Tattoo Granulomas With Uveitis Successfully Treated With CO_2 Laser Ablation

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PRACTICE **POINTS**

- Dermatologists should be aware that uveitis can develop as a delayed hypersensitivity reaction to tattoo ink, particularly in patients with blue ink tattoos.
- It is important to rule out systemic conditions such as sarcoidosis in patients presenting with uveitis and a history of tattoos.
- In a patient with progressive ocular symptoms, carbon dioxide laser ablation may be an effective treatment option if other potential rheumatologic conditions and sarcoidosis have been ruled out and other therapies have not resulted in improvement of symptoms.
- Continuous monitoring of ocular symptoms and intraocular pressure is vital to prevent complications such as glaucoma and potential blindness.

To the Editor:

Uveitis associated with tattoos is common, yet the etiology and optimal treatment options for this phenomenon remain unclear. Possible causes include a delayed hypersensitivity reaction to tattoo ink antigen or systemic sarcoidosis localized to the skin.[1] Long-term treatment options include topical, intralesional, and systemic corticosteroids or immunosuppressants.[2] Short-term options often include direct surgical excision and laser treatment. However, laser removal of tattoo pigment typically involves multiple sessions over the course of years, and there is a risk for antigen dispersal that may lead to anaphylaxis. Determining the most effective and safe treatment for a patient with progressive and severe ocular symptoms can be challenging. We describe a patient with cutaneous blue ink tattoos who developed chronic bilateral glaucoma, iritis, uveitis, and ocular hypertension that was refractory to multiple systemic medications and ophthalmologic procedures but responded to CO_2 laser ablation.

A 27-year-old man with an active smoking history presented to our laser surgery center with a rash of approximately 4 years' duration in areas with blue tattoo ink on both forearms. He was referred by his ophthalmologist due to bilateral uveitis and iritis and subsequent ocular hypertension and glaucoma that developed approximately 5 years after tattoo placement on the bilateral forearms. When the rash first appeared, the skin in the areas of the blue tattoo ink had hyperpigmented pruritic plaques. The patient was treated by a dermatologist with topical steroids to help reduce the itching and inflammation. Around the same time, he also started having ocular symptoms—vitreous floaters, erythema, eye pain, and blurriness—and was diagnosed with iritis of unclear etiology by ophthalmology. Figure 1 documents the patient's clinical course. Due to escalating intraocular pressure and symptoms, he was referred to a glaucoma specialist and a rheumatologist. Systemic and rheumatologic medical conditions were ruled out with negative results on a series of blood tests (eg, rheumatoid factor, HLA-B27, antinuclear antibody, lysozyme, interferon gamma release assay, erythrocyte sedimentation rate, C-reactive protein, hepatitis B/C virus, *Treponema pallidum*, HIV), and magnetic resonance imaging of the brain was negative, ruling out demyelinating disease. Laboratory workup for sarcoidosis also was performed. The angiotensin-converting

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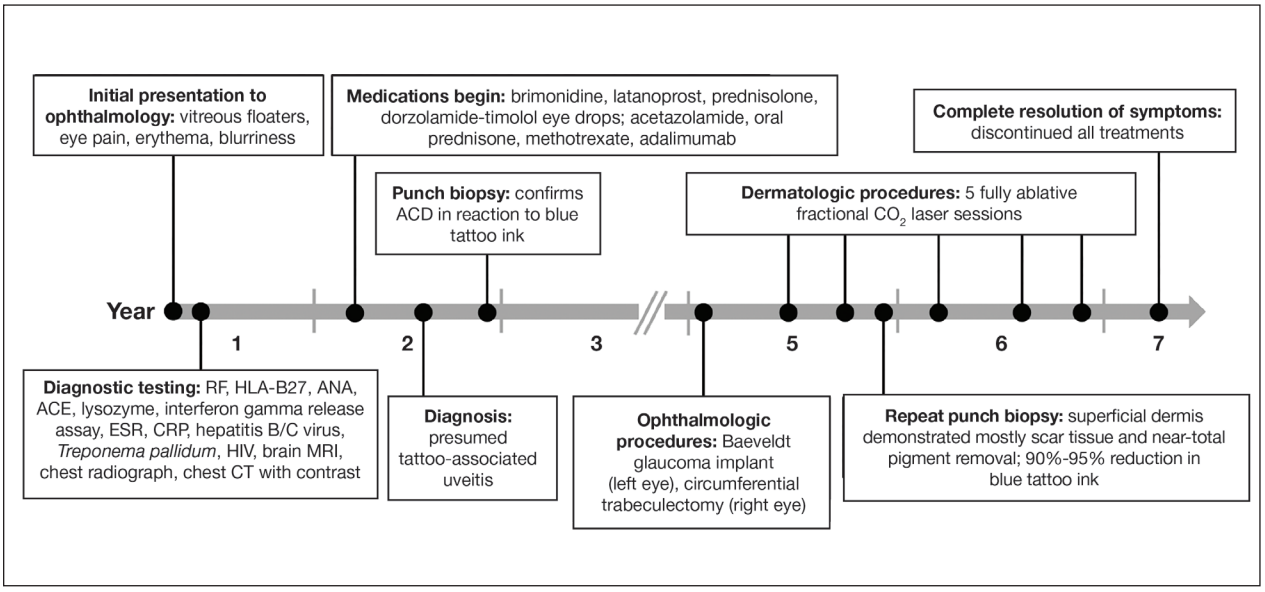

FIGURE 1. Clinical timeline for a 27-year-old man with tattoos on both arms who presented with bilateral iritis and uveitis as well as subsequent ocular hypertension and glaucoma approximately 5 years after tattoo placement. Abbreviations: ACD, allergic contact dermatitis; ACE, angiotensin-converting enzyme; ANA, antinuclear antibody; CRP, C-reactive protein; CT, computed tomography; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; RF, rheumatoid factor.

enzyme level was 30 U/L (reference range, 9-67 U/L), and a chest radiograph and computed tomography with contrast indicated no evidence of cardiopulmonary involvement. Although sarcoidosis could not be definitively ruled out, no other cause could be determined, and the patient's glaucoma specialist diagnosed him with tattoo-associated uveitis. The patient was started on brimonidine, latanoprost, prednisolone, and dorzolamide-timolol eye drops, as well as acetazolamide (500 mg twice daily) and oral prednisone (various doses). Over the next 3 years, the patient continued to have symptoms, and immunosuppressant medications—methotrexate 20-25 mg weekly and adalimumab 40 mg every 2 weeks—were added to his treatment regimen. The patient also underwent bilateral ophthalmologic procedures, including a Baerveldt glaucoma implant procedure in the left eye and circumferential trabeculectomy in the right eye.

Despite these medications and procedures, the patient's symptoms and intraocular pressure had not improved. At the current visit, punch biopsy of the tattooed skin and histologic examination showed dermal lymphoplasmacytic inflammation with scattered foreign-body giant cells associated with blue tattoo ink

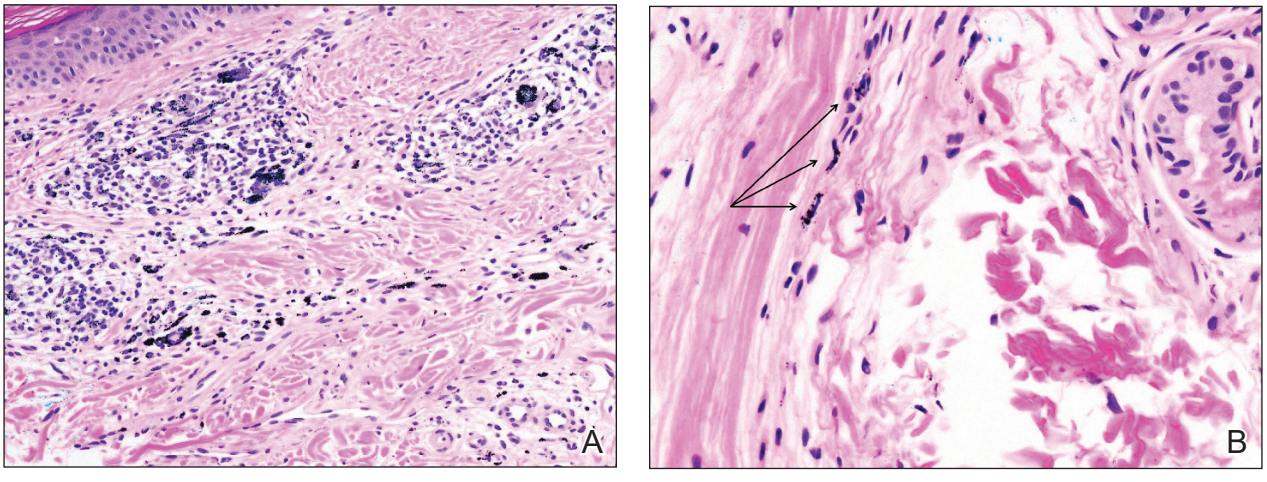

FIGURE 2. A and B, Histopathology from punch biopsies 5 years after tattoo placement demonstrated dermal lymphoplasmacytic inflammation with scattered foreign-body giant cells associated with the blue tattoo ink and overlying hyperkeratosis and spongiosis (H&E, original magnification ×10) and pigment in the deep dermis next to the eccrine glands (arrows)(H&E, original magnification ×40).

and overlying hyperkeratosis and spongiosis, consistent with allergic contact dermatitis (Figure 2). Because both immunosuppressant medications and ophthalmologic procedures had failed to control the progression of the ocular symptoms and the patient was at risk for permanent blindness, surgical excision and laser tattoo removal were considered as potential treatment options. Due to the large surface area and circumferential nature of the tattoos, there was a notable risk for disfiguring scars at both recipient and donor sites with surgical excision followed by graft placement. Thus, CO_2 laser ablation was the preferred treatment option. However, this procedure was not without risk for anaphylaxis if the tattoo pigment were to be released into systemic circulation. Thus, at the first visit, ablation was performed on 3 test spots and the patient was prescribed cetirizine, diphenhydramine, and prophylactic prednisone for a few days. The patient then received a total of 5 fully ablative CO_2 laser sessions (pulse energy: 200 mJ [15 J/cm^2]; computerized pattern generator: 2-8-9 [85.2 J/cm^2]; rate: 200 Hz [20 W], 3 passes) over 13 months to remove all visible blue ink in stages (Figure 3). Even with a shortened time course (as more time between laser sessions typically is preferred), the treatments were well tolerated with only mild hypertrophic scarring that responded to intralesional steroids (triamcinolone 10 mg/mL). On repeat skin biopsy during the treatment course, the superficial dermis demonstrated mostly scar tissue and near-total pigment removal—a 90% to 95% reduction in blue ink from prior biopsy—and minimal inflammation (Figure 4). Scant fine to coarse pigment deposition was seen in the deep dermis next to subcutaneous fat, which was unchanged from the previous biopsy. The patient's ophthalmologic symptoms were tracked via improvement in intraocular pressure and stabilization of his vision, indicating rapid and complete resolution of the glaucoma after the last laser treatment. With resolution of his ocular symptoms, the patient was tapered off all immunosuppressant medications. The patient was lost to follow-up approximately 2 years after the final laser treatment.

Tattoo-associated uveitis initially was described in 1969 in 3 patients with light blue tattoos who developed tattoo granulomas and simultaneous uveitis. These cases were successfully treated with excision.[3] Multiple cases have been reported since, often with bilateral uveitis and tattoos demonstrating noncaseating granulomatous inflammation that were treated with steroids.[4] In 2018, a diagnosis of exclusion was proposed for uveitis associated with granulomatous tattoo reaction without sarcoidosis: tattoo granulomas with uveitis (TAGU).[1]

In this case, sarcoidosis initially was high on the differential diagnosis. Sarcoidosis is an immune-mediated systemic disease of unknown etiology characterized by the presence of widespread noncaseating epithelioid cell granulomas, primarily seen in the pulmonary and lymphatic systems. However, it often initially manifests

FIGURE 3. A and B, Tattoo immediately prior to CO_2 laser ablation and 18 months after 5 treatments with a fully ablative fractional CO_2 laser.

with cutaneous involvement with noncaseating "naked" granulomas in the dermis and subcutaneous tissue. Although TAGU cases have demonstrated noncaseating granulomas in association with dermal tattoo pigment on histopathology,[1,4] dermal lymphoplasmacytic inflammation with scattered foreign body giant cells was noted in our patient, which was more consistent with allergic contact dermatitis. Thus, it is important to consider that TAGU can be seen with varying histologic patterns. In patients with tattoos, sarcoidosis can manifest grossly as a papulonodular cutaneous reaction.[5] Active smoking is associated with a decreased risk for sarcoidosis, and those who smoke are statistically more likely to have tattoos than the general population,[6,7] so our patient's smoking history may be relevant. However, sarcoidosis was an unlikely diagnosis due to the serum angiotensin-converting enzyme level; results of a chest radiograph (bilateral adenopathy and coarse reticular opacities) and computed tomography (hilar and mediastinal adenopathy); and nonsarcoidal histopathology.

An allergic reaction to tattoo ink is caused by a delayed-type hypersensitivity reaction to a pigment hapten that can develop abruptly months to years after tattoo placement—1 year after tattoo placement in our patient. This reaction was seen in our patient's blue pigment tattoos, although it is more commonly seen in red pigment tattoos.[8] Although the etiology of TAGU is poorly understood, it also is hypothesized to be a delayed-type

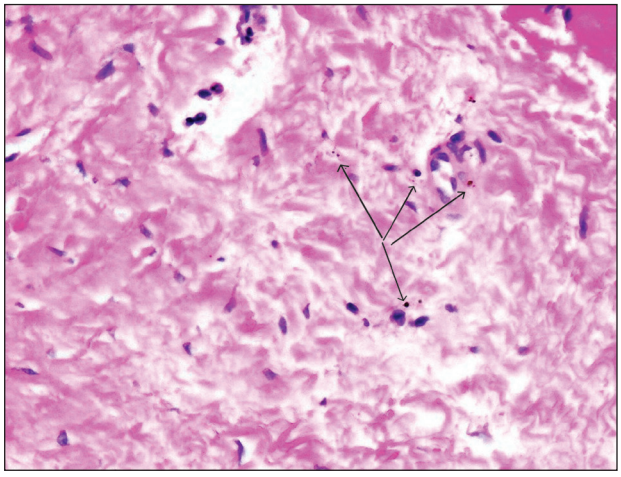

FIGURE 4. Histopathology from repeat punch biopsies 8 years after tattoo placement showing near total tattoo pigment removal (arrows) in the superficial dermis along with a considerable reduction in the lymphoplasmacytic infiltrate, demonstrating mostly scar tissue and a 90%-95% reduction in blue ink (H&E, original magnification ×40).

hypersensitivity response to tattoo ink particles, suggested by the pattern of lymphocytes infiltrating the tattoo and atypical T-cell infiltrate on vitreous biopsy.[9,10] Further research is required to elucidate the relationship between tattoos and uveitis.

Q-switched lasers (eg, 532-nm or 1064-nm Nd:YAG, alexandrite, or ruby lasers) are the standard treatment options for uncomplicated tattoo removal and employ a high-intensity, ultrashort pulse duration.[11] However, Q-switched lasers require multiple sessions and target pigment-containing cells, releasing the tattoo particles into systemic circulation, which can potentially induce a severe allergic response.[12] In contrast, CO_2 lasers use a different mechanism, emitting energy at a wavelength of 10,600 nm, which is absorbed by intracellular water and allows for the ablation of the superficial epidermis along with the embedded ink with subsequent re-epithelialization, as well as heat-mediated thermal injury to allow for dermal collagen remodeling.[13] In a 2021 retrospective study of ablative laser therapy for allergic tattoo reactions, patients were treated with the 10,600-nm ablative CO_2 laser and noted improvements in itching and burning with minimal adverse events.[12] Although using a CO_2 laser may not be considered a first-line treatment option for TAGU, the refractory clinical course and notable morbidity of surgical excision necessitated the use of ablative laser in our case.

Tattoo granulomas with uveitis is a rare diagnosis with the potential for serious permanent sequelae including blindness. Existing treatments such as topical and oral corticosteroids, immunosuppressants, surgical excision, and Q-switched lasers all are possible options, but in a patient with progressive ocular symptoms with other potential rheumatologic conditions and sarcoidosis ruled out, fully ablative CO_2 laser may be an effective treatment option. Our case demonstrated the successful treatment of TAGU with CO_2 laser ablation. Given the unclear etiology of TAGU and the limited evidence on treatment options and efficacy, our case contributes to the body of literature that can inform clinical management of this unusual and serious reaction.

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