INTRODUCTION

Injectable hyaluronic acid derivatives are the most used re-absorbable dermal fillers for soft tissue augmentation and volume expansion as they provide a nonsurgical alternative procedure for the temporary correction of age-related skin defects (facial rejuvenation), postsurgical, and post-traumatic skin facial alterations, increasing of the lip volume. Their utilization is considered overall safe and well tolerable because of biocompatibility and biodegradability of hyaluronic acid, with minimal adverse events secondary to the intradermic injection. Nevertheless, late or early adverse reactions may occur although with an incidence ranging from 0.02% to 0.4%. We report on a female patient showing a delayed onset (10 years later) of a sclerosing granulomatous reaction due to the intradermal filler (poly-hydroxyethyl-methacrylate suspended in hyaluronic acid) injection for lip augmentation, with histochemical and confocal laser scanning microscopical analysis of the lesion.

Abstract
Re-absorbable dermal fillers of poly-hydroxyethyl-methacrylate suspended in hyaluronic acid are considered overall safe and well tolerable because of biocompatibility; nevertheless, rarely, late, or early adverse reactions may occur.

KEYWORDS
delayed granuloma, dermal filler, foreign body reaction, hyaluronic acid, sclerosing granuloma
are consistent with previous injection of HA + HEMA, and the prolonged time interval from injection to clinical manifestations indicates the adverse reaction was slowly progressive. Also, it was postulated that macrophages would incorporate foreign particles, thus keeping the foreign particles in a latent stage. Subsequently, additional priming events (eg, supervening infections) would be needed to re-activate macrophages, lead to multinucleated giant cell accumulation, and, finally, to fully developed granulomatous reaction.\textsuperscript{6,8,10,12-14} Such pathogenetic mechanism may explain the prolonged course of the disease, with only late development of clinically detectable nodular lesions.

## 2 | CASE REPORT

The patient, a 50-year-old woman, had undergone filler injection for lip augmentation 10 years earlier. She presented a slowly growing nodular lesion (Figure 1) of the right lower hemi-lip of hard consistency, not ulcerated, painless, and without signs of infection. With the provisional clinical diagnosis of benign nodular lesion, surgical excision was performed followed by histologic examination. The nodular lesion (Figure 2A) was mainly composed of many clear polygonal spaces, surrounded by fibrous collagen, small lymphocytes, macrophages with occasional cytoplasmic clearing, and sparse multinucleated giant cells (Figure 2B), pointing at long-standing FBG. The polygonal spaces were 20-120 µm in size and partly filled with translucent particles, with a broken-glass appearance (Figure 2C). Histochemical stains (Alcian, Giemsa, May–Grunwald–Giemsa, Grocott) and confocal laser scanning microscopical analysis were performed in order to better characterize the morphological features of the foreign material. With Alcian Blue stain (Figure 3A), the material filling the polygonal spaces was stained in light blue and appeared irregularly condensed toward the center, leaving an empty-looking space at the periphery. Giemsa and May–Grunwald–Giemsa (Figure 3B,C) stains highlighted a homogeneous, centrally placed component, which was deeply stained in blue, which appeared encircled, in most instances, by unstained or light brown, granular to crystalline material. The Grocott stain only showed very light purplish discoloration of the acellular material, centrally placed in the lacunae (Figure 3D). By confocal laser scanning microscopy, we could detect (Figure 4A) more intense autofluorescence of the peripheral content of the lacunae, which progressively vanished toward the center, with a sort of onion-skin pattern. The most intensely autofluorescent material more or less corresponded to crystalline-like material demonstrated by the Giemsa stain (Figure 4B).

## 3 | DISCUSSION

Hyaluronic acid (HA) fillers in cosmetic medicine are widely used and considered relatively safe, though not all the fillers used in European countries and throughout the world have been approved by the Regulatory Agencies.\textsuperscript{2,5,6,15,16} Nevertheless, a wide range of medical compounds has been authorized as fillers for HA injections.\textsuperscript{8,9,16,17} Despite the obvious cosmetic benefits allowed by such fillers, a wide range of possible complications, such as immediate, late, delayed, temporary, or irreversible inflammatory reactions, has been reported in the literature.\textsuperscript{1,5,11}

Filler adverse effects can be classified according to the technical procedure, onset (early or late), filler type, and host factors.\textsuperscript{6,11} Technical errors may be due to too much or too little volume injection, incorrect depth or wrong localization of filler placement, and inappropriate product choice, the latter possibly being the most relevant topic. In fact, fillers are usually divided into reversible and irreversible; in the first group are included early or temporary fillers (collagens and hyaluronic acid), late or long-term (HA with dextranomer beads, poly-L-lactic acid [PLL] and calcium hydroxylapatite), and delayed or permanent fillers (paraffin, silicon preparations, polymethyl methacrylate microspheres, hydroxyethyl-methacrylate fragments, polyalkylimide gel, polyacrylamide hydrogel, polyvinyl hydroxide microspheres in polyacrylamide gel).\textsuperscript{10,13,15} Although it is generally accepted that temporary fillers are better tolerated than permanent ones, the frequency of short-term adverse reactions is similar because filler into tissues is perceived as a foreign substance, with an initial challenge to the host's immune system and with possible early complications (erythema, edema, and allergy) in less than 2 weeks.\textsuperscript{10,15}
It is generally accepted that HA (crosslinked or not) induced erythema and swelling few days after injection, as resulting from the little foreign body reaction observable on the histologic examination; the blue-stained hyaluronic acid is slowly degraded by macrophages and invading capillaries at the circumference of the HA implant in the following 30-60 days; this process goes along with a slower resorption for the cross-linked HA fillers, but generally with a gradual and scarce inflammatory infiltrate, absence or little deposition of structures resembling new collagen fibers at 3-4 months, while clusters of macrophages and giant cells are detectable also after 4-6 months. Overall, no residue of HA is usually identifiable at 6-9 months.8-11

Bumps and lumps following superficial filler placement usually are visible immediately after the injection or shortly thereafter, while necrosis due to intra-arterial injection becomes evident within a day.13

Late complications, instead, may develop over weeks, months, or even years after the injection and may include diffuse chronic inflammation, nodular outgrowth (usually granulomas), late allergic reactions, hypertrophic scars, and telangiectasia.4,5,12 In such instances, patients usually are unable to properly recall which kind of filler was injected. HA preparations with a longevity of approximately 6 months (with highly variable molecular weight and cross-linking properties) are the most commonly used fillers and considered the safest in view of HA being universally present in all animal species, its non-species specificity, free from foreign proteins, with very low propensity to adverse effects in good filler preparations by well-reputed manufacturers.

**FIGURE 2** A-C, Histologic examination showing several clear polygonal spaces surrounded by fibrous collagen, small lymphocytes, macrophages with occasional cytoplasmic clearing, and sparse multinucleated giant cells (A, H&E, original magnification x2) (B, H&E, original magnification x10); the polygonal spaces were 20-120 µm in size and partly filled with translucent particles, with a broken-glass appearance (C, H&E, original magnification x20)

**FIGURE 3** A-D, Alcian Blue stain (A, original magnification x20) showing a light blue coloration of the filling material, irregularly condensed toward the center, leaving an empty-looking space at the periphery. Giemsa (B, original magnification x20) and May–Grunwald–Giemsa (C, original magnification x20) stains highlighting a homogeneous, centrally placed component deeply stained in blue, appearing encircled in most instances, by unstained or light brown, granular to crystalline material. Grocott stain (D) showing a very light purplish discolouration of the acellular material centrally in the lacunae
Indeed, many complications can occur, like in the current case, when using long-term filler reinforced with hydroxyethyl-methacrylate fragments, and they usually are represented by late granuloma formations.\textsuperscript{10,11} The results of previous histologic studies on tissues examined over the first few months after injection of these reinforced fillers appear promising, having shown the hydrophilic polygonal, translucent, not birefringent particles were surrounded by normal tissues, in the absence of inflammatory reactions, thus appearing fully biocompatible products.\textsuperscript{1,10,13,18,19} The HA carriers were included in empty lacunae within the first days after the injection.\textsuperscript{8,10} In cases in which granulomatous reactions developed, inflammatory lymphocytic infiltrates, foreign body giant cells, sometimes containing asteroid bodies, and increased fibrillary collagen accumulation usually appeared suddenly.\textsuperscript{8,10,17-19}

Many possible causes may lead to early and late granuloma formation, such as the volume of injected dermal fillers, impurities within the filler substance with biofilm formation, local infection unrelated to the filler site, and severe systemic infections with subsequent immunologic alterations.\textsuperscript{6,8,12} Surely, the presence of impurities may facilitate late granuloma formation, especially when including particles <20 \textmu m in size, as phagocytosis and immunologic memory are more efficiently stimulated by smaller particles than by larger ones.\textsuperscript{9,10,13,14} Furthermore, irregularities of the particle surface, with pointed edges and corners, seem to further stimulate late granuloma formation.\textsuperscript{7,8,10,11,17,18}

In conclusion, clinicians should be aware that adverse reactions to fillers should be expected, especially when stabilizers or carriers are suspended in HA; therefore, prolonged follow-up of the patients should be carried out, to possibly detect such events at early stages.

**CONFLICT OF INTEREST**

Authors declare no conflict of interest.

**AUTHORS CONTRIBUTION**

SC: involved in surgical procedure and confocal laser scanning examination. PS: involved in surgical procedure. LL: prepared the manuscript. FD: prepared the manuscript and reviewed the literature. AT: corrected the manuscript. GF: involved in surgical procedure and review of the manuscript. EM: involved in histologic examination and review of the manuscript.

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