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Late granuloma formation secondary to hyaluronic acid injection

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Abstract

Hyaluronic acid injection to rejuvenate or to correct defects is a very common practice in aesthetic medicine. Although it is considered highly safe because of biocompatibility and biodegradability, adverse reactions can occur. Herein, we report a patient with foreign body granuloma formation that presented as multiple subcutaneous nodules on both arms, following injections of hyaluronic acid performed about six years earlier. Our case is unique with respect to timing and area of granuloma appearance.

Keywords: hyaluronic acid filler, foreign body granuloma

Introduction

Different types of complications have been observed using hyaluronic acid filler. The most common adverse events are early and transient inflammatory reactions, such as redness, swelling, bruising, tenderness, and pain. Normally, these events disappear after a short time without leaving any trace. Reports about long-term adverse events secondary to hyaluronic acid injections are rare. We describe the clinicopathological findings and the course of a late cutaneous granulomatous reaction to hyaluronic acid injections. The nodules completely disappeared following systemic corticosteroid therapy but two months later, they surprisingly relapsed.

Case Synopsis

A 70-year-old otherwise healthy woman presented to our clinic complaining about multiple subcutaneous nodules on both arms that had been present for about two months. On physical examination, multiple small, painless and firm nodules were appreciated by palpation, with symmetrical distribution on the inner face of both arms (**Figure 1**). She exhibited neither lymphadenopathy nor fever. In the same sites, about six years earlier, the patient had had filler injections for aesthetic purposes to counteract flaccidity and wrinkles in the upper arm skin. The patient did not remember the name of the product, but she could only report that it had been injected by a *physician in a private medical office*. Routine laboratory tests, including blood count, liver and renal function tests, erythrocyte sedimentation rate, and C-reactive protein level were within normal limits.



Figure 1: Clinical photograph demonstrating left arm with multiple subcutaneous nodules.

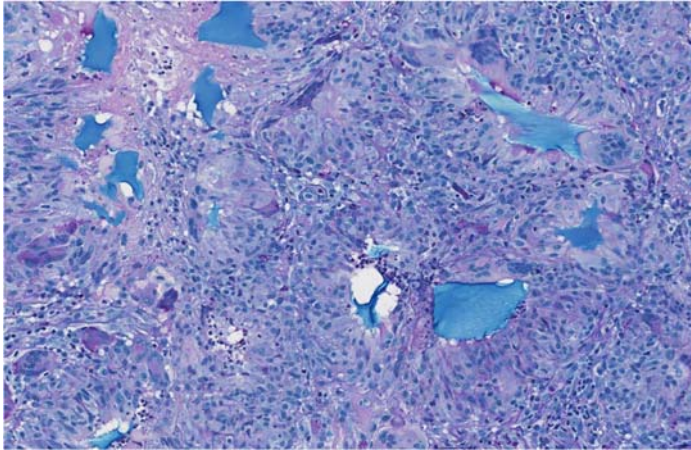


Figure 2. Histopathological image demonstrating amorphous bluish material, Alcian-positive, consistent with hyaluronic acid within the granulomas in the dermis. Alcian-periodic acid Schiff, 20x.

The patient agreed to a diagnostic cutaneous biopsy, which was performed on a nodule localized on the left arm. Upon examination of the histology, the intermediate and deep dermis and the subcutis showed a florid giant cell granulomatous reaction related to a foreign body incorporating amorphous bluish, Alcian-positive, material referable to hyaluronic acid (**Figure 2**). The dermis interposed between the granulomas appeared fibrotic and thickened. Additionally, there was a modest lymphocytic infiltrate with eosinophils. The histological examination supported the diagnosis of granuloma related to hyaluronic acid (**Figure 3**).

Initially, we considered the possibility of treating the patient with hyaluronidase injections, but the patient refused the treatment because she did not want to have any further injections in those areas. Therefore, oral therapy with prednisone 25mg daily was initiated and all lesions disappeared two weeks later. Complete remission was confirmed by a soft tissue ultrasound. Two months later the nodules relapsed in the same sites, but the patient decided not to entertain further treatment.

Case Discussion

The forefather of reabsorbable fillers, hyaluronic acid, is widely used in the field of aesthetic medicine to correct rhytids, folds, and volume deficits induced by aging or disease. Although rare, hyaluronic acid is

injected in the upper arms to counteract age-associated skin laxity and the exaggerated appearance of fat deposits [1]. Hyaluronic acid is a uniform linear polysaccharide derived from fermentation of bacteria. The material is subjected to sterilization and stabilization by a cross-linkage process and becomes, for some months, resistant to the attack of human hyaluronidases and therefore not immediately degradable and reabsorbable. Long-term complications of hyaluronic acid fillers include displacement of product, mainly because of intramuscular placement, inflammatory or non-inflammatory nodules, and granuloma [2]. Delayed granulomatous reactions are extremely rare [3-5]. To date, the pathogenesis of late adverse events is still unknown.

Several hypotheses have been suggested. First, the impurities deriving from the bacterial fermentation during production may elicit hypersensitivity responses, particularly in patients who undergo repeated filler injections. Indeed, antibody formation against hyaluronic acid is possible [6]. Second, the disintegration of the cross-linked material may be responsible for an inflammatory reaction. Third, the concomitant inoculation of bacteria during the filler injection may provoke a foreign body granulomatous reaction to the bacterial biofilm [7]. Biofilm is composed of structured microorganisms surrounded by a self-developed polymeric matrix [8]. These quiescent communities can be activated by repeated injections. In our case, it was possible to document the presence of hyaluronic acid material within the tissue reaction six years after injection, suggesting some defects in degrading the material as this generally occurs in most patients within a limited time frame. This long persistence may have elicited a sort of foreign body tissue reaction.

There is no standardized treatment for foreign body granuloma induced by fillers. The strategies for treatment include the use of hyaluronidase alone or in combination with intralesional corticosteroid. Empiric antibiotic therapy is another option. Oral corticosteroids should be taken into consideration after infection is ruled out. Surgical excision can be the solution in cases of failure of other treatments [9]. Laser-assisted evacuation of filler material and

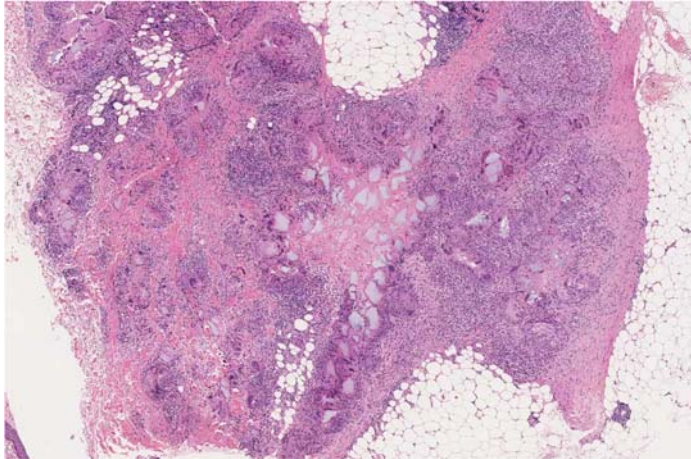


Figure 3. Histopathological image demonstrating giant foreign body granulomatous reaction incorporating hyaluronic acid. H&E, 4x.

inflammatory and necrotic granulomatous tissue is also described in the literature [10].

Conclusion

Long-term complications of hyaluronic acid fillers may continue to be seen in clinical practice. Foreign body granuloma can appear months and even years after injections and patients should be informed of this potential adverse event. Although different strategies of treatment are currently available, optimal management of late granuloma remains a challenge for clinicians.

Potential conflicts of interest

The authors declare no conflicts of interest.

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