

Late Complications of Biopolymers in Aesthetic Medicine: Clinical Presentation, Diagnosis, and Management

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ABSTRACT

Permanent biopolymers used as dermal fillers may cause delayed complications due to chronic foreign body inflammation, progressive fibrosis, and, in severe cases, systemic manifestations such as granulomatous hypercalcemia and renal impairment. Late complications may occur years after injection and range from localized nodules, induration, and deformity to material migration and systemic involvement, often mimicking infectious, neoplastic, or autoimmune conditions. Diagnosis relies on clinicoradiographic correlation, with magnetic resonance imaging playing a central role in defining disease extent and ultrasound serving as a useful adjunct for initial evaluation. Management should be individualized according to disease severity. Medical therapy has a limited role because of the persistence of the material, whereas surgery remains the cornerstone of treatment in moderate to severe disease despite challenges in complete resection. Early recognition, multidisciplinary evaluation, and severity-based management are essential to optimize clinical and aesthetic outcomes.

Keywords: biopolymers, dermal fillers, foreign-body granulomas, foreign-body reaction, reconstructive surgical procedures.

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INTRODUCTION

The use of biopolymers as permanent dermal fillers has increased significantly in aesthetic procedures, particularly in areas such as the gluteal region, face, and lips. However, their long-term safety profile remains limited and has been associated with potentially severe delayed complications [1,2].

Unlike resorbable fillers, biopolymers induce a persistent inflammatory response that may progress to chronic granulomatous reactions, progressive fibrosis, and systemic manifestations [1,3]. In recent years, a broader clinical spectrum has been recognized, including granulomatous hypercalcemia, renal insufficiency, and reported autoimmune-like phenomena such as ASIA syndrome, highlighting the need for a structured diagnostic and therapeutic approach [4,5].

TYPES OF BIOPOLYMERS USED IN AESTHETIC PRACTICE AND THEIR CLINICAL RELEVANCE

Biopolymers used in aesthetic procedures are non-resorbable or very slowly degradable materials, whose persistence in tissues is associated with a higher risk of delayed

complications [1,2]. Their classification is essential to understand their biological behavior and to guide therapeutic planning, particularly in patients with advanced disease.

The main types include:

- Polymethylmethacrylate (PMMA): consists of synthetic microspheres suspended in a carrier, usually collagen. It is a permanent material that induces fibrosis and granulomatous reaction and has been associated with granulomas, extensive fibrosis, and hypercalcemia. Its typically diffuse infiltration makes surgical resection challenging [1,3,6].
- Liquid silicone: a non-biodegradable material with high migratory potential and variable inflammatory response. It has been associated with necrosis, distant migration, and chronic granulomas, often leading to multicompartiment involvement [1,2].
- Synthetic hydrogels (polyacrylamide, polyalkylimide): highly hydrophilic materials with initially homogeneous appearance, later prone to encapsulation or dispersion. They may form pseudotumoral masses and induce chronic inflammation [1].

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- Unregulated substances (oils and mixtures): non-approved materials with variable and unpredictable composition, associated with severe inflammation, necrosis, and systemic complications [2,5].
- Biostimulatory agents (differential diagnosis): calcium hydroxyapatite and poly-L-lactic acid are biodegradable materials that may induce granulomatous reactions but generally respond better to medical treatment and should be distinguished from permanent biopolymers [3].

PATHOPHYSIOLOGY OF LATE COMPLICATIONS

Biopolymers, being non-biodegradable, persist indefinitely in tissues and act as continuous antigenic stimuli, triggering a chronic inflammatory response dominated by innate immunity, particularly macrophages and multinucleated giant cells [6,7].

Unlike resorbable fillers, which induce transient responses, biopolymers lead to sustained activation and chronic granuloma formation, which represents the central pathophysiological mechanism of delayed complications [1,3].

This process evolves dynamically: initially, the material is recognized as a foreign body, triggering macrophage infiltration and proinflammatory cytokine release. Subsequently, the inability to degrade the material leads to organized granuloma formation. In parallel, progressive fibrosis develops, distorting tissue architecture and surgical planes. Over time, the material may migrate through anatomical planes, extending inflammation beyond the original injection site.

A key mechanism is macrophage-mediated extrarenal 1α -hydroxylase activity, promoting conversion of vitamin D to its active form (1,25-dihydroxyvitamin D), leading to granulomatous hypercalcemia and potential renal impairment [1,4].

From a surgical perspective, this explains the absence of clear planes, dense fibrosis, and the frequent impossibility of complete resection in advanced disease.

CLASSIFICATION OF LATE COMPLICATIONS

Late complications encompass a broad clinical spectrum, ranging from progressive local alterations to severe systemic manifestations [1,2,5]. For practical and surgical purposes, they can be classified into local and systemic complications, often overlapping [1,5].

Local complications

Local manifestations are the most common presentation and represent the primary reason for consultation in plastic surgery settings [1,6]. They are typically characterized by a progressive and often insidious course, reflecting the chronic inflammatory response of the tissue induced by the exogenous material [1,3].

- Nodules and granulomas, which may be painful or asymptomatic and result from a persistent foreign body reaction.
- Tissue induration and fibrosis, leading to diffuse hardening, loss of elasticity, and distortion of normal anatomical planes, thereby increasing surgical complexity.
- Cutaneous necrosis, usually secondary to chronic vascular compromise or severe localized inflammation.
- Migration of the material through anatomical planes, with involvement of regions distant from the original injection site.

In addition, severe aesthetic deformity may occur as a consequence of fibrosis, asymmetry, and irregular redistribution of the injected material. The combination of diffuse fibrosis and material migration typically indicates advanced disease and significantly limits the feasibility of complete surgical resection [1,6].



Figure 1. Facial nodular deformities secondary to delayed granulomatous reaction to biopolymer fillers.

Adapted from Poveda et al. (2006) [8].

Clinical photograph demonstrating multiple subcutaneous nodular lesions involving the perioral and mandibular regions (highlighted in red). These findings are consistent with a delayed foreign body granulomatous reaction following cosmetic filler injection. The asymmetric distribution, firm induration, and irregular contour reflect chronic inflammation, progressive fibrosis, and migration of the injected material, which are hallmark features of late complications.

Systemic complications

Although less common, systemic complications represent the most severe clinical manifestation of this condition and are indicative of sustained immune activation.

- Granulomatous hypercalcemia: secondary to extrarenal production of calcitriol by activated macrophages within granulomas [1,4].
- Renal insufficiency: typically associated with prolonged hypercalcemia or chronic systemic inflammation.

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- Autoimmune/inflammatory syndrome induced by adjuvants (ASIA syndrome): immune-mediated systemic manifestations related to the presence of biomaterials [5].
- Post-infectious inflammatory reactivation: exacerbation of the granulomatous response following viral infections, including COVID-19 [9].

CLINICAL PRESENTATION

Late complications associated with biopolymers may present insidiously, occurring months to even decades after the initial injection, which significantly hinders early recognition. The clinical presentation is heterogeneous and depends on the extent, anatomical location, and degree of inflammatory response; however, it is typically characterized by a gradual progression of local symptoms that may evolve into systemic manifestations [10].

Key Clinical Findings

- Chronic pain and induration: progressive hardening of the tissues, often associated with tenderness or persistent pain.
- Cutaneous alterations: erythema, discoloration, surface irregularities, or compromise of skin integrity.
- Progressive asymmetry: deformity secondary to fibrosis, material migration, and tissue redistribution.
- Fistulas, ulceration, or suppuration: manifestations of advanced disease, frequently associated with severe chronic inflammation or superinfection [1,2,6].
- Systemic symptoms: include fatigue, malaise, and, in more severe cases, manifestations related to hypercalcemia, such as weakness, polyuria, or neurological disturbances [1,4,5].



Figure 2. Advanced gluteal necrosis and soft tissue destruction secondary to late biopolymer complications.

Adapted from Duarte et al. (2016) [11].

Clinical photograph of a 50-year-old woman demonstrating severe bilateral involvement of the gluteal region following prior biopolymer injection. Extensive areas of tissue induration, hyperpigmentation, and deformity are observed, along with a large ulcerated defect exposing underlying necrotic tissue, consistent with advanced chronic inflammatory reaction and soft tissue breakdown. These findings represent a late-stage complication characterized by progressive fibrosis, vascular compromise, and secondary infection, often requiring complex surgical management.

From a diagnostic standpoint, late-onset granulomas may mimic chronic infections, soft tissue neoplasms, or autoimmune diseases, often leading to delays in diagnosis and initiation of appropriate treatment [3,10]. In this context, the combination of progressive induration, asymmetry, and a remote history of filler injection should be considered highly suggestive of biopolymer-related complications, even in the absence of documentation of the initial procedure [1,3,10].

DIAGNOSIS

The diagnosis of late complications associated with biopolymers is primarily clinicoradiographic correlation, requiring a high index of suspicion and supported by imaging studies that allow for accurate assessment of disease extent and infiltration patterns [1,3,6]. Histopathological confirmation is reserved for selected cases, particularly when diagnostic uncertainty exists or when there is a need to exclude neoplastic or infectious processes [1,3]. From a surgical perspective, thorough preoperative characterization is essential to guide the resection strategy and anticipate procedural complexity [1,6].

Ultrasound (US)

US is an accessible and useful tool for initial evaluation, particularly in superficial lesions [3,6]. The most common findings include:

- Hypoechoic or heterogeneous areas
- Irregular and poorly defined distribution of the material
- Identification of fluid collections or associated inflammatory changes

It is useful as guidance for diagnostic or therapeutic procedures, such as biopsy or targeted infiltration.

Magnetic Resonance Imaging (MRI)

MRI is generally considered the preferred imaging modality due to its superior soft tissue resolution and its ability to accurately delineate the true extent of disease involvement [3,6]. Characteristic findings include:

- A diffuse infiltrative pattern without a well-defined capsule
- Heterogeneous signal intensity on T1- and T2-weighted sequences
- Evidence of migration into deeper anatomical planes
- Assessment of muscular and fascial involvement

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MRI allows differentiation between localized and diffuse disease, which is critical for determining the appropriate surgical approach, including in bloc resection versus staged management [4,6].

Computed Tomography (CT)

CT is useful in selected scenarios, particularly for evaluating deep or retrofascial involvement, identifying associated calcifications, and assessing systemic complications such as nephrocalcinosis in the context of hypercalcemia [2,6].

Histopathology

Histopathological evaluation is not required in all cases but is essential when the diagnosis is uncertain [3]. Characteristic findings include foreign body-type granulomas, multinucleated giant cells, amorphous or vacuolated exogenous material, and dense fibrosis with tissue remodeling. These features reflect the persistent chronic inflammatory response induced by biopolymers [3].

DIFFERENTIAL DIAGNOSIS

The clinical spectrum of these complications may mimic a wide range of conditions, contributing to diagnostic delays [3,10]. The differential diagnosis includes chronic infections (such as abscesses or atypical mycobacterial infections), granulomatous diseases (such as sarcoidosis), soft tissue neoplasms (such as liposarcoma and fibrosarcoma), and reactions to resorbable fillers, particularly hyaluronic acid, which typically follow a more benign and reversible course [3,10,12].

MANAGEMENT: SEVERITY-BASED STEPWISE APPROACH

The management of late complications associated with biopolymers should be individualized based on anatomical extent, clinical severity, and the presence of systemic manifestations, often requiring a multidisciplinary approach. Due to the permanent nature of these materials, medical treatment is generally limited and, in many cases, serves as a bridge to definitive surgical management [5,6].

Conservative Management: Mild or Selected Cases

Medical therapy may be beneficial in early stages or in patients who are not candidates for immediate surgical intervention, with the aim of modulating the inflammatory response.

- Systemic or intralesional corticosteroids: reduce granulomatous inflammation and local edema.
- Immunomodulators (e.g., methotrexate, hydroxychloroquine): indicated in cases with an autoimmune component or persistent inflammation [5].

- Antibiotics: reserved for suspected superinfection or inflammatory processes with a possible infectious component.
- Other adjuvant approaches: include anti-inflammatory agents and, in selected cases, biologic therapies.

However, the response is often partial or transient due to the persistence of the exogenous material, which limits definitive resolution of the inflammatory process [5].

Persistence of symptoms despite medical therapy is a strong predictor of the need for surgical intervention.

Indications for Surgical Management

Surgical intervention is indicated in patients with moderate to severe disease or in those who fail conservative treatment. The main indications include:

- Refractory chronic pain.
- Significant or progressive aesthetic deformity.
- Cutaneous necrosis or recurrent infection.
- Extensive migration of the material.
- Systemic manifestations, particularly granulomatous hypercalcemia [3,4].
- Failure of medical therapy.

These indications reflect disease progression to a stage at which removal or reduction of the biopolymer burden becomes necessary to achieve clinical control [4,5].

Surgical Management (Therapeutic Cornerstone)

Surgical treatment represents the definitive therapeutic strategy in most advanced cases; however, it poses significant technical challenges due to diffuse infiltration, dense fibrosis, and distortion of normal anatomical planes [3,4,6].

Surgical Principles

The surgical approach may incorporate principles analogous to soft tissue oncologic surgery adapted to chronic inflammatory disease:

- Maximal safe resection of the material while preserving vital structures.
- Functional and aesthetic preservation of adjacent tissues.
- Staged approach in cases of extensive or multifocal disease.
- Careful dissection through fibrotic and frequently distorted planes.
- Meticulous hemostasis due to reactive neovascularization.

Complete resection is rarely achievable in diffuse disease; therefore, the realistic objective is a substantial reduction of the inflammatory burden [3,6].

Surgical Techniques

1. Open in bloc excision. Indicated for localized and relatively well-defined lesions, this approach allows for more complete removal of the infiltrated material and affected tissues [3,6]. It follows principles similar to soft tissue

oncologic surgery, prioritizing adequate margins and local control of the inflammatory process [3].

2. Partial resection with tissue remodeling. Indicated in cases of diffuse infiltration where complete excision is not feasible without compromising critical structures [3,6]. This approach aims to balance reduction of the inflammatory burden with preservation of functional and aesthetic outcomes and is often combined with reconstructive procedures [6].

3. Assisted liposuction (controversial use). This technique may facilitate volume reduction in extensive areas; however, it carries a risk of material dissemination and exacerbation of the inflammatory response. Therefore, its use should be limited to carefully selected cases [6].

4. Reconstruction and secondary management. Reconstructive options include local or regional flaps for defect coverage, as well as delayed fat grafting, which should be performed with caution in previously inflamed tissues. Secondary aesthetic procedures may be considered once the inflammatory process has been adequately controlled [6].

Surgical management should be integrated within a longitudinal treatment approach, taking into account the risk of disease recurrence or persistence, the potential need for staged procedures, and the fact that final aesthetic outcomes largely depend on the stability of the inflammatory process. Overall, the management of biopolymer-related complications should be understood as a stepwise process in which medical therapy has a limited role, while surgery represents the cornerstone of treatment in advanced disease, aiming to control inflammation, preserve function, and restore aesthetic outcomes [4,5,6].

Surgical Complications

Surgical management of biopolymer-related complications, although representing the main therapeutic approach in advanced disease, is associated with a considerable rate of adverse events due to diffuse material infiltration, dense fibrosis, and distortion of normal anatomical planes [3,6].

The main complications include:

- Recurrence or persistence of disease: common in cases of incomplete resection, particularly when the material is widely disseminated within the tissues [3,6].
- Neurovascular injury: resulting from the difficulty in identifying anatomical structures within a fibrotic surgical field, with a risk of permanent functional deficits.
- Residual aesthetic deformities: including asymmetry, contour irregularities, and volume loss, which may require secondary reconstructive procedures [1,6].
- Seroma, hematoma, and infection: relatively common postoperative complications, particularly following extensive resections or in the presence of active inflammation [5,6].

Additionally, in advanced cases, the following may occur:

- Pathologic scarring, including excessive fibrosis or tissue contracture.

- Need for staged or multiple surgical procedures.
- Suboptimal functional and aesthetic outcomes, even after appropriate management.

The risk of complications increases significantly in diffuse disease; therefore, thorough preoperative imaging assessment (particularly MRI) and careful patient selection are critical to optimizing clinical outcomes [3,6].

DISCUSSION

Biopolymers used in aesthetic procedures are associated with significant delayed complications due to their non-biodegradable nature and their ability to induce a persistent chronic inflammatory response, characterized by foreign body granuloma formation and progressive fibrosis [1,2,4]. This process may extend beyond the injection site and, in advanced cases, lead to systemic manifestations such as granulomatous hypercalcemia and renal impairment [3,4,14]. One of the main clinical challenges is their delayed and heterogeneous presentation, which may occur years after the initial procedure, increasing the likelihood of misdiagnosis by mimicking infections, neoplasms, or autoimmune diseases [3,10]. In this context, a history of prior filler injection, even if remote, is critical for clinical suspicion.

Diagnosis relies on clinicoradiographic correlation. MRI allows accurate delineation of disease extent and differentiation between localized and diffuse involvement, while US is useful for initial evaluation and interventional guidance [6,13,15]. Histopathological evaluation is reserved for cases with diagnostic uncertainty [3].

Management should be individualized according to disease severity. Medical treatment has a limited role and is primarily adjunctive, as it does not eliminate the causative material [5,6]. In contrast, surgical intervention remains the cornerstone of treatment in moderate to advanced disease, although it is often limited by diffuse infiltration, fibrosis, and the difficulty of achieving complete resection [3,6,16,17].

Controversies persist regarding certain techniques, such as assisted liposuction, due to the risk of material dissemination and exacerbation of the inflammatory response [6,17]. Additionally, inflammatory reactivation phenomena following infections have been reported, suggesting a dynamic immunological component in disease progression [4,18].

Finally, the current evidence is largely based on case reports and clinical series, which limits the standardization of management and underscores the need for prospective studies to establish more robust therapeutic guidelines.

LIMITATIONS

Current evidence is largely derived from case reports and small clinical series, limiting generalizability. Heterogeneity in injected materials and variability in management approaches further preclude standardized treatment recommendations. Prospective comparative studies are needed to validate severity-based management algorithms.

CONCLUSION

Late complications associated with biopolymers represent a complex entity arising from a persistent chronic inflammatory response, with manifestations ranging from progressive local alterations to potentially severe systemic manifestations. Their recognition requires a high index of clinical suspicion, particularly in patients with a history of aesthetic procedures, even when remote.

Diagnosis should be based on appropriate clinicoradiographic correlation to define disease extent and guide therapeutic decision-making. Management must be individualized according to severity within a multidisciplinary framework. Although medical treatment may provide symptomatic improvement in selected cases, its effectiveness is limited due to the permanent nature of the material.

In this context, surgical intervention represents the cornerstone of treatment in moderate to advanced disease; however, it is associated with significant technical challenges and a considerable risk of recurrence. The complexity of this condition and the lack of standardized guidelines highlight the need for comprehensive evaluation and individualized therapeutic strategies to optimize clinical outcomes. Prospective studies are needed to establish evidence-based diagnostic and therapeutic guidelines.

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