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Mild Allergic Reactions after Botulinum Toxin Injection: A Case Series and Literature Review

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Background: Botulinum toxin type A (BTA) is becoming more and more prevalent as an injection agent in cosmetic surgery. However, there is an increasing amount of cases reporting unexpected adverse reactions related to BTA injection. BTA can invoke many kinds of hypersensitive reactions, some of which can be delayed-type or even fatal; hence, it is of crucial importance to pay close attention to atypical and early symptoms that may indicate the presence of BTA allergy in patients.
Methods: In this study, we reported three cases of mild and unexpected BTA-related hypersensitive reaction with a symptom of nonpruritic erythema on the chest that happened after BTA treatment of upper facial wrinkles and proposed several suggestions based on our practical experience and literature review.
Results: Two patients' symptoms were alleviated spontaneously, and one patient's were alleviated after taking oral corticosteroid. According to our literature review, we believe that these incidences indicate a kind of unreported allergic reaction relevant to botulinum toxin.
Conclusions: We suggest clinicians consider warily patients' subsequent BTA injection schedule if any suspicious reaction occurs after treatment. We suggest that patients who experience nonpruritic erythema after botulinum toxin injection should suspend subsequent injection plans for at least 3 months to prevent more severe consequences.
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INTRODUCTION

Botulinum toxin type A (BTA) is a kind of neurotoxin produced by *Clostridium botulinum*. It can effectively paralyze muscles and remove wrinkles by reversibly inhibiting the release of acetylcholine at the motor end plate.[1] Due to its safety and effectiveness, BTA is prevalent in cosmetic surgery applications, and simultaneously, cases reporting unexpected BTA-related adverse reactions are also multiplying. Although most of these are mild, severe hypersensitive reactions are not rare in clinical practice.[2] Usually, cosmetic surgeons tend to inject BTA multiple times and repeatedly for an ideal wrinkle removal effect. Despite its favorable safety profile, research showed that multiple BTA injections might induce BTA-related immunoreaction in some individuals, hence invoking a delayed-type hypersensitive reaction, which can lead to serious consequences if early allergic symptoms are not taken seriously or even ignored.[3–5]

The BTA allergic symptoms reported so far all occurred around the injection sites or primarily occurred in the injection sites before spreading to other sites.[6] We have noticed several patients in our clinical practice who experienced inconspicuous and nonpruritic erythema on the chest after BTA injection into the upper face, but the injection sites showed no anomaly. We speculate that some of the BTA we injected may have diffused into the blood and invoked some kind of hypersensitive reaction

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on the chest. The symptoms could be alleviated by dexamethasone tablets, in a short time. If these symptoms do not attract timely attention, we suspect serious events may occur in further BTA treatment.[7,9,10]

Therefore, we reported three cases of BTA-related acute hypersensitive reaction that occurred in other sites besides the injection position. Although it has not invoked serious consequences for now, timely attention to these mild symptoms may help clinicians evaluate if there is any hypersensitive reaction to BTA in patients, thereby determining whether to continue or postpone subsequent BTA injection treatments.

Takeaways

Question: Is non-pruritic erythema a kind of unreported adverse reaction to BTA that indicates mild hypersensitive reactions which may lead to more severe consequences?

Findings: Clinical experiences indicate that non-pruritic erythema on the chest is a kind of unreported BTA allergic reaction that should be alerted.

Meaning: Non-pruritic erythema on the chest after BTA injection is a kind of allergic reaction and should be alerted and recorded.

CASE REPORT

Case 1

A healthy 46-year-old woman with no allergic history experienced nonpruritic chest erythema after receiving BTA injection in the glabella and crow's feet. No local anesthetic was applied before injection, and a total of 40U BTXA (Hengli, Lanzhou Institute of Biological Products, China) was injected into her glabella and crow's feet. Two minutes after injection, she reported nonpainful erythema on the chest with no other symptoms (Fig. 1). After 5 minutes of observation, the erythema spontaneously resolved, and the patient did not complain of any other discomfort; thus, she was dismissed after the observation was made.

Case 2

A healthy 28-year-old woman experienced nonpruritic chest erythema after receiving BTA injection in the glabella and crow's feet. The patient reported a history of rash on the chest with unknown inducement. She suspected that it may be related to shrimp allergy but cannot provide hypersensitive test proof. An estimated 0.2 mL of lidocaine diluted in 1.8 mL saline was administered as local anesthetic, and a total of 50U BTXA (Hengli, Lanzhou Institute of Biological Products, China) was injected into her glabella and crow's feet. Five minutes after injection, she reported nonpainful erythema on the chest with no other symptoms (Figs. 2–4), which resembled her previous rash. After 20 minutes of observation with no alleviation of the erythema, we gave her 1.5 mg dexamethasone tablets. After another 20 minutes, we gave her 1.5 mg dexamethasone tablets again, and then the erythema gradually disappeared. Because no other discomfort was reported, she was dismissed after the observation was made.

Case 3

A healthy 33-year-old woman with no allergic history experienced nonpruritic chest erythema after receiving BTA injection in the glabella and crow's feet. No local anesthetic was applied before injection, and a total of 50U Onabotulinum toxin-A (BOTOX, Allergan, Inc, Irvine, Calif.) was injected into her glabella and crow's feet. Five minutes after injection, she reported nonpainful erythema on the chest with no other symptoms (Figs. 5–6). After 15 minutes of observation, the erythema spontaneously resolved, and the patient did not complain of any other discomfort; thus, she was dismissed after the observation was made.

MATERIALS AND METHODS

A systematic search for all relevant articles up to January 2024 was conducted in PubMed with a search term of "botulinum toxin AND (allergy OR hypersensitive reaction

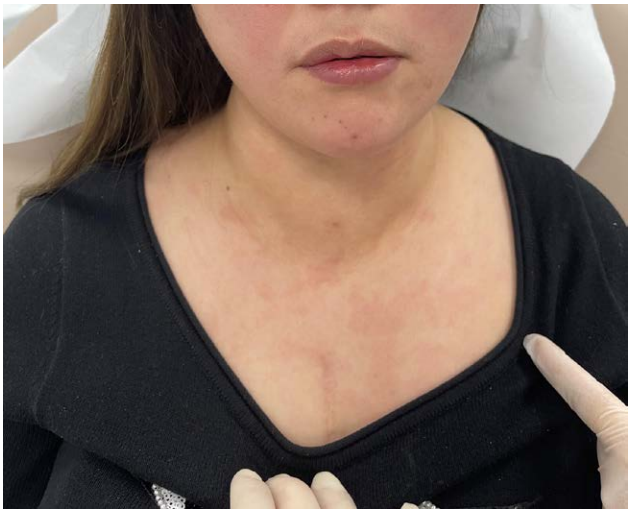

Fig. 1. Case 1. A 46-year-old woman experienced erythema after BTA injection.

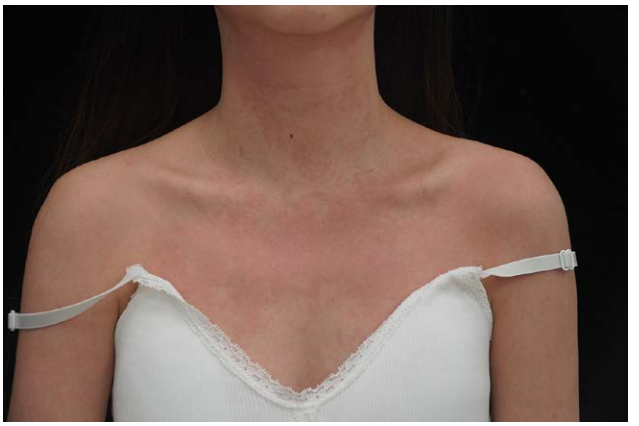

Fig. 2. Case 2. A 28-year-old woman experienced erythema after receiving BTA injection, anterior position.

Fig. 3. Case 2, left position.

Fig. 4. Case 2, posterior position (no erythema on her back).

OR hypersensitive response OR erythema)," and we got a total of 304 results. Only 29 relevant English articles were included and summarized in our research (Fig. 7), as listed in Supplemental Digital Content 1. (**See table, Supplemental Digital Content 1**, which displays the cases of botulinum toxin type A related allergy: symptoms, treatment and duration. **http://links.lww.com/PRSGO/D233**.)

DISCUSSION

BTA is a kind of purified neurotoxin produced by *Clostridium botulinum* that can reversibly inhibit the release

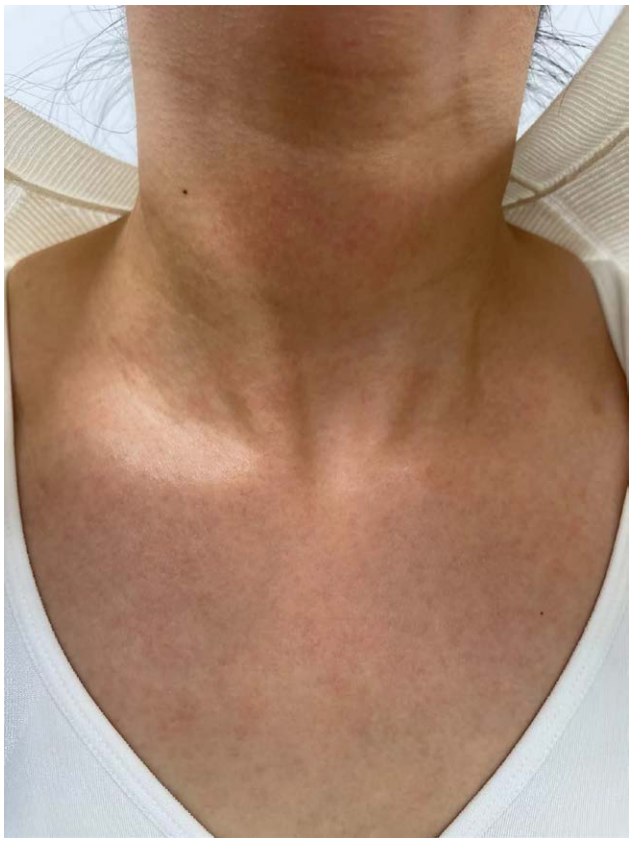

Fig. 5. Case 3. A 33-year-old woman experienced chest erythema after BTA injection.

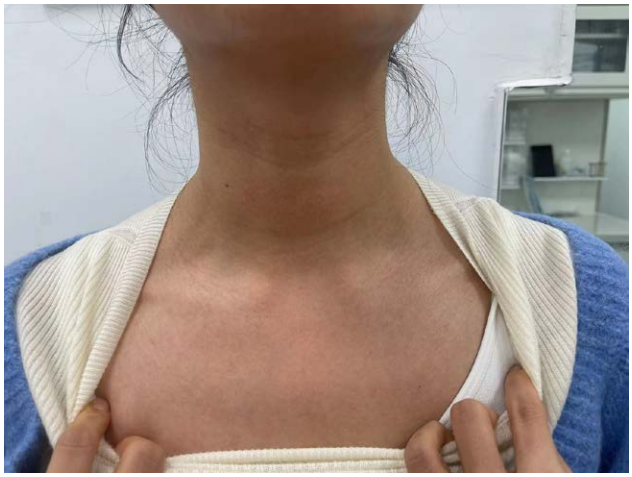

Fig. 6. Case 3. After 15 minutes, the erythema spontaneously resolved.

of neurotransmitter acetylcholine and thus paralyze muscles and remove wrinkles effectively, which makes it a safe and prevailing cosmetic injection for wrinkle removal.[1] However, BTA also has some sort of immunogenicity, which can invoke many adverse reactions such as pain, swelling, and edema of face and eyes, but severe events related to BTA are rare.[8] Recently, some clinical follow-up

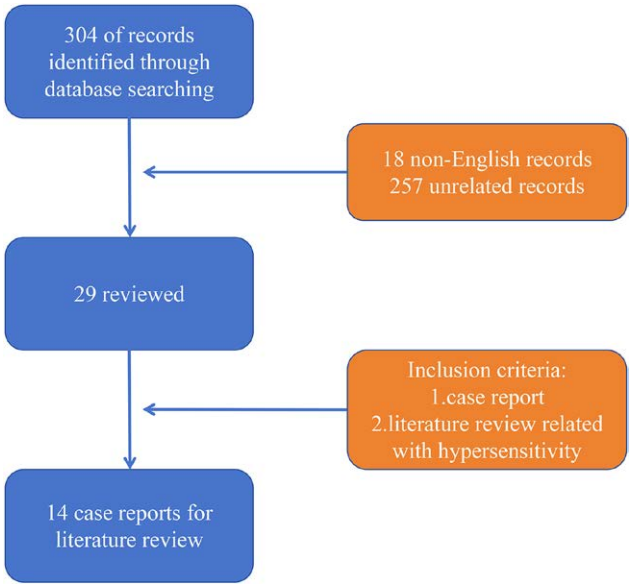

Fig. 7. The cases including criteria.

reports indicated that injecting BTA multiple times and repeatedly might aggravate the immunoreaction to BTA in some individuals, and some patients with no BTA allergic history recording might also confront unexpected delayed-type hypersensitive reaction at months or even years after injection.[7,9,10] Some studies reported severe and subacute allergic events that occurred in some patients with no BTA allergic history recording, after they took vaccination or were asymptomatically infected by herpes zoster virus.[11,12] Simultaneously, a clinical survey focusing on BTA adverse reactions in clinical practice proved the adverse reaction of BTA is actually not rare but usually inconspicuous, thus almost having no influence on subsequent treatment procedure and patients' satisfaction.[6] We suspected that most clinicians and patients might ignore some early and inconspicuous BTA hypersensitive reactions in the first place, but the subsequent injection without protective measures could lead to a severe and unexpected consequence and invoke serious medical accidents. According to the literature review, we noticed that the BTA allergic symptoms reported so far all occurred around the injection sites or primarily occurred in the injection sites before spreading to other sites.[13] With a different clinical practical experience, we proposed that BTA-related hypersensitive reaction is not necessarily notable only in the injection sites; instead, relevant symptoms happening in other sites besides the injection sites also require particular awareness.

Therefore, we reported three patients who all received upper facial wrinkle removal treatment with BTA, and acute, mild, and inconspicuous chest erythema occurred shortly after the injection, which soon spontaneously resolved or was alleviated by dexamethasone tablets. Despite the curative effect and patients' satisfaction still being ideal, we made a decision to record this incident and suggest that the patients postpone BTA treatment temporarily if they have any subsequent BTA injection scheduled in 6 months to improve long-term safety.

Drug hypersensitivity was divided into four major pathophysiologic types: type-I hypersensitivity, which is mediated by IgE and mast cells and usually occurs soon after administration; type-II hypersensitivity, which is mediated by IgG or IgM and immune cells; type-III hypersensitivity, which is mediated by antigen-antibody immune complexes; and type-IV hypersensitivity, which is mediated by T cells.[26,27] We speculate that the BTA injection might infiltrate into the facial capillary, then enter the superficial facial veins and then the anterior jugular vein, ultimately redistributing to the anterior chest wall through vascular and invoke type-I hypersensitive reaction. We do not think other types of hypersensitivity were concerned because the clinical manifestations occurred and resolved very fast. Unfortunately, we have no reason to conduct any hypersensitivity test to verify our hypothesis considering patients' prognosis and their wishes. Schiavo et al[28] reported that botulinum toxin type A is connected by a disulfide bond between the light chain (~50 KDa) and the heavy chain (~100 KDa). The heavy chain is the receptor binding region and protective antigen of botulinum toxin, thus having immunogenicity and containing neutralizing B cell epitopes.[29,30] The light chain's roles in hypersensitivity have not been sufficiently understood yet. As we suspected, if the B cell was activated by the heavy chain, type-I hypersensitivity could occur and may have invoked erythema.

A literature review including 15 case reports and one clinical trial was conducted, including a total of 20 cases and one double-blind trial (**Supplemental Digital Content 1**, **http://links.lww.com/PRSGO/D233**). The most common symptoms include swelling and edema[9,11,12,14–19,24] (11 of 20, 55%), erythema[9–11,14,16,19,20] (six of 20, 30%), rash[10,15,19,21,31] (six of 20, 30%), pruritus[9,15,18,19,31] (seven of 20, 35%), and granulomatous inflammation[7,10,31] (four of 20, 20%). Guo et al[12] reported two cases of severe and subacute hypersensitive reaction that occurred in patients with a history of corona virus 2019 vaccination but with no BTA allergic history. Zhuang et al[11] reported a case of herpes zoster that occurred in a patient with no BTA allergic history after receiving BTA injection. Balighi et al[10] reported a case of delayed-type BTA allergy and granulomatous inflammation that occurred 11 months after the patient received BTA injection. All allergic symptoms listed in Supplemental Digital Content 1 (**http://links.lww.com/PRSGO/D233** [7,9–12,14–19,21,23–25,31]) could be alleviated with corticosteroids. However, there have been no articles reporting allergic symptoms occurring in other sites instead of the injection sites so far.

The three cases we reported all exhibited erythema on the anterior chest wall, two of which spontaneously resolved and one of which was alleviated by dexamethasone tablets. We feel it is unlikely for the expression of a rash in a remote location after BTA injection to be a coincidence. Although BTA allergies are usually temporary and not difficult to deal with, it is still recommended to identify early symptoms and take timely measures to prevent worse allergic reactions.[22] Maybe these inconspicuous hypersensitive reactions we reported can help clinicians determine whether the patients have allergic reactions to BTA and adjust dosage of BTA according to individual conditions,

or even temporarily stop injecting BTA agents in some cases. Simultaneously, we provisionally recommend clinicians reduce the BTA injection dosage or even stop subsequent injection for patients who have herpes zoster history, corona virus 2019 history, and vaccination history within 6 months. Any suspicious reaction to BTA should be taken seriously unless further sensitivity tests reveal no anomaly.

CONCLUSIONS

This article suggests cosmetic surgeons should pay special attention to patients' mild and inconspicuous BTA-related hypersensitive reactions that occur in other sites besides the injection sites. We suggest clinicians consider warily patients' subsequent BTA injection schedule if any suspicious reaction occurs after treatment.

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DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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