During the initial hours post-procedure, neutrophils are the first immune responders to rapidly infiltrate the tattooed site (8,17). Neutrophils release multiple signaling molecules, such as cytokines, chemokines, and growth factors, that mediate communication between damage-associated molecular patterns (DAMPs) and epithelial cells and support tissue repair.

Following that phase, pigment particles can be found enclosed within phagosomes of multiple cell types, including mast cells, keratinocytes, histiocytes, and fibroblasts. Larger particles tend to remain localized within dermal macrophages, fibroblasts, or within the extracellular matrix. In contrast, smaller particles may disseminate more deeply by being engulfed by Langerhans cells and other antigen-presenting cells (8). These can take up antigen-associated substances and subsequently transport them to regional lymph nodes, where they present these antigens to T-lymphocytes (17). This process may result in conditions such as lymphadenopathy, characterized by pigment accumulation within lymph nodes and increased proliferation of histiocytes and Langerhans cells, thereby linking local skin injury to systemic immune activation (15,17).

Within the early post-tattooing period, the reconstruction of the basal membrane remains incomplete, and a proportion of the pigment undergoes transepidermal elimination. In this phase, the skin is more susceptible to secondary microbial invasion. When the basal membrane barrier is fully restored, further transepidermal pigment loss and the likelihood of microbial infection decrease. Subsequently, the initial inflammatory cascade evolves into a foreign-body immune response directed against the deposited material. Histopathologically, this response is characterized by a dense lymphocytic infiltrate within the dermis. Dysregulated immune activity or exposure to toxic ink components may further exacerbate local or systemic manifestations, contributing to the broad spectrum of tattoo-associated complications (8).

4.2.2 HYPERSENSITIVITY AND INFLAMMATORY RESPONSES

Hypersensitivity responses have been documented in association with both temporary and permanent tattoos (19). These are often referred to as tattoo allergies, characterized by long-lasting inflammatory manifestations that may involve one or more tattoos. Such reactions are typically limited to a specific pigment color and can develop either shortly after skin pigmentation or a few years later. Of the adverse reactions associated with tattooing, allergic complications are reported most frequently (3). Current data suggest that the majority of tattoo-related allergic reactions are mediated by T-lymphocytes and are therefore classified as delayed-type (type IV) hypersensitivity reactions. This

immunological process generally includes two stages: an initial sensitization phase, during which the immune system becomes primed to the antigen, followed by an elicitation phase in which re-exposure leads to a clinically apparent inflammatory effect (17,20).

4.3 CLASSIFICATION OF REACTIONS

Complaints after marking the body can be considered relatively minor symptoms or observable changes that arise in connection with a tattoo. These may be limited to a local area or involve more generalized discomfort. Such manifestations can occur shortly after tattooing or develop gradually. Some diminish as the skin heals (2). Tattoo *complications,* on the contrary, represent clinically significant adverse outcomes following body modification. They are characterized by clear pathological findings accompanied by pronounced clinical signs that may impair health or daily functioning. Due to the severity of the condition, affected individuals seek professional evaluation and therapeutic intervention (2).

Cutaneous complications associated with tattooing cover a broad clinical spectrum, ranging from mild manifestations such as erythema, edema, pruritus, localized pain, or papular eruptions to more prominent findings, including nodules, marked inflammation, or even neoplastic transformation.

In particular, tattoos containing para-phenylenediamine may induce acute eczematous reactions that can progress to pigmented alterations, hypertrophic scarring, or even severe lichenoid dermatitis (8).

4.3.1 ALLERGIC REACTIONS

An allergic reaction after tattooing typically manifests as allergic dermatitis, granulomatous or lichenoid patterns, limited to specific pigmented areas (2). Clinical observations indicate that red colorants containing mercury compounds are most frequently implicated in hypersensitivity reactions (8). Kluger's retrospective Finnish study described tattoo-related skin reactions, most of which were hypersensitivity responses (21). Morphologically, these reactions can present as papules or nodules, swelling, plaque-like or lichenoid lesions, hyperkeratosis, or ulcero-necrotic lesions. They usually remain confined to the tattooed areas containing the pigment, although widespread eczema or generalized eruptions may develop, especially in sensitized individuals. Symptoms are often nonspecific and may comprise tenderness, swelling, pruritic or non-pruritic papules and nodules, sometimes accompanied by secondary crusting from excoriation. Pruritus is common, whereas pain is uncommon (3,21). Although sensitivity may arise to any pigment shade, the onset of allergic reactions can be delayed, sometimes appearing many months or even years after tattoo placement (2,21). This latency is thought to result from gradual chemical modification of ink components over time, a process in which exposure to ultraviolet radiation plays a significant role (2).

Large patch-test studies frequently yield negative results (8). Therefore, a skin biopsy is essential. Histology typically reveals epidermal changes such as acanthosis, hyperkeratosis, or parakeratosis, along with a dense lymphocytic dermal infiltrate, sometimes accompanied by macrophages and histiocytes (21). Affected patients are predominantly young adults, with a higher prevalence among women.

Para-phenylenediamine (PPD) is the primary allergen found in temporary tattoos, specifically in "black henna," where it is added to intensify color and durability. Although PPD is not typically found in permanent tattoo inks nowadays, it can still trigger allergic reactions through cross-reactivity with azo pigments, especially those used in red and green shades (19,22). In addition, topical products used for tattoo aftercare often contain potential sensitizers, which can provoke allergic contact dermatitis (2,23).

4.3.2 INFLAMMATORY COMPLICATIONS

4.3.2.1 LICHENOID REACTIONS

Among hypersensitivity reactions to tattoo pigments, local lichenoid responses are very common and may occur in tattoos of any color (8,24). However, they show a clear dominance in red pigment (fig 2) (25). This is likely due to metals such as nickel, mercury, and cadmium, which are frequently incorporated into red formulations and can provoke inflammatory changes.

Clinically, lichenoid tattoo lesions manifest as papular or plaque-like lesions and may mimic idiopathic lichen planus or coexist with allergic mechanisms, making a differentiation between these etiologies challenging (8,20). In some individuals, the tattoo-related lichenoid patterns reflect a Koebner phenomenon in the context of previously unrecognized lichen planus. When this possibility is suspected, a full-body examination is recommended. From a histological standpoint, lichenoid changes are seen as a dense, band-like lymphocytic infiltrate at the dermoepidermal junction, accompanied by interface dermatitis, basal vacuolar alteration, and the presence of dyskeratotic keratinocytes (8).

4.3.2.2 GRANULOMAS

Granulomatous reactions within tattooed skin represent a cascade of inflammatory responses mediated primarily by macrophages, which accumulate at the site of pigment deposition and may form granulomas to isolate and contain the persistent foreign particles (26). Typical features include small nodules, papules, or plaques that usually appear weeks to months following tattoo placement. These lesions may cause pruritus or tenderness (20). Definitive confirmation requires histological examination (3,20). Under the microscope, they are characterized by the presence of epithelioid histiocytes, multinucleated giant cells, and variable lymphocytic or neutrophilic infiltrates (8). The

two most frequently observed patterns are foreign-body granulomas and sarcoidal granulomas (fig. 3) (8,27). Foreign-body-type granulomas are marked by multinucleated giant cells containing intracellular tattoo pigment particles, which the body attempts to isolate and remove (20).

In contrast, sarcoidal granulomatous infiltrates consist of compact, non-caseating aggregates of epithelioid histiocytes with minimal surrounding inflammation, mimicking cutaneous sarcoidosis (3,8). If histopathological analysis reveals sarcoid-like granulomas in the tattooed tissue, further clinical evaluation is necessary to rule out systemic involvement, as skin findings may represent the first sign of a more widespread disease process (20,28). Granulomatous reactions have been reported in tattoos containing a wide range of pigments, such as black, red, blue, purple, and green inks (3).

4.3.3 INFECTION

When tattoo needles breach the protective cutaneous barrier, infectious agents can be carried into the dermis, bloodstream, and lymphatic system, thereby increasing the risk of infectious complications, particularly in patients with immunosuppression (2,8,29). Pathogens can also invade the human body during wound healing and when the barrier function has not yet been fully restored (2).

A nonprofessional or non-sterile setting is associated with a higher risk. Inadequate sterilization can lead to contamination by bacteria, viruses, fungi, mycobacteria, and, less commonly, parasites (8,29). Due to these potential hazards, several countries recommend deferring blood donations following tattooing for a time period varying between 4 months and 1 year. When tattooing is performed by trained professionals who adhere to strict aseptic protocols and if clients have intact skin and follow appropriate aftercare, the overall risk of infection is significantly reduced (8).

4.3.3.1 BACTERIAL INFECTIONS

The incidence of bacterial infections among tattooed people ranges from approximately 1% to 5% (8). The microorganisms most commonly causing these diseases are *Staphylococcus aureus, Streptococcus pyogenes*, and *Escherichia coli*, while other pathogens such as Pseudomonas aeruginosa and anaerobic bacteria, including Clostridium species, have also been described (2,8). The clinical spectrum of bacterial diseases ranges from superficial to deeper skin and soft tissue involvement, comprising impetigo and localized pyogenic infections, abscess formation, erysipelas, folliculitis, and, in rare cases, even gangrene (2,3,8).

Symptoms usually develop within a few days to several weeks after applying the ink. Typical clinical signs include localized pain, erythema, hyperthermia, and edema; purulent exudate may also be observed (8). In severe cases, bacteria enter the bloodstream, leading to sepsis, multiorgan dysfunction, and in rare circumstances, death (2,17). Contamination of tattoo formulations and equipment is considered an important contributing factor to these infectious complications. Studies

have demonstrated that a substantial number of ink containers are inadequately sealed, and a subset of these products may contain non-pathogenic and pathogenic microorganisms. In this regard, it is crucial to recognize the potential risk of infection, highlighting the importance of strict hygiene measures during tattooing (8,17). Nonetheless, infectious agents can arise from multiple sources, including the tattooed individual, the tattoo artist, the working environment, inadequately sterilized equipment, reused needles, or non-sterile water used for pigment dilution (2). In addition, mycobacterial diseases represent a clinically relevant subgroup of infectious complications. They are most commonly caused by atypical, non-tuberculous mycobacteria that are widely found in aqueous sources and may be introduced when non-sterile or non-distilled tap water is used to dilute tattoo preparations (2,8).

Most causative agents identified in tattoo-related cases are *Mycobacterium chelonae*, especially associated with the production of grey coloration by diluting black pigment with water (fig. 4) (3). Lesions such as papules, pustules, or nodules with ulceration confined to the tattooed skin may be seen. Less common cases of *Mycobacterium tuberculosis* and *Mycobacterium bovis* have been reported. In individuals without prior immunity, direct exposure to these pathogens may lead to primary cutaneous tuberculosis. Clinically, lesions occur two to four weeks after tattooing with erythematous nodules or papules present at the tattoo site, which may later develop into a superficial ulcer referred to as a tuberculous chancre. Painless lymphadenopathy can be observed (3,8).

4.3.3.2 VIRAL INFECTIONS

Another potential complication associated with contaminated instruments or inks is virus-related infection (8). Several viral pathogens have been reported to be associated with tattooing, including hepatitis B virus, hepatitis C virus, human immunodeficiency virus, herpes simplex virus, and human papillomavirus (3,8,30). Sterile techniques, disposable needles, and protective gloves have substantially reduced the risk of virus transmission during professional tattooing procedures (2,8). Despite improved hygiene standards, hepatitis cases linked to dermal pigmentation may remain undiagnosed for prolonged periods, as early infection is often asymptomatic and the progression to liver disease can take years or even decades. Transmission of human immunodeficiency virus through tattooing is considered uncommon because a relatively high viral load is required. Moreover, such cases may be overlooked or attributable to alternative exposure routes (2). One possible reason could be that HIV transmission can occur through skin breaches, often linked to inadequate hygiene and the use of non-sterile instruments (30). In addition to systemic viral infections, localized cutaneous manifestations have been described within tattooed skin. Inclusive of herpes simplex virus infections, human papillomavirus-related warts, molluscum contagiosum (fig. 5), and condylomata (8,31). Molluscum contagiosum can develop weeks to months after tattooing and typically presents as small,

umbilicated papules confined to the marked region (8,31). Herpes simplex virus type 1 infection may be transmitted during the tattooing process itself or arise during the healing period. Local trauma associated with tattooing can trigger viral reactivation in previously infected individuals, a phenomenon known as *herpes compunctorum* (8). In some cases, viral lesions have appeared following episodes of intense sun exposure. Ultraviolet radiation may induce local immune dysregulation in the dermis, thereby facilitating activation or reactivation of latent human papillomavirus. For this reason, protecting the newly inked skin from UV radiation is recommended (3,8). Furthermore, the sudden onset of multiple infectious lesions in a tattooed area should prompt evaluation for potential underlying immune deficiencies (3). Owing to widespread childhood vaccination programs and the expansion of standardized aseptic practices during body art application, the overall incidence of virus-associated tattoo infections remains minimal (8).

4.3.3.3 FUNGAL INFECTIONS

Only a few cases in the literature describe fungal complications arising within tattooed areas. Reported cases include both superficial and deep mycoses, such as dermatophytosis, pityriasis versicolor, and candidiasis, and, more rarely, diseases caused by *Sporothrix species, Aspergillus species, zygomycetes,* or *Acremonium species* (3,8). Superficial mycoses may occur, particularly during the healing period when the skin barrier is weakened. Dermatophytes such as *Microsporum canis*, often transmitted from domestic animals, have been implicated, with inadequate hygiene or improper aftercare increasing the likelihood of infection (8). A fungal etiology should be considered if cutaneous complications intensify or fail to improve during topical corticosteroid therapy (3).

Parasitic complications are exceptionally uncommon. Isolated cases have described cutaneous leishmaniasis in tattooed tissue, which has been observed exclusively in patients with underlying immunosuppressive conditions, such as visceral leishmaniasis or human immunodeficiency virus infection. In such instances, the use of previously used needles has been suggested as a possible route of parasite transmission (3,8).

4.3.4 NEOPLASMS ASSOCIATED WITH TATTOOING

Various benign and malignant skin tumors have been reported in areas of tattooed skin. However, strong epidemiological evidence for a direct cause is limited (2,8). Benign tumors observed in tattooed areas include dermatofibroma, epidermal cysts, seborrheic keratosis, and pseudoepitheliomatous hyperplasia, although these neoplasms are documented only sporadically (3,8,10). Malignant neoplasms more commonly described in association with tattoos are melanoma

(MM), basal cell carcinoma (BCC) (fig. 6), squamous cell carcinoma (SCC), leiomyosarcoma, and keratoacanthoma (KA) (3,8,32,33).

The occurrence of neoplasms within tattoos is likely to have multiple factors. Proposed mechanisms include exposure to potentially carcinogenic chemicals introduced via tattoo pigments, such as aromatic amines, polycyclic aromatic hydrocarbons, and benzopyrene, as well as mechanical trauma during the tattooing process (3,8,33). Chronic inflammation in response to exogenous pigment particles, ultraviolet radiation exposure, and individual genetic susceptibility may promote further carcinogenesis in tattooed skin (3,8). Tumor types appear to be influenced by tattoo color. Dark inks, especially black and dark blue shades, are more commonly associated with reports of melanoma and basal cell carcinoma, whereas red pigments are more often linked to squamous cell carcinoma, keratoacanthoma, and pseudoepitheliomatous hyperplasia (3,8).

Tattooing over pre-existing melanocytic nevi may pose additional concerns, as procedural skin trauma and ink-related carcinogens could promote dysplastic changes or mask early malignant transformation (3,8,32). Moreover, tattoos may interfere with clinical inspection of the integument, potentially delaying the detection of neoplasms during dermatological examination (3,20).

4.3.5 PSEUDOLYMPHOMAS

Cutaneous pseudolymphoma represents a benign, reactive lymphoproliferative disorder that mimics malignant lymphoma. The exact pathogenesis of tattoo-associated pseudolymphoma is not fully understood, but chronic antigen stimulation by tattoo pigments is considered a key triggering factor, particularly in red ink (8,34). Pseudolymphomas have been reported to have a delayed onset, developing from months to several years after tattoo placement (29,34). Clinically, tattoo-induced pseudolymphomas are rare, with only a limited number of cases reported to date (29,34). They have been most frequently associated with red tattoo pigments, particularly those containing mercuric sulfate, but similar findings have also been observed in blue- and green-colored tattoos composed of cobalt or chromium salts (8,34)

Malignancy is considered uncommon, but isolated cases of primary cutaneous B-cell lymphoma in tattooed skin have been reported, which warrant regular clinical follow-up (8,34). Histologically, pseudolymphoma is characterized by dense lymphocytic infiltrates within the dermis, presenting as either nodular aggregates or a band-like (lichenoid) pattern. Immunohistochemistry typically demonstrates a mixed population of B and T-lymphocytes (8,29). Predominant involvement of the superficial dermis, increased vascularity, and the absence of deep dermal infiltration help distinguish pseudolymphoma from malignant lymphoma (33). Regarding the differential diagnosis of pseudolymphoma, it is important to consider allergic inflammatory reactions to tattoo pigments,

primary cutaneous B-cell and T-cell lymphomas, lymphomatoid papulosis, as well as infectious conditions (8,34).

In addition to lymphoid proliferations within the skin, tattoo pigments may induce lymphatic changes. Excess pigment particles can migrate via lymphatic vessels to regional lymph nodes, where they accumulate and may cause visible pigmentation of the nodes. In some cases, deep dermal pigment deposition may impair lymphatic drainage, resulting in lymphatic obstruction, soft tissue swelling, and clinically significant lymphedema (2).

4.3.6 OTHER COMPLICATIONS

Temporary edema is a frequent and usually expected short-term reaction following tattooing. It typically manifests as transient swelling of the tattooed skin and may also be accompanied by slight changes in pigmentation, minor localized bleeding, pruritus, slight oozing, and discomfort. These findings are typically self-limiting and resolve within two to three weeks, so they should be regarded as part of normal healing rather than true complications. A study of tattooed adults from 38 U.S. states also reported pain, infection, and itching after the initial tattoo application (8,20). The etiology is mainly mechanical and chemical trauma. Repeated needle penetration causes microtrauma to the dermis, which can be further irritated by the application of disinfectants such as alcohol. In addition, an acute inflammatory response to the tattoo inks or their diluents may occur. These factors can disrupt the epidermal basal membrane and cause limited necrosis of epidermal and dermal cells, resulting in localized swelling and inflammation that gradually subside as the skin heals (8).

Photoinduced reactions are also important to mention. As demonstrated by the Danish "beach study", the prevalence of tattoo-associated discomfort is high. 42 of 144 subjects reported some form of manifestation, with 52% induced by ultraviolet exposure (2,8). Symptoms typically manifest as localized erythema and edema after exposure to solar radiation and are associated with tattoos containing cadmium sulfide, commonly used in yellow and sometimes red pigments (3,8,29). These reactions are generally interpreted as phototoxic: light exposure is thought to generate reactive intermediates that damage cellular components, including deoxyribonucleic acid, proteins, and membrane lipids, thereby provoking symptoms such as pain, pruritus, and, in severe cases, cell injury or necrosis (8).

Rarely, tattoos are followed by persistent pain, dysesthesia, or pruritus without an obvious trigger. Clinical work-up and biopsy may reveal underlying pathology. Isolated reports of complex regional pain syndrome have been described, particularly after tattooing in sensitive sites such as the wrist,

where superficial sensory nerve branches lie close to the dermis. Mechanical needle trauma and pigment chemicals have been proposed to affect unmyelinated C-fibers and induce chronic neuropathic symptoms (2,3).

Conventional tattooing is commonly associated with a limited degree of dermal fibrosis as a physiological response to repeated needle injury. As stated above, the procedure involves numerous punctures into the mid-dermis and thus constitutes a substantial mechanical insult to the skin. This trauma may result in hypertrophic scarring or, more rarely, keloid formation (fig. 7) (2,3,35).

This occurs particularly in areas such as the anterior chest, shoulders, and upper arms. The likelihood of pathological scarring increases when pigment is deposited too deeply, especially within the lower dermis, or when suboptimal or damaged needles are used. Careful technique and precise depth control significantly reduce tissue damage. Notably, even individuals with a known tendency toward keloid formation may undergo tattooing without any abnormal scarring if the procedure is confined to the superficial dermis, high-risk anatomical sites are avoided, and is applied with minimal trauma (2).

Some clients are dissatisfied after the cutaneous marking because the results appear unnatural, with issues such as an undesired or irregular shape, fading, or blurred margins. Expectations should therefore be managed in advance. Overall, the leading causes of complications and dissatisfaction are technical errors, particularly improper pigment placement, pigment migration, and color fanning. Such errors are difficult to correct precisely because the pigment is intended to be permanent (2).
Tattoos in visible regions such as the face, neck, and hands can lead to substantial psychosocial consequences. Ongoing stigma may contribute to discrimination, reduced employment opportunities, and barriers to social integration. In addition, incomplete removal outcomes occur even with modern lasers, and certain socially sensitive motifs provoke social exclusion or raise personal safety concerns. As a result, unwanted or socially disadvantageous tattoos can negatively affect mental well-being and quality of life (2,20).

4.4 DIAGNOSTIC AND EVALUATION METHODS

Given the wide spectrum of tattoo-associated complications, accurate diagnosis requires a structured and multidisciplinary approach. Some reactions are delayed, persistent, and more severe, affecting approximately 6–8% of tattooed individuals, who reportedly require medical evaluation (36).

Diagnosis is challenging due to overlapping clinical presentations and a lack of standardized tools, particularly for allergic tattoo reactions, where the causative allergens are often unknown (17).

Laboratory-based tests, histopathologic assessment, and imaging techniques serve as important extensions of the clinical assessment, particularly for distinguishing reactive from malignant conditions. Together, these tools support the differentiation between allergic, infectious, inflammatory, and neoplastic processes, thereby enabling a more precise and evidence-based diagnostic conclusion (17,33).

4.4.1 CLINICAL EXAMINATION AND PATIENT HISTORY

In clinical practice, the diagnostic process sometimes begins before laboratory investigations. Visual clinical examination combined with a detailed history often provides the first essential clues regarding the nature of the reaction (17,37).

Taking a comprehensive case history is a fundamental component of evaluation. The anamnesis should include information on the patient´s personal and medical background, notably pre-existing allergies, prior infectious diseases such as HIV or hepatitis, previous chronic dermatological conditions such as psoriasis, atopic eczema, or lichen planus (10).

Furthermore, it is essential to assess the circumstances under which the individual was tattooed, including hygienic conditions and whether the tattoo was applied in a professional studio. The exact duration from application and the appearance of symptoms must be documented to allow classification as an early (≤1 month) or late (>1 month) reaction (fig. 8) (10,38).

A structured symptom assessment should evaluate the presence of pruritus, pain, local hyperthermia, swelling, purulent discharge, or even ulceration. Systemic conditions such as fever, lymphadenopathy, or arthralgia should be considered, as they may indicate an infectious or systemic inflammatory process. Additionally, any information regarding previous treatments or diagnostic investigations should be obtained, as well as any occurrence of similar reactions in previous tattoos, particularly with the same pigment color (10).

Therefore, a detailed anamnesis provides essential guidance for further clinical, laboratory, and histopathological investigations. As tattoo-associated reactions are often atypical and may overlap with other inflammatory or infectious dermatoses, clinical inspection alone is insufficient to establish a definitive diagnosis (10).

4.4.2 LABORATORY AND IMAGING TESTS

Assessing pigmented lesions on tattooed skin poses a significant difficulty for dermatologists, as the ink can partially or completely obscure an underlying skin change. In such cases, certain diagnostic tools may become extremely valuable (3).

Dermatoscopy can serve as a useful modality for examining lesions in tattoos. For instance, case reports have demonstrated that both in vivo and ex vivo dermoscopy can identify pathological alterations in tattooed skin, such as verrucous lesions caused by HPV infection (39,40).
Additionally, it is beneficial for evaluating melanocytic nevi when a tattoo covers a pre-existing lesion, especially in areas with low pigmentation (40,41). Several reports highlight the occurrence of benign and malignant tumors within tattoos, underscoring the need for careful evaluation (3,8). At the same time, interpreting findings on decorated skin can be challenging due to the density of tattoo pigments. These external color particles can obscure key dermatoscopic features, complicating the identification of pathological signs (2).
In such cases, non-invasive Reflectance confocal microscopy (RCM) serves as an additional diagnostic tool to assess hidden nevi. Unlike the gold-standard biopsy used for melanomas, RCM enables diagnosis without damaging the tissue artwork. An observational retrospective study by Reilly et al. (2021) demonstrated that 18 out of 19 melanocytic lesions were evaluated as benign based on RCM (40).

Early reactions with clinical signs of infection may present with pain, localized warmth, oozing, and ulceration. When present, microbiological culture of purulent discharge is required, and empiric antibiotic therapy should be initiated. If an early reaction shows clear clinical evidence of infection, both culture of the purulent material and a skin biopsy for histological and microbiological examination, including bacterial and mycobacterial cultures, are mandatory. In contrast, early complications without signs of infection should initially be treated with topical corticosteroids. If the inflammatory response does not improve under therapy, a biopsy is helpful to exclude underlying contamination or other pathological processes (36).

In late or refractory reactions, a skin biopsy is strongly essential to exclude infectious causes, systemic granulomatous diseases, and lymphoproliferative disorders (36,38). Across published case reports, histopathological examination is the gold-standard method for clarifying the underlying cause of tattoo-related skin reactions and is an important tool for distinguishing among differential diagnoses (10,17,40). When tattooed skin develops papules or nodules, histopathological assessment becomes mandatory (fig. 9). An early biopsy should therefore be performed when malignancy is suspected, such as in cases of BCC, SCC, or Melanomas that may develop within a tattooed area. Additionally, Pseudolymphoma can clinically resemble an allergy, which is why a biopsy can provide a histopathological diagnosis. It is also very crucial to differentiate pseudolymphoma from lymphoma (2,42,43).

An optional biopsy can be avoided in cases of small reactions that occur immediately after tattooing and resolve within 1 to 2 weeks, in patients with known dermatological conditions, including psoriasis or lichen planus, exhibiting the Koebner phenomenon, or when symptoms respond adequately to topical corticosteroid therapy (8,36,43).

Establishing a definitive diagnosis of allergy to tattoo pigments is often problematic because tattoo inks contain complex mixtures of ingredients that are not fully identifiable (10,17,43). In hypersensitivity reactions, a biopsy is essential to classify the reaction. It could possibly be lichen planus or another condition, such as sarcoidosis (21). In the context of granulomatous tattoo reactions, further systemic evaluation is necessary to rule out underlying sarcoidosis (21,36). Investigations may include chest X-ray, ophthalmologic and cardiac assessments (echocardiography), abdominal imaging, and laboratory tests for angiotensin-converting enzyme and soluble interleukin-2 receptor levels as supportive markers; assessment for pulmonary involvement has been used to exclude systemic involvement (26,32). If histopathology reveals a lichenoid or spongiotic pattern and the clinical presentation is consistent with an allergic reaction, patch testing may be considered (36).

Under these conditions, patch testing (the gold standard for diagnosing allergic contact dermatitis) may have limited value and present negative or inconsistent results in tattoo reactions, as the responsible allergens and T-cell epitopes often remain unknown due to complex ink formulations (10,17,20).

Intradermal testing would better mimic exposure, but is considered inappropriate due to the risk of permanent pigment deposition and chronic inflammation. Even with dedicated tattoo patch series, allergen selection is uncertain, ink composition can change over time, and late reactions may be driven by photochemical breakdown of pigments. Therefore, skin biopsy supports the diagnosis by excluding infections, systemic diseases, or lymphomatous infiltrates and may show patterns compatible with delayed-type hypersensitivity (17).

A strong diagnostic approach combines biopsy with chemical ink/tissue analysis. Metals such as chromium, mercury, cobalt, and nickel can be identified and linked to sensitization, whereas allergy to organic substances is harder to prove due to the large number of possible colorants and the potential role of decomposition products for which no standard test reagents exist (17).

Pigment identification has been performed using high-performance liquid chromatography (HPLC), which can provide quantitative results but is severely limited by the poor solubility of many compounds in standard organic solvents. Alternatively, matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS) is utilized. This method applies to a broader range of color agents, although its sensitivity is substance-dependent and typically requires relatively high concentrations.

Emerging diagnostic strategies focus on *in vitro* detection of allergen-specific T-lymphocyte responses, including proliferation assays, cytokine readouts, and rapid activation markers such as CD154/CD40L. These methods face the challenge of detecting rare specific T cells and require careful comparison with non-allergic controls. An enrichment of reactive cellular T-cell clonotypes within the inflamed tattoo area provides strong evidence for a type IV hypersensitivity reaction to a compound found in the biopsy or ink. In the future, integrating *in vitro* assays with high-throughput T-cell receptor sequencing to demonstrate overlap between blood-reactive sequences and cells enriched in inflamed tattoo skin may provide more causal evidence than patch testing alone (17).
Following diagnostic confirmation, appropriate targeted management should be initiated to ensure adequate treatment and to prevent persistence or progression of the pathological process (37).

4.4.3 DIFFERENTIATIONS BETWEEN TATTOO REACTIONS AND OTHER DERMATOLOGICAL CONDITIONS

During the evaluation of a suspected type IV hypersensitivity reaction to tattoo pigments, the differential diagnosis should encompass other late-onset cutaneous complications, notably foreign body granulomas, systemic granulomatous diseases such as sarcoidosis, infectious etiologies, and pseudolymphomatous infiltrations (3).

In addition, the pigment application process can induce or exacerbate pre-existing dermatoses, typically within days to weeks or even months, through trauma-related mechanisms, namely the Koebner phenomenon. Flares have been described primarily in psoriasis, lichen planus, and vitiligo. Individual case reports also document cutaneous lupus erythematosus and pyoderma gangrenosum arising at the affected sites (8,26,42). In atopic dermatitis, procedural exposures may facilitate contact allergy or photosensitivity, resulting in eczematous flares (8). Regarding pyoderma gangrenosum, pathergy may trigger ulceration within the design, particularly on the lower extremities (8,36). Because some of these entities can clinically resemble allergic tattoo responses, dermatologic evaluation prior to tattooing should be considered in patients with known inflammatory skin disease (8).
Cutaneous pseudolymphoma is an important additional consideration in the differential diagnosis of suspected contact dermatitis in ornamented skin, characterized by multiple pigment shades within the same dermal area. Clinically, it may closely mimic an allergic manifestation, necessitating histopathological confirmation (34).

Vasculitis has been reported only rarely after tattooing, and a causal relationship remains unclear. When this condition is suspected, other etiologies, especially infection, medications, systemic inflammatory disorders, or underlying malignancy, should be ruled out (8).

4.5 MANAGEMENT AND TREATMENT APPROACHES

Therapeutic interventions for skin reactions range from non-invasive to surgical procedures and are guided by the severity of inflammation, symptoms, and cosmetic considerations. Mild to moderate cases are often treated conservatively with topical, systemic, or intralesional corticosteroids and, where appropriate, antihistamines. In addition, avoiding sun exposure is strongly recommended, as ultraviolet radiation may exacerbate inflammatory and allergic responses. If conservative measures fail or lesions persist, more invasive treatment options are considered. These include surgical excision of affected skin, cryotherapy, electrosurgical techniques, dermabrasion, and, of course, various selected laser modalities. Notably, such procedures increase the risk of permanent scarring (17).

4.5.1 FIRST-LINE TREATMENT

Initial management primarily is symptom control and inflammation reduction. In allergic or inflammatory reactions, conservative measures include oral antihistamines for pruritus and wheal-and-flare responses, particularly in acute presentations (3,8,20). In cases of suspected photosensitivity, strict photoprotection is recommended (3).

Topical corticosteroids represent the first-line anti-inflammatory therapy, with high-potency agents such as clobetasol propionate indicated for pronounced erythema, induration, and eczematous or lichenoid patterns. These agents are particularly effective in localized and mild to moderate reactions (2,3). First-line treatment in lichenoid tattoo reactions involves topical corticosteroids. In selected cases, topical calcineurin inhibitors, such as tacrolimus ointment, may also be used as a nonsteroidal alternative (44). For pseudolymphomatous reactions after dermal pigmentation, topical management may also be considered as an initial conservative therapeutic approach (8,34,45).

For infectious complications, early differentiation is needed. Superficial bacterial infections are treated according to standard protocols for skin and soft-tissue infections, including topical or systemic antibiotics and antiseptics (2,3). Superficial fungal infections are managed with topical antifungal agents such as clotrimazole, econazole, or terbinafine. Viral lesions, such as warts, are initially treated with keratolytics or cryotherapy (3).

4.5.2 SECOND-LINE TREATMENT

If first-line therapy is insufficient, widespread lesions persist, escalation to targeted intralesional or systemic therapy is indicated (2,3). Intralesional corticosteroid injections provide a localized, anti-inflammatory effect, particularly in persistent nodular or granulomatous lesions (2,3).

In selected foreign-body reactions, combination therapy with intralesional corticosteroids and 5-fluorouracil has shown efficacy (2).

Sarcoidosis-type granulomatous reactions are generally managed using therapeutic approaches typical of sarcoidosis care, including topical or systemic corticosteroids; in selected cases, additional immunomodulation if needed, or hydroxychloroquine as an antimalarial agent (26).

Lichenoid tattoo reactions that do not respond adequately to topical therapy may be managed further with intralesional corticosteroid injection (44).

Pseudolymphoma therapeutic measures are typically individualized and may include intralesional corticosteroids as a second-line option. Because rare progression to lymphoma has been discussed, long-term follow-up is recommended, even after apparent clinical remission (8,34,45).

The second-line management becomes specific to each etiology. Mycobacterial infections require prolonged therapy and are important to recognize early, as they may clinically resemble inflammatory responses and worsen if treated only with corticosteroids (2,46). In tuberculosis-related disease (Mycobacterium tuberculosis or Mycobacterium bovis), multidrug therapy is administered in two phases, typically using isoniazid, rifampicin, pyrazinamide, and ethambutol or, in some regimens, streptomycin. For non-tuberculous mycobacterial infections strains reported after tattooing (Mycobacterium chelonae, Mycobacterium abscessus, and Mycobacterium fortuitum), therapy is typically macrolide-based, often with clarithromycin. Treatment durations span approximately four months in mild cases and six to twelve months in severe or persistent disease, adjusted based on response and resistance testing (3). Extensive fungal infections need systemic antifungal management, including itraconazole, fluconazole, or amphotericin B (3).

Refractory cases of viral warts require topical immunotherapy or intralesional or topical cytotoxic approaches, such as bleomycin or fluorouracil. Molluscum contagiosum is generally managed with lesion-directed methods such as cryotherapy, curettage, cantharidin, or podophyllotoxin. Additional options used in selected cases include imiquimod, salicylic acid, and topical retinoids. For systemic viral infections (HBV, HCV, HIV, HPV, HSV), care follows specific antiviral guidelines, typically under multidisciplinary supervision (3).

4.5.3 THIRD-LINE TREATMENT

When cutaneous lesions persist despite prior pharmacological management and procedural interventions, including surgical approaches and, in selected cases, laser-based modalities are indicated (42).

In refractory lichenoid tattoo reactions, removal of affected areas may be necessary (44). Likewise, pseudolymphomatous reaction requires surgical excision, and in selected cases, laser removal approaches have been described (8,34,45).

Removing unsatisfactory body modifications historically relied on non-selective destructive techniques, including dermabrasion, chemical ablation, salabrasion, electrosurgery, cryosurgery, and surgical removal (47–49). Dermabrasion constitutes either a manual or mechanical abrasion with a rapidly rotating wheel or wire brush, whereas salabrasion works by debriding the superficial dermis using sodium chloride in combination with abrasive pads (50,51). Cryotherapy involves localized freezing of the targeted tissue with liquid nitrogen, resulting in cellular injury and subsequent tissue sloughing. Thermal destruction refers to non-selective coagulative injury aimed at dye-containing tissue, achieved through thermal cautery, electrocautery, or coagulation (51). In addition, chemical destruction is used, involving puncture or incision of the skin, followed by application of substances such as tannic acid or silver nitrate, or direct application of chemicals such as phenol or trichloroacetic acid to the affected area (49).

Nevertheless, invasive methods frequently yielded limited satisfaction, associated with incomplete ink clearance, prolonged healing, and a substantial risk of scarring and dyspigmentation (2,48,49). Decorating skin over pigmented lesions, such as naevi, should be actively discouraged. Synthetic pigment can impair clinical monitoring of the lesion and may also be associated with changes that subsequently necessitate surgical excision, resulting in avoidable disruption of the artwork. Individuals with nevi in the intended tattoo area should either refrain from that region or select a design that spares the pigmented lesion to preserve future surveillance (2).

Before any intervention, such as tattoo removal, a comprehensive pre-treatment assessment is essential. This should include detailed documentation of the following ink characteristics: color distribution, layering, and the patient’s skin type, together with a targeted history for factors associated with increased risk of complications (47,48).

Relevant considerations encompass prior isotretinoin exposure, previous systemic gold therapy, a history of herpes infections, keloid predisposition, and UV exposure, as these may necessitate modified therapeutic planning. Baseline standardized digital photography is recommended to objectively record the initial clinical appearance and to enable reliable comparison during follow-up.

In parallel, patients should receive clear counseling on the treatment objectives, realistic expectations, available options, anticipated outcomes, potential adverse effects, including scarring and pigmentary changes, and post-procedural care (47).

Laser therapy is usually contraindicated for allergic responses because the energy can break down pigment molecules, potentially releasing allergenic substances such as azo compounds or quinacridones into adjacent tissue. This may lead to local or serious systemic reactions. Early side effects often include pain, blistering, crusting, and small bleeding. Therefore, photo-thermal treatment in active lesions should be avoided. For reactive or severe cases, surgical removal is the preferred method. Dermabrasion or dermatome shaving is suggested for chronic allergic reactions because these techniques remove the affected tissue, although deeper procedures may result in delayed healing and scarring (48,51–53).

4.5.3.1 LASER TATTOO REMOVAL

Contemporary laser and light-based technologies have improved outcomes by using pigment-targeting wavelengths calibrated to different ink colors, generally allowing more controlled removal with fewer complications, such as reduced injury to adjacent tissue, pigment retention, or scarring, compared with older destructive approaches (2,47,52).

Although therapeutic outcomes cannot be predicted with absolute certainty, estimation tools such as the Kirby–Desai scoring system (fig. 10) can be used to estimate how many sessions will be required for ink clearance. This scale incorporates anatomical location, noting that proximal areas such as the head and neck generally respond more favorably to treatment than distal extremities. It further incorporates technical factors, such as ink depth, scarring, and pigment layering, along with color characteristics, favoring black ink over multicolored designs. Lower scores across these parameters are associated with improved procedural efficiency and fewer required appointments (47,50,51).

Before initiating laser tattoo removal, patients must be thoroughly informed that successful resolution typically requires multiple interventions, commonly ranging from several to more than a dozen applications (50). The exact number of visits depends on multiple variables, including the age of the artwork, chemical composition (e.g., orange, yellow, or white pigments are more challenging to clear), ink density, and depth of dermal deposition. Strict avoidance of ultraviolet exposure before and after each session is essential, as sun exposure significantly increases the risk of pigmentary disturbances following photo-thermal therapy (50).

Comprehensive documentation is a critical component of the clinical evaluation. Accordingly, patients should be aware of the potential adverse effects of laser tattoo removal, including procedural discomfort, hemorrhage, infectious complications, injury to adjacent tissues or sensory organs, and incomplete clearance that may require further measures. Additional risks encompass inflammatory reactions such as burns and blister formation, permanent or temporary scarring, alterations in skin texture, and unpredictable pigmentary outcomes, including both hyperpigmentation and hypopigmentation. Changes in ink coloration, such as the unexpected darkening of certain compounds, as well as dissatisfaction with the aesthetic results, should also be addressed during counseling (50).

Prior to the procedure, the skin is typically cleansed with alcohol or chlorhexidine. If alcohol is used, it must be fully evaporated to avoid ignition risk. Laser procedures are frequently unpleasant. Analgesia can be achieved with topical anesthetics, such as lidocaine–prilocaine combinations applied under occlusion for approximately 45-60 minutes, or via local anesthetic techniques (47,48,50). During treatment, eye protection rated for the specific wavelength is mandatory for all individuals in the room. Patients may use goggles or, for periocular tattoos, metal ocular shields or corneal protectors, depending on the anatomical location (48,50).

4.5.3.1.1 EVOLUTION AND PRINCIPLES IN LASER TATTOO REMOVAL

Historically, tattoo removal was attempted with crude thermal ablation, including the application of open flames, heated charcoal, or even cigarettes, to cauterize pigment-containing tissue. The concept of selective photothermolysis, introduced by Anderson and Parrish in the 1980s, forms the scientific basis for modern interventions: when wavelength selection and pulse duration are matched to the target chromophore and its thermal relaxation time, energy deposition is preferentially confined to pigment particles with relative sparing of surrounding structures (2).

Quality-switched (QS) laser platforms, introduced in the 1990s, became the gold standard by combining ink-specific wavelengths with very high peak power over nanosecond timescales, thereby enabling efficient pigment fragmentation (2,51,53).

Exogenous colorants show distinct absorption characteristics across the visible spectrum (approximately 420–800 nm), and device selection is typically guided by the dominant ink colors. However, contemporary professional designs frequently contain complex pigment blends and are often multilayered, particularly in cover-up applications, which makes the clinical response to a chosen wavelength less predictable. This variability underscores the need for individualized modality selection and cautious, stepwise adjustment of treatment parameters to balance efficacy and safety (2).

Laser choice is largely determined by ink color and the patient's skin type. Q-switched ruby (694 nm; ~28–40 ns), Q-switched alexandrite (755 nm; ~50–100 ns), and Q-switched neodymium-doped yttrium-aluminum-garnet (QS Nd: YAG) lasers (1064 nm; ~5–10 ns and frequency-doubled 532 nm) remain the principal technologies in current use (47,50,53). Dark blue and black tattoos can respond well to multiple platforms, but the longer 1064 nm wavelength of neodymium-doped yttrium-aluminum-garnet is often favored in darker phenotypes because it is less absorbed by epidermal melanin and penetrates more deeply, thereby reducing the risk of pigmentary complications. Shorter wavelengths, as seen in ruby, may achieve strong clearance in some settings but are associated with a higher incidence of hypopigmentation due to greater melanin absorption (47,50). Warm-spectrum inks such as red and orange shades typically respond best to 532 nm (frequency-doubled) neodymium-doped yttrium-aluminum-garnet treatment, whereas green inks generally respond to alexandrite or ruby, with alexandrite often preferred (fig. 11) (47,50). Cosmetic and light-colored inks can be problematic because iron oxides and titanium dioxide may darken after irradiation. While additional sessions can sometimes reverse this, prolonged treatment courses may be required, and ablative laser resurfacing with CO_2 and erbium-doped YAG lasers has been described as an alternative in selected cases (47).

Recent developments aim to improve both treatment efficacy and clinical outcomes. It has been reported that fractional skin resurfacing, whether ablative or non-ablative, enhances ink clearance, reduces blistering and downtime, and may lower the risk of treatment-related hypopigmentation. The latest generation of picosecond lasers emits shorter pulses that better match the physical properties of tattoo colorants. Consequently, photomechanical fragmentation is refined. Clinical studies suggest that these devices can achieve faster and more complete clearance, particularly for blue and green inks. Optimally, in fewer treatment sessions than conventional nanosecond lasers. Although they remain more expensive, the long-term evidence is not yet complete (47).

Following irradiation, the treated area typically shows an immediate tissue whitening, indicating effective pigment–light interaction (fig. 12). This transient change reflects steam-related vacuole formation within the epidermis and dermis and may be accompanied by mild pinpoint bleeding from superficial epidermal disruption (2). Re-epithelialization usually occurs within 2–7 days. During this period, antiseptic agents or dressings are commonly used to reduce the risk of infection. Over subsequent weeks, fragmented particles are progressively removed through immune-cell uptake (primarily by macrophages) and lymphatic transport, although the fate of ink particles beyond regional lymph nodes remains unclear. This uncertainty has raised concerns regarding potential toxic,

allergenic, or carcinogenic effects of degradation products before and after laser fragmentation, contributing to ongoing debate about long-term safety (2).

4.5.4 COMPLICATIONS AND PROGNOSIS

The most frequent complications of laser tattoo removal are suboptimal therapeutic outcomes rather than acute medical harm. In many cases, complete pigment elimination is not achieved within the initially projected number of sessions, resulting in residual dye, incomplete fading, persistent contours of the original design, or unintended chromatic alterations, including darkening. In addition, permanent or long-lasting cutaneous changes may develop, affecting both skin texture and coloration (50).

Patients can experience short-term local manifestations, most commonly blistering, edema, crusting, pruritus, erythema, and pain. Although these effects are usually transient, permanent adverse reactions are possible, including scarring, hyperpigmentation, or hypopigmentation, and unintended pigment color shifts. The risk profile is less favorable in darker skin types, as they are more susceptible to pigmentary adverse events, and skin texture changes may accumulate with repeated treatment sessions (26,50). Post-inflammatory hyperpigmentation occurs more frequently than hypopigmentation, whereas hypopigmentation tends to be more persistent once established. Hyperpigmentation is commonly managed with topical lightening agents such as 4% hydroquinone, whereas hypopigmentation may improve by reducing inflammation with corticosteroids or by exposure to blue or ultraviolet light to stimulate melanogenesis (50). Medical factors may influence eligibility and risk, including pregnancy and lactation, impaired wound healing in diabetic patients, and medication exposures such as retinoids, which may predispose to scarring. Prior systemic gold therapy poses a risk of chrysiasis-related hyperpigmentation. A thorough allergy history and assessment of hypertrophic scar or keloid tendency are important (2).

Although scarring rates are generally low with Q-switched systems, overly aggressive settings increase the risk of fibrosis and dyspigmentation. Pigmentary changes are more frequent overall than cicatrization, with hyperpigmentation often managed with longer intervals and bleaching agents. Hypopigmentation is mitigated by using longer wavelengths, lower fluence, and extended recovery time between sessions (2).

After QS-treatment, fragmented ink is transported via the lymphatic system. Consequently, systemic hypersensitivity is possible, especially in patients with pre-existing local ink allergy. Most reported responses manifest as mild-to-moderate dermatitis. Nonetheless, generalized reactions have been reported in isolated cases. Some professionals, therefore, prefer carbon dioxide or erbium-doped

yttrium-aluminum-garnet lasers over Q-switched therapy. However, QS Nd: YAG intervention has been successfully performed in allergic patients using a cautious protocol with pre-treatment corticosteroids, peri-procedural antihistamines, and close observation, without systemic complications (2).

For the first 24 - 48 hours, patients should avoid activities that elevate body temperature, such as intense workouts, hot showers, or saunas. For at least two weeks post-procedure, ultraviolet exposure should be minimized to reduce the risk of post-inflammatory dyspigmentation. When avoidance is impractical, a broad-spectrum sunscreen with a sun protection factor (SPF) ≥30 should be applied consistently (50).

5 CASE REPORT

This case, adapted from Szulia et al. (2022), illustrates a generalized inflammatory response to red tattoo pigment. The patient developed widespread skin inflammation associated with a red-pigmented design, posing significant diagnostic and therapeutic challenges. Management took place at the Military Medical Faculty and the Plastic, Reconstructive and Aesthetic Surgery Clinic of the Medical University of Lodz (54).

A 36-year-old Caucasian male presented to a plastic and reconstructive surgery clinic for evaluation of persistent inflammatory changes affecting the red portions of a forearm tattoo, accompanied by systemic symptoms.

The patient had multiple large tattoos on the chest and upper extremities. Most had been applied years earlier without complications. Approximately six weeks after receiving new red, black, and green ink on the right forearm, he developed diffuse erythema involving the arms and chest (fig. 13 and fig. 14). At presentation to the surgical clinic, the patient exhibited generalized erythroderma with pronounced xerosis and anhidrosis, accompanied by complete loss of scalp and body hair. Examination of the right forearm revealed firm, elevated granulomatous plaques sharply limited to the red-tattooed areas. In addition, generalized lymphadenopathy was palpable. The patient also reported marked fatigue and substantial impairment of daily functioning, with reduced ability to participate in both occupational and social activities. His medical history was notable for Hashimoto's thyroiditis managed with levothyroxine and prior testosterone misuse. During immunosuppressive therapy for erythroderma and cutaneous alterations, he was hospitalized for COVID-19-associated pneumonia. There was no personal or family history of sarcoidosis or other autoimmune dermatoses (54).

Laboratory evaluation showed a mildly increased C-reactive protein level (8.9 mg/L) and marked eosinophilia (2.4 × 103/μL, 31.7%). Serologic tests for human immunodeficiency virus, hepatitis B

and C, and parasitic infections were negative. Cross-sectional imaging revealed no findings suggestive of malignancy. Histopathological assessment of a biopsied inguinal lymph node demonstrated deposits of red pigment with reactive lymphocytic infiltration. Multiple skin biopsies were obtained at different stages of the disease course: specimens from tattooed, clinically affected skin showed intradermal pigment deposition, a dense inflammatory infiltrate, and epidermal erosion, whereas biopsies from non-tattooed erythrodermic skin were nonspecific. No features of lymphoproliferative disease were identified. Patch testing for metal hypersensitivity was negative. The particularly strict localization of granulomatous inflammation to red pigment regions and the exclusion of alternative systemic causes supported a diagnosis of a systemic delayed-type hypersensitivity reaction to red tattoo pigment (54).

Over the subsequent year, the patient underwent extensive evaluation in dermatology, internal medicine, hematology, and allergology departments. Differential diagnoses included atopic dermatitis, pityriasis rubra pilaris, follicular mucinosis, and cutaneous lymphoma. Multiple therapeutic regimens were attempted, including systemic corticosteroids, cyclosporine A, methotrexate, retinoids, antihistamines, antibiotics, and phototherapy. While high-dose immunosuppression temporarily reduced inflammation, symptoms recurred upon dose reduction. Given the refractory course despite prolonged topical and systemic immunosuppressive therapy, definitive surgical management was pursued. Systemic corticosteroids were discontinued at the initiation of operative treatment. The male subsequently underwent six staged excisions at approximately monthly intervals, aiming to completely remove all clinically reactive tattooed tissue (fig. 15). Reconstruction was achieved using a combination of primary direct closure, local flap procedures, and full-thickness skin grafts harvested from the inguinal region. Excision was carried through the full thickness of the dermis to maximize pigment clearance and reduce the risk of persistent antigenic stimulus (54).
Postoperative recovery after each stage was uncomplicated. Progressive improvement in systemic symptoms was observed following each surgical step. After complete removal of all reactive tattoo segments, erythroderma resolved entirely. Eosinophil counts normalized, and inflammatory markers returned to reference ranges. At the three-month follow-up, no recurrence of systemic or localized symptoms was noted. (fig. 16) The patient reported marked improvement in quality of life and return to full professional activity.

This case demonstrates a rare but severe systemic manifestation of delayed hypersensitivity to red tattoo pigment. The pathogenesis likely involves antigen processing and T-cell–mediated immune activation triggered by pigment components or contaminants. The confinement of granulomatous

inflammation to red-shaded areas and the resolution of systemic disease after complete tissue excision strongly support a causal relationship.

Medical therapy alone may be insufficient in extensive or systemic reactions. In such cases, complete surgical removal represents a definitive and effective treatment option (54).

6 DISCUSSION

Among adverse tattoo reactions, allergic and granulomatous responses are most commonly reported in the literature, particularly with red pigments, as shown by Kluger (2017). This observation has also been noted in earlier reports involving mercury-based pigments and in a cohort study by Serup et al. (2020). In that study, 104 human skin biopsies were examined, predominantly showing allergic reactions to red tattoos, suggesting a connection with modern organic red colors or shades (21,55,56). The persistent link across various ink formulations indicates that the issue persists not only with old compounds but also after reformulation attempts.

These findings have significant clinical implications. Up to 30% of adults bear tattoos, with an estimated complication rate of about 2.1%. However, the actual prevalence is probably greater due to underrecognition, as many individuals don´t seek professional medical help unless symptoms become severe. This issue is further complicated by the inconsistent and often delayed onset of tattoo allergy symptoms (8). Serup et al. (2025) report that long-term reactions can be mild and intermittently chronic, with photosensitivity involving around 20% of those affected. Although about 40% of tattooed individuals report mild issues, only 2–3% seek medical help or visit a clinic (57). The gap between self-reported symptoms and medical consultation means that clinicians likely see only the most severe condition, underestimating the true burden of disease.

A concrete illustration of this diagnostic challenge is provided by Shao et al. (2024) in a case in which a patient with allergic contact dermatitis from tattoo ink was misdiagnosed with cellulitis multiple times by different clinicians. After several antibiotic treatments without clinical improvement, the accurate diagnosis was made only upon presentation to the emergency department, approximately 1 month later. This case underscores why awareness across all clinical specialties, not just dermatologists, is essential (58).

Diagnosing the condition is further complicated by the limitations of standard patch testing. Often, the exact allergen remains unidentified. Some research indicates that the allergen might not be the pigment itself but a degradation product created within the skin, possibly as a result of sunlight exposure, metabolic processes, or laser fragmentation (2,55).

Patch testing frequently generates negative results even in patients with clear symptoms and histological signs of allergy, making its clinical value uncertain (59). A negative patch test cannot rule out a tattoo allergy. Physicians should not be falsely reassured by a negative result alone and

should instead depend on histological evaluation and clinical assessment. The delay of months or years between tattooing and the onset of allergic symptoms further supports the hypothesis that the allergen is a hapten formed over time in the skin rather than a direct component of the original ink (57).
Although Serup et al. (2020) examined dermatome-shaving biopsies, the study included only patients with symptoms. This creates selection bias because people with red tattoos and without symptoms were not included. Overall, the data strongly support a link between red pigments and allergic reactions, although the exact molecular trigger remains uncertain and the true prevalence is difficult to determine (28,55,56).

In contrast, the evidence for neoplastic complications remains weak and controversial. Case reports and systematic reviews, such as Lebhar et al. (2024), have documented melanomas, squamous cell carcinomas, basal cell carcinomas, and other tumors in tattooed skin. Although the number of cases has increased in recent years (especially from 2016 to 2023), also in tattoos with red pigmentation, it is currently impossible to determine whether this is coincidental or due to a true pathological effect. Some speculations include trauma, inflammation, melanocytic mutations, or UV radiation as etiology. The current literature is limited by reporting bias, and systematic reviews of clinical trials have not established a definitive link between tattoos and skin cancer. From an academic point of view, tattoos should not be described as a proven cause of skin cancer, but it is important to acknowledge that carcinogenic contaminants may be present in inks (60,61). A critical methodological challenge further complicates the interpretation. The tattooed population differs systematically from the non-tattooed population in topics of lifestyle and socioeconomics, including education, income, smoking, and alcohol consumption. As shown by the CRABAT (Cancer Risk Attributable to the Body Art of Tattooing) cohort study, the potential impact of tattoos on cancer can only be meaningfully assessed when these factors are taken into account (62). This problem represents a major unresolved challenge for this area of research.

Therapeutically, the evidence indicates a more differentiated rather than a uniform approach. Conservative anti-inflammatory treatments, particularly topical or intralesional corticosteroids, are commonly used for inflammatory or allergic reactions, with surgical excision reserved for more severe cases. Infectious complications require pathogen-specific management. These recommendations are primarily based on case reports and expert opinion rather than randomized controlled trials. This shows that strong therapeutic evidence for tattoo-associated reactions is still lacking. Developing clear guidelines would be beneficial for the future. However, one of the clearest therapeutic conclusions in the literature is that laser tattoo removal should be avoided to prevent

allergic reactions to tattoos. Multiple reports, such as Tjipta et al. (2023) and Werpachowski et al. (2025), state that laser fragmentation may worsen hypersensitivity and provoke systemic reactions, sometimes rare cases of anaphylaxis. In refractory allergic cases, especially in severe or persistent symptoms, surgical excision remains the best intervention despite the cosmetic contraindications. This is an important example in the literature showing what clinicians should refrain from (48,52,63).

The introduction of European REACH regulations marked a milestone in tattoo safety. The most important recent update is Commission Regulation (EU) 2020/2208, which modified Annex XVII of REACH. Since the 4th of January 2022, it has restricted the use of hazardous substances in tattoos and permanent make-up throughout the EU. ECHA and the European Commission state that this regulation applies to over 4,000 chemicals, including carcinogens, mutagens, metals, methanols, reproductive toxins, and substances with sensitizing or irritating effects (57,64,65).

Why red pigment remains a particularly persistent problem despite regulatory intervention is instructive. Between January 2022 and October 2024, following the implementation of the new REACH regulations, one dermatology clinic documented 220 complications related to tattoos, including 41 cases of allergic responses to red tattoo ink. This suggests that REACH, while a significant regulatory milestone, has not eliminated red pigment allergy (66). The reason is following: the allergen and epitope responsible for red tattoo allergy have not yet been clearly identified. In addition, haptenization may develop over time within the skin, arising from the chemical breakdown of the pigment. This means the allergen is not expected to be in the original ink bottle. Therefore, it cannot simply be banned as a specific chemical substance (57,66). REACH operates on the principle of restricting known hazardous compounds, but it cannot address an allergen that forms in the body after ink is injected. Clinically, this implies that even red tattoos that meet REACH standards still carry a residual and currently unmeasurable allergic risk.

Moreover, REACH functions primarily as a negative list, restricting substances known or suspected to be hazardous, but there is no positive list providing a comprehensive overview of proven-safe ingredients (2,67). Moseman et al. (2025) analyzed blue and green REACH-compliant tattoo inks and found that tattoo ink labeling remains incorrect and is still a global issue. Recently, Pigment Green 7 and Pigment Blue 15:3 were banned from application, even though they were commonly used pigments. This is also confirmed by the Bundesinstitut für Risikobewertung (BfR). Additionally, REACH requires that all labels include a precise and complete list of ingredients along with warnings about hazardous substances. Moseman et al. (2025) discovered that 9 out of 10 ink samples from five brands did not meet REACH standards, indicating ongoing concerns about their composition.

Manufacturers may lack full knowledge of the materials they use, underscoring the importance of proper testing and accurate labeling to ensure safety. However, the sample size of 10 inks from five brands limits generality. It is unclear whether these findings reflect an industry-wide problem or just isolated cases (65,68). Furthermore, even post-REACH analyses reveal persistent exceedances of heavy metals. A study by Ćwielag-Drabek et al. (2025) evaluating 41 commercially available EU inks found that limits were exceeded for multiple metals, including nickel in 24 samples, arsenic in 20, and chromium(VI) in 16, with copper raising the most widespread non-cancer risk concerns. This demonstrates that chemical safety challenges persist even after regulatory implementation, and that compliance cannot be assumed from REACH certification alone (69).

Additionally, some questions still remain open, like degradation products, systemic bioavailability, and long-term toxic effects of ink components (57,67). Not all health risks are addressed, such as infection risk. This risk still depends on manufacturing sterility, contamination, and the tattooist's technique or dilution practice. In the future, it is important not only to ban chemical hazards but also to strengthen manufacturing processes, analytical transparency, and surveillance of adverse reactions. (57). In a Danish study by Serup et al (2025) about tattoo ink products and Pigments, 39,687 tattooed clients with ink from 109,720 bottles were analyzed. The study states, for example, that granulomatous reaction in black tattoos can manifest with or without systemic sarcoidosis. Certain tattoo inks containing carbon black can trigger this immune reaction. In these cases, the specific ink product and its manufacturer can often be traced, enabling risk investigation, though this is not mentioned in REACH. (57) Although REACH represents a major regulatory advance, its direct effect on clinical complications has not yet been clearly demonstrated.

Beyond the clinical perspective, broader public health issues are raised. Clinical management of tattoo complications must include the following steps: Clinicians should be aware of the potential risks associated with tattoos and consistently exercise careful assessment when evaluating and monitoring lesions during skin examinations and throughout therapeutic management. Risk counseling should be more explicit in some patient groups. Individuals with a history of keloids or hypertrophic scarring should be informed that tattooing is a form of skin injury and therefore carries a risk of abnormal scar formation, even though published evidence specifically linking tattoos to keloids is limited and largely based on case reports rather than solid epidemiological evidence. This indicates that keloids are a relative, not absolute, contraindication. Patients should exercise caution, particularly if keloids develop after previous trauma like surgery or piercings. (2,35,47).
The potential for disease exacerbation is shown by Orzan et al. (2014), who described a case of tattoo-induced psoriasis likely triggered by the Koebner phenomenon. Similarly, immunocompromised

patients and those with chronic inflammatory diseases should not automatically be excluded from tattooing, but they require individualized counseling as well. They may face a higher risk of infection, delayed healing, unusual inflammatory reactions, or worsening disease. In these groups, clinicians should advise against tattooing during periods of active disease or intensive immunosuppression and should emphasize the importance of medical consultation before the procedure (2,70).

Furthermore, tattoos should never be applied over existing melanocytic nevi, premalignant lesions, or heavily pigmented lesions, as they can obscure early melanoma warning signs and complicate dermoscopic follow-up (60). Diverse dermatological literature advises against tattooing in areas with dense nevi. This advice is based less on confirmed cases of tattoo-induced cancer and more on the significant diagnostic challenge of hiding malignant changes (2,8,60,71).

Clients should always choose licensed studios with certified tattooists who adhere to hygiene standards and avoid unprofessional home tattooing or unhygienic conditions, which increase the risk of hepatitis B/C and bacterial infections. Additionally, training programs for tattoo artists accentuate sterile techniques and infection control, including the use of single-use needles, disinfectants, and sterilization procedures (2,8,72,73).
On top of that, proper aftercare is essential to prevent infections. Follow precise aftercare guidelines: avoid picking scabs and exposure to sunlight to prevent fading, irritation, or scarring. Reviews consistently highlight that poor hygiene, contaminated inks, unsafe dilution practices, and unprofessional tattooing are key factors in infection risks. Therefore, prevention is best achieved through licensed studios, sterile single-use equipment, correct skin preparation, and standardized aftercare routines (2,8,72,73).

7 LIMITATIONS

This review has several limitations that must be taken into consideration. The literature search was limited to PubMed and Scopus, so relevant studies from other sources or non-conventional literature may not have been identified. Furthermore, this is a narrative review rather than a systematic review, which means that structured study selection, formal quality assessment, and transparent reproducibility are limited. Much of the available evidence is based on case reports, which limits the level of evidence and restricts the generalizability of the conclusions. Furthermore, heterogeneity in definitions, diagnostics, and therapeutic approaches across the included studies and information, as well as potential publication and language biases (such as a preference for studies with positive outcomes or English-language studies), may further affect the validity of the findings.

8 CONCLUSIONS

As the ancient Roman term *stigma* already implies, tattoos have long carried a negative connotation. Although body art has gained broader social acceptance in modern times due to increased visibility and changing cultural attitudes, they still present a range of medical concerns. While many tattooed people remain completely asymptomatic, some may develop inflammatory, allergic, infectious, granulomatous, lymphoproliferative, or even neoplastic manifestations.

The toxicological and immunological complexity of tattooing agents remains not fully understood, yet. Modern formulations consist of chemical mixtures that contain substances of toxicological concern, including heavy metals, aromatic amine precursors, and polycyclic aromatic hydrocarbons. Pigment persistence within dermal macrophages, potential lymphatic migration, and photochemical modifications induced by ultraviolet radiation or laser exposure highlight the dynamic, long-term interaction between implanted colorants and the immune system. Despite limited epidemiological evidence directly linking these substances to carcinogenesis, the biological possibility of adverse systemic effects warrants continued investigation.

Diagnosis of tattoo-associated complications relies on a structured, sometimes multidisciplinary approach that integrates clinical assessment, comprehensive history, histopathological evaluation, and, when needed, microbiological and systemic investigations. Patch testing is often insensitive because of limited knowledge of pigment composition and degradation products. Emerging immunological techniques, including in vitro T-cell assays and receptor sequencing, may improve causal attribution in the future.

Therapeutic strategies should be selected based on the underlying pathological mechanism. Conservative anti-inflammatory or immunosuppressive treatments may temporarily alleviate symptoms, but infectious complications require pathogen-specific therapy. Laser-assisted removal, although effective for cosmetic purposes, may exacerbate allergic reactions by fragmenting the ink. In severe, refractory, or systemic hypersensitivity reactions, complete surgical excision of the reactive pigment remains the only definitive curative method.

In summary, adverse tattoo reactions are a complex clinical issue involving dermatology, immunology, toxicology, and surgery. Greater interdisciplinary awareness improved diagnostic approaches, and ongoing research into chemical components and complications is essential to enhance prevention, treatment, and long-term safety.

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10 ANNEXES

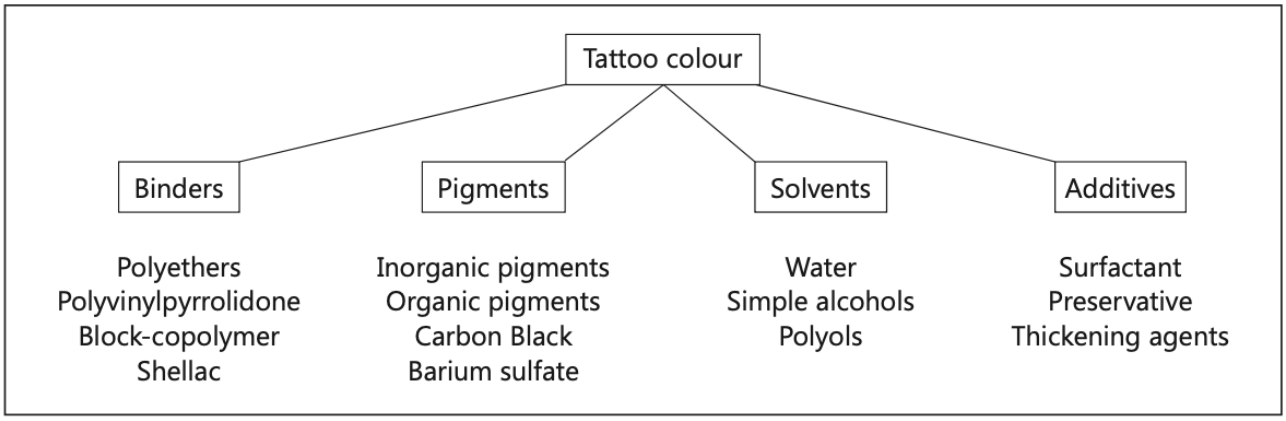

***Figure 1**. Simple illustration of tattoo ink composition (2).*

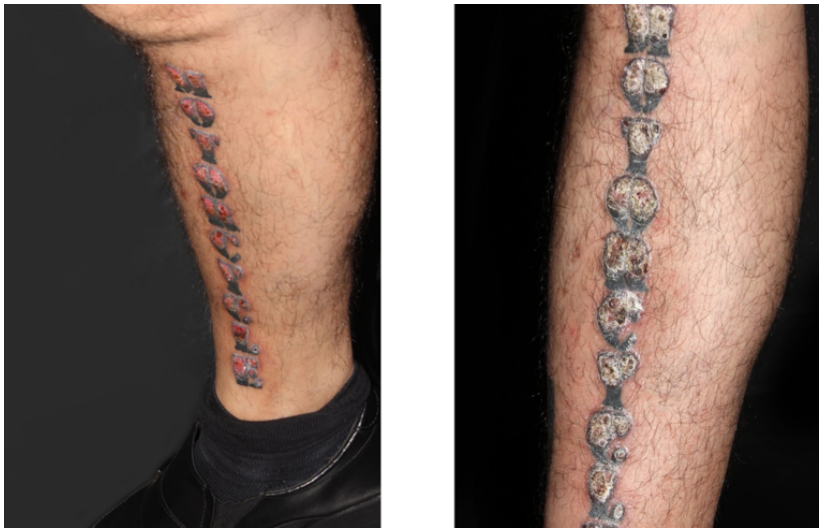

***Figure 2**. Clinical appearance, showing a verrucous reaction in the red-pigmented regions (25).*

***Figure 3.** Firm sarcoidal papules observed within a multicolored tattoo on the upper left arm (27).*

Figure 4. *Clinical appearance of scaly plaques confined to an area of a gray-colored tattoo (74).*

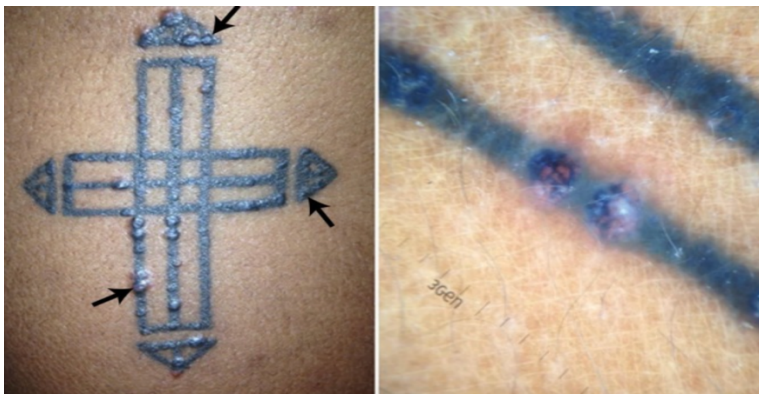

Figure 5. ***(A)*** *Multiple pearly molluscum contagiosum papules measuring 0.3 – 0.5 cm are located within a tattoo on the arm.* ***(B)*** *Dermoscopic image demonstrating umbilicated papules distributed along the tattooed lines (31).*

Figure 6. *Basal cell carcinoma with nodular and superficial components developing in a right shoulder tattoo (28).*

Figure 7. *Keloid scar formation following tattooing on the upper arm (3).*

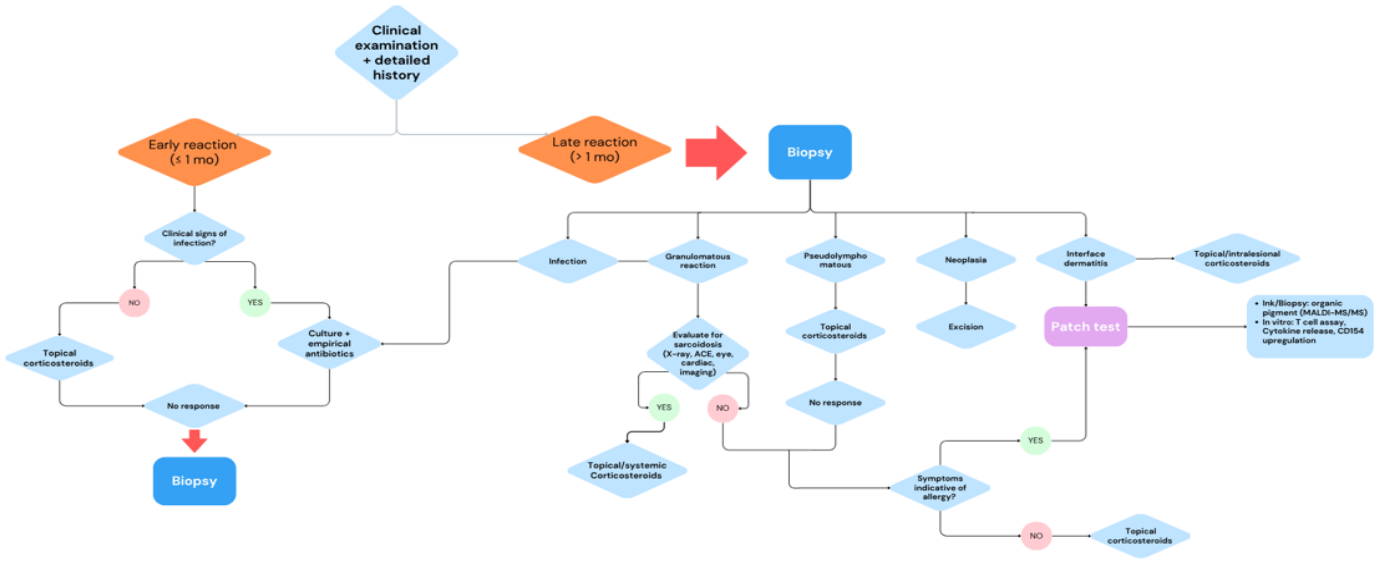

Figure 8. *Diagnostic flow chart. Topical or intralesional corticosteroids remain the first-line treatment; however, other valid therapeutic options include surgery and excision for refractory or severe cases, Q-switched lasers, ablative carbon dioxide lasers, and erbium lasers (17,38).*

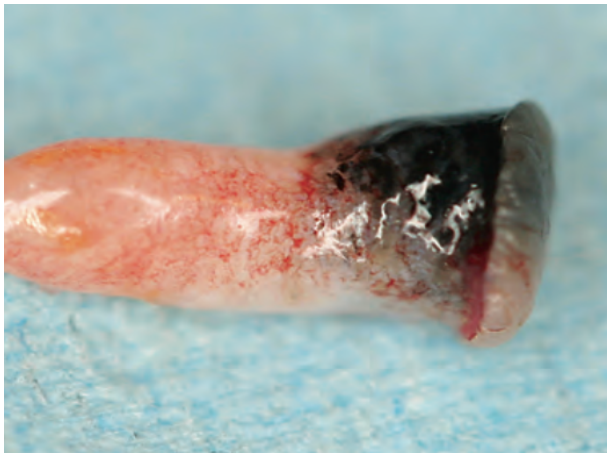

Figure 9. *Punch biopsy specimen of a nodular lesion with aggregated black pigment particles (2).*

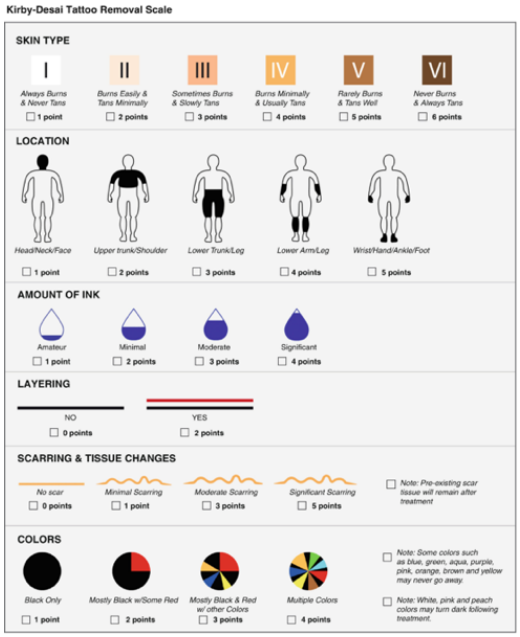

Figure 10. *Kirby Desai Scale (49).*

QS Laser	Black	Blue	Green	Red	Orange	Purple
Ruby 694 nm	√	√	√			√
Alexandrite 755 nm	√	√	√			
Nd:YAG 1064 nm	√	√				
Nd:YAG 532 nm				√	√	

Figure 11. *Response of tattoo pigments to different laser wavelengths (47).*

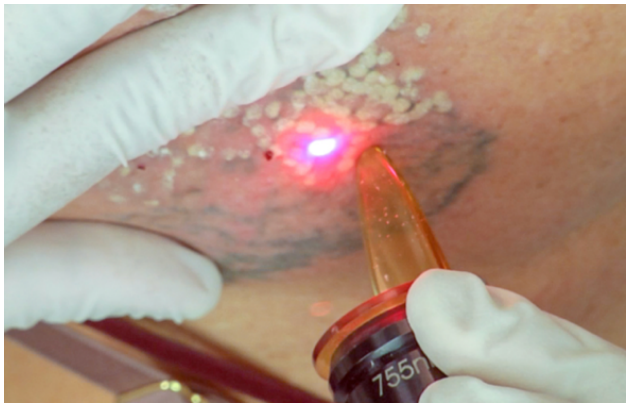

Figure 12*. Q-switched alexandrite laser used for black tattoo removal. The transient "frosting" effect results from intradermal gas bubble formation and usually subsides within 20 minutes (50).*

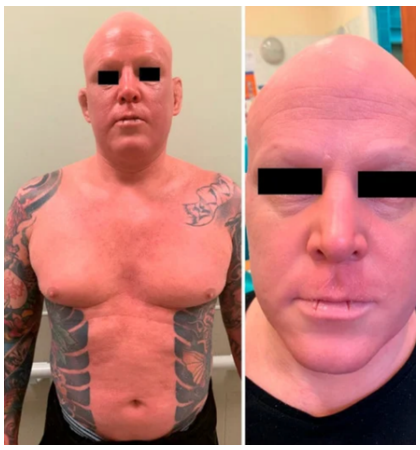

Figure 13. *Patient's presentation at the plastic surgery clinic with systemic erythroderma, xerosis, skin discoloration, and loss of skin appendages, including hair and sebaceous glands (54).*

Figure 14. *Edema and granulomas confined to the red tattooed areas (flame and floral motifs) on the patient´s right forearm (54).*

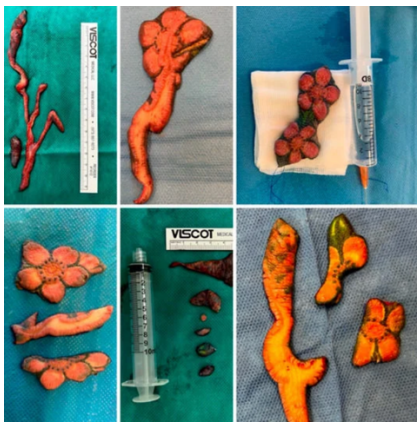

Figure 15*. Surgically excises segments of the right forearm tattoo (54).*

Figure 16. *Clinical outcome three months after treatment. The patient´s forearm, following the gradual removal of the red -pigmented tattooed areas, presents with resolution of the erythroderma and associated skin changes (the arrows indicate skin grafts and scars) (54).*