SARCOIDOSIS AS A GRANULOMATOUS DYSIMMUNE REACTION CAUSED BY COSMETIC LIP TATTOOING

Summary. Sarcoidosis is an uncommon granulomatous inflammatory disease of unknown aetiology, which may affect multiple organ systems. A peculiar form of cutaneous sarcoidosis is represented by the occurrence of sarcoidal lesions on traumatized skin sites by tattooing. Currently, the use of cosmetic lip tattooing is on the rise. With the increasing prevalence of lip tattoo, there is also an increased risk of adverse effects. The purpose of the present study is to review of the English-language literature regarding the risk of developing adverse effects such as sarcoidosis caused by cosmetic lip tattooing, and thus guide physicians in their approach to these patients. Although the mechanism of tattoo-associated sarcoidosis is not definitively known, sarcoidosis is believed to result from a complex interaction between host, genetic and environmental factors leading to a dysimmune response. The clinical and histopathological examination along with a detailed history about this condition is very important to management of patients with sarcoid type of granuloma formation secondary to lip tattoo procedure.

Keywords: sarcoidosis, lip tattooing, oral granuloma, tattoo inks, immunocompromised cutaneous district, COVID-19.
Introduction. Sarcoidosis is a systemic autoimmune disease of unknown etiology defined by the presence of noncaseating granulomatous inflammation that can cause organ damage and diminished quality of life [1, p. 766]. The prevalence of sarcoidosis amongst the female population is found to be higher than in the male population.

Sarcoidosis has numerous clinical manifestations, but respiratory tract involvement occurs at some point in nearly all patients. Cutaneous lesions are present in about one quarter of the patients and are generally observed at the onset of the disease, coincident with or after systemic involvement [2, p. e28053].

A peculiar form of cutaneous sarcoidosis is represented by the occurrence of sarcoidal lesions after tattooing [3, p. 44]. Tattoo-associated sarcoidosis is thought to represent approximately 6-14% of cutaneous sarcoidosis in adults and can be the first manifestation of systemic disease. It is estimated that 74% of patients who develop cutaneous sarcoidosis in tattoo sites are later diagnosed with systemic sarcoidosis [4, p. 358].

Nowadays, patients are more worried about beauty standards and the interest for lip tattooing has increased. At the moment, there are no official data describing the percentage of tattooed individuals in the general Ukrainian population or in specific age groups. Some partial data show that the percentage of young people with lip tattoos has increased [5, p. e30918]. Consequently, the tattoo-associated complications in oral region will become more common, but also more rejuvenated. On the other hand, practitioners must be aware of adverse reactions to lip tattooing.

The health risk associated with the practice of cosmetic makeup and body art has been in the field of vision of our team for a long time. It would be appropriate to provide data from our 2019 study [6, p. 143] conducted in university freshmen and 5 year dental students evaluated the awareness of health-related risks of obtain body art. The majority (85.4%) indicated the possible local infectious risk of body modifications, and only half of them correctly indicated the risk of developing systemic complications. At the same time, the respondents did not have a strong negative attitude towards such risky behavior. This could imply that the systemic health hazards related to body modification practice are underestimated by both potential customers and future physicians.

The purpose of the present study is to review the English-language literature regarding the risk of developing adverse effects such as sarcoidosis caused by cosmetic lip tattooing, and thus guide physicians in their approach to these patients.

Methods and materials. An online electronic search was performed in PubMed with the keywords "cosmetic makeup", "lip tattooing" matched with "granulomatous reaction", "sarcoidosis". Head-searching of selected reviews and publications was also conducted.

Results and discussions. The true incidence and prevalence of sarcoïdal granulomatous reactions to red cosmetic lip tattoos are unknown because of the rarity of the disease and small number of reported cases in literature [7, p. 245]. In contrast, the development of the granulomatous dysimmune reaction within decorative body tattoos is a well-described phenomenon [3, p. 43; 7, p. 245; 8, p. 167; 9, p. e2021030].

Lip lesions of sarcoidosis are psychologically devastating, especially in individuals with concern regarding esthetic [10, p. 552]. That’s way recognition of such lesions may facilitate prompt diagnosis and treatment of underlying disease with overall improvement in patient quality of life.

The available literary data convincingly indicate that the clinical manifestations of sarcoidosis associated with a tattoo are localized exclusively in the area of the tattoo — along the vermilion borders or overlying the entire tattooed vermillion (only in correspondence to the treated area) [10, p. 552].

Affected areas are characterized by papules, nodules, or plaques of 2 to 5 mm in diameter with poor demarcations, which sometimes may be pruritic or tender. Their palpation is painless. Nodules may be secondarily traumatized and partly scaled, but this is not a primary feature of the condition. Adjacent uninvolved tissue which were not tattooed appears completely normal. Taking into consideration that lip tattooing is done in the red zone, there is no mucosal involvement. Apart from cosmetic, the lesions are asymptomatic [10, p. 553; 11, p. 870; 12, p. 229; 13, p. 59]. Clinical manifestations are unusual in their exceptionally long period of persistence. Lip lesions do not change over months and years.

A diagnosis of cutaneous sarcoidosis occurring on the lips after cosmetic tattooing may be easy if there is a known history of systemic sarcoidosis such as in clinical case reported by Yesudian P.D., Azurdia R.M. [10, p. 552]. A young woman presented with a 12-month history of an asymptomatic raised parts of the lips along the outer margins that were corresponded to nodular lesions. The angles of the mouth (which were not tattooed) were spared. Two years earlier, she had undergone cosmetic tattooing of the margins of the lips to enhance their appearance. Violaceous infiltration of old scar of the right forearm was next clinical sign of sarcoidosis. These symptoms were consistent with sarcoidosis that had lasted for 12 years. The authors concluded that patients with pre-existing sarcoidosis should be generally counseled to avoid tattooing for cosmetic or decorative purposes.

Two other cases, which were later reported, involved patients in whom similar manifestations were present simultaneously in the eyebrows and lips [11, p. 869; 12, p. 229]. In both cases, the women had lesions of only the upper lip.

In first clinical case, a 41-year-old woman had a 2-month history of the translucent papules linearly arranged along the vermilion border of the upper lip and her eyebrows. Cosmetic tattooing of the patient’s eyebrows and lips was done 3 years ago. An additional feature of sarcoidosis was a nodular lesion involving previously healthy skin on her forearm. She also described the onset of shortness of breath beginning [11, p. 871].

Martín JM et al. [13, p. 59] reported a late granulomatous reaction complicating cosmetic tattooing for the purpose of permanent makeup in a 59-year-old woman who complained of asymptomatic nodular lesions on her eyebrows and lips for 2 years. She tattooed these areas 6 years before the presentation. The patient had no significant medical history, and
there were no ocular manifestations or systemic symptoms suggestive of sarcoidosis [12, p. 229].

A 27-year-old native Ireland presented with a 4-month history of asymptomatic growth on the upper and lower lip along vermilion borders. Patient reported previous tattoo procedure 4 years earlier [13, p. 59].

Thus, the latency period between lip tattooing and the progression of cutaneous or systemic sarcoidosis is variable. The time from tattoo procedure until recognition of lesions ranged from 2 years to as long as 6 years (mean, 3.8 years). This shows that patients who submit to lip tattooing should undergo close short-term and long-term follow-up.

The diagnosis of oral sarcoidosis may be challenging even for experienced clinicians because a broad range of conditions can mimic sarcoidosis and need to be excluded. Label cases presenting as single nodule suggest salivary-gland cysts (mucoceles) and tumors, as well as soft-tissue neoplasms and cysts. A clinical presentation of multiple nodules should be distinguished from Heck’s disease, neurofibromatosis, amyloidosis, multiple endocrine neoplasia type 2b syndrome, and tuberous sclerosis [14, p. 140].

Histopathological study remains as the gold standard technique to diagnose sarcoidosis [1, p. 766]. The characteristic histopathological finding of sarcoidosis is the presence of noncaseating epithelioid granulomas with multinucleate giant cells surrounded by lymphocytic infiltration in the dermis.

Histopathological characteristics of sarcoidal granulomas may detected resemblance to granulomatous reaction to foreign body, because of the presence of foreign particles in granulomatous lesions [15, p. 744]. Since tissue injury in the setting of a tattoo introduces pigments into the dermis and hypodermic, this can trigger a normal foreign body granulomatous response. In fact, in a recent study, the presence of foreign particles in granulomatous cutaneous lesions was demonstrated in 22% of patients with systemic sarcoidosis and skin involvement [2, p. e28053]. Thus, foreign-body granuloma and systemic sarcoidosis are not mutually exclusive. There is probably a continuum between foreign-body and sarcoidal granulomas, and the differential diagnosis between a non-inmunogenic granuloma, such as foreign-body reaction, and an immunogenic granuloma, such as sarcoidosis, is not possible in most cases.

Some authors suppose that the foreignbody granulomas hypothesis cannot explain the prolonged time interval between primary skin injury and secondary disease (sarcoïdosis), which may develop months to decades after the tattoo was placed [3, p. 47; 5, p. e30918].

The biopsy finding of sarcoidal granulomas in tattoos will be followed by search of other manifestations of sarcoidosis through patient history and diagnostic examinations to exclude pulmonary, ocular, and other organ manifestations.

The management of tattoo sarcoidosis depends on the extent of systemic involvement and is the same as management of non-tattoo-associated sarcoidosis. Widespread cutaneous disease or systemic disease may warrant a multidisciplinary approach and systemic treatment with antimalarial agents, oral corticosteroids, methotrexate, or biologic therapy [4, p. 370].

For many patients, systemic treatment is not necessary. The first-line treatment of limited cutaneous sarcoidosis is topical steroids or intralesional corticosteroids. Oral lesions in sarcoidosis have been reported to respond to 0.1% dexamethasone gel, intralesional betamethasone or oral corticosteroids [7, p. 249; 11, p. 871]. Treatment with oral hydroxychloroquine also resulted in significant remission with flattening of the lip nodules to normal. Allopurinol has also been reported as an option for a granulomatous reaction, especially when using red inks [12, p. 230].

In the case described by Jones B et al., 2008, within 4 weeks of the punch biopsy, all of the lip lesions began to resolve spontaneously and were not clinically evident at a follow-up review. The authors speculate that possible reasons for resolution of the granulomas could be related to the inflammatory process and woundhealing mechanism following biopsy. This process changes the cellular and cytokine environment in the granuloma and along with the subsequent remodelling of the extracellular matrix may lead to ultimate resolution of the lesions. However, this does not fully explain why all the lesions resolved in this case and not just the lesion where biopsy specimen was taken [13, p. 60].

Cosmetic lip tattooing share basic principles and to some degree types and spectrum of technical and clinical complications known from decorative tattooing of other parts of the body.

Tattooing involves both skin trauma and implantation of a foreign body were revealed [5, p. e30918].

The procedures used in applying a tattoo involve either the use of a tattoo machine with the introduction of pigments into the dermis (to a depth of approx. 1–2 mm), or the micropigmentation technique where inks are introduced into the second or third layer of the epidermis (approx. 0.3–0.5 mm). Both techniques result in a disruption of the continuity of the tissue and damage to the skin barrier [16, p. e1360].

Cosmetic tattoos despite their small size and therefore low relative dose of pigment injected into the skin, can trigger fully developed systemic sarcoidosis, say most authors [3, p. 45; 5, p. e30918; 7, p. 245; 8, p. 167; 9, p. e2021030; 10, p. 900].

The inks used for tattooing contain a multi-component mixture of chemical compounds, with the colouring components (pigments and colourants) being the main components responsible for the visual effect and color. Dyes are suspended in a solvent, most often in water or alcohol and supplemented with other auxiliary components, such as preservatives and thickeners or binders [17, p. 287].

The components of tattoo ink are frequently undefined and also highly variable. Additionally, it is common practice for tattooists to prepare their own mixtures to obtain a better visual effect or color, which makes it very difficult to determine the content of substances present in the applied ink and trigger for granulomatous reaction. The inks contain heavy metals such as chromium (green and blue colourants), cobalt (e.g., yellow and blue colourants), lead, antimony, arsenic, beryllium as well as nickel and mercury (red colourant). Also, the presence of aromatic amines, phthalates, polycyclic aromatic hydrocarbons, and nanoparticles has been confirmed [18, p. 399].
The injected tattoo ink is identified by the immune system as a foreign substance, is absorbed by monocytes, and is encapsulated in fibroblasts in the dermis. Engel et al. 8 proved that part of the pigment remains at the injection site, and its remaining nanoparticles enter the lymph nodes via the bloodstream, and it is possible that they are transported and accumulated in larger organs of the body along with impurities which may be present [19, p. 56].

Sarcoidal granulomatous reactions have been reported to occur in multiple colors of multipigment tattoos as well as to be limited to a single color of multipigmented tattoos. Tattoo reactions may occur to various colors such as red, purple, yellow, green, blue and black, while red tattoo is the most frequently blamed colour [3, p. 46; 10, p. 901; 18, p. 400].

It is known that the commonest trigger of black and blue-black tattoo inks is carbon black (amorphous carbon compounds) when its nanoparticles are agglomerate in the dermis over time, forming sarcoid granulomas [17, p. 289; 19, p. 55]. In pigment blue and pink and orange inks, metallic salts also may be responsible for the granulomatous reaction. It has been speculated that either iron oxide or titanium dioxide as the causative agent of the red ink may be prone to elicit sarcoid reactions and thus carry a special risk of sarcoid granuloma [16, p. e1360]. Similarly, the authors of two reports also suggest that iron oxide or titanium dioxide are the trigger [10, p. 552; 13, p. 59], while the rest of the studies analyzed in detail do not indicate the chemical composition of lip tattoo inks at all.

When speaking about the invasiveness of the lip tattoo procedure, as well as the injection the pigment into the tissue, it should be remembered that the current trend in cosmetic make-up is a tattoo crease in both the dose of injected pigment and the expectation of the abnormal tattoo reactions.

Sarcoidal granulomatous reaction secondary to lip tattoo procedure also may validate the novel unifying concept of immunocompromised district (ICD), even if the complex mechanisms at the basis of this phenomenon require further investigation. The ICD is a quite recently introduced concept, which gathers under its definition the whole group of opportunistic disorders (tumors, infections, and immune disorders) that develop at cutaneous sites immunologically marked by previous clinical events, including herpetic infection, vaccination, burn, trauma, and physical injuries [20, p. 565].

Whatever the cause, the concept of ICD refers to a skin site of local immune dysregulation due to an obstacle to the normal trafficking of immunocompetent cells through lymphatic channels and/or an interference with the signals that the neuropeptides and neurotransmitters, related to peripheral nerves, send to cell membrane receptors of immunocompetent cells. Depending on which of the neurotransmitters and immune cells are involved, this destabilization could be either defective (thus predisposing to infections and tumors) or excessive (thus favoring the occurrence of some immune disorders or dysimmune reactions at the sites marked by previous clinical events or injury) [8, p. 170; 21, p. 260].

Current evidence does not allow for the prediction of whether or not a granulomatous reaction will occur at the site of skin injury or even whether an ICD will exhibit an exaggerated or reduced immune response; thus, a genetic predisposition as well as an intact immune system are also instrumental for the persistence of local granuloma formation in the ICD. There is now evidence that a genetic predisposition for human leukocyte antigen B27 (HLA-B27) is implicated in the pathogenesis of this condition [2, p. e28053].

T helper cells, T regulatory cells, and macrophages, as well as a number of antigenic proteins, have been identified as potential contributing factors. A local inflammatory focus containing proinflammatory and regulatory cytokines such as TNFa, IL-6, IL-12, IL-18, TGFb, and IL-10, is a consequence of their activity [1, p. 766; 7, p. 245; 15, p. 744].

The hypothesis of active cell-mediated hypersensitivity is also supported by recent literature reports. To date, the incidence of COVID-19 and vaccination against COVID-19 have been identified as a trigger for granulomatous inflammation that is confined to the patient’s tattooed areas, i.e., areas with high antigen content [22, p. 6244]. Cytokine storms associated with COVID-19 and COVID-19 vaccination; T cell release of interferon gamma and its activating role for macrophages seems to be the key players in tattoo reactions and in sarcoidosis.

Thus, beyond exogenous antigen retention, overactive immune response in ICD with or without loss of immune tolerance; overall reduce immune response or a combination of all these processes can be considered as possible explanations for the formation of granulomas. However, the exact mechanism of a granulomatous dysimmune reaction caused by cosmetic lip tattooing requires further study. An individual's genetic background almost certainly plays a crucial role in driving the granulomatous response toward a given direction in each patient.

**Conclusion.** It is crucial to keep sarcoidosis in the differential diagnoses and screen patients who are presenting with unusually behaving lesions at the pre-existing lip tattoo sites. Detailed history-taking is essential to reach a correct diagnosis and biopsy is very useful for an early diagnosis and thus prompt treatment.

**References:**

Список літератури:


