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"Delayed reactions after hyaluronic acid injections – a review for physicians outside aesthetic medicine"

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Abstract

Background. Delayed reactions after hyaluronic acid (HA) injections are rare but clinically significant complications that may occur months or years after aesthetic procedures. Their nonspecific presentation may mimic infections, cysts, salivary gland disorders, or neoplasms, causing diagnostic difficulties for physicians outside aesthetic medicine.

Aim. To review current evidence on the epidemiology, pathogenesis, clinical presentation, diagnosis, and management of delayed reactions after HA injections, with emphasis on practical aspects for non-aesthetic physicians.

Material and methods. A narrative review was conducted using PubMed publications from 2015–2026 and the ISAPS report. Reviews, expert consensus statements, case reports/series, observational studies, post-marketing surveillance analyses, and diagnostic/therapeutic algorithms were analyzed.

Results. Delayed reactions after HA fillers include swelling, erythema, induration, inflammatory and non-inflammatory nodules, granulomas, and delayed infections. Pathogenesis is multifactorial, involving foreign body reactions, immune-mediated mechanisms, and infectious processes, including biofilm formation. Manifestations may be triggered by infections, vaccination, trauma, or dental procedures. Diagnosis relies on history, clinical examination, and differential diagnosis, with imaging, microbiological testing, or histopathology needed in selected cases. Treatment depends on the mechanism and may include antibiotics, hyaluronidase, corticosteroids, or procedural interventions.

Conclusions. Delayed reactions after HA injections should be considered in the differential diagnosis of persistent facial nodules, swelling, and inflammatory lesions, even years after cosmetic procedures. Routine inquiry about previous aesthetic treatments is essential to avoid misdiagnosis.

Key words: hyaluronic acid, dermal fillers, delayed reactions, granuloma, differential diagnosis, general practice

1. Introduction

Patients experiencing delayed reactions following hyaluronic acid (HA) injections may not associate symptoms that develop months or even years later with a previous aesthetic procedure. As a result, they often initially present to physicians who do not specialize in aesthetic medicine, including primary care physicians and emergency department clinicians. [1, 2, 3, 4, 5] In a survey study based on a simulated case of a delayed reaction, most physicians initially referred the patient to the emergency department, including 91.2% of dentists, 68% of dermatologists, and 65% of plastic surgeons. [6] This highlights the need to increase awareness of these complications, as failure to obtain a history of previous aesthetic procedures contributes to misdiagnosis. [2, 4, 5, 7, 8]

The prolonged latency period of these complications, which may exceed 10 years after the procedure, may lead clinicians to dismiss the association between the patient's symptoms and previous filler injections, despite evidence that filler material can persist in tissues for many years. [4, 9, 10] The nonspecific clinical presentation of delayed complications may result in their misinterpretation as soft tissue neoplasms, cysts, sialadenitis, or nonspecific infectious processes, potentially leading to inappropriate treatment or unnecessary surgical interventions. [4, 9, 10, 11] Furthermore, the absence of information regarding previous aesthetic procedures may complicate histopathological interpretation, as the diagnosis of a filler-related reaction requires recognition of the characteristic features of the implanted material together with correlation with the patient's procedural history. [4]

Greater awareness of potential triggering factors, including infections, vaccinations, dental procedures, and trauma, may facilitate recognition of the relationship between seemingly nonspecific symptoms and previous HA filler injections. [12, 13, 14, 15, 16, 17] Therefore, physicians across different specialties should routinely inquire about a history of aesthetic procedures, particularly in middle-aged women presenting with unexplained inflammatory lesions or nodules in the orofacial region, as failure to obtain this information may result in diagnostic errors, inappropriate treatment, and unnecessary interventions. [4, 9, 10]

2. Research materials and methods

This study is a narrative review. The material was developed based on literature indexed in the PubMed database published between 2015 and 2026 and supplemented with the statistical report of the International Society of Aesthetic Plastic Surgery (ISAPS). The review included narrative reviews, systematic reviews, expert consensus statements, case reports and case series, observational studies, post-marketing surveillance analyses, and publications presenting diagnostic and therapeutic algorithms.

The literature search was conducted using the following keywords: *"hyaluronic acid filler," "dermal filler," "delayed inflammatory reaction," "late-onset reaction," "delayed-onset nodules," "granuloma," "complications," "diagnosis," "treatment," "primary care," "general practice," "soft tissue infection,"* and *"differential diagnosis."* Publications addressing the definition, epidemiology, pathogenesis, clinical presentation, diagnosis, and treatment of delayed reactions following hyaluronic acid injections were included. Studies focusing exclusively on acute vascular complications, other types of dermal fillers, or topics unrelated to practical clinical management were excluded. Owing to the narrative nature of this review, neither a meta-analysis nor a systematic assessment of study quality was performed.

3. Research results

3.1. Definition and Classification

In most publications, delayed reactions following hyaluronic acid (HA) injections are defined as adverse events occurring after an initial symptom-free period, usually at least two weeks after the procedure. This definition helps distinguish them from conditions such as prolonged post-procedural edema or hematoma, which are present from the time of injection. [1, 6, 12, 18] The terminology used to describe this group of complications is not entirely consistent, as terms such as *"delayed-onset," "late-onset," "delayed reaction,"* and *"delayed complication"* are often used interchangeably in the literature. [1, 6, 12, 13, 15]

The most fundamental classification is based on the time of symptom onset and distinguishes early reactions, which develop immediately after injection or within the first days or weeks following the procedure, from delayed reactions, which may occur after a longer symptom-free interval, ranging from several weeks to many months or even years. [2, 6, 11, 13, 14]

Clinically, delayed complications following HA injections include swelling, induration, inflammatory and non-inflammatory nodules, granulomas, abscesses, delayed infections, filler migration, and persistent filler deposits. In rare and severe cases, tissue necrosis has also been reported. [2, 6, 7, 11, 13, 14, 15, 19] Alternatively, these reactions may be classified according to their presumed underlying mechanism as foreign body reactions, immunological reactions, and infectious reactions, including those associated with biofilm formation. [1, 3, 7, 12, 13, 15, 19]

These classification systems are not mutually exclusive and frequently overlap in clinical practice, reflecting the complex and multifactorial nature of delayed reactions following HA injections.

3.2. Epidemiology

As the number of hyaluronic acid (HA) procedures continues to increase, a corresponding rise in the number of reported complications has also been observed, reflecting the growing popularity and availability of these aesthetic treatments. [2, 11, 15] According to the available literature, the vast majority of affected patients are women, representing between 96.8% and 100% of cases depending on the study, with the mean patient age most commonly falling within the middle-aged population. [4, 5, 7, 9]

According to the International Society of Aesthetic Plastic Surgery (ISAPS), more than 6 million hyaluronic acid procedures were performed worldwide in 2024, indicating that even rare complications may be encountered in routine clinical practice. [20] In a post-marketing surveillance analysis based on voluntary adverse event reports collected between 2016 and 2020, delayed reactions accounted for 195 of 585 reported adverse events (33.3%), with nodules representing the most common clinical manifestation. [1]

Delayed complications following HA injections are considered uncommon, with an estimated incidence ranging from 0.3% to 4.25%; higher rates have been reported in some studies

involving Vycross-based fillers. [1, 4, 16, 18] However, these epidemiological data should be interpreted with caution, as much of the available evidence is derived from case reports, small case series, questionnaire-based studies, and passive adverse event reporting systems, which may both underestimate the true number of complications and preclude accurate estimation of their actual incidence. [1, 4, 6, 9] Furthermore, the absence of national registries makes it difficult to assess the true scale of the problem in Poland.

3.3. Pathogenesis

The pathogenesis of delayed reactions following hyaluronic acid (HA) injections has not been fully elucidated and is considered multifactorial, involving foreign body reactions, immunological mechanisms, and infectious factors. [2, 12, 13, 15] A foreign body reaction represents a host defense response to the deposited material and may result in fibrosis and granulomatous inflammation surrounding the filler. [4, 10, 13, 15] It develops when the size of HA particles exceeds the phagocytic capacity of a single macrophage, leading to macrophage aggregation and fusion into foreign body giant cells. [4, 15]

T-cell-mediated immune reactions (type IV hypersensitivity) also play an important role in the pathogenesis of delayed reactions, distinguishing them from early allergic reactions mediated by IgE antibodies (type I hypersensitivity). [3, 11, 13, 16] One proposed mechanism involves the degradation of the filler into low-molecular-weight HA fragments, which may exert pro-inflammatory effects and enhance the immune response, particularly in the presence of concurrent immune stimulation or infection. [12, 13, 16]

Another possible mechanism involves delayed infectious complications resulting from contamination of the filler with skin commensal bacteria or pathogenic microorganisms at the time of injection. This may lead to the formation of a biofilm, an organized community of microorganisms embedded within an extracellular matrix, which impairs microbial clearance by the host immune system and reduces the effectiveness of antibiotic therapy. [5, 12, 13, 15, 19] Microorganisms within a biofilm may remain dormant for months or even years without causing clinical symptoms until an external triggering factor induces an abrupt inflammatory response. [5, 9, 15]

Some publications have also highlighted the potential role of genetic predisposition in the development of delayed reactions following HA injections. [12, 13, 14] An increased risk of

inflammatory reactions has been reported in patients carrying the HLA-B*08 and HLA-DRB1*03 haplotypes, which are thought to modify immune response pathways and increase susceptibility to T-cell-mediated reactions. [12, 13] Similar mechanisms of immune susceptibility have also been discussed in the context of autoimmune/inflammatory syndrome induced by adjuvants (ASIA), in which biomaterials may act as triggers for an abnormal inflammatory and autoimmune response. [13, 14]

The development of delayed reactions may also be influenced by triggering factors, which are discussed in the following section.

3.4. Triggering and predisposing factors

Factors preceding the onset of delayed reactions after hyaluronic acid include both systemic events, such as infections and vaccinations, and local factors, including trauma, dental procedures, laser procedures, and disruption of the skin barrier. [3, 12, 13, 16, 17] A separate group consists of factors predisposing to the occurrence of reactions, related to the patient's health status, the properties of the preparation, the presence of biofilm, contaminants, or the injection technique. [2, 7, 12, 13, 14, 15] Among the best-described triggers are infections, especially viral and bacterial ones in the form of, for example, flu-like syndromes and gastrointestinal or urinary tract infections, which may precede the occurrence of delayed reactions, sometimes appearing several days after the illness. [3, 12, 13, 15] Interestingly, one study noted that as many as 71% of delayed reactions occur in the autumn-winter period, which correlates with flu season and supports the involvement of infections as a triggering factor. [13] The literature has also mentioned herpes zoster infection, sinusitis and tonsillitis, as well as inflammatory skin conditions, including acne. [14] Reactions following vaccinations, especially against COVID-19, have also been described, although this data comes mainly from case reports and clinical observations. [12, 14, 15, 16] Local factors include dental procedures, trauma, microtrauma, laser procedures, and disruption of the skin barrier. [13, 14, 15, 17, 19] A separate group consists of factors related to the preparation and the injection technique, which may predispose to the development of late reactions, especially foreign body-type or inflammatory reactions. [12, 13, 15] Hyaluronic acid fillers may contain trace amounts of silicone oil (syringe lubricant), aluminum (particularly in factory-filled glass syringes), fragments of stainless steel originating from manufacturing machinery, or bacterial endotoxins resulting from the fact that the substance is produced using bacterial fermentation, including

Streptococcus strains, which, despite purification processes, may be present as trace contaminants. [12, 13] In addition, injecting too large a volume of material at a single point, too fast an injection rate, and aggressive introduction of the preparation using the fanning technique may increase the risk of tissue irritation and favor foreign body-type reactions and granuloma formation. [12, 13] It should be emphasized, however, that the presence of a triggering factor does not conclusively determine the mechanism of the reaction, since in many cases it remains not fully explained. [12, 17]

3.5. Clinical presentation

The clinical presentation of delayed reactions after hyaluronic acid injections is varied and primarily includes nodules, edema, erythema, induration, and infections, which may appear after an initial period free of symptoms. [2, 6, 21] Nodules are divided in the literature into inflammatory and non-inflammatory lesions, which has clinical significance, since they differ in the time of occurrence and possible mechanism. [1, 15] Non-inflammatory nodules usually appear directly or shortly after implantation of the preparation and are most often associated with technical factors, such as excessive volume or improper placement of the filler. [15, 22] Inflammatory nodules may appear much later, from several days to many months or years after the injection, and in clinical descriptions, reactions of this type most often concern a period of several months after the procedure. [11, 15] Clinically, they are described as single or multiple lesions of firm, hard consistency, which may be accompanied by edema, induration, and erythema, although they are not always painful or clearly visible on examination. [9, 15] Depending on the location of the procedure, nodules have been described, among others, within the lips, cheeks, chin, and temples, and the lip area is indicated in the literature as a frequent location of nodular lesions after fillers. [4, 9, 15] Nodular lesions have also been described outside the primary injection site, which in some cases may be related to displacement or migration of the preparation. [7, 15] Nodules appearing many months or years after the procedure may correspond to granulomas. [4, 9, 15] However, a definitive diagnosis of a foreign body-type granuloma requires histopathological confirmation, in which the presence of material surrounded by giant cells and macrophages is found. [4, 15] Delayed reactions also often manifest as edema at the site of the previous injection, which may appear after at least two weeks from the procedure. [8, 12] A particular form of edema is PIDS, manifesting as persistent and recurrent, non-pitting edema, which may last several months with episodes of exacerbation

and remission. [2] It is often not accompanied by clearly palpable nodules, but rather by diffuse tissue induration. [2] Another type of edema is lymphatic malar edema, manifesting as localized, painless swelling of tissues, appearing in the infraorbital area, after injections in the so-called tear trough. [7, 18] The Tyndall effect may also occur in the same area, i.e., a blue-gray discoloration of the skin, resulting from too superficial administration of the acid. [7, 22] Edema may be accompanied by erythema, in a diffuse or patchy form, which, in reactions of an immunological nature, may co-occur with itching and simultaneously involve all areas where the preparation was previously injected. [3, 14, 17] In infectious complications, erythema may be asymmetric in nature, with a dark red center and gradually fading edges, and coexist with burning, pain, and edema. [14] Prolonged erythema may result from the filler's pressure on tissues, which impairs circulation and forces the body to form new blood vessels. [14] In clinical practice, diffuse erythema and edema should be differentiated from severe infectious or vascular complications, especially when the symptoms are accompanied by sudden pain, a reticulated pattern of bruising, or rapid progression of lesions, which suggests the development of necrosis. [14, 19] It is therefore worth carefully monitoring cases of cellulitis, abscess, intensified local pain, or warming of the surrounding tissues. [6, 19, 21] However, the clinical presentation of delayed reactions does not always have to be limited to the face alone, since some sources discuss case reports of ASIA syndrome, in which the patient may report chronic fatigue, muscle and joint pain, sleep disturbances, dry mouth, memory problems, and urticaria over the entire body. [13, 14] The same symptom, especially edema or a nodule, may have a different basis, and therefore the clinical presentation should be interpreted together with the timing of the lesions, procedural history, and additional tests. [13, 14, 15]

3.6. Diagnostics

The diagnosis of delayed reactions after hyaluronic acid injections should be based on a structured analysis including history taking, assessment of the timing of symptom onset, the presence of triggering factors and their clinical nature, as well as, if necessary, the use of additional tests. [2, 4] The first step is a thorough history, with particular attention to previous aesthetic procedures, since the connection between symptoms and filler administration may be difficult to capture, especially when many months or years have passed since the procedure. [4] It is also worth, if possible, establishing the type of preparation, the date and site of administration, the injection technique, the volume, and the person performing the procedure,

since this information may facilitate assessment of the complication mechanism and the choice of further management. [2, 13, 15] It is also essential to determine the timing of symptom onset, since delayed reactions are defined as appearing after an asymptomatic period, usually after at least 2 weeks from the procedure. [1, 12, 13, 18] In the next step, the nature of the lesions should be assessed, paying attention to the presence of nodules, edema, erythema, induration, or signs of infection, since different reaction mechanisms may produce a similar clinical picture. [2, 6, 21] Of particular importance is differentiating between an immunological reaction and an infectious process, since they may manifest with similar inflammatory symptoms, although the presence of abscess, exudate, or systemic symptoms may suggest an infectious etiology. [6, 13, 19, 21] It may also be helpful to consider potential triggering factors, such as infections, vaccinations, or trauma, which may precede the onset of symptoms and indicate a possible reaction mechanism. [12, 14, 15, 17] In ambiguous cases, ultrasonography is applicable, especially high-frequency ultrasonography, which allows assessment of the location, depth, and volume of the deposited filler, as well as the presence of nodules, abscesses, material deposits, or diffuse tissue edema. [2, 10, 22] It is particularly useful as an auxiliary diagnostic tool during targeted treatment, for example when administering hyaluronidase, since it increases the precision of lesion localization and needle guidance. [2, 15, 22] On ultrasound imaging, hypoechogenic, often lobulated nodules corresponding to granulomatous reactions, poorly demarcated HA deposits in the subcutaneous tissue, and diffuse thickening with increased echogenicity of the subcutaneous tissue have been described. [2] In selected cases, especially with deep or extensive lesions, magnetic resonance imaging may be considered. [2, 5, 10, 13] In unclear situations, particularly when a granuloma is suspected, a biopsy may be necessary, since the definitive diagnosis of a granulomatous reaction requires histopathological confirmation, in which the presence of material surrounded by giant cells and macrophages is found. [4, 9, 15] During histopathological evaluation, alcian blue staining may be helpful, as it reveals mucinous/glycosaminoglycan material and may support the identification of HA deposits and their differentiation from other materials. [4, 21] When an intensified inflammatory process or infection is suspected, CRP and complete blood count may be additionally determined to assess possible leukocytosis, although these results are nonspecific and should be interpreted together with the clinical picture. [5, 6, 19, 21] To extend infectious diagnostics, in the case of material collected from the lesion, it is worth performing a culture for aerobic bacteria, anaerobic bacteria, and fungi. [6, 19, 21] In selected, diagnostically difficult cases, molecular methods such as PCR or FISH may be considered, which may

increase the chance of identifying microorganisms in the biofilm, especially with negative results of classic cultures. [6, 15, 19, 21] In the case of systemic symptoms suggesting a possible ASIA syndrome, the diagnostic workup may be extended to include immunological tests, such as ANA and complement components, although this diagnostic direction should be considered individually and interpreted with caution. [13, 14] In clinical practice, it should also be remembered that delayed reactions after fillers may be confused with other disease entities, such as benign and malignant soft tissue and salivary gland tumors, stagnant cysts, skin and soft tissue infections, inflammatory diseases, or allergic reactions, whose nonspecific clinical picture may mimic delayed reactions after hyaluronic acid. [2, 4, 6, 9, 14]

3.7. Treatment

At the very outset, it should be emphasized that the treatment of delayed reactions after HA is not fully standardized, and the available regimens are based mainly on expert consensus, treatment algorithms, case reports, and clinical experience. [6, 15, 21, 22] Before choosing a therapy, it should be assessed whether the lesion is inflammatory or non-inflammatory in nature, since this determines further management. [13, 21, 22] Treatment of delayed inflammatory reactions should take into account the possibility of an infectious, immunological, or mixed background, since these mechanisms may produce a similar clinical picture. [13, 15, 21] In the case of inflammatory nodules of infectious origin, the presence or absence of fluctuation of the lesion should be assessed. [13, 21] Its presence, suggesting abscess formation or active infection, requires above all incision and drainage of the lesion along with collection of material for culture. [2, 13, 14, 16, 21] In the case of non-fluctuant inflammatory lesions of infectious background, it is recommended to perform a biopsy along with tissue culture for precise pathogen identification. [13] While awaiting the test results, empirical broad-spectrum oral antibiotic therapy is recommended, and after obtaining the culture result, targeted treatment should be implemented. [6, 7, 13, 15, 21] Algorithms and expert recommendations have described the use of combination therapy for 3-6 weeks, including a fluoroquinolone combined with a tetracycline or a macrolide, due to their assumed antibacterial and anti-inflammatory action. [21] Macrolides, such as clarithromycin, are particularly recommended in the treatment of inflammatory lesions after fillers due to their ability to accumulate in adipose tissue and to inhibit the quorum sensing mechanism of bacteria in the biofilm. [21] The literature has also described combinations of ciprofloxacin (500 mg twice daily) with minocycline (100 mg/day)

or clarithromycin (500 mg twice daily). [6, 14, 15, 21] If clear clinical improvement occurs after the drugs are implemented, confirming the infectious background of the lesion, therapy should be continued for 2 weeks after complete resolution of all symptoms. [15] When antibiotic therapy does not bring the expected results, the use of hyaluronidase may be considered. [13] The effectiveness of hyaluronidase depends on its contact with the HA material, therefore, in the case of nodules or compact deposits, precise administration into the interior of the lesion is recommended, sometimes with mechanical disruption of the deposit and tissue massage after the injection. [15, 21, 22] The dosing of hyaluronidase depends on the location, volume, and physicochemical properties of the administered filler, with the use of 30 to 300 units per lesion described for inflammatory nodules, with the possibility of repeating the therapy. [16, 21, 22] Before starting therapy, allergy to insect venoms (bees, wasps) should be excluded as far as possible due to the risk of cross-reaction, and an intradermal test should be considered, particularly when using an enzyme of animal origin. [13, 22, 23] However, the absence of insect venom allergy does not exclude a reaction to hyaluronidase, since rare cases of delayed hypersensitivity to the enzyme itself have been described, probably related to its repeated administration, since the treatment itself may need to be repeated in 2-3 cycles at 2-3 week intervals. [21, 22, 23] At the same time, it is worth remembering that it should not be a first-line treatment, and its introduction is recommended only after starting antibiotic therapy, in order to prevent the spread of microorganisms. [13, 15, 21, 22] An exception is made for certain highly cross-linked preparations, including the filler using Vycross technology described in the literature, for which the authors of the algorithms suggest earlier consideration of hyaluronidase, usually with antibiotic cover, due to the more difficult degradation of the material and the risk of persistence of the reaction. [21, 22] Treatment of delayed inflammatory reactions of immunological background is based on suppressing an excessive cellular response (most often type IV hypersensitivity). [3, 13] It is worth remembering that type IV usually does not respond to antihistamines. [3] In the case of small nodules, observation is recommended, and in the absence of improvement, further treatment should be introduced according to the regimen for moderate and severe immunological reactions. [13] The basis of treatment is oral glucocorticosteroids (e.g., prednisone), which allow rapid control of the inflammatory state, but they should be used only after active infection has been excluded. [3, 13, 15, 21] In the absence of improvement, hyaluronidase can be added to glucocorticosteroid therapy due to its key role in eliminating the HA substrate that triggers the inflammatory process. [13, 15, 17, 22] If the treatment effect is still unsatisfactory, intralesional glucocorticosteroid injections can be

considered, most often triamcinolone, and in fibrotic lesions also in combination with 5-FU. [2, 13, 16, 17, 21] The therapeutic protocol described in the literature recommends the use of triamcinolone (10-20 mg/mL), 5-FU (50 mg/mL), and lidocaine or saline in a 1:1:1 ratio, which allows minimizing the risk of skin atrophy. [15, 21] Injections should be administered precisely into the interior of the lesion at intervals of 2-4 weeks, until full remission is achieved, with particular caution maintained in the periorbital area. [15, 21, 22] In recurrent inflammatory reactions requiring repeated steroid therapy, the use of colchicine at a dose of 0.6 mg every 12 hours has been described, and after resolution of symptoms, reducing the dose to 0.6 mg per day. [15] Laser therapy using an Nd:YAG laser with a wavelength of 1064 nm may be considered as an alternative method in the treatment of persistent, treatment-resistant nodules and granulomas. [9, 21] The literature has described, among others, its subcutaneous use in combination with cannula aspiration. [9, 21] The use of vascular lasers may also be considered to alleviate symptoms of delayed, diffuse erythema, which occurs as a result of the filler's pressure on surrounding tissues and secondary neovascularization. [14] In descriptions of reactions after COVID-19 vaccination, the use of angiotensin-converting enzyme inhibitors, such as lisinopril, was mentioned to modify the local inflammatory response, although the data are limited and this approach should not be treated as a routine treatment standard. [12, 16] In rare situations of ASIA syndrome diagnosis, treatment in the form of long-term immunosuppressive pharmacotherapy, e.g., using cyclosporine A, has been described. [13, 14] In the case of small, non-inflammatory, invisible, and asymptomatic nodules with a diameter <0.5 cm, observation or massage may be considered, due to their tendency to resolve spontaneously; in the absence of results, hyaluronidase injections may be considered. [13, 15, 16, 21, 22] In situations where the lesion does not respond to the enzyme, short-term oral steroid therapy may be considered to reduce edema and induration. [13, 22] Surgical excision of delayed reactions after hyaluronic acid injections is treated as a last-resort method in the therapeutic algorithm, implemented only after all other medical options have been exhausted. [4, 9, 19, 21, 22]

4. Discussion

The available evidence indicates that delayed reactions after hyaluronic acid (HA) filler injections, although statistically uncommon, represent a clinically important and likely underrecognized diagnostic challenge, particularly for physicians who do not routinely work in

aesthetic medicine. The reviewed literature consistently shows that the diagnostic difficulty of these complications does not stem from a lack of described clinical features, but rather from their nonspecific character and the long, often multi-year, latency period that separates the causative procedure from symptom onset. This temporal gap creates a substantial risk that patients will not spontaneously report a history of filler injections, and that clinicians will not think to ask about it, resulting in a diagnostic blind spot that is well illustrated by survey data showing that the large majority of physicians confronted with a simulated delayed-reaction case chose to refer the patient directly to the emergency department rather than considering a filler-related etiology.

A recurring theme across the pathogenesis, clinical presentation, and diagnostic sections of this review is the overlap between immunological, infectious, and foreign-body mechanisms. Rather than representing distinct, easily separable entities, these mechanisms frequently coexist or transition into one another over the course of a single reaction, which has direct practical consequences: it explains why treatment algorithms proposed in the literature are staged and sequential (e.g., antibiotics before hyaluronidase, hyaluronidase before corticosteroids) rather than mechanism-specific from the outset. This layered approach reflects the genuine diagnostic uncertainty that persists even after a structured work-up, since clinical, ultrasonographic, and even histopathological findings may not reliably distinguish between an infectious and a purely immune-mediated process.

The role of triggering factors, especially infections and vaccinations, deserves particular attention. The seasonal clustering of delayed reactions in the autumn-winter period, coinciding with the influenza season, is one of the more compelling pieces of indirect evidence supporting an infection-triggered immune mechanism, and it offers a practical clinical clue: a patient presenting with a new orofacial nodule during flu season, with a remote history of filler injection, should raise suspicion for this diagnosis even in the absence of an obvious local trigger. At the same time, it must be acknowledged that much of the evidence linking specific triggers (vaccination, dental procedures, herpes zoster) to delayed reactions is derived from case reports and small case series, which limits the strength of causal inference that can be drawn.

From a methodological standpoint, several limitations of the underlying evidence base should be highlighted. First, epidemiological estimates of incidence are drawn largely from passive post-marketing surveillance systems and voluntary reporting, both of which are prone to

underreporting and selection bias, meaning that the true incidence of delayed reactions is likely higher than the commonly cited range. Second, the absence of standardized terminology, with "delayed-onset," "late-onset," and "delayed complication" used interchangeably, complicates comparison across studies and may obscure clinically meaningful subgroups. Third, no national or international registry currently captures these complications systematically, which is particularly relevant in the Polish context, where the true scale of the problem cannot be reliably estimated. Fourth, treatment recommendations, while increasingly organized into algorithms, remain based predominantly on expert consensus and retrospective case series rather than randomized controlled trials, reflecting the practical and ethical difficulty of conducting prospective interventional research on a rare, heterogeneous, and unpredictable complication.

For clinical practice outside aesthetic medicine, the most actionable conclusion of this review is straightforward: a history of aesthetic filler procedures, irrespective of how remote in time, should become a routine element of the differential diagnostic work-up for unexplained facial nodules, swelling, or erythema, especially in middle-aged women. Recognizing this possibility early can prevent unnecessary invasive investigations, inappropriate empirical treatment of presumed neoplastic or purely infectious disease, and delays in initiating the staged, filler-specific management strategies described in this review.

This review has several limitations inherent to its narrative design. Because no systematic methodology or formal quality assessment was applied, the selection of included studies may be subject to bias, and the relative weight given to different mechanisms or treatment strategies reflects the current state and emphasis of the literature rather than a quantitatively validated hierarchy of evidence. Given the increasing global volume of HA procedures, prospective, multicenter studies with standardized definitions and outcome reporting are needed to refine incidence estimates, clarify the relative contribution of the proposed pathogenic mechanisms, and validate treatment algorithms in a more rigorous, evidence-based manner.

5. Conclusion

Delayed reactions after hyaluronic acid injections constitute rare but potentially diagnostically challenging complications, which may manifest after a long asymptomatic period and take on a nonspecific clinical presentation, often mimicking other disease entities, including tumors.

Consequently, patients most often present to primary care physicians or emergency departments, and a lack of information about previous aesthetic procedures may lead to misdiagnosis and inadequate treatment. From the point of view of a physician outside of aesthetic medicine, it is of key importance to include previous injections in the medical history, even if they were performed many months or years earlier, and to be aware that symptoms such as nodules, edema, or erythema may be related to fillers. The nonspecificity of the clinical presentation and the possibility of coexisting immunological and infectious mechanisms require a broad diagnostic approach and careful differentiation. Therapeutic management is staged in nature and depends on the presumed mechanism of the reaction, although in many cases it is based on antibiotic therapy and steroid therapy, supplemented if necessary with other methods. Due to the increasing number of procedures using fillers, raising awareness of these complications among physicians of various specialties constitutes an important element in improving patient safety and treatment effectiveness.

Disclosure

All authors have read and approved the final version of the manuscript for publication.

Author Contributions

Conceptualization, J.K. and O.G.; methodology, W.N.; software, W.K.; validation A.Z. and J.C.; formal analysis Ł.K.; investigation, M.S.; resources J.K.; data curation A.N.; writing—original draft preparation J.K.; writing—review and editing M.Z. and A.Z.; visualization J.K.; supervision M.S.; project administration, J.K.; funding acquisition O.G. All authors have read and agreed to the published version of the manuscript.

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Declaration of the Use of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used ChatGPT for the purpose of language editing and grammar correction of the English text to improve readability and linguistic accuracy. After using thi stool, the authors reviewed and edited the content as needed and take full responsibility for the substantive content of the publication.

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