Case report

Injectable hyaluronic acid (HA) derivatives are the most used reabsorbable dermal fillers for soft tissue augmentation today and their utilization is considered safe. We report a cutaneous granulomatous reaction that developed in a woman 5 weeks after the first treatment with a nonanimal HA derivative for the correction of facial wrinkling. We describe the clinicopathological findings and course of the cutaneous reaction. The adverse reaction showed clinical and histopathological characteristics comparable to the few previously reported cases. All cutaneous lesions spontaneously disappeared without scars within 3 months. We conclude that even nonanimal injectable HA derivatives can be associated with delayed granulomatous reactions. The patient should be informed of this potential long-term complication.

Case report

In February 1999, a 41-year-old female was treated with intradermal injections of Restylane for correction of facial wrinkling by an aesthetic surgeon. It was the first time the patient had undergone such a treatment for which there were no contraindications. No pretreatment skin testing for filler tolerance was performed.

Restylane was first approved for marketing and sale in September 1996 in the European Union and then registration was obtained in several other countries, including the U.S.A. More or less important adverse events have been observed when using both injectable Restylane and Hylaform. Transient inflammatory reactions such as severe redness, severe bruising, severe swelling, severe pain and severe tenderness have been reported by 3–5% of patients within 14 days following the first treatment and in a lower percentage with follow-up injections. These inflammatory reactions disappeared within 2–3 days, only rarely persisting for several weeks.1–3

Reports about long-term adverse events secondary to Restylane injections are, on the contrary, very rare.4–8 We report the clinicopathological findings and course of a cutaneous reaction to Restylane, which developed 5 weeks after the first injection of the gel for correction of facial wrinkling and lasted for 3 months.
Five weeks after the treatment, the patient gradually developed erythematous nodules, which appeared simultaneously at all sites of injection. One month later, she was referred to our institute for dermatological evaluation.

Cutaneous examination revealed multiple erythematous nodular lesions, which measured 0.5–1 cm or more in diameter and showed a linear distribution along the treated wrinkles (Figs 1 and 2). The nodules were painless, hard at palpation and covered by intact skin. The patient agreed to a diagnostic biopsy, which was performed on a nodule localized in the glabellar fold.

Histopathological examination showed a dense multinodular infiltration involving the deep part of the dermis and the subcutaneous fat (Fig. 3). Each nodule was found to be composed of several drops of a basophilic material showing a honeycomb aspect, surrounded by a layer of multinucleated giant cells with a dense peripheral infiltration of neutrophils and eosinophils (Fig. 4). Routine laboratory tests, including the IgE level, were within normal limits.

Topical treatment with antibiotics and steroids was suggested. Three months later, all nodules had completely disappeared, leaving no residual postinflammatory scars.

**Discussion**

During the past 100 years, several materials have been developed for soft tissue augmentation, improving contour deficiencies and facial wrinkles without major surgical procedures. Injectable paraffin and liquid silicones were used for a long time, but they are no longer employed because of the high
incidence of undesirable foreign body granuloma formation. Injectable bovine collagen has been the most popular filler for years and is still used even if it can occasionally cause nonhypersensitive adverse treatment responses such as local necrosis. Moreover, it is responsible for hypersensitive reactions associated with antibovine antibodies in about 1% of treated patients.

The ideal soft tissue filler substance for wrinkles, skin defects and sphincters is biocompatible and safe, is stable at the implantation site, keeps its volume and remains pliable, does not cause protrusion of the skin or mucosa, induces minimal foreign body reaction, will not be removed by phagocytosis, has no migration potential to distant locations and does not cause foreign body granuloma. These characteristics are far from reached, but HA derivatives are no doubt a step forward.

HA is a ubiquitous polysaccharide in that it is distributed widely in vertebrates and is present as a component of the cell coat of many strains of bacteria. HA in combination with other glycosaminoglycans, such as dermatan sulphate, chondroitin sulphate and keratan sulphate, is prominent in tissues such as the skin. HA is found to exist together with protein cores (aggregans) to which others such as chondroitin sulphate, dermatan sulphate and keratan sulphate are attached.

Commercially available injectable HA derivatives are isolated either from animal sources, such as rooster comb, or from bacteria, through a process of fermentation, or by direct isolation. Thanks to their versatile properties, such as their biocompatibility, nonimmunogenicity, biodegradability and viscoelasticity, HA derivatives are regarded as ideal biomaterials for cosmetic, medical and pharmaceutical applications. Nevertheless, not only do immediate adverse reactions such as redness, swelling, bruising and slight discomfort manifest in 3–5% of treated patients, but also some cases of delayed granulomatous reaction have been observed.

Lupton and Alster reported a 54-year-old woman who developed indurated and erythematous papulocystic nodules in the melolabial folds bilaterally at the site of intradermal injection of a modified HA gel after the third treatment session. Shaﬁr et al. described localized swellings that looked like white abscesses at the injection sites, the upper and lower lips and the nasolabial folds, 2 months after injection of Restylane. Micheels, using both Hylaform and Restylene for treating 219 patients, had eight patients with delayed inﬂammatory reactions which lasted up to 4–5 months. Histology, performed in seven patients, showed strong granulomatous reactions to a foreign body, with giant cells. Some patients also had skin test positivity for either one or both the injectable HA preparations and had positive antibodies against Hylaform and/or Restylane at serum analysis. A granulomatous reaction, which occurred after the first intradermal injection of Resty-lane gel, was observed by Rongioletti followed by scleromyxoedematous lesions on the patient’s trunk and extremities. Honig et al. reported a 48-year-old healthy woman who, several days after injection of the HA gel for correction of her nasolabial folds, complained of redness and intermittent swelling, followed by the development of severe, palpable and painful erythematous nodular papulocystic lesions 3 months after injection.

The time of presentation and clinical findings as well as histopathological findings in our patient were comparable to those of the 12 above reported cases. Fortunately, our case did not evolve to scleromyxoedema as in the patient reported by Rongioletti.

Studying 10 commercially available ﬁller substances for biocompatibility and durability by histopathological examination at 1, 3, 6 and 9 months after dermal injection, Lemperle et al. found that all reabsorbable or nonreabsorbable substances appeared to be clinically and histopathologically safe, although all exhibited undesirable side-effects. Natural ﬁller substances such as bovine collagen and HA are phagocytized slowly, usually with minimal histological reaction.

The cause of late inﬂammation or granuloma formation in some patients after intradermal injection of the nonanimal HA Restylane is not yet known, but it has been suggested that it could be allergic in nature and due to proteic impurities of bacterial fermentation. Whatever the explanation may be, products that can possibly cause complications after their use cannot be considered innocuous or nonallergic, and the patient should be informed of the potential complications.

References