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Abstract

Background: The pathogenesis of delayed-onset tissue nodules (DTNs) due to hyaluronic acid (HA) injections is uncertain.
Objectives: To formulate a rational theory for DTN development and their avoidance and treatment.
Methods: A multidisciplinary and multicountry DTN consensus panel was established, with 20 questions posed and consensus sought. Consensus was set at 75% agreement.
Results: Consensus was reached in 16 of 20 questions regarding the pathogenesis of DTNs, forming the basis for a classification and treatment guide.
Conclusions: The group believes that filler, pathogens, and inflammation are all involved in DTNs and that DTNs most likely are infection initiated with a variable immune response. Injected filler may incorporate surface bacteria, either a commensal or a true pathogen, if the skin barrier is altered. The initially high molecular weight HA filler is degraded to low molecular weight HA (LMWHA) at the edge of the filler. Commensals positioned within the filler bolus may be well tolerated until the filler is degraded and the commensal becomes visible to the immune system. LMWHA is particularly inflammatory in the presence of any local bacteria. Commensals may still be tolerated unless the immune system is generally heightened by viremia or vaccination. Systemic pathogenic bacteremia may also interact with the filler peripheral LMWHA, activating Toll-like receptors that induce DTN formation. Given this scenario, attention to practitioner and patient hygiene and early systemic infection treatment deserve attention. Classification and treatment systems were devised by considering each of the 3 factors—filler, inflammation, and infection—separately.

Level of Evidence: 4

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The etiology and pathogenesis of delayed tissue nodules from injected hyaluronic acid (HA) have been a source of confusion for much of this current century.[1,2] Many experts in this field extol a view on pathogenesis with vigor to form a logical treatment regimen, yet there are as many strident views as there are experts.[3,4] True agreement on pathophysiology and best management has not been reached despite multiple consensus meetings and guidelines. Often disagreements among key opinion leaders considerably dilute the utility of any published protocols. There is little cohesive understanding of what causes the different scenarios of delayed tissue nodules, and a resultant logical treatment guideline has not found completion.[5–9] To this end, in 2019, just before the COVID-19 pandemic was upon us, a consensus group was convened in Melbourne, Australia, at a meeting of the Australasian Society of Cosmetic Dermatologists to consider 3 main aspects of nodule formation: the filler itself, the patient's immune reaction to HA, and the possibility of coexistent infection or colonization. This consensus group was restarted in 2022, posing 18 questions and further dividing question 11 into 11a and 11b and question 18 into 18a and 18b after the first round of consensus establishment.

Because most fillers injected and filler reactions seen are due to hyaluronic acid (HA) in Australia and New Zealand, we felt that the discussion should begin with the nature of the hyaluronic acid moiety itself. Hyaluronic acid is a glycosaminoglycan defined by the disaccharide unit (GlcNacb1-4GlcAb1-3), which is neither sulphated nor covalently linked to protein. Native hyaluronic acid is synthesized on the inside of the cell membrane and translocated outside the cell where long 5000 kDa chains are created by repeating the disaccharide thousands of times.[10] All endogenous hyaluronic acid starts out as high molecular weight hyaluronic acid (HMWHA) because of this process.

Although there is no real consensus as to what constitutes low molecular weight and high molecular weight hyaluronic acid, an accepted definition may be that high molecular weight hyaluronic acid is greater than 1000 kDa. In skin most hyaluronic acid exists natively in the papillary dermis, which decreases with endogenous and exogenous (sun exposure) aging over the years. In youth, there is also some hyaluronic acid high up in the epidermis produced by keratinocytes, but this decreases with age.

Hyaluronic acid is eventually degraded by hyaluronidase 1 and 2 (Hyal-1 and Hyal-2) and reactive oxygen species into 20 kDa fragments extracellularly and then undergoes endocytosis and is dropped into lysosomes where it is further degraded by Hyal-1. In injured tissue, reactive oxygen species free radicals will also decompose hyaluronic acid polymers into smaller fragments for endocytosis. As will be explained further below, these methods of degradation are likely to be critically important in the ongoing process that we feel fuels the delayed-onset nodule situation.

The immune system is central with respect to hyaluronic acid metabolism and nodules. Hyaluronic acid is not an inert molecule but interacts widely with the body, signaling

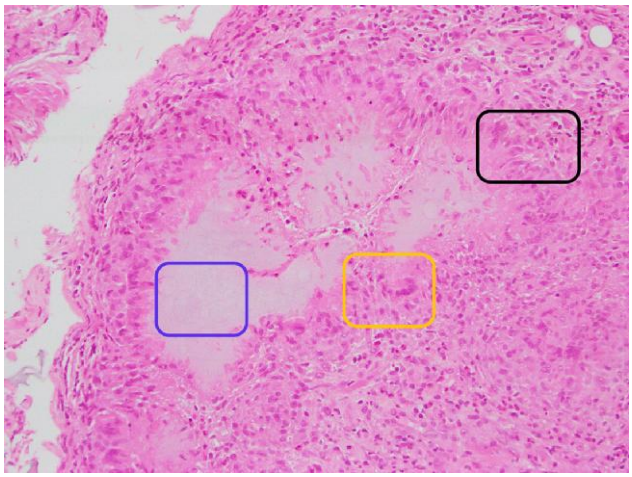

Figure 1. Inflammatory nodule showing filler by the blue rectangle (blue amorphous material) surrounded by chronic inflammatory cells comprising epithelial cells, macrophages, lymphocytes (black rectangle), and giant cells (yellow rectangle).

many complex molecular interactions.[11,12] There are several pathways for recognition of hyaluronic acid by the immune system and other cells. Clustered CD44 receptors produce anti-inflammatory cytokines in conjunction with their interaction with HMWHA and inhibit the Toll-like receptor activity and degradation of bound hyaluronic acid.[13,14] High molecular weight hyaluronic acid binding to CD44 also affects cell motility, cell growth, and longevity. The RHAMM receptor binding of HMWHA is important in cell motility and wound healing. The presence of HMWHA (more than 1000 kDa) signals that all is well with the world and intrinsically inhibits inflammation.

However, fragments of hyaluronic acid below this size are variably proinflammatory. These smaller HA fragments can activate an array of receptors including Toll-like 2 and 4 (TLR2 and TLR4), which form part of the early warning or innate immune system engaging immunologically active cells to initiate an inflammatory response.[15] This system is activated nonspecifically by viruses, certain bacteria, and other endogenous agents and is highly inflammatory. Histologically it appears that inflammation is occurring at the periphery of implanted filler material (Figure 1).

METHODS

A literature search was conducted, searching consensus papers and original manuscripts centering on the theories of delayed nodule development and the delay in their onset and subsequent treatment employing the Ovid MEDLINE (National Library of Medicine, National Institutes of Health; Bethesda, MD) and Google Scholar (Google; Mountain View, CA) databases. Search terms included

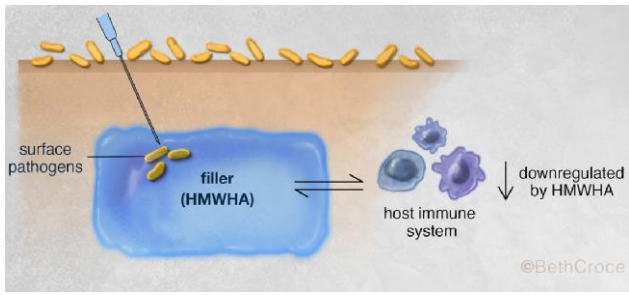

Figure 2. Day of implantation. All fillers are high molecular weight hyaluronic acid (HMWHA) at time of implantation. HMWHA is anti-inflammatory even in the presence of implanted bacteria. Illustration created by and published with permission from Beth Croce.

"delayed filler nodules," "delayed dermal filler nodules," "filler nodules," "hyaluronic acid nodules," "filler complications," "hyaluronic acid injection complications," and "dermal filler complications." A theory was then developed during the consensus meeting held in September 2019 and its elements discussed in a modified Delphi method with the consensus group. These centered on the theories of delayed nodule development and the theories behind the delay experienced with many nodule complications as well as treatment options. Once this investigation was completed, the consensus group tasked itself with developing a simple grading system and logical treatment options for these nodules.

Consensus Development

To develop a unifying theory of delayed nodule development a series of questions were asked of the consensus group (Table 1). These questions were discussed in 2019 and posed formally in 2022 to a consensus group of 25 plastic surgeons, dermatologists, and aesthetic medical and nursing practitioners from Australia, New Zealand, the UK, and the USA.

A degree of background information was presented to the panel to aid their deliberations on these questions, which is outlined in the explanatory notes in Appendix A (see supplemental material online at www.aestheticsurgeryjournal.com).

The consensus questions comprising the survey are found in Appendix B (see supplemental material online at www.aestheticsurgeryjournal.com). The survey was conducted solely online with a modified Delphi approach. Modifications were made to questions after group feedback and the original set and final set of questions are shown in Appendix B.

RESULTS

The answers to the posed questions showed varying degrees of agreement. Consensus was determined to have

Table 1. Results of Consensus Questions and Degree of Agreement

Question number	Question	Agreement number (%)	Consensus achieved (75% or greater)
1	Does the consensus group believe that the filler, pathogens, and inflammatory factors are all involved in many of the tissue filler nodules?	25 (100%)	Yes
2	Does the consensus group believe that a very plausible explanation for other hyaluronic acid–associated delayed nodules is that most late-onset nodules are infection initiated with a variable immune response? This requires a hyaluronic acid tissue filler, a pathogen, and an immune response.	23 (92%)	Yes
3	Does the consensus group believe that surface bacteria are involved in some late nodule formation and that the quality of skin barrier function, skin commensal carriage, and the cleanliness of the practitioner's procedure are all variables that may dictate this likelihood?	24 (96%)	Yes
4	Does the consensus group believe that bolus size is important in the likelihood of delayed tissue nodules?	19 (76%)	Yes
5	Does the site of bacteria within the filler and the degree of pathogenicity of the implanted bacteria relate to a variability in the host response?	23 (92%)	Yes
6	Do you feel that the body is likely to tolerate a normal skin commensal implanted into a filler in a more benign fashion than a true pathogen?	23 (92%)	Yes
7	Do you feel that a commensal will contribute to a delayed tissue nodular response largely when visible to the immune system at the periphery of a bolus of filler?	22 (88%)	Yes
8	Do you feel a generalized immune response generated by a viremia or post-vaccination status contributes to temporary or prolonged delayed nodule formation?	25 (100%)	Yes
9	Do you feel that implanted bacteria may amplify or contribute to this issue in the presence of this heightened immune activity if now visible at the periphery of the filler material?	25 (100%)	Yes
10	Do you feel that more virulent bacteria seeded via a bacteremia will induce a more significant inflammatory response?	24 (96%)	Yes
11	Do you feel that the degree of inflammation is contributed to by a combination of the virulence and number of bacteria as well as the age and condition of the filler?	22 (88%)	Yes, but N/A because this was split into 2 further questions (11a and b)
11a	Do you feel that the degree of inflammation is contributed to by the virulence and number of bacteria in or around the filler?	23 (92%)	Yes
11b	Do you feel that the degree of inflammation is contributed to by the age and condition of the filler?	17 (68%)	No
12	Regarding the inflammatory response, do you feel that LMWHA is involved through activation of Toll-like receptors via the LMWHA and that the ensuing inflammation may be enhanced by reactive oxygen species and further production of LMWHA by the inflammatory process?	23 (92%)	Yes
13	Regarding long-standing nodules—do you feel these are more difficult to dissolve?	18 (72%)	No
14	Do you feel that it is important for a practitioner to be injecting through a skin surface that has a normal barrier function?	25 (100%)	Yes
15	Do you feel that it is important to treat generalized infection early or to warn filler patients to seek early treatment because of their fillers?	25 (100%)	Yes
16	Do you agree that the suggested table meets the need to classify tissue filler nodules in a logical manner and is one that would allow practitioners to follow and grade (Table 2)?	25 (100%)	Yes, after second round of discussion and slight changes
17	Do you agree that the suggested treatment algorithm table (Table 3) meets the need to classify treatment of tissue filler nodules in a logical manner and is one that practitioners would readily follow?	25 (100%)	Yes, after second round of discussion and slight changes
18a	Do you feel that the amount of filler per session contributes to the likelihood of late-onset tissue nodules?	17 (68%)	No
18b	Is there a suggested upper limit for filler quantity per session?	No upper limit 9 (36%) 4 mL 10 (40%) 3 mL 5 (20%) 2 mL 1 (4%)	No

LMWHA, low molecular weight hyaluronic acid.

Table 2. Classification System for Nodules

Category	Primarily filler related	Primarily inflammatory	Primarily infective
Reaction pattern	1	2	3
Description	Tissue edema or late appearance of product (for example in tear trough)	Cold inflammatory delayed nodules	Hot delayed nodules
Summary	Edematous change due to altered lymphatic drainage and/or chronic low-grade inflammation or late displacement of filler	Swelling or nodules that arise intermittently and settle spontaneously or persistent cold inflammatory delayed nodules most likely due to a combined pathogenic-immunologic trigger	Hot infective delayed nodules most likely due to pathogen through hematogenous spread or local infiltration of a virulent skin pathogen

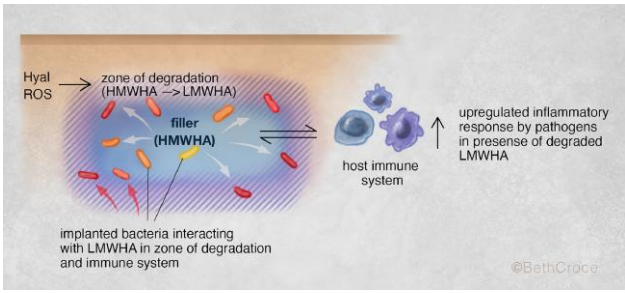

Figure 3. Delay to nodule development: Scenario 1. As the filler ages, it is degraded by reactive oxygen species (ROS) and native hyaluronidases (Hyal). The bacteria implanted with the filler may be destroyed immediately or become sequestered within the filler and become visible after a delay at the periphery of the filler as the filler is degraded or by growth of the bacterial colony. There the bacteria may interact with the immune system in an environment of proinflammatory degraded hyaluronic acid fragments. Illustration created by and published with permission from Beth Croce. HMWHA, high molecular weight hyaluronic acid; LMWHA, low molecular weight hyaluronic acid.

been agreed upon for individual answers if at least 18 of the group of 25 voted in the affirmative and those voting in the negative were less than 6 of 25. Although framed as yes/no answers, consensus members were permitted to express a variation in responses given the lack of evidence-based medicine available. Unsure, or variations of this, were taken as "no," whereas probably or most likely were deemed to be "yes" for the purpose of consensus.

As part of their deliberations classification and treatment tables were circulated to the consensus panel, debated, modified, and submitted for final vote (Tables 2, 3). Results to posed questions are found in Table 1. The supplemental questions 18a and 18b on volume implanted in a single session, effect of the age and condition of the filler on tissue reactivity, and whether long-standing filler complications were more difficult to resolve did not achieve consensus (4/20). Even though these questions did not receive 75% or greater agreement, no question received less than 67% agreement. All other questions (16/20) achieved 75% agreement or higher (Table 1).

DISCUSSION

Summary of Findings

The consensus group agreed that the filler, pathogens, and inflammatory factors were all involved in many tissue reactions and that most late-onset nodules were infection initiated with a variable immune response. However, reservations were expressed about the rarity with which standard testing isolated bacteria from nodules. Whether this was due to relatively insensitive laboratory methods or pathogens being overwhelmed by the immune response was debated but not agreed upon because of lack of evidence.

Initially most implanted hyaluronic acids are of high molecular weight, and bacteria may be carried from the surface with the injection process (Figure 2). The group felt that the quality of the skin barrier with its normal skin commensal carriage and the cleanliness of the procedure were important variables in the likelihood of nodule development. The group recommends that practitioners attempt to inject through a skin surface that has normal skin barrier function.

They also felt that the pathogenicity of any implanted surface bacteria would make a difference to the patient's immune response and that a patient was more likely to tolerate an implanted normal skin commensal than a true pathogen. It may be that an implanted commensal activates an immune response when it is seen at the periphery of a filler bolus (Figure 3). Bolus size only just passed consensus for being a risk factor for delayed nodule development, with group members expressing reservations that even small boluses or linear threads could cause nodules.

The group felt that a viremia or post-vaccination immune response might contribute to temporary or prolonged nodule formation. COVID-19 vaccinations and viremia were found to be potent causes of delayed nodule formation by upregulation of the immune response, possibly through CD44 activation, and blockade with low-dose angiotensin converting enzyme inhibition (ACE-1) was a useful anti-inflammatory strategy (Table 3).[16] Any implanted bacteria sitting peripherally on the filler bolus may get caught up

Table 3. Treatment Algorithm for Treatment-Related Hyaluronic Acid Nodules

Therapy	Primarily filler related	Primarily inflammatory	Primarily infective
Best therapy considered for subtype	1. Removal of product required—hyaluronidase if appropriate	1. Either allow to settle if minor and possibly self-limiting once immunologic challenge has settled 2. Anti-inflammatory treatment such as prednisolone or colchicine and nonsteroidal anti-inflammatories 3. May include anti-inflammatory aspects of antibiotics such as tetracyclines; if COVID-19 related the use of ACE-1 inhibitors may be considered	1. Appropriate antibiotic treatment if source of infection known or suspected (for example dental abscess, sinus infection, urinary tract infection, or local abscess from injected pathogen) 2. If source not known, generic choice of agents such as doxycycline, clarithromycin, or cephalosporins may be considered 3. Removal of product or drainage if resistant to treatment. This may require antibiotic and steroid coverage before and after the dissolution process
Alternative therapies for subtype	2. Oral steroids/nonsteroidal immune suppressant or anti-inflammatory treatment 3. Intralesional steroids or fluorouracil if persistent edematous swelling 4. Physical energy-based devices such as shockwave therapy, laser treatment	4. Product removal if deemed necessary 5. If resistant to treatment may require intralesional steroids or 5-fluorouracil	4. May require intralesional steroids or 5-fluorouracil in difficult cases

in this heightened immune response and amplify this reaction (Figure 4).

In a similar manner to viremia and post-vaccination status with a heightened immune status, virulent bacteria seeding the surface of the filler in a bacteremia would be likely to induce a significant immune response, with both virulence and the number of bacteria contributing to this (Figure 4). However, the group could not reach consensus as to whether the age and condition of the filler were contributing factors to this outcome.

Low molecular weight hyaluronic acid (LMWHA) is the inevitable metabolic breakdown product of high molecular weight hyaluronic acid fillers. These LMWHAs are proinflammatory, and the consensus group judged that these agents were involved in inflammatory delayed nodules through the activation of Toll-like receptors and magnification by inflammation-induced reactive oxygen species (Figures 4, 5).

Tables 2 and 3 delineate the group's agreed classification system and treatment algorithm, which seek to guide practitioners in recognizing and treating tissue filler reactions. The group did not reach consensus that longstanding fillers were more difficult to dissolve, nor that there was an upper limit on the volume of filler that should be injected in any given session.

Theories of Delayed Nodule Development

The candidates for explanation of delayed nodule activity are 3 in number—immune response, infection, and the filler itself—and it is debatable whether one of these on its own is sufficient. The contention of this paper is that all 3 are involved to varying degrees in most cases. There have been advocates for the immune argument alone, suggesting that LMWHAs have been shown to elicit an immune response on skin testing in some patients.[17,18] These immune responses have been quite specific in some cases, with only 1 specific injected filler agent being involved. It has also been shown that some fillers are more prone than others to produce these changes.[3,19] Additional arguments of the immune protagonists relate to the delayed immune response, stating that antibiotics and anti-infective agents do not work in all cases and that steroids and anti-inflammatories alone have worked well in some cases.[20,21] The variability in an individual's immune response looks likely to play a part in the development of late nodules. Certain HLA haplotypes (HLA-B × 08 and DRB1 × 03) appear to place the individual at risk by altering immune responsiveness.[22]

Although there are endotoxins in all injected hyaluronic acid products because they are produced by fermented streptococcal species, the agents are purified to such an extent that the endotoxin is less than 20 endotoxin units per syringe.[23] This endotoxin load is felt to be insufficient to be involved in delayed nodule development. It has been shown that all injectable forms of hyaluronic acid are anti-inflammatory in vitro. Additionally, any argument regarding the possibility of cross-linking structures being involved in an immune response appears moot, because these structures have been shown to be inert.[24]

Those supporting the central role of infection argue essentially the opposite—that antibiotics do work well in many cases and most cases do not have specific immune reactions. Degradation of the hyaluronic acid on the surface of the bolus producing LMWHA may make it easier

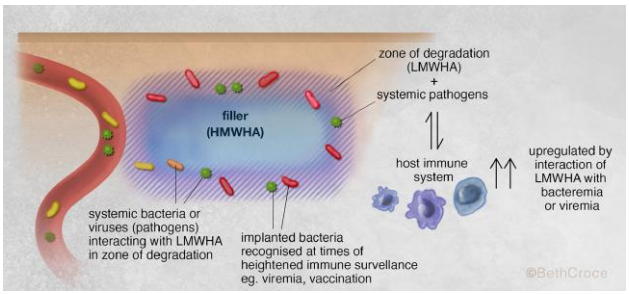

Figure 4. Delay to nodule development: Scenario 2. The high molecular weight hyaluronic acid (HMWHA) filler ages and degrades to low molecular weight hyaluronic acid (LMWHA). Viremia or bacteremia may seed to the periphery of filler where this LMWHA degradation zone exists. LMWHA in the presence of viremia or bacteremia will exert a variable upregulation of the immune system, dependent on the virulence of the systemic infection. A viremia may just generally upregulate immune surveillance allowing "recognition" of previously tolerated implanted bacteremia. Illustration created by and published with permission from Beth Croce.

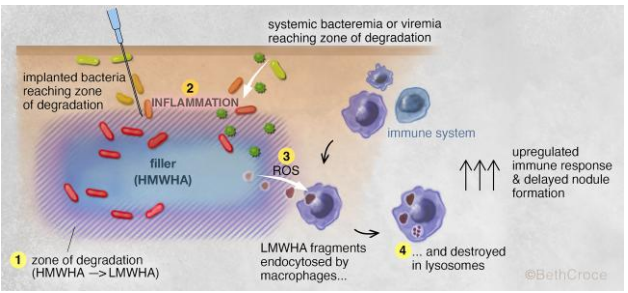

Figure 5. Overview of inflammation in delayed hyaluronic acid filler nodules. (1) Over time, high molecular weight hyaluronic acid (HMWHA) fillers degrade to low molecular weight hyaluronic acid (LMWHA). (2) In the presence of pathogens, either implanted or systemic, LMWHA is inflammatory. (3) This inflammation induces reactive oxygen species (ROS) which hasten dissolution of the filler HMWHA and further degrade LMWHA into macrophage digestible fragments. (4) These small fragments of LMWHA attract macrophages to the zone of degradation for endocytosis of these fragments and final destruction by endocellular lysosomes. Illustration created by and published with permission from Beth Croce.

for any infection to seed there; what follows will address this. It is not only possible but probable that there are elements of both these views that are correct and incorrect.

Two manuscripts describe a unifying theory of these conflicting views. They find that HMWHAs suppress immune response even in the presence of endotoxin load (bacteria), whereas LMWHAs stimulate immune responses in the presence of an endotoxin load.[25,26] However, if one suppresses the endotoxin load to very low levels (less than 0.03 EU/mg), LMWHAs no longer stimulate the immune response in the same way.

There are some fillers that are initially a mixture of HMWHAs and what we previously called LMWHAs. However, these LMWHAs are not less than 500 kDa, so are best classed as intermediate hyaluronic acid compounds. These LMWHAs remain incapable of undergoing endocytosis at that level of molecular weight. Injected HA filler products vary in their composition, ratio of HA molecule sizes, cross-linking technology, and ease of ability to break down into degradation products, which may include proinflammatory-size molecules before further breakdown into noninflammatory HA-size molecules.

The Delay Before Nodule Development

An interval after injection of 1 to 2 weeks before the presentation of inflammation may denote an implanted virulent pathogen such as *Staphylococcus aureus*, but most commonly the delay is considerably longer than this. The variable delay before some nodules become inflamed has always been a source of mystery, and very little literature exists regarding this point. This may be due to the time necessary for HMWHA filler to degrade to proinflammatory LMWHA particles. This degradation may be influenced by the nature of the filler, including factors such as tenacity and quantity of cross-linking utilized, volume of product utilized in a treatment session, the original molecular weight of the hyaluronic acid, and the concentration of HA in the product. If a product degrades to LMWHA, it may hasten or make more likely developmental characteristics favoring nodule development. Certainly, several articles have suggested in retrospective incident reports that a widely used range of products with a mixture of high and intermediate molecular weight HA appears more likely to lead to nodule formation.[3,27–29] However, this is still debated, and furthermore some articles quote only numbers of nodules and not how many injections of that material were involved.[30,31] Degradation into shorter HA molecules would be expected to preferentially occur at the periphery of the injected material where there is exposure to native tissue hyaluronidases and any reactive oxygen species (ROS). In the absence of endotoxin or commensal bacterial presence, a slow, controlled process would be expected (Figure 3).[32]

Treatment Options

Treatment options in the literature have largely followed algorithms centering on success or failure of simpler and more generic treatments.[7,21,33] These have included antibiotics either separately or in combination, anti-inflammatory steroidal and nonsteroidal oral or intralesional therapies, and removal of the filler when appropriate.[3,34,35]

Table 3 simplifies the approach to treatment centered around each of the elements (the filler, the patient's inflammatory response, and the infective element). We will illustrate

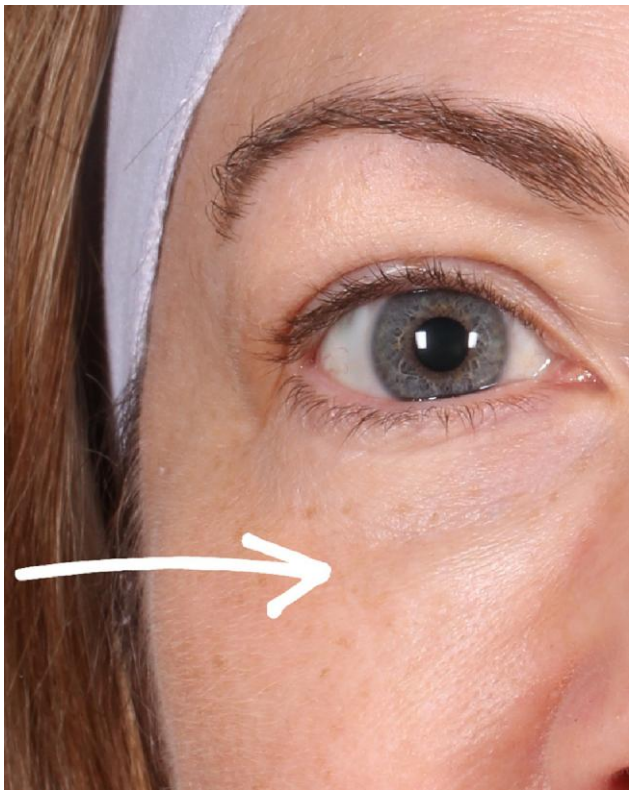

Figure 6. Migration of product over time resulting in visible product or swelling, as in this typical example seen in the tear trough of a 56-year-old female.

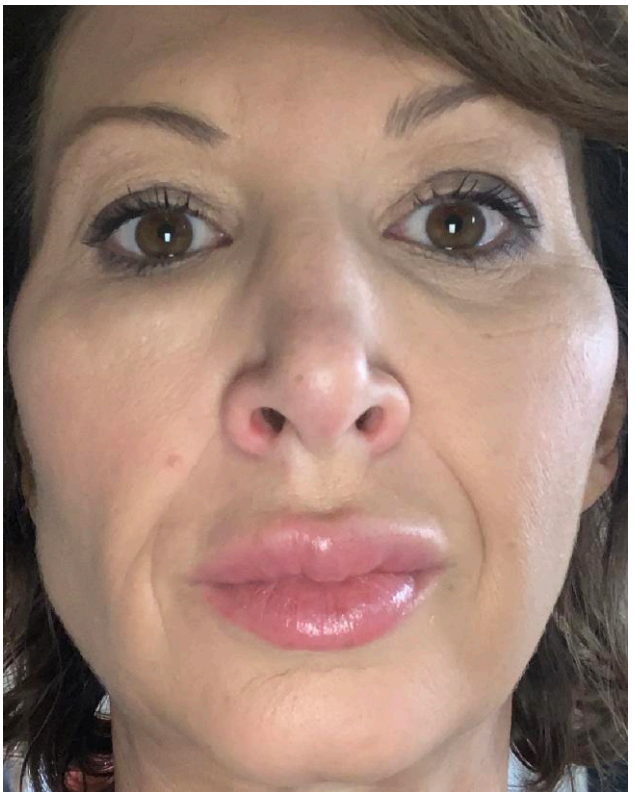

Figure 7. Multiple nodules affecting lips, cheeks, and tear trough of a 48-year-old female.

this approach utilizing the following patient examples, describing the preferred approach in each scenario.

These cases were given to the consensus group with other examples. The cases chosen below were those that the group felt most closely correlated with the classification system (Table 2).

Case Example 1

A female patient presents with a gradually increasing asymptomatic swelling under each eye. She remembers having filler placed in this position, but not for many years. When the patient is asked to smile the lumps do not disappear, but in fact seem more obvious, suggesting that these are not her own fat pads but swelling in or external to her orbicularis oculi muscle. The diagnosis is the late appearance of injected filler. In this case, we would follow the advice for management of primarily filler-related nodules (Table 3). The initial approach would favor dissolution of this product with multiple sessions of hyaluronidase alone (Figure 6).

Case Example 2

A patient presents with a history of fillers injected 6 months earlier in multiple areas without incident. She has had an incidental upper respiratory tract infection, possibly influenza, and complains that all the areas in her face where fillers were injected have become swollen. These areas are otherwise asymptomatic but are clinically obvious and distressing for the patient (Figure 7). She has swelling in her lip as well as other sites. The approach here favors the use of anti-inflammatory agents in the first instance (Table 3). Treatment could include oral steroids or nonsteroidal anti-inflammatory agents.

An approach suggested in 2018 considered the possibility that delayed tissue nodules might be treated as a gout analogue.[36] In gout, uric acid crystals, which are reasonably innocuous, are dealt with by the body with a very severe inflamed immune response. In a similar way, it was reasoned that dermal nodules excited the Toll-like receptors to produce an excessive inflammatory response, above that required to handle the threat. In gout the arachidonic acid pathway is activated, with both the lipoxygenase and cyclooxygenase pathways involved in this inflammatory response. These may be blocked with the combined use of colchicine and nonsteroidal anti-inflammatories.

Case Example 3

A female patient was acutely unwell with a suspected bacteremia following systemic infection. She noted the

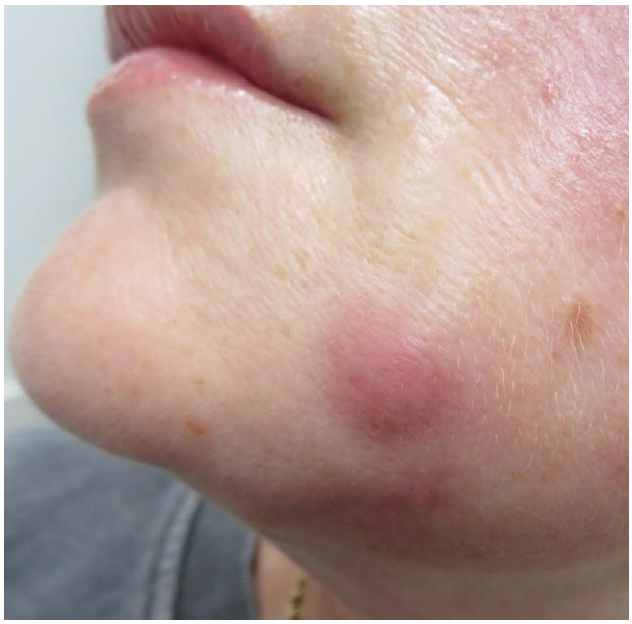

Figure 8. Hot inflammatory nodule following a systemic illness in a 54-year-old female.

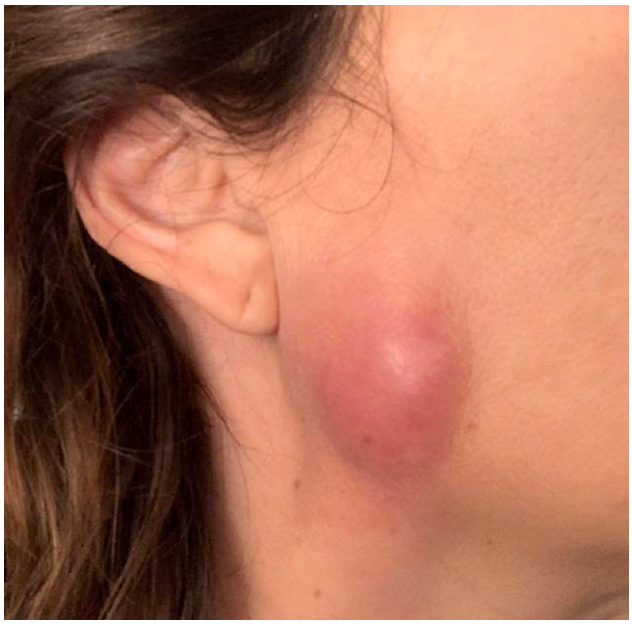

Figure 9. Acute infection producing an abscess following procedure in a 48-year-old female.

appearance of symptomatic swelling in areas of previous fillers over the ensuing days migrating to other areas of the face (Figure 8).

Because these nodules were erythematous with substantial inflammation and swelling and followed a significant bacteremia, antibiotics appeared to be required in the first instance, rather than an anti-inflammatory or removal of the product (Table 3). If the history indicated a possible source, such as a urinary tract infection, gastroenteritis, sinusitis, or dental abscesses, appropriate antibacterial agents for that source could be considered first-line treatment. If no source was discernible broad-spectrum antibiotics would be called for (Table 3).

Case Example 4

A patient presented 10 days after extensive facial injection of hyaluronic acid filler with a hot painful nodule at the angle of the jaw (Figure 9). She was febrile and felt unwell. This was acutely tender to palpation. It was deemed to be an abscess, and that the patient should be treated for an infective process with drainage, culture, and appropriate antibiotics (Table 3) .

Treatment Algorithm

Although the preferred option may be derived from Table 3, there are many nodules that will require more than 1 approach. In general, the approach may be to assess the likely pathophysiology, with preservation of the filler as the preferred outcome. However, if the process difficult to control completely, removal of the product should always be considered (Table 3).

If the presentation is apparently solely a filler issue, such as the Tyndall effect or noninflammatory edema, consider removal with hyaluronidase or management with anti-inflammatory agents.

If inflammation of the filler appears to follow viral infection or heightened immune surveillance, then consider a primarily "watch-and-see" approach with or without anti-inflammatory medication. However, if inflammation persists product removal or intralesional therapies may be needed. Recently there also has been a case report on shockwave therapy.[37]

If infection is considered an etiological factor, either from local pathogen implantation or through a bacteremia, relevant antibiotics are recommended. Drainage of a fluctuant mass may be necessary, or removal of product considered.

Limitations of this article include that it is a consensus document and by its nature has a low level of evidence. Added to this, some conjecture and assumptions were involved in the consensus points discussed. Nevertheless, this consensus group was highly experienced in the diagnosis and management of delayed tissue nodules, and individual points were debated at length over many revisions of this paper.

CONCLUSIONS

We as a group believe that the filler, the patient's immune system, and infection are likely all involved to a variable degree in the development of nodules and that the risk is

increased by injection into patients with a compromised barrier function. The delay often seen with inflammatory nodules is in all likelihood due to the perfect storm of degradation of high molecular weight to very low molecular weight hyaluronic acid, together with a pathogen present on the periphery of the filler (where the HA degradation is occurring) either from its emergence over time from its intrafiller placement at the time of injection or through later bacteremia. The inflammatory response to this pathogen may vary dependent on the host immune system (Figures 4, 5).

Treatment should be directed to the aspect of the nodule that is most apparently involved. The filler, the inflammatory response, or the infection may take primacy in treatment, but addressing all may be needed for resistant lesions. This is a difficult area in which to build prospective in vivo studies with high levels of evidence, and alternative concepts involving imaginative and more experimental models would be welcome advances.

Supplemental Material

This article contains supplemental material located online at www.aestheticsurgeryjournal.com.

Disclosures

Dr Goodman is a speaker, investigator, and consultant for Allergan, Inc. (Irvine, CA) and Galderma (Lausanne, Switzerland). Dr McDonald is a trainer, speaker, investigator, and consultant for Allergan, Inc. Dr Lim holds partner employment with EBOS Healthcare Australia (New South Wales, Australia). Dr Porter is a consultant for Abbvie (Allergan) and Galderma. Dr Deva is a consultant and research coordinator for Allergan, Mentor (Irvine, CA), and 3 M (Saint Paul, MN). Dr Magnusson is a consultant and investigator for Abbvie (Allergan), and an investor in Strathspey Crown Funding (Newport, CA). Dr Hart is a consultant and lecturer for Allergan, Inc. Dr Callan is a consultant for Allergan and Merz (Frankfurt, Germany). Dr Roberts is a consultant, lecturer, and investigator for Abbvie, Inc. (North Chicago, IL), and a consultant for Dermocosmetica (Melbourne, Victoria, Australia). Mr Clague is a former employee and consultant for Allergan, a trainer and consultant for Croma (Leobendorf, Austria), a speaker for Alma Lasers (Buffalo Grove, IL), a board member of the Cosmetic Nurse Association, and an owner and trainer for Facecoach and facecoachlive (South Yarra, Victoria, Australia). Dr Williams is a trainer for Abbvie (Allergan) and Teoxane (Geneva, Switzerland). Dr Corduff is a consultant and speaker for Merz. Dr Arendse is a consultant and speaker for Galderma and Envogue (New York, NY). The remaining authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

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