



Foreign Body Granuloma Formation after Dermal Fillers – A Review & Comparison of Literature

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Abstract

Hyaluronic acid based dermal filler injections to correct skin deformities, volume loss, facelift and counteracting is a common practice in aesthetic medicine. (1) although these fillers are considered safe because of their biodegradability but advanced reactions can occur. (2) Here, we discuss and compare a rare case of foreign body granulomas formation in the parotid and submandibular region presented as painful subcutaneous nodules, following injection of hyaluronic acid performed 1 year ago for strengthening of jawline. A review of 16 publications in literature presenting with similar presentation or formation of granulomas after filler injection, who underwent a biopsy for confirmation, was conducted to determine the diagnosis, presentation and management of the nodule after derma filler injections.

Introduction:

Dermal fillers are gel like substances mostly hyaluronic acid, calcium Hydroxyl apatite (CaHA) or Poly-L- lactic acid that are injected beneath the skin to restore the lost volume, smoothen lines and soften creases, or enhance facial contouring. (3) Among them the most widely used filler is hyaluronic acid based fillers. Dermal fillers are gaining in popularity and frequently use to treat aging skin. Although, a large variety of fillers is present in the market to achieve satisfactory results if injected with accuracy and guidelines, however adverse reactions can also be observed and complications can happen. (4) All dermal fillers carry a risk of adverse reactions ranging from transient reactions like erythema, redness, swelling, bruising and inflammation that disappear after a short time to vascular occlusion, chronic inflammation and infection, filler migration and foreign body granulomas that are challenges for the physicians. (5)(6).

Methods & Materials:

An Extensive manual literature search was performed to review the complications that can happen with dermal fillers. Specifically, the occurrence of foreign body granuloma after dermal fillers.

A complete review of articles published upto 2022 on pubmed, Science direct, Embase, Google Scholar, Cochrane database and Medline database was conducted to correctly describe the proposed mechanism of actions, the factors involved in Granuloma formations, its presentation and correct treatment options. The initial search for filler- related nodules or granulomas yielded 2,955 articles and 16 cases with complete case reporting in which the confirmation was made with histopathological examination were manually searched for other potential eligible studies.

Cases/ Reference	Age/ Sex	Age of FBGF	Presentation	Filler type/Years	Histopathological findings	Treatment
1 (11)	80/F	Oral (left side of the lower lip)	Circumscribed, pendunculated, painless soft nodule was noted on the left side of the lowerlip	Hyaluronic Acid 1.5 years ago	Amorphous eosinophilic material, interspersed in a fibrous connective tissue strome. (Granulomatous)	Excisional Biopsy
2 (11)	48/F	Oral/upper lip	Well- defined submucosal firm nodule on the upper lip, painless and soft on palpation	Hyaluronic Acid 6 months	Pools of amorphous basophilic material compatible with hyaluronic acid that were surrounded by epithelioid macrophages and mild lymphocytic inflammation.	Excision
3 (12)	69/F	Parotid Cheeks/	2 mm nodule in the right superficial parotid mass was palpable and approximately 0.5cm	Hyaluronic acid or polyacrylamide gel Patient not sure many years ago	Epithelioid histiocytic and gaint cell reaction of amorphous, non polarizable foreign material (0.5 cm) involving per parotid soft tissue	Excision

4 (13)	56/F	Glabella/ nasolabial Fold	Indurated mobile mass	Silicone on findings/ patient informed it was hyaluronic acid 5 years	Granulomatous finings suggestive of silicone based filler	Intralesional steroid injection followed by excision
5 (14)	62/F	Oral upper lip	Well-defined submucosal firm nodule on the upper lip	Hyaluronic acid Polylactic acid Many years ago	Granulomatous finings suggestive of HA based filler	Intra lesional steroid injection followed by antibiotics.
6 (15)	68/ F	Cheeks	Nodules accompanied by bluisn skin discoloration	Polycaprolactone based dermal filler (PCL) 1 year back	Amorphous eosinophilic material, interspersed in a fibrous connective tissue stroma (Granulomatous)	Steroids followed by antibiotics
7 (16)	52/F	Oral upper lip	Well defined submucosal firm nodule on the upper lip	Not known 2 year	Granulomatous finings suggestive of HA based filler	Excision
8 (17)	54/F	Oral Upper lip	Well-defined submucosal firm nodule on the upper lip	Hyaluronic acid 1 year	Amorphous eosinophilic material with multinucleated cells suggestive of granuloma due to fillers	Excision
9 (18)	48/F	Oral/Upper lip	Erythematous nodules painless on the upper lip	Hyaluronic acid 2 Years	Granulomatous finings suggestive of HA Based filler	Oral Steroids
10 (19)	47/F	Cheeks / Nasolabial folds	Painful well circumscribed nodules on cheeks and NLF	Hyaluronic acid 1.5 years	Granulomatous finings suggestive of HA Based filler	Antibiotics Nsaids oral prednisolone + Hydroxy chloroquin
11 (20)	23/F	Oral/ Lower lips	Erythematous painful firm nodule on lower lip	N/A 3 years	Epitheloid histiocytic and gaint cell reaction of amorphous, non	Hyalauronidase steroids and antibiotics

					polarizable foreign material shown	
12 (21)	65/F	Oral (upper lip)	Painless nodules on upper lips	Hyaluronic Acid 1 year	Granulomatous findings suggestive of HA based filler	HD dase oral steroids
13 (22)	70/F	Arms	Multiple subcutaneous painless firm nodules	Hyaluronic acid 6 years	Amorphous bluish material Alcian positive PAS, Cocsistent with HA within granuloma	Oral Prednisone
14 (22)	58/F	Cheek/Glabella infatemporal region	Erythematous painful skin lesion on right side of face	Hyaluronic Acid 2 years	Diffuse infalmmatory cells infiltration, predominantly lymphocytes, swiss cheese appearance suggestive of FBG	Hyaluronidase intralesional & oral Antibiotics
15 (23)	40/F	Nasolabial Fold	Dusty red Firm rash	Hyaluronic Acid Acrylic hydrogel 4 months	Multiple small fragments within cystic spaces refractive material of gaint cells histiocytic fibrosis clacification	Antibiotics oral steroids
16 (24)	66/F	NLF Chin Upper lip	Purplish hard lumps & Plaques	Hyaluronic Acid 5 years	Granulomatous inflammation with gaint cells epithelios histocytic & with pink fragments of foreign body.	Responded poorly to treatment

Case Analysis:

A 26 years old otherwise healthy Arab women presented with history of tenderness and swelling in her jawline, complaining about multiple subcutaneous lumps in her jawline that has been presented for almost 1 month.

On physical examination, multiple small to large firm, round to symmetrical nodules were noticed in the parotid & Submandibular area on Palpation. The nodules were tender, firm in consistency and not fixed. She exhibited neither lymphadenopathy nor fever. Her medical history was unremarkable. In the same area, she had a history of taking 5 ml of hyaluronic acid based filler for straightish for her jawline 1 year ago that had been injected by a physician in a private medical clinic. On investigations, routine laboratory examination, CBC, liver function test, renal function test, erythrocyte sedimentation rate, C- reactive protein all were within normal range. On MRI scan, there were numerous fluid filled low intensity well circumscribed rounded lesions in the parotid and submandibular area. Patient was referred for histopathological examination of these nodules & Incisional biopsy was performed and histopathological analysis showed a well circumscribed granulomatous reaction without central necrosis, characterized by an epithelioid histiocytic organization, numerous multinucleated giant cells with peripheral disposition of nuclei, PAS positive stain suggesting hyaluronic acid with the granuloma.

The patient was treated with hyaluronidase and intralesional steroidal injections followed by antibiotics. The nodules disappear after 2 weeks complete remission was confirmed by soft tissue ultrasound. patient was fully explained about the long term adverse effects of filler and the follow up was made to check further reoccurrence and relapse.

Discussion

Hyaluronic acid-based fillers are widely used to correct facial deformities, enhancement of volume and facial counter, loss of volume in hands and lip enhancement in aesthetic medicine. (1) they are generally considered Safe. Though adverse reactions can happen. Swelling, redness, inflammation, erythema, tenderness can occur an immediate side effect after procedure, these adverse effects go shortly without leaving any trace. however late complications like foreign body granulomatous, inflammatory reactions, fillers displacement can happen even after many months and years. (2) (6)

Delayed reaction due to dermal filler injection have appeared in various studies in the past even until recent times previously silicon fillers were considered the culprit but HA fillers are also causing this complication.

A review of 16 publications in literature presenting with similar presentation of formation of granulomas after filler injection who underwent a biopsy and radiological assessment for facial nodule formation from the period of 4 months to 6 years after filler injections, was conducted to determine the diagnosis presentation and management of the nodule after filler injection and to determine type of filler used.

All patients were women (mean age 60.6 years) some patients suffered from different localizations lip 09; glabella 02; cases nasolabial folds 04; cheeks 04; the parotid region 1; and arms 1; case 90% patients know the type of filter used and in other cases histopathological findings were able to provide some information.

The histopathological findings in most cases of foreign body granuloma formation due to dermal fillers show a dense lymphocytic infiltration with eosinophils and granulomatous infiltrates with multinucleated giant cells often containing basophilic amorphous material multiple vacuolated cystic like structure and Swiss cheese appearance are also possible.

Typical presentations include Erythematous painful nodules but subcutaneous painless nodules have also been reported.

The strategies for treatment involves hyaluronidase injection alone or in combination with intralesional or oral steroid injections. Empirical antibiotics is also an option to treat granulomas in response to fillers. In resistance and a long standing cases or in case of failure to medical treatment surgical excision of nodules and granulomas is considered. (7,8,9,10)

Hyaluronic acid is produced by biotechnology it is obtained by fermentation of bacteria a process using lactic acid bacteria then it is collected stabilised, sterilised, purified, cross linked and dehydrated to form a powder when added to water it forms a more or less tested gel cross linked HA is more durable it involves a process that allows linear hyaluronic acid molecules to be linked together to form a HA filament with higher molecular weight. (2)

the exact pathogenesis of late onset granulomas is still in debate but several hypothesis have been suggested. These involved derivation of impurities during bio fermentation hypersensitivity responses in patients who undergo repeated filler injections antibody formation could be possibility or disintegration of cross linking may be responsible for an inflammatory reaction. (3-6)

Conclusion

Long term complications due to dermal fillers can happen after months and years patients undergoing cosmetic procedures may be fully informed regarding the late possible adverse effects that can happen. The diagnosis and treatment of this complication is a challenging for physicians proper history, examination radiological and histopathological examination play a main role in making diagnosis of foreign body granulomas and its management.

References

- 1) Trinh LN, McGuigan KC, Gupta A. Delayed Granulomas as a Complication Secondary to Lip Augmentation with Dermal Fillers: A Systematic Review. *Surg J (N Y)*. 2022 Mar 3;8(1):e69-e79. doi: 10.1055/s-0042-1743524. PMID: 35252562; PMCID: PMC8894086.
- 2) Rossatto A, Trocado Dos Santos J, Zimmer Ferreira Arlindo M, Saraiva de Morais M, Denardi de Souza T, Saraiva Ogradowski C. Hyaluronic acid production and purification techniques: a review. *Prep Biochem Biotechnol*. 2023;53(1):1-11. doi: 10.1080/10826068.2022.2042822. Epub 2022 Mar 24. PMID: 35323089.
- 3) Micheels P. Human anti-hyaluronic acid antibodies: is it possible? *Dermatol Surg*. 2001 Feb;27(2):185-91. doi: 10.1046/j.1524-4725.2001.00248.x. PMID: 11207696.
- 4) Lee JM, Kim YJ. Foreign body granulomas after the use of dermal fillers: pathophysiology, clinical appearance, histologic features, and treatment. *Arch Plast Surg*. 2015 Mar;42(2):232-9. doi: 10.5999/aps.2015.42.2.232. Epub 2015 Mar 16. PMID: 25798398; PMCID: PMC4366708.
- 5) Zhang FF, Xu ZX, Chen Y. Delayed Foreign Body Granulomas in the Orofacial Region after Hyaluronic Acid Injection. *Chin J Dent Res*. 2020;23(4):289-296. doi: 10.3290/j.cjdr.b867893. PMID: 33491361.

- 6) [Jeong Min Lee, Yu Jin Kim, Foreign body granulomas after the use of dermal fillers; pathophysiology, clinical appearance, histological appearance, treatment; Pastic Surgery 42\(2\):232-9, March 2015\[PubMed\]](#)
- 7) Funt D, Pavicic T. Dermal fillers in aesthetics: an overview of adverse events and treatment approaches. *Plast Surg Nurs*. 2015 Jan-Mar;35(1):13-32. doi: 10.1097/PSN.0000000000000087. PMID: 25730536.
- 8) Ali Modarressi, Christophe Nizet, Tommaso Lombardi,
- 9) Granulomas and nongranulomatous nodules after filler injection: Different complications require different treatments, *Journal of Plastic, Reconstructive & Aesthetic Surgery*, Volume 73, Issue, 2020,
- 10) Gottfried Lemperle, MD, PhD, David M. Duffy, MD, Treatment Options for Dermal Filler Complications, *Aesthetic Surgery Journal*, Volume 26, Issue 3, May 2006, Pages 356–364,
- 11) Tamiolakis P, Piperi E, Christopoulos P, Sklavounou-Andrikopoulou A. Oral foreign body granuloma to soft tissue fillers. Report of two cases and review of the literature. *Journal of Clinical and Experimental Dentistry*. 2018 Feb;10(2):e177-e184. DOI: 10.4317/jced.54191. PMID: 29670737; PMCID: PMC5899785.
- 12) Coughlin A, Gray ML, Westra WH, Teng MS, Rosenberg JD. Dermal Filler Presenting as Parotid Mass: A Case Report. *Head Neck Pathol*. 2021 Jun;15(2):638-641. doi: 10.1007/s12105-020-01197-1. Epub 2020 Jul 8. PMID: 32642936; PMCID: PMC8134640.
- 13) Liu A, Hoss E, Kollipara R, Goldman MP. Granulomatous Reaction to Silicone Filler Injections on the Glabella and Nasolabial Folds. *Dermatol Surg*. 2021 Jun 1;47(6):851-853. doi: 10.1097/DSS.0000000000002707. PMID: 32897948.
- 14) Masui, hoss, Granulomas Of The Lips A Rare Complication After Injection Poly lactic Acid For Aesthetic Augmentation *Journal Plastic Reconstructive Surgery*. jun 2021
- 15) Skrzypek E, Górnicka B, Skrzypek DM, Krzysztof MR. Granuloma as a complication of polycaprolactone-based dermal filler injection: ultrasound and histopathology studies. *J Cosmet Laser Ther*. 2019;21(2):65-68. doi: 10.1080/14764172.2018.1461229. Epub 2018 May 14. PMID: 29757038.
- 16) Kaczorowski M, Nelke K, Luczak K, Halon A, Filler migration and florid granulomatous reaction to hyaluronic acid mimicking a buccal tumour. *J Craniofac Surg*. 2020;31(01):e78-e79.[PubMe] [Google Scholar]
- 17) Alcantara C EP, Noronha M S, Cumha J F, Flores I L, Mesquita R A. Granulomatous reaction to hyaluronic acid filler material in oral and perioral region: a case report and review of literature. *J Cosmet Dermatol*. 2018;17(04):578-583. [Pubmed] [Google scholar]
- 18) Fernandez-Acenero M J, Zamora E, Borbujo j. Granulomatous foreign body reaction against hyaluronic acid: report of a case after lip augmentation.

Dermatol Surg. 2003;29(12):1225-1226.[Pubmed] [Google Scholar]

19) Alijotas-Reig j, Fernandez-Figueras M T, Puig L. Pseudocytic encapsulation: a late noninflammatory complication of hyaluronic acid filler injections. Dermatol Surg.2013;39(11):1726-1728.[Pubmed] [Google Scholar]

20) Park T H,Seo S W, Kim J K, Chang C H. Clinical experience with hyaluronic acid-filler complication. J Plast Reconstr Aestht Surg.2011;64(07):892-896. [Pubmed][Google Scholar]

21) Curi M M, Cardoso C L, Curra C, Koga D, Benini M B. Late onset adverse reaction to hyaluronic acid dermal filler for aesthetic soft tissue augmentation. J Craniofac Surg.2015;26(03):782-784.[Pub Med] [Google Scholar]

22) Yo Sup Shin, Won Joo Kwon, Eun Byul Cho, Eun Joo Park, Kwang Ho Kim, Kwag Joong Kim,A case of cellulitis- like foreign body reaction after hyaluronic acid dermal filler injection, Dermatologica Sinica, Vol 36, Issue 1, 2018, 46-49. ISSN 1027-8177

23) R.U. Sidwell. A.P. Dhillon, P.E. Butler, M.H. Rustin Localized granulomatous reaction to a semipermanent hyaluronic acid and acryliv hydrogel cosmetic filler Clin Exp Dermatol,29(2004), pp.630-632

24) J.E.Angus, A.G.Affleck, I.H.Leach, L.G.Millard Two cases of delayed granulomatous reactions to the cosmetic filler Dermalive, a hyaluronic acid and acrylic hydrogel Br J Dermatol,155(2006), pp. 1077-1078