# Delayed Superficial Migration of Retained Hyaluronic Acid Years Following Periocular Injection

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***Abstract:*** **Cosmetic injection of hyaluronic acid (HA) and other fillers is increasingly common, and the late complications of these relatively new procedures are now coming to medical attention. Three patients with delayed periocular swelling that began years after injection of HA are described, with CT, MRI, and histopathologic characterization. While HA fillers are marketed as having a temporary effect of several months, the authors demonstrate that they may persist in the body for up to 9 years. Unlike most previous reports, there was no inflammatory reaction or encapsulation, simply infiltration into more superficial subcutaneous layers. All cases improved after surgical biopsy and hyaluronidase injections. Delayed periocular swelling after filler injections from several years prior can mimic serious medical conditions. With a detailed history and high index of suspicion, one may avoid a costly and invasive workup.**

Non-animal hyaluronic acid (HA) has been used as a dermal filler for facial augmentation since 1996,[1] and while it is one of the safest filler options, complications still occur even several years after injection. There are many reports of late-onset granulomatous inflammation[2] and one case of encapsulation without inflammation.[3] Recently, Kopp et al.[4] described a delayed-onset Tyndall effect in 3 patients who had received multiple tear trough injections, suggesting superficial migration up to 5 years after last injection. Nathoo et al.[5] also described one case of likely HA migration 4 years after injection. The authors further characterize the clinical presentation of this late adverse effect with MRI, CT, histopathology, and clinical photographs of 3 patients with periocular swelling detected 3 to 8 years after injection of HA. All patient care and handling of patient information was performed in compliance with Health Insurance Portability and Accountability Act regulations.

## CASE 1

A 53-year-old man with medical history of hypertension and Lyme disease was referred for the evaluation of bilateral lower eyelid swelling and discoloration of 4 months duration (Fig. 1). There was a translucent appearance of the skin with marked transillumination in the affected area, but no pain, itching, or erythema; ophthalmologic examination was otherwise normal.

Accepted for publication January 17, 2015.

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Cosmetic hyaluronic acid injection: Delayed periocular edema as an uncommon complication. ASOPRS 45th Annual Fall Scientific Symposium, 2014, Chicago, IL, U.S.A.

The authors have no financial or conflicts of interest to disclose.

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**DOI: 10.1097/IOP.0000000000000434**

The patient was presumptively diagnosed with Graves ophthalmopathy. Laboratory studies were within normal limits (thyroid stimulating hormone 1.92 uIU/ml, free T4 0.92 ng/dl, thyroid stimulating immunoglobulin 25). His orbital ultrasound was interpreted as "suggestive" of thyroid eye disease. No improvement was seen with a trial of weekly intravenous methylprednisolone 250 mg for 6 weeks. He was then referred to the authors' service.

On closer questioning, the patient disclosed a history of Juvéderm (Allergan, Inc., Irvine, CA) injection to the glabellar region and possibly the lower eyelids 5 years prior. MRI showed hyperintensity in the subcutaneous tissue plane on T2 fat-suppressed images, consistent with HA (Fig. 1).[6] Surgical biopsy revealed copious gray gelatinous material just beneath the skin. Histopathology showed amorphous acellular material dissecting through the soft tissues, highlighted by colloidal iron and Alcian blue stains, consistent with HA. After surgical debulking, 2 injections of hyaluronidase (50 and 60 units) resolved the swelling.

## CASE 2

A 47-year-old woman with medical history of hypothyroidism, gastroesophageal reflux, and depression presented with 1 year of chronic bilateral periorbital swelling (Fig. 2). She had cosmetic Restylane (Medicis Aesthetics Inc., Scottsdale, AZ) injection 4 years prior. Ophthalmologic examination was otherwise normal. MRI showed hyperintensity in fat-suppressed T2-weighted images limited to the subcutaneous plane. On surgical exploration, similar gelatinous material was excised (Fig. 2). Histopathology demonstrated amorphous, acellular gray material infiltrating the muscle fibers without any signs of inflammation. This material stained with colloidal iron and Alcian blue, consistent with retained HA. Surgical debulking followed by hyaluronidase injections resulted in a satisfactory cosmetic result.

## CASE 3

A 39-year-old woman with medical history of idiopathic alopecia and endometriosis presented with 1 year of periocular swelling (Fig. 3) and an otherwise normal examination. She had Restylane injections to the cheeks and eyelids 9 years prior. CT showed homogeneous soft tissue density material in the subcutaneous tissue plane. Surgical biopsy revealed gray amorphous material infiltrating the muscle and subcutaneous tissue without inflammation. This material stained with mucicarmine, consistent with HA. Injection with hyaluronidase resolved the swelling.

## DISCUSSION

HA gels such as Juvéderm and Restylane are commonly used materials for facial volume augmentation. Both products are marketed as having a temporary effect. There have been rare reports of persistence of HA. In 1 report, HA was found 6 years after injection.[5] Foreign body inflammatory reactions have been described as long as 7 years after injection.[2] One case of encapsulation without inflammation has been reported.[3] Most similar to the authors' cases, delayed superficial migration has been described in patients up to 6 years after injection.[4,5]

The authors describe 3 patients with periocular swelling that developed years after cosmetic HA injection. Such remote onset of symptoms made diagnosis difficult without biopsy. On pathology, the HA was seen to have infiltrated

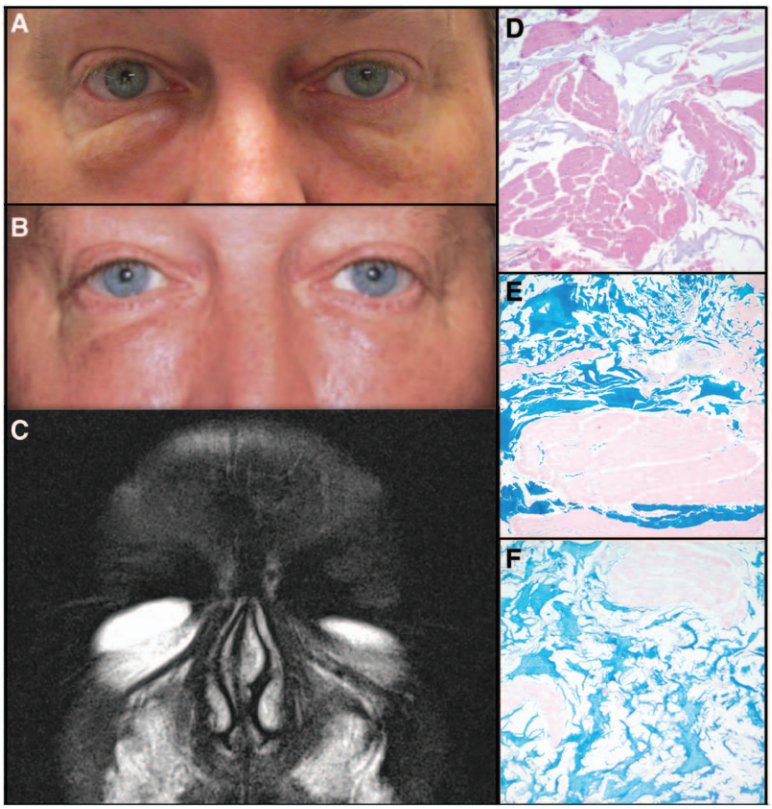


**FIG. 1.** **A**, Initial presentation; (**B**) after surgical biopsy and first injection of hyaluronidase; (**C**) MRI coronal fat-suppressed T2-weighted image; (**D**) ×100 magnification image of hematoxylin and eosin stain of the biopsy sample shows gray amorphous acellular material; hyaluronic acid is highlighted by colloidal iron at ×40 (**E**) and Alcian blue at ×100 magnification (**F**).

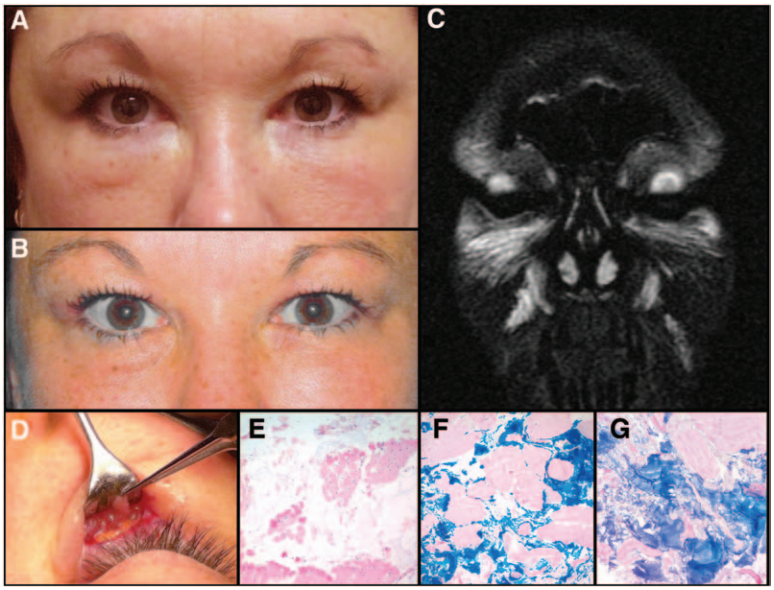


**FIG. 2.** **A**, Initial presentation; (**B**) after surgical biopsy and injection of hyaluronidase; (**C**) MRI coronal fat-suppressed T2-weighted image; (**D**) intraoperative appearance of gray gelatinous material just below the skin; (**E**) ×100 magnification image of hematoxylin and eosin stain of the biopsy sample shows gray amorphous acellular material; hyaluronic acid is highlighted by colloidal iron at ×40 (**F**) and Alcian blue at ×100 magnification (**G**).


**FIG. 3.** **A**, Initial presentation; (**B**) coronal CT shows soft tissue density material extending from cheek to inferior periorbital region.

superficial tissues, without accompanying inflammation. This clinical presentation likely results from filler migration. Other possibilities include improper injection technique, delayed edema related to filler breakdown products, or the presence of contaminants.[1,5]

In summary, the authors present the most comprehensive series to date of retained HA which appeared to migrate, infiltrating superficial tissue in the periocular region. Awareness of this potential complication is important to avoid a delay in diagnosis and unnecessary testing.

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