Case report

Case report and literature review of late inflammatory reactions to hyaluronic acid filler in a 28-year-old female

Vera Vera

Master Program in Biomedical Science, Anti-Aging Medicine, Faculty of Medicine, Universitas Udayana, 80234, Denpasar, Indonesia

Abstract. It is believed that Hyaluronic acid (HA) filler is the second most frequent and favored aesthetic treatment. Although considered as harmless procedures, they can cause significant adverse events. Late inflammatory reactions demonstrate swelling and induration occurring at least 14 days post filler injection, with an incidence of less than 1.0% late onset nodule. Many aspects contribute, including hypersensitivity, injection method, infection, or biofilm. A 28-year-old female underwent cheek HA filler and developed a delayed onset inflammatory reaction 1.5 months later, presenting a purplish nodule on her right cheek. The nodule measured 1x1x0.5 cm. Ultrasonography and biopsy were not carried out because the patient wished to have minimal invasive options to overcome her symptoms promptly. Strategies recommended for managing delayed onset inflammatory reactions require combination therapy. In this patient, symptoms resolved in 3 weeks after being treated with intralesional hyaluronidase and triamcinolone. To the author's knowledge, this is the first case being reported in Indonesia.

Key words: hyaluronic acid, dermal filler, filler complication, adverse events, delayed onset reactions, delayed onset nodule

Introduction

One of the top desired aesthetic procedures is soft tissue filler[1]. After toxin injections, fillers are the second most commonly performed minimally invasive procedure in 2019, according to the American Society of Plastic Surgeons (ASPS)[2,3]. The International Society of Aesthetic Plastic Surgery (ISAPS) also reported that more than 4.3 million aesthetic treatments are Hyaluronic Acid (HA) fillers, which account for a 15.7% increase than in 2018[4]. Although there is a decrease in number as much as 18.3% in 2022 compared to 2021, HA treatments remain the second most favored non-surgical procedures according to ISAPS[5]. In spite of Covid-19, they are still cherished globally. Although it is considered a safe procedure, as more people undergo the treatment, more side effects continue to be reported[1,3]. With an incidence of no more than 1%, Late-onset Inflammatory reactions (LIR) are uncommon[1]. Prior to 1999, the reported rate was 0.7%. After improvements in their manufacturing to elevate the quality of HA products, it decreased to 0.2%[1,4,6].

The cause and pathophysiology of LIR due to HA fillers are not clearly known yet[4,6]. Proposed affecting aspects involving prior infection and trauma, injection method (filler amount, repetitive procedures, and intramuscular injection) and various characteristics of the filler[7]. Hypersensitivity reactions are categorized as acute or late, based on their progression. Type I hypersensitivity takes place in minutes or hours after treatment, and related to immunoglobulin E (IgE) - mediated immune response[2,7].

LIR with HA fillers is thought to be Type IV hypersensitivity[7-9]. Across literature, the rate of this reaction ranges from 0.02% to 4.0%[4,6-9]. Caused by the mediate response of T-lymphocyte, they usually

appear as solid erythematous swelling and tender[10,11] with frequently affected areas being the cheeks, tear trough, and lips[12]. They appear as swelling and soreness 14-21 days after the treatment[6], and, in addition, chronic inflammation can induce granuloma[13]. Covid-19 spike protein has been proposed as a trigger to induce delayed inflammatory reactions, therefore reports have escalated after Covid-19 vaccinations and infections[6,9]. Similar reactions were outlined following flu-like illnesses or gastrointestinal issues[1,10,14].

The phrase Delayed-onset Nodules (DONs) is a descriptive phrase instead of a diagnosis[9]. Nodule formation can take place after treatment with all sorts of fillers. The nodule can be classified as inflammatory (appear days to years after injection and varies due to the etiology) or non-inflammatory (usually seen straight away or soon after injection, commonly technique-related, inappropriate volumes)[1,15]. Histologic examination (biopsy) verifies the diagnosis of a foreign-body granulomatous reaction[1].

Nodules were predominantly recorded as a late event, and most of them were inflammatory. The second and third were hypersensitivity reactions and granulomas, respectively. Nearly all of them began in 2 to 4 months. The lips turned out to be more vulnerable in evolving nodules[8].

Case report

A 28-year-old healthy female patient underwent HA dermal filler (INFINI®, Infini Lab S.R.L., Milano Italia) for her cheek at Plasthetic Clinic Alam Sutera, September 15th 2023, as stated by the author. The injection was performed using a 27G x ½" TW Terumo to lessen the possibility of injection trauma and obtain better accuracy. A retrograde injection technique was performed in the cheek area (CK2 and CK1, MD Codes) with the needle inserted in a bevel down manner with a 90^0 angle to the skin surface, until touching the bone, and withdrawn slightly before depositing the filler placing 0.3 cc (CK2) and 0.2 cc (CK1).

October 31st 2023 (1.5 months after the procedure) she complained about a purplish nodule on her right cheek at the implantation site. Photographs and complete medical history were required (Figure 1).

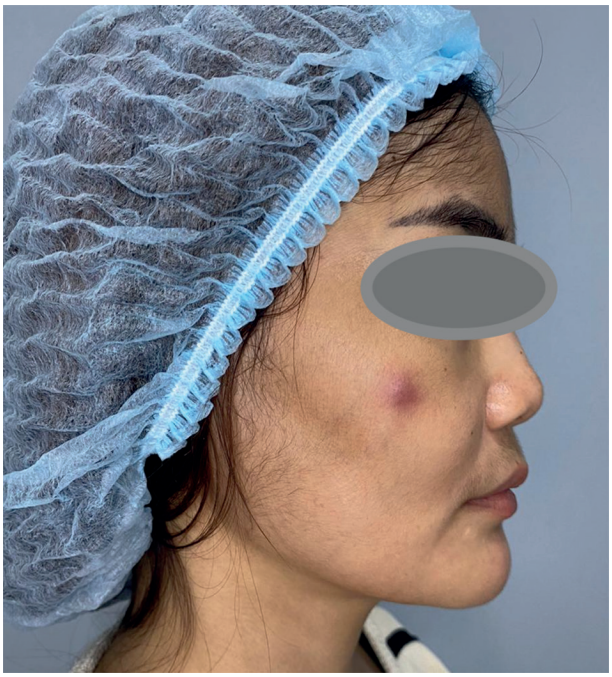

Figure 1. Picture taken three days after occurrence of purplish nodule on her right cheek when patient came to the author's clinic (3rd November 2023).

She did not experience any trauma or infection in the treatment location or facial area, nor did she undergo dental treatment, start any new drugs, or undergo any medical procedures between the cheek treatment and the onset of swelling. Additionally, she has no history of previous treatment with non-absorbable or absorbable fillers.

The physical examination revealed a localized, palpable purplish nodule with no pain or warmth. It was best described as a firm soft tissue nodule. She did not report any further systemic symptoms, nor did she have a history of allergies or autoimmune disease. She experienced gastrointestinal upset a couple of days before the onset of filler inflammation and reported slight itching prior to the appearance of the nodule. She has never had a COVID-19 infection but has received three vaccinations, with the last one administered over a year ago.

The author suggested that the patient undergo blood tests, ultrasonography, cultures, and biopsy before initiating any treatment. However, the patient refused to undergo any examinations of the nodule. Due

to the difficulty in determining the pathophysiological mechanism, a trial of therapy was pursued. The patient was prescribed ciprofloxacin 500 mg twice daily for 7 days, along with fusidic acid cream. No improvement was noted during this time.

Intralesional hyaluronidase, with or without corticosteroids, is advisable to expedite the healing process if nodules are present on the face or if they are causing discomfort for the patient. On November 5, 2023, she received treatment with 400 IU of intralesional hyaluronidase. Initially, the purplish nodule measured 1x1x0.5 cm. Despite not agreeing to receive steroids, the nodule decreased in size to 0.8 cm in diameter. On November 10, 2023, she received an additional 200 IU of intralesional hyaluronidase and 0.05 cc of triamcinolone (10 mg/mL). Three days later, the nodule further reduced in size to approximately 0.4 cm in diameter. Subsequently, she received 0.05 cc of triamcinolone. Photographs were taken to document the reduction in the size of the nodule (Figure 2).

On November 16, 2023, she returned with a nodule measuring approximately 0.1 cm in size. She was administered 0.03 cc of triamcinolone intralesionally. The intralesional triamcinolone was administered in a low dose to prevent skin atrophy. Following the last treatment, the nodule continued to shrink, and her quality of life significantly improved. Photographs were taken to document the progress (Figure 3). A definitive diagnosis could not be reached since a biopsy and histological examination were not performed.

Discussion

HA is a natural part of the human tissue[6]. In its original form, hyaluronic acid (HA) does not typically stimulate an immune response since it is naturally found in the extracellular matrix (ECM) of both humans and animals. Additionally, it lacks species idiosyncrasy and therefore is not usually identified as a foreign material. However, HA filler, when crosslinked, can potentially be recognized as a foreign body by the immune system. Residues of DNA fragments, endotoxins, and proteins are considered potential triggers for an immune response. While there is no direct evidence proving that impurities cause late inflammatory reactions (LIR), it is essential for HA filler products to be pure.

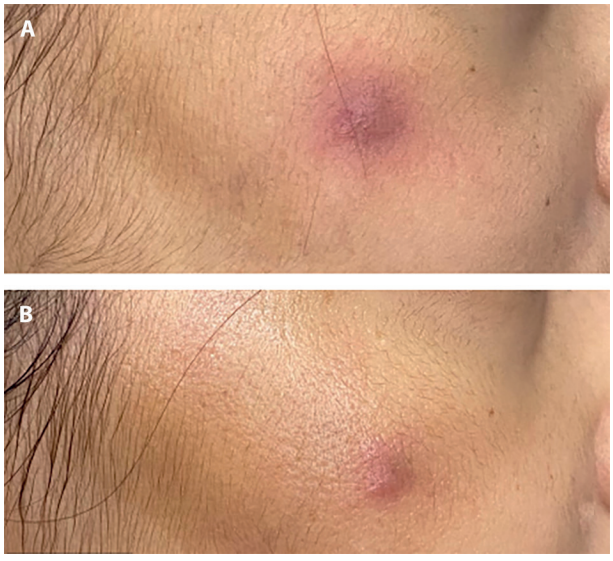

Figure 2. Comparison between: (A) 10th November 2023, after first hyaluronidase. Nodule was decreased from 1 cm to 0.8 cm in diameter. (B) 13th November 2023, after second hyaluronidase and first triamcinolone. Nodule was decreased from 0.8 cm to 0.4 cm in diameter.

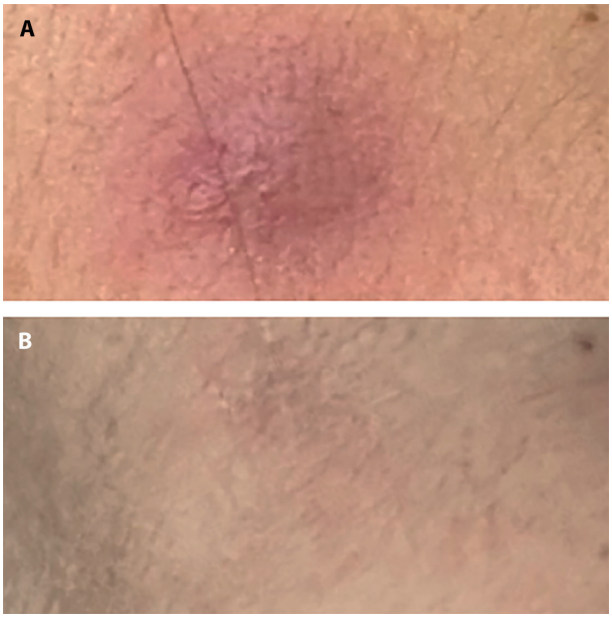

Figure 3. Comparison between: (A) 3rd November 2023, photographs taken on the first visit after onset of delayed onset inflammatory reactions. (B) 21th November 2023, resolution after couple course of intralesional hyaluronidase and triamcinolone.

Countless late complications could happen after HA injections. No common terminology is present to describe such unfavourable reactions. The term was presented by Beleznay et al in 2015; Delayed-Onset Nodules and by Snozzi et al; Late Inflammatory Response Syndrome (LIRS). Another was presented in 2020; Delayed Inflammatory Reactions (DIR) [4].

Frequency of LIR due to the HA dermal filler is unforeseeable and can happen as a late complication from weeks to months after treatment[10]. Several schemes have been proposed, which include the patient's immunologic status (common cold/ depressed immunologic status)[13], systemic infection, trauma, injection method (including filler amount, repetitive procedures, and intramuscular injection), vaccine, anti-HA antibodies, and immunogenic reaction (disintegration of cross-linked agents)[7,10]. Four feasible concepts for such complications, namely foreign-body reactions, infectious (biofilms or else), Type IV hypersensitivity reactions, or adjuvant-based reactions[9].

Foreign-body Reaction (FBR)

Like most foreign properties, injecting fillers can induce various inflammatory responses, called the FBR[9]. The body's response also differs based on the filler's formulation. HA drives more of a lymphocytic penetration, as Calcium hydroxylapatite induces more macrophages[1].

A Foreign Body Granuloma (FBG), enclosed by epithelial macrophages, and different types of giant cells is the result due to failure of productive phagocytosis[9]. It can take place subsequent to a latent period, from couple months up to years following treatment, and any properties described are mainly culture negative[1]. Non-infectious late-onset inflammatory nodules or suspected granuloma terms are applied if there is no histology, because usually the patient is unwilling to give tissue samples[9].

The growth of foreign-body granulomas is believed to be bound by humoral and cell-mediated immune system pathways in addition to presumptively characterize a type IV hypersensitivity reaction to foreign antigens[1]. The very least granuloma develops in 3 months, begins with a minor nodule prior to a solid, frail granuloma; thereafter an asymmetrical, hard granuloma is shaped[13].

In short, the immune granuloma involving T cells of adaptive immunity, and non-immune or FBG involving macrophages. The formation of granulomas due to the immune reaction of chronic inflammations does not always come from infections, but also foreign bodies.

Immune mediated delayed nodules

Delayed onset nodules (DON) typically manifest from weeks to more than a year after treatment, with an average occurrence around 4 months post-treatment. Initially, these nodules are soft and loose, comprising varying degrees of inflammation, and may exhibit a purplish hue due to the obstruction of dermal capillaries[9]. Over time, they tend to become firmer, sometimes including or excluding features such as edema, induration, and erythema in the surrounding area[1,14]. These nodules may occur as single or multiple entities, initially positioned at the site of HA filler injection, but they can also migrate to other sites[1].

The etiology of DON is complex and not yet fully understood[1,16]. Previous studies have suggested that DON may be associated with filler composition and injection technique[4]. Variations in cross-linking level and pattern, particle size, chain lengths, as well as the ratio of high molecular weight HA (HMW-HA) to low molecular weight HA (LMW-HA), contribute to the filler's rheological properties, hydrophilicity, susceptibility to enzymatic degradation, and subsequent clinical duration of effect. HMW-HA is known to have anti-inflammatory effects, whereas LMW-HA, particularly those less than 500 kDA, tends to be pro-inflammatory[1,4,10,14,16]. LMW-HA fillers have been associated with a higher incidence of DON, with reported rates ranging from 1 to 4.25%[9].

Some studies linked the formation of delayed-onset inflammatory nodule with the growth of foreign body granulomas[16]. FBG is easily confused with nodules and delayed hypersensitivity. FBG usually has a 6-24 months onset, growing larger than the injected volume with skin discoloration and edema, while said nodule usually has an onset of several weeks, the same size as injected volume with skin discoloration and edema. Delayed hypersensitivity usually has a 1 month

onset, growing larger than the volume injected with erythema, edema, and indurated nodule.

Infectious processes

During hyaluronic acid (HA) filler injections, it is essential to maintain an aseptic environment, including the use of antiseptic solutions[6,15]. Biofilm refers to a cluster of microbial cells associated with an implant, surrounded by Extracellular Polymeric Substances (EPS) derived from bacteria[9]. The polymeric matrix shields the biofilm complex, enabling its survival, proliferation, and resistance to antibiotics[14].

If the injected filler is tainted with pathogens, it could cause a biofilm[17]. The threshold for microbial infection to occur dramatically decreases from 100,000 to 100 per gram of tissue in the presence of filler[9]. This typically occurs at the site of the first filler injection. Differentiating between inflammation, biofilm, or a low-grade hypersensitivity reaction can be challenging. However, the presence of a red lesion with induration at any time after treatment should raise suspicion of biofilm formation[1,4].

If filler is injected in large volume, the patient's immune response extends longer, thus enhancing the chance of biofilm development. Therefore, a large bolus of HA filler has a greater chance of inducing FBR and other side effects[6,15]. An example of large volume exceeding 0.5 cc per bolus causing a non-inflammatory nodule was reported in an Asian woman after she had chin filler injection[18]. The recommended injection volume should not exceed 0.2 cc per bolus for the facial area[15]. A biofilm is also suspected if endless inflammatory circumstances do not present amelioration with other therapy, and inflammatory nodules reappear following resolution[1]. Studies propose that the most ideal option to obliterate a biofilm is to manage it with antibiotics during the infection process[9].

Autoimmune Syndrome Induced by Adjuvants (ASIA) - Systemic manifestations

A condition that encompasses numerous correlated, immune-mediated diseases appearing in vulnerable individuals is called ASIA. Contact with an adjuvant (such as fillers) leads to hyperstimulation of the immune system, creation of autoantibodies, and occurrence of autoimmune diseases[9]. Symptoms are heterogeneous and not very specific in patients. Individuals with a history of post-vaccination reactions, personal predisposition to autoimmunization (concurrent disease), a record of severe allergic reactions, and autoimmune diseases have a higher risk[4].

In this case, a bolus injection was not given in large volume (not exceeding 0.5 cc) yet causing a late onset nodule. The patient has no history of infection, trauma, allergy, nor any other treatment before and after the injection. Repeated filler injections and LMW-HA have been proposed in increasing the risk of late inflammatory reactions, although in this case she had never had filler injections before (both non-absorbable and absorbable) and the filler injected is HMW-HA.

Undoubtedly the hardest thing of hypersensitivity reactions is that their presence is not feasible to be calculated[12]. Delayed complications especially, are hard to diagnose and manage because of the interval from their last treatment[7]. They do not get better with antihistamines[10]. Differentiating the inflammatory nodule from infectious paths versus immune-mediated, can be hard as in both cases aspirations are usually culture negative[1]. For non-inflammatory nodules, watchful waiting is appropiate[15]. Although no therapy is given, most HA-related granulomas settle within a year[9]. Some resolved impromptu in the absence of any therapy, though others need considerable therapy[16].

The patient wished to have minimal invasive management options to overcome her symptoms as soon as possible without conducting any other examination such as blood test, ultrasonography, and biopsy. Therefore, a therapy trial was the right choice.

The most effective way of treating DON is combination management[15]. The presented path ought to be followed consecutively[1].

1. Patient counselling. Therapy might be lengthy and include treatments[9].
2. First-line therapy with a broad-spectrum oral antibiotic, like ciprofloxacin (500-750 mg bid), clarithromycin (500 mg bid), or doxycycline (100 mg/ day), when contagious cause is alleged. After all signs and symptoms have settled, the treatment is ought to be extended for 14 days[1,19].

3. Begin with oral steroids when systemic edema or induration are present. Steroids are given after the antibiotics. Administer a tapering 7-day course of prednisone (60, 40, 40, 20, 20, 10, and 5 mg) followed by Intralesional (IL) therapy. The course may be extended if the patients relapse as the 7-day course is fulfilled. 0.6 mg oral colchicine every 12 hours might be needed for multiple courses. Lessen to 0.6 mg daily after swelling settles. Keep the dosage for 7 days after the patient is symptomless[1].
4. Remove filler with IL hyaluronidase, it might be advantageous for solitary granulomatous nodules[19]. It is wise to perform this therapy prompt into area of edema or nodule. Commonly it is necessary to have multiple injections (30-100 IU into solitary nodule), repeated every 1 to 2 days until there is no farther amelioration[1,11,15].
5. IL corticosteroid (triamcinolone 10 mg/mL) is given when certain nodules endure, in a small dose to avoid atrophy[1,20].
6. The Mixture of triamcinolone 10 mg/mL (1-3 parts) and 5 fluorouracil (5-FU) 50 mg/mL with lidocaine 2% (7-9 parts) should be given every 14 days for long-lasting or fibrotic lesions insusceptible to steroids alone[1,15].
7. Angiotensin Converting Enzyme (ACE-1) inhibitors may be given due consideration in cases related to Covid-19, as a practical anti-inflammatory approach to reduce dermal inflammation in 72 hours[9,21].
8. Radiofrequency produces arise in hypodermic temperature (up to 42°C), flattening the area or ruining the filler, subsequently settled[14].
9. The last option for refractory nodules is excision. It is not recommended due to its adverse effects, such as scarring and discoloration[8,12,14].

At first, she was given oral antibiotics and topical antibiotic cream, but no improvement was noted. Steroids were not given because the patient did not agree and based on the author's assessment oral steroids was not needed, there were no other external symptoms aside from a localized nodule at the injection site. She was treated with repeated intralesional hyaluronidase and triamcinolone and the nodule shrunk in three weeks.

Raising awareness among patients about the potential for reactions after vaccination, including Covid-19 vaccines, has been proposed by the Italian Society of Aesthetic Medicine. There should be an interval of at least a month between vaccination and treatment[4]. If, following therapy, the symptoms have not settled, a biopsy and tissue culture must be performed. Ultrasound has been regarded as the 'gold standard' due to its ability to identify the precise position of delayed onset nodules (DON), as well as to show the texture of filler[13,20].

In this case, a definitive diagnosis could not be concluded as both the biopsy and histological examination were not done due to the patient's lack of consent. The term "non-infectious late-onset inflammatory nodule" is applied when there is no histological examination available to confirm the nature of the nodule.

Conclusion

Regardless of the assertion that HA fillers are non-immunostimulatory and that side effects are very rare, adverse events do occur. Late inflammation linked to HA fillers does not depend on the brand, and the cause is not clearly known yet. It might be related to the filler substance itself, the patient's medical history (including gastrointestinal, respiratory, and allergic history), and the physician's injection method. It has been suggested that large volume bolus injections increase the risk of causing non-inflammatory nodules, although, in some cases, such as this one, nodule formation can occur with filler volumes not exceeding 0.5 cc. Symptoms are considered to be related to Type IV hypersensitivity reactions, manifesting as firm, erythematous swelling or Foreign Body Reaction (FBR) at least 14 days after the injection. Immediate recognition and appropriate therapy enable effective resolution of inflammatory reactions. The significance of this case report lies in the fact that, to the author's knowledge, only a few cases of Late Inflammatory Reactions (LIR) to HA fillers have been published, and this is the first case reported in Indonesia. The main

limitation of this article is the lack of histological examination to identify macrophages. Therefore, a definitive diagnosis of granulomatous reaction to HA could not be concluded.

Acknowledgment: The author would like to thank the patient for giving permission to publish this information.

Author Disclosure Statement: No conflict of interest.

Funding Information: No funding was granted.

References

1. Funt DK. Treatment of Delayed-onset Inflammatory Reactions to Hyaluronic Acid Filler: An Algorithmic Approach Special Topic. Plast Reconstr Surg Glob Open. 2022; 10(6):e4362.
2. Alawami AZ, Tannous Z. Late onset hypersensitivity reaction to hyaluronic acid dermal fillers manifesting as cutaneous and visceral angioedema. J Cosmet Dermatol. 2020; 20(5):1483–1485.
3. Chung KL, Convery C, Ejikeme I, Ghanem AM. A Systematic Review of the Literature of Delayed Inflammatory Reactions After Hyaluronic Acid Filler Injection to Estimate the Incidence of Delayed Type Hypersensitivity Reaction. Aesthetic Surgery Journal. 2020; 40(5):NP286–NP300.
4. Owczarczyk-Saczonek A, Zdanowska N, Wygonowska E, Placek W. The Immunogenicity of Hyaluronic Fillers and Its Consequences. Clin Cosmet Investig Dermatol. 2021; 14:921–934.
5. International Society of Aesthetic Plastic Surgery (ISAPS). ISAPS Global Survey on Aesthetic/ Cosmetic Procedures in 2022. Available from: https://www.isaps.org/discover/about-isaps/global-statistics/reports-and-press-releases/global-survey-2022-full-report-and-press-releases/ (accessed on 24 January 2024).
6. Lee W, Shah-Desai S, Rho N-K, Cho J. Etiology of Delayed Inflammatory Reaction Induced by Hyaluronic Acid Filler. Arch Plast Surg. 2024; 51(1):20–26.
7. Bhojani-Lynch T. Late-Onset Inflammatory Response to Hyaluronic Acid Dermal Fillers. Plast Reconstr Surg Glob Open. 2017; 5(12):e1532.
8. Cohen JL, Hicks J, Nogueira A, Lane V, Andriopoulos B. Postmarket Safety Surveillance of Delayed Complications for Recent FDA-Approved Hyaluronic Acid Dermal Fillers. Dermatol Surg. 2022; 48(2):220–224.
9. Convery C, Davies E, Murray G, Walker L. Delayed-onset Nodules (DONs) and Considering Their Treatment Following Use of Hyaluronic Acid (HA) Fillers. J Clin Aesthet Dermatol. 2021; 14(7):E59–E67.
10. Rowland-Warmann MJ. Hypersensitivity Reaction to Hyaluronic Acid Dermal Filler following novel coronavirus infection – a case report. J Cosmet Dermatol. 2021; 20(5):1557–1562.
11. Artzi O, Loizides C, Verner I, Landau M. Resistant and Recurrent Late Reaction to Hyaluronic Acid–Based Gel. Dermatol Surg. 2016; 42(1):31–37.
12. Mikkilineni R, Wipf A, Farah R, Sadick N. New Classification Schemata of Hypersensitivity Adverse Effects after Hyaluronic Acid Injections: Pathophysiology, Treatment Algorithm, and Prevention. Dermatol Surg. 2020; 46(11):1404–1409.
13. Koh IS, Lee W, in: Filler-Induced Hypersensitivity Inflammation and Granuloma. Springer Nature, Singapore; 2019 pp.41–51.
14. Tomescu R, Nasturica I, Grigorescu A, Dodan G, Leventer M. Delayed Complications during Aesthetic Procedures after Injection of Hyaluronic Acid Dermal Filler and Their Management. DermatoVenerol (Buc.). 2020; 65(3):19–30.
15. Philipp-Dormston WG, Goodman GJ, Bouelle KD, et al. Global Approaches to the Prevention and Management of Delayed-onset Adverse Reactions with Hyaluronic Acid-based Fillers. Plast Reconstr Surg Glob Open. 2020; 8(4):e2730.
16. Rivers JK. incidence and treatment of delayed-onset nodules after VYC filler injections to 2139 patients at a single Canadian clinic. J Cosmet Dermatol. 2022; 21(6):2379–2386.
17. Ibrahim O, Overman J, Arndt KA, Dover JS. Filler Nodules: Inflammatory or Infectious? a Review of Biofilms and Their Implications on Clinical Practice. Dermatol Surg. 2018; 44(1):53–60.
18. Saputra DI, Kapoor KM. Management of noninflammatory nodule in chin after a large volume bolus injection of hyaluronic acid filler. Dermatol Ther. 2020; 33(3):e13424.
19. Grass J, Majenka P, Sedlaczek OL, Toberer F, Lonsdorf AS. Granulomatous Reaction to Cosmetic Soft Tissue Filler with Late-onset Inflammatory Response. Acta Derm Venereol 2020; 100(15):5850.
20. Artzi O, Cohen JL, Dover JS, et al. Delayed Inflammatory Reactions to Hyaluronic Acid Fillers: A Literature Review and Proposed Treatment Algorithm. Clin Cosmet Investig Dermatol. 2020; 13:371–378.
21. Goodman GJ, McDonald CB, Lim A, et al. Making Sense of Late Tissue Nodules Associated with Hyaluronic Acid Injections. Aesthet Surg J. 2023; 43(6):NP438-NP448.

Correspondence:
Received: 21 December 2023
Accepted: 8 April 2024
Vera Vera
Master Program in Biomedical Science, Anti-Aging Medicine, Faculty of Medicine, Universitas Udayana, 80234, Denpasar, Indonesia
E-mail: radcliffe.vera@gmail.com