

Foreign Body Reaction to Injectable Hyaluronic Acid: Late Granuloma Formation

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Dear Editor:

Injectable hyaluronic acid (HA) derivatives are widely used as soft tissue fillers for facial rejuvenation. Because of the biocompatibility and biodegradability of HA, adverse events secondary to this application are minimal. Nevertheless, we report a rare case of a long-term adverse event following the injection of a non-animal-sourced HA derivative. A 21-year-old female presented at our clinic complaining of a 0.5 cm-sized, soft, fixed nodule on the right side of the dorsum of the nose (Fig. 1A, B). The patient had been injected with a HA filler Restylane (Q-Med AB, Uppsala, Sweden) once in this region two years previously, and about 10 months later an asymptomatic nodule had gradually developed. A diagnostic 3-mm punch biopsy was performed, and whitish gelatinous material was drained. A bacterial culture of the drainage or the tissue was not performed. The histological examination revealed inflammatory cell infiltrations with foreign body giant cells, macrophages, and lymphocytes with fibrotic change in the deep dermis surrounding scattered bluish material (Fig. 2A). Alcian blue staining (pH 2.7) strongly stained the formless substance (Fig. 2B). A Gram stain of the paraffin-embedded tissue block was negative. The size of the nodule was markedly reduced after biopsy, and no further management was necessary.

Received August 29, 2013, Revised June 19, 2014, Accepted for publication June 23, 2014

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Although HA derivatives are considered to be well tolerated, very few cases of delayed adverse effects have been observed. There are several theories for the etiology of this reaction. First, impurities in the bacterial fermentation may lead to hypersensitivity responses. This type of reaction, which is plausible in a patient with repeated filler injections, is confirmed by intradermal injection or circulating antibodies of HA¹. Second, others suggest that disintegration of the cross-linked product may provoke an inflammatory response². Third, recent studies propose that concomitant bacterial inoculation during the filler injection may cause late granuloma formation. In most cases, bacterial infections become clinically apparent within several days after HA injection. However, biofilms consisting of bacteria, their nutrients, and wastes on the surface of foreign bodies enable persistent minimal infection with little host response, and they become symptomatic months or even years after³. Foreign body reactions to biofilm rather than to pathogenic bacteria may produce delayed granuloma formation. Recent polymerase chain reaction (PCR)-based studies have shown that nonpathogenic species that are not usually detected by bacterial culture are responsible for biofilm formation⁴. In addition, Bjarnsholt et al.⁵ demonstrated biofilms from culture-negative long-lasting nodules formed after the injection of a polyacrylamide gel using the fluorescence *in situ* hybridization (FISH) technique.

Although we do not have evidence such as PCR or FISH data to prove the existence of biofilm, we assume that 10 months of an asymptomatic period after the injection and no history of prophylactic antibiotics therapy provide the possibility of biofilm formation as the underlying pathogenesis.

We report on a delayed granulomatous response after HA injection, which is unique with regard to the time of presentation. We recommend that practitioners consider

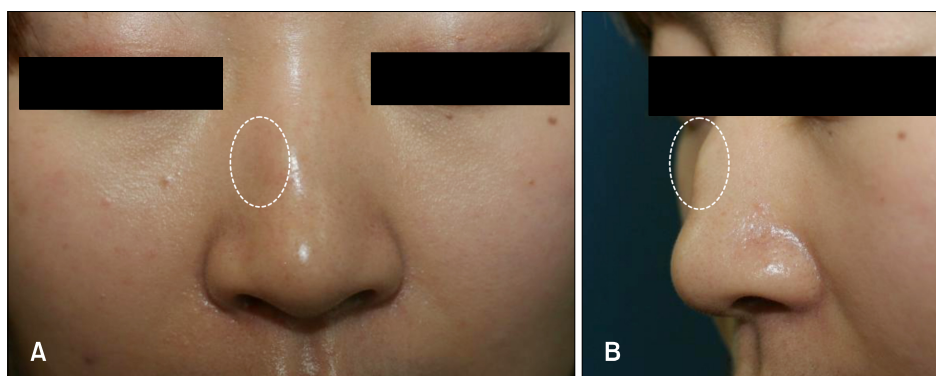


Fig. 1. A slightly erythematous nodule covered by intact skin on the dorsum of the nose. (A) Frontal and (B) side view.

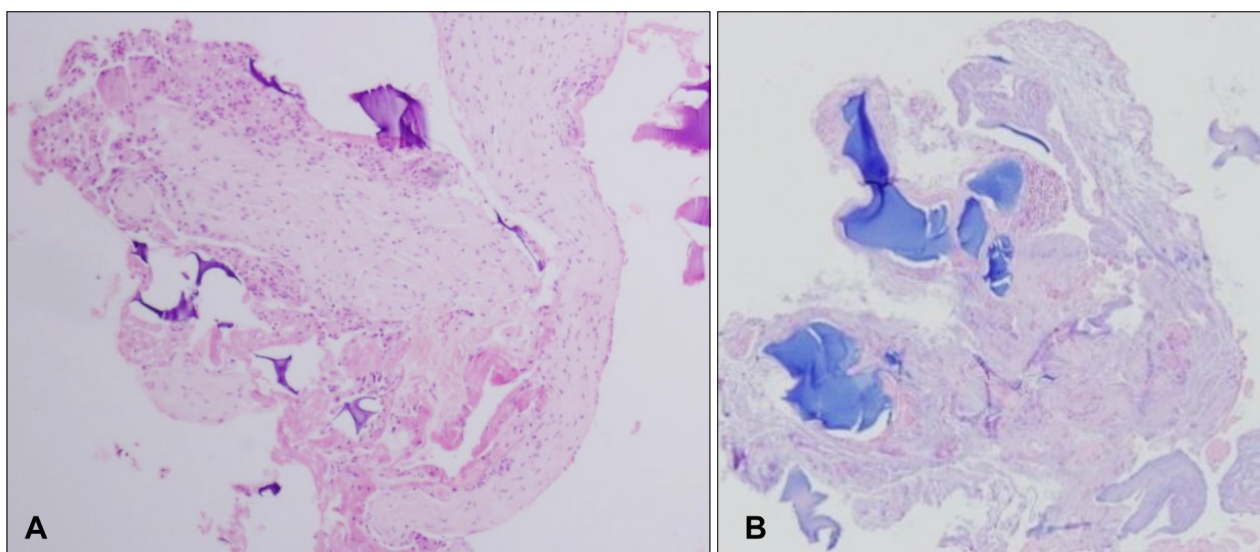


Fig. 2. (A) A 3-mm punch biopsy shows amorphous material surrounded by fibrotic tissue with inflammatory cell infiltration (H&E, $\times 40$). (B) An intensely blue staining substance within the granuloma (Alcian blue at pH 2.7, $\times 40$).

potential complications when using an HA filler and investigate the underlying cause of reactions by using appropriate tools.

ACKNOWLEDGMENT

The authors wish to acknowledge the financial support received from the Gachon University, Graduate School of Medicine and the Gil Hospital Research Foundation.

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