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LETTER TO THE EDITOR

COVID-19 vaccine and oral lesions: Putative pathogenic mechanisms

Dear Editor,

Although effective and sufficiently safe, COVID-19 vaccines may report metabolic, immune-inflammatory, and infectious adverse reactions (ARs) with prevalent renal, musculoskeletal, and gastrointestinal involvement (Caggiano et al., 2022). Orofacial ARs to COVID-19 vaccines are still rarely (1:1000) reported (Cirillo, 2021). Specifically, oral lesions have generally been described in association with skin lesions, showing heterogeneous macro-microscopic features and a slight predilection for females and subjects with previous dermatological disorders (Caggiano et al., 2022; Riad, 2021).

The main pathogenic mechanisms potentially implied in the onset of oral lesions following the COVID-19 vaccination comprise hypersensitivity reactions, molecular mimicry, immune cross-reactivity and autoimmunity, allergy to vaccine excipients, and reactivation of latent viral infections.

The typical phenotypes reported for mucocutaneous hypersensitivity reactions are the lichenoid and erythema multiforme-like patterns, putatively secondary to an immune response against coating lipid nanoparticles in mRNA vaccines (Hertel et al., 2022), or CD8+ cytotoxic T lymphocytes targeting vaccine antigens expressed on the oral epitheliocytes surface, thus causing their death (Caggiano et al., 2022).

Although a cause–effect relationship has not been established yet, SARS-CoV-2 and COVID-19 vaccine-associated autoimmunity, resulting from molecular mimicry and immune cross-reactivity, has also been noticed with flare-ups of an underlying disease and new onsets in individuals susceptible to immune dysregulation. Anti-SARS-CoV-2 antibodies may cross-react with unknown aminoacidic sequences of glycoproteins on the host oral epitheliocytes, structurally similar to the viral ones (Shafie'ei et al., 2022), promoting autoreactive B or T lymphocytes activation, as previously hypothesized for antibodies targeting protein S in hepatitis B vaccines (Drago & Rebora, 2002). Alternatively, vaccines generated Spike proteins may bind angiotensin-converting enzyme-2 (ACE-2) receptors on oral epitheliocytes, recruiting CD4+ lymphocytes (Zengarini et al., 2022). In addition, vaccine adjuvants, enhancing immune response, may determine the autoimmune/inflammatory syndrome induced by adjuvants known as ASIA (Gambichler et al., 2022).

Oral lesions may also be the epiphenomenon of allergic reactions to excipients in vaccine preparations. Among them, polysorbate 80 (PS80), a vaccine excipient preventing mRNA rapid degradation, was proven to cross-react with polyethylene glycol, which is involved in delayed (>24 h) mucocutaneous lesions following mRNA-based COVID-19 vaccines (Hatami et al., 2021). Accordingly, Manfredi et al. reported diffuse erythematous and ulcerative lesions in a subject vaccinated with mRNA BNT162b2 Comirnaty (Pfizer-BioNTech) containing PS80 (Di Spirito, Amato, et al., 2022; Di Spirito, Pelella, et al., 2022).

A further pathogenic hypothesis may be linked to the reactivation of herpes simplex virus type 1 and varicella-zoster virus (Di Spirito, Amato, et al., 2022; Di Spirito, Pelella, et al., 2022; Shafie'ei et al., 2022), observed in oral mucosal and cutaneous adverse reactions. Both viruses are also involved in the genesis of erythema multiforme and Bell's palsy (Cirillo & Doan, 2022), the last seeming increasingly documented following mRNA and inactivated COVID-19 vaccines compared with the background rate. Herpesviruses establish a well-known life-long latent infection in neuronal ganglion cells, surveilled by resident ganglionic virus-specific CD8+ cytotoxic T lymphocytes preventing viral reactivation. In this scenario, COVID-19 vaccines could act similarly to psychophysical stress or hormonal changes by promoting a massive T lymphocytes polarization toward the spike protein, thus temporarily disabling their surveillance on Herpesviridae, and indirectly favoring their reactivation, also supported by type I interferon and proinflammatory cytokine increase, after the corresponding reduction of toll-like receptor signaling. Such viral reactivations may be more frequent in immunocompromised subjects and the elderly due to their immunosenescence, reducing the cell-mediated immune response and facilitating viral reactivation.

In conclusion, the proposed pathogenic mechanisms should be furtherly elucidated, given the rapidly evolving findings concerning oral lesions following COVID-19 vaccines, and considering the continuously emerging SARS-CoV-2 variants (Di Spirito, Pelella, et al., 2022) and the newly developed vaccines (Di Spirito, Amato, et al., 2022).

AUTHOR CONTRIBUTIONS

Federica Di Spirito: Conceptualization; investigation; writing – original draft; writing – review and editing. **Maria Contaldo:** Conceptualization; writing – original draft; writing – review and editing. **Alessandra Amato:** Investigation; methodology; writing – review and editing. **Maria Pia Di Palo:** Investigation; methodology; writing

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– review and editing. **Giuseppe Pantaleo:** Methodology; visualization; writing – review and editing. **Massimo Amato:** Supervision; validation; writing – review and editing.

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KEYWORDS

adverse reaction, COVID-19, oral care, oral lesions, oral manifestations, SARS-CoV-2, vaccine

CONFLICT OF INTEREST

All the authors declare that no conflict of interest.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this article.

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