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DOI: https://doi.org/10.1007/s00238-013-0883-7

Eur J Plast Surg (2014) 37:45–48
DOI 10.1007/s00238-013-0883-7

CASE REPORT

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Received: 7 June 2013 / Accepted: 31 July 2013 / Published online: 22 August 2013

Abstract Injectable hyaluronic acid (HA) derivatives are the most used resorbable dermal fillers used for soft tissue augmentation. While their use is considered safe, there have been reports of cutaneous granulomatous reactions. We describe the clinical, radiological, and cytological findings in a patient who presented a full year after cosmetic treatment with HA injections and discuss the various treatment options.
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Keywords Hyaluronic acid · Granuloma · Cosmetic surgery · Dermal filler

Introduction

Cosmetic procedures are becoming ever more popular [1] but standards among clinics and practitioners varies. Aggressive marketing techniques are sometimes used, and patients are often under the impression that the procedure is risk free and may be undertaken lightly. Indeed, when asked if they have ever had an operation, many patients fail to include cosmetic procedures as they do not view them as "proper" operations. Furthermore, regulation in many countries is lacking[2]. Public hospitals are sometimes left with the impression that when things go wrong, they are left to salvage the situation and deal with the dissatisfied patient.

It is against this backdrop that we report a case of delayed granulomatous reaction to a facial filler.

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Case report

The 53-year-old female patient presented to the University Hospital Zurich Eye clinic in January 2013. She had been seen 3 days previously in an external walk-in clinic with unspecific complaints relating to her left cheek. Despite receiving no diagnosis, she had been prescribed co-amoxiclav orally and told to return if the symptoms did not improve. The patient, unsatisfied with this course of action, self-referred to the Eye clinic where, after a normal ophthalmological examination was referred for an ear, nose and throat (ENT) consult.

A detailed history revealed the patient to be in good health with occasional sinusitis symptoms and a watery rhinorrhea. She regularly took euthyrox for hypothyroidism and symbicort for light asthma symptoms. She had a strong history of atopy with allergies to dog hair, house dust mites, birch, and books.

Clinical examination revealed a very discrete asymmetry of the nasolabial fold without overlying skin changes or associated pain (Fig. 1). Naso-endoscopy was poorly tolerated with repeated sneezing but showed no signs of polyposis, pathological secretions, or signs of acute sinusitis. Oral examination showed a good dentition without any root canal work.

The patient was asked to finish her course of antibiotics and return in 1 week or sooner if there were any substantial changes. At follow-up examination, she presented with three palpable pea-sized lesions, two in the left nasolabial fold and one on the inferior left lip. All lesions were bimanually intra/extra-orally palpable, nonpainful, smooth, and rubbery in consistency. Despite being easily palpable, they were not obvious on visual inspection or on ultrasound examination. Magnetic resonance imaging (MRI, Fig. 2) showed two poorly demarcated lesions with contrast uptake, and computed tomography (CT) showed reactive inflammatory changes of the underlying bone thought to represent an atypical infective process such as actinomycosis.

Freehand fine needle aspiration cytology showed a granulomatous reaction with foreign body giant cells on a

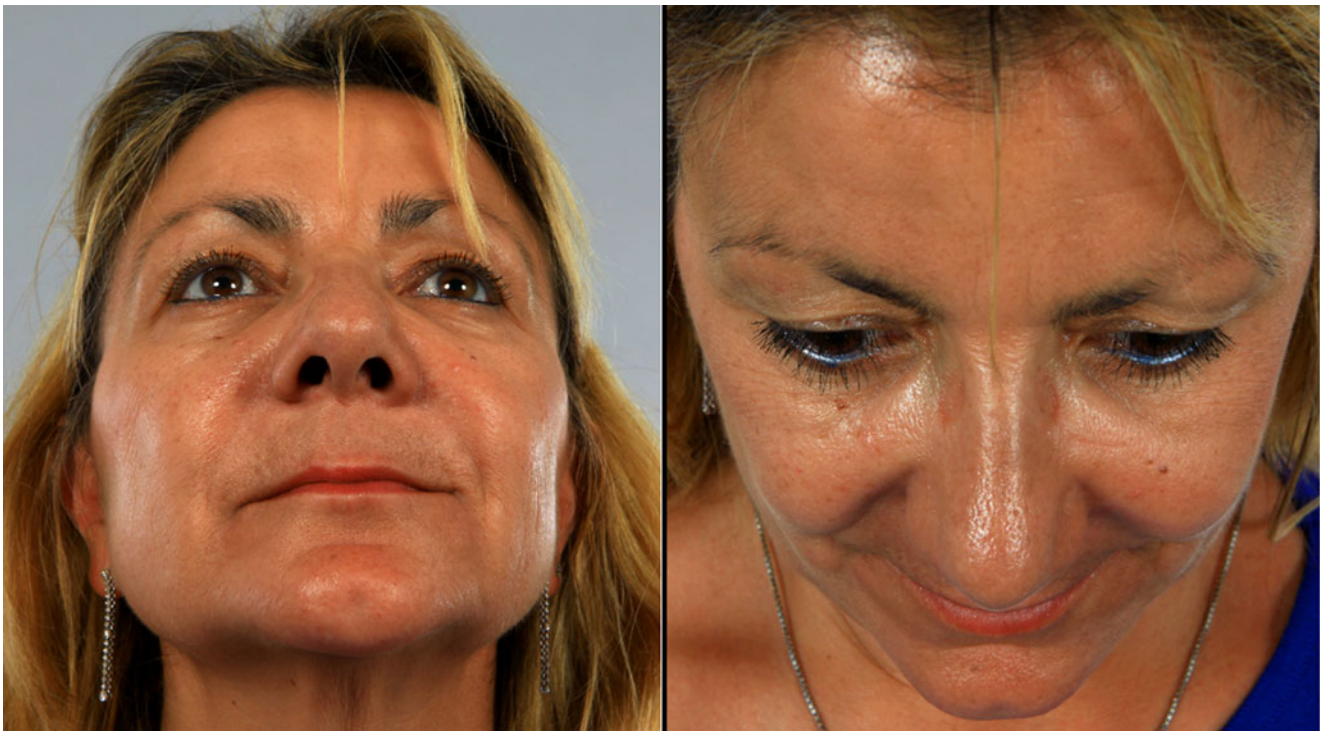

Fig. 1 Clinical photos showing subtle swelling on the left nasolabial fold

nonbirefringent gelatinous violet substance in direct smears stained with papanicolaou and cytoblocks stained with hematoxylin and eosin (H&E) (Fig. 3). Localization of the material together with the cytomorphology and review of the literature was suggestive of a foreign body reaction to cosmetic filler.

When told of the results, the patient admitted to multiple cosmetic injections in the nasolabial folds as well as the lips bilaterally, a full year previously with Belotero®, (Merz Pharma GmbH, Dassau-Rosslau, Germany). The supplier was contacted and the serial number of the injection noted. The patient was treated expectantly without any steroids or further antibiotics, but a week later, presented with two further pea-sized finds in the left nasolabial fold. Despite having also had simultaneous injections on the right, there were no clinical findings on this side. A further 2 weeks later, however, she had multiple further lesions bilaterally.

Steroids were discussed with the patient, but in the end, she was given ibuprofen with a proton pump inhibitor for stomach protection. The lesions were waxed and waned over the ensuing 3 months, and she is still under observation.

Discussion

Dermal fillers are a nonsurgical alternative used in facial cosmetics to eliminate wrinkles and contour tissue, allowing a temporary amelioration of age-related or posttraumatic/surgical facial findings. They can also be used to increase lip volume. Over the years, many different substances have been used including injectable paraffin and liquid silicones. Bovine collagen was popular for many years but can cause

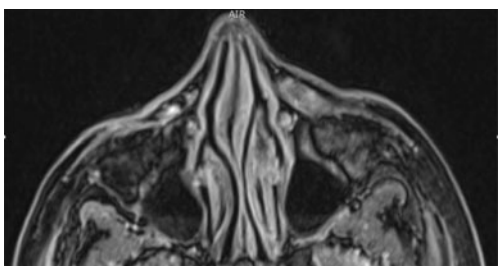

Fig. 2 T1 axial MRI showing left-sided diffuse lesion in the nasolabial fold

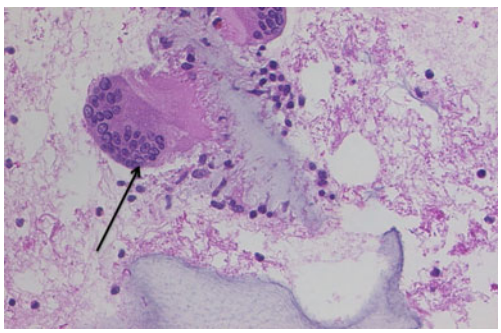

Fig. 3 Foreign body giant cells (*arrow*) and pale blue material corresponding to hyaluronic acid (cell block from FNA, H&E staining)

nonhypersensitivity necrosis or hypersensitivity reactions with antibovine antibodies. More recently, hyaluronic acid (HA) derivatives have gained widespread popularity. They not only have an immediate physical affect but also induce natural collagen production. Normally, age-related decreased production of collagen by fibroblasts occurs[3], resulting in loss of tissue bulk and elasticity. By providing a scaffold, HA fillers can stimulate collagen production and thereby strengthen and support the skin.

HA derivatives are polysaccharides naturally found throughout the body and in the cell coat of many strains of bacteria[4]. As a biodegradable filler, they are thought to be safer to use than nonbiodegradable fillers. When appropriately cross-linked with denser molecular structures, they have a lifespan of up to a year before being degraded by the body[5, 6]. Two different processes are available to obtain HA derivatives: extraction from cock's combs or by bacterial fermentation of specific strains of streptococci [7]. The synthetic HA filler is biocompatible, biodegradable, nonantigenic, nontoxic, and though long lasting, fully absorbable.

The perfect dermal filler should be safe, easy to use, cost-effective, adequately restore tissue contour, and have a low risk of complications [8]. Beyond this, patient factors such as autoimmune disorders, immunosuppressive therapy, and cosmetic factors, such as size and location of the defect, need to be borne in mind before choosing the appropriate interventional course. For a thorough overview of available fillers, the reader is referred to another publication [9].

Preoperative testing is encouraged with many dermal fillers. For example, bovine collagen has a 3 % patient sensitivity, and it is therefore recommended that two separate skin tests are preoperatively performed [10, 11]. Despite this, late reactions have still been reported [7]. Skin testing is not routinely performed with HA injections as it is thought to be less immunogenic [12].

When complications occurs, they can be categorized as immediate (allergy/hypersensitivity, anaphylaxis), early (swelling, erythema, infection), late (granuloma), or permanent (scarring) [13]. Transient redness, bruising, swelling, pain, and tenderness have been reported in 3–5 % of patients within 14 days of HA injections [6], but long term complications are rare [14, 15].

Granuloma development following HA injections has even been reported up to 4 years after injection in between 0.01 and 1.0 % of the patients [7, 16–18] [19, 20]. This despite the fact that the body in theory should have biodegraded the filler well before.

Microscopically, the foreign body granuloma consists of macrophages congregating in multinucleated giant cells attempting to phagocytose the filler. The resulting mass takes on an epithelial-like appearance and is often referred to as epithelioid. Lymphocytes surround the epithelioid mass and produce cytokines leading to chronic inflammation [12].

Unfortunately, it remains unclear what the risk factors and triggers for late granuloma are. One possibility is that an infectious agent, introduced at the time of injection, forms a relatively inert biofilm around the filler. At a later stage, a trigger such as surgery, trauma, or infection can lead to an acute inflammatory response [12, 21]. Though immediate hypersensitivity reactions to HA are rare, another possibility is a late hypersensitivity reaction [16]. Often, reactions can remain discrete despite extensive and bilateral initial injections. We can speculate that our patient's strong history of atopy might have played a role in her late reaction.

In terms of treatment options, spontaneous resolution has been observed but may take several months [17]. However, further progression, as in our case, can also occur. Furthermore, because often the granulomas are in particularly cosmetically sensitive areas, even small reactions can be very distressing for the patient. A variety of treatments are available, though with varying levels of evidence. Simple massage therapy may help to disperse the reaction and at least gives the patient the impression that they are taking action. Medications such as steroids can be used to suppress the immune reaction and both intralesional injections and systemic steroids have been used [16]. More exotic medications such as minocycline and imiquimod can modulate the immune response [16, 17], and even powerful immune suppressants such as cyclosporine [7] and tacrolimus [7, 11] have been reported. Surgery can be used on well-defined, excisable lesions when the resulting scar can be well disguised, for example in the nasolabial fold.

On a closing note, we would like to highlight that the regulatory background as to who can administer what fillers varies from country to country. Often, there is actually very little regulation. In the UK, the Medicine and Healthcare Products Regulatory Agency specifically has not licensed many products for general cosmetic procedures despite their widespread use. In the aftermath of recent PIP breast implant scandal, which resulted in thousands of women being scheduled for reoperation, this regulatory environment is certain to change. To what extent, a manufacturer is liable for the undesired affects of a product and what disclaimers should be included in the insert is also unclear. Furthermore, "who" is allowed to perform cosmetic procedures, in what setting, and what training they should have are also contentious. If cosmetic surgeons are not to fall into disrepute, it will be important for patients to trust their surgeon and some form of increased regulation is likely inevitable.

Conclusions

HA dermal fillers, while representing a major step forward from older preparations, are not risk free. Patients are often very aware of their appearance and are quick to notice small irregularities. The optimal treatment of late granulomas is

controversial though many surgeons advocate the use of steroids. We therefore recommend careful pretreatment counseling of patients with respect to this complication.

Conflict of interest None.

Patient consent Patients provided written consent for the use of their images.

References

1. Rohrich RJ (2000) The increasing popularity of cosmetic surgery procedures: a look at statistics in plastic surgery. Plast Reconstr Surg 106(6):1363–1365
2. Orton C (2002) Regulating cosmetic surgery. BMJ 324(7348):1229–1230
3. Christensen LH (2009) Host tissue interaction, fate, and risks of degradable and nondegradable gel fillers. Dermatol Surg 35(Suppl 2):1612–1619
4. Brown MB, Jones SA (2005) Hyaluronic acid: a unique topical vehicle for the localized delivery of drugs to the skin. J Eur Acad Dermatol Venereol 19(3):308–318
5. Kablik J, Monheit GD, Yu L, Chang G, Gershkovich J (2009) Comparative physical properties of hyaluronic acid dermal fillers. Dermatol Surg 35(Suppl 1):302–312
6. Duranti F, Salti G, Bovani B, Calandra M, Rosati ML (1998) Injectable hyaluronic acid gel for soft tissue augmentation. A clinical and histological study. Dermatol Surg 24(12):1317–1325
7. Requena L, Requena C, Christensen L, Zimmermann US, Kutzner H, Cerroni L (2011) Adverse reactions to injectable soft tissue fillers. J Am Acad Dermatol 64(1):1–34, quiz 35–6
8. Cockerham K, Hsu VJ (2009) Collagen-based dermal fillers: past, present, future. Facial Plast Surg 25(2):106–113
9. Ryssel H, Germann G, Koellensperger E (2012) An overview of current biomaterials in aesthetic soft tissue augmentation. Eur J Plast Surg 35(2):121–133
10. Bailey SH, Cohen JL, Kenkel JM (2011) Etiology, prevention, and treatment of dermal filler complications. Aesthet Surg J 31(1):110–121
11. Moody BR, Sengelmann RD (2001) Topical tacrolimus in the treatment of bovine collagen hypersensitivity. Dermatol Surg 27(9):789–791
12. Bentkover SH (2009) The biology of facial fillers. Facial Plast Surg 25(2):73–85
13. Bray D, Hopkins C, Roberts DN (2010) A review of dermal fillers in facial plastic surgery. Curr Opin Otolaryngol Head Neck Surg 18(4):295–302
14. Shafir R, Amir A, Gur E (2000) Long-term complications of facial injections with Restylane (injectable hyaluronic acid). Plast Reconstr Surg 106(5):1215–1216
15. Honig JF, Brink U, Korabiowska M (2003) Severe granulomatous allergic tissue reaction after hyaluronic acid injection in the treatment of facial lines and its surgical correction. J Craniofac Surg 14(2):197–200
16. Wolfram D, Tzankov A, Piza-Katzer H (2006) Surgery for foreign body reactions due to injectable fillers. Dermatology 213(4):300–304
17. Sanchis-Bielsa JM, Bagan JV, Poveda R, Salvador I (2009) Foreign body granulomatous reactions to cosmetic fillers: a clinical study of 15 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 108(2):237–241
18. Sclafani AP, Fagien S (2009) Treatment of injectable soft tissue filler complications. Dermatol Surg 35(Suppl 2):1672–1680
19. Al-Shraim M, Jaragh M, Geddie W (2007) Granulomatous reaction to injectable hyaluronic acid (Restylane) diagnosed by fine needle biopsy. J Clin Pathol 60(9):1060–1061
20. Bardazzi F, Ruffato A, Antonucci A, Balestri R, Tabanelli M (2007) Cutaneous granulomatous reaction to injectable hyaluronic acid gel: another case. J Dermatolog Treat 18(1):59–62
21. Monheit GD, Rohrich RJ (2009) The nature of long-term fillers and the risk of complications. Dermatol Surg 35(Suppl 2):1598–1604