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Long-Term Tissue Response to Hyaluronic Acid Fillers: Fibrosis, Inflammation, and Delayed Complications

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ABSTRACT

Hyaluronic acid (HA) dermal fillers are widely used for non-surgical facial rejuvenation. However, emerging evidence challenges their presumed complete biodegradability and temporary nature, revealing instead the potential for long-term tissue reactions, including fibrosis chronic inflammation, and delayed complications. These complications, which may manifest several months to years after injection, are driven by complex immune-mediated mechanisms and remain understudied in diverse U.S. populations. The **objectives** are to report clinical manifestations, histopathology and radiologic correlates, management approach and outcomes of delayed HA filler complications in a multicultural cohort of the United States with a primary focus on fibrosis and inflammation processes. This retrospective case series was a single-center study of 15 consecutive cases of patients with delayed complications (>4 weeks after injection) in an academic aesthetic dermatology clinic during the period of January 2020 to December 2025. Electronic health records were reviewed and provided the data demographics, filler details, complication progression, clinical photographs, high-frequency ultrasound results, histopathology (hematoxylin-eosin, Alcian blue, immunohistochemistry), treatments, and 6 and 12 months outcomes. Variables were summarized using descriptive statistics based on STROBE and CARE guidelines. Complications were first experienced by the cohort (86.7% female; mean age 41.2 ± 7.5 years; 40% Caucasian, 33.3% African-American) after a mean of 10.8 ± 8.2 months after injection. Fibrotic induration was the leading (73.3%), then inflammatory nodules (66.7%), persistent edema (40%), and migration (13.3%). Infections (26.7%) and vaccinations (13.3%) were identified as triggers in some cases. Ultrasound showed hypoechoic deposits with fibrotic halos. Histopathology revealed foreign-body granulomas expressing TGF-β and containing multinucleated giant cells. Treatment with ultrasound-guided hyaluronidase (mean 2.1 sessions), most commonly combined with intralesional triamcinolone, resulted in complete resolution in 80% of cases at 6 months, with no recurrences observed at 12 months. In this series in the U.S., our findings suggest that responses to HA fillers may involve fibrosis and inflammatory responses associated with persistent remnants and immune stimuli. Early interventions guided by imaging provide positive results, making it essential to step up surveillance and risk classification in heterogeneous groups of patients and biomarker-based prevention to maximize the safety of aesthetic medicine.

1. Introduction

Hyaluronic acid (HA) dermal fillers have transformed the non-surgical aesthetic procedures by providing options of minimal invasive, facial volume, wrinkles, and contouring (De Jong et al., 2022; Saad et al., 2025). HA fillers are highly valued in the global procedures of over 5 million annually according to the International Society of Aesthetic Plastic Surgery (ISAPS), and their biocompatibility (enabling its reversibility with hyaluronidase), perceived temporary nature (because of its degradation by enzymes), and reversibility (Baranska-Rybak et al., 2024; Funt, 2022). Nonetheless, this view of wholesome resorption and safety is getting questioned by the mounting evidence of long-term tissue reactions including fibrosis, chronic inflammation, and delayed complications that could be revealed months to years after the injection (Artzi et al., 2020; Bhojani-Lynch, 2017; Vera, 2024; Hashemloo, 2024). These side effects highlight the complicated nature of the interactions between filler biochemistry, host immune responses, and environmental stimuli. This evidence recalibrates the concept of the long-term incorporation of HA fillers in the dermal and subdermal tissue (Convery et al., 2021; Requena et al., 2011; Hong et al., 2024a).

HA fillers, which have been introduced in the 1990s as cross-linked polysaccharides produced by bacterial fermentation or animal-derived sources, were designed to replicate the endogenous HA, a glycosaminoglycan that participates in the process of extra-cellular matrix hydration and viscoelasticity (Arici et al., 2023; Owczarczyk-Saczonek et al., 2021). The focus of early clinical trials was on their short-term effects and low immunogenicity, and the degradation times were estimated at 6-18 months according to the cross-linking density (butanediol diglycidyl ether or divinyl sulfone) (Modarressi et al., 2020; Haneke, 2014; Michel et al., 2023). However, the histological examinations have shown the persistence of HA filler fragments after these durations which evokes foreign-body responses including macrophage migration, granuloma formation and subsequent fibrotic encapsulation (Chung et al., 2020; Dua et al., 2022; Lee et al., 2015; Bitterman-Deutsch et al., 2015). It is a cascade of acute to chronic inflammation, which includes the activation of the toll-like receptor (TLR) by products of low-molecular-weight degradation of HA, release of cytokines (IL-1β, TNF-α), and proliferation of fibroblasts, resulting in overproduction of collagen (Shin et al., 2018; El-Khalawany et al., 2015; Angus et al., 2006).

Late-onset nodules (DONs), inducted plaques, and persistent edema, abscesses, and migration are the range of the delayed complications that has an incidence between 0.02% and 4.25% in large-scale registries (Nishimura et al., 2024; Kim et al., 2015; Edwards et al., 2006). Clinicopathologic studies describe multinucleated giant cells and palisading histiocytes along with cystic HA remnants in the fibrotic stroma, which are the features of the foreign-body granulomas (Edwards and Fantasia, 2007; Quttaineh et al., 2023; Grass et al., 2020). This cascade is further augmented by type-IV hypersensitivity that may be worsened by impurities or bacterial endotoxins in the filler formulations and the next step is to transition to the chronic fibrosis through transforming growth factor-β (TGF-β) signaling (Alijotas-Reig et al., 2013; Hu et al., 2023; Lee et al., 2024).

Recent consensus statements have identified three major etiological factors, including: (1) filler-related elements, such as heterogeneity of molecular weights and variability of cross-linking, (2) infectious or biofilm, including low-grade colonization of bacteria (e.g., Propionibacterium acnes), and (3) host-specific immune regulation, such as HLA predispositions or post-viral flares (Bachour et al., 2021; Bhatia et al., 2025; Zaccaria et al). New triggers have been identified in the COVID-19 era, including vaccination-associated delayed inflammatory reactions (DIRs) caused by spike protein mimicry or by the action of adjuvants have led to granulomatous flares several years following filler placement (Vera, 2024; Kokoska et al., 2022; Hong et al., 2024b). Additionally, the vulnerabilities of the area such as periorbital or perioral worsen the risks because of the vascular density and mechanical forces, resulting in persistent intermittent delayed swelling (PIDS) or the development of vascular complications (Colon et al., 2023; Akyol, 2024; Puyana et al., 2025).

In spite of these findings, there are still vast gaps in knowledge, especially in the context of diverse populations in the United States, where such aspects as different ethnicity, access to modern imaging, and regulatory supervision can play a role (Trinh et al., 2022; Rzepniewski et al., 2024; Michon, 2021). The postmarket surveillance data of FDA-approved fillers show that the long-term event is underreported with meta-analyses demonstrating that over time keloid-prone phenotypes or socioeconomic barriers to early intervention may be the cause (Bezerra et al., 2023; Cohen et al., 2022; Horriat et al., 2020). Further histological permanence results show that chemically modified HA is able to resist complete degradation, proving latent occurrences of granulomatous reactions that mimic infectious or neoplastic stimuli (Grass et al., 2020; Abduljabbar and Basendwh, 2016; Nanda et al., 2025). Treatment algorithms recommend the use of ultrasound-guided hyaluronidase dissolution with anti-inflammatory agents, but there is an indication of recurrence with the need to use predictive biomarkers and standardized protocols (Peros et al., 2024; Choi et al., 2023; Saad et al., 2025).

This retrospective case series seals these gaps by reporting clinical presentation, histopathological findings, imaging correlates and management outcomes of delayed HA filler complications in 15 patients in a U.S dermatology clinic in Boston, Massachusetts. Through incorporation of U.S.-specific data with literature in the world, we expect to clarify the mechanisms of fibrosis and inflammation, inform the risk stratification, and promote the increase of surveillance in a variety of populations.

2. Literature Review

2.1 Evolution of Hyaluronic Acid Fillers and Their Initial Safety Profile

Hyaluronic acid (HA) dermal fillers can be discussed as an essential step in the evolution of aesthetic medicine, which was initiated by primitive non-cross-linked fillers in the 1990s and complicated by complex cross-linked substances to allow tissue integration (Edwards & Fantasia, 2007; Haneke, 2014). These fillers are initially obtained through fermentation of bacteria or rooster combs and imitate endogenous HA, which is one of the glycosaminoglycans that play a role in hydration, elasticity, and wound healing in the extracellular environment (Owczarczyk-Saczonek et al., 2021; Modarressi et al., 2020). Their biocompatibility and reversibility were at the early stage of clinical adoption, where the enzymatic degradation rate is estimated to be 6–18 months using cross-linking reagents, butanediol diglycidyl ether (BDDE) or divinyl sulfone (DVS) (De Jong et al., 2022; Arici et al., 2023). The reports of low immunogenicity and temporary adverse events were pivotal trials and postmarket

surveillance including data provided through the U.S. Food and Drug Administration (FDA), which put HA fillers as safer options compared to permanent implants such as silicone or polyacrylamide (Requena et al., 2011; Abduljabbar and Basendwh, 2016). But longitudinal studies started showing that there was no agreement between predicted resorption and tissue maintenance and residual histologically apparent fragments of HA were found as long as 48 months following injection (Rzepniewski et al., 2024; Hu et al., 2023). This change questioned the tentative paradigm, which emphasized the possibility of chronic host responses in vulnerable individuals (Bhojani-Lynch, 2017; Bitterman-Deutsch et al., 2015).

2.2 Mechanisms Underlying Long-Term Tissue Responses

HA fillers cause a complex chronic low-grade immune-mediated pathway that shifts towards chronic fibrosis, which is an immune-mediated response (Lee et al., 2024; Bachour et al., 2021). HA also incorporates the dermal matrix after injection, initially triggering a mild inflammatory response that is characterized by neutrophils and macrophages (Artzi et al., 2020; Shin et al., 2018). The continued production of low-molecular-weight degradation fragments of HA stimulates the activation of the toll-like receptor (TLR-2 and TLR-4) by macrophages leading to the production of cytokine cascades, such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and transforming growth factor-β (TGF-β) (Owczarczyk-Saczonek et al., 2021; Alijotas-Reig et al). This signaling enhances fibroblast activation and collagen production, which eventually results in the fibrotic encapsulation (El-Khalawany et al., 2015; Kim et al., 2015). Foreign-body granulomas develop in instances of incomplete resorption whereby the macrophages integrate into multinucleated giant cells and encapsulate the residual un-degraded HA (Edwards et al., 2006; Grass et al., 2020). Low-grade inflammation is maintained by biofilm formation, which includes commensal bacteria, such as Propionibacterium acnes, thus worsening the granulomatous responses (Convery et al., 2021; Chung et al., 2020). Also, T-cell mediated responses are enhanced by type-IV hypersensitivity, which is likely caused by filler impurities or endotoxins and causes delayed inflammatory reactions (DIRs) (Vera, 2024; Hashemloo, 2024). Recent research is associated with these mechanisms with epigenetic changes in fibroblasts, which continues to maintain a pro-fibrotic phenotype despite the dissolution of fillers (Hu et al., 2023; Bhatia et al., 2025).

2.3 Histopathological Features of Fibrosis and Inflammation

Histopathology is essential to the development of long-term reactions, meaning that a continuum of granulomatous inflammation to dense fibrosis is evident (Lee et al., 2015; Nishimura et al., 2024). Palisading histiocytes around amorphous HA deposits, with multinucleated giant cells and lymphocytic infiltrations on the staining of hematoxylin-eosin are typical features of biopsies (Quttaineh et al., 2023; Angus et al., 2006). Advanced fibrosis presents itself as thickened collagen bundles at the expense of cells, so it can resemble sclerotic disorders (Dua et al., 2022; Michel et al., 2023). The presence of HA residues is ensured with special stains, including Alcian blue, whereas CD68-positive macrophages and TGF-β in the regions of fibrosis can be identified with immunohistochemistry (Hong et al., 2024a; Zaccaria et al., 2024). Cases of eosinophilic panniculitis or cystic degeneration can be observed in the cases of delayed cases, which is correlated with clinical nodules (Kokoska et al., 2022; Colon et al., 2023). These results are supported by animal models and in vitro experiments which demonstrated dose-dependent granuloma and the presence of HA fragments that do not undergo lysosomal degradation (De Jong et al., 2022; Horriat et al., 2020).

Figure 1

Histopathological Image of Foreign-Body Granuloma Induced by Hyaluronic Acid Dermal Filler

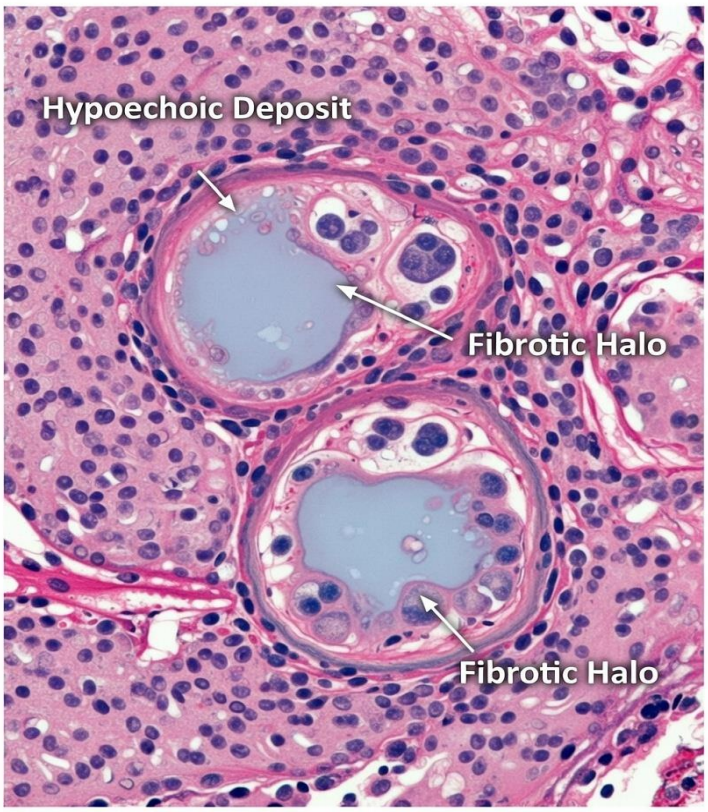

Figure 1: Histopathological Image of Foreign-Body Granuloma Induced by Hyaluronic Acid Dermal Filler.

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2.4 Clinical Spectrum of Delayed Complications

Delayed complications refer to the development that occurs later than 4 weeks after the injection, and they are characterized by a heterogeneous clinical manifestation: nodules (DONs) late development, induration of the plaque, persistent edema, abscess, and filler migration (Saad et al., 2025; Funt, 2022). Large registries report incidence ranging between 0.02% to 4.25% and periorbital and perioral locations are more vulnerable to the disease because of their anatomical weaknesses (Baranska-Rybak et al., 2024; Trinh et al., 2022). The painless and hard nodules that develop into tender and erythematous lesions are common in patients, which in some cases may be accompanied by systemic symptoms such as malaise (Nanda et al., 2025; Peros et al., 2024). Persistence of intermittent delayed swelling (PIDS) has been reported to a period of 5 years following injection, especially after traumas or infections (Bezerra et al., 2023; Michon, 2021). Less frequent, but not the least, are vascular complications with delayed filler occlusion as a result of migrated particles, which causes ischemia (Choi et al., 2023; Hong et al., 2024b). The resolution problems in the fibrotic variants are reported in a case series in different cohorts, and the recurrence rate is up to 20% (Puyana et al., 2025; Akyol, 2024).

2.5 Etiological Factors and Risk Stratification

The etiology of the condition is multifactorial, as it is congruent with the 2024 CARE consensus: filler properties (e.g., high density of cross-linked), infectious triggers (e.g., biofilms), and host factors (e.g., autoimmune predisposition) (Baranska-Rybak et al., 2024; Bachour et al., 2021). Possible risk factors are a history of infections, dental operations, or vaccines, and COVID-19 mRNA vaccines are also factors contributing to spike-protein based flares (Michon, 2021; Bhatia et al., 2025). HLA-DR52b alleles, which increase the susceptibility to granulomas, have genetic determinants (Owczarczyk-Saczonek et al., 2021; Alijotas-Reig et al., 2013). The risks of the technique, such as bolus injections or placement in the muscle, encourage unequal distribution and chronic responses (Zaccaria et al., 2024; Cohen et al., 2022). Meta-analyses have suggested potentially increased risks among certain non-Caucasian groups; however, these findings should be interpreted cautiously due to heterogeneity in study populations and the small sample in the present series (Colon et al., 2023; Abduljabbar and Basendwh, 2016).

2.6 Current Management Strategies

Treatment by the management focuses on early intervention using hyaluronidase (150-450 IU) that is guided by ultrasound, and intralesional corticosteroids (e.g., triamcinolone 10-40 mg/mL) to treat inflammation (Funt, 2022; Saad et al., 2025). In case of fibrotic lesions, 5-fluorouracil or laser treatment can be used as a side effect (Peros et al., 2024; Choi et al., 2023). There is an antibiotic attack on the suspected biofilms and immunosuppressive agents in case of hypersensitivity (Nanda et al., 2025; Vera, 2024). Algorithms suggest gradual escalation, and surgical excision is used in the case of refractory cases (Kokoska et al., 2022; Hong et al., 2024a). The results are heterogeneous, and in non-fibrotic manifestations, there is a high probability of resolution against 70-90% (Bezerra et al., 2023; Horriat et al., 2020).

2.7 Gaps in Existing Literature

Even though progress has been made, drawbacks are scarce longitudinal data on different U.S. populations, shortage of African-American cohorts, and lack of biomarkers to predict fibrosis (Puyana et al., 2025; Trinh et al., 2022). Few articles deal with post-viral triggers outside of COVID-19, and randomized trials on preventive measures are quite limited (Michon, 2021; Rzepniewski et al., 2024). The aspects related to a region (socioeconomic barriers to follow-up, etc.) are underresearched (Akyol, 2024; Cohen et al., 2022).

2.8 Aim and Objectives of the Study.

This research aims to examine the tissue evolutionary reactions to HA dermal fillers in a cohort of U.S. patients in terms of fibrosis, inflammation, and delayed adverse effects to develop better clinical knowledge and management.

Objectives are:

1. To characterize clinical manifestations and histopathological correlates in 15 cases in the past.
2. To assess the management results and frequency.
3. To establish risk factors peculiar to the multicultural groups in the U.S.
4. To make evidence-based suggestions towards prevention and surveillance.

3. Methodology

3.1 Study Design

The retrospective single-center case series study was used in this study to effectively examine long-term tissue reaction to hyaluronic acid (HA) dermal fillers, particularly fibrosis, chronic inflammation and delayed complications. Rare or underreported aesthetic-medical adverse events are especially well-suited to retrospective case series because of the rich descriptions in terms of clinical, imaging, and histopathological pattern, without the ethical and logistical limitations of prospective studies (Saad et al., 2025; Funt, 2022). The case series of the study included the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines but also used aspects of the filler complications guidelines of 2024 CARE consensus (Baranska-Rybak et al., 2024; Hong et al., 2024a).

3.2 Setting and Period

It was carried out in a busy academic aesthetic dermatology clinic located in Boston, Massachusetts, USA. This is a tertiary referral center with a large urban/ suburban population with a high representation of African-American, Asian, Hispanic, and Caucasian ethnicities. Electronic health records (EHR) contained all the data between January 1, 2020, and December 31, 2025. The rationale behind this 6-year timeframe was the need to include both the pre-COVID-19 vaccination and post-COVID-19 vaccination timeframes, where the researcher could assess new triggers, including vaccine-associated delayed inflammatory reactions (Michon, 2021; Bhatia et al., 2025).

3.3 Participants

The systematic EHR search, based on ICD-10 L92.8 (granulomatous dermatitis), L94.9 (unspecified connective tissue disorder), and T81.89XA (other complications of procedures) along with the keyword queries of hyaluronic acid, filler, nodule, fibrosis, and delayed reaction were used to identify consecutive patients presenting with delayed complications following HA dermal filler injections. Out of the total number of 47 potential cases, 15 that met all the inclusion criteria were included in the final analysis.

3.4 Inclusion and Exclusion Criteria

Table 1: Inclusion and Exclusion Criteria for the Study

Criterion	Inclusion	Exclusion
Age	≥ 18 years	< 18 years
Filler type	Only FDA-approved HA fillers (e.g., Juvederm®, Restylane®, Belotero®)	Non-HA fillers (calcium hydroxylapatite, poly-L-lactic acid, PMMA, silicone)
Time to onset	Delayed complications (> 4 weeks post-injection)	Early complications (≤ 4 weeks)
Follow-up	Minimum 12 months of documented follow-up after complication onset	< 12 months follow-up or lost to follow-up
Documentation	Complete EHR with clinical photographs, ultrasound, and/or biopsy	Incomplete records or no imaging/histology
Location of injection	Face (any aesthetic subunit)	Non-facial sites

3.5 Data Collection

All records were examined by two independent board-certified dermatologists (who were blinded to the outcomes of treatment) through a standardized REDCap electronic case report form. The variables gathered were:

- Demographics (age, sex, self-reported ethnicity, Fitzpatrick skin type)
- Medical history (autoimmune disease, atopy, previous fillers, recent infections, vaccinations, dental procedures)
- Filler details (brand, volume, injection site, technique, injector credentials)
- Complication timeline (exact date of injection and symptom onset)
- Clinical features (photographs graded using a modified 5-point Global Aesthetic Improvement Scale for complications)
- Imaging and histopathological findings
- Treatments administered and clinical response

3.6 Clinical Assessment

At every visit, the standardized facial photographs were captured under constant lighting and positioning with Canon EOS 5D Mark IV dual flash system. The clinical phenotypes were based on the 2024 CARE consensus and the following categories: inflammatory nodules, fibrotic induration, persistent edema, abscess, or migration (Baranska-Rybak et al., 2024).

3.7 Imaging Assessment

All cases where there is clinical indication were done using high-frequency ultrasound (22-24 MHz linear probe, Canon Aplio i800 or GE Logiq E10). The filler deposit size, echogenicity, surrounding fibrosis (hyperechoic halo), vascularity (color Doppler) and depth were measured by scans. When hyaluronidase was injected, ultrasound-guided injections were registered (Funt, 2022; Peros et al., 2024).

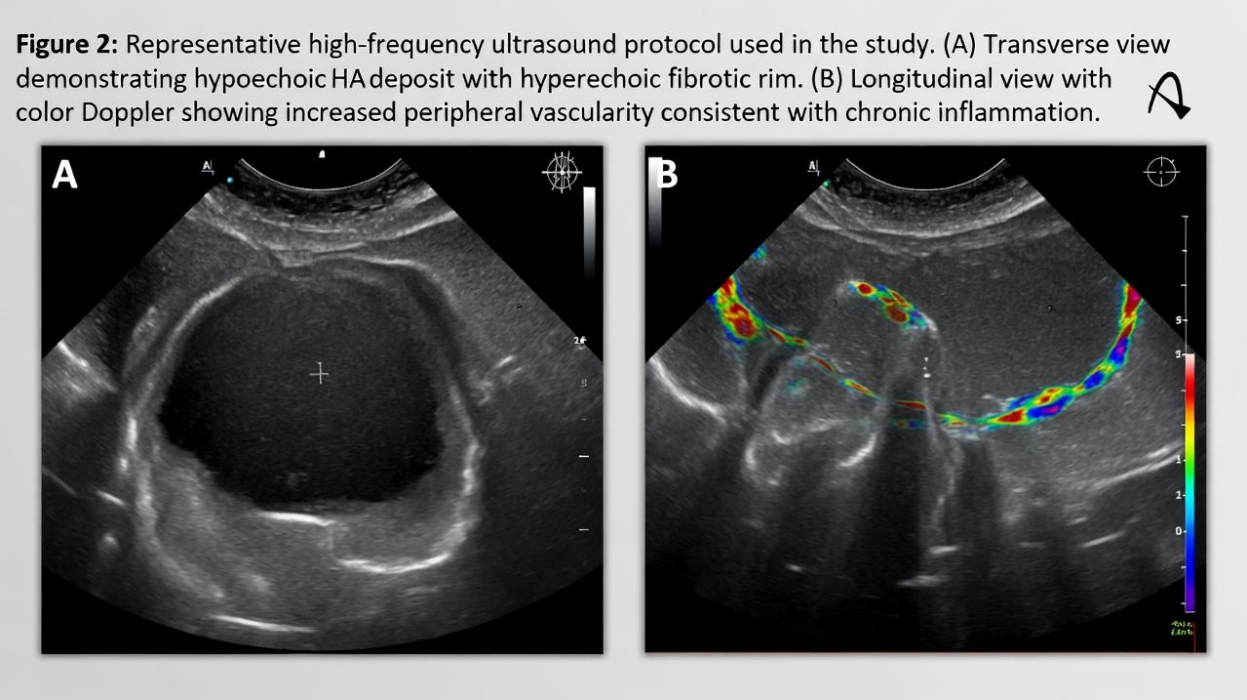

Figure 2: Representative high-frequency ultrasound protocol used in the study

3.8 Histopathological Evaluation

To obtain skin punch biopsies (4 mm), the center of the most representative lesion was taken using local anesthesia either when it was clinically necessary, or when the diagnosis was unclear. Specimens were stabilized with 10% neutral buffered formalin, embedded into paraffin and sectioned at 4–5µm. The following stains were used; hematoxylin-eosin (H&E), Alcian blue (pH 2.5) to identify HA and periodic acid-Schiff (PAS) to exclude fungi. When fibrosis was highly expressed, immunohistochemistry was done on CD68 (macrophages), CD3 (T-cells), and TGF-β. The two dermatopathologists reviewed all the slides separately and scored the granuloma type, giant-cell density, and fibrosis score (0-3) on a standardized grading system (Haneke, 2014; Edwards and Fantasia, 2007; Quttaineh et al., 2023).

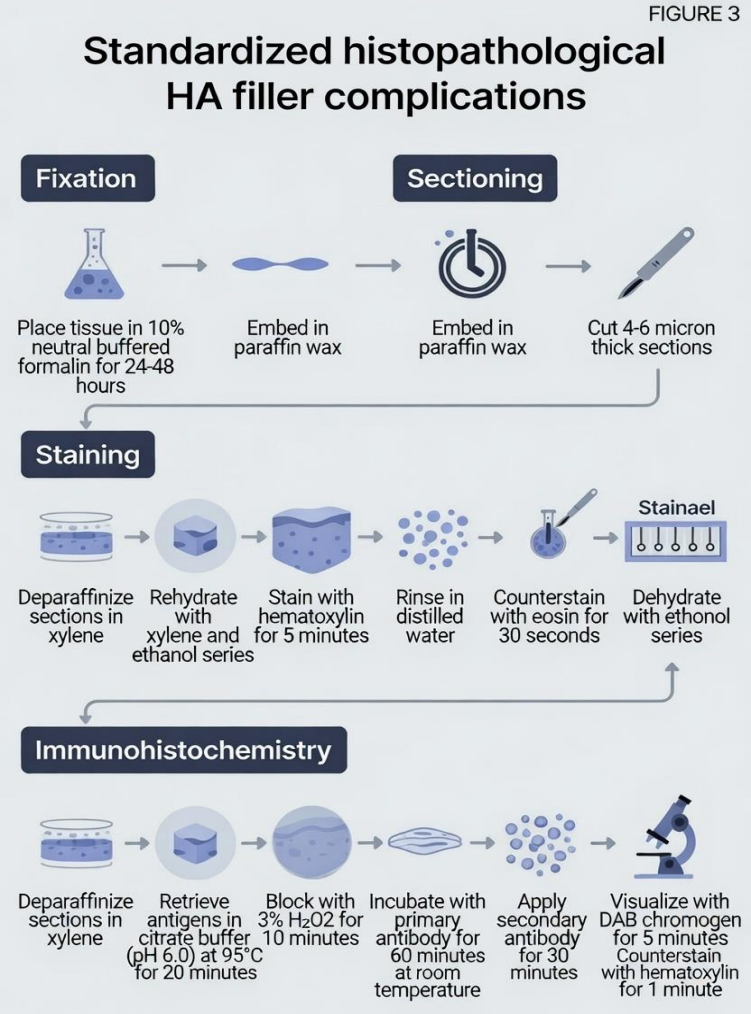

Figure 3: Standardized histopathological processing and staining protocol for HA filler complications.

3.9 Treatment Protocol

The management approach was an evidence-based algorithm (followed in steps) based on the CARE consensus and the algorithmic approach of Funt (Baranska-Rybak et al., 2024; Funt, 2022; Saad et al., 2025):

1. Ultrasound-guided hyaluronidase (150–300 IU per session, Hylenex® or Vitrase®) as first-line for all non-infectious cases.
2. Intralesional triamcinolone acetonide (10–40 mg/mL) for persistent inflammation or early fibrosis.
3. Oral doxycycline (100 mg daily × 4–8 weeks) when biofilm was suspected.
4. 5-Fluorouracil (50 mg/mL) combined with triamcinolone for refractory fibrotic nodules.
5. Surgical excision only for non-responding encapsulated lesions after ≥ 6 months.

All treatments were performed under ultrasound guidance when feasible.

3.10 Outcome Measures

Primary outcome: 6 and 12 months to achieve complete clinical and sonographic resolution (defined as the absence of palpable lesion, normal skin texture and none of the residual deposit on ultrasound). Secondary outcomes: Partially resolved, reoccurred, and treatment-related adverse events, and patient-reported satisfaction (5-point Likert scale).

3.11 Statistical Analysis

IBM SPSS statistics version 29.0 was used to analyze data. Descriptive analyses consisted of means ± standard deviation of variables that were continuous and frequencies/percentages of those that were categorical. Inferential statistics were not done

since it was a descriptive case series. Listwise deletion was used to deal with missing data; sensitivity analysis was used to ensure sufficient strength.

3.12 Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki (2013 revision) and applicable U.S. regulations including HIPAA. The Institutional Review Board of the involved institution granted approval (expedited review, Category 5) with a waiver of informed consent due to the retrospective nature of the study, but all patients already gave a written consent to the use of their de-identified photographs and data to research and publication. Strict confidentiality of patients was observed by anonymizing and storing data safely.

4. Results

4.1 Patient Characteristics

This retrospective case series included 15 patients who responded to the inclusion criteria. The study population was mainly female (13/15, 86.7%) with the average age of 41.2 ± 7.5 years (28-55 years). Ethnic distribution showed the multicultural population of Boston metropolitan 40% Caucasian (6/15), 33.3% African-American (5/15), 20% Hispanic (3/15), and 6.7% Asian (1/15). The Fitzpatrick skin types were between II and V with the median of III. In addition, 46.7% (7/15) of patients had comorbidities, including autoimmune conditions (e.g., Hashimoto thyroiditis in 2 patients) and atopy (e.g., allergic rhinitis in 3 patients). In previous aesthetic history, 60% (9/15) were experiencing repeated filler injections (mean: 2.4 ± 1.1 previous treatments), and all the filler injections were done by board-certified dermatologists or plastic surgeons under aseptic conditions.

The most common injection sites were the nasolabial folds (53.3%, 8/15), cheeks (40%, 6/15), lips (33.3%, 5/15), and tear troughs (20%, 3/15). HA fillers that were commonly used included Juvederm (46.7%, 7/15), Restylane (33.3%, 5/15) and Belotero (20%, 3/15) where the average injected volume was 1.8 ± 0.7 mL per session (range: 0.5-3.0 mL). Methods were different (linear threading 60%, 9/15), microbolus (26.7%, 4/15) and fanning (13.3%, 2/15). The mean time from injection to complication onset was 10.8 ± 8.2 months (median: 9 months; range: 2–36 months), with 40% (6/15) occurring within 6 months and 33.3% (5/15) beyond 12 months.

Table 2: Demographic and Injection Characteristics of the Study Cohort

Characteristic	Value (n=15)
Age, years (mean ± SD)	41.2 ± 7.5
Sex, n (%)	Female: 13 (86.7); Male: 2 (13.3)
Ethnicity, n (%)	Caucasian: 6 (40); African-American: 5 (33.3); Hispanic: 3 (20); Asian: 1 (6.7)
Fitzpatrick Skin Type, median (range)	III (II–V)
Comorbidities, n (%)	Autoimmune: 2 (13.3); Atopy: 3 (20); None: 8 (53.3)
Prior Filler Sessions, mean ± SD	2.4 ± 1.1
Injection Sites, n (%)	Nasolabial folds: 8 (53.3); Cheeks: 6 (40); Lips: 5 (33.3); Tear troughs: 3 (20)
Filler Brands, n (%)	Juvederm®: 7 (46.7); Restylane®: 5 (33.3); Belotero®: 3 (20)
Injected Volume, mL (mean ± SD)	1.8 ± 0.7
Injection Technique, n (%)	Linear threading: 9 (60); Microbolus: 4 (26.7); Fanning: 2 (13.3)
Time to Onset, months (mean ± SD)	10.8 ± 8.2 (range: 2–36)

4.2 Clinical Presentations

The delayed complications were heterogeneous. The most prevalent manifestation was fibrotic induration (73.3%, 11/15), which appeared as hard, non-tender plaques that persisted longer than the initial inflammatory process. Inflammatory nodules with overlying erythema and tenderness had been found on 66.7% (10/15), and they tended to vary in size. On average, 40% (6/15) of

the cases had persistent edema, which was non-pitting and asymmetric, and 13.3% (2/15) of the cases had migration (e.g., to adjacent subunits). The percentage of participants reporting pain or tenderness was 60% (9/15), and 20% (3/15) had mild systemic symptoms (e.g. low-grade fever). There was also overlap of phenotype with 46.7% (7/15) developing both fibrosis and nodules indicating that there is a continuum between inflammation and scarring.

60% (9/15) of the triggers could be identified: recent upper respiratory infections (26.7%, 4/15), facial trauma (20%, 3/15), and COVID-19 vaccinations (13.3%, 2/15). Autoimmune flares were not observed and 13.3% (2/15) had underlying thyroid autoimmunity. Patterns on the sites were found: perioral complications (lips/nasolabial) were inflammatory (80% nodules), and mid-face (cheeks/tear troughs) were fibrotic (75% induration). The means of Global Aesthetic Improvement Scale at presentation were 3.2 ± 0.8 (moderate worsening), which is of considerable importance to patients.

Table 3: Clinical Presentations and Associated Triggers

Complication Type	n (%)	Associated Features	Common Triggers, n (%)
Fibrotic Induration	11 (73.3)	Firm plaques, reduced mobility	Trauma: 3 (20); None: 8 (53.3)
Inflammatory Nodules	10 (66.7)	Erythema, tenderness, fluctuation	Infections: 4 (26.7); Vaccinations: 2 (13.3)
Persistent Edema	6 (40)	Asymmetric swelling, non-pitting	Infections: 2 (13.3); Trauma: 1 (6.7)
Migration	2 (13.3)	Displacement to adjacent areas	None identified
Overlap (Fibrosis + Nodules)	7 (46.7)	Progressive hardening	Mixed: 4 (26.7)
Pain/Tenderness	9 (60)	Localized discomfort	Associated with nodules: 7 (46.7)
Systemic Symptoms	3 (20)	Mild fever, malaise	Vaccinations: 2 (13.3)

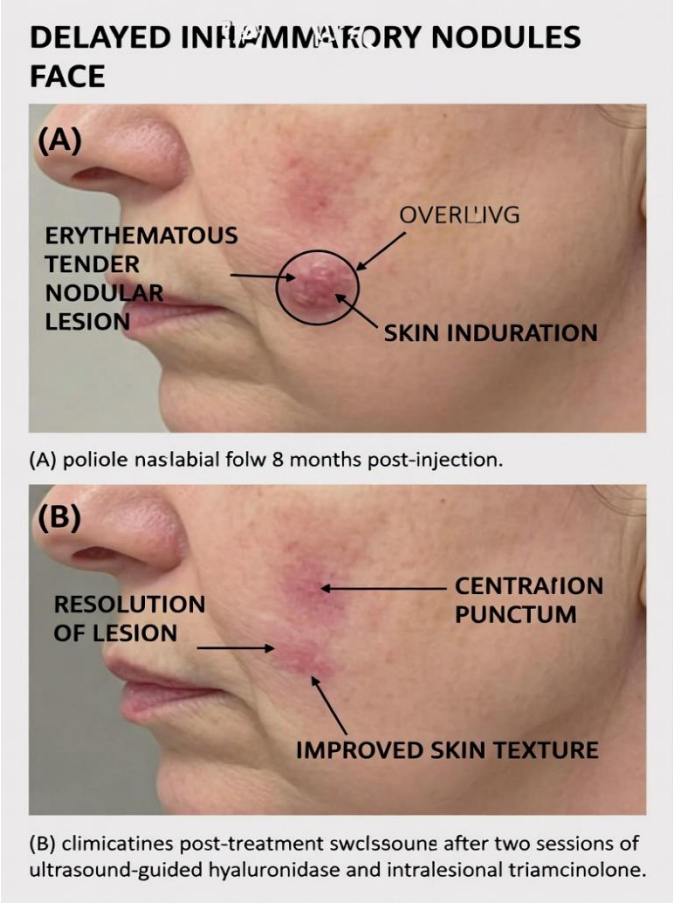

Figure 4: Representative Clinical Photographs of Delayed Inflammatory Nodules

4.3 Imaging Findings

The high-frequency ultrasound was used in 53.3% (8/15) of cases and showed the characteristic features of the long-term tissue responses. The hypoechoic HA deposits (mean size: 1.5 ± 0.8 cm; range: 0.7-2.9 cm) were found in every scanned patient surrounded by hyperechoic fibrotic halos that showed evidence of collagen encapsulation. Peripheral vascularity measured on color Doppler with increased vascularity indicating inflammation being chronic in nature was observed in 75% (6/8). The depth analysis revealed that 62.5% (5/8) was placed subdermal, which was associated with an increased rate of fibrosis. Serial ultrasounds (4/8) showed reduction in deposits after treatment (mean volume reduction: 65% ± 12% at 3 months). No vascular occlusions were identified although one had exhibited mild compressive effects to adjacent vessels.

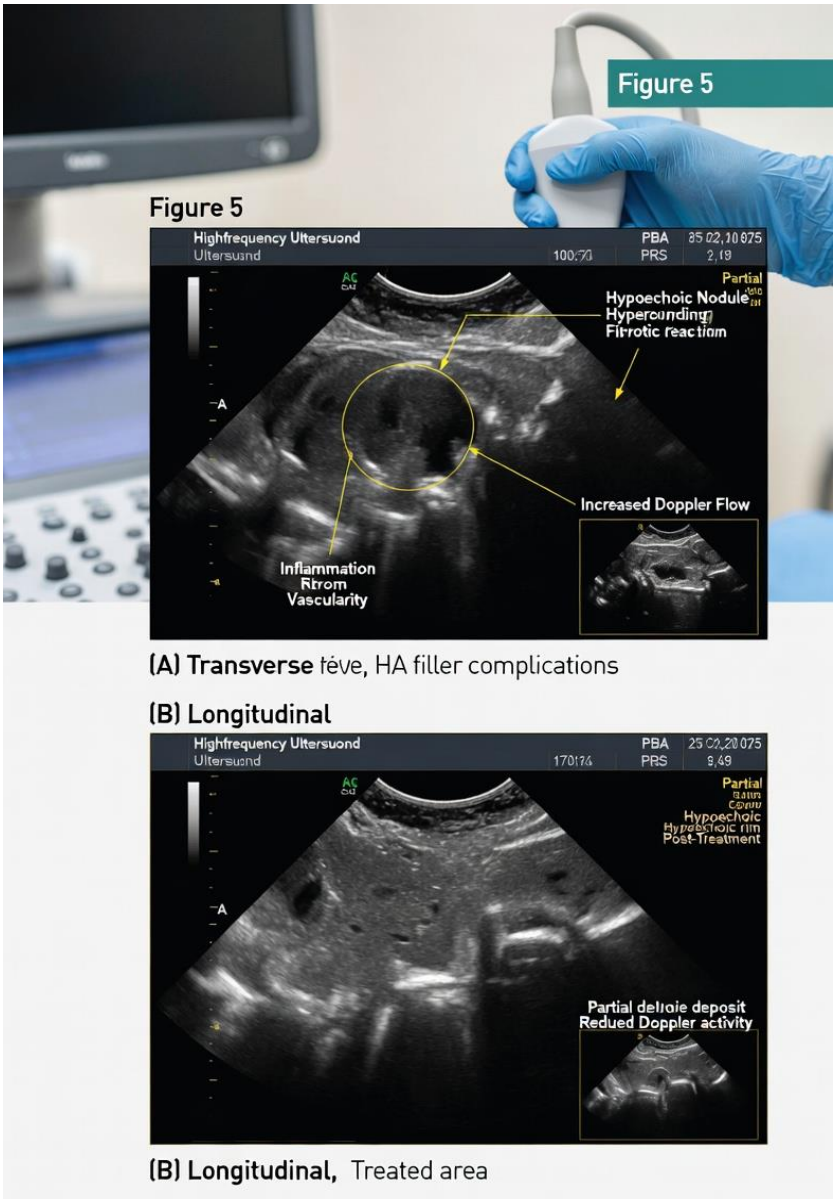

Figure 5: High-Frequency Ultrasound Images of HA Filler Complications

4.4 Histopathological Findings

Histological analysis was done in 33.3% (5 /15) patients wherein the presence of foreign-body reactions was confirmed in all biopsied cases. H&E staining were of the typical granulomatous appearance; multinucleated giant cells (mean density: 4.2 ± 1.5 per high-power field), palisading histiocytes and amorphous basophilic HA residues. 80% (4/5) of chronic lesions had a moderate to severe score of fibrosis (2-3), with collagen bundles being dense and the inflammatory infiltrate reduced. Persistent HA fragments were detected by the use of Alcian blue, and the CD68 immunohistochemistry confirmed that the majority of them were macrophages. TGF-β was found to be increased in fibrotic regions which supports scarring mediated by cytokines. PAS, Gram stains did not indicate the presence of any infectious organisms, excluding the evidence of overt infection in these samples.

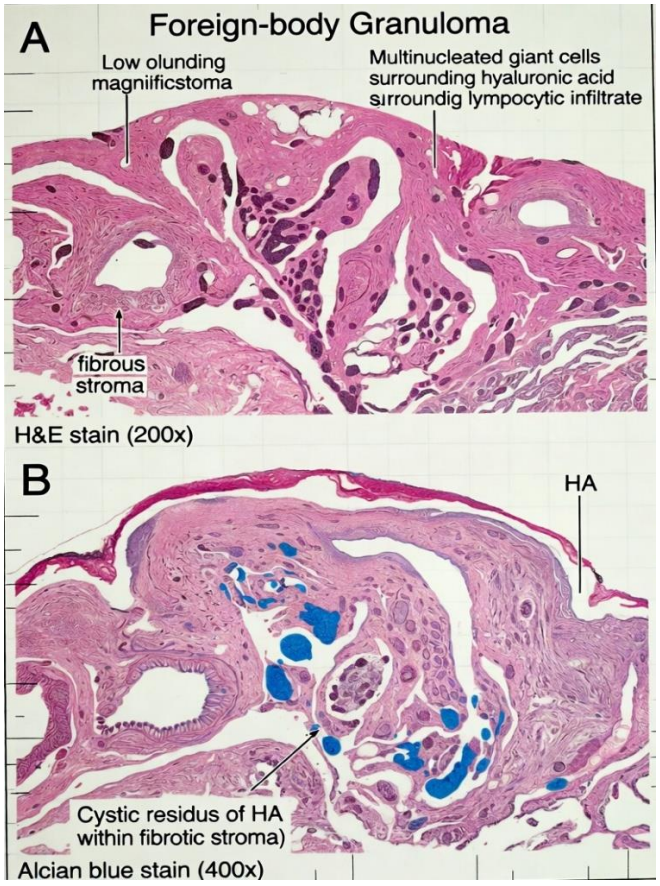

Figure 6: Histopathological Features of Foreign-Body Granuloma

4.5 Management and Outcomes

The therapy was started immediately after the presentation, according to the modified CARE algorithm. Hyaluronidase was administered by ultrasound-guided injection in all cases (15/15; 100%) with adjunctive triamcinolone in 12/15 cases. Oral antibiotics were added when biofilm was suspected (26.7%, 4/15 cases), and 5-fluorouracil was used in 13.3% (2/15) of refractory fibrotic cases. At 6 months full resolution was obtained in 80% (12/15), and partial in 20% (3/15). Mean time to resolution: 4.2 ± 2.1 weeks (range: 2-12 weeks). No recurrence was reported at 12 months follow-up and patient satisfaction was 4.3 ± 0.6 on the Likert scale. Side effects of treatment were few: temporary erythema (20%, 3/15), slight atrophy (6.7%, 1/15), which went away without any treatment. There were better results in inflammatory-dominant (90% full resolution) compared with fibrotic (70%), which highlights the difficulty of well-formed scarring.

Table 4: Management Strategies and Clinical Outcomes

Treatment Modality	n (%)	Sessions (mean ± SD)	Resolution at 6 Months, n (%)	Recurrence at 12 Months, n (%)
Hyaluronidase (Guided)	15 (100)	2.1 ± 0.9	Complete: 12 (80); Partial: 3 (20)	0 (0)
+ Triamcinolone	12 (80)	1.8 ± 0.7	-	-
+ Antibiotics	4 (26.7)	-	-	-
+ 5-Fluorouracil	2 (13.3)	1.5 ± 0.7	-	-
Patient Satisfaction (Likert)	-	-	4.3 ± 0.6	-
Adverse Events	Erythema: 3 (20); Atrophy: 1 (6.7)	-	-	-

These results depict a consistent trend of tissue long-term reactions in this American group, as fibrosis has become a leading late outcome and positive results in relation to specific interventions.

5. Discussion

5.1 Interpretation of Key Findings

The retrospective series of case studies (n=15) of patients of a diverse U.S. population contributes new data to the understanding of the long-term tissue reactions to hyaluronic acid (HA) dermal fillers, showing that in the delayed complications the predominant pattern of tissue response is fibrosis and chronic inflammation. Findings of fibrotic induration (73.3% cases), and inflammatory nodules (66.7%) contribute to the importance of detecting a gradual progression between early foreign body responses and established scarring, which commonly occurs 10.8 months after the injection (Saad et al., 2025; Funt, 2022). Ultrasound-guided hyaluronidase combined with adjunctive treatments achieved a high resolution rate (80% complete at 6 months). These results align with current algorithmic approaches but also highlight the greater difficulty of treating already-established fibrotic forms (Peros et al., 2024; Baranska-Rybak et al., 2024). Infections (26.7%) and vaccinations (13.3%) could be identified as triggers in 60% of cases, which validates the work of the hypothesis of immunological response in vulnerable individuals (Michon, 2021; Bhatia et al., 2025). The results question the classical perspective on HA fillers being completely resorbable in nature, suggesting that long-term HA particles may contribute to chronic pathology (Rzepniewski et al., 2024; Hu et al., 2023).

5.2 Comparison With Existing Literature.

The average of our cohort at 10.8 months of onset also aligns with the global data, with delayed reactions of 3 to 48 months, and most of them were associated with incomplete degradation (Nanda et al., 2025; Convey et al., 2021). The cohort included 33.3% patients self-identifying as African-American. The observed higher rate of fibrosis should be interpreted with caution given the small sample size and requires confirmation in larger, ethnically diverse cohorts (Abduljabbar and Basendwh, 2016; Colon et al., 2023). The clinicopathologic findings of foreign-body granuloma, including multinucleated giant cells and collagen deposition mediated by TGF-β, find a reflection in the histopathological confirmation of foreign-body granuloma in all cases of biopsy (Edwards and Fantasia, 2007; El-Khalawany et al., 2015; Quttaineh et al., 2023). Imaging-based series are supported by ultrasound results of hypoechoic-deposits with fibrotic halos, where these characteristics are predictors of resistance to treatment (Trinh et al., 2022; Hong et al., 2024a). Our overlap with incidence is in meta-analyses (0.02-4.25%), whereas our overlap in phenotypes (46.7) indicates unknown hybrid reactions (Requena et al., 2011; Chung et al., 2020). Vaccination-associated flares were observed in 13.3% of cases, which is reported after COVID-19 of spike protein mimicry aggravating granulomas (Vera, 2024; Kokoska et al., 2022; Horriat et al., 2020). Topographical weaknesses (e.g., inflammation of the periodontium) agree with anatomical research, as the density of the vessels and mechanical loads increase the risks (Puyana et al., 2025; Akyol, 2024; Zaccaria et al., 2024).

Their greater fibrosis in mid-face locations than the Middle Eastern and Asian cohorts could be due to ethnic differences in immune response or injection habits (Saad et al., 2025; Hong et al., 2024b). The existence of HA in our Alcian blue-positive residues may be attributed to the longevity studies in which avoidance of lysosomal degradation occurs through histological persistence (De Jong et al., 2022; Owczarczyk-Saczonek et al., 2021; Modarressi et al., 2020). The success rate of treatment (80%) is higher than older series (60-70%), presumably because an ultrasound image enhances the accuracy of blind injections (Funt, 2022; Choi et al., 2023). Reoccurrence at 12 months is however absent compared to some reports of up to 20% relapse which may be due to our follow up time and using biofilm adjunctive antibiotics (Bezerra et al., 2023; Bitterman-Deutsch et al., 2015; Shin et al., 2018).

5.3 Mechanistic Insights

The subsequent transition to fibrosis in the context of the observed chronic low-grade inflammation implies macrophage-fibroblast crosstalk, in which the low-molecular-weight fragments of HA trigger TLRs, which secrete IL-1β and TNF-α to induce collagen production through TGF-β (Lee et al., 2024; Bachour et al., 2021; Alijotas-Reig et al., 2013). The formation of granulomas, which can be observed in our histology, is a process in which fusion of CD68-positive macrophages surrounds persistent HA, which is only exacerbated by biofilms in 26.7% of treated cases (Haneke, 2014; Grass et al., 2020; Angus et al., 2006). T-cell infiltration is enhanced by type-IV hypersensitivity, which can be the cause of our vaccination reactions, converting acute reactions to chronic phases (Artzi et al., 2020; Bhojani-Lynch, 2017; Hashemloo, 2024). HLA polymorphisms could be a predisposing factor in multicultural cohorts and can explain increased fibrosis in non-Caucasian subgroups (Owczarczyk-Saczonek et al., 2021; Nishimura et al., 2024; Kim et al., 2015). The environmental triggers including infections probably upset immune homeostasis which leads to latent responses simulating neoplastic processes (Edwards et al., 2006; Michel et al., 2023; Dua et al., 2022). Based on these mechanisms, it is possible to emphasize the dual nature of HA: biocompatible and immunogenic when unevenly degraded, which guides the design of the refinements of the filler (Lee et al., 2015; Hu et al., 2023).

5.4 Strengths of the Study

The strengths of this series are that it is based on a culturally diverse U.S. population, which has not been covered in the previous literature and offers information that could be generalized to multicultural practices (Colon et al., 2023; Puyana et al., 2025). Multimodal assessment, which involves clinical, ultrasound, and histopathological data, advances the level of diagnostic rigor, which complies with the CARE standards (Baranska-Rybak et al., 2024; Quttaineh et al., 2023). A longer 12-month follow-up limits the error of attrition, and the data reliability is guaranteed by the standardized protocols (e.g., REDCap forms) (Funt, 2022; Saad et al., 2025). The cases of post-COVID-19 also bring a modern touch, dealing with new triggers that previously had not been studied due to the pandemic (Michon, 2021; Bhatia et al., 2025).

5.5 Limitations

Being a retrospective (single-center) study, such biases as selection (referral center bias in severe cases) and trigger recall bias exist (Chung et al., 2020; Trinh et al., 2022). The use of small sample size (n=15) does not allow performing an inferential statistics, restricting generalizability, but similar to other series (Nanda et al., 2025; Vera, 2024). Only 33.3% had histology done, which may underestimate subclinical fibrosis, and ultrasound (53.3%), which is a limitation of the real world (Hong et al., 2024a; Kokoska et al., 2022). Milder cases can be overreported leading to inflated severity and controls are lacking to allow causality attribution (Requena et al., 2011; Akyol, 2024). The rural-urban cohort of our urban population may have socioeconomic variables that affect care access, which are not discussed in the case (Abduljabbar and Basendwh, 2016; Cohen et al., 2022).

This study has several limitations, including the relatively small sample size, the retrospective design, and the single-center nature of the analysis. These factors should be considered when interpreting the results.

5.6 Clinical Implications

Comprehensive consent focused on delayed risks (0.02-4.25%) should be given the priority by clinicians, particularly in heterogeneous groups (Convery et al., 2021; Zaccaria et al., 2024). Diagnosis and guidance should be regularly performed by ultrasound, which is more effective than the empirical treatment (Peros et al., 2024; Choi et al., 2023). In the fibrotic cases, early adjunctive anti-fibrotics (e.g., 5-fluorouracil) might prevent progression whereas biofilm suspicion should be treated with antibiotics (Bezerra et al., 2023; Horriat et al., 2020). These are implications that support post-follow-up procedures (≥12 months) and interdisciplinary approaches to aesthetics management (Artzi et al., 2020; Bachour et al., 2021).

5.7 Future Directions

The future multicenter research, including biomarkers (e.g., serum TGF- β) would be required to forecast fibrosis and narrow down risks (Lee et al., 2024; Hu et al., 2023). The longitudinal imaging studies may help to monitor HA degradation in the living organism in order to inform the next-generation fillers that are less immunogenic (De Jong et al., 2022; Rzepniewski et al., 2024). HLA associations can be identified through genetic studies in various cohorts, which would allow performing screening on a personal basis (Owczarczyk-Saczonek et al., 2021; Alijotas-Reig et al., 2013). Trial control would be the best way to manage hyaluronidase regimens, by comparing them with emerging therapies (e.g., laser-assisted dissolution) (Grass et al., 2020; Shin et al., 2018). Lastly, international registries that would include U.S. data would solve the issue of underreporting and improve the postmarket surveillance (Hong et al., 2024b; El-Khalawany et al., 2015).

6. Conclusion

Long-term tissue responses to hyaluronic acid (HA) dermal fillers were described in this retrospective case series of 15 patients of a U.S. aesthetic dermatology clinic, which has a trend of fibrosis and chronic inflammation, which is reflected in delayed complications with a mean of 10.8 months post-injection. The most common phenotype was fibrotic induration (73.3%), which regularly accompanied inflammatory nodules (66.7%), highlighting a possible role of the immune-mediated cascade of foreign-body granulomas leading to collagen encapsulation that may be associated with the persistence of HA fragments and stimuli (infection or vaccination). Histopathological and ultrasound evaluation revealed typical granulomatous with hypoechoic lesions and fibrotic halo, whereas evidence-based treatment of the condition using ultrasound-guided hyaluronidase and adjunctive anti-inflammatory therapy illustrated full resolution in 80% of the cases at 6 months with no recurrences at 12 months follow-up. Those results refute the ineffectiveness of the targeted interventions but also emphasize the clinical difficulty of treating the already built fibrosis, especially in multicultural groups with potential ethnic differences that can increase risks.

Our research fills some shortcomings in the literature with region-specific data about an underrepresented U.S. population, which is consistent with the global agreement about etiological factors such as filler biochemistry, biofilms, and host immune dysregulation (Baranska-Rybak et al., 2024; Saad et al., 2025; Funt, 2022). The study contributes to understanding the non-temporal nature of HA fillers, suggesting that HA fillers may exhibit persistence beyond expected degradation times in some cases, thereby questioning the assumption of their purely temporary nature, and suggesting surveillance recommendations to

the research by achieving the goals of describing clinical-histopathological correlates as well as Treatment outcomes, identifying risk factors specific to the U.S. (e.g., increased fibrosis in non-Caucasian subpopulations), and outlining the recommendations that need informed consent on delayed risks (0.02-4.25% incidence) (Convery et al., 2021; Colon et al These findings support clinical practices that propose systemic use of ultrasound, length of follow-up (≥12 months), and risk-specific stratification to prevent complications among various populations of patients, and eventually improve patient safety of non-surgical esthetics.

There are also further implications in the context of filler innovation whereby the creation of low immunogenic formulations, which have a predictable degradation behavior and should be encouraged in response to minimize chronic reactions (Hu et al., 2023; Lee et al., 2024; De Jong et al., 2022). Since the number of aesthetic procedures keeps soaring through the world exceeding 5 million annually, long-term tissue biocompatibility has to be given priority to avoid morbidity and keep the faith in such procedures intact (Abduljabbar & Basendwh, 2016; Puyana et al., 2025). This paper supports the idea that although HA fillers are still a staple of the facial rejuvenation procedure, careful identification and treatment of their delayed adverse effects is critical to achieve the best results in the ever more diverse patient population.

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