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Review

Oral lesions after COVID-19 vaccination: Immune mechanisms and clinical approach

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ABSTRACT

COVID-19 vaccination, although is a promising tool to overcome the pandemic, has side effects. There are increasing reports of oral lesions after COVID-19 vaccination. The aim of this review is to identify the occurrence of some oral lesions after COVID-19 vaccination, and highlight the underlying immune mechanisms involved. A narrative literature review was performed by searching electronic databases including PubMed, Scopus and Web of Science to investigate the oral lesions after COVID-19 vaccination. The inclusion criteria were original studies, including the case reports, case series, letter to the editor, and cross-sectional studies. The exclusion criteria included the studies which examined the oral lesions caused by COVID-19 infection. The information, including the number of participant(s) receiving vaccine, type of vaccine, dose number, side effect(s), time of onset following vaccination, healing time, treatment strategies for the existing lesions, and related mechanisms were then summarized in a data extraction sheet. The results of this review showed that some vaccines had side effects with oral involvement such as pemphigus vulgaris, bullous pemphigoid, herpes zoster, lichen planus, Stevens-Johnson syndrome and Behçet's disease. Future research needs to elucidate the physiopathology of oral manifestations after the COVID-19 vaccination, and better understand the risk factors associated with such responses. Sometimes vaccine's side effects may be due to the nocebo effect, which means that the person expects some adverse events to occur following the vaccine administration.

1. Introduction

The new Corona Virus Disease 2019 (COVID-19) is caused by a new strain of coronavirus, known as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), which has become a worldwide pandemic burden with severe health, social and economic consequences [1]. Currently, there are no approved specific COVID-19 therapies. Most current therapies aim to relieve symptoms or interfere with the immune response [2]. However, vaccinations are promising to be the essential medical tool for preventing and controlling the current COVID-19 pandemic [3].

The vaccines now available against SARS-CoV-2 are produced using one of the following technologies: (a) mRNA-based vaccines, (b) viral vector-based vaccines, (c) protein subunit vaccines and (d) inactivated or whole virus vaccines [4]. Developing a safe, effective vaccination is a lengthy and resource-intensive procedure that takes up to 10–15 years to accomplish completely. On the other hand, such a lengthy approach may endanger many more lives than it saves in a fast-growing pandemic. As the

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result of the COVID-19 epidemic's emergency condition, vaccines were licensed without long-term monitoring or standard procedures. So, it has raised concerns regarding vaccination effectiveness and safety in the long run [5].

Adverse drug reactions are serious side effects of medications, including vaccinations [6]. By and large, the advantages of vaccination obviously outweigh the risks. A study estimated that vaccination over the age of 60 in 33 countries prevented half a million deaths in about 1 year [7]. However, adverse reactions must be identified and addressed as soon as possible to minimize potential injury. Orofacial adverse reactions are reported increasingly after COVID-19 vaccination, including facial paralysis, oral mucosa ulcers, posterior palatal swelling and pain, pain on lips, gingiva, tongue or palatal area of the central incisor [8]. Dentists, dermatologists, and other health care providers should be prepared to identify oral lesions after the COVID-19 vaccination [9]. As a result, this review aims to evaluate the oral lesions after the COVID-19 vaccination and the immune mechanis involved.

2. Pathophysiology of oral lesions after COVID-19 vaccination

It has been reported by several studies in the literature that patients infected with COVID-19 show different manifestations of orofacial signs and symptoms. These lesions might be seen on the skin and the mucosa including maculopapular rash, urticaria, vesicles, ulceration, chilblain, petechiae, stomatitis, necrotizing periodontal disease, livedo reticularis, and erythema multiforme-like (EM) like lesions [10].

The ability of the SARS-CoV-2 for interacting with or binding to different cells in the body other than just type 2 alveolar cells in the lung, explains the wide range of symptoms and multi-organ failure which can be caused by the virus. However, immunosuppressive drug regimens suggested for the treatment of COVID-19, predispose patients to be infected with opportunistic microorganisms such as Candida. Another study conducted by Temo et al. [11] after the description of a COVID-19 patient with diffuse erythema on the lateral borders of tongue, suggested that mucosal hypersensitivity and immune system impairment can be associated with the oral manifestations of the patient.

Similarly, triggered immune response following the COVID-19 vaccination is a justification for causing lesions of the same appearance in vaccinated people. Genetic susceptibility for specific disorders is highly associated with the adverse events following vaccine administration. For instance, it was reported by Zermatten et al. [12] that a heterozygous Factor V Leiden mutation is accompanied by an increased risk of thromboembolism and may trigger the onset of oral mucositis after COVID-19 vaccination.

Among all the types of vaccines and vaccine designs developed against COVID-19, few of them are approved or authorized for emergency or full use, and are categorized into component viral or whole virus vaccines. Pfizer/BioNTech (BNT162b2) and Moderna (mRNA-1273) are mRNA vaccines, while the Johnson & Johnson and Astra Zeneca (ChAdOx1) contain a type of viral vector. Both types of vaccine mentioned, serve as T-cell-mediated immunity triggers, and T-cell activation following inflammatory cytokines secretion can cause possible adverse effects (see Fig. 1). A case of oral mucositis after the first dose of the ChAdOx1 vaccine was reported by Azzi et al. [13], owing to the mucosal hypersensitivity and autoimmunity induced by hereditary Factor V Leiden mutation.

Additionally, mRNA vaccines might trigger myeloid or plasmacytoid dendritic cells which are associated with hypersensitivity or autoimmunity. The other ingredients of mRNA were reported to be associated with the allergic reactions induced after vaccine administration. Polysorbate 80 is added to mRNA-based vaccines as a constituent component to dissolve mRNA in lipid nanoparticles, and is possibly involved in the cross-link reaction with polyethylene glycol (PEG), the other component of the mRNA-based vaccines that have been authenticated to enhance the immunogenicity and stability of vaccine particles [14].

Extensive vaccination of individuals and increasing the number of doses administered could be another justification for the high incidence rate of oral adverse reactions.

Based on a study conducted by Klugar et al. [15], more than one-sixth of the participants, among German healthcare workers, were referred with at least one oral adverse effect. The most prevalent oral manifestation of vaccine-related side effects was vesicles, with an incidence rate of 6.3%. Other adverse effects reported, in order of prevalence, were as followed: gingival bleeding (4.3%), halitosis (3.7%), oral paresthesia (2.2%), swollen mucosa (2.2%), and ulcers (2%), and with the time of onset ranging 1–28 days after vaccination. A summary of the recent publications on oral lesion following COVID-19 vaccination is available in Table 1.

3. Pemphigus vulgaris

Pemphigus vulgaris (PV) is an autoimmune condition reported following COVID-19 vaccination. Improper production of autoantibodies against desmosomal proteins localized in the lower epidermis of skin or mucosa called desmoglein (Dsg) 1 and 3, give rise to a damaging inflammatory response characterized by blistering and multiple erosions. Clinical manifestations of the disease appear in the form of painful, non-healing, and erosive lesions affecting oral mucosa or the upper part of the body skin.

Table 1
The summary of the available data on COVID-19 vaccines oral side effects.

Author	Type of article	Participant(s) receiving vaccines	Vaccine	Dose number	Side effect(s)	Time of onset following vaccination	Healing time	Treatment	Related mechanisms
Azzi et al. [37]	Letter to the editor	A 31-year-old woman	ChAdOx1	First dose	Oral mucositis	24 hours	3 days	Topical corticosteroids (i.e., Betamethasone effervescent tablets 1 mg three times per day, with progressive dose reduction) and topical miconazole oral gel 2%	Heterozygous Factor V Leiden mutation as a risk factor, mucosal hypersensitivity and autoimmunity
Thongprasom et al. [38]	Letter to the editor	A 38-year-old woman	ChAdOx1	First dose	Oral pemphigus lesion	1 week	1 week	a potent topical steroid, fluocinolone acetonide 0.05% mouthwash	-
Solimani et al. [16]	Letter to the editor	A 40-year-old female	BNT162b2	First and second dose	Pemphigus vulgaris	5 days after the first and 3 days after the second dose	-	Oral prednisone (1 mg per kg body weight, eventually tapered) and azathioprine (100 mg/day)	Autoimmunity (molecular mimicry, inflammatory dysregulation, epitope spreading or bystander activation)
Kulkarni et al. [39]	Letter to the editor	A 65-year-old female patient with multifocal lichen planus	-	First dose	Symptomatic recurrence of multifocal lichen planus	Immediately following the administration	3 weeks	-	T-cell activation
Manfredi et al. [13]	Letter to the editor	A 34-year-old healthy woman	BNT162b2	First dose	Diffuse ulcerative lesions on the floor of the mouth, oral erythema, angular cheilitis	2 days	15 days	Topical antibacterial agents and moisturizing lip balm	Hypersensitivity due to a cross-link reaction between Polysorbate 80 and Poly(ethylene glycol) (PEG)
Riad et al. [40]	Cross-sectional survey	522 participants	BNT162b2	First and second dose	The most common oral side effect was burning or bleeding gingiva (3.3%), followed by blisters (2.1%), ulcers (1.9%), and vesicles (1.5%).	1–21 days	-	-	The allergy to mRNA-based vaccine ingredients, inflammatory response, direct infiltration of SARS-CoV-2 to the lining epithelium of the oral cavity and secondary infection
Young et al. [19]	Case report	A 68-year-old man	BNT162b2	First and second dose	Bullous pemphigoid	3 days after first dose and 3 weeks after second dose	3 months after the first dose	Topical treatment of corticosteroids	Age-induced thymic atrophy and autoimmunity
Klugar et al. [15]	Cross-sectional survey	599 participants	BNT162b2 (386 participants), mRNA-1273 (88 participants) and ChAdOx1 (125 participants)	First and second dose	The most prevalent oral side effect was vesicles (6.3%), followed by bleeding gingiva (4.3%), halitosis (3.7%), oral paranesthesia (2.2%), swollen mucosa (2.2%), and ulcers (2%).	1 to 28 days (More than three-fourths of oral side effects emerged within the first week after vaccination)	-	-	-

(*continued on next page*)

Table 1 (*continued*)

Author	Type of article	Participant(s) receiving vaccines	Vaccine	Dose number	Side effect(s)	Time of onset following vaccination	Healing time	Treatment	Related mechanisms
Mazur et al. [35]	Cross-sectional survey	223 participants	BNT162b2 (217 partic-ipants), ChAdOx1 (5 partici-pants) and mRNA-1273 (1 partici-pants)	First and second dose	No significant correlation between vaccine administration for COVID-19 and facial and oral manifestations was observed.	1–28 days	-	-	-
Riad et al. [41]	Cross-sectional survey	539 participants	mRNA-based COVID-19 vaccines	First and second dose	Oral paraesthesia (1.3%) was the most common side effect, followed by oral ulcers (1.1%), taste disturbance (0.4%), skin rash (0.4%), and skin eruptions (0.4%).	-	-	-	-
Sharda et al. [10]	Letter to the editor	A 35-year-old female	BNT162b2,	-	Oral lichen planus erythematous base lesions with white reticular streaks over them, some of them had erosions	2 weeks	-	Short term course of steroids	-
Babazadeh et al. [28]	Case report	A 52-year-old woman	BBIBP-CorV	Second dose	Oral lichen planus Buccal lesions/ Desquamation of the lips	1 week	-	Oral antihistamines and topical corticosteroids	The Th1 response is elicited, increase in IL-2, TNF-α, and IFN-γ levels
Elboraey et al. [29]	Case report	A middle-aged female	BNT162b2	Second dose	SJS Large, red-colored bullae at the left retromolar area Whitish-yellow patches all over the tongue dorsal surface and upper and lower lips Multiple large ulcers at the buccal mucosa, labial mucosa, tongue, and palate	5 days	-	Mouthwash corticosteroids with addition of triamcinolone acetonide to 100 mL of sterile saline	Specific drugs stimulate immune cells such as cytotoxic T cells and natural killer cells that secrete granulysin, which destroys cells in the skin and mucous membrane by dysregulation of specific transmembrane protein pathways
Dash et al. [30]	Case report	A 60-year-old male	-	First dose	SJS Hemorrhagic crusting lesions over the lips, epidermal keratinocyte necrosis.	3 days	7 days	Oral cyclosporine 300 mg	Virotpes of the vaccine has been believed to cause SJS. $CD8^+$ T-lymphocyte response against epidermal cells causes apoptosis of keratinocytes and detachment of dermo-epidermal junction

(*continued on next page*)

Table 1 (*continued*)

Author	Type of article	Participant(s) receiving vaccines	Vaccine	Dose number	Side effect(s)	Time of onset following vaccination	Healing time	Treatment	Related mechanisms
Tagini et al. [32]	Letter to the editor	A woman in her late 20s	mRNA-1273	Second dose	Inaugural BD or a BD-like adverse event Painful oral ulcers	15 days	-	Colchicine 2×0.5mg/day Prednisone 1 mg/kg/day At the 1.5-month follow-up visit, azathioprine and acetazolamide were added to her treatment due to persistent papillary edema and intracranial hypertension findings.	-
Foster et al. [25]	Letter to the editor	A 17-year-old female with acute lymphoblastic leukemia (ALL) and a 20-year-old male with relapsed ALL	BNT162b2	First and second dose	VZV reactivation, a cluster of fluid-filled lesions on the face Oral lesions and a right-sided facial droop	In first case, 2 and 5 days following the first and second dose, respectively. In the second case, 17 days after his second dose.	7 days for the second case	2 week course of intravenous acyclovir transitioned to oral valacyclovir, for the first case. A 2-week course of valacyclovir with a steroid taper, in second case.	A reduction in lymphocytes, especially $CD3^+$ $CD8^+$ lymphocytes, which can occur during infection with SARS-CoV-2, has been proposed as a potential mechanism triggering reactivation of herpesviruses.
Fukuoka H., et al. [26]	Report of five cases	Five Japanese patients (four females and one male), whose age range was 59–97 years	BNT162b2	First and second dose	Oral herpes zoster Unilateral acute rash	Ranged from 1–3 weeks	-	Four patients did not receive any treatment for their oral HZ, but one patient also had skin reactions on her right orbit and ear and was thus treated with an antiviral drug.	-

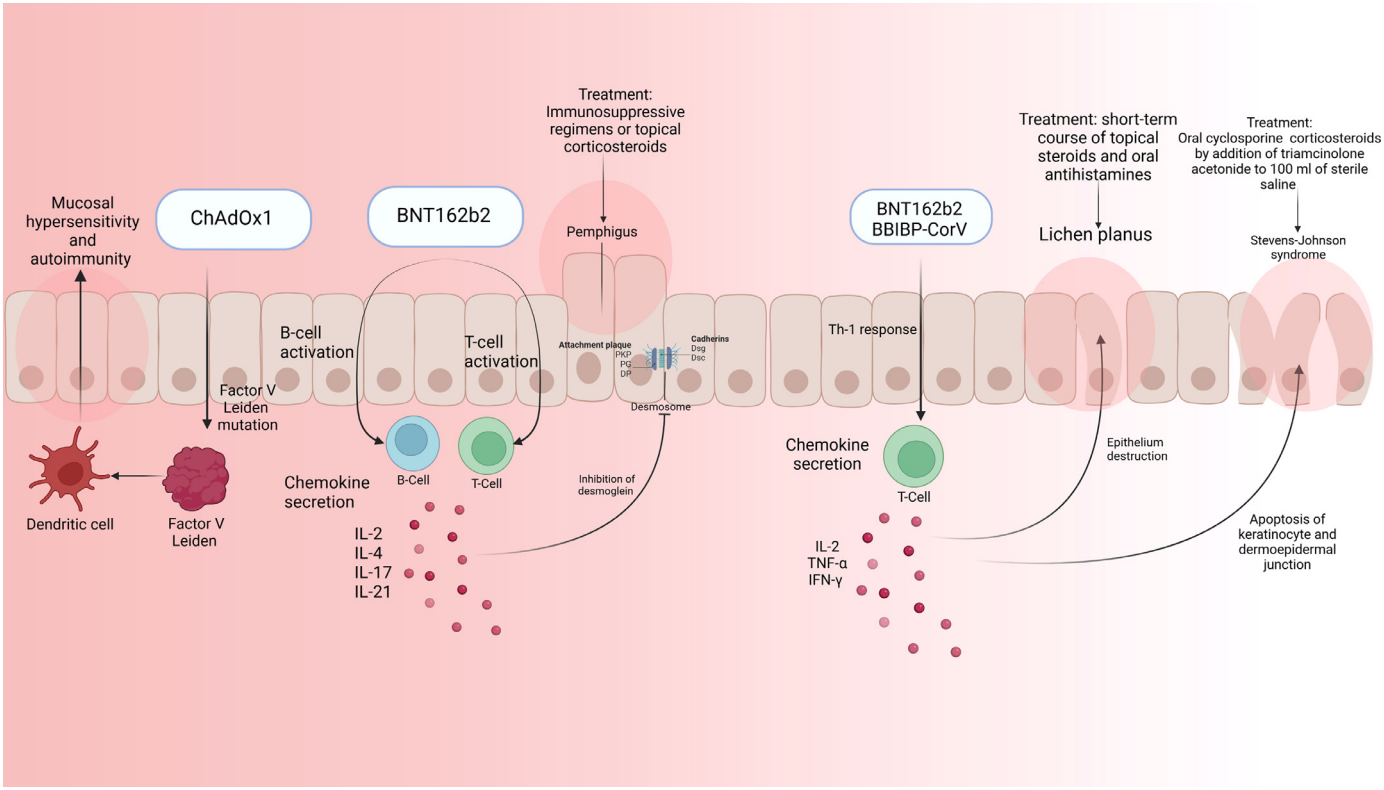

Fig. 1. Pathophysiology of the COVID-19 vaccines oral lesions.

In a case reported by Solimani et al. [16], oral lesions appeared 3 days after receiving the first dose of the BNT162b2 vaccine, and worsened 5 days after administration of the second dose. The histopathologic and direct immunofluorescence evaluation of the lesions with a view of honeycomb-like epidermal pattern of intercellular Immunoglobulin G (IgG) confirm the diagnosis of PV along with detection of anti-Dsg3 and Dsg1 autoantibodies in serum. Immunosuppressive regimens or topical corticosteroids are recommended.

Activation of T and B cells followed by BNT162b2 administration, and increased production of related cytokines including interleukin (IL)-2, IL-4, IL-17, and IL-21 is associated with the onset of possible autoimmune disorders like pemphigus in genetically susceptible individuals [17,18].

4. Bullous pemphigoid

Bullous pemphigoid (BP) is an autoimmune condition that causes large, fluid-filled blisters on skin and/or mucosa due to the production of autoantibodies against hemi-desmosomal proteins. A case of BP related to the SARS-CoV-2 mRNA vaccine (BNT162b2) was reported by Young et al., and a single ulcer appeared 2 weeks after the patient received the second dose of vaccine along with cutaneous blisters and lesions located over his back. With the help of topical treatment of corticosteroids, all the blisters were resolved by the next follow-up. The exact mechanism by which vaccines induce BP still remains unclear. However, considering the higher incidence of disease in older adults, immunosenescence leads to changes in the immune function of the elderly, and might be associated with autoimmune disease [19].

5. Oral herpes zoster

Recently some cases have been reported in the literature characterized by oral herpes zoster (HZ) following COVID-19 vaccination. It is believed that the varicella-zoster virus (VZV) is latent in the spinal dorsal root ganglia (DRG) and trigeminal ganglia (TG). Previous studies have demonstrated that vaccines like hepatitis A, influenza, rabies and Japanese encephalitis vaccines can also cause HZ [20–22, 23]. In these cases, after COVID-19 vaccination, reactivation of the VZV caused oral HZ. The mechanism is still unclear. However, some studies suggested the immune-modulatory effect of vaccines might lead to VZV reactivation. Oral HZ can appear after the first or second dose of the BNT162b2, mRNA-1273, AZD1222 (AstraZeneca), mRNA COVID vaccine (not specified) and inactivated SARS-CoV-2 vaccine [24].

It can happen from 2 days to 38 days after the vaccine administration. Symptoms included a cluster of fluid-filled lesions on the face, multiple unilateral small ulcers in the mouth, and one-sided facial droop [24–26].

VZV can also be reactivated with symptomatic COVID-19 [26]. The SARS-Cov-2 virus causes immune dysfunc-

tion and decreased body resistance to infections, therefore, it may lead to oral HZ [27]. In one study which reported the recurrent oral HZ in 2 patients with leukemia after COVID-19 infection, one of the patients was treated by a 2-week course of valacyclovir with a steroid taper, and the other patient was treated with acyclovir intravenously, and then converted to oral valacyclovir to complete in a 2-week treatment period, and thereafter received prophylactic dosing of valacyclovir [25]. Thus, dentists and dermatologists should be aware of the probable presence of the oral HZ in their patients with a history of COVID-19 vaccination or SARS-CoV-2 infection.

6. Oral lichen planus

Oral lichen planus (OLP) is an inflammatory, chronic, autoimmune and T cell-mediated disease. Its origin is not exactly known. In the oral cavity, it commonly affects the oral mucosa and the lips. Vaccination is one of the predisposing factors of OLP. Tetanus-diphtheria–acellular pertussis (Tdap), hepatitis B vaccine, measles–mumps–rubella (MMR), rabies, and influenza vaccines have been reported to provoke OLP [28].

The reported cases presented erythematous-based lesions with white reticular streaks over them, and some of them had erosions. Also, the patients presented desquamation of the lips. These lesions appeared 1 week to 2 weeks after the second dose administration of the BBIBP-CorV (Sinopharm) and BNT162b2. Patients were treated by a short-term course of topical steroids and oral antihistamines [10,28].

In the literature the related mechanism suggested for OLP following COVID-19 vaccination was the increased Th1 response, which sequentially leads to the increase of IL-2, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ levels [28].

Studies have shown that COVID-19 might be a potential trigger for OLP. Therefore, in the reported cases of OLP due to COVID-19 vaccination, infection with SARS-CoV-2 must be ruled out. In P. Sharda et al.'s study, patients' RT-PCR tests were negative, and they did not have any symptoms of COVID-19. However, we must be aware of the subclinical COVID-19 which cannot be ruled out [10].

7. Stevens-Johnson syndrome

Stevens-Johnson syndrome (SJS) is an acute hypersensitivity reaction that affects mucous membrane and skin, and leads to their necrosis. The prevalence of SJS is less than 1 to 2 cases per 100 million people per year. The related mechanism of SJS is a cytotoxic reaction of the immune system in keratinocytes which leads to extensive apoptosis in these cells. Factors like medications, bacterial and viral infections, and some vaccines such as smallpox, varicella, MMR, and influenza vaccine have been reported to cause the SJS. However, in rare cases of SJS, vaccination has been reported as a causative factor [29].

In the literature, two cases have been reported for SJS after the COVID-19 vaccination so far. Generally, oral manifestations of SJS are described as polymorphic, erosive, ampullary and erythematous lesions. In these two cases oral manifestations were large, red-colored bullae at the retromolar area, whitish-yellow patches all over the tongue, dorsal surface, upper and lower lips, and multiple large ulcers at the buccal mucosa, labial mucosa, tongue and palate, and hemorrhagic crusting over the lips. One of the cases showed the symptoms 5 days after the second dose of the BNT162b1 vaccine. The other case showed the symptoms 7 days after vaccination (The vaccine type and the dose number of the latter case were not mentioned) [29,30].

COVID-19 vaccines have two components: virotopes and excipients. Dash S. et al. hypothesized that virotopes of the vaccine caused the SJS in the reported case. They believed in genetically predisposed individuals, the virotopes component induced $CD8^+$ T-lymphocyte response against epidermal cells and the keratinocytes apoptosis, and dermo-epidermal junction detachment resulted in SJS. However, this hypothesis must be further investigated [30].

Both of the patients were fully recovered. One of them was treated with oral cyclosporine 300 mg daily, and the other with mouthwash corticosteroids by addition of triamcinolone acetonide to 100 mL of sterile saline [29,30].

8. Behçet's-like adverse event or inaugural Behçet's disease

Bechet's disease (BD) is an inflammatory disease of unknown etiology, presented by painful oral and genitalia ulcers, eye involvement and other systemic manifestations [31].

One case of new-onset Behçet's disease or a BD-like adverse event occurring 15 days after the second dose of the SARS-CoV-2 mRNA-1273 vaccine has been reported so far. The oral manifestation was painful ulcers. The patient was prescribed colchicine 2×0.5 mg/day and prednisone 1 mg/kg/day. However, she was not fully recovered after 1.5 months. This patient was the first reported case of Behçet's-like adverse event following the COVID-19 vaccination. The possible mechanism that induced this inflammatory reaction needs to be investigated [32].

9. Discussion on reports of the oral side effects of COVID-19 vaccination

Developing a safe and effective vaccine is a time- and resource-intensive procedure. As the result of the COVID-19 pandemic's emergency, several phases in vaccine development have been expedited. This has raised concerns

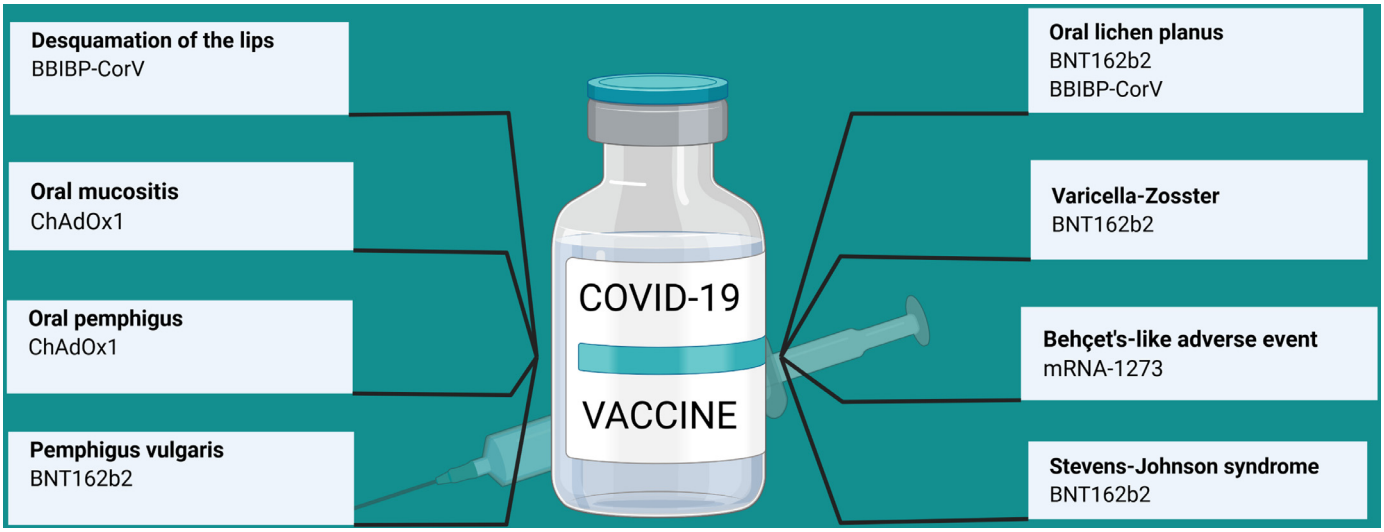

Fig. 2. Summary of the clinical presentations of oral side effects of COVID-19 vaccines.

regarding safety in the long run. Our study evaluates oral manifestations after the COVID-19 vaccination (see Fig. 2). The study examined the oral side effects of different types of vaccines, the dose of the vaccine, the time of onset of side effects, the type of treatment and the duration of treatment.

Side effects from vaccinations could be the result of existing medical disorders interfering with the vaccine, or they could be the result of a new condition. Various articles have hypothesized that VZV activation is due to the immune-modulatory effect of the vaccine [24]. The development of autoimmune diseases such as OLP, PV and BV can be linked to the activation of T and B cells, which leads to an increase in the production of related cytokines after vaccination [17–19,28]. In addition, hypersensitivity reactions such as SJS may be due to the induction of $CD8^+$ T-lymphocyte response against epidermal cells [30]. On the other hand, side effects may represent a complication of COVID-19 disease in patients who already have a concomitant with SARS-CoV-2. Some studies have shown that COVID-19 might be a potential trigger for OLP [10], and it can also reactive VZV [26]. Physicians and dentists should consider that the mentioned oral lesions could be a complication of either COVID-19 infection or vaccination.

There are still ambiguities regarding the interaction of COVID-19 vaccines with other drugs. Kow et al. [33] proposed COVID-19 vaccines (mRNA-based and viral vector-based ones) might interfere with antiepileptic drugs owing to the production of interferon-gamma generated by the vaccines. In Riadet al.'s [34] study, antihistamines usage were accompanied by higher adjusted odds of various side effects, for instance, injection site redness, headache, nausea, fever, chills and lymphadenopathy.

The COVID-19 vaccination procedure may be one of the first observed in the twenty-first century, spreading globally in a short period of time and on a scale that includes practically all ethnic, geographical, and age groupings [35]. This situation increases the possibility of seeing the incidence of side effects including oral signs, which may have been seen as coincidental with other vaccinations.

Sometimes vaccine's side effects may be due to the nocebo effect, which means that the person expects some adverse events to occur following the administration of the vaccine. For example, In the case of lichen planus, Kalkur et al. [36] claimed that it was possibly linked to stress.

Future research needs to elucidate the physiopathology of oral manifestations after the COVID-19 vaccination, and better understand the risk factors associated with such responses. The relationship between a patient's medical history, genetic profile and the vaccine's probable allergic and non-allergic adverse effects remains unknown. The majority of the research included in this review were case reports and case series, which can make interpreting their findings difficult. As a result, further research with robust designs, such as cohort studies, is required in this sector to provide more accurate and detailed data.

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Declaration of competing interest

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Data available statement

No data, models, or code were generated or used during the study.

Ethics statement

Ethics approval were waived for this study because no patients' data were reported. We declare that our research thoroughly adheres to all the ethical guidelines in concern.

Informed consent

Informed consent was waived for this study because no patients' data were reported.

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