

# Lip Nodules Caused by Hyaluronic Acid Filler Injection: Report of Three Cases

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Received: 22 August 2011 / Accepted: 26 September 2011 / Published online: 8 October 2011  
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**Abstract** Many dermal fillers have been used for reducing facial skin lines and for providing lip augmentation, and hyaluronic acid (HA) is one of the most widely used agents. One of the main commercial forms of HA is Restylane (Q Med, Sweden) produced by microbiological engineering techniques. Although HA is non-immunogenic, hypersensitivity and Granulomatous foreign body reactions have been reported. Herein, we report three female patients (average age 56 years) who presented with firm nodular lesions of the lip and a history of injection with HA (Restylane, Q Med, Sweden). Histopathologically, all cases showed pools of amorphous hematoxyphilic material surrounded by bands of densely collagenized connective tissue with no inflammation or foreign body reaction. Histochemical stains confirmed the presence of acid mucopolysaccharides such as hyaluronic acid. We conclude HA (Restylane, Q Med, Sweden) is an inert filler

that may persist at an injection site, resulting in a tumor-like nodule.

**Keywords** Cosmetic filler · Hyaluronic acid · Restylane · Lip nodule

## Introduction

Many dermal fillers have been used for reducing facial skin lines and wrinkles, and for providing lip augmentation and hyaluronic acid (HA) is one the most widely used agents [1]. This was first used as an injectable dermal filler by Balazs et al. in [2] and it was introduced on the market in Europe in 1996 as a biodegradable product [3].

In 2003, the hyaluronic acid filler Restylane (Q Med, Uppsala, Sweden) was approved by the FDA in the US for soft tissue augmentation and since then its use has increased by 70% [4]. Although HA fillers are non-toxic and non-immunogenic, hypersensitivity and granulomatous foreign body reaction have been reported [5–15].

Here we report three new patients who developed lip nodules after injection with Restylane (Q Med, Uppsala, Sweden).

## Report of the Cases

All three cases were females, with an average age of 56 years, who each presented with a painless discrete nodule on the labial mucosa. All patients had a history of Restylane (Q Med, Uppsala, Sweden) injection into their lips and had undergone biopsy. The characteristics of the current cases are presented in Table 1.

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**Table 1** Clinical features of current cases and similar previously reported cases with lip nodules and history of Restylane injection

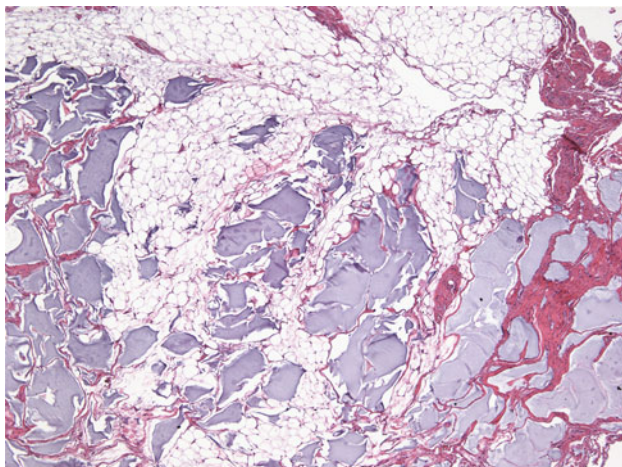
Cases	Gender/age	Site/size (cm)	Clinical diagnosis	Period of time between restylane injection and biopsy
Current case #1	F/55	Upper lip/0.5	Adenoma/fibrous hyperplasia	4 months
Current case #2	F/57	Lower lip/1.0	Sclerotic/inflamed minor salivary gland	24 months
Current case #3	F/56	Lower lip/0.8	Fibroma	Unknown
Bennett et al. [16]	F/61	Upper lip/0.6	Basal cell carcinoma	23 months
Anatelli et al. [17]	F/80	Upper lip/0.3	Basal cell carcinoma	Not specified

**Histopathologic Findings**

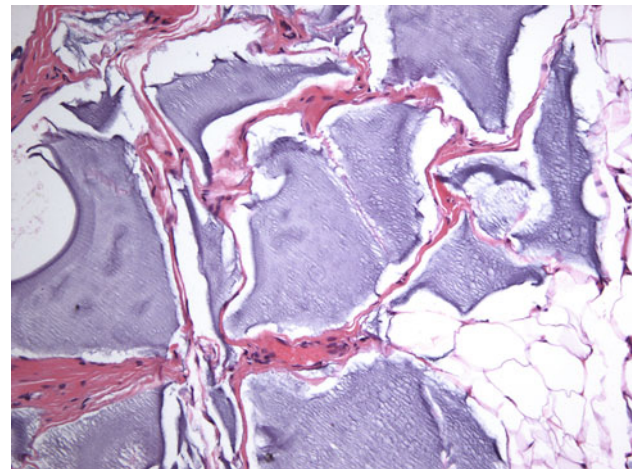
All cases were identical histopathologically. They consisted of pools of amorphous hematoxyphilic material surrounded by collagenized connective tissue and mature adipose tissue without inflammation or foreign body reaction (Figs. 1, 2). Alcian blue and colloidal iron stains confirmed the presence of acid mucopolysaccharides such as HA (Figs. 3, 4). In case 2, salivary gland lobules were also noted and these exhibited very mild chronic obstructive sialadenitis.

Case 3 demonstrated a nodule of densely collagenized fibrovascular tissue covered by hyperkeratotic stratified squamous epithelium typical for a fibroma (Fig. 5) Pools of basophilic and alcianophilic material, surrounded by thin septa of fibrous tissue and unassociated with inflammation or giant cell reaction, identical to what was seen in cases 1 and 2, were noted as an incidental finding at the base of the fibroma.

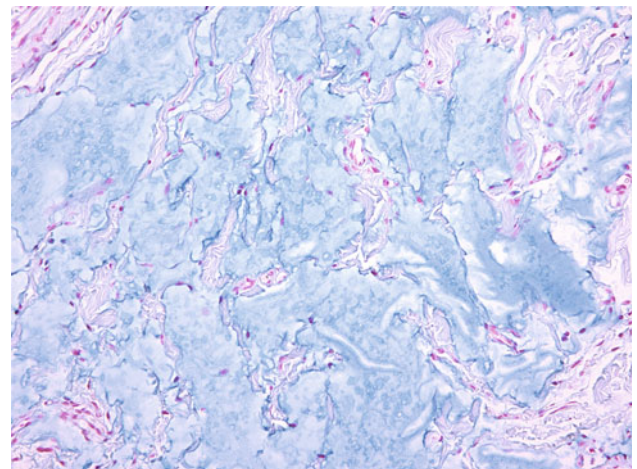
All cases were diagnosed as “inert foreign material consistent with hyaluronic acid filler (Restylane; Q Med, Uppsala, Sweden) unassociated with foreign body reaction”.



**Fig. 1** Pools of hematoxyphilic material surrounded by fibro-fatty tissue (H&E, ×40)



**Fig. 2** Amorphous hematoxyphilic material surrounded by densely collagenized connective tissue (H&E, ×200)

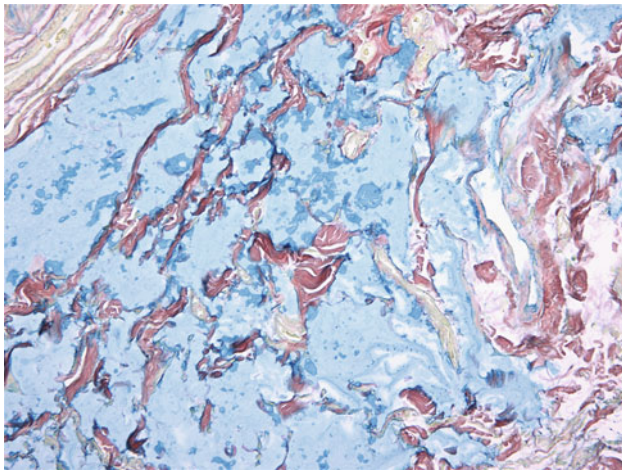


**Fig. 3** Pools of alcianophilic acid mucopolysaccharides (Alcian blue, ×200)

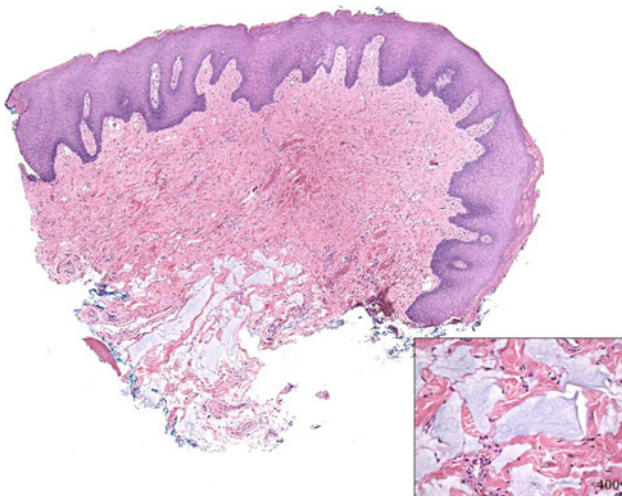
**Discussion**

The use of cosmetic dermal fillers is on the rise [18]. The ideal filler should be efficacious in reducing wrinkles and plumping the tissues without looking unnatural, be easy





**Fig. 4** Pools of acid mucopolysaccharides positive for colloidal iron (Colloidal iron,  $\times 200$ )



**Fig. 5** Case 3 showing a nodule of densely collagenized fibrovascular tissue with pools of basophilic material at the base (*inset*) and overlying hyperkeratotic squamous epithelium (H&E,  $\times 40$ )

and safe to introduce into the tissues, have a long duration of action, be relatively inert and not incite a painful or bulky tissue response, and have acceptable cost [19].

Dermal fillers may be classified as permanent or degradable [19, 20]. Permanent fillers tend to be synthetic or alloplastic and show a very low rate of breakdown or may even remain permanently in the dermis. Examples of these include silicone and polymethylmethacrylate [19, 21].

Non-permanent or degradable fillers are generally made up of naturally-occurring biological agents such as collagen or hyaluronic acid that undergo degradation at variable rates [19, 21]. Collagen dermal fillers are available in the form of bovine collagen and human-based collagen [14, 22].

HA is a non-sulfated glycosaminoglycan polysaccharide composed of repeating disaccharide units of glucuronic acid and N-acetylglucosamine. HA is a major and natural component of the extracellular matrix in all animal tissues produced by mesenchymal cells with no organ or species specificity; as such, there is no risk for immunogenicity and it is non-toxic and biocompatible [19, 23]. It is highly hydrophilic and this property helps it to retain water and occupy larger volumes relative to its mass [22].

HA fillers have been used to eliminate photoaging wrinkles such as are often present on the nasolabial fold and lip, as well as peri-oral rhytides, and marionette lines. Such fillers may also be used for lip filling or contouring and chin and cheek augmentation [24]. Other indications for HA are noted in otologic surgery for regeneration of perforated tympanic membrane, in ophthalmic surgery for production of artificial tears, and in orthopedics as an anti-inflammatory lubricant [19]. Its use should be avoided in pregnant/breast feeding women, in patients younger than 18 and patients with history of allergy or anaphylaxis to the filler or one of its components [25].

HA fillers may be obtained from both animal and non-animal sources and there are two main commercial forms of HA. One is Hyaloform (Biomatrix, USA), an extract derived from rooster combs and the other is Restylane (Q Med, Uppsala, Sweden) which is a cross-linked HA produced by microbiologic engineering techniques (generated by streptococcus equi) [5, 19]; this latter product is more resistant to early degradation by hyaluronidase and rendered more water-insoluble because of cross-linkage [19, 24].

Adverse reactions to HA consisting primarily of localized hypersensitivity reactions and injection site inflammation are uncommon and occur in 0.05–0.15% of cases (Friedman et al. [26]). The most common early or immediate, non-allergic, local, and transient side effects are injection site reactions such as pain, mild to moderate edema, ecchymoses and hematoma; palpability, hypercorrection, and bluish discoloration may also occur secondary to superficial injection of the implant and inappropriate technique [19, 27]. The incidence of such reactions has been noted in approximately 2% of treatments for Hylaform [28]. Delayed adverse reactions include hypersensitivity and granulomatous foreign body reaction that occur in up to 0.6% of cases [3, 5]. This may result from reactivity of some patients to the protein residues of bacterial or avian origin, or impurities from the cross-linking process [19]. Uncommon non-allergic adverse reactions include bacterial infection, aseptic or cold abscess, herpes reactivation [29], generalized scleromyxedema [30], scar sarcoidosis [31], interferon-induced systemic sarcoidosis in patients with chronic hepatitis C [32], and necrosis and livedoid pattern due to accidental arterial embolization

[33]. Migration of the filler into a tunnel or track created by a large needle or cannula may manifest as a single and well-defined nodule 1–2 months after injection and may persist until resorption [34, 35].

HA is an inert and non-immunogenic filler and is usually resorbed within 4–6 months with no evidence of filler at nine months [19, 36]. However, a few cases of hypersensitivity and foreign body reaction have been documented, usually developing within 6–24 months [5–15, 35].

In this paper, we report three patients with a history of Restylane (Q Med, Uppsala, Sweden) injection to their lips who presented with lip nodules. Two other previously reported cases included female patients who presented similarly (Table 1). Histologic sections revealed pools of basophilic amorphous material within the fibro-fatty tissue of the lip typical for HA, unassociated with a foreign body reaction; one of our three cases was a fibroma with the HA present as an incidental finding at the base. The time period to development in the first two cases was 4 and 24 months, respectively. Case 2 was unusual in its exceptionally long period of persistence, similar to one other case in the literature [16]. Such persistence may be related to the cross-linking process, which makes Restylane more resistant to breakdown.

The basophilic nature of HA may be mistaken for the myxoid fibroplasias often seen around tumor islands in basal cell carcinomas [16, 17].

## Conclusion

This is a report of three cases of lip nodules with a history of Restylane (Q Med, Uppsala, Sweden) injection into the lip. Such nodules may clinically resemble other conditions such as mucocele, fibroma, benign salivary gland lesions/tumors, and other benign soft tissue tumors. Histologically, HA filler, which is inert, is seen as pools of amorphous basophilic material unassociated with a foreign body reaction.

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