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CASE REPORT

Unveiling the Hidden Dangers: Massive Allergic Dermatitis After Hyaluronic Acid Injection

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Abstract: The increasing use of hyaluronic acid (HA) implants has made adverse effects more apparent. Here, we present a rare case of massive allergic dermatitis due to HA injections. We performed dermoscopy and color ultrasound, which clarified that this was an allergic dermatitis caused by fillers, and analyzed the possible causes of the allergy. Common treatments were compared, and the advantages of 5-FU-based treatment regimens and their associated mechanisms were noted. A low dose of 5-fluorouracil and triamcinolone acetonide was administered to the patient's entire face and neck, and significant efficacy was achieved. We aimed to gather evidence on extensive dermatitis caused by HA injection, provide new perspectives and solutions for subsequent HA injections, and promote further research on the potential mechanisms of extensive skin inflammation and allergies caused by local HA injections.

Keywords: hyaluronic acid, massive allergic dermatitis, 5-fluorouracil

Introduction

Hyaluronic acid (HA) is a multifunctional agent that regulates diverse biological processes, including dermal repair, wound healing, tissue regeneration, anti-inflammatory effects, and immunoregulation. It induces fibroblast production, stimulates collagen synthesis, and enhances skin hydration and soft tissue enlargement.[1] In the last 25 years, the use of HA has increased, and complications resulting from its use must be taken seriously. Agents of unknown origin, low purity, or contaminated with bacterial DNA pose significant risks. Patients often underestimate the consequences of inexpensive procedures performed by individuals lacking proper training and using unregistered products. Common minor adverse reactions include transient local reactions, such as erythema, bruising, and pain, while less common serious complications include nodules, vascular occlusion, visual disturbances, and ocular alteration reactions. The inflammatory reaction that occurs with HA injections is often treated with nonsteroidal anti-inflammatory drugs (eg ibuprofen), antihistamines, antibiotics (eg doxycycline, clarithromycin), and hyaluronidase; surgical drainage is necessary for severe nodules or abscesses.[2]

Herein, we report on a rare case of extensive skin inflammation triggered by HA injection, with favorable therapeutic results from treatment with 5-fluorouracil (5-FU) and triamcinolone acetonide (TAC) over a large area.

Case Report

A 47-year-old woman experienced itching at an injection site near the eyebrow arch two days after the injection of unknown HA products into the eyebrow arch, nasolabial folds, labial folds, and malar muscles at a private clinic. Symptoms began on the second day after the injection. Over the next 4 months, redness, swelling, molting, dryness, increased itching, and pain gradually appeared, and the area of dermatitis gradually expanded to the entire face and the skin of the neck. During this period, the patient used medications such as tacrolimus on her own to relieve the symptoms, but these were not effective; therefore, she visited our clinic for treatment.

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Photographs (Figure 1), color ultrasound, and 10× and 30× dermoscopic examinations (Figure 2) were performed before treatment. Color ultrasound revealed multiple areas of abnormal echogenicity that were considered fillers. Considering that the patient was injected with HA for the first time and that no symptoms of infection were detected, allergic dermatitis was suspected. For anti-inflammatory and anti-allergic effects and to prevent infection, treatment with a regimen of low-dose 5-FU and TAC in the patient's skin lesions was initiated. The concentration of the 5-FU stock solution was 25 mg per mL, diluted 6 times. The concentration of TAC was 40 mg per mL, diluted 20 times. The diluted fluids were mixed and injected. A total of 3 injections were performed, with 2 months between the 1st and 2nd injections and 1 month between the 2nd and 3rd injections. The final results show that the patient was stable and recovered well. Post-treatment photographs (Figure 3) and 10× and 30× dermoscopic examinations (Figure 4) confirmed these observations.

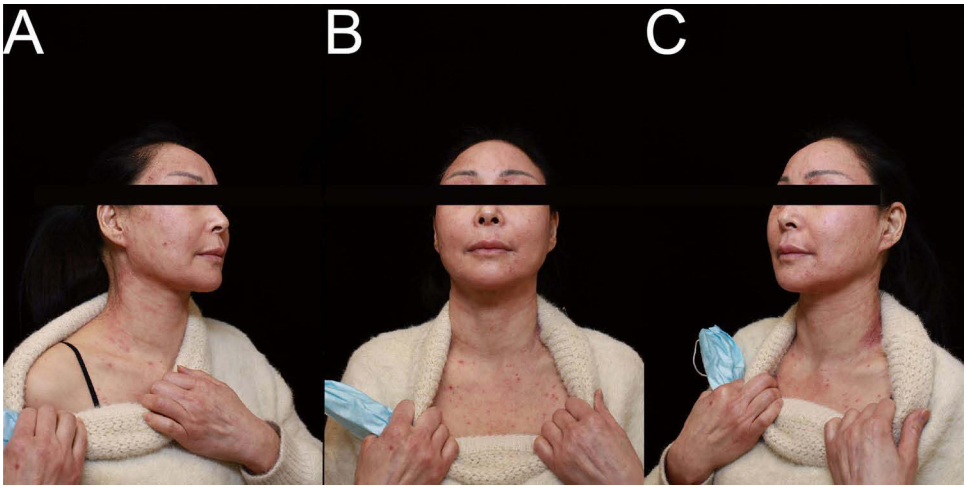

Figure 1 Patient's condition before the treatment.

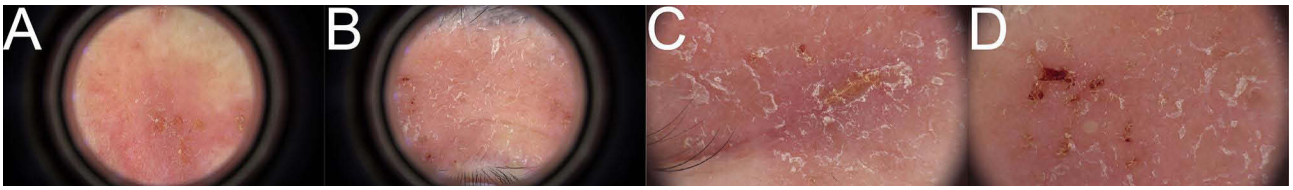

Figure 2 Redness, dryness and severe molting of the skin.

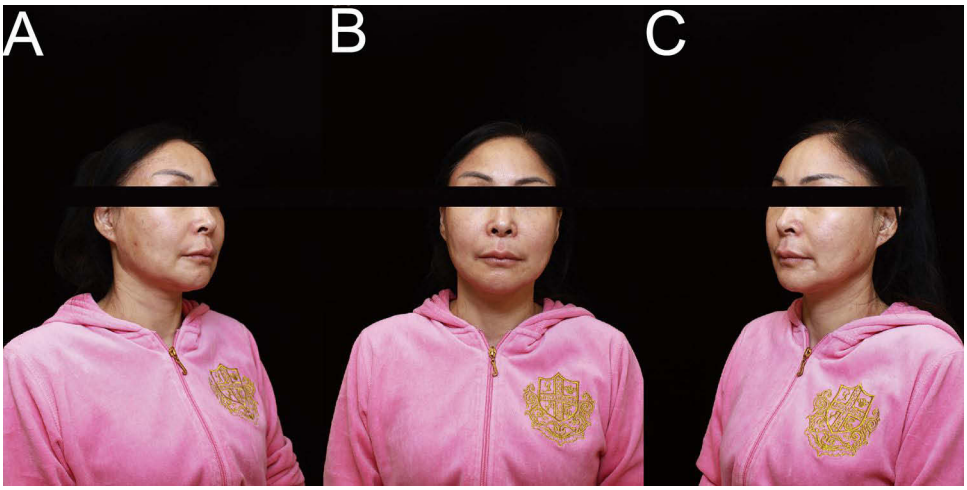

Figure 3 Patient's condition after the injection treatment.

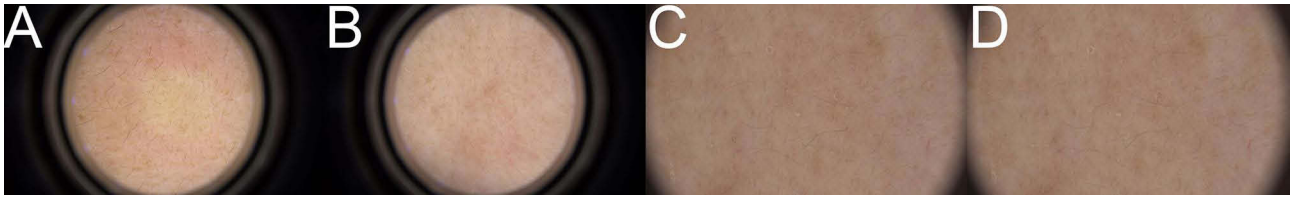

Figure 4 The skin returns to the normal state.

Discussion

HA is a naturally occurring polymer, produced from endogenous sources within the human body. It has distinctive physicochemical and biological properties and excellent biocompatibility and biodegradability. HA is not organ- or species-specific and is therefore presumed to be non-allergenic. Instead, HA may function as an anti-inflammatory agent by inhibiting the release of inflammatory mediators, reducing oxidative stress, promoting tissue repair, and modulating immune responses.[3] However, injectable products also include other substances, such as additives. Various crosslinking chemicals, including 1.4-butanediol diglycidyl ether (BDDE) (found in Juvederm, Restylane, Princess), divinyl sulfone (used in Captique, Hylaform, Prevelle), and diepoxyoctane (in Puragen) are employed to stabilize the HA chain. To enhance hydrophilicity, some producers include additional agents such as dextran or mannitol. Various additives may trigger immune responses as antigens.[4] As of now, HA formulations have been obtained from specific strains of Streptococcus (*S. equi* or *S. zooepidemicus*) through bacterial fermentation. However, this does not eliminate contamination by protein molecules, bacterial nucleic acids, or stabilizers. They can act as antigens and stimulate a hypersensitivity reaction in the host,[5] which can lead to the aggregation of immune cells and the release of inflammatory factors. Factors contributing to adverse reactions include the quality of the HA filler, the patient's immune status, infection, and the injection technique.[6] In addition, mechanical damage caused by massive HA injections and local osmotic pressure changes may also contribute to the inflammatory response.

HA causes early reactions with a rapid onset, with tachyphylactic hypersensitivity reactions striking within minutes of injection and IgE-mediated histamine release from stimulated mast cells and basophils. These manifest as urticaria, angioedema, and anaphylactic reactions.[5] In contrast, clinical manifestations of HA-induced delayed inflammatory reaction (DIR) include recurrent localized solid edema with erythema and tenderness, or injection site nodules caused by HA soft tissue filler injections,[7] mediated by T-lymphocytes rather than antibodies. These reactions typically manifest 48–72 h post-injection, but may appear weeks later and continue for months.[8] In the present case, the patient presented with extensive desquamative dryness, itchy redness, and swelling that persisted for several months, which was different from previously reported cases of sensitization due to HA injections. Considering that the patient was injected with HA for the first time, the onset occurred on day 2 post-injection. Our analysis of the timing of symptom onset, presentation, and duration strongly indicates an association with DIR. Previously reported cases associated with DIR due to HA injection have presented with erythema in the neck 3 weeks after HA injection that resolved on its own after 2 weeks.[9] Common adverse effects include tender granulomas, skin edema, and dermatosclerosis. The widespread dermatitis due to HA injection that we report on is rare.

Considering that hyaluronidase is effective only within 4 hours after HA injection and that it is not effective in the treatment of skin necrosis,[10] it was not used to treat this patient. Clinicians often use nonsteroidal anti-inflammatory drugs (NSAIDs) or steroids for treatment; however, the use of NSAIDs may lead to adverse effects such as insomnia, dry mouth, dizziness, tinnitus, and cardiotoxicity. Steroid hormone use may lead to decreased immune function. 5-FU and TAC are administered subcutaneously at low doses to achieve immunosuppression by inhibiting T cell proliferation.[11] This helps reduce serum levels of TNF-α and IFN-γ in vivo without inducing cutaneous atrophy and rebound lesions.[12] Additionally, considering that patients present with extensive desquamation and thin skin prone to infection, 5-FU can inhibit bacterial DNA and RNA synthesis by inhibiting thymidine synthase, which is necessary for DNA synthesis,[13] especially in methicillin-resistant *Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli*, and *Vibrio harveyi*, which in turn strongly inhibits autoinducer-2 production and release[14] and prevents infection by pathogens. It

should be noted that after observation during the treatment period, the patient's dermatitis had improved significantly after the 2nd injection. After the 3rd injection, the dermatitis was basically cured. Compared with conventional anti-allergic drugs, such as loratadine, levocetirizine, and tacrolimus, the treatment regimen of 5-FU combined with TAC not only has a more significant therapeutic effect but also allows the appropriate concentration of drug to be injected directly into the lesion site, which avoids many of the possible side effects associated with systemic administration of the drug.

However, this study still has limitations. First, the diagnosis is usually confirmed using tests such as histologic biopsy and blood tests, but we made the diagnosis only on the symptoms, ultrasound, and dermoscopy, which needs to be noted for improvement in future clinical practice. Second, this combination therapy option is primarily used to treat keloids and is essentially for patients with hyperproliferation of collagen fibers or excess collagen. TAC reduces levels of α-2 macroglobulin and α-1 antitrypsin, which are natural inhibitors of collagenase. 5-FU inhibits fibroblast proliferation and TGF-β induced type I collagen gene expression. Studies have shown that using 5-FU and TAC together is more effective and safer than using 5-FU or TAC alone.[15] However, vasoconstriction induced by combination therapy with 5-FU and TA also plays an important role, and this enhanced vasoconstriction can promote local thrombosis or embolization and closure of capillaries, leading to local tissue hypoxia. These effects can lead to localized tissue atrophy, and in extreme cases to linear necrotic atrophy. Injecting too close to the epidermis can result in epidermal atrophy, and injecting too deeply can result in subcutaneous atrophy.[16] Therefore, in the process of treatment, the dosage is very important to grasp, as well as control of the injection level. There is a certain degree of risk and further research is needed to improve and perfect the program.

Conclusion

To treat our patient with HA-induced allergic dermatitis, we administered a combination of 5-FU and TAC. In the future, the regimen of 5-FU in combination with TAC should not be limited to anti-keloid therapy, and broader clinical attempts could be made based on the mechanisms of inhibiting cell proliferation, decreasing collagen synthesis, and increasing collagen degradation. However, our regimen as a clinical attempt has shortcomings and requires more clinical practice as well as further research.

Abbreviations

HA, Hyaluronic acid; 5-FU, 5-fluorouracil; NSAID, nonsteroidal anti-inflammatory drugs; TAC, triamcinolone acetonide; DIR, Delayed Inflammatory Reactions.

Ethical Approval

The study was approved by the Ethics Committee of Peking Union Medical College.

Consent for Publication

We have obtained the patient's consent and signed patient photographic consent forms.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest to disclose.

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