**Case Report**

**First reported case of delayed-type hypersensitivity reaction to non-hyaluronic acid Polycaprolactone dermal filler following COVID-19 vaccination: A case report and a review of the literature**

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**Abstract**

Cases of filler reactions after COVID-19 vaccination have been reported. Here, we present the first case of delayed-type reaction (DTR) to non-hyaluronic acid Polycaprolactone dermal filler after the second dose of Sinopharm COVID-19 vaccine which was improved with administration of topical and intraleisional steroids.

**Keywords**

adverse effects, augmentation, case report, coronavirus, cosmetic, cosmetic filler, COVID-19, COVID-19 vaccines, delayed-type reaction, dermal fillers, hyaluronic acid, hyaluronic acid fillers, non-hyaluronic acid fillers, review, side effects, swelling, vaccination

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**1 | Introduction**

Dermal filler injections are among the most popular minimally-invasive cosmetic procedures performed globally.\(^1\) There exist different types of fillers such as hyaluronic acid (HA), calcium hydroxylapatite, poly-L-lactic acid, and collagen-based fillers.\(^2\) Polycaprolactone (PCL) derivatives are soft dermal fillers that are biodegradable.\(^3\) While PCL fillers have a proven safety profile, many adverse effects associated with these fillers such as nodules, granuloma, edema, and bruising have been reported.\(^4\) Acute type 1 hypersensitivity reactions, which are immunoglobulin E (IgE)-mediated, can occur within minutes or hours after filler injection while delayed-type reactions (DTR), which are T-cell mediated, can happen between hours or days after the filler placement.\(^5\)

With the onset of vaccination against the SARS-CoV-2 virus (COVID-19 virus), various adverse effects associated
with these vaccines were reported. As well, filler reactions following COVID-19 vaccination have been observed in practice. Herein, we present a case of DTR to previously placed PCL filler after getting the Sinopharm vaccine against COVID-19.

2 | CASE PRESENTATION

A 62-year-old woman without any past medical history or allergies presented to our clinic complaining of multiple nodules with stone-like firmness in the back of her hands. She had previously received PCL filler within the back of her both hands 2 years ago. She had never experienced any complications with her hand fillers during the past 2 years. Fourteen days after getting the second dose of Sinopharm vaccine, she noticed painless swelling in the dorsum of her hands without any other symptoms. After 2 weeks, she developed multiple hard nodules in the back of her both hands and no extra-site symptom was noticed. Notably, she did not have any complications after receiving the first dose of Sinopharm vaccine.

After taking a thorough history from our patient, it was proved that she did not suffer from any infection or trauma in that area. Furthermore, she had not started a new medication and she had not undergone any dental or medical procedures between the time of vaccination and symptoms' manifestation.

Examination revealed multiple nodules with stone-like firmness in palpation located in the back of our patient’s both hands in the first visit (Figure 1). Dorsal hands soft tissue ultrasound imaging showed interstitial edema with low-level echo fluid without any signs of collection.

What do we know?
- Various adverse effects associated with COVID-19 vaccines have been reported.
- Cases of filler reactions following COVID-19 vaccination have been observed in practice.

What does this article add?
- While rare, reactions to previously placed Polycaprolactone (PCL) fillers can happen following COVID-19 vaccinations.
- Individuals seeking both COVID-19 vaccines namely Sinopharm and PCL fillers should be aware of this phenomenon.

FIGURE 1 (A and B) Multiple nodules with stone-like firmness in the back of our patient’s both hands in the first visit

FIGURE 2 (A and B) Lesions improvement after 4 weeks of treatment
As a result, a DTR reaction following the second dose of COVID-19 vaccination was made. Single dose of dexamethasone in addition to topical corticosteroid was prescribed. Gradual improvement of lesions was observed after using the topical corticosteroid. Intraläsional triamcinolone injection in nodules resulted in a significant improvement. Our patient is still under treatment with topical steroids. During our 4 week follow-up, no recurrence of the lesions was observed (Figure 2).

3 | DISCUSSION

Recently, experts defined delayed inflammatory reactions (DIRs) as reactions occurring 2–4 weeks after injections. The exact mechanisms for DTRs following the filler injection remain unclear, but various factors such as infections, filler properties, trauma, vaccinations, and injection technique are reported to be responsible. PCL-based fillers are collagen stimulators stimulating neocollagenesis providing an immediate and temporary filling effect in the target tissue. In this article, we have provided the first reported case of DTR reaction to PCL filler following Sinopharm vaccination. As well, we reviewed the literature regarding the reported cases of DTR reactions after PCL placement. Furthermore, most reported cases of DTR to dermal fillers following COVID-19 vaccinations are against HA fillers.

Polycaprolactone-based fillers are safe and well-tolerated choices for hand rejuvenation with minimal chance of migration. In a study done by Figueiredo et al. on 5 women evaluating the efficacy and safety of a PCL-based filler for dorsal hand rejuvenation using a visual analog scale, satisfaction was rated at 82% at 24 weeks, and patients were 88% likely to re-treat the same procedure on average.

In a study done by Lin et al. reviewing 1111 treatments with PCL injections, the incidence rate of adverse effects was 4.5% such as bruising/hematoma, swelling, color change, or palpable lumps. It is worth mentioning that no cases of nodule formation nor granulomas were reported in that study. There has long been a concern about collagen-stimulating products causing nodules to develop and the injection technique is considered to be one of the most important factors in nodule formation. In order to prevent nodule development, it has been recommended to use linear threading, fanning, and cross-hatching techniques in the subcutaneous plane and to avoid injecting more than 0.2 mL. Histopathology of a nodule shows an overabundance of product, as opposed to granulomas, which reflect an immune origin that depends on the immune status or specific incidents that make alterations in the immune status. As well, cases of PCL-induced granuloma have been reported in the literature.

| Reference number | First author and year of publication | Age and gender | Location | Clinical presentation and type of reaction | Interval between injection and reaction | Management | Outcome |
|-------------------|-------------------------------------|----------------|----------|------------------------------------------|----------------------------------------|------------|---------|
| 3                  | Moon et al./2017                    | 36/male        | Cheek, nasolabial folds, infraorbital    | Granuloma                              | 2 years                                | Doxycycline 100 mg twice daily for 1 month | Decreased lesion size |
| 9                  | Skrzypek et al./2019                | 68/female      | Marionette line                          | Granuloma                              | 13 months                               | Doxycycline 100 mg twice daily for 1 month | Decreased lesion size |
| 8                  | Chiang et al./2021                  | 57/female      | Tear trough                              | Granuloma                              | 7 months                                | Excision                                           | No recurrence |
| 10                 | Philibert et al./2020               | 47/female      | Cheeks and nasolabial folds              | Granuloma                              | 9 months                                | Methotrexate, 10 mg per week for 3 months, then 20 mg per week for 9 months | Complete regression |
| 11                 | Ortiz-Alvarez et al.                | 74/female      | Nasolabial folds and over both zygomatic arches | Granuloma                              | 3 months                                | Methotrexate (20 mg subcutaneous weekly) with prednisone (0.17 mg/kg/day) | Significant improvement |
In contrast to HA fillers which can be dissolved by injecting enzymes (hyaluronidase), PCL-based fillers cannot be instantly removed with enzyme injections. Observation may be the best approach for treating filler-induced nodules, because most nodules will disappear spontaneously within a year, and short-term overcorrection might result in deformity. In comparison, treatment for filler-induced granulomas consists of observing, massaging, saline or water dilution, intralesional steroids injection, oral antibiotics administration, curettage, and lesion removal. Moreover, methotrexate has been used in a case of eruptive granuloma following PCL filler placement. In our case, topical and intralesional steroids were prescribed and a significant improvement of the lesions was observed.

In this article, we performed a brief review of the literature in the Pubmed/MedLine database to address complications including reported granulomas and nodules formation following PCL injection (Table 1). Unfortunately, we were not able to provide a pathologic and histologic assessment in our patient, which is considered as a limitation of our study.

4 | CONCLUSION

Cases of filler reactions after COVID-19 vaccination have been reported. Notably, most of them were HA-based fillers reaction to Moderna and Pfizer COVID-19 vaccines that may well be because HA fillers are by far the most frequently used ones, and the Moderna and Pfizer COVID-19 vaccines are also most frequently used. It is worth mentioning that the authors of this manuscript have broadly worked on COVID-19 and skin as well as cosmetic fields. To the best of our knowledge, this is the first reported case of nodule formation due to the PCL reaction following Sinopharm COVID-19 vaccination and further investigations with longer follow-ups are recommended. Our case highlights the importance of reporting similar cases in order to better understand this phenomenon and its management. Of note, individuals and physician should be aware of such reactions in practice.

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1. Ortiz-Álvarez J, Lebrón-Martín JA, Rodríguez Fernández-Freire L, Zulueta Dorado T, García Morillo JS. Cutaneous and ganglion sarcoïdosis induced by polyacrylactone facial filler: a new expression of ASIA syndrome? Eur J Case Rep Intern Med. 2021;8(7):002652. doi:10.12890/2021_002652

2. Savva D, Battineni G, Amenta F, Nittari G. Hypersensitivity reaction to hyaluronic acid dermal filler after the Pfizer vaccination against SARS-CoV-2. Int J Infect Dis. 2021;113:233-235. doi:10.1016/j.ijid.2021.09.066

3. Michon A. Hyaluronic acid soft tissue filler delayed inflammatory reaction following COVID-19 vaccination - A case report. J Cosmet Dermatol. 2021;20(9):2684-2690. doi:10.1111/jocd.14312

4. Lajevardi V, Mahmoudi H, Karimi F, Kalantari Y, Etesami KALANTARI et al. Histopathologic survey on lung necropsy specimens of 15 patients who died from COVID-19: a large study from Iran with a high rate of anthracosis. Acta Medica Iranica. 2021;14:4-14.

5. Mohamadi M, Fattahi N, Goodarzi A, et al. A comprehensive review on COVID-19 infection and comorbidities of various organs. Acta Medica Iranica. 2021;14:4-14.

6. Behrangi E, Goodarzi A. First reported case of delayed-type hypersensitivity reaction to non-hyaluronic acid polycaprolactone dermal filler following COVID-19 vaccination: A case report and a review of the literature. Clin Case Rep. 2022;10:e05343. doi:10.1002/ccr3.5343

7. Mohamadi MM, Goodarzi A, Aryannejad A, et al. Geriatric challenges in the new coronavirus disease-19 (COVID-19) pandemic: a systematic review. Med J Islam Repub Iran. 2020;34(4):e841-848. doi:10.47176/mjri.34.123

8. Seirafianpour F, Mozafarpoor S, Fattahi N, et al. Treatment of COVID-19 with pentoxifylline: could it be a potential adjuvant therapy? Dermatol Ther. 2020;33(4):e13733. doi:10.1111/dth.13733

9. Seirafianpour F, Sodagar S, Pour Mohammad A, et al. Cutaneous manifestations and considerations in COVID-19 pandemic: a systematic review. Dermatol Ther. 2020;33(6):e13986. doi:10.1111/dth.13986

10. Najar Nobari N, Goodarzi A. Patients with specific skin disorders who are affected by COVID-19: what do experiences say about management strategies? A systematic review. Dermatol Ther. 33(6):e13733. doi:10.1111/dth.13986

11. Najar Nobari N, Seirafianpour F, Mashayekhi F, Goodarzi A. Systematic review on treatment-related mucocutaneous reactions in COVID-19 patients. Dermatol Ther. 2020;34(1). doi:10.1111/dth.14662

12. Kalantari S, Sadeghzadeh-Bazargan A, Ebrhami S, et al. The effect of influenza vaccine on severity of COVID-19 infection: an original study from Iran. Med J Islam Repub Iran. 35:114.

13. Tavakolpour S, Aryanian Z, Seirafianpour F, et al. A systematic review on efficacy, safety, and treatment-durability of low-dose rituximab for the treatment of Pemphigus: special focus on COVID-19 pandemic concerns. Immunopharmacology and Immunotoxicology. 2021;43(5):507-518. doi:10.1080/0893973.2021.1953063

14. Mashayekhi F, Seirafianpour F, Pour Mohammad A, Goodarzi A. Severe and life-threatening COVID-19-related mucocutaneous eruptions: a systematic review. Int J Clin Pract. 2021;75(12):e14720. doi:10.1111/iicp.14720

15. Lotfi Z, Haghighi A, Akbarzadehpasha A, Mozafarpoor S, Goodarzi A. Pansclerotic morphea following COVID-19: a case report and review of literature on rheumatologic and non-rheumatologic dermatologic immune-mediated disorders induced by SARS-CoV-2. Front Med. 2021;8:728411.

16. Behrangi E, Ghassemi M, Sadeghzadeh-Bazargan A, Roohaninasab M, Najar Nobari N, Goodarzi A. A systematic review of clinical studies on mucocutaneous manifestations of COVID-19: virus-related and drug-related. Acta Med Iran. 2021;59(12):687-698.

17. Hatami P, Aryanian Z, Nicknam ASL H, Goodarzi A. Mucocutaneous adverse effects following COVID-19 vaccination: a comprehensive review of the literature with a presentation of some cases from Iran. Iran J Dermatol. 2021;24(4). doi:10.22034/IJD.2021.31094.1451