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REVIEW ARTICLE

Inflammatory Nodules Following Soft Tissue Filler Use: A Review of Causative Agents, Pathology and Treatment Options

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Abstract Nodule development is a common complication following the use of fillers for soft tissue augmentation and is commonly categorized as inflammatory or non-inflammatory in nature. Inflammatory nodules may appear anywhere from days to years after treatment, whereas non-inflammatory nodules are typically seen immediately following implantation and are usually secondary to improper placement of the filler. Although inflammatory nodules are more common with permanent fillers such as silicone, inflammatory nodule development following administration of temporary fillers such as hyaluronic acid and collagen has also been reported. Treated many times with corticosteroids due to their anti-inflammatory properties, inflammatory nodules may be secondary to infection or biofilm formation, warranting the use of alternative agents. Appropriate and prompt diagnosis is important in avoiding delay of treatment or long-term complications for the patient. This paper addresses the etiology, development, and studied treatment options available for inflammatory nodules secondary to each of the major classes of fillers. With this knowledge, practitioners may expeditiously recognize and manage this common side effect and thus maximize functional and aesthetic benefit.

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1 Introduction

Fillers for the correction of scars, lipoatrophy, or overall cosmesis are widely used in dermatology, plastic surgery, and general medicine. The use of harvested material to correct defects in appearance was first recorded over a century ago, with the use of autologous fat transplantation [1]. Intradermal fillers quickly evolved to include synthetic materials such as paraffin and silicone, and were used in Japan during World War II to help women appear more westernized, as well as in Nevada during the 1960s for unregulated breast enhancement [1, 2]. Initially thought to be a cosmetic panacea, these intradermal fillers soon began to manifest serious side effects, including migration, severe inflammatory responses, and granulomatous reactions [3].

One common method of classifying fillers is by duration of action (Table 1). Temporary fillers include collagen and hyaluronic acid, while permanent fillers include silicone, polymethylmethacrylate (PMMA), and polyacrylamides. Calcium hydroxylapatite and poly- L-lactic acid maintain a semi-permanent duration of up to and around 2 years [4, 5]. Autologous fat transplantation cannot be reliably classified by duration; it is believed that handling, processing, and overall quality of the adipose tissue account for such variability [6].

Fillers for soft tissue augmentation can also be delineated by mechanism of action, either serving as direct volumizers or relying on a secondary foreign-body host response to achieve the desired effect (Table 1). Volumizers typically include hydrophilic substances such as collagen, hyaluronic acid, and polyacrylamides, or, in the case of silicone, oil. Fillers that primarily rely upon eliciting a foreign-body reaction (calcium hydroxylapatite, poly-L-lactic acid, PMMA) contain synthetic particulate materials that serve as the nidus for such a response [7].

Table 1 Mechanism of action and duration of major soft tissue filler classes

Soft tissue filler	Mechanism of action	Approximate duration
Collagen	Direct volume	Temporary (3–6 months)
Hyaluronic acid (HA)	Direct volume	Temporary (6–9 months)
Poly-L-lactic acid (PLLA)	Secondary foreign-body host response	Semi-permanent (up to 2 years)
Calcium hydroxylapatite	Secondary foreign-body host response	Semi-permanent (2–5 years)
Silicone	Direct volume and secondary foreign-body host response	Permanent
Polymethylmethacrylate (PMMA)	Secondary foreign-body host response	Permanent
Polyacrylamides	Direct volume and integration into host tissue	Permanent
Autologous fat	Direct volume and integration into host tissue	Variable

Polyacrylamide gels and silicone both serve as direct volumizers but also maintain secondary mechanisms of action such as integration into host tissues or generation of a foreign-body reaction, respectively.

US FDA regulation of filler production and administration has greatly reduced, but has not eliminated, the incidence of adverse effects in the US. Rare long-term and/or serious adverse events associated with filler use include the development of fistulas [8], migration or displacement [9], sensory dysfunction [10], scarring [11], embolization [12], necrosis [13], and chronic infection [7]. Nodule formation is a much more common complication with significant morbidity to the patient in both the short- and long-term. While non-inflammatory nodules secondary to improper placement are those typically seen immediately following implantation, inflammatory nodules may appear at any time from days to years after treatment.

Inflammatory nodules have historically been thought of as granulomatous reactions occurring many months or years after treatment. While this is often true, they can also result from varied etiologies, including infection, hypersensitivity reactions, or sterile abscesses. The time course and clinical presentation of these inflammatory nodules also varies widely. For example, presentation several months to years after treatment is typically more indicative of a foreign-body granulomatous reaction (Table 2) [14]. In order to identify the proper treatment, it is important to establish the type and quantity of filler used, the time to development of the nodule, and the initial clinical presentation. Unfortunately, this information is often lacking due to poor patient recall, making treatment decisions difficult. In these cases, therapies are typically focused on reducing the inflammatory response, which is generally suspected to be responsible for the development of these nodules.

Many therapies have been used for the treatment of inflammatory nodules following filler use, albeit the choice of therapy is often based on practitioner expertise. These therapies include, but are not limited to, topical, oral or intralesional corticosteroids, oral antibiotics, intralesional hyaluronidase, 5-fluorouracil (5-FU), allopurinol, surgical excision, lasers, warm compresses and massage, or a combination of the aforementioned. This review will address various treatment options for each of the major classes of fillers used today, with the goal of helping practitioners better understand the etiology of inflammatory nodules following filler use and therefore better tailor treatment strategies.

2 Collagen

Currently, collagen fillers have been voluntarily withdrawn from the US market and are rarely used in Europe and other parts of the world. Despite this recent decrease in availability, the difficulty in predicting the likelihood of a future resurgence or the development of other collagen-based filler materials warrants discussion of collagen-based filler complications. Approximately 5 % of the population are allergic to, or prone to, developing a hypersensitivity to bovine collagen [6].

Heise and colleagues have reported a case of chronic granulomatous inflammation secondary to a delayed-type hypersensitivity reaction to bovine collagen, despite negative skin testing. Nine days after filler administration and 19 days after a single negative skin test, one patient developed a granulomatous reaction at the original testing site [15]. Topical corticosteroids were administered twice daily for 5 weeks, daily for 6 additional weeks, and, finally, every 2 days until the nodules eventually resolved, either a result of corticosteroid administration or natural degradation of the implanted collagen. Two skin tests, spaced 4 weeks apart, may therefore be beneficial prior to bovine collagen filler use [16].

Porcine- and human-derived collagen fillers have since been developed in an attempt to reduce the incidence of this adverse event [17, 18]. Despite the reduced

Table 2 Time frame of nodule development for certain fillers

Appearance of 'nodules'	Possible symptoms	Pathophysiologic process	Responsible fillers
Immediately	None	Uneven filler placement	Any
Days–weeks	Self-limited	Reaction to injury	Any
	Erythema, pain	Infection	Polyacrylamide, any
Weeks–months	Palpable but not visible, pruritus, erythema	Hypersensitivity reactions	Collagen, HA, PLLA
	Pain, erythema	Sterile abscesses	HA
	Induration, erythema	Infection	Polyacrylamide
Months–years	Gross disfigurement, pain, pruritus	Foreign-body granuloma or chronic, low-grade infection	PMMA, silicone, HA + acrylics
	Firm, mobile, photosensitive	Cyst (unknown etiology)	Polyacrylamide
	Soft, non-tender	Fat hypertrophy	Autologous fat

HA hyaluronic acid, *PLLA* poly-L-lactic acid, *PMMA* polymethylmethacrylate

immunogenicity found in porcine collagen, as well as a relatively short duration of effect lasting 3–6 months, nodule formation has been reported after use of collagen fillers several months after treatment [19].

Although not thought to be representative, in one 2008 study there was a reported 80 % (16 out of 20) incidence of nodule formation when using porcine collagen for lip augmentation [19]. Furthermore, collagenase was ineffective in dissolution of these nodules. In order to achieve resolution with no recurrence, surgical excision and drainage were required. In the patients who did not undergo surgical removal, hyaluronic acid was placed between nodules to help even irregularities. At 15 months' follow-up, six of these patients continued to suffer from visible and palpable nodules in the lips.

Aside from hypersensitivity reactions, collagen fillers are thought to possess an overall decreased incidence of side effects when compared with other forms of biological implants.

3 Hyaluronic Acid

Hyaluronic acid is a polysaccharide present in nearly all species, including bacteria and mammals [20]. For this reason, it is generally considered immunologically inert, enabling it to serve as an ideal biological implant. Given its compatibility and temporary duration of approximately 6–9 months, hyaluronic acid is not typically associated with many long-term side effects. However, a recent study demonstrated nodule formation from 1 month to 3 years after hyaluronic acid implantation [13]. Despite its low immunogenicity, hyaluronic acid implantation in soft tissue can also lead to delayed-type hypersensitivity reactions that may present as foreign-body granulomas, sterile abscesses, or non-inflammatory fibromas (Table 3) [7, 21]. Histology of the granulomatous reaction reveals a lymphocytic infiltrate with macrophages and the presence of foreign-body giant cells. As the name suggests, abscess content culture is typically negative, yet this does not exclude the presence of bacteria [7, 22–24]. In comparison to other non-epidermal tissues, hyaluronic acid has a higher (600 ms) T2-weighted magnetic resonance imaging (MRI) relaxation time [25]. Additionally, if placed too superficially under the skin, 'blue' nodules may appear as a result of light scattering through the clear filler, otherwise known as the Tyndall effect [26].

The reported incidence of hypersensitivity reactions to hyaluronic acid is typically low; one 4-year retrospective study reported a rate of approximately 0.6–0.8 % [22]. Although minimal, this level of risk may warrant skin testing prior to use [27, 28]. Improvement of nodules secondary to hypersensitivity reactions has been reported with administration of antibiotics alone [22, 29] or in combination with hyaluronidase [10, 13], as well as intralesional [30], topical [31] or oral corticosteroids [22, 30, 31], and surgical drainage or excision [31]. Nodules in these cases have also been reported to resolve spontaneously [31].

4 Hyaluronic Acid with Acrylic Hydrogels

In an attempt to increase the duration of hyaluronic acid fillers to a semi-permanent state, formulations of hyaluronic acid with acrylic hydrogels have been developed. With the addition of acrylic hydrogels such as ethylmethacrylate (EMA) and polyhydroxyethylmethacrylate (PHEMA), however, the incidence of nodule formation has increased secondary to the introduction of foreign-body particles. This has resulted in reported cases of palpable red nodules developing months to years after injection [24, 32–34].

Table 3 Reported delayed-type hypersensitivity nodule formation following hyaluronic acid filler use

Reference	*n*	Time to development	Pathology	Treatment	Resolution
Raulin et al. [94]	1	3 days after last session, 18 months after first	FBG	None	Spontaneous resolution after 6 weeks
Shafir et al. [23]	1	2 months after last session	Sterile abscess	Drainage IL corticosteroids	No complete follow-up
Lupton and Alster [95]	1	2 weeks after third session; 14 months after first session	Sterile abscesses and fibrotic nodules	PO minocycline PO corticosteroids Warm compresses IL corticosteroids	Resolved with one episode of recurrence
Lowe et al. [96]	6	6–8 weeks after injection (first injection in 3 patients)	Inflammatory nodules, no FBGs	IL corticosteroids in 3 patients	Eventual resolution of all lesions
Honig et al. [31]	1	3 months after last session	Sterile abscesses and FBG	Drainage	Resolution with several recurrences
Andre [22]	18	Few weeks to 6 months	Inflammatory nodules, non-inflammatory nodules, sterile abscesses	Topical corticosteroids ($n = 2$) IL corticosteroids ($n = 13$)	Complete resolution ($n = 18$) Spontaneous resolution ($n = 3$)
Pinheiro et al. [97]	1	6 days after last session, 5 months after first	FBG	IL corticosteroids Oral corticosteroids	Complete resolution
Ghislanzoni et al. [98]	1	5 weeks after first session	FBG	Topical antibiotics Topical corticosteroids	Complete resolution
Bardazzi et al. [21]	1	10 days after final session, 2 years after first session	FBG	Topical corticosteroids IL corticosteroids	Mild improvement with corticosteroids, spontaneous resolution 1 year later
Alijotas-Reig and Garcia-Gimenez [99]	10	Average 10 months after last session	Inflammatory nodules ($n = 7$), sterile abscess ($n = 1$)	NSAIDs Antihistamines HCQ Oral corticosteroids	Complete resolution ($n = 4$), recurrences ($n = 4$), lost to follow-up ($n = 2$)
Micheels [28]	4	2 days to 11 months after treatment	FBGs	Not mentioned	Not mentioned
Shahrabi Farahani et al. [100]	3	4 and 24 months after session. Third patient unknown duration	Fibroma; unassociated with foreign-body reaction	Not mentioned	Not mentioned

FBG foreign-body granuloma, *HCQ* hydroxychloroquine, *IL* intralesional, *n* number of cases, *NSAIDs* non-steroidal anti-inflammatory drugs, *PO* per oral

Histologically, a foreign-body reaction within these nodules is noted, with marked accumulations of macrophages and giant cells [33, 34]. In addition, there is evident fibrosis and necrosis, as well as pink polygonal foreign bodies trapped within cystic spaces, a finding that is similarly seen in biopsies of nodules taken from patients treated with PMMA [24]. In nodules appearing years after initial filler application, calcifications may also be appreciated [34]. While these foreign-body granulomas are likely to be caused by the acrylic materials within the formulation, hyaluronic acid itself has been implicated in the development of foreign-body granulomas as well. Nodule formation in hyaluronic acid/acrylic hydrogel compounds therefore may be a result of both hyaluronic acid itself as well as its synthetic additives [33].

In a study evaluating the natural host response to hyaluronic acid/acrylic hydrogel filler implantation, Bergeret-Galley and colleagues [32] found that fibroblasts develop around the particles approximately 1 month after implantation, with full infiltration at 6 months. By implanting the material into the dermal-hypodermal junction and maintaining a retrograde linear technique, these authors noted an overall decreased incidence of nodule formation and adverse events. The authors recommended against injecting into the mucosal lips or vertical lip lines in healthy patients and recommended avoidance of treating patients with autoimmune inflammatory disease.

Both intralesional corticosteroids and intralesional 5-FU have been reported to be effective in treating nodules following hyaluronic acid/acrylic hydrogel injection [32, 33]. Oral antibiotics may also demonstrate significant benefit [29, 35].

5 Poly-L-Lactic Acid

Poly-L-lactic acid, the L-isomer of polylactic acid, is currently FDA-approved for the treatment of facial lipoatrophy in patients with human immunodeficiency virus (HIV) but can be used off-label for other forms of soft tissue augmentation [36, 37]. Aside from silicone, poly-L-lactic acid is most commonly implicated in delayed-onset inflammatory nodule formation. One study reported an incidence of nodules in approximately 44 % of patients 24 months after treatment [38]. While not typically visible, these nodules are almost always palpable and can appear anywhere from 6 to 60 months following implantation [38–40]. It is important to stress that most nodules due to poly-L-lactic acid are secondary to improper (superficial) placement or too-high concentrations [24, 41]. Gentle massage may help to alleviate the acute appearance of lumpiness after implantation.

Clinically, these nodules may appear as cystic reactions or inflammatory nodules [24]. Histologically, biopsies of nodules demonstrate a granulomatous reaction with heavy lymphocytic infiltrate and cystic spaces that exhibit birefringence under polarized light [24]. Unlike with hyaluronic acid/acrylic hydrogels, use of poly-L-lactic acid typically does not result in fibrosis or necrosis [34]. Unfortunately, minimally invasive techniques have demonstrated little success in reducing or eliminating these nodules. While they have been reported to resolve spontaneously, nodules formed after poly-L-lactic acid use are resistant to many therapies and are most successfully treated with surgical excision [24, 34, 38–40].

6 Calcium Hydroxylapatite

Calcium hydroxylapatite is the heaviest of all fillers; it is semi-permanent and is comprised of calcium hydroxylapatite crystals suspended in carboxymethylcellulose gel. It has low immunogenicity due to synthetic production, and is typically used for moderate to severe soft tissue volume loss.

Placement of the filler into the deep dermis and subcutaneous fat as well as avoidance of dynamic areas, such as the perioral region, is recommended to minimize risk of migration and nodule formation. Because of the deep placement of the filler, however, intra-procedural correction is difficult. Gentle massage several times a day for 2–3 weeks may help the acute appearance of lumpiness after implantation, although this technique is more successful with poly-L-lactic acid [42].

Delayed-onset nodules secondary to calcium hydroxylapatite implantation appear white or yellow under the skin and occur almost exclusively in the lips, likely as a result of migration [7, 43, 44]. They typically appear within 12 weeks of treatment and can be painful [42]. Upon microscopic examination, calcium hydroxylapatite crystals can be appreciated within diffuse areas of fibrosis or within macrophages [42]. Computed tomography (CT) reveals relatively highly attenuated linear streaks or clumps between 280 and 700 HU [25]. To treat nodules secondary to calcium hydroxylapatite implantation, it has been shown that minimally invasive therapies such as intralesional corticosteroids or fractional carbon dioxide (CO_2) laser may be helpful, but in refractory cases surgical excision is the most definitive option [42, 44, 45]. While implantation of calcium hydroxylapatite into the lips is not recommended, decreasing the overall quantity of injected filler and placing the implantation between the orbicularis oris muscle and mucosa, may help to minimize the development of nodules in this area [42, 44].

7 Silicone

Despite advances in purification processes and surgical technique, injectable silicone for soft tissue augmentation maintains a high incidence of adverse events, particularly migration and diffuse granulomatous reactions years after injection. Several therapies for these disfiguring events have been studied, yet none have proven universally successful. While surgical excision is considered the final recourse, it is often difficult to excise the entirety of the affected area due to migration and spread of the granulomatous reaction to distant sites [46]. These aptly named 'siliconomas' have been extensively reported in the literature. A recently described perilesional surgical approach may prove of benefit in long-standing lesions secondary to materials such as unregulated silicone [47, 48]. These authors found that creating perilesional excisions along relaxed skin tension lines not only aids in removal of the foreign substance, but also reduces the appearance of post-surgical scarring.

In one study, Christensen and colleagues [34] compiled 88 published cases of silicone granulomas between 1969 and 2004, along with any available outcomes to therapy. Of these cases, 29 were excised, 13 were treated with intralesional corticosteroids, 9 with antibiotics, 7 with oral corticosteroids, and 3 resolved spontaneously. While some of these modalities were used in combination, and the outcomes of each intervention were not always reported, trends in efficacy could be appreciated. Intralesional corticosteroids, for example, had little to no effect on silicone-induced nodules and the addition of antibiotics led to some level of improvement in approximately half of the cases, although it is unclear whether this was due to antibacterial or anti-inflammatory mechanisms. The results of excision, however, were largely underreported.

More recently, additional therapeutic modalities have been evaluated for the resolution of inflammatory nodules secondary to silicone soft tissue augmentation. Chui and Fong [49], for example, investigated the use of the intralesional CO_2 laser by making an incision in the affected area and applying the laser to each granuloma, causing minimal ablation with satisfactory results. Oral isotretinoin alone, or in conjunction with tetracycline, has also led to resolution in two cases of painful lower extremity silicone granulomas refractory to steroid therapy [50]. Furthermore, tetracyclines alone have improved both the pain associated with nodules as well as overall appearance [51–53]. Although the proposed mechanism of tetracycline use for the treatment of granulomas is thought to be due to the anti-inflammatory effects of the agent, systemic corticosteroids, in contradistinction, have demonstrated mixed results [54–56]. Tumor necrosis factor alpha (TNF-α) inhibitors, methotrexate, allopurinol, and tacrolimus have also been investigated with promising results (Table 4).

Many patients currently presenting with inflammatory nodule formation may have undergone soft tissue augmentation several years ago, when silicone administration was not as heavily regulated. For these patients, biopsies and/or imaging can be extremely useful to identify silicone granulomas and subsequently make a correct diagnosis. Liposarcomas, cellulitis, angioedema, and metastatic breast cancer have all been misdiagnosed in patients with silicone granulomas [57–62]. On histology, a 'Swiss-cheese' appearance of empty vacuoles throughout a sea of multinucleated giant cells and fibrosis, without birefringence, is

Table 4 'Alternative' treatment for silicone-induced granulomatous reactions

Technique	Reports	*n*	Results	Notes
Tetracyclines	Senet et al. [101]	2	Improvement	Minocycline + prednisone
	Arin et al. [53]	1	Resolution	Minocycline + NSAIDS
	Beer [52]	1	Resolution	Minocycline + prednisone
	Schwartzfarb et al. [59]	1	Temporary resolution	Pain resolved, lumpiness remained
	Lopiccolo et al. [51]	1	Partial resolution	
Allopurinol	Redondo et al. [102]	1	Resolution	
Tacrolimus	Alijotas-Reig et al. [103]	7	Resolution ($n = 3$), mild recurrences ($n = 4$)	All refractory cases
Etanercept	Pasternack et al. [104]	2	Resolution	Refractory to other treatments
	Rapaport [105]	1	Worsened	Etanercept given for another condition, triggered granuloma formation in face
	Desai et al. [106]	1	Resolution	
Methotrexate	Kluger et al. [107]	1	Resolution	In conjunction with oral corticosteroids
CO_2 laser	Chui and Fong [49]	1	Resolution	Intralesional laser therapy, through incision

CO_2 carbon dioxide, *NSAIDs* non-steroidal anti-inflammatory drugs

characteristic for silicone-induced granulomatous reaction [24]. In lesions secondary to silicone-polypyrrolidone formulations, a combination that was created to help minimize migration, asteroid bodies may be identified within giant cells [63]. Liquid silicone has a similar attenuation to soft tissue on CT [25].

8 Polymethylmethacrylate (PMMA)

PMMA fillers, a combination of PMMA crystals, bovine collagen and lidocaine, act by re-volumizing and subsequently serving as a scaffold for new collagen production over time [64]. Skin testing is required prior to use of PMMA because of the presence of bovine collagen, but it is theorized that its decreased electrostatic charge reduces the incidence of foreign-body granulomas [65]. Granulomas secondary to PMMA typically appear white under the skin.

While it has been reported that PMMA granulomas may spontaneously resolve after 2–3 years, corticosteroids, surgical excision, or superficial dermabrasion can augment reduction of these lesions if they are bothersome to the patient [64, 66, 67]. Less invasive techniques such as oral antibiotics or intralesional corticosteroids are recommended prior to surgical excision, with oral antibiotics considered first-line treatment [68]. In contrast to silicone nodules, PMMA nodules have been shown to respond to intralesional corticosteroids; systemic corticosteroids may also lead to some improvement, but lesions may recur with cessation of treatment [34, 69–71]. Allopurinol has also been reported to be effective for symptomatic treatment of PMMA nodules that developed on the face following scar revision in some cases; however, lesions may remain palpable [71, 72].

In order to avoid the presence of palpable nodules, PMMA should never be injected into thin skin, such as around the eyes or in very elderly skin. Nodules may also be palpable if using PMMA to correct subcutaneous fat atrophy. Implantation should be made subdermally, taking care not to implant into the papillary dermis. If mistakenly placed superficially, massage may help. Immobility is also beneficial in avoiding nodule formation if using PMMA to inject the lips or perioral region, although injection in this region is not recommended [67].

9 Autologous Fat Transplantation

Autologous fat transplantation is appealing to both physicians and patients because of the advantages of reduced immunogenicity and incorporation into existing tissue. However, the formation of lipogranulomas months after implantation has been reported [73]. Sa and colleagues reported several cases of such a reaction. In all cases, the patients denied any filler placement within the orbital socket, and were injected only in the cheek, forehead, and temporal areas. For these patients, surgical excision was attempted following failure with intralesional corticosteroids.

In addition to lipogranulomas, other nodules may present themselves in patients previously implanted with autologous fat. Faulty technique may lead to immediate irregularities and clumping that could be permanent. In addition, areas previously treated with autologous fat may increase in size following weight gain. Unlike lipogranulomas, these 'lumps' are soft, with a consistency similar to adipose tissue. In two separate cases, lipohypertrophy of previously treated areas occurred 10 years after implantation, with only a 10–15 lb weight gain [74, 75]. In these case studies, both patients improved with surgical correction.

10 Polyacrylamides

Polyacrylamides are permanent hydrogels that correct soft tissue defects by providing an immediate volumizing effect and over time become integrated into host tissues. They are highly biocompatible, allowing them to avoid both degradation and foreign-body reactions. Due to their high biocompatibility, however, polyacrylamides also serve as an ideal medium for the low-virulence bacteria found in the normal skin flora and mucosa [7]. Within the hydrogel, these bacteria can flourish to cause chronic infections, often in conjunction with bio-film formation [76, 77]. For this reason, polyacrylamides are the most commonly infected filler implants and warrant thorough evaluation prior to immediate corticosteroid therapy.

Infectious polyacrylamide nodules can appear days, weeks, or months after implantation and are typically associated with non-specific findings such as erythema and pain [34, 78, 79]. One recent case-control study detected the presence of bacteria in nodules up to 5 years following implantation [80]. They may also resemble cysts. Identifying the filler agent is critical as initial treatment with corticosteroids can intensify the infection and promote the formation of biofilms, ultimately making treatment more difficult [7, 76, 78]. Sterile technique is imperative when using polyacrylamide fillers, and a short course of prophylactic antibiotics either immediately before or following administration is recommended [78, 81]. Patients should also avoid touching the injected site in the days following implantation. To avoid irregularities seen immediately after implantation, practitioners may benefit from a fan-shaped technique rather than a superficial, linear approach [81].

Diagnosing these infections via culture is difficult because of sequestering of the infection within the

protective environment of the biofilm; cultures are often negative [78]. Broad-spectrum antibiotics, however, are typically sufficient to eradicate the infectious nodules, given no prior corticosteroid use. Excision or manual extraction of the material can also be performed to purge the material even if the nodule does not show signs of infection [81–84].

11 Discussion

Overall, soft tissue fillers are a safe option for soft tissue augmentation if performed by experienced physicians, in the appropriate patients, and with the correct agents and proper techniques. While the formation of nodules or granulomas is one of the most commonly cited long-term complications associated with filler implants, the overall incidence is variable and depends on the location and agent used [19, 77, 83]. Because these nodules can be painful, debilitating, and both psychologically and physically scarring, it is critical they are treated swiftly. Several options are currently available to practitioners; however, these largely depend on the agents used and extent of the disease.

Unfortunately, delay in diagnosing adverse events such as nodule, granuloma, or sterile abscess formation may be a result of many factors and, therefore, timely recognition, diagnosis, and appropriate management are of the upmost importance. For example, many fillers are indicated for the amelioration of HIV-associated lipoatrophy; however, in these and other immunocompromised populations, the presence of erythematous, indurated, or painful nodules may lead to a work-up for opportunistic infections [85]. While this course of action is completely warranted and necessary considering the dangerous sequelae that may occur in this population, negative cultures and serologies as well as a history of soft tissue augmentation should warrant the inclusion of a delayed-type reaction to fillers in the differential diagnosis. Furthermore, for various reasons, patients may neglect to inform their physicians of past soft-tissue augmentation, leading to misdiagnoses of cellulitis and various forms of cancer [57–59, 61, 62, 86, 87].

Despite its disreputable history, some purport that with proper technique and careful patient selection, high-grade silicone can be used safely with minimal complications [88, 89]. Because of the delayed nature of silicone granuloma formation, however, adverse effects from silicone implantation several years ago are still seen today. Oral antibiotic therapy appears to have the most promise, likely due to its anti-inflammatory properties. Systemic corticosteroids seem to ease symptoms temporarily, but patients often develop recurrences once treatment is stopped. Surgical excision is difficult in diffuse disease, but may provide some aesthetic improvement for patients who are grossly disfigured. Furthermore, while only one case evaluated the role of lasers, it may be a modality that is explored in future. In order to fully evaluate the efficacy of newer modalities, it is important that negative findings also be reported.

When evaluating site-specific risk, the lips appear to be more prone to developing nodules, either due to the thin mucosa, increased amounts of bacterial flora, or increased mobility of the perioral region. When using calcium hydroxylapatite, several authors report nodule formation only within the lips, with no evidence of nodule formation when injecting anywhere else in the face [42–44]. Furthermore, hyaluronic acid/acrylic hydrogel complexes are contraindicated for implantation into labial mucosa or vertical lip lines [32]. It is also thought that scarring within the lips is more likely after the injection of an implant, making it more difficult to re-fill the area in subsequent sessions, contributing to irregularity in the region [90]. Fillers should never be injected into muscle, especially into the orbicularis oris due to increased nodule formation; muscle movement should be restricted after implantation with tape and patients should try to minimize movement for 1–3 days after the procedure [90].

Technical approach is also greatly varied depending on type of filler used. Depth, distribution, and dilution of the implant each play an important role in minimizing the incidence of adverse events. For example, calcium hydroxylapatite fillers should be placed in the subcutaneous fat, whereas PMMA fillers are more suitably placed in the deep dermis. Typically, a fan-shaped approach is recommended for polyacrylamide fillers, but retrograde linear and microdroplet placement have also been shown to decrease the incidence of nodule formation with hyaluronic acid/acrylic hydrogel and silicone fillers, respectively. Lastly, diluting poly-L-lactic acid fillers has been positively associated with reducing nodule formations. Appropriate training, for that reason, is warranted for all kinds of practitioners wishing to implement fillers for soft-tissue augmentation into their daily practice.

It has been suggested that individuals who are predisposed to the development of hypertrophic scars or keloids, as well as patients who suffer from autoimmune conditions, are more likely to form nodules following filler use [32, 90, 91]. A newly described syndrome, autoimmune/inflammatory syndrome induced by adjuvants (ASIA), is categorized by the development of an autoimmune or inflammatory disease following exposure to a certain agent, most likely in a genetically susceptible individual [92]. In a study of 185 patients without a history of direct adverse reactions to silicone, one study found that 8 % of patients potentially met the criteria for ASIA [93]. Furthermore, 11 of these 15 patients presented with localized symptoms prior to systemic manifestations of their conditions. These conditions included sarcoidosis, Sjogren's syndrome,

primary biliary cirrhosis, and monoclonal gammopathy of unknown significance. While still considered controversial, a thorough medical history and physical exam should be performed prior to using fillers for soft tissue augmentation. Risks and alternatives should also be presented to patients and thoroughly explained.

12 Conclusion

As used today, soft tissue fillers are a safe and effective means of tissue augmentation in the appropriate population. While the risk of nodule formation is always present, appropriate selection of the agent, patient, location, and technique, as well as the ability to expeditiously recognize and manage any complications, will allow the physician to maximize aesthetic benefit while simultaneously minimizing potential harm to the patient. Lastly, given advancing technology in the detection and isolation of biofilms, investigation into the role of low-grade bacterial infection, as well as first-line use of corticosteroids, in the development and treatment of inflammatory nodules secondary to soft tissue fillers is warranted.

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References

1. Klein AW, Elson ML. The history of substances for soft tissue augmentation. Dermatol Surg. 2000;26:1096–105.
2. Chasan PE. The history of injectable silicone fluids for soft-tissue augmentation. Plast Reconstr Surg. 2007;120:2034–40 discussion 41–3.
3. Glicenstein J. The first "fillers", vaseline and paraffin: from miracle to disaster. Annales de chirurgie plastique et esthetique. 2007;52:157–61.
4. Broder KW, Cohen SR. An overview of permanent and semi-permanent fillers. Plast Reconstr Surg. 2006;118:7S–14S.
5. Narins RS, Bowman PH. Injectable skin fillers. Clin Plast Surg. 2005;32:151–62.
6. Cheng JT, Perkins SW, Hamilton MM. Collagen and injectable fillers. Otolaryngol Clin N Am. 2002;35:73–85 vi.
7. Christensen LH. Host tissue interaction, fate, and risks of degradable and nondegradable gel fillers. Dermatol Surg. 2009;35(Suppl 2):1612–9.
8. Omranifard M, Taheri S. Filler augmentation, safe or unsafe: a case series of severe complications of fillers. J Res Med Sci. 2011;16:1627–31.
9. Buchanan AG, Holds JB, Vagefi MR, Bidar M, McCann JD, Anderson RL. Anterior filler displacement following injection of calcium hydroxylapatite gel (Radiesse) for anophthalmic orbital volume augmentation. Ophthalmic Plast Reconstr Surg. 2012;28:335–7.
10. Park TH, Yeo KK, Seo SW, et al. Clinical experience with complications of hand rejuvenation. J Plast Reconstr Aesthet Surg. 2012;65:1627–31.
11. Lemperle G, Hazan-Gauthier N, Lemperle M. PMMA microspheres (Artecoll) for skin and soft-tissue augmentation. Part II: clinical investigations. Plast Reconstr Surg. 1995;96:627–34.
12. Lazzeri D, Agostini T, Figus M, Nardi M, Pantaloni M, Lazzeri S. Blindness following cosmetic injections of the face. Plast Reconstr Surg. 2012;129:995–1012.
13. Park TH, Seo SW, Kim JK, Chang CH. Clinical experience with hyaluronic acid-filler complications. J Plast Reconstr Aesthet Surg. 2011;64:892–6.
14. Lowe NJ, Maxwell CA, Patnaik R. Adverse reactions to dermal fillers: review. Dermatol Surg. 2005;31:1616–25.
15. Heise H, Zimmermann R, Heise P. Temporary granulomatous inflammation following collagen implantation. J Cranio Maxillo-Facial Surg. 2001;29:238–41.
16. Matarasso SL. The use of injectable collagens for aesthetic rejuvenation. Semin Cutan Med Surg. 2006;25:151–7.
17. Lorenc ZP, Nir E, Azachi M. Characterization of physical properties and histologic evaluation of injectable Dermicol-p35 porcine-collagen dermal filler. Plast Reconstr Surg. 2010;125:1805–13.
18. Shoshani D, Markovitz E, Cohen Y, Heremans A, Goldlust A. Skin test hypersensitivity study of a cross-linked, porcine collagen implant for aesthetic surgery. Dermatol Surg. 2007;33(Suppl 2): S152–8.
19. Braun M, Braun S. Nodule formation following lip augmentation using porcine collagen-derived filler. J Drugs Dermatol. 2008;7:579–81.
20. Naoum C, Dasiou-Plakida D. Dermal filler materials and botulin toxin. Int J Dermatol. 2001;40:609–21.
21. Bardazzi F, Ruffato A, Antonucci A, Balestri R, Tabanelli M. Cutaneous granulomatous reaction to injectable hyaluronic acid gel: another case. J Dermatol Treat. 2007;18:59–62.
22. Andre P. Evaluation of the safety of a non-animal stabilized hyaluronic acid (NASHA-Q-Medical, Sweden) in European countries: a retrospective study from 1997 to 2001. J Eur Acad Dermatol Venereol. 2004;18:422–5.
23. Shafir R, Amir A, Gur E. Long-term complications of facial injections with Restylane (injectable hyaluronic acid). Plast Reconstr Surg. 2000;106:1215–6.
24. Andre P, Lowe NJ, Parc A, Clerici TH, Zimmermann U. Adverse reactions to dermal fillers: a review of European experiences. J Cosmet Laser Ther. 2005;7:171–6.
25. Ginat DT, Schatz CJ. Imaging features of midface injectable fillers and associated complications. AJNR Am J Neuroradiol. 2013;34:1488–95.
26. Hirsch RJ, Narurkar V, Carruthers J. Management of injected hyaluronic acid induced Tyndall effects. Lasers Surg Med. 2006;38:202–4.
27. Grossman KL. Hyaluronic acid gel fillers: hypersensitivity reactions. Aesthet Surg J Am Soc Aesthet Plast Surg. 2005;25: 403–5.
28. Micheels P. Human anti-hyaluronic acid antibodies: is it possible? Dermatol Surg. 2001;27:185–91.
29. Sclafani AP, Fagien S. Treatment of injectable soft tissue filler complications. Dermatol Surg. 2009;35(Suppl 2):1672–80.
30. Patel VJ, Bruck MC, Katz BE. Hypersensitivity reaction to hyaluronic acid with negative skin testing. Plast Reconstr Surg. 2006;117:92e–4e.
31. Honig JF, Brink U, Korabiowska M. Severe granulomatous allergic tissue reaction after hyaluronic acid injection in the treatment of facial lines and its surgical correction. J Craniofac Surg. 2003;14:197–200.
32. Bergeret-Galley C, Latouche X, Illouz YG. The value of a new filler material in corrective and cosmetic surgery: DermaLive and DermaDeep. Aesthet Plast Surg. 2001;25:249–55.

33. Sidwell RU, Dhillon AP, Butler PE, Rustin MH. Localized granulomatous reaction to a semi-permanent hyaluronic acid and acrylic hydrogel cosmetic filler. Clin Exp Dermatol. 2004;29:630–2.
34. Christensen L, Breiting V, Janssen M, Vuust J, Hogdall E. Adverse reactions to injectable soft tissue permanent fillers. Aesthet Plast Surg. 2005;29:34–48.
35. Rohrich RJ, Monheit G, Nguyen AT, Brown SA, Fagien S. Soft-tissue filler complications: the important role of biofilms. Plast Reconstr Surg. 2010;125:1250–6.
36. Sadick NS, Palmisano L. Case study involving use of injectable poly-L-lactic acid (PLLA) for acne scars. J Dermatol Treat. 2009;20:302–7.
37. Sadove R. Injectable poly-L-lactic acid: a novel sculpting agent for the treatment of dermal fat atrophy after severe acne. Aesthet Plast Surg. 2009;33:113–6.
38. Valantin MA, Aubron-Olivier C, Ghosn J, et al. Polylactic acid implants (New-Fill) to correct facial lipoatrophy in HIV-infected patients: results of the open-label study VEGA. AIDS. 2003;17:2471–7.
39. Alijotas-Reig J, Garcia-Gimenez V, Vilardell-Tarres M. Late-onset immune-mediated adverse effects after poly-L-lactic acid injection in non-HIV patients: clinical findings and long-term follow-up. Dermatology. 2009;219:303–8.
40. Dijkema SJ, van der Lei B, Kibbelaar RE. New-fill injections may induce late-onset foreign body granulomatous reaction. Plast Reconstr Surg. 2005;115:76e–8e.
41. Rossner F, Rossner M, Hartmann V, Erdmann R, Wiest LG, Rzany B. Decrease of reported adverse events to injectable polylactic acid after recommending an increased dilution: 8-year results from the Injectable Filler Safety study. J Cosmetic Dermatol. 2009;8:14–8.
42. Jansen DA, Graivier MH. Evaluation of a calcium hydroxylapatite-based implant (Radiesse) for facial soft-tissue augmentation. Plast Reconstr Surg. 2006;118:22S–30S discussion 1S-3S.
43. Sadick NS, Katz BE, Roy D. A multicenter, 47-month study of safety and efficacy of calcium hydroxylapatite for soft tissue augmentation of nasolabial folds and other areas of the face. Dermatol Surg. 2007;33(Suppl 2):S122–6 discussion S6–7.
44. Tzikas TL. Evaluation of the radiance FN soft tissue filler for facial soft tissue augmentation. Arch Facial Plast Surg. 2004;6:234–9.
45. Reddy KK, Brauer JA, Anolik R, et al. Calcium hydroxylapatite nodule resolution after fractional carbon dioxide laser therapy. Arch Dermatol. 2012;148:634–6.
46. Rapaport MJ, Vinnik C, Zarem H. Injectable silicone: cause of facial nodules, cellulitis, ulceration, and migration. Aesthet Plast Surg. 1996;20:267–76.
47. Park TH, Seo SW, Kim JK, Chang CH. The efficacy of perilesional surgical approach for foreign body granuloma. Plast Reconstr Surg. 2011;127:121e–3e.
48. Park TH, Seo SW, Kim JK, Chang CH. Clinical outcome in a series of 173 cases of foreign body granuloma: improved outcomes with a novel surgical technique. J Plast Reconstr Aesthet Surg. 2012;65:29–34.
49. Chui CH, Fong PH. Carbon dioxide laser vaporization of facial siliconomas: flash in the pan or way of the future? Ann Plast Surg. 2008;60:272–5.
50. Lloret P, Espana A, Leache A, et al. Successful treatment of granulomatous reactions secondary to injection of esthetic implants. Dermatol Surg. 2005;31:486–90.
51. Lopiccolo MC, Workman BJ, Chaffins ML, Kerr HA. Silicone granulomas after soft-tissue augmentation of the buttocks: a case report and review of management. Dermatol Surg. 2011;37:720–5.
52. Beer K. Delayed onset nodules from liquid injectable silicone: report of a case, evaluation of associated histopathology and results of treatment with minocycline and celocoxib. J Drugs Dermatol. 2009;8:952–4.
53. Arin MJ, Bate J, Krieg T, Hunzelmann N. Silicone granuloma of the face treated with minocycline. J Am Acad Dermatol. 2005;52:53–6.
54. Celerier P, Litoux P, Dreno B. In vitro modulation of epidermal inflammatory cytokines (IL-1 alpha, IL-6, TNF alpha) by minocycline. Arch Dermatol Res. 1996;288:411–4.
55. Ficarra G, Mosqueda-Taylor A, Carlos R. Silicone granuloma of the facial tissues: a report of seven cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2002;94:65–73.
56. Poveda R, Bagan JV, Murillo J, Jimenez Y. Granulomatous facial reaction to injected cosmetic fillers: a presentation of five cases. Medicina oral patologia oral y cirugia bucal. 2006;11: E1–5.
57. Mustacchio V, Cabibi D, Minervini MI, Barresi E, Amato S. A diagnostic trap for the dermatopathologist: granulomatous reactions from cutaneous microimplants for cosmetic purposes. J Cutan Pathol. 2007;34:281–3.
58. Goncales ES, Almeida AS, Soares S, Oliveira DT. Silicone implant for chin augmentation mimicking a low-grade liposarcoma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009;107:e21–3.
59. Schwartzfarb EM, Hametti JM, Romanelli P, Ricotti C. Foreign body granuloma formation secondary to silicone injection. Dermatol Online J. 2008;14:20.
60. Chen YC, Chen ML, Chiu YM. A case of mimicking angioedema: chin silicone granulomatous reaction spreading all over the face after receiving liquid silicone injection forty years previously. Chin Med J. 2011;124:1747–50.
61. Gundeslioglu AO, Hakverdi S, Erdem O, Ozen EC, Inan I, Emlik D. Axillary lipogranuloma mimicking carcinoma metastasis after silicone breast implant rupture: a case report. J Plast Reconstr Aesthet Surg. 2013;66:e72–5.
62. Shepherd SM, Makariou E. Silicone granuloma mimicking breast cancer recurrence on PET CT. Breast J. 2010;16:551–3.
63. Rudolph CM, Soyer HP, Schuller-Petrovic S, Kerl H. Foreign body granulomas due to injectable aesthetic microimplants. Am J Surg Pathol. 1999;23:113–7.
64. Broder KW, Cohen SR. ArteFill: a permanent skin filler. Expert Rev Med Devices. 2006;3:281–9.
65. Haneke E. Polymethyl methacrylate microspheres in collagen. Semin Cutan Med Surg. 2004;23:227–32.
66. Hoffmann C, Schuller-Petrovic S, Soyer HP, Kerl H. Adverse reactions after cosmetic lip augmentation with permanent biologically inert implant materials. J Am Acad Dermatol. 1999;40: 100–2.
67. Lemperle G, Romano JJ, Busso M. Soft tissue augmentation with artecoll: 10-year history, indications, techniques, and complications. Dermatol Surg. 2003;29:573–87 discussion 87.
68. Park TH, Seo SW, Kim JK, Chang CH. Clinical experience with polymethylmethacrylate microsphere filler complications. Aesthetic Plast Surg. 2012;36:421–6.
69. Cohen SR, Berner CF, Busso M, et al. ArteFill: a long-lasting injectable wrinkle filler material—summary of the U.S. Food and Drug Administration trials and a progress report on 4- to 5-year outcomes. Plast Reconstr Surg. 2006;118:64S–76S.
70. Pearl RM, Laub DR, Kaplan EN. Complications following silicone injections for augmentation of the contours of the face. Plast Reconstr Surg. 1978;61:888–91.
71. Reisberger EM, Landthaler M, Wiest L, Schroder J, Stolz W. Foreign body granulomas caused by polymethylmethacrylate microspheres: successful treatment with allopurinol. Arch Dermatol. 2003;139:17–20.
72. de Barros Silveira LK, de Oliveira FL, AlvesTde B, et al. The therapeutic benefit of allopurinol in the treatment of foreign

body granulomas caused by polymethylmethacrylate microspheres. Case Rep Dermatol Med. 2012;2012:945205.
73. Sa HS, Woo KI, Suh YL, Kim YD. Periorbital lipogranuloma: a previously unknown complication of autologous fat injections for facial augmentation. Br J Ophthalmol. 2011;95:1259–63.
74. Latoni JD, Marshall DM, Wolfe SA. Overgrowth of fat autotransplanted for correction of localized steroid-induced atrophy. Plast Reconstr Surg. 2000;106:1566–9.
75. Miller JJ, Popp JC. Fat hypertrophy after autologous fat transfer. Ophthalmic Plast Reconst Surg. 2002;18:228–31.
76. Bjornsdottir K, Bolton GE, McClellan-Green PD, Jaykus LA, Green DP. Detection of gram-negative histamine-producing bacteria in fish: a comparative study. J Food Protect. 2009;72:1987–91.
77. Bello G, Jackson IT, Keskin M, et al. The use of polyacrylamide gel in soft-tissue augmentation: an experimental assessment. Plast Reconstr Surg. 2007;119:1326–36.
78. Bjarnsholt T, Tolker-Nielsen T, Givskov M, Janssen M, Christensen LH. Detection of bacteria by fluorescence in situ hybridization in culture-negative soft tissue filler lesions. Dermatol Surg. 2009;35(Suppl 2):1620–4.
79. Alijotas-Reig J, Garcia-Gimenez V, Miro-Mur F, Vilardell-Tarres M. Delayed immune-mediated adverse effects related to polyacrylamide dermal fillers: clinical findings, management, and follow-up. Dermatol Surg. 2009;35(Suppl 1):360–6.
80. Christensen L, Breiting V, Bjarnsholt T, et al. Bacterial infection as a likely cause of adverse reactions to polyacrylamide hydrogel fillers in cosmetic surgery. Clin Infect Dis. 2013;56:1438–44.
81. Yagi Y, Kato K, Murakami D, et al. Use of Aquamid as a filler for facial rejuvenation in orientals. J Plast Reconstr Aesthet Surg. 2009;62:1245–9.
82. von Buelow S, Pallua N. Efficacy and safety of polyacrylamide hydrogel for facial soft-tissue augmentation in a 2-year follow-up: a prospective multicenter study for evaluation of safety and aesthetic results in 101 patients. Plast Reconstr Surg. 2006;118:85S–91S.
83. Pallua N, Wolter TP. A 5-year assessment of safety and aesthetic results after facial soft-tissue augmentation with polyacrylamide hydrogel (Aquamid): a prospective multicenter study of 251 patients. Plast Reconstr Surg. 2010;125:1797–804.
84. Wolter TP, Pallua N. Removal of the permanent filler polyacrylamide hydrogel (aquamid) is possible and easy even after several years. Plast Reconstr Surg. 2010;126:138e–9e.
85. Males S, Joly V, Adle-Biassette H, et al. Silicone in HIV-1-infected patients: a cause of misdiagnosed granulomatous disease. Int J Infect Dis. 2010;14(Suppl 3):e277–9.
86. Bennett R, Taher M. Restylane persistent for 23 months found during Mohs micrographic surgery: a source of confusion with hyaluronic acid surrounding basal cell carcinoma. Dermatol Surg. 2005;31:1366–9.
87. Anatelli F, Chapman MS, Brennick J. Amorphous basophilic deposit in the superficial dermis of the lip in an 80 year old. Am J Dermatopathol. 2010;32:306–9.
88. Duffy DM. Liquid silicone for soft tissue augmentation. Dermatol Surg. 2005;31:1530–41.
89. Barnett JG, Barnett CR. Treatment of acne scars with liquid silicone injections: 30-year perspective. Dermatol Surg. 2005;31:1542–9.
90. Lemperle G, Rullan PP, Gauthier-Hazan N. Avoiding and treating dermal filler complications. Plast Reconstr Surg. 2006;118:92S–107S.
91. Cabral AR, Alcocer-Varela J, Orozco-Topete R, Reyes E, Fernandez-Dominguez L, Alarcon-Segovia D. Clinical, histopathological, immunological and fibroblast studies in 30 patients with subcutaneous injections of modelants including silicone and mineral oils. Revista de investigacion clinica; organo del Hospital de Enfermedades de la Nutricion. 1994;46:257–66.
92. Shoenfeld Y, Agmon-Levin N. 'ASIA'—autoimmune/inflammatory syndrome induced by adjuvants. J Autoim. 2011;36:4–8.
93. Alijotas-Reig J, Garcia-Gimenez V, Llurba E, Vilardell-Tarres M. Autoimmune/inflammatory syndrome (ASIA) induced by biomaterials injection other than silicone medical grade. Lupus. 2012;21:1326–34.
94. Raulin C, Greve B, Hartschuh W, Soegding K. Exudative granulomatous reaction to hyaluronic acid (Hylaform). Contact Dermat. 2000;43:178–9.
95. Lupton JR, Alster TS. Cutaneous hypersensitivity reaction to injectable hyaluronic acid gel. Dermatol Surg. 2000;26:135–7.
96. Lowe NJ, Maxwell CA, Lowe P, Duick MG, Shah K. Hyaluronic acid skin fillers: adverse reactions and skin testing. J Am Acad Dermatol. 2001;45:930–3.
97. Pinheiro MV, Bagatin E, Hassun KM, Talarico S. Adverse effect of soft tissue augmentation with hyaluronic acid. J Cosmet Dermatol. 2005;4:184–6.
98. Ghislanzoni M, Bianchi F, Barbareschi M, Alessi E. Cutaneous granulomatous reaction to injectable hyaluronic acid gel. Br J Dermatol. 2006;154:755–8.
99. Alijotas-Reig J, Garcia-Gimenez V. Delayed immune-mediated adverse effects related to hyaluronic acid and acrylic hydrogel dermal fillers: clinical findings, long-term follow-up and review of the literature. J Eur Acad Dermatol Venereol. 2008;22:150–61.
100. Shahrabi Farahani S, Sexton J, Stone JD, Quinn K, Woo SB. Lip nodules caused by hyaluronic acid filler injection: report of three cases. Head Neck Pathol. 2012;6:16–20.
101. Senet P, Bachelez H, Ollivaud L, Vignon-Pennamen D, Dubertret L. Minocycline for the treatment of cutaneous silicone granulomas. Br J Dermatol. 1999;140:985–7.
102. Redondo P, Del Olmo J, Alberola I. In situ and distant foreign body granulomas caused by silicone: treatment with allopurinol. Br J Dermatol. 2005;152:1064–5.
103. Alijotas-Reig J, Garcia-Gimenez V, Vilardell-Tarres M. Tacrolimus in the treatment of chronic and refractory late-onset immune-mediated adverse effects related to silicone injections. Dermatol Surg. 2012;38:38–47.
104. Pasternack FR, Fox LP, Engler DE. Silicone granulomas treated with etanercept. Arch Dermatol. 2005;141:13–5.
105. Rapaport MJ. Silicone granulomas treated with etanercept. Arch Dermatol. 2005;141:1171.
106. Desai AM, Browning J, Rosen T. Etanercept therapy for silicone granuloma. J Drugs Dermatol. 2006;5:894–6.
107. Kluger N, Plantier F, Carlotti A, Guillevin L. Facial granuloma after occult silicone injection (siliconoma): a diagnosis not to be missed. Eur J Int Med. 2009;20:e120–1.