OPEN

PRS GLOBAL OPEN

SPECIAL TOPIC

Cosmetic

Treatment of Delayed-onset Inflammatory Reactions to Hyaluronic Acid Filler: An Algorithmic Approach

David K. Funt, MD, FACS

Summary: Hyaluronic acid fillers are one of the most widely used and versatile fillers worldwide. Although traditionally regarded as immunologically inert, many currently available products have been substantially modified to improve longevity and to optimize properties for specific indications. Such modifications, either alone or in combination with other factors (such as the immune status of the patient, immune-triggering events, and bacterial contamination), may lead to the development of late-onset inflammatory nodules in some patients. This article discusses the clinical presentation of late-onset adverse inflammatory reactions to hyaluronic acid injections, describes their likely triggers, and presents the author's treatment algorithm for successful resolution. *(Plast Reconstr Surg Glob Open 2022;10:e4362; doi: 10.1097/GOX.0000000000004362; Published online 20 June 2022.)*

INTRODUCTION

Aesthetic treatments with soft-tissue fillers remain one of the most requested cosmetic procedures.[1] Expanding indications combined with tailored treatments offers individuals a minimally invasive and more affordable means of enhancing their appearance compared with surgical techniques. This has led to rising demand worldwide, despite the COVID-19 pandemic.[1] When injected by well-trained, experienced, knowledgeable practitioners, filler treatment is regarded as a safe procedure, but complications still occur. With more people undergoing treatment, statistically we can expect that more adverse events will be reported.

Nodule development is one such event and can occur after injection with all filler types. Nodules are commonly categorized as inflammatory or noninflammatory. Noninflammatory nodules are typically seen immediately or shortly after implantation and are usually technique-related, secondary to improper volumes and/or placement of the filler. Inflammatory nodules can occur anywhere from days to years after filler placement and vary according to their etiology. The focus of this article will be on delayed-onset inflammatory reactions and nodules as a result of reactions to hyaluronic acid (HA) fillers.

From the Division of Surgery, Department of Plastic Surgery, Icahn School of Medicine, Mount Sinai Hospital, New York, N.Y.

Received for publication March 1, 2022; accepted April 11, 2022.

Presented at the American Society for Aesthetic Plastic Surgery (ASAPS) Aesthetic Meeting, Miami Beach, Fla., April 29–May 3, 2021.

DOI: 10.1097/GOX.0000000000004362

ETIOLOGY OF DELAYED-ONSET INFLAMMATORY NODULES

There are three schools of thought related to the etiology of nodular inflammatory reactions in the medical literature: foreign-body reactions; immune-mediated, delayed reactions (delayed hypersensitivity); and infectious processes (or immune processes initiated only with the presence of bacterial contamination).[2] Regardless of etiology, when biopsies of inflammatory nodules have been performed, histologic examination invariably confirms a diagnosis of a foreign-body granulomatous response.

Two broad forms of well-defined granuloma exist, defined by their etiology: foreign-body giant cell granulomas without an adaptive immune response, and immune granulomas.

Foreign-body Granulomatous Delayed Nodules

All injected fillers are foreign to the immune system, and inflammation around an implant particle is a normal host reaction, which eventually leads to resorption in the case of biodegradable fillers.[3] The host response can range from limited macrophage infiltration to a foreign-body granulomatous reaction with fibrosis.[2] The body's response also varies by the composition of the filler. Calcium hydroxylapatite generates more of a macrophage response, while HA generates more of a lymphocytic infiltrate. The intensity of the reaction will depend on how immunologically inert the injected material is.[4] This is determined by numerous factors, including the composition and quantity of the material involved, the shape and size of the injected particles, and its biodegradability, and in the case of HA fillers, the concentration, the degree of

Disclosure: *Dr. Funt is a paid consultant in adverse events at Galderma, a paid consultant and speaker at Merz, and a paid consultant in adverse events at Revance. No funding was received for this study.*

cross-linking, and the proprietary HA structure and cross-linking technique.[4]

Foreign-body granuloma is an inflammatory response to exogenous material that has a low potential for degradation by macrophages.[5] It can occur after a latent period, which can be several months to years after injection, and any material expressed is generally culture negative. They present clinically as red, indurated papules, plaques, or nodules. Additional clinical findings may include ulceration and erythema.[6]

The development of foreign-body granulomas is thought to be under the control of both the humoral and cell-mediated immune system pathways and most likely represents a type IV hypersensitivity reaction to a foreign antigen (that antigen may be from bacteria that have contaminated the filler).[7] The purpose of a foreign-body granulomatous reaction is to encapsulate and isolate the foreign material that cannot immediately be removed by enzymatic breakdown or phagocytosis. It is defined by the presence of mononuclear leukocytes, specifically histiocytes (macrophages), which respond to various chemical mediators of cell injury. When observed under light microscopy, the activated histiocytes appear as epithelioid cells with round to oval nuclei, often with irregular contours and abundant granular eosinophilic cytoplasm with indistinct cell borders.[8] They may also coalesce to form multinucleated giant cells. A true granulomatous reaction can only be confirmed histologically. Phagocytized material may remain sequestered in the macrophage. Activated macrophages attract fibroblasts and signal them to produce collagen. Erythematous nodules that persist for months and which become firmer over time due to fibrosis likely are foreign-body granulomas (Fig. 1).

IMMUNE-MEDIATED DELAYED NODULES

Delayed inflammatory nodules typically present at weeks to over a year after injection (most frequent at around 4 months). They are firm to hard, with or without surrounding edema and/or induration and erythema. The nodules may be solitary or multiple and are located at the sites of HA filler injection. Alternatively, they may be solitary at the time of initial injection and then migrate to other sites of injection. The author has also observed another nodule emerging, as one resolves. The nodules are generally not painful and may or may not be visible. They are most frequent with dermal/subdermal injections, followed by those in subcutaneous fat, and then preperiosteal injections. Lips are also a frequent location for delayed-onset nodule formation (Fig. 2).

Takeaways

Question: How do late-onset adverse inflammatory reactions to hyaluronic acid filler injections arise? What is their clinical presentation? How can they be managed?

Findings: Immune-triggering events, bacterial contamination, and the physiochemical structure of the filler at various stages of degradation may individually or in combination cause a delayed inflammatory response or delayed-onset nodules.

Meaning: The treatment algorithm presented has been developed with years of experience, and it has proven reliable for the successful resolution of delayed-onset inflammatory reactions.

The etiology of delayed nodules is still debated, but is likely multifactorial.[9] It is the author's opinion that these reactions are an interaction between the physiochemical characteristics of the filler at that point in its degradation, the patient's immune characteristics at the time of the reaction, and a degree of bacterial contamination that occurred at the time of injection.

In its native form, HA is not immunostimulatory because it is found in the extracellular matrix of human and animal dermis and has no species specificity.[10] As a result, immune responses to HA fillers were initially thought to be caused by impurities such as DNA fragments, endotoxins, and proteins. Before 1999, the reported rate of delayed inflammatory reactions to HA fillers was 0.7%.[11] Following manufacturing improvements to increase the purity of the HA products, the rate subsequently began to decline to a level of around 0.2%. Although the antigenicity of the filler still plays a role, recent research suggests that other factors may also be involved.

Each vendor has proprietary techniques used in the manufacturing of their fillers.[12] These cause differences in the degree and pattern of cross-linking, particle size, and chain lengths, and thus the blend of high molecular weight HA (HMW-HA) and low molecular weight HA (LMW-HA) that comprise their products. These characteristics are responsible for the fillers' rheological characteristics, hydrophilicity, and resistance to enzymatic degradation, and resultant duration of clinical effect. For example, Vycross technology produces a hybrid complex comprising a high proportion (approximately 90%) of short-chain

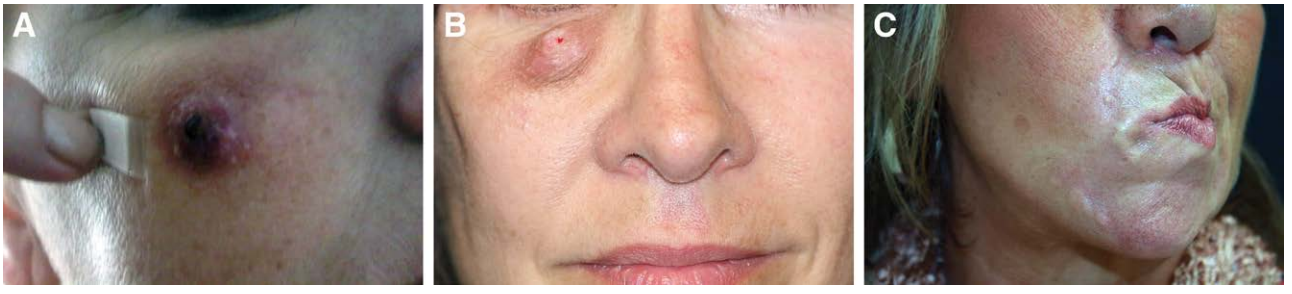

Fig. 1. Examples of inflammatory nodules, post filler. All are confirmed as foreign-body granulomas, on biopsy (A-C).

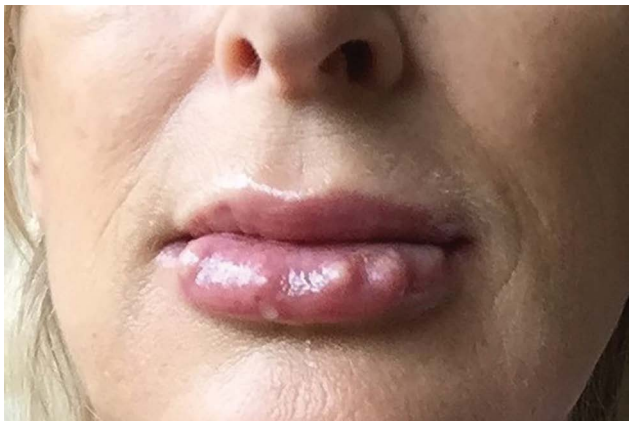

Fig. 2. Late-onset lip nodules 4 months after Volbella injection.

LMW-HA (according to Allergan, chain lengths are not shorter than 500 kDa) cross linked with a low proportion (approximately 10%) of long-chain HMW-HA (>1 MDa).[13] HA products manufactured with this technology, such as Juvederm Voluma XC 20 mg/mL (VYC-20), Juvederm Vollure XC 17.5 mg/mL (VYC-17.5), and Juvederm Volbella XC 15 mg/mL (VYC-15), have varying properties depending on the HA concentration and ratio of long- and short-HA chains.[13] Although no safety concerns were raised in the initial 6-month trials with these products, a number of retrospective chart reviews have subsequently documented reports of delayed-onset nodules with rates ranging from 0.5%[14] to 0.98%, which is higher than that seen with other HA fillers.[15]

Native HA has numerous biological and physiological functions.[16,17] Its abundance and high turnover—nearly one-third is removed and replaced each day[18]—suggest a highly regulated molecule with functional importance. Endogenous HA is degraded by a family of hyaluronidase enzymes to progressively smaller fragments, with the different-sized HA molecules having varied biological effects.[16,19] It has been shown that intact HMW-HA tends to exert anti-inflammatory effects, whereas mid-sized and small fragments have pro-inflammatory effects, depending on which cell-surface receptor they bind to.[20,21] Smaller HA molecules (usually with an average molecular weight ranging from 5 to 20 kDa) are often promoters of early inflammatory responses,[22] which activate signaling cascades to prompt cell migration and proliferation toward repair.[23] In vitro studies suggest that this may also depend on the existing inflammatory state, with LMW-HA not directly provoking macrophage-mediated inflammatory reactions when the inflammatory state is extremely low (eg, in the presence of very low endotoxin levels).[24,25] The LMW HA found in the fillers sold in the US market today are greater than 500 kDa and likely do not produce an inflammatory response, but these fragments change in size upon degradation. In addition, the presence of even small degrees of bacterial contamination can increase the inflammatory potential of the injected filler. This effect, alone or in combination with an immune-triggering event, may produce an inflammatory response. Examples of late-onset nodules after injection of various HA products are shown in Figure 3.

Potential triggers for the onset of delayed inflammatory nodules include local trauma, infections, dental cleanings, and vaccine administration.[26] The latter has been at the forefront of attention recently because of reports of delayed inflammatory reactions to HA dermal fillers following exposure to COVID-19 or following vaccination against the virus.[27–29] Similar reactions have been reported after flu-like illness or gastrointestinal upset.[30,31] It is the author's opinion that these responses are not a result of bacterial seeding, but rather due to heightening of the immune status of the individual.

INFECTIOUS PROCESSES

In some cases, the development of chronic nodules and granulomatous inflammation after filler injections can be attributed to bacterial, fungal, polymicrobial, or viral infection. In vitro assays have shown that filler materials, including HA, can support the growth of bacterial biofilms.[32] Biofilms occur when injected filler material becomes contaminated with bacteria.[33] This generally takes place at the time of initial filler injection. It can also occur by reactivating a previously quiescent biofilm that formed after a previous filler treatment or after a bacteremia (following dental cleaning, upper respiratory infection, urinary tract infection, and so on), but this is less likely.

Biofilms consist of densely packed communities of bacteria that adhere to a living structure or an inert surface. They surround themselves with secreted polymers and, consequently, are very difficult to treat. Once mature, a

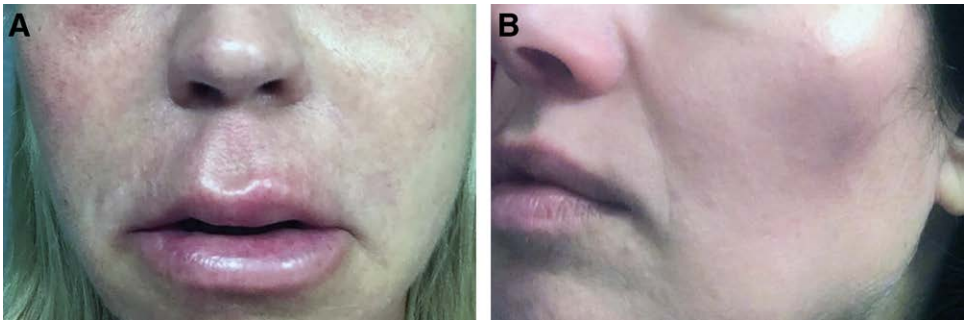

Fig. 3. Examples of late-onset hyaluronic acid nodules. A, 4 months after injection of Restylane, Refyne, and Defyne. B, 4 months after Voluma injection. Both of these reactions had initial induration and edema and responded to the protocol presented.

biofilm gives rise to a low-grade chronic infection that is resistant to antibiotics and difficult to culture.[34] When activated, for example by trauma from a subsequent dermal filler procedure, the biofilm can cause a local infection, a systemic infection, or a granulomatous or inflammatory response. Distinguishing inflammation due to a bacterial biofilm from a low-grade hypersensitivity reaction is difficult. If an erythematous and/or indurated area appears at any time after treatment, regardless of duration, a biofilm should be suspected.[34] Persistent inflammatory conditions not showing improvement with other therapy and inflammatory nodules that recur after resolution may also indicate a biofilm.

It is the author's opinion that many filler adverse events, including nodules and persistent, fluctuating edema and erythema, are, at least in part, caused by bacterial contamination. This bacterial contamination does not have to be sufficient to cause frank infection or the formation of a biofilm but can be sufficient to cause the patient's immune system to recognize and react to the injected filler.[35] Immune-triggering events (as described above), bacterial contamination, and the physiochemical structure of the filler at that point in its degradation—individually or in combination—cause a delayed inflammatory response or delayed-onset nodules.

AUTHOR'S TREATMENT ALGORITHM

The author has had the privilege of working as a consultant for many years for Galderma, Allergan, Merz, and Revance, assisting in the management of adverse events, including delayed-onset inflammatory reactions and nodules. This algorithm was developed over time, based on clinical efficacy and a literature review.

It can be difficult to distinguish between inflammatory nodules that result from infectious processes versus those that are immune-mediated as in both cases, and aspirations taken from the lesions are usually culture negative.

The following steps should be performed sequentially.

1. If there is warmth, tenderness, erythema, induration, or edema, an infective etiology should be suspected. First-line treatment is with a broad-spectrum oral antibiotic, such as ciprofloxacin, clarithromycin, or doxycycline. If a significant response to antibiotics is seen, this indicates an infective process, and treatment should be continued for 2 weeks after all signs and symptoms have resolved. More frequently, a minimal effect is seen (antibiotics can exert an anti-inflammatory effect).
2. If generalized edema or induration is present, the patient should be started with oral steroids, unless an infection is suspected. In the latter case, steroids should only be administered after the antibiotics have been initiated. The author uses a tapering 7-day course of prednisone (60, 40, 40, 20, 20, 10, and 5 mg). The above treatment allows the individual nodules to become delineated for subsequent intralesional treatment. Also, in "hot" cases where nodules are increasing in size or number, or when they wax and wane, oral steroids seem to be the most effective therapy. In some cases, the patients flare when the 7-day course is completed and, here, a longer course of steroids may be necessary. When multiple courses of steroids are necessary, the author has had good results with the use of 0.6-mg oral colchicine every 12 hours. This can be reduced to 0.6 mg daily after swelling resolves. Maintain the daily colchicine dose for a week after the patient is asymptomatic.
3. Concurrently, hyaluronidase should be injected to remove the HA filler because this is what initiated the process. It is recommended that this be performed early into the areas of edema or nodularity. This frequently requires multiple injections of hyaluronidase, repeated every 1 to 2 days until no further improvement is noted.[36] It must be remembered that hyaluronidase is an enzyme and it must be in direct physical contact with its substrate to work; so after injection, massage should be performed. As the exact location of the HA cannot be determined, hyaluronidase should be liberally used. Hyaluronidase is a safe product and should not be diluted before injection. It will not cause any loss of native HA because this is quickly replaced by the body.
4. If any discrete nodules persist, they should be treated with intralesional corticosteroid injection (triamcinolone 10 mg/mL). Efforts should be made to keep the injected steroid within the nodule to avoid atrophy of the surrounding skin and soft tissue that may persist long after the nodule has resolved. Intralesional steroid injection can be performed at 2-week intervals.
5. Long-standing or fibrotic lesions resistant to steroid alone should be treated with a combination of triamcinolone 10 mg/mL and 5 fluorouracil (5-FU) 50 mg/mL with lidocaine 2%. 5-FU, a pyrimidine analog, acts to decrease fibroblasts' collagen production, reducing the fibrosis through its antimetabolite function. It also has direct antibacterial and anti-inflammatory effects. The combination also reduces the amount of steroid injected and thereby, the risk of steroid-related adverse events such as tissue atrophy and telangiectasia.[37] Clindamycin can also be added to the mix if there is a strong suspicion of a biofilm. Injections should be performed at 2-week intervals. Once the practitioner feels that an adequate quantity of triamcinolone has been successfully delivered into the nodule (initially nodules are firm, making intralesional injection difficult), the triamcinolone should be discontinued, and subsequent injections should contain 5-FU and lidocaine alone. The author uses a mixture of 0.4 cm^3 of 10-mg/mL triamcinolone and 0.4 cm^3 of 50-mg/mL 5-FU with 0.2 cm^3 of 2% lidocaine in a 1-cm^3 syringe with a 30-G needle.
6. Small nodules that are asymptomatic and nonvisible do not have to be treated because they seem to resolve over time.

High-frequency ultrasound has been used to evaluate the nature of these responses and to more accurately deliver intralesional therapy. The author is now using this technology in his practice and anticipates that it will

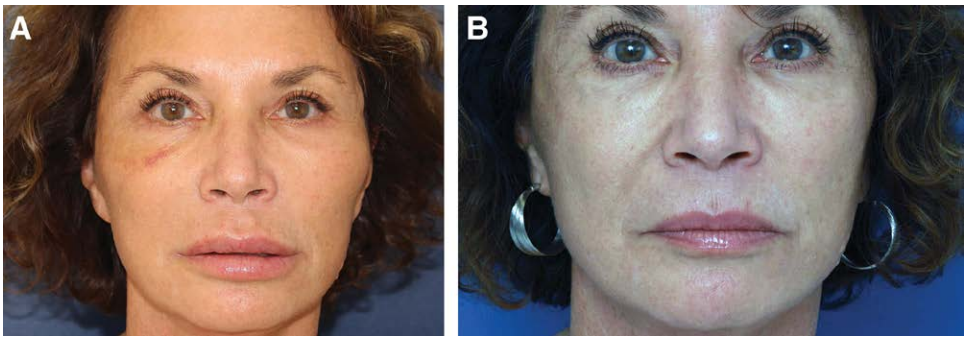

Fig. 4. Example of delayed onset nodules after injection of Voluma and Volbella and their resolution after treatment. A, Late-onset reaction 3.5 months after Vollure and Voluma injections. B, Total resolution after treatment following the discussed algorithm.

provide further insights because with this technique one could visualize the filler location, the characteristics of the response, and the real-time response to therapy.

Figure 4 shows an example of a delayed-onset nodule and its resolution after treatment.

DISCUSSION

Delayed-onset inflammatory reactions are rare events occurring with an incidence of less than 1%. However, as the popularity and acceptance of soft-tissue fillers continues to grow, so too will the occurrence of adverse events. Although delayed-onset reactions may not be the most feared complication of treatment, they nevertheless can be disfiguring and, until their resolution, can significantly affect patients' quality of life.[38]

HA fillers have traditionally been regarded as immunologically inert because of their presence in all living organisms and lack of tissue specificity. However, the degree of cross-linking technology used by manufacturers to improve longevity and modify properties of the individual HA fillers varies considerably. The extent to which the HA molecule can be modified before it is no longer recognized as native HA is not known, but it is conceivable that significant alteration could increase the risk of an inflammatory reaction. Inherent qualities of the filler or its degradation products may be proinflammatory. The author has seen cases in which two fillers were injected in the same patient, by the same injector, at the same session, and only one of the fillers produced an inflammatory response. In other cases, the patient has received the particular filler in the past without adverse response. The immune status and immune-triggering events seem to be etiologic in some cases, though none can be discerned in others. The role of bacterial contamination can never be ignored. Biopsy specimens can only rarely be obtained and examined and, as a result, much of our understanding of these events remains based on clinical presentation and response to treatment. Recently published recommendations for the management of delayed-onset nodules[39] reflect those published by the author some years ago, which continue to be relevant.[6]

The treatment algorithm presented here has been successfully used by the author and practitioners with whom he has consulted for many years. Patients should be seen frequently and should be emotionally supported by the injector until resolution has occurred. Although multiple treatment sessions are frequently required, all cases that the author has been involved with have eventually been resolved.

David K. Funt, MD, FACS
19 Irving Place
Woodmere, NY 11598
E-mail: dkfuntmd@gmail.com

PATIENT CONSENT

The patient provided written consent for the use of her image.

REFERENCES

1. The Aesthetic Society. Aesthetic plastic surgery national databank statistics 2020. Available at https://cdn.theaestheticsociety.org/media/statistics/aestheticplasticsurgerynationaldatabank-2020stats.pdf. Published 2020. Accessed August 12, 2021.
2. Alijotas-Reig J, Fernández-Figueras MT, Puig L. Late-onset inflammatory adverse reactions related to soft tissue filler injections. *Clin Rev Allergy Immunol.* 2013;45:97–108.
3. Lee JM, Kim YJ. Foreign body granulomas after the use of dermal fillers: pathophysiology, clinical appearance, histologic features, and treatment. *Arch Plast Surg.* 2015;42:232–239.
4. Lemperle G, Gauthier-Hazan N, Wolters M, et al. Foreign body granulomas after all injectable dermal fillers: part 1. Possible causes. *Plast Reconstr Surg.* 2009;123:1842–1863.
5. Anderson JM, Rodriguez A, Chang DT. Foreign body reaction to biomaterials. *Semin Immunol.* 2008;20:86–100.
6. Funt D, Pavicic T. Dermal fillers in aesthetics: an overview of adverse events and treatment approaches. *Clin Cosmet Investig Dermatol.* 2013;6:295–316.
7. Marwa K, Kondamudi NP. Type IV hypersensitivity reaction. *StatPearls* [Internet]. Treasure Island, Fla. StatPearls Publishing; 2021. Available at https://www.ncbi.nlm.nih.gov/books/NBK562228. Accessed April 26, 2021.
8. Shah KK, Pritt BS, Alexander MP. Histopathologic review of granulomatous inflammation. *J Clin Tuberc Other Mycobact Dis.* 2017;7:1–12.
9. Decates T, Kadouch J, Velthuis P, et al. Immediate nor delayed type hypersensitivity plays a role in late inflammatory reactions after hyaluronic acid filler injections. *Clin Cosmet Investig Dermatol.* 2021;14:581–589.

10. Owczarczyk-Saczonek A, Zdanowska N, Wygonowska E, et al. The immunogenicity of hyaluronic fillers and its consequences. *Clin Cosmet Investig Dermatol.* 2021;14:921–934.
11. Artzi O, Loizides C, Verner I, et al. Resistant and recurrent late reaction to hyaluronic acid-based gel. *Dermatol Surg.* 2016;42:31–37.
12. Herrmann JL, Hoffmann RK, Ward CE, et al. Biochemistry, physiology, and tissue interactions of contemporary biodegradable injectable dermal fillers. *Dermatol Surg.* 2018;44(suppl 1):S19–S31.
13. Bernardin A, Pierre S, Pather S, et al. VYCROSS: an innovative dermal filler technology. Paper presented at: Anti-aging Medicine European Congress (AMEC); October 11-12, 2013; Paris, France.
14. Beleznay K, Carruthers JD, Carruthers A, et al. Delayed-onset nodules secondary to a smooth cohesive 20 mg/mL hyaluronic acid filler: cause and management. *Dermatol Surg.* 2015;41:929–939.
15. Humphrey S, Jones DH, Carruthers JD, et al. Retrospective review of delayed adverse events secondary to treatment with a smooth, cohesive 20-mg/mL hyaluronic acid filler in 4500 patients. *J Am Acad Dermatol.* 2020;83:86–95.
16. Stern R, Asari AA, Sugahara KN. Hyaluronan fragments: an information-rich system. *Eur J Cell Biol.* 2006;85:699–715.
17. Maytin EV. Hyaluronan: more than just a wrinkle filler. *Glycobiology.* 2016;26:553–559.
18. Fraser JR, Laurent TC, Laurent UB. Hyaluronan: its nature, distribution, functions and turnover. *J Intern Med.* 1997;242:27–33.
19. Stern R. Devising a pathway for hyaluronan catabolism: are we there yet? *Glycobiology.* 2003;13:105R–115R.
20. Petrey AC, de la Motte CA. Hyaluronan, a crucial regulator of inflammation. *Front Immunol.* 2014;5:101.
21. Scheibner KA, Lutz MA, Boodoo S, et al. Hyaluronan fragments act as an endogenous danger signal by engaging TLR2. *J Immunol.* 2006;177:1272–1281.
22. D'Agostino A, Stellavato A, Busico T, et al. *In vitro* analysis of the effects on wound healing of high- and low-molecular weight chains of hyaluronan and their hybrid H-HA/L-HA complexes. *BMC Cell Biol.* 2015;16:19.
23. Maneiro E, de Andres MC, Fernández-Sueiro JL, et al. The biological action of hyaluronan on human osteoartritic articular chondrocytes: the importance of molecular weight. *Clin Exp Rheumatol.* 2004;22:307–312.
24. Lyle DB, Breger JC, Baeva LF, et al. Low molecular weight hyaluronic acid effects on murine macrophage nitric oxide production. *J Biomed Mater Res A.* 2010;94:893–904.
25. Baeva LF, Lyle DB, Rios M, et al. Different molecular weight hyaluronic acid effects on human macrophage interleukin 1β production. *J Biomed Mater Res A.* 2014;102:305–314.
26. 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.
27. Rice SM, Ferree SD, Atanaskova Mesinkovska N, et al. The art of prevention: COVID-19 vaccine preparedness for the dermatologist. *Int J Womens Dermatol.* 2021;7:209–212. .
28. Munavalli GG, Guthridge R, Knutsen-Larson S, et al. "COVID-19/SARS-CoV-2 virus spike protein-related delayed inflammatory reaction to hyaluronic acid dermal fillers: a challenging clinical conundrum in diagnosis and treatment." *Arch Dermatol Res.* 2022;314:1–15.
29. Rowland-Warmann MJ. Hypersensitivity reaction to hyaluronic acid dermal filler following novel coronavirus infection—a case report. *J Cosmet Dermatol.* 2021;20:1557–1562.
30. Bhojani-Lynch T. Late-onset inflammatory response to hyaluronic acid dermal fillers. *Plast Reconstr Surg Glob Open.* 2017;5:e1532.
31. Turkmani MG, De Boulle K, Philipp-Dormston WG. Delayed hypersensitivity reaction to hyaluronic acid dermal filler following influenza-like illness. *Clin Cosmet Investig Dermatol.* 2019;12:277–283.
32. Saththianathan M, Johani K, Taylor A, et al. The role of bacterial biofilm in adverse soft-tissue filler reactions: a combined laboratory and clinical study. *Plast Reconstr Surg.* 2017;139:613–621.
33. Ibrahim O, Overman J, Arndt KA, et al. Filler nodules: inflammatory or infectious? A review of biofilms and their implications on clinical practice. *Derm Surg.* 2018;44:53–60.
34. Dayan SH, Arkins JP, Brindise R. Soft tissue fillers and biofilms. *Facial Plast Surg.* 2011;27:23–28.
35. Hee C, Messina D. Role of bacteria on the in vitro immune response to hyaluronic acid fillers. *J Am Acad Dermatol.* 2018;79(suppl 1):AB248.
36. Brody HJ. Use of hyaluronidase in the treatment of granulomatous hyaluronic acid reactions or unwanted hyaluronic acid misplacement. *Dermatol Surg.* 2005;31(8 Pt 1):893–897.
37. Wiest LG, Stolz W, Schroeder JA. Electron microscopic documentation of late changes in permanent fillers and clinical management of granulomas in affected patients. *Dermatol Surg.* 2009;35(suppl 2):1681–1688.
38. Düker D, Erdmann R, Hartmann V, et al. The impact of adverse reactions to injectable filler substances on quality of life: results from the Berlin Injectable Filler Safety (IFS) – study. *J Eur Acad Dermatol Venereol.* 2016;30:1013–1020.
39. King M, Bassett S, Davies E, et al. Management of delayed onset nodules. *J Clin Aesthet Dermatol.* 2016;9:E1–E5.