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Mini review

Granulomatous reaction to hyaluronic acid dermal filler: clinical and histological features

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Abstract. The use of soft tissue fillers has greatly increased in the past years; indeed, it is now one of the most frequent non-surgical cosmetic procedures performed all over the world. Due to its safety profile, hyaluronic acid is the most injected substance. Although the use of hyaluronic acid in aesthetic medicine is safe, as any other medical procedure it carries its own risk of developing complications and adverse effects. The aim of this article is to focus on one specific complication: the granulomatous foreign body reaction. This mini review summarizes clinical and histological features of the granulomatous foreign body reaction in hyaluronic acid fillers.

Keywords: Granuloma, filler, hyaluronic acid, histology

Introduction to Hyaluronic Acid filler

The use of Soft Tissue fillers (STF) has greatly increased in the past years, becoming one of the most performed non-surgical cosmetic procedures all over the world. STFs are used to treat many aesthetic blemishes such as volume deficiency, rhytids and face contouring.

Nowadays various types of STF are available on the market, each having different properties and being made from different substances (autologous or heterologous). There is only one "permanent" (long-lasting) filler substance approved by FDA and EMA, the polymethylmethacrylate (or PMMA); while numerous non-permanent fillers are permitted including collagen, hyaluronic acid, poly-L-lactic acid, and calcium hydroxyapatite[1].

Hyaluronic acid (HA), approved by FDA in 2003[2] , is the most widely used cosmetic substance[3]. HA is a common glycosaminoglycan present in different connective tissues, especially in the dermis, where it provides hydration and volume. The HA used for filler maintains the same biocompatibility and biological activity as the human HA, although it has more molecular binding (cross-link) between different molecules. This different structure enhances its biomechanical properties[4], resulting in increased density and duration of the filler over time, ranging from 3 to 12 months[5], as more molecules become cross-linked.

Its safety profile is the reason why this type of injectable filler is the most used by aesthetic doctors. Indeed, HA has a very high level of biocompatibility and, if needed, it can be easily metabolized within a few minutes by injecting hyaluronidase enzymes in the same area as the STF[6].

Dermal filler adverse effects

Although the use of HA in STF is safe, like any other medical procedure it also carries the risk of developing complications and adverse effects (AEs). Most of the time complications are mild and temporary due to reactions at the site of injection and they resolve in few hours/days without treatment[7]. However, severe and long-lasting complications may also occur. The risk of developing AEs to fillers depends on many factors such as the procedure site, the type of substance injected and its duration. The risk lasts as long as the

filler remains in the tissue, indeed the permanent ones may develop complications over a longer period than the others and often require more complex treatment[8].

AEs can be classified according to different aspects, such as severity (mild, moderate or severe), pathologic mechanism (ischaemic and not-ischaemic) or time of onset. Two main time-based classifications of AEs to STF have been proposed. The first classification, proposed by Rohrich et al in 2009[9], distinguishes complication into early, late, and delayed with an onset time of 14 days, 14 days to 1 year and more than one year, respectively. The second, proposed by Urdiales-Gálvez et al in 2018[10], classifies complication into immediate onset (up to 24h after procedure), early onset (24h to 4 weeks after the procedure) and delayed onset (more the 4 weeks after the procedure). Although there are not so many data available on the true incidence of the AEs to STF, it seems that most of them are injection related effects[2,11]. A meta-analysis from 2021 including 1,488 participants overall revealed that among AEs the most common are tenderness (88,7%), injection site swelling (74,3%), contusion (48,7%), injection site mass (27,3%), site pain (19,7%), erythema (7,3%) and Tyndall effect/discolouration (5,7%)[11]. Luckily, other more severe and dangerous AEs such as granulomatous foreign body reactions (0,6%), paraesthesia (0,6%), herpes labialis (0,6%), angioedema (0,3%) or anaesthesia (0,1%)[11] are very infrequent or rare. Moreover, during the Covid-19 Pandemic period, some patients developed AEs (swelling, oedema, granuloma...) after getting infected by the virus or after being vaccinated. It has been hypothesized that the Covid-19 causing a protein spike may evoke a delayed type IV hypersensitivity reaction to HA filler[12].

Histology of HA filler in the skin

The presence of STF in cutaneous biopsy is easy to identify, although different injected substances have different histological appearances. In the case of HA fillers, it appears as a single compact large nodule or multiple small fragments of a homogeneous hyaline gel-like material, surrounded by the collagen mesh and the connective structures of the dermis or the superficial subcutaneous fat. Multiple stains could be used to identify the presence of the HA deposit. The first and most common stain used to evaluate a cutaneous biopsy is hematoxylin-eosin (HE), in which the HA shows a grey/pale-blue colour (Figure 1 A-B). Although it's not mandatory for diagnosis, the use of

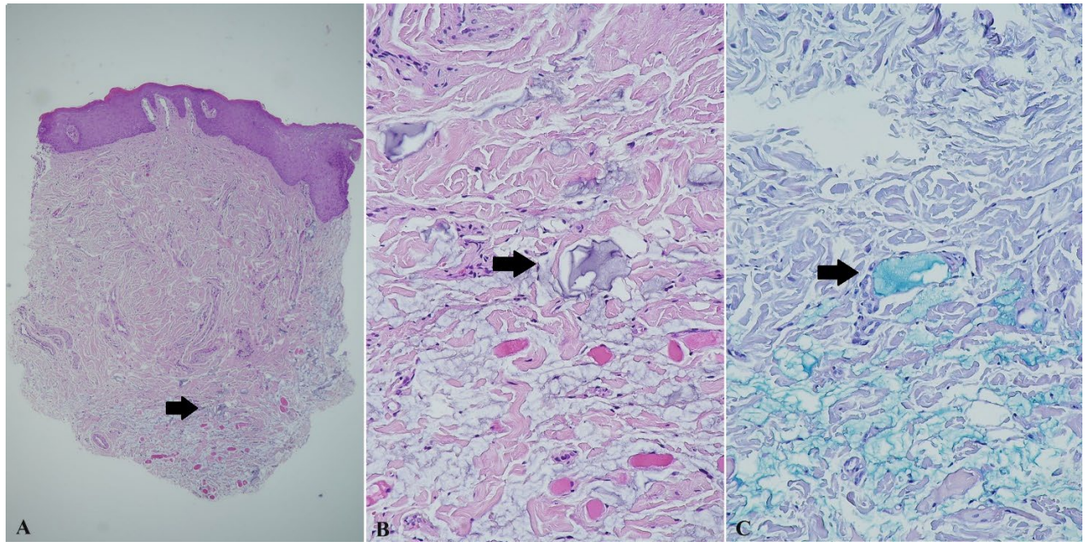

Figure 1. Cutaneous biopsy showing a homogeneous hyaline nodule in the dermis (arrow). A: HE staining 4x; B: same biopsy HE staining 20x; C: same biopsy Alcian-Blue staining 20x.

Alcian-Blue and colloidal iron stains helps to better identify and confirm the presence of HA, which shows a brighter blue/green-blue colour (Figure 1 C).

The HA is physiologically broken down enzymatically and metabolized by the immune system of the organism within 3 to 12 months[5], so the presence of some lymphocytes and some macrophages around the material should not be considered pathological.

Granulomatous foreign body reaction

Granulomatous foreign body reaction (GR) is a common response of the human immune system to a foreign body or to a pathogen (bacteria, parasites, or fungi) that cannot be metabolized by usual mechanisms. Moreover, GR is also associated with the presence of many other inflammatory and autoimmune diseases (such as sarcoidosis or Crohn's disease). The presence of a persistent antigen and/or chronic inflammation causes the release of many cytokines by the immune system's cells, especially lymphocytes T. All these cells and cytokines attract and over-activate macrophages, which fuse together to form the "Multinucleated Giant Cells" (MGC) that characterized the GR[13]. The most used classification, proposed by Adams in 1976[14], distinguishes the granulomas according to structure and composition into three different categories: epithelioid, necrotic, or complex (if different types of cells are present).

The injection of any foreign substance, including STF, causes an initial collagen deposition and inflammatory response that could result in GR in some patients. As seen above, although GR represents only 0,6% of all the AEs to STF, it is one of the most common among the delay-onset ones[11] and sometimes develops more serious consequences, such as pain and superinfection. Unsurprisingly, GR seems to be more frequent using long-lasting substances compared to the re-absorbable ones[5].

Sometimes other infections (such as the flu or gastroenteritis) or some drugs (especially IFN-therapy) may trigger GR to STF[15,16].

Although someone has suggested that the contamination of the STF could be a reason for hypersensitivity and chronic inflammation[17], the causes for GR development have not been fully understood yet. For this reason, it is not possible to predict which patients will develop GR and decide which of them is better not to treat.

Usually, GR to STF appears in the same site of the injection from 6 to 24 months after the cosmetic treatment, but can also occur many years later[18]. Moreover, some patients develop GR at the first STF procedure, while some others after a subsequent injection; this fact, and the presence of an unknown or unclear aesthetic medicine anamnesis could complicate the diagnosis.

The GR has typical signs and symptoms prompting an easy clinical diagnosis. When the inflammatory response begins, the site of injection initially increases in size and skin redness due to the oedema and erythema of the area; these symptoms are usually accompanied by an uncomfortable tension and occasional suppuration. After this initial phase, it results in a painless, undefined, and rather soft nodule/lump clinically appreciable that *can increase or maintain the same size until a spontaneous resolution after some years*. In patients who have undergone multiple STF procedures, one or more injection sites could be affected by this process.

However, the distinction between GR and the nodular STF deposit is not always easy to make. In all these cases imaging procedures, especially high-frequency ultrasounds, could support the diagnosis. Indeed, GR appears as an oval shape with blurred irregular outer edges and a small hyperechoic area inside, while nodular STF deposits are hypo-anechogenic with sharp and regular borders[19] .

The treatment and management of GR to STF is well described in literature and changes according to the substance used and to the presence of superinfection[8,15,20]. In case of active cellulitis or concurrent infection, all the treatments should be performed 24-48 hours after the use of antibiotics to not spread the infection to other areas[15]. The best treatment for GR is the intralesional injection of corticosteroid, which usually resolves the AE in a few days/weeks; if the lesion is unresponsive to that, it is recommended to intake antimitotic drugs (such as 5-FU). In case of GR due to HA it is also possible to use a hyaluronidase injection

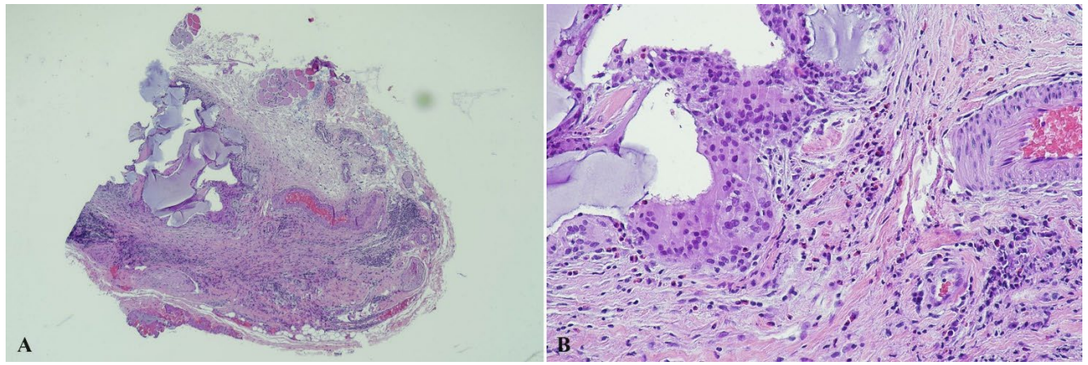

Figure 2. Cutaneous biopsy showing *a homogeneous hyaline nodule in the dermis surrounded by inflammatory infiltrate with MGC and eosinophils. A: HE staining 4x; B: same biopsy HE staining 20x*

as treatment, as it accelerates the resolution of the granuloma by cleaving the HA molecules[21]. The combination of these treatments is rarely not sufficient to resolve the GR and therefore in which case it becomes necessary to remove the STF with more invasive procedures such as surgical excision or intralesional diode laser[15,22].

Histology of GR

Histologically it is possible to observe the presence of both the STF and the inflammatory infiltrate that characterize the GR. As in "normal" STF histology the HA maintains its homogenous hyaline gel-like appearance, but most of the time it is divided into many different fragments rather than being a single nodule. Around the foreign material there is a moderate inflammatory infiltrate composed of lymphocytes, plasma cells, neutrophils, eosinophils, and macrophages; the latter fuse together to form the MGC (Figure 2 A-B).

MGC exhibit distinctive cytological features that made them easily recognizable by pathologists. MGC are very large cells with irregular borders, multiple nuclei, abundant and often granular cytoplasm in which, sometimes, it's possible to observe vacuoles or phagocytised material (such as asteroid bodies in polycaprolactone filler[23]). Although unnecessary, the identification of MGC can also be confirmed by the positivity of these cells to CD68 immunohistochemical staining. In case of the presence of necrosis, uncommon in GR to STF, it is recommended to perform Ziehl-Neelsen, PAS and Grocott stains to exclude an infective process. In case of long-lasting inflammation, it is also possible to observe a stromal reaction with the proliferation of fibroblasts and the deposition of fibrous tissue.

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