

Case Report/Case Series

Facial Allergic Granulomatous Reaction and Systemic Hypersensitivity Associated With Microneedle Therapy for Skin Rejuvenation

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IMPORTANCE Microneedle therapy includes skin puncture with multiple micro-sized needles to promote skin rejuvenation or increase transdermal delivery of topical medications. In cosmetic practices, various cosmeceuticals are applied before microneedling to enhance the therapeutic effects. This results in intradermal tattooing of the topical product. Despite rapid increase in the use of microneedles in dermatology, there are few data about their safety.

OBSERVATIONS We describe 3 women, aged 40s to 60s, who developed facial granulomas following microneedle therapy for skin rejuvenation. Two patients had undergone microinjection of the same branded topical moisturizer (Vita C Serum; Sanitas Skincare) during microneedle therapy. Biopsy in all cases showed foreign body-type granulomas. Results of tissue cultures were negative. Chest radiography and serum angiotensin-converting enzyme findings were normal. The first 2 patients had a positive patch test reaction to Vita C Serum. Initial treatment with topical and oral corticosteroids was ineffective. Therapy with doxycycline hydrochloride and minocycline hydrochloride led to partial improvement in one case and resolution in another.

CONCLUSIONS AND RELEVANCE Application of topical products prior to microneedling can introduce immunogenic particles into the dermis and potentiate local or systemic hypersensitivity reactions. Because the microneedle therapy system is accessible for home use, health care providers need to be aware of its potential consequences.

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Microneedles are solid- or hollow-cannula micro-sized needles developed to increase transdermal delivery of various topically applied products.¹ They have been used to deliver macromolecules, such as growth hormones, insulin, and immunobiologics. In dermatology practice, microneedles have been used to increase skin penetration of depigmenting serum to treat melasma.² However, the most common use of microneedles in dermatology is skin needling with solid microneedles to create a field of microinjuries that leads to increased collagen and elastin production and skin rejuvenation. Various cosmeceuticals are applied before microneedling to enhance the therapeutic effect and improve wrinkles, traumatic and acne scars, and dyspigmentation.^{3,4} Microneedling can be accomplished by rolling a microneedle device or using an electronically powered “pen” that uses an automated, stamp-like suit. The Dermapen fraction microneedling device (Dermapen, LLC) is one type of microneedling pen used to tighten the skin. Rapid response is observed with the insertion of the microneedles into the stratum corneum, with penetration depth of 0.25 to 2.00 mm.

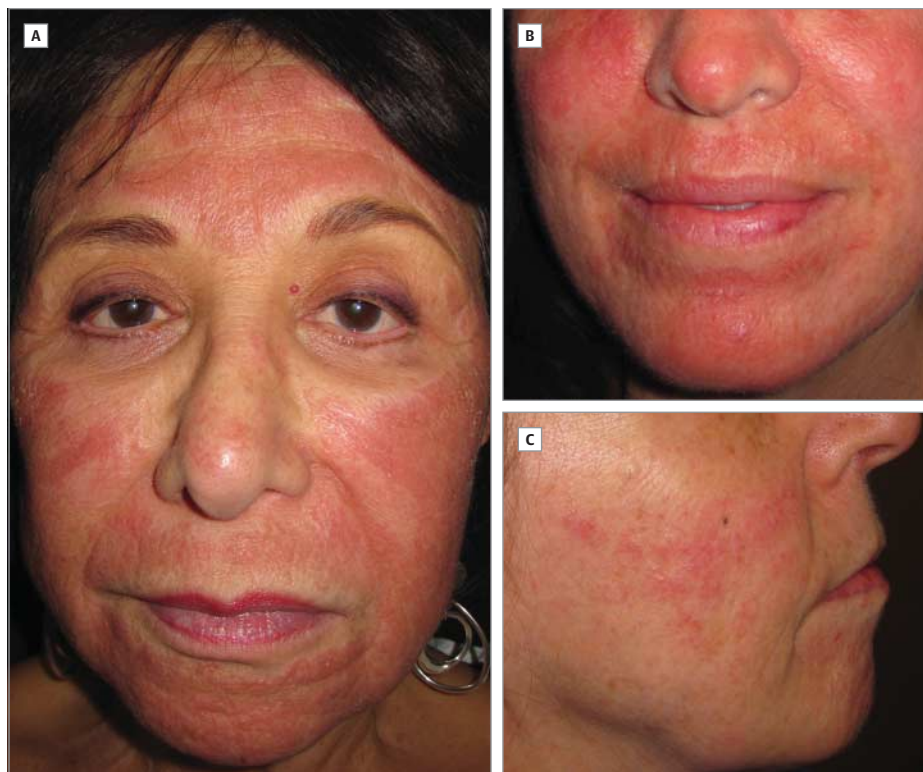
Despite the rapidly increasing use of microneedle therapy in outpatient and cosmetic dermatology practices, there are few data about the safety of this procedure. We present 3 patients who developed granulomatous reactions following microneedle therapy for skin rejuvenation. One of the patients also developed signs of systemic hypersensitivity.

Report of Cases

Case 1

A woman in her 60s was referred to our clinic for evaluation and management of a diffuse facial rash. She had received microneedle therapy using a Dermapen for facial skin rejuvenation at a local medical spa. The procedure was performed using topical anesthetics (benzocaine hydrochloride, lidocaine hydrochloride, and tetracaine hydrochloride cream), which were washed off before the procedure. A high dose of lipophilic vitamin C (Vita C Serum; Sanitas Skincare) was then applied to the skin surface, followed by microneedling treatment. Two weeks after treatment, the woman

Figure 1. Facial Granulomatous Reaction After Microneedle Therapy in 3 Women



Indurated erythematous plaques affected the entire face, sparing the untreated periorbital area, immediate periorbital area, and nasal sidewalls in the patients described in case 1 (A) and case 2 (B) 3 months after microneedle therapy for skin rejuvenation. Similar indurated erythematous papules developed on the cheeks and chin in the patient presented in case 3 (C).

developed a progressive erythematous rash on her face. A 5-day tapering dose of methylprednisolone led to minimal improvement. During the next 2 to 4 weeks, she developed arthralgias, most prominent in the knees, followed by a temperature of 40°C, fatigue, and erythema nodosum. The patient was hospitalized. She had elevated erythrocyte sedimentation rates of 123 and 83 mm/h (reference range, 0-20 mm/h) on 2 occasions. Extensive infectious and rheumatology workup, including a tuberculin test, gold test (QuantiFERON-TB Gold; Cellestis Limited), chest radiography, complete blood cell count, blood cultures, antinuclear antibody screening, and rheumatoid factor, were unrevealing. The patient received empirical treatment with antibiotics but continued to have progressive facial rash, persistent fatigue, and knee pain. She was referred to our clinic 3 months after the procedure.

Her medical history was significant for ductal invasive breast carcinoma with lumpectomy, mitral valve regurgitation, anxiety, depression, lymphocytic colitis, hypertension controlled with atenolol base, and hypercholesterolemia controlled with simvastatin. She reported no prior skin diseases, prior cosmetic procedures, or allergies. On examination, we noted well-demarcated erythematous indurated plaques with minimal overlying scale over the forehead, temples, cheeks, and chin with sparing of the nontreated areas of the face, including the perioral and periorbital regions and the nasal sidewalls (Figure 1A). On the left lower extremity, a 1-cm subcutaneous nodule with hyperpigmentation suggested resolving erythema nodosum.

Case 2

A woman in her 40s with a long-standing history of acne treated in the past with oral isotretinoin underwent microneedling treatment for facial acne scars at the same medical spa as the patient in case 1. Before microneedling, a hyaluronic acid-based moisturizer supplied by Dermapen, LLC was applied to the face. On the same day, the woman had received laser treatment (Fraxel re:store, Solta Medical Inc) for a scar on her chest, using 8 passes at 25 mJ and treatment level 9 with a 15-mm tip. Vita C Serum (Sanitas Skincare) was applied to the skin on the chest prior to laser treatment. A few days after the procedure, she noticed redness, pruritus, and blistering at the site treated with the laser. Two weeks later, she had a second session of microneedling performed on her face, this time using Vita C Serum. Within 3 days, she developed progressive facial redness and swelling. After 2 months, she developed arthralgias in her lower limbs.

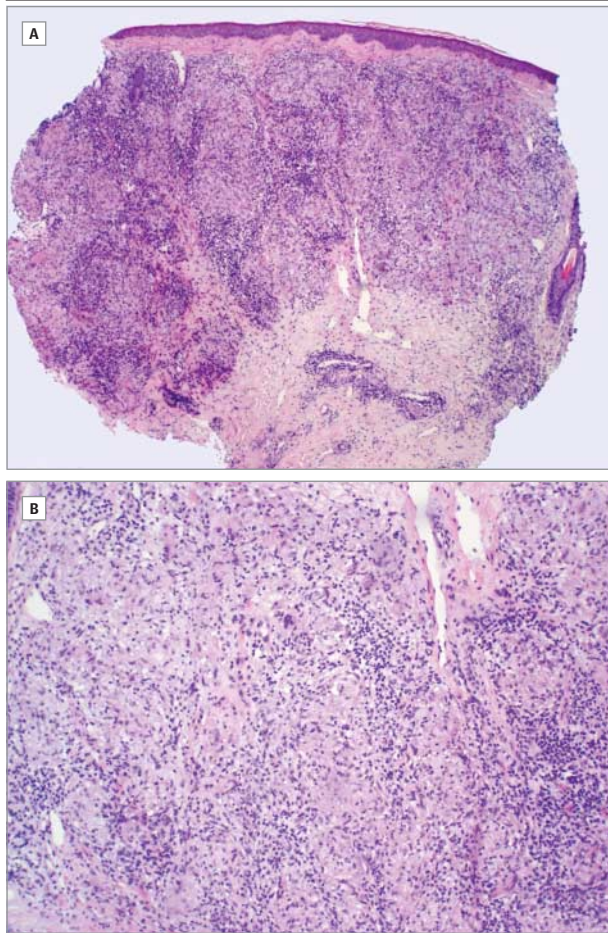
She presented 2 months after the last microneedling session. Her dermatologic history was significant for treatment with botulinum toxin A, hyaluronic acid fillers, and intense pulse light treatment. She had experienced no adverse reactions after the prior procedures and reported no allergies. She was not taking any medications. Her skin examination showed indurated erythematous papules coalescing into plaques over the forehead, cheeks, and chin (Figure 1B).

Further Investigations and Follow-up

Cases 1 and 2

Biopsy of indurated papules in both cases showed foreign body-type granulomatous reaction (Figure 2A and B). Focal, polar-

Figure 2. Skin Biopsy Specimen From Facial Granulomas After Microneedle Therapy



Skin biopsy showed a foreign body-type granulomatous reaction with dermal histiocytes and foreign body giant cells surrounded by lymphocytes and few plasma cells. Hematoxylin-eosin; original magnification $\times 40$ (A) and $\times 200$ (B).

izable material was detectable in the cytoplasm of few giant cells. Chest radiography findings and the serum angiotensin-converting enzyme and total serum calcium levels were normal. Results of tissue bacterial, mycobacterial, and fungal cultures were negative.

Given the high clinical suspicion for delayed hypersensitivity granulomas after intradermal injection of Vita C Serum, we conducted patch testing with a standard tray, cosmetic tray, mixture of topical anesthetics, and Vita C Serum. Both patients showed a 1+ reaction to Vita C Serum at the 96-hour reading (Figure 3). Prick testing for contact urticaria (immunoglobulin E-mediated type I hypersensitivity reaction) was negative. A biopsy specimen of the patch test area showed spongiotic dermatitis with follicular, perivascular, and periadnexal lymphocytic inflammation, without any evidence of granulomas. The patch test reaction faded after 4 to 5 days. Subsequent control patch testing of 5 healthy volunteers to Vita C Serum was negative.

Treatment with midpotency topical corticosteroids alternating with a topical calcineurin inhibitor for 6 months was ineffective. Because doxycycline has been used suc-

Figure 3. Patch Test in a Patient With Granulomatous Reaction After Microneedle Therapy



Patch testing with a standard tray, cosmetic tray, and Vita C Serum showed a +1 positive reaction consisting of grouped erythematous edematous papules after 96 hours.

cessfully in various granulomatous processes, the second patient received empirical treatment with a twice-daily regimen of doxycycline, 100 mg/d. This resulted in partial improvement after 3 months of therapy. At a 9-month follow-up check, these women had persistent, mildly indurated erythematous papules and plaques on the microneedle-treated areas.

Case 3

An otherwise healthy woman in her 50s underwent 3 sessions of microneedle therapy at a local spa using the Dermalpen device for facial skin rejuvenation. During the first and third treatments, a gel product (Boske Hydra-Boost Gel; Boske Dermaceuticals) was applied to the skin surface before the microneedling. The second microneedling session was done using pretreatment with Vital Pigment Stabilizer (Dermalpen, LLC). The patient reported an erythematous rash affecting the entire treated area of the face a few days after the first procedure. The rash progressively worsened with subsequent microneedling sessions and became papular after the third session. Her medical and family histories were nonsignificant and she had no allergies. She was taking no medications other than multivitamins. She presented to our clinic 3 months after the third microneedling session. Her skin examination revealed indurated erythematous papules on her bilateral cheeks and chin (Figure 1C). Examination of a skin biopsy specimen confirmed a foreign body-type granulomatous reaction with evidence of polarizable foreign material in giant cells. Tissue cultures were negative and she had normal chest radiography findings and a normal serum angiotensin-converting enzyme level. The patient refused a patch test. Given our experience with the first 2 cases, we suspected delayed-type allergic granulomas. Therapy was started with a topical midpotency corticosteroid and oral minocycline hydrochloride, 100 mg, twice a day. After 3 weeks, the woman had almost complete clinical resolution.

Discussion

Our cases represent granulomatous reactions after intradermal tattooing with an antigenic topical product. Given the positive patch test results in the first 2 cases, we believe that these cases were true delayed-type hypersensitivity granulomas. Granulomatous hypersensitivity reaction has traditionally been associated⁵ with intradermal tattooing of metallic elements in the red dyes, including mercury, cadmium, aluminum, calcium, silicon, iron, and titanium. Similar reactions have been reported⁶ with skin penetration of topically applied products containing zirconium and silica after injection of dermal fillers, such as bovine and human collagen, polymerized silicones, hyaluronic acid, and polylactic acid,⁷ and more recently with transdermal permeation of topical products through a skin rejuvenation technology called *electroporation*.⁸ Allergic granulomas represent persistent delayed-type hypersensitivity reaction to an allergen that has been injected into the dermis. Topical application of the culprit antigen (ie, during patch testing) results in allergic contact dermatitis. This explains the histologic findings of spongiotic dermatitis that were seen on biopsy specimens from the patch test site in our first 2 patients. However, intradermal injection of the allergen (ie, intradermal testing) results in the development of granulomas.^{9,10} Given the potential for long-term persistence of granulomatous reactions resulting from intradermal testing, we did not perform that testing in our patients.

Systemic symptoms, including fever, malaise, and arthralgia as well as erythema nodosum in one of the patients, suggest systemic hypersensitivity. Similar findings have been reported with other cosmetic injections, including red tattoos¹¹ and silicone implants.¹² Whether this represents a true systemic immunologic reaction, dissemination of the granuloma-inducing injected material through lymphatics, or a mere coincidence is controversial. Management of potential systemic hypersensitivity symptoms can require prolonged courses of anti-inflammatory or immunomodulator medications. Our first patient did not respond to a short course of systemic corticosteroids; instead, she required long-term nonsteroidal anti-inflammatory drugs.

The ingredients of Vita C Serum include botanical squalane, ascorbyl tetraisopalmitate, retinyl palmitate, cholecalciferol, *Carthamus tinctorius*, ω -6 ceramides, oleic/stearic/myristic/lauric triglycerides, palm alcohol, lecithin, and vegetable stearyl esters. The prevalence of allergic reactions to this topical product is not known. Based on the data voluntarily provided by the cosmetic treatment facility, 60 patients had received microneedling using Vita C Serum during 3 weeks, and none had developed a similar hypersensitivity reaction. Despite several attempts to contact the manufac-

turer (Sanitas Skincare), we were unable to obtain samples of the ingredients for patch testing. Results of patch testing to the ingredients that we were able to obtain from other sources, including retinyl palmitate, cholecalciferol, *C tinctorius*, and lecithin, were negative. We hypothesize that the culprit allergenic chemical is one of the nontested ingredients or an unlisted ingredient of Vita C Serum, such as an unknown fragrance or preservative.

Differential diagnosis of granulomatous reaction at the site of injection of foreign materials includes bacterial, mycobacterial, and fungal infections as well as sarcoidosis, which has been reported at the site of tattoos¹³ and dermal fillers.¹⁴ All 3 patients had negative infectious workup results and no evidence of systemic sarcoidosis. Topical, oral, and/or intralesional corticosteroids may decrease granulomatous reactions to tattoos or other cosmetic products. Other treatments include oral antihistamines and UV light therapy, imiquimod, isotretinoin, allopurinol, tacrolimus, doxycycline, minocycline, and cyclosporine.¹⁵ One of our patients did not respond to a short course of systemic corticosteroids early in her therapy, suggesting that if systemic treatments are to be implemented, a prolonged course is needed.

These patients experienced a disfiguring adverse effect resulting from unauthorized use of topical products that were not designed for intradermal injection. Microneedles are powerful means of transdermal delivery of drugs. Thus, only chemicals approved for intradermal injection are safe to be used in conjunction with microneedling. At the time of preparation of this article, there were neither regulations from the US Food and Drug Administration nor specific guidelines from the manufacturers about application of cosmeceuticals prior to microneedling. Microneedle rollers, stamps, and pens are accessible for home use and are widely applied in cosmetic practices and medical spas. Most of these treatments are performed without the direct supervision of a physician. We believe that numerous similar adverse reactions are happening and are not reported in the medical literature.

Conclusions

Application of various nonapproved topical products before a microneedling procedure can introduce immunogenic particles into the dermis and potentiate local or systemic hypersensitivity reactions. Given the increasing popularity of microneedling in cosmetic practices, dermatologists should be aware of its potential consequences. The use of topical products in conjunction with microneedling needs to be regulated and limited to products approved for intradermal injection in humans.

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Acquisition of data: Soltani-Arabshahi, Wong.

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Drafting of the manuscript: Soltani-Arabshahi, Wong.

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Correction: This article was corrected on November 19, 2013, to fix the Abstract.

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NOTABLE NOTES

It's a Small and Dangerous World Global Dermatologic Toponyms

Walter H. C. Burgdorf, MD; Leonard J. Hoenig, MD

Many diseases are identified by toponyms or place names. Most are infectious diseases, but others are genodermatoses found in isolated populations. Toponyms are not always viewed favorably; Q fever referred to Queensland, but after protests, its name was changed to query fever to avoid reflecting badly on the Australian state.¹

The most toponymous disease is Old World cutaneous leishmaniasis. Names for its primary lesion include Aleppo (Syria) boil, Baghdad (Iraq) boil, Biskra (Algeria) button, Jericho (West Bank) button, Delhi (India) boil, Kandahar (Afghanistan) sore, and Lahore (Pakistan) sore, reflecting its wide distribution. Dum-dum fever is a synonym for visceral leishmaniasis; William Leishman worked at Camp Dum-Dum near Calcutta, India.

Names may change as one crosses borders; Rocky Mountain spotted fever, caused by *Rickettsia rickettsii*, is known as São Paulo fever in South America.

Mycobacterium ulcerans causes widespread, surprisingly painless cutaneous and subcutaneous necrosis. The lesion's most common name is Buruli ulcer, after the Buruli region of Uganda. In Australia it is known as Bairnsdale (Victoria) or Daintree (Queensland) ulcer.

Trench fever caused by *Bartonella quintana* and spread by the body louse caused widespread problems during World War I, infecting around one-fifth of troops on both sides of the trenches. An alternative name is Volhynia fever, named after the region of Ruthenia, which straddles the border between today's Poland and Ukraine.

Contact with the spicules of *Hylesia* moths produces pruritic papulovesicular dermatitis. Massive outbreaks have occurred when swarms of moths were attracted by the lights of ships in the Venezuelan port of Caripito; today, Caripito itch is a recognized occupational dermatitis.²

Several genodermatoses carry place names: Mljet or Meleda (Croatia) palmoplantar keratoderma, Ognå (Norway) epidermolysis bullosa simplex, Oudtshoorn (Cape Province of South Africa) keratolytic winter erythema,³ and Rheydt (Germany) ichthyosis hystrix.

Merseburg triad is one of the few toponyms attached to an endocrine disease. Carl Adolph von Basedow, working in the city of Merseburg in Sachsen-Anhalt, Germany, identified the triad of exophthalmos, tachycardia, and goiter for autoimmune thyroid disease just a few years after Robert James Graves in Ireland. Another uncommon toponym is Mallorca acne, a form of polymorphic light eruption that was first identified when Europeans starting flying to southern isles during the winter without any prior hardening to UV light.

Hopefully, these examples will not discourage travelers but instead pique their curiosity about the many skin diseases with geographic names.

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