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Review

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Non-ischemic complications of dermal fillers

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Abstract

Dermal fillers have been commonly used for the filling of facial rhytids. As the use of dermal fillers has grown, so has the incidence of non-ischemic complications. These complications range from edema, bruising, and erythema to more complex conditions such as delayed hypersensitivity nodules and biofilms. This article sought to review the causes of various non-ischemic complications, discuss their risk factors, and review management techniques. Certain predisposing factors to delayed hypersensitivity nodules, such as Vycross technology, a history of viral illness, or coronavirus disease 19 (COVID-19) infections, are discussed in detail in this review. Prevention techniques such as patient counseling, elucidating certain patient history (viral illness, dental procedures), the use of aseptic technique, and procedural factors are also discussed. Understanding appropriate management for these complications can also help in treatment. Imaging, such as ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI), has taken on a larger role in the management of non-ischemic complications.

Keywords: Non-ischemic complications, delayed hypersensitivity nodules, COVID-19 hypersensitivity nodules, prevention techniques, granulomas, biofilms, imaging

INTRODUCTION

Dermal fillers have been commonly used to fill rhytids and folds and to correct soft tissue volume loss from disease and skin aging[1]. There are now an estimated 160 products available worldwide, with about 3.4

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million soft tissue injections being provided in 2020[2,3]. While dermal fillers are generally considered a safe procedure, there are inherent risks and complications.

Our narrative literature review aimed to discuss various non-ischemic complications seen after injection. A literature search was performed on PubMed and Google Scholar on the complications, management, and prevention strategies seen for dermal fillers. Broadly, our initial search terms were "dermal filler complications" and "filler complications" on both PubMed and Google Scholar. We then individually evaluated the full papers for a discussion on non-ischemic complications. Once we identified non-ischemic complications that we wanted to include and discuss in further detail, we specifically searched for articles discussing those complications. For example, search terms for malar edema included "malar edema anatomy", while COVID-19 complications were searched using terms like "covid-19 fillers" and "COVID-19 fillers case report." Articles until August 2022 were included in our study. We excluded articles that were published before 2000 or that only discussed ischemic complications, for inclusion in our review on ischemic complications of dermal fillers[4]. Figure 1 discusses our search process in a visual format. Given that we performed a narrative literature review rather than a systematic review, we listed our exclusion criteria in broad terms. The overarching goal of this review was to focus on non-ischemic complications seen after filler injections and discuss prevention strategies, management, and the recent use of imaging within the field.

COMPLICATIONS

Bruising

Bruising is commonly seen after filler injections, secondary to needle-associated perforation or vessel rupture from pressure in the injected area[5]. The most common location for bruising includes the perioral rhytid, lower eyelids, the upper third of the nasolabial fold, upper lip, and lateral edge of the lower lip[5]. The bruising tends to darken for a day and resolves in approximately 5 to 10 days, with minimal effect on clinical outcomes[5].

Bruising is generally managed by applying immediate firm pressure and ice packs, both during and after the injections[5]. Vitamin K oxide gel may also be considered in the treatment of bruising[6,7]. Shah *et al.* conducted a study that evaluated patients who received topical vitamin K for two weeks before and after laser treatment[6]. While pretreatment with Vitamin K cream did not reduce bruising severity, Vitamin K treatment after the laser significantly decreased the severity of bruising[6]. However, Kovacs *et al.* used a more objective method of counting petechiae and found that there was no difference between Vitamin K treatment and placebo[8]. Cohen *et al.* also conducted a randomized double-blinded, placebo-controlled, split-face study that found that there was no statistical significance between vitamin K oxide gel and placebo, although there did appear to be a trend towards faster resolution with the gel[7]. Tao *et al.* recently published a review paper analyzing Vitamin K among other treatments and concluded no benefit of Vitamin K compared to placebo in reducing ecchymosis after oculofacial surgery[9].

Patients who are on anti-inflammatory or anticoagulation medications may see an increased risk of bruising[10]. However, the risk of stopping the medicine for that individual patient should be evaluated before recommending that option[10]. However, if deemed appropriate, non-essential medications with anticoagulation effects may be paused one week prior to injection[10,11].

Erythema

Another complication seen in patients after filler injections is erythema secondary to puncture trauma and inflammation[5,12,13]. Firm pressure and ice-packs during and after the injection can help with resolution[2,12].

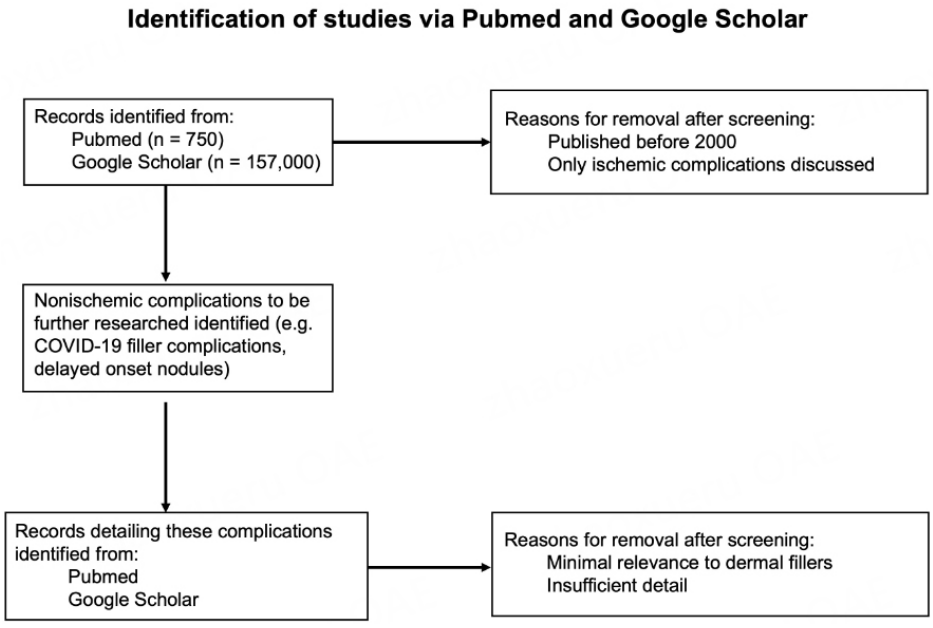

Figure 1. Identification of studies for inclusion in this narrative review of non-ischemic complications.

While the erythema generally tends to resolve within a couple of h, it is best to inform the patient of this expected side effect[5]. If patients are interested in covering up the erythema, make-up with a green tint can be used to help hide the redness[5].

Edema

Edema is another common complication seen after filler injection. A blunt-tip cannula has been shown to produce less edema, pain, and bruising at injection sites with faster recovery times[14,15]. Similar to bruising management, firm pressure and ice-packs during and after the injection can help with resolution[2,12]. Edema tends to resolve after several days, but can sometimes take up to a week[2]. The areas most commonly affected are the lips and periorbital region[16]. Edema tends to be worse in the mornings after patients wake up, due to dependent edema, and gradually improves throughout the day. This cycle tends to repeat itself daily until it all resolves in 5-10 days. It is worth noting that shorter-chain hyaluronic acids have a higher tendency to cause inflammation upon injection, which can cause increased edema[17]. Other more severe or prolonged forms of edema include angioedema and malar edema.

Angioedema

Angioedema occurs due to a Type I hypersensitivity response to dermal fillers[2]. The release of IgE, a B cell response, degranulates mast cells to cause a classic triad of swelling, edema, and itching associated with an allergic response[2]. While fillers are essentially foreign bodies, hyaluronic acid (HA) fillers have been seen to be less immunogenic compared to bovine collagen fillers[18]. The onset of this edematous response occurs within h and lasts up to 3 to 7 days[18]. Rapidly progressing edema has the potential to cause airway obstruction, leading to emergent treatment[2]. For resistant or persistent edema, oral prednisone, cortisone tablets, or injections can be considered for treatment[2,18]. If the edema lasts for more than 6 weeks, it is classified as chronic angioedema[2]. This can be managed with nonsedating antihistamines to sedating antihistamines and eventually oral steroids or immunosuppressants, being careful to use the smallest dose of steroids necessary[2]. Funt *et al.* also mention the use of leukotriene receptor antagonist to reduce the oral steroid dose[2]. As the severity of this rare complication can be significant, Chiang *et al.* recommend keeping

an emergency kit of epinephrine pens, oral corticosteroids, and antihistamines in the treatment room[12].

Malar edema

Malar edema is commonly reported after filler injections in the infraorbital hollow or "tear trough" in the lid/cheek junction area[19]. It is defined as a collection of fluid over the malar eminence below the level of the infraorbital rim[20]. A recent study found an incidence of approximately 11% for malar edema following periorbital filler injection[21]. Older patients with thinner skin tend to be at higher risk[19].

The malar fat pad is a triangular-shaped area of subcutaneous fat based at the nasolabial fold with its apex at the malar eminence[22]. The malar septum has been described in multiple ways, first by Pessa *et al.* as originating from the orbital rim, along the arcus marginalis, which is also a fusion point of the orbital rim periosteum, orbital septum, and maxilla periosteum[23]. The malar septum works to divide the suborbicularis oculi fat (SOOF) into superior and inferior components [Figure 2A][23,24]. This septum creates a relatively impermeable barrier from the orbital rim to the cheek skin, allowing for edema to accumulate. This description seems to be similar to the zygomaticocutaneous ligament (ZCL). However, Newberry *et al.*, Alghoul *et al.*, and Mendelson *et al.* describe it as more diagonal coming from the orbital rim down toward the ZCL[25-27].

The placement of filler superficial to the malar septum and ZCL may lead to additional impermeability, limiting lymphatic drainage and resulting in fluid accumulation and prolonged edema[22]. Fillers may also cause edema by putting direct pressure on the lymphatics, depending on the elasticity or elastic modulus (G')[22]. Funt *et al.* recommend injecting filler directly on the periosteum within the boundaries of the malar septum and placing small boluses of filler directly on the bone[22]. Another alternative was using a less refractive hyaluronic acid filler that could be placed in the subdermal plane[22].

There are two important considerations in individuals who present with malar edema. The first is differentiating malar edema from orbital fat prolapse as depicted in Figure 2A and B. Orbital fat prolapse tends to present more superiorly than malar edema and would require different management [Figure 2B]. Secondarily, patients with pre-existing malar edema should also be counseled that receiving tear trough fillers could worsen their edema [Figure 3]. There are some patients in whom this malar edema may not resolve, and it is best to avoid filler injections entirely.

General management of malar edema involves head elevation, cool compresses, manual lymphatic compression, hyaluronidase, and methylprednisolone for HA fillers[12,28]. In one study of 19 patients with malar edema, an injection of 15-30 U/cm^2 of hyaluronidase appeared to be sufficient to resolve edema for 15 patients[29]. Another patient, who developed malar edema 1 year after receiving hyaluronic acid filler, received 120 U hyaluronidase into the left eyelid and 80 U hyaluronidase into the right, with a dramatic resolution of the edema[30]. We have also included an example of treating malar edema with hyaluronidase [Supplementary Video 1]. This patient received hyaluronidase and initially looked well treated [Figure 4]. However, her fillers hydrated and caused her to develop edema. However, after treatment with hyaluronidase, her malar edema resolved. When a diffuse area, such as the undereye area, needs to be dissolved gradually (and incompletely to avoid completely wasting the filler), the dissolvability of the filler should also be considered (see the Reversibility section below). With a more reversible filler, a 150 U/1 mL mixture of hyaluronidase can be further diluted with bacteriostatic saline, such as 5-10 U of hyaluronidase diluted in 0.5 mL of saline and can be infiltrated throughout the filled area to reduce the malar edema. Reassessment in 1-2 weeks is advised, with further dissolution as needed.

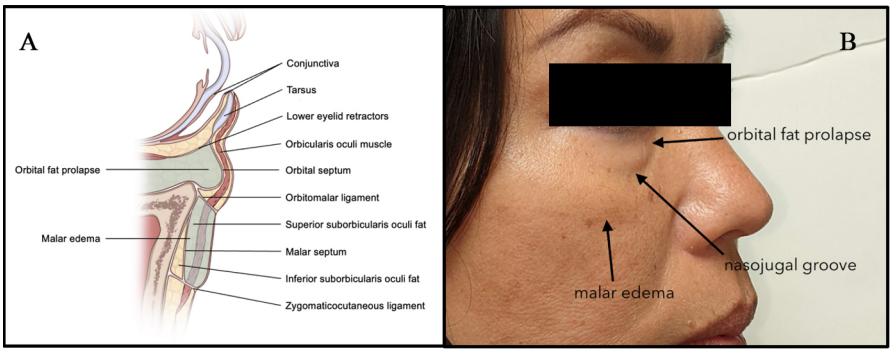

Figure 2. (A): Anatomy of malar edema and an orbital fat prolapse; (B): Representative image of pre-existing mild malar edema and orbital fat prolapse.

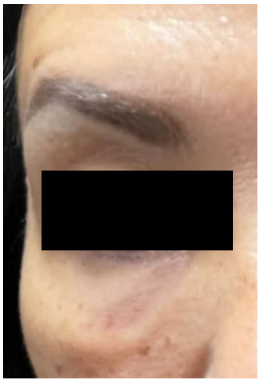

Figure 3. Malar edema worsening after undereye injection of hyaluronic acid filler.

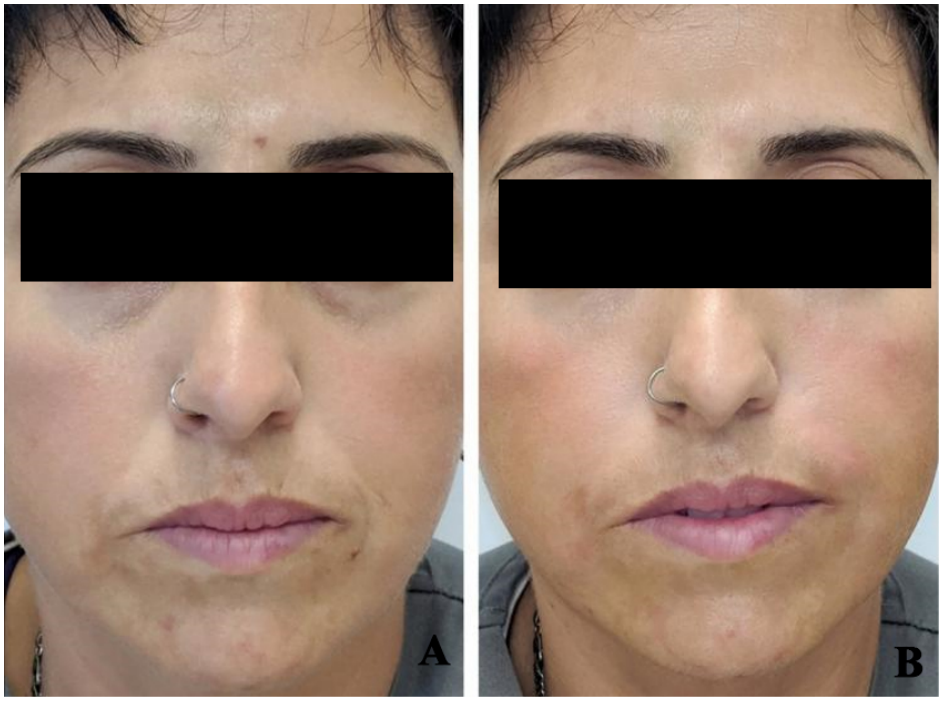

Figure 4. (A): Patient prior to receiving undereye and nasolabial filler; (B): Immediately after receiving Revanesse Versa filler.

Paresthesia/nerve injury

Nerve damage is a rare complication that can occur due to direct trauma from the needle, injection of filler into the nerve, or tissue compression[2]. The most common area of nerve damage is the infraorbital nerve, occurring more frequently if the intraoral approach is used[2]. This nerve damage can vary from being transient to permanent[2]. The most important strategy to avoid this type of complication is to be aware of the anatomy and neurovascular bundles around the area of injection[2,16]. Treatment is with triamcinolone at the infraorbital foramen as well as breaking up the material with lidocaine or saline[2]. Less commonly, Bell's palsy can also be seen secondary to filler injection[16]. While almost 70% of patients experience complete resolution, 30% can have remaining weakness[31]. The recommended treatment for Bell's palsy is a short course of high-dose steroids[32]. While various other treatments have been proposed, including surgical decompression, antiviral therapy, electrotherapy, physical therapy, and acupuncture, there is currently no significant evidence to support their use[32-36].

Skin discoloration

Neovascularization

Neovascularization is usually secondary to tissue expansion by the product[2,16]. These vessels will eventually fade within 3-12 months without additional treatment[2,16]. However, if they are persistent, laser treatment can be considered as a treatment[2,16]. Lasers that have been shown to be effective include the 532-nm KTP, 532-nvm diode copper vapor, the 585-nm pulsed dye laser, and intense pulsed light (IPL)[2].

Hyperpigmentation

Post-injection hyperpigmentation can be seen in patients with Fitzpatrick skin types IV-VI[2,16]. Reducing the skin punctures by using a linear threading or fanning technique may help reduce post-injection erythema and, therefore, inflammatory hyperpigmentation[2]. Typically, a bleaching agent such as topical hydroquinone (2%-8%) and Retin-A (tretinoin) combined with daily full-spectrum sunscreen application can be used[2]. If the hyperpigmentation remains resistant, chemical peels may also be considered[2,16]. Additionally, intense pulsed light, a pulsed dye laser, or a fractional laser may be considered to improve hyperpigmentation[2].

Blue-grey dyschromia

If the filler is placed in the superficial dermis or epidermis, it can often cause a bluish hue[2,16]. This is thought to be secondary to greater light scattering of blue waves compared to red wives, creating the blue color perception[2,37]. However, this theory has been disputed and has been hypothesized to be a deficit in red light intensity over veins combined with deoxyhemoglobin absorbing more red to create a color perception as blue[2,37]. One study found that blue-gray dyschromia was seen more often in patients with repeat injections[21]. Hyaluronidase can be considered as an initial approach to treatment[2].

Nodules

Nodules have generally been divided into non-inflammatory and inflammatory categories[2]. Inflammatory nodules are secondary to infection or foreign body reactions, while non-inflammatory nodules are due to superficial injections or improper filler placement[38,39]. In this section, we will discuss the various causes of nodules, predisposing factors, and their management techniques.

Inflammatory nodules

Infection

Early infection can present as a fluctuant and tender lump a few days after injection[40]. It has been noted to be the second most common complication seen after filler injections, with a reported rate of 41%[41], and the most common complication in the nasolabial folds[41]. Infection risk does not appear to be dependent on filler type, but rather more on breaks in sterile technique[40,41].

These infections are often secondary to Staphylococcus aureus, but can also be caused by other viral and fungal species such as Candida[40,42,43]. It can be managed with incision and drainage along with first-generation cephalosporins[40,42,43]. If an abscess is present, incision, drainage, cultures, and antibiotics are recommended[40,43]. It is best to avoid massages or treatment with hyaluronidase until the infection is cleared, as this may spread the infection[12,43,44]. Patients who have developed midfacial and periorbital infection should be carefully monitored for intracerebral complications[2]. It is worth noting that if a late-onset infection occurs after 2 weeks, it may be secondary to atypical mycobacteria[40]. These mycobacteria are often drug-resistant and very difficult to treat[45]. A panel of experts recommended obtaining bacterial cultures for these late-onset infections and performing sensitivity reports to help tailor the antibiotic regimen[16].

Herpes reactivation

Filler injections can also lead to the reactivation of a herpes virus infection (HSV)[2]. Herpes reactivation secondary to dermal filler injections tends to occur in the perioral area, nasal mucosa, and mucosa of the hard palate[2,11,16]. If a reaction occurs outside the areas of recurrent herpes simplex virus infections, it is important to rule out vascular compromise given the possibility of similar presentations[2,46]. The symptoms of HSV reactivation include angioedema-like swelling, erythema, and local pain and crusting between 24 and 48 h of injection[46,47]. One case details a 24-year-old woman who presented with a vesicle on her nose the day after filler injection, which was positive for herpes simplex virus[47]. If patients have a history of cold sores (> 3), they should be prescribed anti-herpes medication as prophylaxis[16]. Any active herpes lesions should warrant a delay of injection[11,16]. Other therapy recommendations include 2 g valacyclovir hydrochloride twice a day for 1 day or 400 mg acyclovir five times a day for 5 days[48]. It is important to elicit a detailed clinical history and, if a history of HSV is present, provide prophylaxis with valacyclovir 500 mg twice daily 2-3 days before the procedure and 5-7 days after the procedure[49].

Delayed hypersensitivity nodules

Delayed hypersensitivity nodules have been described as “angry red bumps” that occur in the area of the filler injection and are characterized by induration, erythema, and edema[50,51]. The pathophysiology of these nodules involves T-lymphocytes and macrophages[52]. These reactions can occur anytime from 24 h after injection to several months[16,51,53]. The nodules can eventually progress to a specific granulomatous reaction[52,54].

While various reasons have been proposed for these reactions including infections, immunogenic triggers, and HA-breakdown byproducts, the exact etiology of the delayed reaction is multifactorial[55]. An increase in proinflammatory levels of C-reactive protein, fibrinogen, and angiotensin convertase (which appears to also play a role in delayed nodules after COVID-19 reactions) has been seen in patients with delayed hypersensitivity reactions[53]. On the other hand, Decates *et al.* showed that in 12 patients who experienced a delayed hypersensitivity reaction and underwent intradermal testing, none had a reaction[56]. The paper postulates that neither type I nor type IV hypersensitivity plays a role in these late inflammatory reactions[56]. However, there does appear to be an element of inflammatory process causing these nodules.

For example, in one of the authors' experience, anything that flares up the immune system, including dental work, cutaneous surgery/lasers, sinus infection, UTI, irritable bowel syndrome, or autoimmune conditions, can lead to the presentation of these nodules. They usually resolve in 1-2 days with diphenhydramine or doxycycline at an inflammatory dose and are not granulomas. Another etiology for these nodules includes filler byproducts. While hyaluronic acid is not typically immunogenic, other components that stabilize these molecules may predispose the filler product to become immunogenic[57]. It has also been theorized that glycosaminoglycans can act as superantigens and activate immune reactive cells[54]. After changes in the manufacturing process reduced the protein load in HA by six-fold, the incidence of inflammatory reactions decreased from 0.15 to 0.06 percent[58-60]. Delayed hypersensitivity nodules are now more commonly reported after permanent fillers such as silicone or polymethylmethacrylate rather than HA[61]. In reviewing the literature, it appears that further data is needed to determine the exact etiology of these nodules.

These delayed hypersensitivity nodules often lead to granulomas[54]. A granuloma is considered a form of chronic inflammation that occurs in response to a foreign material that has not been able to be phagocytosed by macrophages[62]. Several factors can increase the likelihood of granulomas. Lemperle *et al.* found that an irregularity in the particle surface could cause a longer-lasting inflammatory reaction as well as severe systemic infection[63]. While a relationship between biofilms and granulomas has been considered, this hypothesis is still being debated[64,65]. Other factors that lead to the development of granulomas include superficial placement, hydrophobic polymer gels, smaller particle size, volume of the filler, intramuscular injection, and previous infections[2,51,63].

Lemperle *et al.* classify granulomas into three separate types. A cystic granuloma tends to develop after intradermal collagen and hyaluronic acid and results in a sterile abscess[63,66,67]. Histologically, this granuloma is defined by neutrophils, lymphoid cells, macrophages, and giant cells[63]. Edematous granulomas are usually caused by silicone or polyacrylamide injection[63]. In this type of granuloma, histology shows infiltration of the tissue by lymphocytes and macrophages rather than giant cells[63]. Lastly, sclerosing granulomas occur after implantation of particulate material, such as Artecoll, Dermalive, and Sculptra, and can last for several years if untreated[63]. The histology of this granuloma shows widely separated spaces between the microspheres due to the production of fibers from fibroblasts[63].

The treatment goal for granulomas is to stop cell invasion and interstitial substance secretion[67]. Treatment must involve ruling out infection with bacteriological sampling before starting steroids and immunosuppressants[62]. Hyaluronidase should be considered, as well as steroids, 5-FU injections, and triamcinolone injections[5,67]. If the granuloma is obviously sterile or has little capsule formation, incision and drainage can be considered[67]. If hyaluronidase fails to improve the nodule, a surgical approach can be considered[62,67,68]. Complete removal of these granulomas can prove to be difficult secondary to ill-defined margins[69]. Methotrexate was also studied to see if it improved granulomatous lesions[70]. One patient who received liquid injectable silicone was found to have a diffuse dermal granulomatous reaction seventeen years after her initial injections[70]. After receiving a weekly dose of subcutaneous methotrexate, there was a significant regression of her nodules[70]. Another 73-year-old woman had been treated with silicone filler 30 years ago and developed glabellar inflammatory lesions in the past 2 years[70]. While corticosteroids led to some improvement, 15 mg of weekly methotrexate for 6 months resulted in complete regression. However, the dose did lead to hepatic cytolysis which eventually resolved[70].

In the corresponding author's experience, a 40-year-old female patient developed delayed hypersensitivity 2 weeks after filler injections [Figure 5]. While aspiration and culture did not grow any organisms, she eventually improved with hyaluronidase. Of note, antibiotics were given to be safe in the case of an

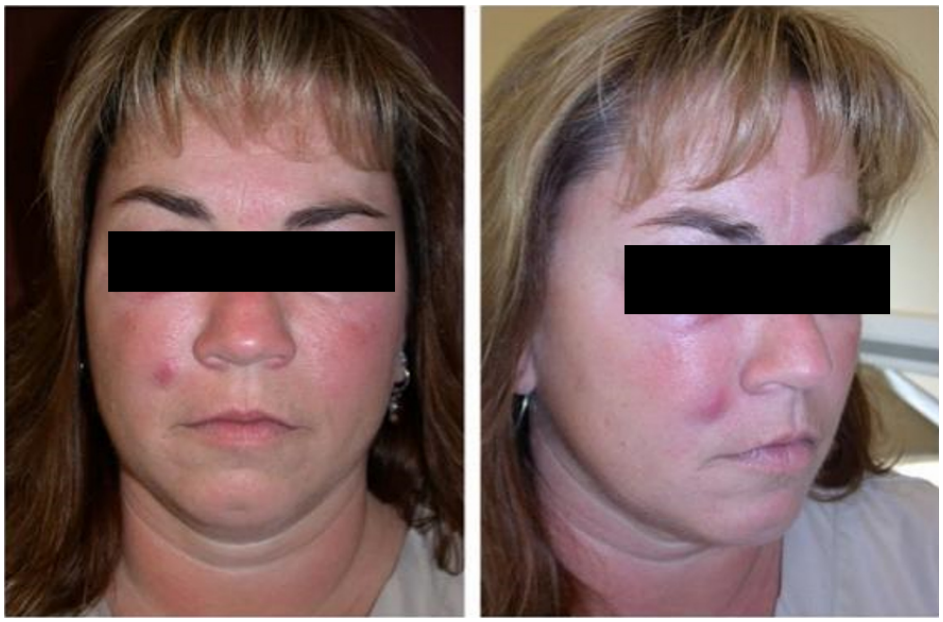

Figure 5. A 40-year-old female who presented two weeks after hyaluronic acid gel injections. Culture and aspiration showed no growth, and she improved with hyaluronidase. (Figure courtesy of Jill Foster, M.D.)

infectious etiology such as a biofilm. A similar algorithm was recommended by Alijotas-Reig *et al.*[54]. If a patient presents with a late inflammatory nodule, and there is fluctuation, incision and drainage should be performed to assess for infectious causes[54]. If there is no clinical improvement after 1 week, biopsy specimens should be assessed for histopathology and microbiological cultures. Meanwhile, antibiotics should be continued for several weeks[54].

Vycross

One factor that has been studied as a cause for delayed hypersensitivity reactions is inherent filler properties. Vycross (VYC) technology incorporates high-molecular-weight hyaluronic acid with low-molecular-weight hyaluronic acid and has been shown in studies to increase the number of delayed-onset nodules[17]. While the incidence of nodules was originally 0.02% as reported in 2002[71], the incidence increased to 0.5% to 4.25% after products from the VYC family were released[50,72]. One theory for why VYC technology has a higher incidence of these inflammatory reactions is that this form of HA has a higher proportion of low-molecular-weight hyaluronic acid, which has been shown to be proinflammatory[73,74].

In a paper reviewing 17 patients who developed these reactions after Juvederm Volbella filler, they noted that these nodules were characterized by a waxing and waning appearance, a location away from the injection site, a resistance to antibiotics, and a negative bacterial culture[72]. The authors recommended treating these delayed reactions with broad-spectrum antibiotics to ensure treatment of any potential biofilms, along with repeated hyaluronidase (30-100 IU) injections into the nodule, and short-term systemic steroids for severe inflammation or swelling[72]. Another paper described 23 cases of nodules after VYC, with symptoms including swelling, firm nodules, and lumps[50]. The authors recommended several treatment strategies as first-line therapies, including watchful waiting, intralesional hyaluronidase, oral prednisone, intralesional triamcinolone, and clarithromycin if a biofilm is suspected[50]. It is worth noting that individuals who developed these reactions and then retreated with VYC fillers did not develop repeated

episodes[50]. Interestingly, almost 40% of patients who developed a reaction had a flu-like illness or dental procedure before the reaction[50]. The rate of nodules did decrease from 1 case per 2.67 months to 1 case every 3 months after improved cleaning procedures[50]. Given that 40% of patients had an immune history prior to developing the nodule, the authors theorized that these nodules are more likely to happen when the immune system is already overactivated[50]. The authors theorized that these delayed nodules likely occurred from an inflammatory cause rather than an infectious cause, but mentioned that biofilms and other infectious processes should also be considered in the case of a new onset nodule[50].

Flu-like illness

Turkmani *et al.* published 14 cases of females who had an influenza-like illness and presented with redness and swelling in areas where filler had been previously injected[57]. Even though the injections were done anywhere between 2 to 10 months before the illness, the filler reactions started 3-5 days after the illness[57]. Patients were treated with steroids for 5 days and were tapered for another 5 days[57]. For four patients whose swelling did not resolve for one month , hyaluronidase was injected[57]. While the majority of patients had inflammation at all previously injected sites, a few patients did not have reactions at certain sites[57]. The authors hypothesized that the cause for that difference may have been the time since injection, because the nonreactive site was from injections more than 2 years ago[57]. Bhojani-Lynch also reported on several cases of inflammatory nodule reactions that started after the patients had an illness, including viral, cold sore, and GI symptoms[75]. The fifth case involved a patient who had a long-standing history of hay fever but did not have any systemic illness[75]. The cases mostly resolved with steroids and, in one case, hyaluronidase[75]. The hypothesis for this reaction is that macrophages may be stimulated after a severe systemic infection and begin triggering giant cell formations and foreign body granulomas[18,63,76]. Similar to Turkmani *et al.*, in one of the patients, two different brands were used for her fillers, but only one exhibited a hypersensitivity response[57]. This difference in reaction, combined with the knowledge of vycross technology, merits the question of whether certain filler properties interact more with the immune system to be more immunogenic[75].

These flu-like illnesses seem to have a similar course to the reactions that are being seen after COVID-19 vaccinations and illness. The management approach appears to be fairly consistent among both injections, with steroids serving as the primary management tool, followed by hyaluronidase for any remaining areas of swelling[57,75]. However, it is important to initially consider all clinically inflamed nodules as potential infections, and if certain features are present, the use of antibiotics should be considered[42].

COVID-19

There have been several reports of delayed Type-IV hypersensitivity secondary to SARS-CoV-2 infection as well as vaccination. Table 1 shows a review of all the recent case reports seen both after SARS-CoV-2 infection and vaccination. Munavalli *et al.* detail a case of a 50-year-old female who received two hyaluronic fillers in the cheeks, lips, and tear troughs over the course of a year, and tested positive for COVID-19 about 2 weeks after her last filler injection[55]. Two weeks after her positive test, she developed swelling in her periorbital region, lips, and cheeks, and reported a burning sensation in her lips[55]. She was initially treated with 2CCs of hyaluronidase. Although her pain transiently improved, she had another flare and was given additional hyaluronidase, as well as a 2-week course of prednisone and doxycycline[55]. Given a lack of improvement, she was injected with additional hyaluronidase, prescribed clarithromycin and prednisone, and a radiofrequency microneedling device was used to thermally dissipate the filler[55]. At the time of publication, mild periorbital edema still remained[55]. The recency of filler injection does not seem to play a

Table 1. Recent case reports of covid-19 delayed inflammatory reaction

Author	Demographics	Filler	Site of Injection	Time of filler presence before vaccine or illness	COVID-19	Time from vaccine or illness to symptom onset	Symptoms	Treatment	Resolution
Munavalli *et al.*[55]	50-year-old female	Hyaluronic acid-restylane lyft and restylane l to cheeks, lips, tear troughs	Cheeks, lips, tear troughs	15 days	Infection	(1) 15 days (2) 3 days after initial treatment	(1) Periorbital swelling erythema tenderness (2) Persistent edema erythema tenderness	(1) Hyaluronidase (2) Prednisone and doxycycline hyaluronidase radiofrequency micro-needling device clarithromycin prednisone triamcinolone	Patient reports intermittent mild edema under the eyes at the time of publication
Munavalli *et al.*[55]	36-year-old female	Hyaluronic acid-juvederm voluma to tear troughs juvederm ultra to upper and lower lip	Tear troughs, upper and lower lips	14 months	Moderna vaccine 1st dose	12 h	Tear trough tenderness infraorbital edema periorbital edema	30 mg cetirizine 5 mg lisinopril	Improvemet of tear trough swelling within 5 h of lisinopril At 1 day after treatment, patient returned to baseline
Munavalli *et al.*[55]	43-year-old female	Unknown	Tear trough filler	2.5 years	Pfizer vaccine 2nd dose	24 h	Tenderness under right eye swelling under left eye	Medrol dosepak	At 1 day after treatment, patient noted improvemet with a decrease in swelling
Michon[78]	45-year-old female	Hyaluronic acid-juvederm volift to lips and juvederm volux to chin	Lips chin	9 months	Unknown booster dose	24 h	Swelling at injection sites	Lisinopril 5 mg	Within 72 h, she had complete resolution
Savva *et al.*[121]	38-year-old female	hyaluronic acid-unknown	Lips	2 months	Pfizer vaccine 2nd dose	2 months	Painful erythematous edema on upper and lower lip	Methylprednisolone tablet	At 5 days, improvemet with a reduction in swelling and pain
Michon[122]	39-year-old female	Hyaluronic acid-juvederm volite to tear trough	Tear trough	6 months	Pfizer vaccine 1st dose	48 h	Tender, erythematous swelling at left tear trough	Watchful waiting	At 5 days, spontaneous resolution
Michon[122]	61-year-old female	Hyaluronic acid-juvederm voluma and juvederm volift to cheek, juvederm volux to chin and jaw, juvederm volbella to tear trough	Cheek chin jaw Tear trough	10 months	Pfizer vaccine 1st dose	Few days later	Intermittet facial swelling Left undereye swelling that persisted	75U hyaluronidase	At 48 h, complete resolution
Rowland-Warmann[123]	22-year-old female	Hyaluronic Acid-perfectha subskin for non-surgical	Nasal radix Nasal tip	4 months	COVID-19 infection	3 weeks	Edema, induration, erythema,	Watchful waiting	At 6 days, complete resolution

		rhinoplasty					tenderness around radix		
Shome *et al.*[124]	32-year-old female	Unknown	Periocular area	9 months	COVID-19 infections	1 month	Sudden swelling of periocular area	Oral anti-inflammatory treatment	Complete resolution in a few days
Kalantari *et al.*[125]	62-year-old female	Polycaprolactone in the back of her hands	Hands	2 years	Sinopharm 2nd dose	14 days	Hard nodules on back of hands	Dexamethasone topical corticosteroids Intralesional triamcinolone injections	No recurrence of lesions at 4 weeks
Ortigosa *et al.*[126]	35-year-old female	Hyaluronic acid-restylane classic and restylane lyft to lips, nasojugal furrow, malar, and chin region	Lips nasojugal furrow Malar Chin	16 months	AstraZeneca vaccine	24 h	(1) Induration and edema in lips and chin (2) Edema in malar and nasojugal sulcus	1) Prednisone (2) Prednisone	4 months after reaction, she remains with mild lip edema and is on antihistamines
Ortigosa *et al.*[126]	47-year-old female	Hyaluronic acid-unknown	Eyes	6 months	Pfizer vaccine 1st dose	4 weeks	(1) Edema in lower eyelids (September 2021) (2) Second episode of edema (October 2021) (3) Third episode of edema (December 2021)	(1) Prednisolone (2) Prednisolone 3) Lisinopril 5mg	At 1 day, adequate response after lisinopril 5 mg

role in swelling after COVID-19 vaccination. One patient who received tear trough filler 2.5 years ago developed tenderness and swelling in the area of injection 1 day after her second COVID-19 vaccine [Figure 6][55]. Her swelling improved with a Medrol dose pack[55]. Additional cases are detailed in Table 1.

Given the effect of COVID-19 mRNA on irreversibly binding to angiotensin-converting enzyme 2 (ACE-2), an accumulation of angiotensin II leads to an upregulation of CD44 glycoprotein[77]. This molecule has an affinity for finding free extracellular hyaluronic acid and low molecular-weight hyaluronic acid[77]. Given the proinflammatory effects of low molecular weight hyaluronic acid, this may be a cause for why these quiescent granulomas have an immunogenic reaction after several years[77]. Munavalli *et al.* suggested that lisinopril 5 mg can be considered for these delayed inflammatory reactions, and also recommend using ACE inhibitors prophylactically in a patient who may be at risk for developing this hypersensitivity reaction[77]. The use of lisinopril as a treatment option was also supported by Michon[78].

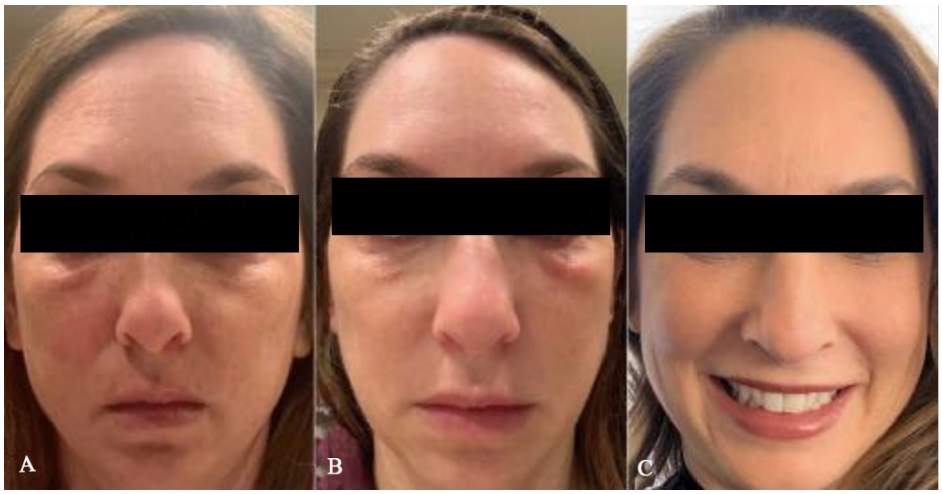

Figure 6. (A): Initial appearance of delayed inflammatory reaction to hyaluronic acid placed in the right tear trough; (B): Inflammation extending to the left tear trough; (C): Resolution of inflammation and majority of the swelling. Reproduced from Munavalli *et al*[55].

Rauso *et al.* published a review of 19 patients who experienced adverse effects after filler injections[79]. His review hypothesized that a high BDDE cross-linking rate or a low molecular weight hyaluronic acid filler would be more likely to have adverse effects[79]. Although the literature has detailed various cases of delayed hypersensitivity events following a generic viral illness, more literature will have to be published and reviewed to determine the best management for these events associated with COVID-19 infection and vaccination[57,75].

Biofilms

A biofilm is defined as a protected complex aggregate in which bacteria adhere to one another and to surfaces by secreting an extracellular matrix that serves as a protective barrier[80,81]. Biofilms are considered a chronic infection that begins at the time of filler injection[82]. Fillers have been shown to create a habitat that supports biofilm growth, with one study showing aggregates of *P. aeruginosa, S. epidermidis,* and *P. acnes in vitro*[83]. However, there may be differences based on the type of filler. For example, in an *in vivo* mouse model, only polyacrylamide hydrogen (PAAG) was able to sustain the growth of biofilm after 7 days, while calcium hydroxyapatite showed limited bacterial growth and HA gel did not show any[83].

The danger with these biofilms is that the bacteria can predispose to a low-grade and ongoing chronic infection, resistant to antibiotics[84]. With a low metabolic rate and an environment that favors plasmid transfer of genetic resistance, these biofilms have been seen to be up to 1000 times more resistant to antibiotics[40]. This is supported by Alhede *et al.* showing that after 72 h, the bacterial sensitivity to antibiotics was seen to be reduced and that while bacterial colonies were reduced, antibiotics were unable to completely eradicate the infection[83]. These infections can occur more frequently after treatment with permanent filler material, which was also supported by Alijotas-Reig *et al.*[54]. Christensen *et al.* conducted a case-control study that found that in patients with a long-term adverse reaction to polyacrylamide gel (swelling, pus, pain, warmth), 98% showed the presence of bacteria (including *Staphylococcus epidermidis* and *Propionibacterium acnes*) compared to 0% in controls[85]. These biofilms, when activated by trauma, can cause local or systemic infections or an inflammatory response[2,54].

Given that the thickness of a biofilm layer can be anywhere from 5-1200 micrometers, the extraction and culture of a sample can be very difficult[86]. However, the following methods are recommended: biopsy with utilization of peptide nucleic acid fluorescence in situ hybridization or with subsequent three-dimensional or direct observation using confocal laser-scanning microscopy[87]. However, cost must be considered for these newer detection methods[40].

In a study of 22 women with symptoms of late bacterial infections (LBI), an evaluation of their treatment regimen was performed[86]. This regimen involved puncturing the lesion and draining the pus and HA twice a week. After an allergy test, local hyaluronidase was injected into the lesion twice a week for 14-21 days[86]. Combination antibiotic therapy of moxifloxacin and clarithromycin was initiated for 14-21 days and a probiotic formulation was provided for the month of treatment with antibiotics to 1 month after completion[86]. If the nodule was between 0-0.5 cm, 45 units of hyaluronidase was given, with an increase in 30 units for every 0.5 cm (e.g., 1.5-2 cm would be given 135 units of hyaluronidase and 2.5-3 cm would be given 195 units of hyaluronidase)[86]. Using their approach, 17 patients were cured of their late bacterial infection (LBI), with five of the patients using it as first-line treatment and 12 patients using it as second-line[86].

A more general treatment approach involves drainage of the lesion, removal of the foreign body with hyaluronidase, combination antibiotic therapy and consideration of probiotics to provide physiological skin flora. A 36-year-old woman who had polyacrylamide dermal filler placed 2 years prior had presented to the surgeon with an abscess over her right cheek and eyelid[88]. Her abscess, which was later found to be positive for *Pseudomonas Aeruginosa,* was drained with an incision, drainage, and clindamycin[88]. Another treatment method that has been studied is low-dose triamcinolone mixed with 5-fluorouracil, as well as the use of an intralesional laser treatment procedure[40]. In a more preventative technique, a recent retrospective paper found that the administration of prophylactic antibiotics (azithromycin + moxifloxacin) in patients with permanent fillers reduced the incidence of inflammation and infection[89].

Non-inflammatory nodules

Although inflammatory nodules and other severe adverse effects are discussed frequently in the literature, non-inflammatory nodules are both common and clinically relevant. These nodules are usually secondary to overcorrection or erroneous placement of filler[58]. Some examples of overcorrection include skin-colored papules after poly-L-lactic acid secondary to superficial injection, sunken eyes, or subocular lines above the infraorbital rim[58]. Lumps are commonly seen in the tear trough, periorbital regions, lips, and perioral areas[90]. Given that these are areas of high mobility that could be difficult to correct, the use of semipermanent fillers is discouraged in this area and overcorrection can lead to irregularity and nodule formation[90]. In these high-risk regions, HA products are preferable as they can be corrected with hyaluronidase[90].

Two early pilot studies looked at how hyaluronidase could be used to correct HA gel injections and showed a trend of a dose-response relationship[91]. Rzany *et al.* conducted a review that looked at how hyaluronidase has been used to reduce these depots[44]. A majority of the studies reviewed by Rzany *et al.* involved 75 units of hyaluronidase to reduce unwanted depots[44]. The recommendation from that paper was to inject 7.5 U to 15 U per injection point[44].

Given that fillers have different properties and resistance, Zhang-Nunes *et al.* and Ryu *et al.* looked at how various hyaluronidase concentrations may affect different fillers both in an *in vivo* and *in vitro* setting[92,93]. In the *in vivo* studies, Voluma was found to require higher doses of recombinant human hyaluronidase

(RHH) for dissolution, requiring more than 20 U of RHH/0.2 mL filler *in vivo*, while Restylane dissolved with 2.5 U of RHH/0.2 mL[92]. All of the fillers also showed a dose-response curve[92]. In an *in vitro* study, Restylane-L and Restylane Lyft were shown to be very dissolvable with 2.5 U of RHH/0.2 mL, while Restylane Refyne, Restylane Defyne, Juvederm Ultra Plus, Vollure, Versa, and Voluma were least dissolvable with 20 U of RHH/0.2 mL[93]. Reversibility is discussed further in this review paper.

It is recommended to use a 30-gauge needle for superficial nodules and a 27-gauge or 26-gauge needle for deeper nodules[44]. If the nodule is superficial, Rzany *et al.* recommend injecting just beneath it[44]. For calcium hydroxyapatite filler, the use of lasers has been shown to improve nodule formation[94,95]. Excision should only be considered as a last resort[2].

It is important to note that hyaluronidase can also be associated with adverse effects such as post-injection pruritus and allergic or anaphylactic reactions[96]. Allergic reactions can manifest as immediate hypersensitivity reactions as well as delayed hypersensitivity reactions[96,97]. One patient developed erythematous edema two h after hyaluronidase injection, which continued for 7 days[97]. After a positive skin test reaction to 15 U hyaluronidase on the right arm, she was diagnosed with an allergic reaction to hyaluronidase[97]. The patient later improved with systemic steroids, antihistamines, and steroid cream[97].

Reversibility

Given the different properties of the available fillers on the market, two studies evaluated the dosages of recombinant human hyaluronidase (RHH) that were needed in the dissolution of various different fillers[92,93]. Our group then measured solubility *in vitro* by injecting a 0.2 mL aliquot of filler with different concentrations of hyaluronidase ranging from 2.5 U to 40 U. Restylane-L and Restylane Lyft were found to be the most dissolvable both *in vivo* and *in vitro*, responding to 2.5 U of R/0.2 mL of filler[92,93]. On the other hand, Juvederm Voluma, Versa, Vollure, Juvederm Ultra Plus, Restylane Refyne, and Restylane Defyne were least dissolvable by hyaluronidase, with Voluma requiring greater than 20 U of RHH/0.2 mL of filler for *in vivo* dissolution and the other fillers were found to be resistant to dissolution with 20 U of RHH/0.2 mL of filler *in vitro*[92,93]. In a recent study conducted by our group, RHA 2, RHA 3, RHA 4, Restylane Contour, and Restylane Kysse were all found to be relatively resistant to dissolution with 40 U of RHH/0.25 mL of filler *in vitro*[98]. However, a difference in consistency was seen between the more superficial RHA2 filler compared to the deeper RHA4 filler, with RHA2 appearing more dissolvable with hyaluronidase[98]. Our group then modified our methods to better assess for solubility-20 units of hyaluronidase were injected into 0.2 mL of filler every 30 min over 3 h. Using this methodology, Restylane-L, Restylane Lyft, and RHA-1 were classified as least resistant. The moderately resistant fillers were Juvéderm Volbella, Revanesse Versa, Belotero Balance, and Restylane Silk. The fillers classified as most resistant were Belotero Volume, Belotero Intense, Juvéderm Ultra XC, Juvéderm Ultra Plus XC, Juvéderm Vollure, Juvéderm Voluma, Juvéderm Volux, Restylane Contour, Restylane Defyne, Restylane Kysse, Restylane Refyne, RHA 2, RHA 3, and RHA 4. These fillers had still not completely dissolved at the three-hour time point, at which a total of 120 units RHH had been injected (data unpublished).

Hyaluronic acid is a naturally occurring polysaccharide of the extracellular matrix and consists of repeating monomers (D-glucuronic acid and N-acetyl-D-glucosamine disaccharide units) linked together by a B-1,4 glycosidic bond. These natural bonds can be degraded by natural enzymes such as hyaluronidase as well as free radical degeneration from local tissue elimination[99]. To strengthen the duration of these fillers, many of these fillers are cross-linked by a variety of agents, most commonly 1,4 butanediol diglycidyl ether (BDDE), and by manufacturing techniques including but not limited to Vycross, Resilient hyaluronic acid,

and nonanimal stabilized hyaluronic acid (NASHA)[93]. One of the main determinants of dissolvability depends upon the (1- > 4) linkages between glucuronate and N-glucosamine, as they are the ones that can be dissolved by hyaluronidase. The number of these bonds will affect the longevity of dissolvability. Additionally, based on the cross-linking pattern, it may prove difficult for the hyaluronidase to get in between the bonds and act as a dissolving agent, especially for the newer fillers. Another contributing factor is the particle size of the HA filler, which is thought to contribute to its duration in the tissue[100]. One of the most dissolvable fillers in our study, Restylane-L, was found to have an average particle size of 472 nm, while Juvederm Voluma, which was in the least dissolvable category, had a particle size of 703 nm[101].

Preventative measures

Given the potential of these complications to affect patient care, prevention is an important consideration. In this section, we discuss the various factors that can reduce the risk of these complications. We conclude with a discussion on the use of imaging in determining both the presence of filler as well as complications.

Patient factors

It is vital to ensure that the right patient is selected for this procedure by evaluating for history that could be a potential contraindication, including allergies, systemic diseases, current medications, and previous procedures[102]. In order to minimize bruising, patients should be advised to stop all blood thinners 1 week prior to the procedure, if medically appropriate[11,103]. Thin skin (0.4 mm thick) is also considered a contraindication for all fillers[11,18]. Inflammatory or infective conditions that cause skin barrier disruption may predispose the patient to future infections[104]. Patients with active skin infections in the area of treatment should not be treated[11,105]. However, pretreatment of these active conditions can allow for restoration of barrier function[102].

Several papers have shown that viral illnesses predispose to nodule formation, so eliciting a history of recent illnesses is very important[50,57,75]. Given the incidence of delayed hypersensitivity reactions after COVID-19 vaccination, we also believe that a recent vaccination or viral illness should warrant a delay of filler injection. Patients with autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, mixed connective tissue disease, and Hashimoto's thyroiditis should also warrant caution before receiving filler treatments, given that the risk of systemic immune upregulation can predispose to delayed inflammatory reactions[11,38,106]. For a similar reason, infections such as sinusitis, periodontal disease, ear, nose, or throat infection or dental abscesses should necessitate a pause in treatment until there is resolution of their condition[38,106]. Getting a thorough history of previous fillers and products that patients have received may also help prevent complications of late-onset nodules[43].

Aseptic technique

Given the inherent risks of filler injections and the potential cause for infection through the introduction of a foreign body, aseptic and clean practices should be highly emphasized[38]. A global panel emphasized the implementation of "continuous prep", in which the entire face is cleansed with make-up removed and applying antiseptic to the full face[38]. Treatment should be initiated in areas away from the nose and mouth, as they are more prone to bacteria[38]. Each injection site should be cleaned and recleaned before treatment and a disposable dressing tray should be used[38]. Other important factors were that alcohol alone was not sufficient and chlorhexidine gluconate (CHG) may be preferable[38]. In the corresponding author's clinic, she uses betadine if she is injecting close to the eyes or chlorhexidine if she is not injecting close to the eyes. The authors recommend using two different types of preparation (hypochlorous acid followed by alcohol), covering the patient's hair, removing all make-up, and advising the patient not to use cosmetics or place tap water on the face for at least 4 h.

Procedure factors

There are some elements of injection technique that can be discussed to prevent complication risk. To avoid the irregular surface contours seen in areas that have low subcutaneous fat, filler should be placed on a deeper plane[107]. In the tear trough region, the authors recommend using a serial puncture technique to advance the needle to the periosteum along the inferior orbital rim and inject small boluses of product[107]. Studies have shown that rapid injection speed, aggressive fanning, high-volume filler deposits, and large bolus size have increased bruising and delayed inflammatory reactions[108,109]. Therefore, the injection technique should usually involve a slow speed and low pressure along with a small bolus size[102]. It is recommended not to exceed a volume of 0.2 cc per bolus[38]. Bruising can also be prevented by using side lighting and cleaning the skin with alcohol pads to distinguish the bluish hue vessels[5]. Additionally, canalization of the superficial fat with a 1.25-inch needle can be considered as it allows for injection without repeated perforation of the dermis[5]. Extra precautions should be taken when injecting the perioral areas and it is preferred to inject these areas last given the high presence of bacteria[38].

Posttreatment care

It is very important to educate the patient about ideal post-injection care including washing hands immediately before treatment, avoiding touching the area after treatment, and keeping hands clean after treatment[38]. Clinicians should ideally provide patient consent forms that explain aseptic guidelines and posttreatment care[38].

Imaging advancement

Imaging has taken on a larger role in diagnosing non-ischemic complications. This portion of the review aims to discuss the different imaging forms and how they are involved in the diagnosis and management of non-ischemic complications.

Ultrasound has been studied to help determine the location of filler in the skin[110]. A recent study characterized how various dermal fillers appeared in ultrasound imaging, with heterogeneous patterns being characteristic of healthy skin or after integration of resorbable fillers[110]. A "fine-grain snowfall pattern" is more typical of silicone or biopolymers-based fillers, while "coarse grain snowfall" is seen in calcium hydroxyapatite fillers and polycaprolactone fillers[110]. This may prove to help with patients who do not remember exactly what type of filler or where they had the filler placed. While previous filler location is usually assessed clinically, the use of ultrasound could assist in determining the true location of filler, and how much it has been incorporated in the tissue with the goal of achieving better aesthetic outcomes. Additionally, ultrasound can also be used to determine where to place hyaluronidase in cases of overcorrection or late-onset nodules[111]. Figure 7 demonstrates the visualization of a filler nodule more than two years after it was initially injected, and after the patient believed it had completely dissolved. Ultrasound has also been able to distinguish between granulomas and dermal filler deposits, highlighting the idea that, in the future, this technology may be able to discern different pathologies as well[112]. Our team evaluated five point-of-care ultrasounds (POCUS) for ophthalmic and facial aesthetic applications. For overall image quality, the Clarius L20 received the highest mean rating, followed by the Clarius L15, Vscan Air, Butterfly IQ$^+$, and the Lumify. The L20 was also ranked first for filler, artery, and orbital imaging[113].

CT and MRI have also been able to identify the different types of fillers. Collagen on CT appears to show fluid attenuation with a streaky appearance; it appears hyperintense on T2-weighted (T2W) and short tau inversion recovery (STIR) images due to high water content[114,115]. Calcium hydroxyapatite appears with well-defined linear streaks and is hyperattenuating on CT; on MRI, calcium hydroxyapatite fillers have low to intermediate signal intensity on T2W images and show mild post-contrast enhancement[115,116].

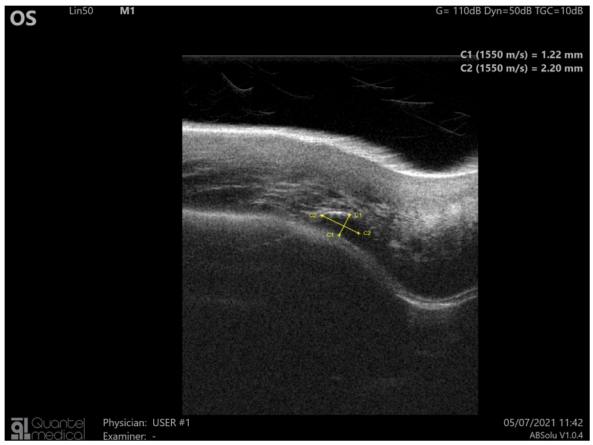

Figure 7. Visualization of a filler nodule more than 2 years after initial injection with the absolu ultrasound biomicroscopy.

Hyaluronic acid, similar to collagen, appears strongly hyperintense on T2W and STIR images on MRI but appears more as areas of soft tissue attenuation on CT[115]. Poly-L-lactic acid appears hypointense on T2W images and shows soft tissue attenuation on CT[115]. In contrast, polyalkylimide and polyacrylamide hydrogels appear hyperintense on T2W and show an area of well-defined fluid attenuation on CT[115]. Silicone fillers show as hypointense on T2W and slightly hyperdense on CT[114,115]. Studies currently differentiate on whether types of fillers can accurately be differentiated based on MRI features[115,116]. MRI has also recently been shown to demonstrate hyaluronic acid imaging almost 6 years after injection[117].

MRI has also been shown to assess the migration of filler[118]. In one study, 27 migrations that had not been recognized clinically had been identified by an MRI[118]. Figure 8 shows the depiction of hyaluronic acid in the mental crease, mentalis, and gnathion after initial injection. MRI has also been studied to look at differentiation between a foreign body granuloma and a non-inflammatory nodule[115]. The MRI of foreign body granulomas has been shown to have post-contrast enhancement, although to varying degrees[115]. The study found that nodular or diffuse enhancement correlated with foreign body granulomas, while a more streaky enhancement pointed more to cellulitis[115]. One study found a 100% correlation between post-contrast enhancement and granuloma formation, while non-inflammatory nodules did not show that same enhancement[119]. Another study also found a strong agreement between non-inflammatory nodules as seen in MRI and clinical assessment (85%), a good correlation between abscesses as seen on MRI and clinical assessment (60%), and a fair correlation between low-grade inflammation and clinical inflammation (32%) [118]. Therefore, it seems that MRI could be clinically useful in the identification of delayed and severe non-ischemic complications.

CONCLUSION

As dermal fillers continue to increase in popularity, the rate of complications continues to rise as well. While many of these complications are benign and self-resolve, several complications including foreign body granulomas, biofilms, and non-inflammatory nodules pose an significant concern and issue for clinicians. The COVID-19 pandemic has also brought up considerations for the management of delayed hypersensitivity nodules that are occurring after vaccination or illness. Proper counseling and selection of the patient, implementation of an aseptic technique, and improving procedure technique can help in the prevention of some of these complications. Understanding the reversibility of the different fillers is important in managing non-ischemic complications such as overfill and nodules, with titration specific to each type of HA filler. The role of imaging appears to be taking on an increasing role in the diagnosis of

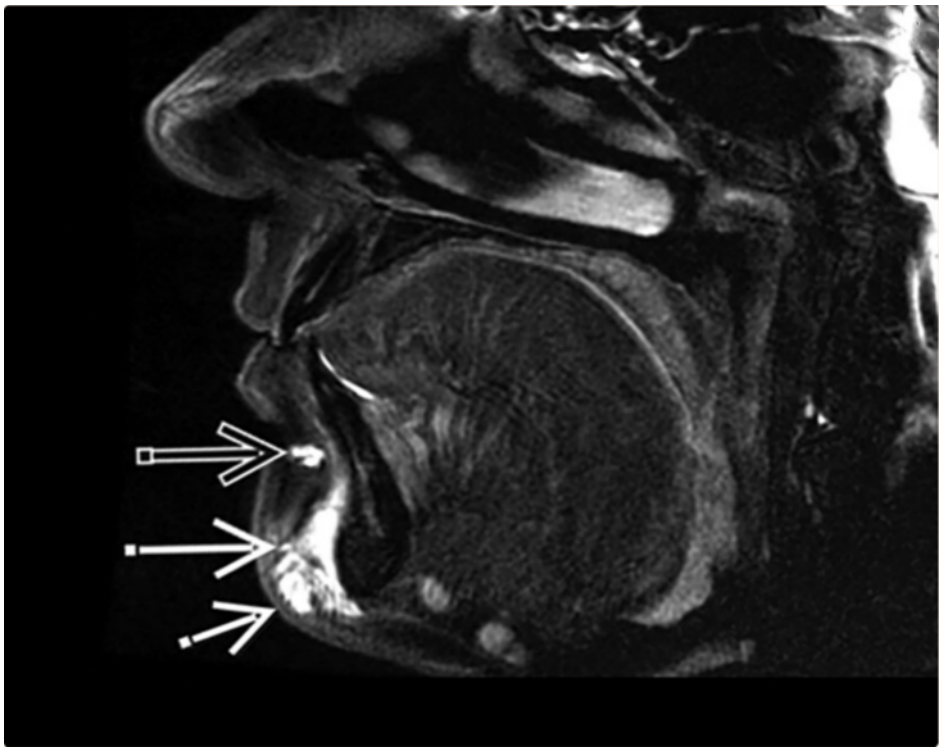

Figure 8. Initial MRI sagittal T2 fat saturation, showing HA signal in the mental crease (open arrow), mentalis and gnathion (closed arrow), and mentalis and the menton (short arrow). Reproduced from Master *et al.*[120].

several non-ischemic complications and will be an area of upcoming innovation to improve patient outcomes.

DECLARATIONS

Authors' contributions

Made substantial contributions to the conception and design of the study and performed data analysis and interpretation: Mehta P, Li J, Woodward J, Zhang-Nunes S

Availability of data and materials

Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable. Informed consent was obtained from the patients involved in this manuscript.

Consent for publication

The pictured patients who were treated by the authors of this manuscript have given their approval to have their images published for research purposes.

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