Journal of Cosmetic Dermatology, **14**, 241–245

Granulomatous reaction to red tattoo pigment treated with allopurinol

Mariana Marteleto Godinho, MD,[1] Felipe Aguinaga, MD,[1] Rachel Grynszpan, MD,[1] Victor Maselli Lima, MD,[2] David Rubem Azulay, MD,[1] Tullia Cuzzi, MD, PhD,[3] Marcia Ramos-e-Silva, MD, PhD,[1] & Mônica Manela-Azulay, MD, PhD[1]

[1]*Sector of Dermatology and Post-Graduation Course in Dermatology, University Hospital and School of Medicine, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil*

[2]*Sector of Plastic Surgery, Ivo Pitanguy Institute/Pontifical Catholic University of Rio de Janeiro, Rio de Janeiro, Brazil*

[3]*Sector of Pathology and Post-Graduation Course, University Hospital and School of Medicine, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil*

Summary

Granulomatous reactions to tattoo ink are most commonly associated with mercury sulfide, a component of red pigments. Treatment options show limited results. Allopurinol, an inhibitor of xanthine oxidase, has been reported as a successful alternative treatment to granulomatous disorders, such as sarcoidosis and granulomatous reactions to fillers and tattoos. We report a case of granulomatous reaction to red tattoo pigment treated with allopurinol for 6 months. Good clinical improvement could be noticed during this time. Two months after we stopped the treatment, the lesion recurred. Allopurinol emerges as an important drug for the management of granulomatous reactions caused by tattoo pigments. Based on the significant clinical improvement noticed during its use, we recommend new studies to elucidate all the potential benefits of the use of allopurinol for the treatment of granulomatous reactions to tattoo ink.

Keywords: allopurinol, tattoo, red pigment, granulomatous reaction

Introduction

Granulomatous reactions to tattoo ink are most commonly associated with mercury sulfide, a component of red pigments.[1–4] The lesion is limited to the red portion of the tattoo[1,2] and shows eczematous eruption, localized edema, and pruritus as the most common signs and symptoms.[1]

Treatment options are limited. Topical and intralesional corticosteroids, surgical removal, cryotherapy, and lasers[1] are some of the therapeutic possibilities, and the response to these treatments depends on the severity and extension of the reaction. Allopurinol (AL), an inhibitor of xanthine oxidase, has shown beneficial effects in patients with cutaneous sarcoidosis and has also been reported as an alternative therapy to granulomatous reactions caused by fillers and tattoos.[5]

The mechanism through which it reduces granulomas is unknown. Free radicals are supposed to play an important role in the pathogenesis of granulomatous disorders, and allopurinol would act as a free radical scavenger.[5–7] Also, the drug has been related to a downregulation of ICAM-1 and P2X7, which are receptors of monocyte/macrophage lineage cells, important in the genesis of multinucleated giant cells.[8]

Correspondence: Mariana Marteleto Godinho, Rua General Glicério 156/706 Laranjeiras, 22245-120 Rio de Janeiro, Brazil.
E-mail: marianamarteleto@yahoo.com.br

Accepted for publication March 15, 2015

For these reasons, we decided to use this drug to treat a young woman with granulomatous reaction to red tattoo pigment.

Case report

A healthy 23-year-old woman had a tattoo done 3 years before she came to our hospital for consultation. For 2 years, it did not show any sign of reaction. After this period, she decided to have her tattoo redone and its old faded red part was replaced with a new red ink. A few days later, erythema, local edema, and pruritus occurred exactly on the red part of the tattoo, located laterally below her right ankle (Figure 1). An incisional biopsy of the lesion was performed. Histologically, epithelioid granulomas could be noticed in close association with the red pigment (Figures 2 and 3). We started allopurinol 300 mg per day and slowly raised the dose to 600 mg per day, which was maintained for 6 months. Good clinical improvement could be noticed during this period (Figure 4). Two months after we stopped the treatment, the lesion recurred (Figure 5).

Discussion

Cases of reactions to tattoo inks are common. They can be classified as acute inflammatory reactions, allergic hypersensitivities and granulomatous, lichenoid and pseudolymphomatous types of reactions.[1,4]

Acute inflammatory reaction occurs during the first 2 to 3 weeks after the tattoo is done. It consists of an acute aseptic inflammatory reaction with erythema, induration, and an edematous "peau d'orange."[9] It is secondary to the injury caused by introduction of the pigment.[2] Some authors believe this should not be

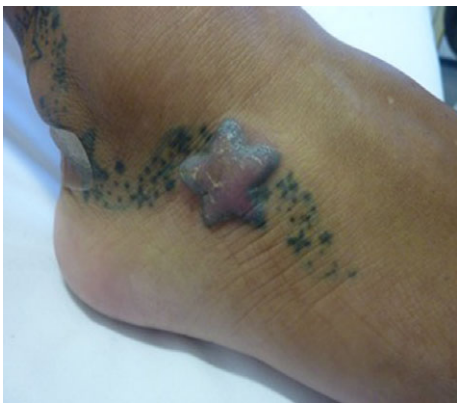

Figure 1 Edema limited to the red portion of the tattoo.

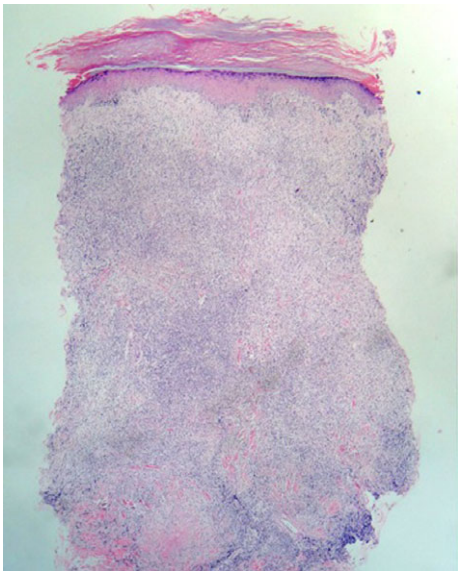

Figure 2 Chronic granulomatous reaction associated with red pigment showing dermal diffuse inflammatory infiltrate with ill-defined granulomas (HE, Obj. 4).

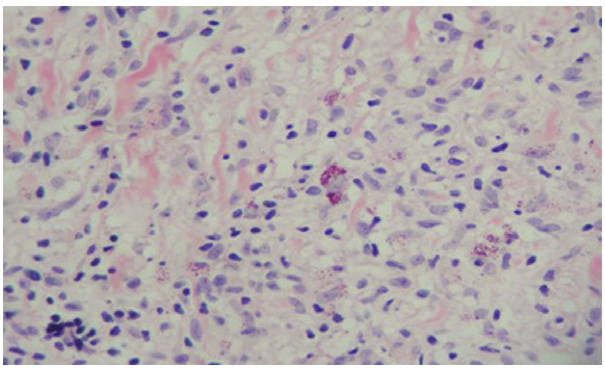

Figure 3 Macrophage engulfing red pigment surrounded by lymphocytes and epithelioid cells (HE, Obj. 40).

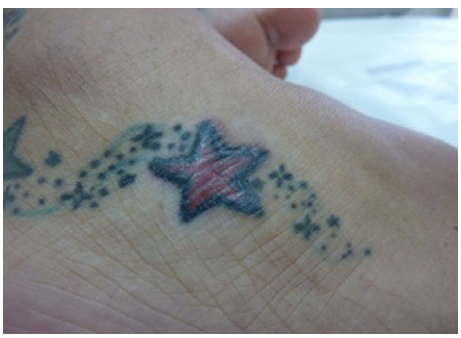

Figure 4 Clinical improvement after 6 months of allopurinol.

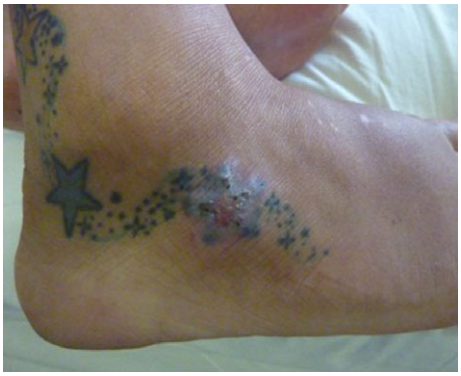

Figure 5 Recurrence after 2 months without treatment.

considered as a complication, but as a natural step of the healing process of the tattoo.[2,9]

Allergic hypersensitivity to tattoo pigment is caused by release of chemical mediators, such as histamine and prostaglandins. On histopathology, eosinophilic cells can be found.[1]

Granulomatous, lichenoid, and pseudolymphomatous types of reactions[1,4] are classified based on the histologic patterns of the reaction.[4] They usually occur months to years after the tattoo is done.[2] Histologically, in granulomatous reactions, there are well-defined epithelioid granulomas in close association with pigment.[5] Lichenoid reaction is composed of a lymphocytic T-cell infiltrate.[1] Pseudolymphomatous reaction shows similar clinical aspect to cutaneous B-cell lymphoma, but different patterns can be found in histologic analysis. For example, there is a predominant involvement of the upper dermis compared with the lower dermis in the cutaneous lymphoma, and lymphocytes are polyclonal in the pseudolymphoma reaction upon immunohistochemical analysis.[1]

Clinically, all of these reactions show pruritus, localized edema, and eczematous eruption as the most common signs and symptoms. Exfoliative dermatitis, verrucous papules or plaques, and lichenoid appearance may occur.[1]

Reactions to red pigments are the most common ones[2,4] and may be caused by a variety of components, particularly mercury sulfide (cinamar).[3,4] In 1976, the FDA limited mercury in tattoo dyes to 3 ppm in the USA.[1,4] In Brazil, such control to limit this component in red ink is not enforced.

Despite this restriction, reactions to red pigment still occur.[1,3,4] Titanium, iron, aluminum, and several metallic elements can be found in red dyes and are some examples of other components that could also cause reactions to the ink.[1] Treatment depends on the severity and extension of the signs and symptoms. Topical, oral and/or intralesional steroids, and oral antihistamines can be used in mild cases. Among destruction methods, there are cryotherapy, electrosurgery, excision, dermabrasion, and laser ablation.[1]

Although there are treatment options available, the results are limited. Extensive lesions cannot be removed by excision in most cases. Moreover, intense reactions do not usually respond to topical and intralesional corticosteroids. Besides, Q-switched laser, the gold standard of tattoo treatment, is not indicated to treat allergic reactions.[1] It can cause an inflammatory response that can intensify the reaction or even cause a generalized inflammatory eruption.[2,4]

Table 1 summarizes some of the treatment options for foreign body granuloma caused by fillers and/or tattoo reactions described in literature.[1–4,6,10–12] The results may vary. Some authors refer good responses with one kind of treatment while others deny any improvement of the lesions with the same treatment option. There are no consistent data for establishing a guideline.

There is one study that suggests that intralesional steroid injections are the treatment of choice for foreign body granuloma caused by fillers butrecurrence may still occur. Antimitotic agents, such as 5-fluorouracil, might reduce the risk of cortisone skin atrophy and mixed with corticosteroids can be injected when necessary. The same study considers surgical excision contraindicated because of the invasiveness and nonconfined borders of the granulomas with the surrounding tissue. Corticosteroids creams may not reach the subdermally located foreign body granuloma because they are usually absorbed superficially. Spontaneous improvement of foreign body granuloma caused by fillers has also been reported.[11]

Table 1 Treatment options for foreign body granuloma reactions caused by fillers and tattoo

Fillers	Tattoo
Oral corticosteroids	Topical corticosteroids
Intralesional corticosteroids	Oral corticosteroids
Colchicine	Intralesional corticosteroids
Imiquimod	Antihistamines
Minoclycline	Surgical excision
Allopurinol	Cryotherapy
Surgical excision	Electrosurgery
	Dermabrasion
	Chemical destruction by acid
	Carbon dioxide laser
	Allopurinol

One case of facial granulomas caused by cosmetic implants was successfully treated with colchicine.[12] Treatments for keloids and hypertrophic scars such as bleomycin injections and a combination of triamcinolone with interferon-α2b injections have been considered as possible alternative options for foreign body granulomas that failed corticosteroid injections.[11]

A recent Brazilian case with a chronic inflammatory pruriginous reaction 4 months after the application of a tattoo with the alteration restricted to the red pigment area was submitted to surgery for removal of the inflamed areas, after no result with local and oral steroids.[13]

Our patient did not want to have her tattoo removed by excision. Despite the lack of consistent data on the use of allopurinol for the treatment of granulomatous reactions to tattoo ink, we suggested this drug as an alternative treatment option and she agreed to try it. The lesion showed clinical improvement during the use of the medication, but after its withdrawal, the original signs and symptoms recurred. No adverse effects related to the drug could be noticed. After the lesion recurred, the patient came back to the clinic but not wanting to take the same drug again, as a personal option and for this reason, it was not possible to observe the reintroduction of allopurinol and its actions and possible adverse effects. We then began corticosteroid injection at the tattoo reaction, but after the first injection, the patient did not return to the clinic anymore.

Allopurinol, a drug widely used for the treatment of hyperuricemia, is proposed to have a therapeutic effect in granulomatous disorders.[14] Multiple case reports document the efficacy of allopurinol in the treatment of cutaneous sarcoidosis.[6,7,14] Noncaseating granuloma is the classic pathologic finding of this disease.[15]

Based on the histopathological similarities between sarcoidosis and foreign body granulomas, cases of granulomatous reactions to cosmetic fillers successfully treated with allopurinol started to be reported after the good responses of sarcoidosis to the drug.[6,7,16] It is well known that foreign body granulomas may appear as late skin reactions to cosmetic fillers. The reaction is usually persistent, and therapeutic options in these cases are also limited.[12] Allopurinol was used to treat granulomatous reactions caused by polymethylmethacrylate microspheres and silicone with no recurrence after 5 and 12 months, respectively.[6,7]

Allopurinol, an inhibitor of xanthine oxidase, a catalyst in the formation of superoxide, acts by reducing free radicals, which supposedly play an important role in the pathogenesis of granulomatous disorders.[5,6,] Xanthine oxidase is an important source of biological free radical generation. Free radicals can be generated by the enzymatic activity for the degradation of purine nucleotides.[17,18]

The drug has also been related to a downregulation of ICAM-1 and $P2X_7$, which are receptors of monocyte/macrophage lineage cells, playing key roles in the genesis of multinucleated giant cells.[8,14]

Multinucleated giant cells (MGCs) are characteristic cells in granulomatous disorders. The MGC formation is complex. MGCs are formed by the fusion of monocyte/macrophage lineage cells.[19,20] Plasma membrane receptors are responsible for recognition, adhesion, activation, and fusion of the process.[8] However, many aspects of this process remain unknown.[20] Adhesion molecules, such as intracellular adhesion molecule-1 (I-CAM1), are known to play a role in MGC formation.[14,20] The downregulation of ICAM1 interferes with cell adhesion, an early event of cell fusion.[8] P2X7 receptors are thought to be involved in the process of cell fusion that leads to MGC formation during granulomatous inflammation.[14,20]

In our experience, allopurinol was effective during its use; with the lesion recurring after it was withdrawn. This outcome, however, raises some relevant issues. Perhaps tapering the medication's dosage instead of abrupt withdrawal could improve clinical outcome or avoid recurrence. Moreover, it should be noted that as skin-tattoo granuloma is a chronic reaction, low-dose, long-term maintenance treatment might be necessary after initial treatment dosage levels. Finally, we must consider the concurrent use of other therapies while using allopurinol. The patient showed remarkable improvement of her symptoms during allopurinol treatment. Thus, allopurinol might create a critical window of opportunity where Q-switched laser could have been used for tattoo pigment removal, thus removing the cause of the granulomatous reaction and enabling complete withdrawal of the drug with no recurrence. Allopurinol can even be used while topical agents, for example, imiquimod 5%, or intralesional injections of corticosteroids are concomitantly applied. These considerations show a clear need for further investigation with long-term prospective studies before establishing allopurinol as a viable treatment modality for tattoo granulomas.

Besides these questions, we have to consider that allopurinol therapy is not without its risks. Although it is a drug widely used for the treatment of hyperuricemia and is generally safe, cutaneous adverse reactions (CARs) affect 2% of the patients who use it.[21] Stevens–Johnson syndrome and toxic epidermal necrolysis are

some examples of possible CARs, and allopurinol is the most frequent drug associated with these conditions.[22]Also, allopurinol hypersensitivity syndrome, a severe cutaneous adverse reaction, affects 0.4% of patients receiving therapy and is associated with high morbidity and mortality (18–25% of mortality). The pathogenesis remains unclear.[21] It is characterized by fever, skin rash, and systemic involvement.[21]

Conclusion

Allopurinol emerges as an important alternative treatment to granulomatous reactions caused by tattoo pigments. In this study, great clinical benefit could be noticed during its use. Further studies must be conducted to elucidate the real benefits of the use of allopurinol for the treatment of granulomatous reactions to tattoo ink. Such studies should consider the risks and safety of the drug, as well as its exact mechanisms of action and new approaches to its use.

References

1 Kaur RR, Kirby W, Maibach H. Cutaneous allergic reactions to tattoo ink. *J Cosmet Dermatol* 2009; **8**: 295–300.
2 Cruz FA, Lage D, Frigério RM *et al.* Reactions to the different pigments in tattoos: a report of two cases. *An Bras Dermatol* 2010; **85**: 708–11.
3 Yazdian-Tehrani H, Shibu MM *et al.* Reaction in a red tattoo in the absence of mercury. *Br J Plast Surg* 2001; **54**: 555–6.
4 Duke D, Urioste SS, Dover JS *et al.* A reaction to a red lip cosmetic tattoo. *J Am Acad Dermatol* 1998; **39**: 488–90.
5 Martín JM, Revert A, Monteagudo C *et al.* Granulomatous reactions to permanent cosmetic tattoos successfully treated with topical steroids and allopurinol. *J Cosmet Dermatol* 2007; **6**: 229–31.
6 Reisberger EM, Landthaler M, Wiest L *et al.* Foreign body granulomas caused by polymethylmethacrylate microspheres: successful treatment with allopurinol. *Arch Dermatol* 2003; **139**: 17–20.
7 Redondo P, Del Olmo J, Alberola I. In situ and distant foreign body granulomas caused by silicone. Treatment with allopurinol. *Br J Dermatol* 2005; **152**: 1064–5.
8 Mizuno K, Okamoto H, Horio T. Inhibitory influences of xanthine oxidase inhibitor and angiotensin I-converting enzyme inhibitor on multinucleated giant cell formation from monocytes by downregulation of adhesion molecules and purinergic receptors. *Br J Dermatol* 2004; **150**: 205–10.
9 Kluger N. Acute complications of tattooing presenting in the ED. *Am J Emerg Med* 2012; **30**: 2055–63.
10 Bassi A, Campolmi P, Cannarozzo G *et al.* Tattoo-associated skin reaction: the importance of an early diagnosis and proper treatment. *Biomed Res Int* 2014; **2014**: 354608.
11 Lemperle G, Gauthier-Hazan N. Foreign body granulomas after all injectable dermal fillers: part 2. Treatment options. *Plast Reconstr Surg* 2009; **123**: 1864–73.
12 Aivaliotis M, Kontochristopoulos G, Hatziolou E *et al.* Successful colchicine administration in facial granulomas caused by cosmetic implants: report of a case. *J Dermatolog Treat* 2007; **18**: 112–4.
13 Ono MCC, Balbinot P, Morais RLSL *et al.* Reactions to red pigment. *Surg Cosmet Dermatol* 2014; **6**: 82–5.
14 Badgwell C, Rosen T. Cutaneous sarcoidosis therapy updated. *J Am Acad Dermatol* 2007; **56**: 69–83.
15 Haimovic A, Sanchez M, Judson MA *et al.* Sarcoidosis: a comprehensive review and update for dermatologist. Part I. Cutaneous Disease. *J Am Acad Dermatol* 2012; **66**: 699.e1-18.
16 Wiest LG, Stolz W, Schroeder JA. Electron microscopic documentation of late changes in permanent fillers and clinical management of granulomas in affected patients. *Dermatol Surg* 2009; **35** (Suppl 2): 1681–8.
17 Kuppusamy P, Zweier JL. Characterization of free radical generation by xanthine oxidase. Evidence for hydroxyl radical generation. *J Biol Chem* 1989; **264**: 9880–4.
18 Chen L, Hu JY, Wang SQ. The role of antioxidants in photoprotection: a critical review. *J Am Acad Dermatol* 2012; **67**: 1013–24.
19 Van Maarsseveen TC, Vos W, van Diest PJ. Giant cell formation in sarcoidosis: cell fusion or proliferation with non-division? *Clin Exp Immunol* 2008; **155**: 476–86.
20 Brodbeck WG, Anderson JM. Giant cell formation and function. *Curr Opin Hematol* 2009; **16**: 53–7.
21 Tsai TF, Yeh TY. Allopurinol in Dermatology. *Am J Clin Dermatol* 2010; **11**: 225–32.
22 Somkrua R, Eickman EE, Saokaew S *et al.* Association of HLA-B*5801 allele and allopurinol-induced Stevens Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. *BMC Med Genet* 2011; **12**: 118.