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ORIGINAL ARTICLE

Inflammatory immune-mediated adverse reactions induced by COVID-19 vaccines in previously injected patients with soft tissue fillers: A case series of 20 patients

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Abstract

Background: Adverse events (AE) after COVID-19 vaccines, particularly, but not solely, with those messenger RNA (mRNA)-based vaccines, have rarely been reported in patients previously treated with dermal fillers (DF).

Objective: To evaluate the morphology, clinical characteristics, the timing of presentation, and outcomes of inflammatory AE appeared in patients injected with DF, after anti-COVID-19 vaccination.

Methods: Descriptive study of a case series of 20 consecutive patients collected after the occurrence of AE in previously filled areas post COVID-19 vaccination.

Results: From January 2021 to July 2021, we analyzed 20 AE reactions triggered by COVID-19 vaccines in the previously mentioned cohort. They were vaccinated with Pfizer/Biontech (11; 55%), Moderna (5; 25%), Astra-Zeneca (3; 15%), and Sputnik (1; 5%). The most common manifestations were oedema/swelling, angioedema, erythema, skin induration, and granuloma. Less common reactions included myalgia and lymphadenopathy. In 13/20 (65%) cases, the AE appeared after the first dose of vaccine. These inflammatory AE appeared more rapidly after the second dose than after the first one. In 13/20 (65%) cases, the symptomatology subsided with anti-inflammatory/antihistaminic drugs, while spontaneously in 3/20 (15%). The manifestations are ongoing.in the remaining four cases (20%).

Conclusion: Although probably rare, both RNA-based and adenovirus-based anti-COVID-19 vaccines can cause inflammatory bouts in patients previously treated with DF. In these cases, caution should be paid on subsequent vaccine doses, considering a tailored risk/benefit for any case before next vaccination.

KEYWORDS
adverse reactions, COVID-19, inflammation, SARS-CoV-2, soft tissue fillers

1 | INTRODUCTION

Interest is growing worldwide in medical treatments with dermal fillers (DF) to prevent or reduce skin aging, both on medical grounds and for aesthetic and cosmetic purposes.[1] Initially, reports on adverse events (AE) were lacking[2]; however, severe late-onset inflammatory—mainly local/regional but also systemic—reactions are also being reported in 1%–5% of cases.[3–5] To trigger these immune reactions, DF may act as a T-cell-directed antigen, as a superantigen or act as an adjuvant. An immunological adjuvant is a substance that enhances the antigen-specific immune response, preferably without triggering one on its own.[6] Vaccines can also act as adjuvants, and inflammatory local or systemic complaints have been reported.[7] As of this article submission, the number of COVID-19 disease continues to rise worldwide. Angiotensin-converting enzyme 2 (ACE2) is a major target for SARS-CoV-2 and essential for virus anchoring and intracellular invasion.[8] ACE2 is ubiquitously expressed in all tissues of the human body. Interestingly, the skin is moderately high in expression of ACE2.[9] ACE2 may act as an inflammatory regulator, inhibiting proinflammatory cascade via angiotensins II-VII. As such, blockade of dermal ACE could provoke a proinflammatory pathway activation causing local inflammation.[10] With the pandemic's intrinsic need to vaccinate people worldwide, the possibility of having people filled with DF and also vaccinated will rise. Thus, a plausible hypothesis is that the COVID-19 vaccine could target the possibility of having AE to fillers. The FDA brief on the Moderna® vaccine already reported reactions to prior DF after vaccination.[11] Pfizer also launched a similar preliminary warming, later followed by other companies manufacturing COVID-19 vaccines.[12] Recently, Munavalli et al[13] reported the first 4 patients previously filled who developed cutaneous adverse reactions after COVID-19 vaccination.

Herein, we report a series of 20 cases with prior facial/breast filler injections complicated with inflammatory adverse reactions after COVID-19 vaccination.

2 | MATERIAL AND METHODS

A case series of 20 patients were recruited from Barcelona (Spain) and Amsterdam (the Netherlands). All had previously injected with DF, and one of them has breast prosthesis.

An oriented survey was delivered to the patients. The major questions were as follows: age, ethnicity, smoking habit, medical history, previous autoimmune disorders, COVID-19 vaccine type, previous dermal filler/s, area/s injected, previous AE, lapse time, post-vaccine AE, lapse time between vaccination and AE; main AE: edema, skin induration, granuloma, lymphadenopathy, panniculitis, fever, systemic complaints—malaise, feverish, arthralgia, myalgia, skin rash—treatment response, relapses, and biopsy.

All patients were vaccinated with one of the following anti-COVID-19 vaccines: BNT162b2 (Comirnaty®, Pfizer); mRNA-1273 (Moderna TX, Inc.); ChAdOx1 nCoV-19 (Astra-Zeneca) and (Sputnik V, Gamaleya Center).

All patients gave their informed consent that was registered in the medical history. In addition, special informed consent was signed in patients (five) when images—photographs—were used. IRB is not required in this study because only clinical data, and no experimental samples were used. Finally, all data used were anonymized.

3 | RESULTS

All cases were female and all but one were Caucasian. The mean age was 45.30 years (range: 21–71 years). Four cases 8, 10, 18, and 20 have allergic history, and cases 18 and 19 had been diagnosed of Hashimoto's disease.

The four previously mentioned anti-COVID-19 vaccines were used, being the BNT162b2 (Comirnaty®, Pfizer) the most frequent in 11/20 cases (55%) followed by mRNA-1273 (Moderna TX, Inc.) 5/20 (25%), ChAdOx1 nCoV-19 (Astra-Zeneca) 3/20 (15%) and 1/20 (5.%) (Sputnik V, Gamaleya Center).

All 20 cases were previously injected with DF, 19 in facial area and 1 in both the facial and buttocks area plus also having breast implants. DF used in patients of this cohort were: hyaluronic acid (HA), fluid silicone (FS), polymethyl methacrylate (PMMA) microspheres and with poly-alkyl-imide (PAI). In more detail, the DF used were as follows: 14/20 with HA, 2/20 HA + SMG, 1/20 HA and methacrylate, 1/20 cases with PMMA, 1/20 with FS and 1/20 with poly-alkyl-imide (PAI). (Table 1). Three cases (15%) had experienced inflammatory late-onset AE related to DF before COVID-19 vaccination. Two of them were on low-dose prednisone plus tacrolimus, and one was taken full-dose of allopurinol plus prednisone. All 20 cases experienced inflammatory signs in previously implanted areas, having only two patients presented with systemic but transitory symptoms.

In 13/20 (65%) cases, the AE appeared after the first dose of vaccine and in 7/20 (35%) after second one. The mean lapse time between the vaccine injection and the occurrence of the inflammatory signs in previous filled areas was 10 days (1–56 days). Interestingly, AE possibly triggered by COVID-19 vaccine in previous filled areas presented more rapidly after the second dose than after the first one (mean: <4 days vs. > 11 days). Three patients received no treatment and clinical signs subsided. Fourteen were treated with antihistamines in possible combination with non-steroidal anti-inflammatory drugs and prednisone, or both, with good responses in all but one of them. An increase in dosage was needed in the three cases already treated with prednisone plus tacrolimus or allopurinol. Clinical improvement, but no full remission with continuous local manifestations, was observed in these three cases (Table 1A and B). Finally, photography of 5 cases can be seen in attached Figures 1 and 2.

4 | DISCUSSION

We report a cohort of consecutive 20 patients that experienced inflammatory bouts in the previously filled areas with DF after receiving anti-SARS-CoV-2 vaccine. In patients treated with biomaterials

TABLE 1 Type of vaccines, clinical findings, treatment response, and follow-up of these 20 patients

A

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Vaccine	Pfizer x1	Pfizer x1	Pfizer x1	Pfizer x2	Sputnik x2	Pfizer x1	Pfizer x2	A-Z x1	Moderna x1	A-Z x1
Previous filler	HA	HA	FS	HA	HA	Methacryl	HA	HA	PAI	HA
Area filled	Facial	Facial	Breast[a]	Facial	Lips	Facial	Facial	Facial	Facial	Lips
Previous AE	No	No	No	No	No	Yes	No	No	No	No
Post-vaccine AE lapse time (days)	7	8	14	10	8	10	1	35	7	14
Edema	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Induration	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Granuloma	Yes	Yes	No	Yes	Yes	Yes	No	No	No	No
Lymphadenopathy	No	No	Yes	No	No	No	No	No	No	No
Fever	Yes	No	ND	No	No	No	No	No	No	No
Systemic complaints	No	No	No	Myalgia	No	No	Arthralgia	No	No	No
Treatment response	Yes	Yes	Yes	No	No	Partial	Yes	Yes	Yes	Yes
Type of treatment	Prednisone Anti-H1	Anti-H1	Prednisone Anti-H1	NSAD Anti-H1	Prednisone Anti-H1	↑Tacrolimus ↑Prednisone	Prednisone Anti-H1	NSAD Anti-H1	Anti-H1	Anti-H1
Relapse	No	No	No	Yes	Yes	No	No	No	No	No

B

	Case 11	Case 12	Case 13	Case 14	Case 15	Case 16	Case 17	Case 18	Case 19	Case 20
Vaccine	A-Z x1	Pfizer x1	Pfizer x1	Moderna x2	Pfizer x1	Moderna x1	Moderna x1	Moderna x2	Pfizer x2	Pfizer x2
Previous filler	HA /FS	HA	HA	HA	HA	HA	HA	HA	HA/Methacryl	HA/FS
Area filled	NSLF	Lips	Facial	Lips	Lips	Facial	Lips	Cheeks	Facial	Lips
Previous AE	Yes	No	No	No	No	No	No	No	Yes	No
Post-vaccine AE lapse time (days)	56	3	4	3	3	1	2	5	7	14
Edema	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Induration	No	No	Yes	No	No	No	No	No	Yes	Yes
Granuloma	Yes	No	No	No	No	No	No	No	Yes	Yes
Lymphadenopathy	Yes	No	No	No	No	No	No	No	No	No
Fever	No	No	No	No	No	No	No	No	No	No
Systemic complaints	No	No	No	No	No	No	No	No	No	No
Treatment response	No	Yes	ND	Yes	Yes	ND	ND	Yes	No	Not fully
Type of treatment	↑Tacrolimus ↑Prednisone	Prednisone Erythromycin	--	Anit-H1	Prednisone	--	Anti-H1	Prednisone Anti-H1	Allopurinol Prednisone	NSAD Anti-H1
Relapse	Yes	No	No	No	ND	No	No	No	Yes	No

Abbreviations: FS, fluid silicone; HA, Hyaluronic acid; Methacryl, polymethyl-Methacrylate; ND, not done; NP, not performed; NSLF, nasolabial folds; Predni, prednisone.

[a]It was her last prostheses. The patient had been previously filled in facial and buttocks areas, with HA, polymethyl methacrylate and FS.

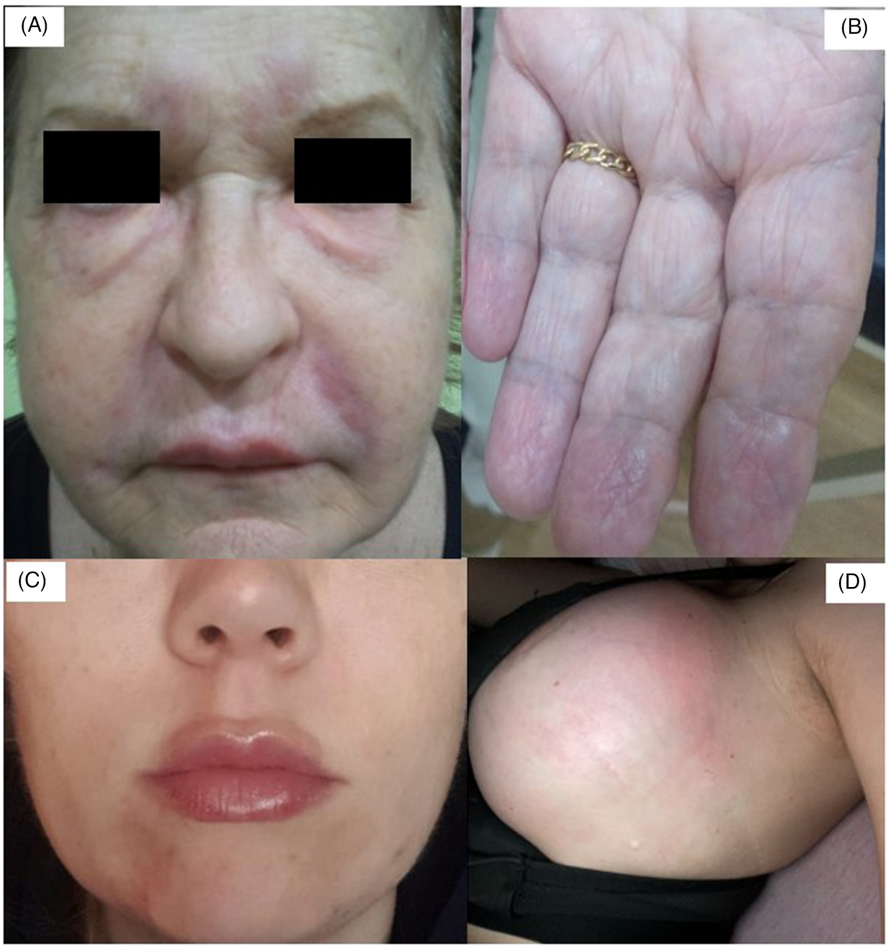

FIGURE 1 Inflammatory, immune-mediated reactions in previously filled patients after receiving an anti-COVID-19 vaccine. (A) A 59-year-old woman, with history of heavy and recurrent facial immune reaction related to previously polymethyl methacrylate injection, treated with low-tacrolimus dose plus low-prednisone dose. 10 days after first shot of Pfizer–Biontech vaccine, she presented with heavy facial oedema that initially provoke a total eye closure, nasolabial folds induration and inflammatory nodules in supraciliary areas and the upper lip. (Case 6). (B) Palm and digital red-purplish erythema of left hand of patient 1A. Right hand had the same kind of lesion. This skin changes appear with relapses. (Case 6). (C) A 21-year-old healthy woman, treated with hyaluronic acid on lips 5 months before COVID-19 vaccination, presented with grave oedema in the prior injected areas a few days after the second dose of Moderna. She was put on prednisone, and the lip swelling disappeared in a few days with no relapses until now. (Case 17). (D) A 50-year-old woman, with history of heavy and recurrent facial and buttocks inflammatory immune reaction related to previously hyaluronic acid, polymethyl-methacrylate and fluid silicone injections. She was asymptomatic taken hydroxychloroquine, antihistamines, and allopurinol when she was vaccinated. 14 days after the first dose of Pfizer–Biontech vaccine, she presented a severe inflammatory reaction in face and breasts with associated axillary lymphadenopathy. Prednisone was added, and a rapid improvement was achieved

or DF, infections and vaccines may act as adjuvants and eventually provoking activation of the immune system.[7] Along these lines, in 2008, Alijotas-Reig J et al[5,14,15] already reported a series of cases of human adjuvant-like disease induced or triggered by synthetic DF. Vaccines can also act as adjuvants, and inflammatory local or systemic complaints have been reported.[7] Acute or delayed AE in areas previously filled with DF appeared after different vaccination have also been reported.[11–13,16,17] The most filled material in these reported cases was HA but also others like calcium-hydroxylapatite or acrylamides, like our cases, reflecting that HA is the most used filler from far. Our patients showed no clinical nor microbiological evidence of acute SARS-CoV-2 infection. Thus, a vaccination increases immunological reactions of the body, and especially, permanent fillers remain in the immune memory of T-cells and macrophages for decades, causing a foreign-body reaction in certain patients. This looked like this in our patients. They were effectively treated with such and such immunosuppressive drugs. Thus, the most probably if not true trigger for these inflammatory AE was COVID-19 vaccination. Some of these AE appeared few days to 2 weeks after vaccination, but in two cases the lapse-time was longer, up to 56 days. Other previously commented small series reported similar data.[13,16–18] The proper explanation for these differences is elusive to us. The genetic background, previous sensitization, the role played for resident immune cells, and the degree

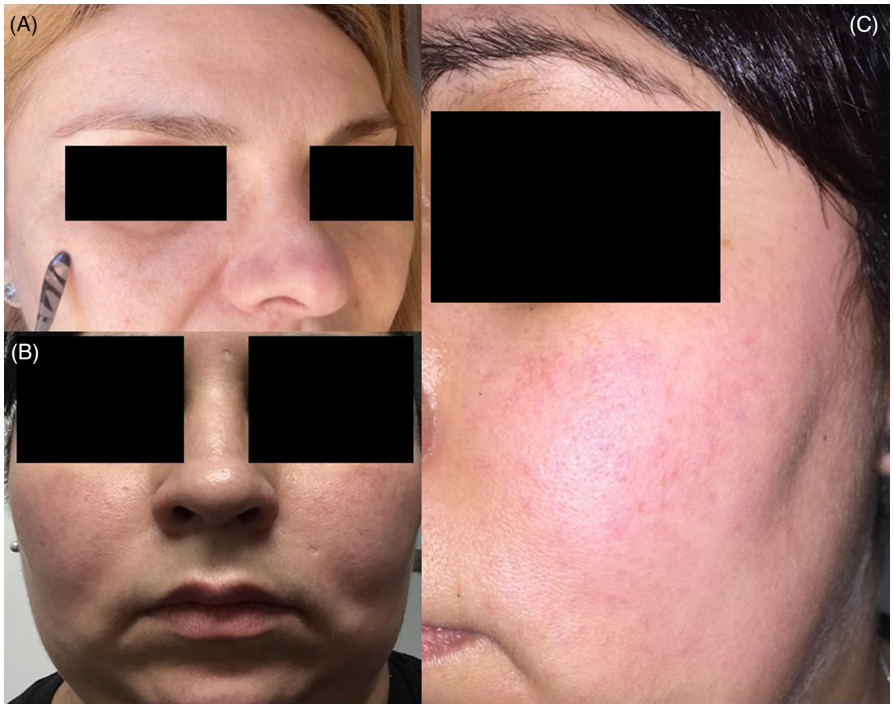

FIGURE 2 Inflammatory, immune-mediated reactions in previously filled patients after receiving an anti-COVID-19 vaccine. (A) A 52-year-old healthy women with HA in zygomatic areas, cheekbones, and lips injected 30 and 52 days before the first and second doses of Sputnik vaccine. Bilateral oedema and painful inflammatory nodules appeared in zygomatic areas, cheekbones, and nose 2 weeks later. She was put on local cold packs and non-steroidal anti-inflammatory drugs, but clinical complaints did not remit (case 5). (B,C) A 48-year-old otherwise healthy women, with history of HA injections in malar areas. She was injected with two doses of Pfizer–Biontech vaccine. 10 days after receiving the second shot, prominent inflammatory signs in the face appeared with big nodule on malar left side. She was put on non-steroidal anti-inflammatory drug plus antihistamines with a slow improvement over weeks (case 4)

of immune stimulation provoked by the vaccine could explain it. Three patients were already on treatment with prednisone, tacrolimus, and allopurinol, because of chronic and recurrent AE before vaccination. In addition, in these 3 cases, the protective role of anti-COVID-19 vaccine is doubtful but sufficient to trigger inflammatory bouts. It is challenging that the patient with breast involvement also had previously and repeatedly been filled in other areas, but only suffered market inflammatory signs in breast, and slight signs in the face and buttocks.

Why have only a few cases of all vaccinated and filled people finally develop these AE? Probably by the similar ground that only 1%–4% of filled cases will develop an intermediate or delayed inflammatory, immune-mediated AE: the genetic background. In these manner, our team[19] recently reported that the HLA-B*08 and DRB1*03 haplotype is related to high risk to develop subacute or late-onset inflammatory, immune reaction to DF. In some instances, suspected allergic reactions to polyethylene glycol, a common excipient in vaccines, should be considered in certain cases). However, the relationship between polyethylene glycol and inflammatory bouts in prior filled areas has not been previously reported. In 16 of our cohort patients, the clinical complaints abated spontaneously in 3 and in 13 after treatment. Interestingly, three cases on treatment before vaccination keep on treatment and are still symptomatic. Patient number 20 presents still local clinical manifestations. Although Gotkin et al[20] stated that the relationship between DF

TABLE 2 Preliminary recommendations on patients filled, inflammatory adverse reactions and COVID-19 vaccines

Q1: The patient has already been treated with dermal fillers/ prosthesis months or years before and had no known problems and wants to be vaccinated:
A1: The patient can be vaccinate.
Q2: The patient has been fully vaccinated without notifying any problem and requests to be treated with fillers/prosthesis:
A2: The patient can be filled I implanted.
Q3: The patient has been vaccinated, has been treated with dermal fillers/prosthesis with no complaints and wants to be vaccinated (next doses):
A3: The patient can receive additional doses.
Q4: The patient has already been treated with dermal fillers/ prosthesis, presented some type of delayed inflammatory reaction or adverse effect related to filler and wants to be vaccinated for the first time:
A4: Currently, there is no sufficient data to answer this question. It must individualize the counseling. Probably the patient can receive vaccine.
Q5: The patient was treated with dermal filler/prosthesis weeks, months or years before and had no known problems. After the first or second dose of COVID-19 vaccine, adverse reactions of inflammatory type appear in the filled/implanted areas:
A5: We suggest avoid or delay the next dose of vaccine. According to the clinical follow-up, comorbidities and personal risk, re-evaluate and reconsider this recommendation.

Note: These recommendations have the endorsement of the Sociedad Española de Medicina y Cirugia Cosmética.

Abbreviations: A, answer; Q, Question.

and AE in filled patients remains unclear, we should be mindful that causality could be present. Special attention will have to be paid in those cases with previous inflammatory AE related to DF. Unfortunately, the accurate estimation of risk and prevalence of vaccine-filler cross reactivity is unknown. More data on this topic are warranted. Meanwhile, we cannot assemble a solid recommendation. Nevertheless, and transiently, we, together with the Sociedad Española de Medicina & Cirugía Cosmética, stablished a set of "preliminary recommendations" that can be seen Table 2.

5 | CONCLUSION

We can state that in small number of patients injected with DF, and probably in relationship with a specific genetic background, the COVID-19 vaccine can trigger an immune-mediated inflammatory hyperresponsiveness in the filled areas. This fact can appear both, in cases who already had inflammatory AE related to fillers and in those who did not experience any previous AE. Special considerations in the former cases must be made. People that have history of AE related to fillers and those who experienced them after the first COVID-19 vaccine doses should receive complete information on the risk of developing AE. In those that first dose of vaccine provokes or induces inflammatory AE, the recommendation would be to delay the next dose according to the clinical follow-up, comorbidities, and overall risk factors for COVID-19. We need to collect more data on this issue as far as possible and are welcome offer suitable counseling considering the primary role of COVID-19 vaccines in controlling the pandemics.

AUTHOR CONTRIBUTIONS

All authors have read and approved the final manuscript. Jaume Alijotas-Reig (JAR), Victor García-Gimenez (VGG), Peter J. Velthuis (PV), Frank B. Niessen (FN), Tom S. Decates (TD). JAR, VGG, PV, FN, and TD involved in conception or design of the work. JAR, PV, FN, and TD involved in data acquisition. JAR and DT involved in drafting the work. All authors involved in agreement to the work contents, final approval of the version to be published, analysis and interpretation of data for the work, and revising the work critically for important intellectual content.

CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

The data that support the findings will be available in [repository name] at [DOI/URL] following an embargo from the date of publication to allow for commercialization of research findings.

ETHICAL APPROVAL

Authors declare human ethics approval was not needed for this study.

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