

ORIGINAL ARTICLE

Increase in the incidence of acute inflammatory reactions to injectable fillers during COVID-19 era

Kiyoko Kato MD¹ | Eiko Inoue MD² | Sakae Tanaka MD, PhD³ | Hiroshi Kawamoto PhD⁴¹Azabu Beauty Clinic, Tokyo, Japan²Jyosui Dermatology Clinic, Fukuoka, Japan³Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo, Tokyo, Japan⁴Laboratory of Immunology, Institute for Frontier Life and Medical Sciences, Kyoto University, Kyoto, Japan**Correspondence**

Kiyoko Kato, Azabu Beauty Clinic, 2-14-11 Azabujuban, Minato-ku, Tokyo 106-0045, Japan.

Email: kato@abcsalon.co.jp**Funding information**

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Abstract

Background: Acute inflammatory reactions (AIRs) are a rare complication following esthetic treatment with hyaluronic acid (HA) and/or human collagen fillers. However, a substantial increase in the frequency of AIRs was observed in the first author's clinic since May 2020.

Aims: To report AIR cases, we experienced and discuss potential underlying mechanisms.

Methods: This was a retrospective review of patients representing AIR symptoms following filler injection with HA or human collagen in our clinic.

Results: Although only one case of an AIR with an incidence rate of 0.01% was recorded following filler treatment between September 2008 and April 2020 in our clinic, we observed 14 AIR cases without anaphylaxis, with an incidence rate of 1.18% between May 2020 and June 2021, in line with the spreading of the new coronavirus pandemic. All cases were females aged 40–57 years, and the time of onset was within hours after filler injection. Three patients had been treated with HA fillers only, 2 with HA plus human collagen, and 9 with human collagen only. Most patients had been treated with these products in the past. Nine patients were treated with oral prednisolone. In all cases, symptoms resolved entirely within a week without sequelae.

Conclusions: The marked increase in AIRs coincided with the COVID-19 pandemic. Possible explanations include immune system alterations caused by extensive changes in domestic and personal hygiene, prolonged and elevated stress levels, and subclinical COVID-19 infection. Further studies may be warranted.

KEYWORDS

acute inflammatory reaction, collagen, COVID-19, filler, hyaluronic acid

1 | INTRODUCTION

Injectable esthetic treatments using fillers—such as hyaluronic acid (HA), collagen, and hydroxyapatite—has become increasingly popular, and the estimated number of procedures based on HA, the

leading filler treatment globally, grew by over 150% between 2010 and 2019, with around 4.3-million sessions performed worldwide in 2019.^{1,2}

Adverse events (AEs) following filler injection are generally mild and self-limiting, and this is one of the key reasons for their popularity.

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Nonetheless, there are potential complications. Bruising, temporary erythema, and local pain are relatively common, while less frequent AEs include vascular occlusion (estimated incidence rate: 0.05%),³ delayed inflammatory reactions (DIRs; 0.02%–4.25%),^{4,5} and acute inflammatory reactions (AIRs).

AIRs are extremely rare AEs, manifesting as localized redness, swelling, edema, heat, pain, and nodules occurring within minutes to hours after injection. In our clinic, only one case of an AIR was recorded following filler treatment in the 12 years between September 2008 and April 2020, with an incidence rate of 0.01%. However, we have observed a marked increase in the frequency of AIRs since May 2020, in line with the spreading of the new coronavirus pandemic. The purpose of this report is to describe these cases and to discuss potential mechanisms underlying them.

2 | MATERIALS AND METHODS

This was a retrospective analysis of patients experiencing an AIR following filler injection with HA or human collagen in the first author's clinic. The assessment was conducted in accordance with the Declaration of Helsinki, and all patients provided informed consent for treatment.

All filler treatments during the study period used one or more the following products: the Vycross range of HA fillers (VYC-25L [Juvéderm Volux], VYC-20L [Juvéderm Voluma], VYC-17.5L [Juvéderm Volift], and VYC-15L [Juvéderm Volbella]; Allergan); the Belotero series of HA fillers (Belotero Balance and Belotero Soft; Merz); the HA filler, Teosyal Redensity 2 (Teoxane Laboratories); and/or the human collagen product, Humallagen (Cosmetic Medicine Enterprises Inc.). Injections were mostly performed using a cannula, except when giving injections onto the bone (e.g., zygomatic arch or temporalis), which were delivered using a sharp needle.

Fifteen minutes before commencing treatment, an anesthetic cream was applied containing 9.6% lidocaine; in addition, 0.025% (w/v) benzalkonium chloride solution was used for skin preparation. For patients treated in the tear trough area with HA, or given four or more HAs, oral prednisolone (PSL) 10 mg was prescribed for use on the same day of treatment. If swelling occurred on the following day, patients were instructed to take another 5 mg of PSL.

There is no well-recognized, standardized definition of AIR, and we defined it as local inflammatory reaction characterized by features such as redness, swelling, edema, heat, pain, and/or nodules that occurred within minutes to hours after filler injection in this study. One individual who developed an AIR that led to an anaphylactic reaction was excluded in the present analysis.

3 | RESULTS

A total of 14 cases of AIRs (without anaphylaxis) were recorded between May 2020 and June 2021 (Table 1; Figure 1). Since 1,180 patients were treated with fillers over the study period, this equates

to an incidence rate of 1.18%. 1,020 patients received HA filler and 882 received human collagen (Humallagen), 722 patients having undergone both procedures. All cases that developed AIRs were females aged 40–57 years, and the time of onset was between a few minutes and a few hours after filler injection. Three patients had been treated only with an HA filler ($n = 2$, Vycross; $n = 1$, Belotero); two patients had received combination therapy with human collagen (Humallagen) plus an HA filler (Vycross), and nine individuals had received a human collagen filler only (Humallagen) (Table 2).

Cases 1, 2, and 8 received HA alone (Table 1), two receiving it for the first time to treat tear trough depression and forehead, and one undergoing a second round of treatment in the cheek and perioral area. Cases 4 and 11 had received combination treatment for tear trough depression using HA and human collagen, and in both cases the HA filler had been used for the first time; case 4 had also received human collagen for the first time, but case 11 had received several injections of collagen before. Simultaneous use of HA and human collagen is common in treating tear trough depression when mid-cheek volumization is also needed. In the 9 cases of AIR following human collagen use alone, 8 had undergone treatment for tear trough depression and 1 for neck wrinkles; all 9 of these patients had received at least two previous rounds of collagen injection, several months apart, but they never experienced AIR before.

Among the 11 patients who received human collagen (alone or in combination), the volume used was between 0.5 and 1.0 ml, which is the usual quantity in our practice.

Symptoms resolved in 7 patients following 2–3 days of oral administration of prednisolone (PSL) (10 mg/day) initiated when the patients returned to the clinic with the complaint. Two individuals exhibited prolonged symptoms and were treated with oral PSL 10 mg/day for 3 days, followed by PSL 5 mg/day for additional 3–4 days, with full resolution in around 1 week. In the other 5 cases, symptoms resolved without the use of drugs. In all patients, symptoms ultimately resolved entirely without any sequelae.

4 | DISCUSSION

This report describes 14 cases of AIRs (without anaphylaxis) following filler treatment between May 2020 and June 2021 in the first author's clinic. Only a few instances of AIRs with injectables have been previously reported. With regard to HA, cases of angioedema-type acute hypersensitivity were reported following lip treatment with non-animal stabilized HA (NASHA) gel (Restylane Lip [Q-Med])⁶ or Juvéderm Ultra Plus XC (Allergan).⁷ In addition, a large retrospective analysis identified acute hypersensitivity reactions in 16 of 4320 patients (0.3%) treated with NASHA between 1997 and 2001.⁸ There are several theories as to the cause of AIRs with HA, including a reaction to small amount of stabilizing proteins required in the manufacturing process,⁸ or a reaction to HA itself through CD44 receptors on mast cells.⁶ However, the exact mechanisms remain unclear.

With regard to collagen, products of bovine origin were once widely utilized. However, since they caused high rates of allergic

TABLE 1 Acute inflammatory reactions

Case	Sex	Age (years)	Occupation	Treatment date	Filler used	Injection history	Treatment area	Onset time	Management
1	F	54	Office worker	June 30, 2020	Belotero Soft 0.5 ml	1st time	Tear trough depression	3 h	PSL 10 mg 2 days
2	F	55	Teacher	September 16, 2020	VM 1.0 ml; VL 1.0 ml	2nd time	Cheek, perioral	Next morning	Resolved without medication ^a
3	F	56	Self-employed	October 21, 2020	Co 0.5 ml	3rd time since 2019	Tear trough depression	Next morning	PSL 10 mg 2 days
4	F	50	Office worker	November 11, 2020	VM 2.0 ml; VL 2.0 ml; Co 0.5 ml	1st time	Tear trough depression	2 h	PSL 10 mg 3 days; 5 mg 3 days
5	F	44	Housewife	December 24, 2020	Co 0.5 ml	9th time since 2018	Tear trough depression	Next morning	PSL 10 mg 2 days
6	F	53	Office worker	January 6, 2021	Co 0.5 ml	6th time since 2017	Tear trough depression	Next morning	PSL 10 mg 2 days
7	F	40	Housewife	January 13, 2021	Co 1.0 ml	5th time since 2017	Neck wrinkles	Next morning	PSL 10 mg 2 days
8	F	45	Office worker	January 20, 2021	VL 1.0 ml	1st time	Forehead	Several hours	Resolved without medication ^a
9	F	57	Office worker	February 4, 2021	Co 0.5 ml	9th time since 2017	Tear trough depression	Next morning	Resolved without medication ^a
10	F	48	Housewife	February 27, 2021	Co 0.5 ml	8th time since 2017	Tear trough depression	Several hours	PSL 10 mg 3 days; 5 mg 4 days
11	F	53	Housewife	March 29, 2021	VM 1.0 ml; Co 0.5 ml	VM, 1st time; Co, 7th time since 2019	Tear trough depression	Next morning	Resolved without medication ^a
12	F	40	Office worker	May 22, 2021	Co 0.5 ml	8th time since 2018	Tear trough depression	Next morning	Resolved without medication ^a
13	F	54	Office worker	June 3, 2021	Co 0.5 ml	3rd time since 2020	Tear trough depression	6 h	PSL 10 mg 2 days
14	F	52	Housewife	June 8, 2021	Co 1.0 ml	7th time since 2015	Tear trough depression	Several minutes	PSL 10 mg 3 days

Abbreviations: Co, Humallagen; F, female; PSL, prednisolone; VL, Volift; VM, Voluma.

^aWithin a few days.

reaction (3%–5%),^{9,10} they were gradually replaced by human collagen. Human tissue-derived CosmoDerm (Inamed) was extensively used for a short period, due to its low allergy incidence and the lack of requirement for prior allergy testing. It was approved by the US FDA in 2003 and was marketed until 2010, with only two cases of AIR reported during that period.¹¹ Nonetheless, CosmoDerm was

ultimately discontinued, owing to its high cost and short duration of efficacy. After that, long-lasting HA products emerged, and human collagen is now available only in Japan (Humallagen) and Korea (Bellacol [Hans Biomed]).¹² The incidence rates of allergy with these products are very low, and to the best of our knowledge, no cases of AIRs have been previously reported.

At the first author's clinic, about 1000 patients per year receive filler treatments, and between September 2008 and April 2019, only one individual developed an AIR following lip augmentation with Juvéderm Volift (Allergan). This patient was allergic to various drugs and had several episodes of anaphylaxis, which may indicate a unique constitution. Over that period, there were no other cases of AIR following HA filler treatment, and none at all resulting from human collagen injection in over 5000 sessions since 2015 when Humallagen first arrived on the Japanese market. Although the exact reason for the rapid increase in AIRs since May 2020 is unknown, we speculate it may be related to the COVID-19 pandemic.

We hypothesize three possible explanations for an association between COVID-19 and AIRs. The first is a rapid change in the lifestyle. Increased handwashing, alcohol disinfection, and the wearing of masks have resulted in cleaner domestic environments than ever before. The risk of viral and bacterial infections has been dramatically decreased. Indeed, reports from Italy, Singapore, and Taiwan have shown that rates of influenza infection during the COVID-19 pandemic were 70%–80% lower compared with previous years.^{13–15} In 1989, Strachan investigated the environmental factors associated with the development of allergic diseases and proposed that there were important differences in the frequency of exposure to infection during infancy, which became the basis for the “hygiene hypothesis.”¹⁶ This idea was later developed in a variety of ways. It has been suggested that during the differentiation of naïve T cells into Th1 and Th2 cells in the neonatal period, exposure to bacteria and viruses induces greater differentiation to Th1 cells—whereas in a more sterile environment this differentiation is Th2-dominant and individuals have increased susceptibility to allergy.¹⁷ More recently, the potential impact of symbiotic intestinal microflora and parasitic helminths has been added to this hypothesis¹⁸; during microflora development in childhood, a hyper-hygienic environment may reduce the diversity of these organisms and thus induce immune diseases.



FIGURE 1 Acute inflammatory reactions. Images were taken by patients within a few hours of filler treatment: case 5 (a 44-year-old woman given 0.5 ml of Humallagen for tear trough depression; part A), case 6 (a 53-year-old woman given 0.5 ml of Humallagen for tear trough depression; part B)

TABLE 2 Composition of products associated with acute inflammatory reactions

Product	Composition
Humallagen	Mixture of types I and III human collagen extracted from the donated human placenta; <0.3% lidocaine
Belotero Soft ²⁸	Cross-linked sodium hyaluronate (20 mg/ml) produced by fermentation of <i>Streptococcus equi</i> ; 0.3% lidocaine hydrochloride; physiologic phosphate buffer
VYC-17.5L (Juvéderm Volift) ²⁹	Hyaluronic acid (produced by <i>Streptococcus</i> species of bacteria) cross-linked with BDDE; formulated to a concentration of 17.5 mg/ml with 0.3% w/w lidocaine in a physiologic buffer
VYC-20L (Juvéderm Voluma) ³⁰	Hyaluronic acid (produced by <i>Streptococcus</i> species of bacteria) cross-linked with BDDE; formulated to a concentration of 20 mg/ml with 0.3% w/w lidocaine in a physiologic buffer

Note: BDDE, 1,4-butanediol diglycidyl ether.

The gut microflora is formed in childhood but can change in adult life according to various factors, including diet, environment, and stress.¹⁹ Some experts have warned that hygiene changes associated with the COVID-19 pandemic could affect the microflora and alter human immune systems, particularly in high-resource countries.²⁰ It is possible that HA and human collagen were not previously significantly allergenic due to their high biocompatibility, but have recently become more so due to immune system changes caused by an ultra-hygienic environment, thereby leading to AIRs. The cases reported here came from various backgrounds, but like most Japanese people, they all complied with advice to wear face masks, wash their hands frequently, and disinfect with alcohol during the pandemic.

A second possible explanation is based on Th2 system activation under stress. Hormones produced as a result of increased stress levels include noradrenaline (NA), adrenaline, and cortisol. Th1 cells have NA receptors that act in an inhibitory manner, whereas Th2 cells do not, and consequently, stress has been shown to activate the Th2 system.²¹ NA receptors are also present on B cells and may induce allergy by increasing immunoglobulin E production from plasma cells.²² Furthermore, cortisol secreted under stress conditions essentially suppresses all immune cells and particularly decreases the production of interleukin-12 by antigen-presenting cells, thereby reducing the activity of the Th1 system and relatively favoring the Th2 system.²³ Persistent mental stress, in particular, stimulates mast cells through the corticotropin-releasing hormone, neurtensin, and substance P to release chemokines and cytokines.²⁴ Hence, it is possible that the Th2 system has been widely activated by chronic stress relating to the COVID-19 pandemic.

A third explanation is that most of our cases had already undergone several previous cycles of injection, which may have resulted in some immunologic reaction rather than AIRs. Previous reports following HA injection occurred after the first round of treatment. The cases in the present analysis were unique because most patients developed swelling and redness after multiple previous cycles of filler treatment. Some viral infections may activate the immune system and cause delayed T-cell-mediated allergies known as DIRs.^{5,25,26} It is, therefore, possible that subclinical COVID-19 infections present at the time of filler injection could have triggered an immune response through a similar mechanism. None of the patients who developed AIRs in the present report had symptoms of COVID-19, but it is plausible that they were subclinically infected, particularly given that up to 80% of such infections are thought to be subclinical.²⁷

It should be noted that the COVID-19 vaccination program in Japan only started in July 2021. Hence, none of the cases reported here had been vaccinated at the time of the AIR development, and vaccines could not have played any role.

Most of our AIR patients had been treated with human collagen. We routinely prescribe PSL 10 mg/day to all individuals receiving HA injections in order to prevent the risk of DIRs; however, PSL was not given to patients receiving human collagen because there were no previous reports of DIRs with this type of filler. That could explain the higher incidence of AIRs in patients using human collagen

versus HA. Indeed, the three cases of AIRs who had received HA alone refused prophylactic PSL. This suggests that the prophylactic corticosteroid use may be recommended in patients receiving filler to mitigate the risk of AIRs.

It is also noteworthy that most AIRs were in patients treated for tear trough depression. However, this is not surprising given that over 80% of individuals at our center receive human collagen for this indication. In addition, the deep fat compartment, which is injected during the treatment of tear trough depression, is an enclosed space that does not allow lymphatic drainage and is, therefore, highly symptom-inducing.

We acknowledge the limitations of this study. First, it reports only cases at one clinic, and most were related to a single product (human collagen) that is not widely used outside Japan and Korea. Nonetheless, the increase in AIRs was both highly pronounced and not limited entirely to collagen. Second, the background of the patients was not uniform and PSL was given prophylactically only to patients receiving HA. However, even taking into account these limitations, it is striking that there was such a large increase in the incidence of AIRs coinciding with the COVID-19 pandemic.

5 | CONCLUSIONS

We have observed a marked increase in cases of acute hypersensitivity reactions to injectable treatment with collagen and/or HA fillers since the beginning of the COVID-19 pandemic, and such adverse events were rarely observed before the pandemic. A larger, multicenter study is required to demonstrate the relationship with COVID-19 in more detail.

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CONFLICTS OF INTEREST

The authors report no conflicts of interest to disclose.

ETHICAL STATEMENT

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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