DELAYED COMPLICATIONS DURING AESTHETIC PROCEDURES AFTER INJECTION OF HYALURONIC ACID DERMAL FILLER AND THEIR MANAGEMENT

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Summary

Fillers are injectable substances used for reduction of wrinkles when they are placed in the skin, or give volume in the tissue, improving the contour and skin texture when they are injected deep (periosteal). In accordance with regulations, fillers are recognized and categorized as medical devices. Among the many fillers that have appeared in recent decades, hyaluronic acid has become widely used by aesthetic doctors and are preferred by patients who are looking for non-invasive methods of rejuvenation. The number of hyaluronic acid injection procedures have risen, so have the number of post-injection complications.

***Methods:** The data of patients with delayed post-injection complications were extracted from the clinic archive and the following information was analysed: complication onset date, last injection date, injected product, injection amount and type, injected area, total amount of hyaluronic acid injected in the last 20 months, history of injected products, treatment of complication(s), and time of remission. We followed 10 patients who presented with late complications from one week to 1 year after the injection. Published articles on late complications and proposed treatment algorithms have been reviewed in the literature.*

***Results:** Over a period of 8 years (2013-2020) 2,418 hyaluronic acid injection procedures were performed in our clinic in a number of 1836 patients with a total volume of 3,855 mL of hyaluronic acid. Over 95% of these patients treated were women. Delayed complications occurred between one week after injection and up to one year.*

The most common complications were visible or only perceived as nodules on palpation and localized edema. Among the possible causes that were discussed—nickel allergy, dental treatments, pre-existing conditions - acne, rosacea, and injection defects.

***Conclusions:** The causes of late complications can be associated with— the injected volume, the number of injected products, the fact that the products were injected simultaneously in the same session, and that they could be related to the patient's allergic pathology.*

***Key words:** hyaluronic acid, filler complications, side effects*

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The popularity of fillers has grown rapidly in recent years because they offer a rapid rejuvenation of the skin and an improvement in aesthetics without a recovery period.

The number of injectable cosmetic treatments globally in 2017 was close to 8.6 million, representing an increase of 50% compared to 2011, according to the annual international survey conducted by the International Society of Plastic and Aesthetic Surgery - ISAPS. [1]

Fillers are currently preferred instead of cosmetic surgical procedures that are invasive and require recovery time. The composition of fillers has changed over time, the most popular product currently used is one based on hyaluronic acid. Hyaluronic acid is a

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polysaccharide that can be synthesized in the laboratory, extracted from the rooster's crest, or obtained by streptococcal fermentation. The viscoelastic gel obtained has a high bio-compatibility, elasticity, and a capacity to maintain shape. Hyaluronic acid is considered a safe product, which adapts to facial movements, does not migrate, and is easy to inject producing a predictable and reproducible result. Hyaluronic acid products have a long duration period lasting anywhere from 12 to 20 months, but are perfectly absorbable. They are considered non-carcinogenic, non-teratogenic, and non-allergenic products.

The main indications of fillers are the filling of aging and expression wrinkles in the glabellar, periocular, perioral area, remodeling and defining of the cheeks, nose, chin, lips, correcting facial asymmetry, and diminishing the effects of aging skin. As the indications, quantities used, and the number of procedures increased, so have the number of complications.

Post-injection filler complications can be divided into early and late. Early ones appear immediately after injection or at a maximum of 24-48 hours. Late side effects are rare and can be described as aspects of neovascularization, biofilm reaction, persistent edema or nodules. We define late-onset side effects as complications that occur weeks, months, or years after injection and can be correlated with it.

Material and Methods

A total of 10 female patients, between the ages of 39 and 66, who presented to our clinic between 2013 and 2020 were analysed. The patients were injected with hyaluronic acid, either in our clinic, or in another medical clinics. Post-injection, at a variable time interval, but longer than a week, presented complications.

All patients had a history of multiple injections in different areas of the face - between 3 and 6 injection sessions - in the last 3 years. The injections were performed by specialists from the clinic, were made by bolus or linear injection technique, and with a needle or cannula. Out of the total number of patients reported, 8 patients were from our clinic and 2 patients were from other medical services.

Another parameter analysed was the total dose of filler injected in the last 20 months which varied between 2 ml and 21 mL per patient.

From the patients' history, it should be noted that none of them reported a history of autoimmune diseases or allergies, subsequently the allergological tests revealed allergies in 4 cases.

The injected substances were produced by Allergan (Vycross technology -Voluma, Volbella, Volift), Allergan Juvederm Ultra (based on Hylacross technology with high molecular weight crosslinked hyaluronic acid chains), Galderma (non-animal stabilized hyaluronic acid, obtained by NASHA technology - Restyline Vital light), Teoxane (stabilized hyaluronic acid, non-animal, with a low level of protein and battery endotoxins - Teosyal Ultra Deep, RHA4). Table 1.

Table 1

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The duration between the last filler injection and the appearance of complications varied between one week and one year.

A biopsy was performed on a case of a patient with two hard nodules, that were palpable unilaterally in the eyelid area, revealed the possibility of the persistence of hyaluronic acid in an inflammatory nodule 2 years after the treatment was performed in another clinic.

Case 4. A 61-year-old female patient was injected with a total amount of 3 mL (Volit- anterior neck, eyelid wrinkles; Volbella- lips; Voluma- ygomatic area) by linear injection and bolus technique. Patient presented, approximately one month after injection with edema in the upper and lower eyelids, and micronodules on the injected area in the neck. Although it was injected in several areas, it developed allergic edema only in the periocular area. Antihistamines and oral cortisone were administered, but the edema continued to occur alternately in one eye and then the other and remitted only by Hyaluronidase injection. According to the patient's history, the total amount of hyaluronic acid injected in the last 20 months was 11.5 mL. Allergic tests have shown an allergy to dust mites (Figure 1).

Case 1. The 66-year-old female patient was injected with 6 mL of Restyline Vital light 2 mL per month for 3 months at periocular and peribuccal wrinkles by linear injection technique; the total amount of hyaluronic acid injected in the last 20 months was 8 mL. One year after the last hydration treatment, the patient presented with lower eyelid edema. Hyaluronidase was injected and the edema resolved in 48 hours (Figure 2).

Case 2. The 62-year-old female patient was injected with 2 mL of Teosyal RHA4 on the chin, anterior cheek, and zygomatic prominence by linear technique. After a week she returned with an erythematous nodule that was warm in the right genial region. We noted that the patient has a seborrheic, acne-prone complexion. The nodule could have produced by the compression given by the filler on an area with inflamed sebaceous glands. Clindamycin and Prednisone were administered and remission occurred within 7 days. (Figure 3)

Biopsy of a persistent nodule 2 years after hyaluronic acid injection.Tissue with nodular infiltrates formed by epithelioid histiocytes that included giant histiocytes, multinucleate foreign bodies, and palisades around deposits of basophilic material with colloid appearance representing the injected hyaluronic acid. The histological aspect is of a granulomatous inflammatory reaction to the remaining hyaluronic acid injected in the area. The patient subsequently received treatment with Hyaluronidase for the nodules. (Figure 4)

Figure 1. Edema of the lower eyelid.

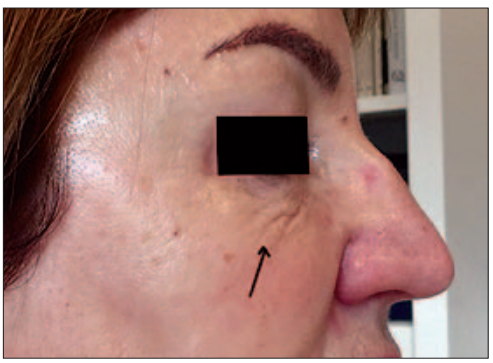

Figure 2. Appearance after Hyaluronidase treatment.

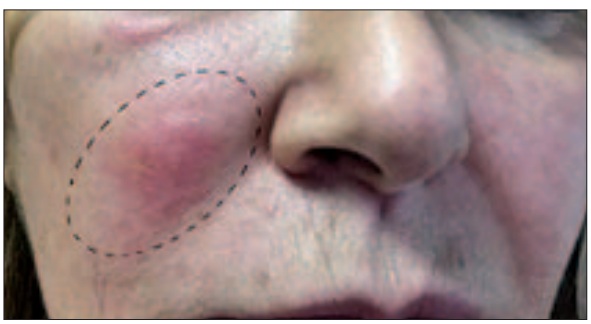

Figure 3. Red warm nodule.

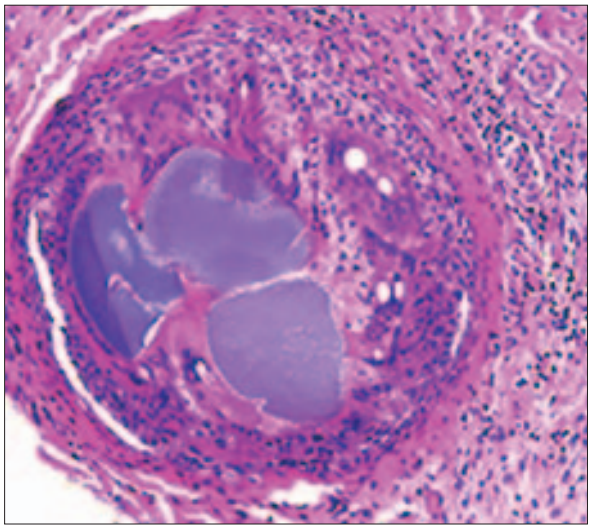

Figure 4. Persistent nodule biopsy 2 years after hyaluronic acid injection.

Case 5. The 51-year-old female patient was injected with 5 mL (Volite anterior neck, Volbella lips and tear through) by linear technique. After about one month she returned with multiple nodules in the neck region. Patient received Radiofrequency treatment and remission occurred within 48 hours (Figure 5).

The treatment was administered for 4 of the patients with Antihistamines and Prednisone. One patient was given Hyaluronidase, one patient was given Antibiotics and Prednisone, and another patient received Antibiotics and drainage. Another patient received treatment with Radiofrequency, and another patient received Radiofrequency and Hyaluronidase.

Only one patient in 10 had a recurrence of reactions but not in the same area where the initial complications were recorded to occur.

Discussions

The most side effects occurred at periocular level (n = 4), cheeks (n = 3), neck area (n = 2), chin (n = 2), then the naso-genian groove (n = 1). The most common types of complications were nodules and edema.

Although patients were injected on several areas, they developed delayed side effects only in certain areas, the lower eyelid area being the most affected even 1 year after treatment.

Analyzing our group of patients, we noticed that allergic edema from one eye to another was

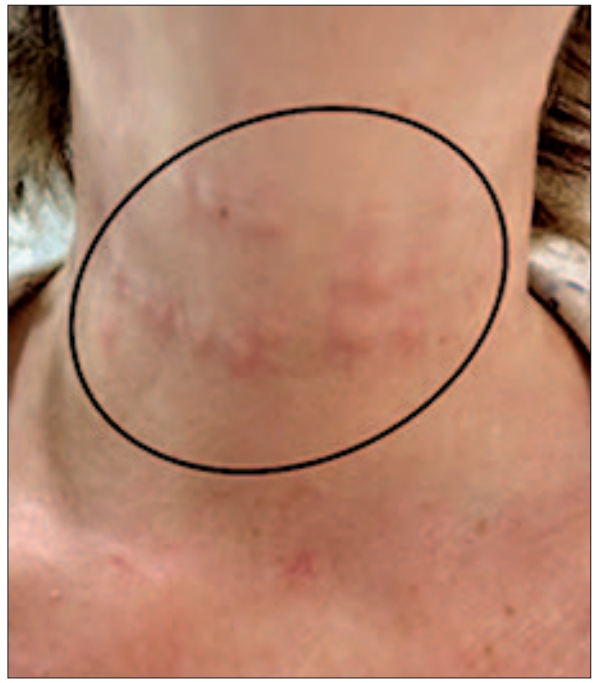

Figure 5. Nodules at the injection site.

recurrent for a long time and did not respond to standard antihistamine treatment. The edema resolved during oral cortisone therapy but recurred upon discontinuation of treatment. All cases showed remission within 48 hours after Hyaluronidase injection. One case started one year after the injection of Volbella probably due to an allergy to one of the degradation products, the other allergological tests being negative. Only one of the analyzed cases showed a biofilm reaction starting more than 3 months after treatment, in a patient who had a dental implant 2 months before cosmetic treatment. Drainage and prolonged antibiotic treatment were required for one month to achieve healing.

Hyaluronic acid is a glycosaminoglycan (GAG), a polysaccharide substance formed by polymerizing repetitive disaccharide units with one or more amino-carbohydrate molecules. Hyaluronic acid is obtained from animal tissues (rooster crest) or from plant sources through fermentation processes. Hyaluronic acid is crosslinked or non-crosslinked.

The molecular weight of hyaluronic acid obtained from animal sources is about 5000 kDa and that extracted from plant sources varies

between 500 and 2000 kDa. Currently low molecular weight hyaluronic acid is most used in cosmetic procedures [19]. A cross-linked hyaluronic acid with a higher concentration has a higher viscosity, higher elasticity, and implicitly higher degradation resistance in case of Hyaluronidase injection. This type of hyaluronic acid has a longer lifespan in the tissue and is thought to increase the risk of inflammation [20].

Also, the larger the particles and the more concentrated they are the more water they absorb and can cause post-injection edema. Depending on the size of the microspheres contained, hyaluronic acid is divided into:

• Biphasic, contains microspheres of various sizes (ex Restylane)

• Single-phase, contains microspheres of the same size (ex Juvedem, Teosyal, Belotero)

Various cross-linking technologies are currently used to obtain hyaluronic acid with different viscoelastic properties: non-animal stabilized hyaluronic acid (NASHA-Restylane), resilient hyaluronic acid (Teosyal RHA), hyaluronic acid obtained with Hylacross technology with chains of high molecular weight crosslinked hyaluronic acid (Allergan Juvederm Ultra), Vycross technology (Alergan Juvederm).

In Vycross technology, 10% is high molecular weight hyaluronic acid and 90% low molecular weight hyaluronic acid, resulting in a product with a high cross-linking coefficient. The body needs a longer time to degrade this type of hyaluronic acid.

The incidence of side effects has increased in parallel with the increase of the number of cosmetic procedures and the number of fillers offered by the industry. Different types of hyaluronic acid are associated with different side effects.

Early complications are immediate reactions that occur 24 to 48 hours after injection, such as bruising, erythema, edema, small nodules, asymmetry, and vascular compression. Poor cleansing and disinfection of the area can cause infections, and injection microtrauma can reactivate herpes simplex. Hypersensitivity reactions are also described, such as the Tyndal effect which consists in the appearance of a local tearing of the tissue with a color change in a translucent - purple. The most important side effects that appear rapidly are generated by intravascular injection which is recognized by acute pain, change of skin color initially in livid white then, formation of a bruise, followed by necrosis or the appearance of foreign body granuloma. The most feared side effect, however, is unilateral blindness by affecting the retinal artery.

How to avoid side effects:

Injection technique: enter with the needle or cannula in the desired direction, aspirate, wait 10 seconds then slowly inject small volumes. The color of the skin is observed, the area is not traumatized by friction, after the treatment gentle compression is applied and increased attention is given to the areas with superficial vessels. For bruises, a light massage with arnica gel or vascular laser Dye is recommended, if you feel a lump, massage it gently until remission. In the case of intravascular injection, apply a warm compress immediately and follow the normal re-coloration of the skin. You can massage with nitroglycerin paste, administer oral aspirin or heparin. If bruising occurs on the vascular path Hyaluronidase (more than 100 IU) or dilute triamcinolone solution is injected. If the patient complains of unilateral visual disturbance after hyaluronic acid injection, an emergency long-needle retrobulbar hyaluronidase injection technique is applied to save vision. A maximum of one hour can elapse from the onset of this major complication to correction. The patient should be educated to report any persistent unpleasant symptoms. Photos should be standardized to observe asymmetries before treatment. An important measure is to plan injections before events so that there is time to resolve possible side effects.

Late complications are those that occur between one week to a year or more after the injection. Thus, we can have:

1. **Neovascularization:** occurs when new blood vessels form at the injection site of hyaluronic acid. Potential pathogenetic mechanisms could be tissue trauma and direct stimulation of angiogenesis by hyaluronic acid. In the case of telangiectasia, the dilation of blood vessels is due to increased pressure in the tissue

after injection. Neovascularization can occur a few weeks after the procedure and should disappear in 3-12 months without treatment. If the appearance does not disappear spontaneously, erythema or telangiectasia can be treated with IPL and vascular lasers. [2]

2. **Edema (delayed type IV hypersensitivity)**: allergic reactions mediated by T lymphocytes and macrophages that are manifested by induration, erythema, and edema. Potential triggers may be the needle used for injection, such as an allergy to nickel or components in the injected product. Reactions of this type may occur within a few weeks after injection and may persist for several months. This type of edema usually does not respond to antihistamine treatment. Oral corticosteroids are recommended followed by Hyaluronidase injection. [3]

3. **Malar Edema:** is a complication that has been reported with injected fillers in the tear troughs and infraorbital area. The malar septum is a band of connective tissue that separates the bundle of superficial subocular fat into two compartments: superficial and deep. Injection of hyaluronic acid into the superficial compartment can make lymphatic drainage difficult at this level and can lead to malarial edema [4]. Also, injecting too much volume or using a hyaluronic acid with an increased viscosity in the deep compartment can cause edema by compressing the lymph. Malar edema persists for a long time and responds modestly to treatment. Initial measures include elevation of the cephalic extremity, cold compresses, massage of the area several times a day, administration of Methylpredninsolone, and injection of Hyaluronidase [4]. The incidence of malar edema can be reduced by careful selection of patients, injection of a small volume of filler deep in the malar septum and with a low viscosity and elasticity. Persistent malarial edema should be differentiated from overcorrection.

4. **Foreign body granuloma:** the inflammatory node that persists for a long time is most often foreign body granuloma. Foreign bodies introduced by injection and which are not immediately removed by enzymatic lysis or phagocytosis are encapsulated with monocytes and macrophages to isolate them and prevent their migration. Activated macrophages secrete cytokines and other inflammatory products that attract other macrophages and monocytes from the bloodstream. Macrophages increase in size and fuse to form giant multinuclear cells [9]. If a biopsy can be obtained, these cells are specific for granulomas and can be highlighted by histopathological examination. Clinically, foreign body granulomas appear as red papules, nodules or plaques with or without ulceration, and bacteriological cultures are negative. The lesions eventually become firm to the touch due to fibrosis. The incidence of foreign body granulomas is rare, estimated at about 1% [10]. The reaction may occur months or years after the injection. Factors that influence their appearance include injection of a large volume of filler, intramuscular injection, infections, or trauma. The purity and stability of the product are also discussed, so it is important to buy fillers from the right sources. Another possible cause is incorrect make-up removal and disinfection with the possibility of transporting makeup microparticles inside the skin. Initial treatment is intralesional injection with triamcinolone acetonide or hyaluronidase.

In patients who do not respond to corticosteroid monotherapy, 5-FU is added. This combination has the advantage of reducing the dose of corticosteroids that are injected and implicitly reduces side effects such as atrophy and telangiectasia [11]. If this therapy has no effect, surgical excision is recommended.

5. **Nodules:** inflammatory or non-inflammatory, can occur for multiple reasons so it is important to determine their nature before starting treatment.

A) **Non-inflammatory nodules**: can be visible and palpable especially in the eyelids, nasal region, and lips [12]. They occur when filler is injected in a large volume, injected superficially, injected in areas with significant muscle activity, (for example at the level of the modiolus) or when the filler is unsuitable for the anatomical area to be injected. Not all nodules require medical treatment. Careful monitoring of them to the point of remission is an accepted strategy. If treatment is required, Hyaluronidase

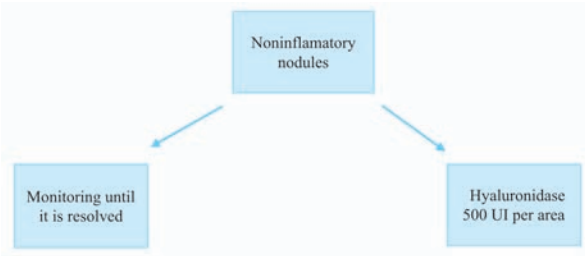

Figure 6. Management of noninflammatory late-onset nodules after hyaluronic acid filler administration.

is injected directly into the center of the nodule within 48 hours until resolved [13]. Ultrasound, when possible, can be used to detect the amount, exact location and depth of the filler and to guide Hyaluronidase injection. Figure 6 [45].

B) **Inflammatory nodules:** any injected filler can initially produce an influx of neutrophils and mononuclear cells, phagocytosis by macrophages, activation of fibroblasts, and the appearance of collagen deposits. These reactions to hyaluronic acid injection are necessary and expected because they stimulate the production of extracellular matrix [14]. If an abnormal process of phagocytosis and inadequate stimulation of immune cells occurs, with a permanent activation of macrophages. These lead to a granulomatous or fibrotic process [15]. Clinically, inflammatory nodules are red, painful and occasionally suppurating [16]. They usually appear a few weeks after treatment. Many factors are involved in the transition from a physiological reaction of a foreign body to a severe granulomatous inflammatory process. Occasionally, a respiratory or gastrointestinal infection or interferon therapy may trigger this inflammatory process. The recommended treatment is a systemic antibiotic for 2 weeks and follow up. If the inflammation and edema are severe, then oral corticosteroid treatment is instituted. If the lesions do not respond to antibiotics and hyaluronidase, intralesional corticosteroids are administered [2]. Figure 7 (includes an example of antibiotic treatment) [45].

Fluoroquinolone antibiotics (Ciprofloxacin) are no longer used as first-line treatment due to adverse effects (cardiovascular toxicity, hepatotoxicity, muscle, joint, tendon damage) [17]. Figure 8 shows an algorithm for the use of broad-

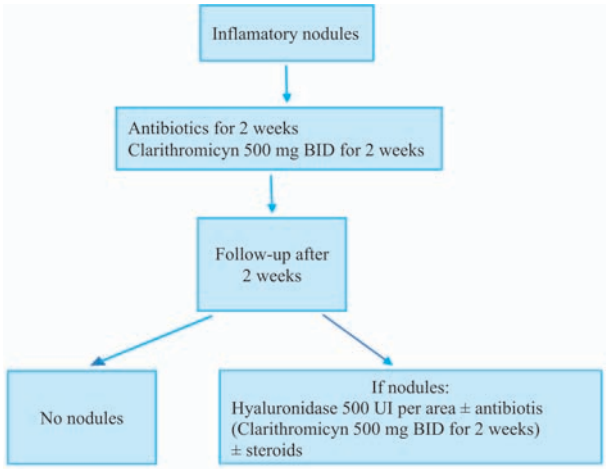

Figure 7. Management of inflammatory late-onset nodules after hyaluronic acid filler administration.

spectrum antibiotics and oral corticosteroids [45]. Non-steroidal anti-inflammatory drugs, antihistamines, and oral corticosteroids can be used in the treatment regimen to reduce inflammation. The presence of an abscess should be ruled out, in which case an incision and drainage are required. Sterile abscesses are characterized by negative bacteriological cultures and can represent the reaction of a biofilm, which are difficult to treat. Failure to diagnose an active infection as a delayed inflammatory reaction can lead to permanent tissue destruction. For nodules refractory to treatment with hyaluronidase and oral corticosteroids, 5-FU (50 mg / mL) is injected in combination with intralesional corticosteroids [18]. The recommended protocols for this combination are:

- 7-9 parts of 5-FU to 1-3 parts of triamcinolone acetonide;
- an 80:20 ratio of 5-FU and triamcinolone acetonides (10 or 40 mg, depending on nodule size):
- mixture of 1 cc 5-FU and 0.1 cc triamcinolone acetonide 40 mg, injected at one month interval until resolution, the injected volume depending on the size of the nodule.

The summary of treatment strategies for late-onset nodules after hyaluronic acid injection is shown in fig. 9 [45]

Late inflammatory reactions after hyaluronic acid injection are usually manifested by the

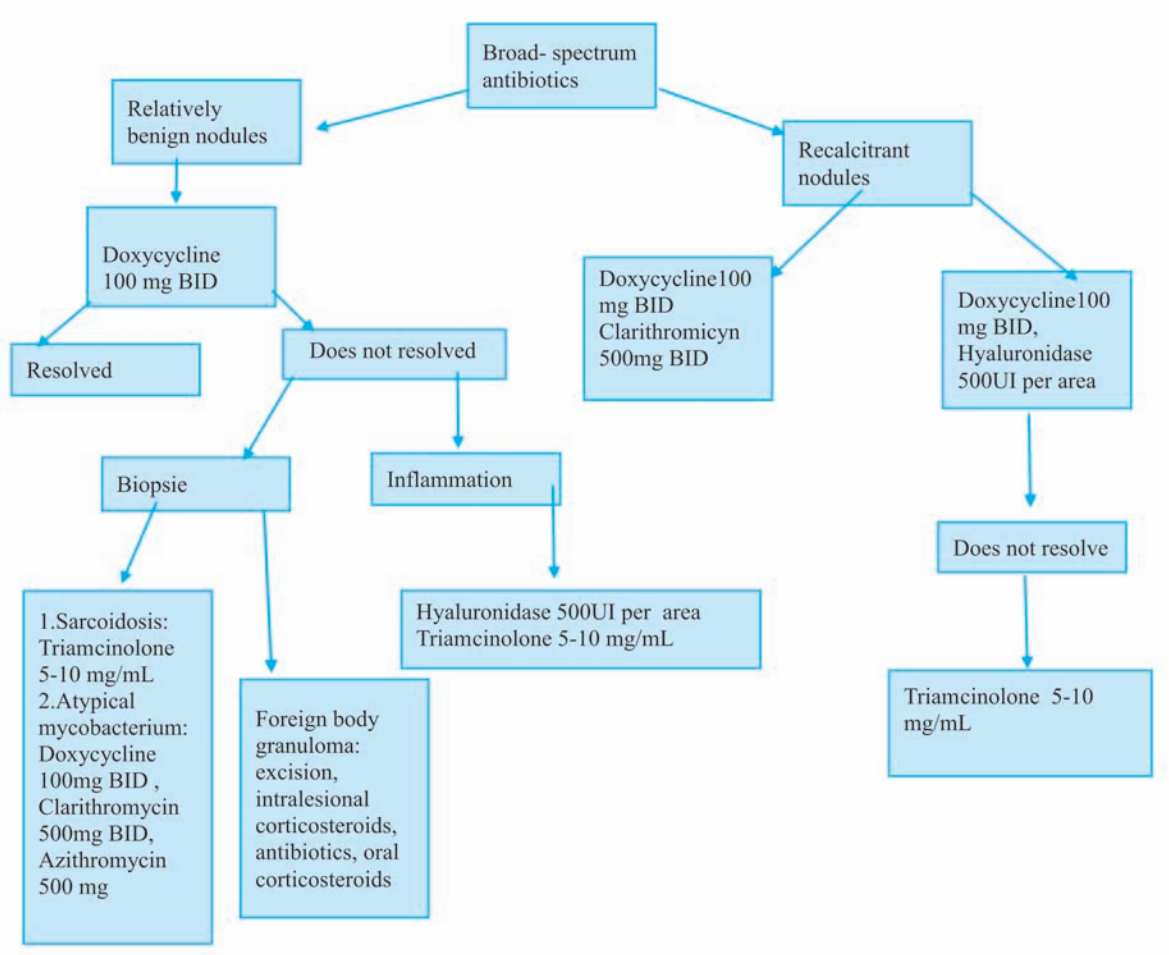

Figure 8. Broad-spectrum antibiotic treatment for late-onset nodules after hyaluronic acid filler administration.

appearance of painful nodules, edema, and erythema [22].

The triggers of late reactions are considered to be viral infections, dental interventions, an incorrect injection technique, active sinusitis, and simultaneous injection of several types of hyaluronic acid [23, 24].

Recent reports in the literature have revealed the occurrence of late inflammatory reactions to the injection of Juvederm Volbella of 1.0% per patient and 0.8% per syringe. Low molecular weight hyaluronic acid degradation products are thought to have high pro-inflammatory activity [21].

In a study performed on 4500 patients for 9 years in which cross-linked hyaluronic acid injections obtained by Vycross technology were performed, there was a late complication rate of 0.98% per patient [43]. According to this study, the etiology of late complications is immune mediated. It is assumed that in the process of degradation of this type of hyaluronic acid the immune system is stimulated and an inflammatory process is triggered.

For the management of late-onset nodules, several other diagnostic and treatment algorithms have been proposed. First of all, it is necessary to exclude a fluctuating node that requires incision, drainage, and bacteriological and fungal examination of the secretion [25, 26]. C-reactive protein assay (PCR) and biopsy are required if treatment is not effective [27, 28].

Skin ultrasound is considered the "gold standard" investigation because it indicates the

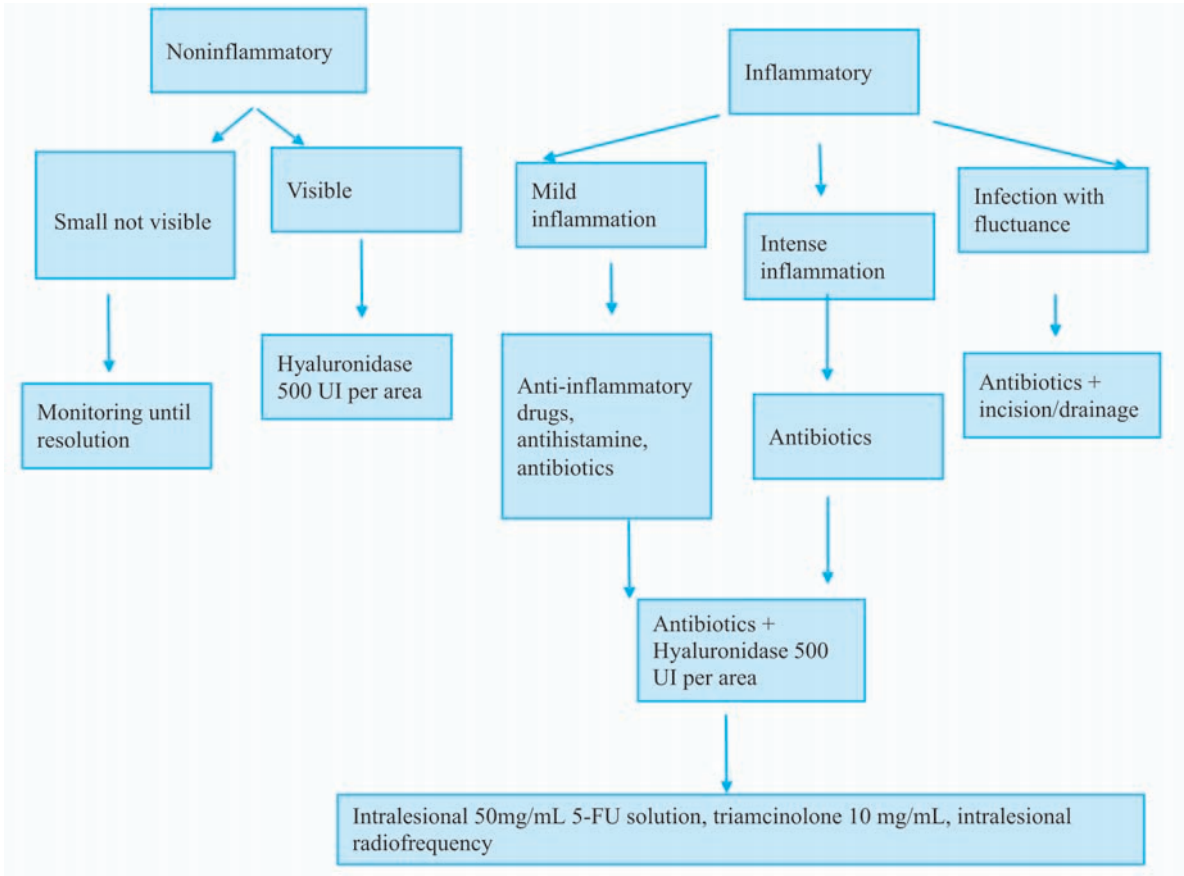

Figure 9. Summary of global treatment strategies for late-onset nodules after hyaluronic acid filler administration.

exact location of the nodule and its relationship with neighboring tissues as well as the density of the injected filler [29, 30].

Regarding the treatment algorithm, the first line therapy is represented by broad-spectrum antibiotics and some authors recommend bi-therapy for several weeks [31-37]. Macrolides are considered very effective due to their ability to concentrate in adipose tissue, given that the vast majority of fillers are located in adipose tissue [38]. Cyclin antibiotics, especially doxycycline, are used for their anti-inflammatory and immunomodulatory effect [44].

Another first-line option is the intralesional injection of Hyaluronidase [39, 40, 41].

Hyaluronidase disintegrates hyaluronic acid by hydrolysis. The recommended dose is 10-20 U for an area <2.5 mm and the dose should be increased in resistant cases or when resistant filler has been injected (for example from the Vycross Juvederm family) [12].

Corticosteroids or a combination of the two are recommended [2, 42].

The second most used treatment line is intralesional steroid injection [2, 42]. Injection of concentrated steroids leads to an area of atrophy.

To reduce the side effects of corticosteroids, some authors suggest reconstituting the solution for injection with 5-FU, lidocaine, or saline. Alternative options for the second line of therapy are antibiotic treatment, radiofrequency, laser therapy, intralesional injection with hyaluronidase or 5-FU, surgical excision is used as a last resort when a granuloma is suspected [2]. Radiofrequency treatment generates an increase in subcutaneous temperature of up to 42°C, smoothing the area or even destroying the injected hyaluronic acid, which is then resorbed.

One possible cause of inflammatory nodules is the biofilm.

Biofilm is a group of microorganisms or cells in which they attach to each other in a three-dimensional structure. The structure is covered by a polymeric substance by a matrix, which gives it the ability to survive, grow, and be resistant to antibiotics [5, 6].

The biofilm uses the implanted filler as a surface to which it attaches and excretes its own matrix.

The biofilm can stay in a dormant state and can be activated, for example, after a trauma or a hematogenous infection. They are found in patients who make cosmetic corrections with hyaluronic acid and dental implant treatments in the same period. A variety of clinical presentations can occur, such as cellulite, abscess, nodules, and granulomatous inflammation, which can occur weeks, months, and years after injection of hyaluronic acid [7]. Bacteriological examinations usually do not identify the bacterium, the diagnosis is confirmed by PCR [8]. Macrolide and quinolone antibiotics are recommended (ex Clarithromycin 500 mg x2 / day and Ciprofloxacin 500 mg x2 / day for 4-6 weeks). Hyaluronidase injection can cause matrix fragmentation and help better penetration of antibiotics.

Conclusions

Immediate side effects have long been reported and late complications have been undiagnosed.

Post-injection complications of hyaluronic acid can also occur over long distances. The main evidence of the cause-effect link is the histopathological examination that highlights the persistence of hyaluronic acid in the tissue and the remission of symptoms after injection of hyaluronidase. The causes of late complications can be associated with the number of products injected, the volume injected, and whether the products were injected simultaneously or in separate sessions, and are related to the patient's related allergic pathology.

For the group of patients analyzed in our clinic, the time of complete remission of symptoms varied between 48 hours and 2 months.

Among the possible causes we mention atopy, nickel allergy, injected products, cosmetics, dental treatments, dental implants, and acne skin.

Recognizing late complications helps the injecting physician to choose the most appropriate treatment.

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Conflict of interest
NONE DECLARED

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