CASE REPORT

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Recurrent delayed hypersensitivity reaction to a hyaluronic acid soft-tissue filler following COVID-19 vaccination: a case report

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Hyaluronic acid soft-tissue fillers are the second most widely used injectable agents in cosmetic surgery. During the coronavirus disease 2019 (COVID-19) pandemic, a few cases of delayed hypersensitivity reactions to hyaluronic acid filler injections have been reported following COVID-19 infection or vaccination against the virus. A 61-year-old woman visited the emergency room with swelling and redness on the entire face that started on the nasolabial area. She had received hyaluronic acid filler injections in her nasolabial area 8 months previously and had completed the primary series of vaccinations and received a booster dose of the mRNA Pfizer-BioNTech COVID-19 vaccine 1 month before the swelling episode. A corticosteroid was added to the antibiotic regimen because of the nonsignificant effect of the antibiotics. The symptoms then resolved, and corticosteroid use was tapered over the course of 2 weeks. Four months later, swelling and redness recurred on both nasolabial folds and chin, but the symptoms were more localized than before. The renewed symptoms regressed with surgical drainage and corticosteroid and antibiotic treatment. This study discusses this extremely rare case of a recurrent delayed hypersensitivity reaction to a hyaluronic acid soft-tissue filler following COVID-19 vaccination.

Keywords Hypersensitivity / Hyaluronic acid / Dermal filler / COVID-19 vaccine / Case reports

INTRODUCTION

Soft-tissue filler injections using hyaluronic acid (HA) are one of the most popular treatments in temporary, noninvasive, relatively low-risk procedures that offer aesthetic improvements. In 2020, HA filler injection was the second most frequently performed nonsurgical procedure worldwide, reported in more than 4 million patients, following only botulinum toxin injection [1]. HA is considered to be safe and biologically inert for use as a soft-tissue filler because it is found naturally in mammalian tissue. However, with the rising demand for noninvasive aesthetic procedures and the resulting creation of new HA fillers, several adverse reactions have been reported. Complications after filler injections vary and can be broadly categorized based on their onset in relation to the filler injection as early events (occurring up to several days after the procedure) or delayed events (occurring weeks to years after the procedure) [2].

Delayed hypersensitivity reactions, also known as type 4 hypersensitivity reactions, are T-cell mediated and generally occur 48 to 72 hours after the injection, though they can follow an asymptomatic period of weeks to months. The reported incidence of delayed hypersensitivity reactions following HA soft-tissue filler injections is about 1.13% [3]. With the emergence of the coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), concerns have arisen about interactions between HA soft-tissue fillers and COVID-19 infection or vaccination. Because a few studies have reported delayed hypersensitivity reactions to soft-tissue fillers following COVID-19

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infection or vaccination, we introduce a case of recurrent delayed hypersensitivity reaction to an HA filler following a booster dose of the Pfizer-BioNTech COVID-19 vaccine.

CASE REPORT

A 61-year-old woman without any allergies or underlying disease except hypertension presented to the emergency room in January 2022. She was taking lercanidipine, which belongs to the dihydropyridine class of calcium-channel blockers (10 mg daily), for hypertension. In June 2021, she received an injection of HA soft-tissue filler (Cleviel Contour; PharmaResearch Co., Ltd.) in her nasolabial area for aesthetic improvement. The first two vaccine doses had been administered without complication, and a booster dose of an mRNA COVID-19 vaccine (Comirnaty; Pfizer-BioNTech) was administered in mid-December 2021. Several days after the booster vaccination, she was diagnosed with COVID-19, but the infection passed without remarkable symptoms.

In the middle of January, about 1 month after the booster vaccination, swelling and redness occurred on her nasolabial area and gradually spread to her whole face (Fig. 1A). Her white blood cell (WBC) count and C-reactive protein (CRP) level, which are representative of serum inflammation, were serially assessed. At the time of presentation, her WBC was elevated to 11,400/mm^3, but her CRP was normal at 0.5 mg/dL. A contrast-enhanced computed tomography (CT) scan was performed for evaluation and showed ill-defined soft tissue densities, suggesting cellulitis (Fig. 1B). She was admitted through the emergency room, and intravenous first-generation cephalosporin (cefazolin, 2 g every 8 hours) was administered primarily because the symptoms indicated likely cellulitis. Three days later, an intravenous corticosteroid (dexamethasone, 5 mg every 24 hours) was added because the effect of the antibiotics was not significant. After that, the symptoms subsided (Fig. 1C). One week later, she was discharged with a tapering dose of the oral corticosteroid. The symptoms were resolved 2 weeks later with no sequelae (Fig. 2). Her WBC and CRP levels decreased to 7,900/mm^3 and 0.1 mg/dL, respectively.

About 4 months later, in May 2022, erythematous swelling recurred on both nasolabial folds and chin, with a pattern that was similar but more localized than the prior event (Fig. 3A). A follow-up contrast-enhanced CT scan was collected and showed ill-defined soft tissue densities with increased enhancement, skin thickening, and subcutaneous fat infiltration, suggesting cellulitis with inflammatory injection granuloma or abscess formation (Fig. 3B and C). The symptoms receded with surgical drainage and intravenous and oral corticosteroid and antibiotic use, as in the prior event (Fig. 3D). The treatments reduced her WBC and CRP level from

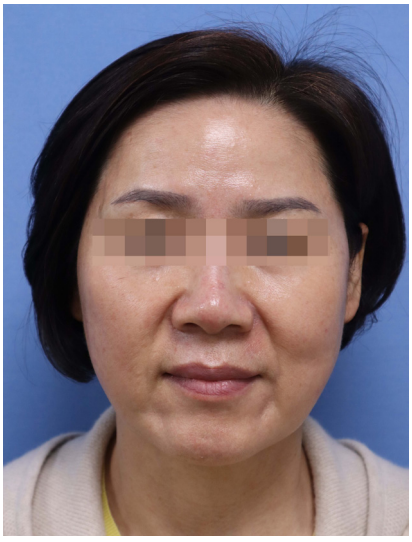

Fig. 2. Symptoms improved 2 weeks after hospitalization without any sequelae.

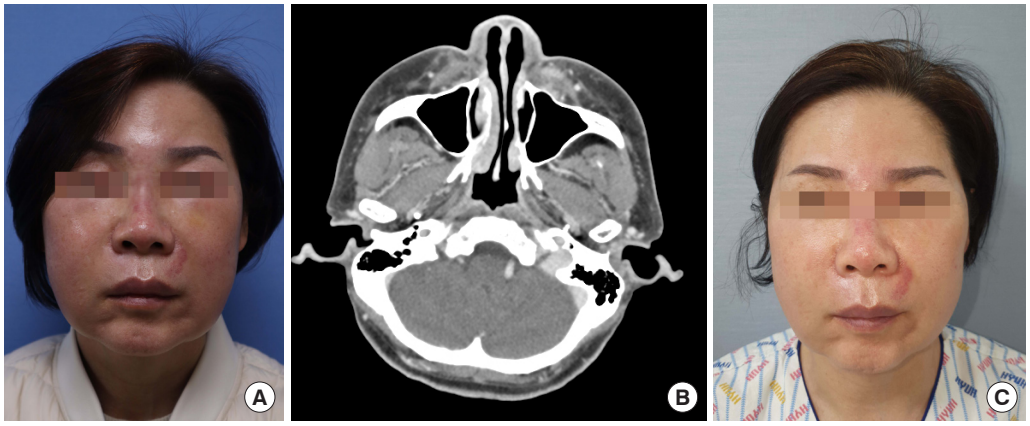

Fig. 1. First delayed hypersensitivity reaction event. (A) Patient's photographs taken on the day she presented to the clinic. (B) Contrast-enhanced facial computed tomography scan shows ill-defined soft tissue densities, suggesting cellulitis. (C) Patient's photographs taken 3 days after hospitalization.

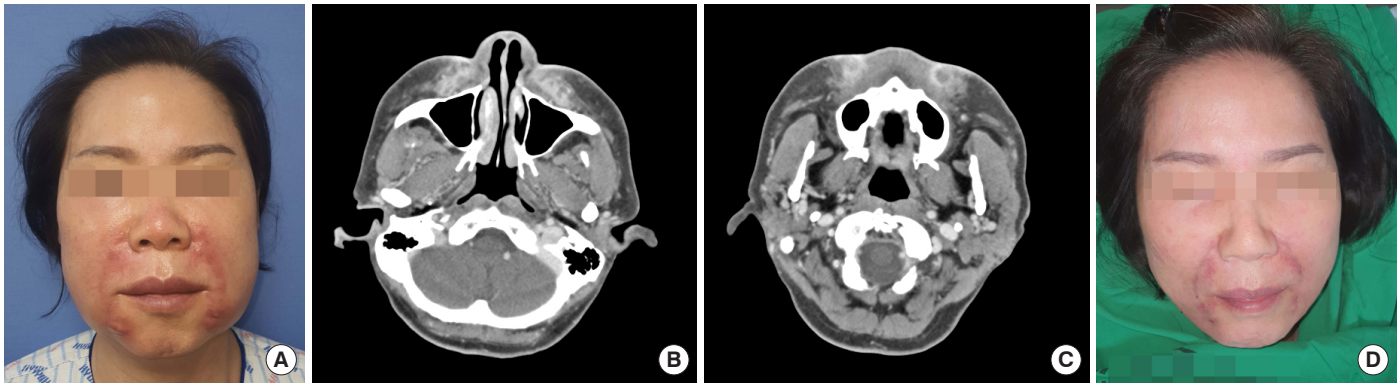

Fig. 3. Recurrent delayed hypersensitivity reaction event. (A) Patient's photographs taken on the day of recurrence. Erythematous swelling recurred on both nasolabial folds and chin, more localized than the prior event. (B, C) Contrast-enhanced facial computed tomography shows a more heterogeneous pattern, with ill-defined soft tissue densities, suggesting aggravated cellulitis and abscess formation. (D) Patient's photographs taken 2 days after surgical drainage. Improved erythema and swelling are seen.

16,500/mm^3 to 7,800/mm^3 and 8.6 mg/dL to 0.5 mg/dL, respectively.

DISCUSSION

The injection of soft-tissue fillers containing HA as a noninvasive aesthetic procedure has become popular in recent years. HA filler injection was the second most frequently performed non-surgical procedure worldwide, after botulinum toxin injection, in 2020 [1]. HA is a high-molecular-weight glycosaminoglycan polysaccharide and a component of tissue matrices and fluids that acts as a stabilizing intracellular component of the dermis [4]. Despite the known safety of procedures with HA soft-tissue fillers, rare adverse events have been reported [5-7].

Hypersensitivity reactions to soft-tissue fillers can be broadly classified as acute or delayed, depending on the time of onset. Acute hypersensitivity reactions, also known as type 1 hypersensitivity reactions, present within minutes or hours of the injections and are caused by an immunoglobulin E–mediated immune response to the filler. They can present as angioedema or anaphylactic reactions after exposure. In contrast, delayed hypersensitivity reactions, also known as type 4 hypersensitivity reactions, are commonly characterized by induration, erythema, and edema. Delayed hypersensitivity reactions typically occur 48 to 72 hours after injection, but can occur as late as several weeks or months later, and are mediated by T lymphocytes rather than antibodies. Unlike acute hypersensitivity reactions, they can occur in both previously injected patients and patients who have received their first injections [3,8]. The incidence of delayed hypersensitivity reactions following HA soft-tissue filler injections was previously reported to be about 1.13% [3].

After the emergence of COVID-19, which is caused by SARS-CoV-2, in December 2019, various vaccines became available, and the number of people vaccinated against COVID-19 rose steadily. Some cases of delayed hypersensitivity reactions to fillers have been reported after vaccinations against influenza, shingles, and COVID-19 [9-11]. In a previous study, Munavalli et al. [11] proposed a mechanism by which the COVID-19 spike protein might act as a triggering factor for delayed hypersensitivity reactions following COVID-19 vaccination. Spike protein interactions with angiotensin-converting enzyme 2 receptors can cause a pro-inflammatory, regional Th1 cascade that promotes a $CD8^+$ T cell-mediated reaction, resulting in a delayed hypersensitivity reaction. Delayed hypersensitivity reactions produced through those processes usually manifest as swelling, erythema, or granuloma formation at the injection site. Similar to HA soft-tissue fillers, delayed hypersensitivity reactions to botulinum toxin type A and non-HA polycaprolactone following COVID-19 vaccination have also been reported [12,13].

Delayed inflammatory reactions associated with COVID-19 were reported to generally self-resolve in days or weeks [14]. In both mild and severe cases, various treatments, including hyaluronidase and oral, intralesional, or intravenous steroids, were applied and had significant effects. Mild to moderate reactions were treated with hyaluronidase, at a dose of 10 units per 1 milliliter of HA filler, or about 30 to 300 units per nodule. Secondary treatments involve the use of an intralesional steroid alone or with 5-fluorouracil. Antibiotics can be added when the symptoms suggest infection, and further surgical procedures such as incision and drainage are needed when a fluctuating mass is identified [14,15]. Some studies questioned the use of immune modulators such as corticosteroids during the COVID-19 pandemic because of concerns about dampening the immune response needed to protect against infection [10]. However, the short-term or low-dose steroids indicated to treat general delayed hypersensitivity can be used safely and present no increased risk of contracting SARS-CoV-2 [4]. Munavalli et al. [11] introduced a novel treatment of low-dose lisinopril, which is an oral angiotensin-converting enzyme inhibitor (ACE-I) that was previously used to treat hypertrophic scars, keloids, and several inflammatory skin disorders.

In this study, we used a combination of intravenous and oral corticosteroids and antibiotics with surgical drainage to successfully treat a patient who presented recurrent delayed hypersensitivity reactions to an HA soft-tissue filler following COVID-19 vaccination. We were concerned that the COVID-19 infection would worsen, but we confirmed the safety of corticosteroid administration through a literature review before prescribing it, and no further worsening of the infection was observed [4,10,11]. Unfortunately, it was not possible to apply an ACE-I in this case. Because our patient was already taking lercanidipine regularly as an antihypertensive medication, we could not add lisinopril due to concerns about hypotension.

Several studies have been conducted and molecular studies are also in progress, but the exact mechanism related to the delayed hypersensitivity reaction between the HA filler and the COVID-19 vaccine is still unknown [9-12,15]. However, there are several reasons for concluding that a delayed hypersensitivity reaction took place in this case. First, the timing of 1 month after the COVID-19 vaccination corresponds to the delayed hypersensitivity reaction [3, 8]. Furthermore, the swelling and redness around the filler injection and the presence of an abscess at the time of recurrence of this case were similar to the previously reported cases [7,9,12]. This is also supported by the rapid resolution of symptoms through proper antibiotics and corticosteroid administration [4]. Considering that there were no other specific events near the onset of symptoms, it is reasonable to conclude that this was a delayed hypersensitivity reaction induced by the COVID-19 vaccine to the HA filler. In addition, this case report has significance as a recurrent case, which has not been previously reported.

In conclusion, although delayed hypersensitivity reactions to HA fillers following vaccination are rare, unwanted side effects do occur. Because they have not been the subject of well-designed studies, management is often difficult. However, considering the ongoing pandemic and the worldwide demand for vaccines against COVID-19, providers of aesthetic procedures should be conscious of the risks posed by the vaccines to patients who have previously received HA filler injections. This case study will be helpful to clinicians who need to manage vaccination-mediated delayed hypersensitivity reactions to HA fillers.

NOTES

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Patient consent

Written informed consent was obtained from the patient for photographs and radiologic images.

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