Review article

CLINICAL AND EXPERIMENTAL VACCINE RESEARCH

Occurrence of erythema multiforme following COVID-19 vaccination: a review

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The fast development of vaccines against the novel coronavirus disease is among the most critical steps taken to control this potentially fatal viral disease. Like other vaccines, the coronavirus disease 2019 (COVID-19) vaccines can also cause unwanted reactions. Erythema multiforme (EM) is among the oral mucocutaneous side effects of COVID-19 vaccines. This study aimed to comprehensively review the reported cases of EM since the global onset of COVID-19 vaccination. Data from 31 relevant studies regarding the type and dose of COVID-19 vaccines administered, time of initiation of symptoms, age, and gender of patients, site of involvement, patients' medical history, and treatment options were extracted. In total, 90 patients were identified with EM as a side effect of COVID-19 vaccination across studies. EM had the highest frequency after receiving the first dose of mRNA vaccines in older individuals. The first symptoms of EM appeared in less than 3 days in 45% and after 3 days in 55% of patients. EM is not a common side effect of COVID-19 vaccination, and fear of its occurrence should not impede vaccination.

Keywords: Erythema multiforme, COVID-19 vaccines, COVID-19

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the seventh human coronavirus which was first detected in Wuhan, China, and led to the recent pneumonia pandemic [1,2]. The coronavirus disease-2019 (COVID-19) afflicted thousands of people worldwide and resulted in hospitalization of 80% of affected individuals and death of 7.4% due to infection complications [3]. COVID-19 vaccines are currently the most efficient intervention to control COVID-19 pandemic [4]. Since April 15, 2021, 13 vaccines have acquired legal approval, including the followings [5]: Moderna's mRNA-1273 , Pfizer-BioNTech's BNT162b2, Oxford-AstraZeneca's AZD1222, Gamaleya's Sputnik V, Johnson & Johnson's Janssen's Ad26.COV2.S, Sinovac's CoronaVac, Sinopharm's BBIBP-CorV, The Vector Institute's EpiVacCorona, CanSino's Convidecia, Bharat's Covaxin, Sinopharm's WIBP-CorV, Chumakov's CoviVac, and Anhui Zhifei Longcom's ZF2001.

Similar to many other medications and vaccines, COVID-19 vaccines can also cause unwanted reactions, which are mainly immune reactions elicited by vaccination [6]. Cutaneous disorders are among the most commonly reported complications following vaccination. Nonetheless, such reactions are mainly limited to redness, swelling, and tenderness of the injection site, which may occur in up to 90% of those receiving the vaccines [7].

Erythema multiforme (EM) is among the cutaneous side effects of COVID-19 vaccination [8]. EM is a cutaneous inflammatory condition, which is classically related to infections, and is most common following herpes simplex virus and mycoplasma infections. However, a wide range of stimulants such as infective agents, medications, and even internal diseases may also trigger its occurrence. Skin lesions in EM mainly include targetoid papules comprised of three distinct concentric regions [9]. EM is classified into two groups of major and minor. In EM minor, cutaneous lesions cause less than 10% body surface involvement especially on the acral extensor surfaces with minimal or no mucosal involvement [10]. EM major has a cutaneous pattern similar to that of EM minor but with greater extension and mucosal involvement [11,12]. Also, some cases of oral mucosal ulcers have been reported without any skin lesions, which are classified under a new category of oral EM [11]. Thus, their identification and differentiation from other oral ulcerative disorders is important for early management and follow-up [11,13].

EM is a rare adverse complication of some other vaccines as well, including mumps, measles, and hepatitis B [8], and to date, 984 cases of EM due to vaccination have been reported [9]. Also, some EM-like reactions related to COVID-19 have been reported which were mainly in the form of acral typical lesions in younger patients and more extensive atypical lesions in adults [14].

To the best of the authors' knowledge, no comprehensive review is available regarding the occurrence of EM after COVID-19 vaccination. Thus, this study was conducted aiming to review all the reported cases of EM with oral and cutaneous lesions since the onset of COVID-19 vaccination.

Methods

Several studies have reported the occurrence of EM following COVID-19 vaccination. This study evaluated all relevant case reports/case series, registry-based studies, and reviews published until April 2022. An electronic search of the literature was carried out in PubMed, Google Scholar, Science Direct, and Scopus databases using the following keywords: Erythema Multiforme, Targetoid Lesion, Iris Lesion, COVID Vaccination, Corona Vaccination, EM, Rowell's Syndrome, Cutaneous Reaction, and Skin Reaction.

Finally, 31 articles were retrieved. Data including type and dose of vaccine, time of onset of symptoms after vaccination, age and gender of patients, site of involvement, medical history of patients, and treatment options were extracted from the articles.

Results

Table 1 [8,15-38] and Table 2 [39-44] presents the results obtained from evaluation of 31 eligible articles retrieved from the databases.

The mean age of 90 patients that developed EM following COVID-19 vaccination was approximately 51 years. The prevalence of EM in females was twice that in males. EM due to COVID-19 vaccination appeared most after the first dose of vaccine. Most of the vaccines were mRNA vaccines (32% Moderna, and 47% Pfizer). 20% of patients had a history of an underlying condition or medication intake. Of all patients who developed EM after COVID-19 vaccination, 37% had oral, 93% had cutaneous, and 31% had both oral and cutaneous manifestations.

Discussion

Widespread administration of COVID-19 vaccines approved by the US Food and Drug Administration has created some concerns regarding their potential side effects [45]. Cutaneous complications are among the most commonly reported side effects of vaccines [9].

EM is an acute self-limiting reaction caused by exaggerated immune response, which is characterized by targetoid skin lesions that may be associated with mucosal involvement as well.

The etiology of EM is unknown; however, it appears that a trigger (usually infection) can elicit a cellular immune response to antigens through CD4 type 1 T-helper cells, and induce the release of interferon IFN-gamma and eventual activation of autoreactive system in genetically susceptible individuals [9]. IFN-gamma has been identified as a marker of T cell response after CoronaVac vaccination [46]. Thus, it appears that COVID-19 vaccination can serve as a stimulant and activate the same pathway that is activated by EM, and lead to type III or type IV hypersensitivity reactions by the vaccine itself or its components [6].

In the present study, data of 31 articles retrieved by electronic search of databases were reviewed, revealing 90 patients that developed EM following COVID-19 vaccination. The mean age of patients with oral and cutaneous manifestations of EM following COVID-19 vaccination was approximately 51 years. In terms of age, patients were categorized in-

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Table 1. Demographic factors and characteristics of coronavirus disease 2019 vaccines received by patients who developed EM following vaccination

No.	Author	Vaccine type	Dose	Latency period of EM after vaccination	Gender	Age (yr)	Medical history	Location (involved areas)	Treatment options
1	Wunderlich et al. [15]	Pfizer	Second	2 days	F	61	Unremarkable	Skin (trunk and the lower extremities) and oral lesions	Symptomatic topical therapy with zinc lotion for areas with incipient blistering and glucocorticoids
2	Lavery et al. [16]	Pfizer	- First - Second	- 12 hours - 1 day	F	58	Rheumatoid arthritis for which she was taking abatacept, endometriosis, hypertension, and a multinodular thyroid goiter	Palms of the hands and soles of the feet	Topical clobetasol ointment
3	Sechi et al. [17]	Pfizer	First	4 days	F	76	Lung adenocarcinoma (stage IV), arterial hypertension, type II diabetes mellitus, chronic obstructive pulmonary disease	Non-coalescing target-like lesions mainly distributed on the limbs	Methylprednisolone 0.1% cream twice daily for 10 days
4	de Las Vecillas et al. [18]	Pfizer	Second	1 day	F	47	Unremarkable	Lesions on the neck, thorax, flexor surface of upper extremities, abdomen, back, groins, and thighs	Cetirizine 10 mg 1 tablet every 12 hours
5	Kothari et al. [19]	AstraZeneca	First	3 days	F	25	Unremarkable	Both arms, face, and upper back	Short course of antihistamines and topical steroids
6	QJM (2022) [20]	Moderna	First	9 days	F	27	Unremarkable	Acral extremities	The rash spontaneously disappeared 10 days after onset
7	Bujan Bonino et al. [8]	Pfizer	Second	6 days	F	91	Unremarkable	Left deltoid area, neck, and extremities	High potency topical corticosteroids (clobetasol propionate ointment)
8	Gambichler et al. [21]	Pfizer	First	1 day	F	74	Severe dementia syndrome; taking pantoprazole	Trunk and extremities	Tapered systemic prednisolone 150 mg/day
9	Kim et al. [22]	Pfizer	First	10 days	F	78	Unremarkable	Entire body (skin rash)+oral mucosa	Systemic corticosteroid treatment with topical agents and oral antihistamine
10	Scharf et al. [23]	Pfizer	NR	3 days	F	27	Unremarkable	Nevocentric EM presenting on arms and hands and thighs	Cetirizine 10 mg and moisturizers
11	Lopes et al. [24]	CoronaVac (Sinovac)	Second	5 days	M	75	Hypertension; use of Ramipril 5 mg for the past 7 years	Knees, face, trunk, and forehead	Topical corticosteroids and oral antihistamines
12	Karatas et al. [25]	Moderna	First	10 days	M	61	Crohn's disease; taking 6-mercaptopurine and adalimumab	Face, trunk, and extremities, with multiple vesicles and erosions on the oral mucosa (oral and nasal involvement)	Symptomatic treatment
		Pfizer	Second	3 days	F	21	Unremarkable	Extremities, including the palms and soles, with rare lesions on the trunk	Prednisone
		Pfizer	Second	5 days	M	50	Hyperlipidemia and anxiety disorder	Trunk and extremities, palmoplantar skin, and hemorrhagic crusts on the oral mucosa	Topical corticosteroid in addition to prednisone
		Moderna	Second	2 days	F	53	Type 2 diabetes mellitus and multinodular goiter	Dorsum of the hands and extremities	Topical corticosteroid

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Table 1. Continued

No.	Author	Vaccine type	Dose	Latency period of EM after vaccination	Gender	Age (yr)	Medical history	Location (involved areas)	Treatment options
13	Iwasawa et al. [26]	Pfizer	Second	1 day	F	52	History of myasthenia gravis and chronic thyroiditis, without therapy	Trunk and extremities	Oral prednisolone 20 mg/day as well as topical corticosteroids and oral antihistamines
14	Saibene et al. [27]	Moderna	Second	1 day	F	58	Recalling an analogous clinical picture after administration of metamizole and penicillin (respectively 27 and 16 years before); under treatment with oral sertraline, lorazepam, and atorvastatin	Oral floor swelling, excruciating oral burning pain, dysphagia and odynophagia, and cutaneous lesions on the right thigh and calf	IV steroids, tapering began on day 5+oral prednisone
15	Ibrahim [28]	Pfizer	First	1 day	F	49	Oral paracetamol 2 weeks ago for headache	Both hands and few small ulcers over buccal mucosa and palatal tonsils	Antihistamine
16	Lefeuvre et al. [29]	Pfizer	First	11 days	M	62	Verapamil for paroxysmal supraventricular tachycardia	Trunk+palms and soles with erosions on the swollen lips and oral mucosa	2 g/kg intravenous immunoglobulin as a single infusion as well as oral aspirin at a dosage of 160 mg/day
17	Borg et al. [30]	Pfizer	First	2 days	M	38	Unremarkable	Hard palate	Prednisolone 40 mg daily for five days and most lesions resolved within seven days
18	Burlando et al. [31]	Moderna	Second	2 days	M	67	NR	Generalized bullous pruritic EM	NR
19	Wang et al. [32]	Pfizer (3 cases)	NR	NR	NR	NR	NR	NR	NR
20	Katayama et al. [33]	Pfizer	Second	3 days	F	60	Unremarkable	Elbows	Topical corticosteroid
21	Petruzzi et al. [34]	Pfizer	- First - Second	- 1–10 days - Immediately	F	55	Mucous membrane pemphigoid	- Lips, oral mucosa, hands, knees, and feet - Hands	Prednisone 25 mg per day, in association with topical 0.05% clobetasol propionate ointment
		Pfizer	First	7 days	M	15	West syndrome	Oral mucosa and whole body	Prednisone 25 mg per day, in association with topical 0.05% clobetasol propionate ointment
		Pfizer	Second	1 day	F	49	Unremarkable	Tongue and the mouth floor	Prednisone 25 mg per day, in association with topical 0.05% clobetasol propionate ointment
		Pfizer	First	18 days	F	20	Celiac disease, lactose intolerance, and spastic colon	Erosions on the gingiva and labial mucosa	Prednisone 25 mg per day, in association with topical 0.05% clobetasol propionate ointment
22	Gimeno Castillo et al. [35]	Moderna	Third	4 days	M	29	Anterior recurrent human leucocyte antigen-b27 negative uveitis under treatment with salazopyrin	Labial and palate mucositis and palms, soles, and ears	Oral prednisone (30 mg/day)+salazopyrin
23	Haranaka et al. [36]	Pfizer	- First - Second	- 1 day - 2 days	F	74	Unremarkable	- Mild swelling and pain at the injection site - Skin rash	Topical steroids, topical antihistamines, and oral antihistamines
24	Majenka et al. [37]	Pfizer	Second	3 days	M	75	NR	Skin involvement	Systemic steroid (prednisolone)
		Moderna	Second	9 days	M	68	NR	Skin involvement	Topical steroid (betamethasone)

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Table 1. Continued

No.	Author	Vaccine type	Dose	Latency period of EM after vaccination	Gender	Age (yr)	Medical history	Location (involved areas)	Treatment options
25	Niebel et al. [38]	Pfizer	First	4 days	M	41	Hydroxychloroquine 200 mg and prednisolone 5 mg for 4 years due to rheumatic joint stiffness as well as Raynaud's syndrome and puffy fingers	Generalized annular plaques	Prednisolone 1 mg/kg body weight in combination with topical corticosteroids+therapy with hydroxychloroquine was maintained and methotrexate 15 mg subcutaneously was added to prevent relapses
		Moderna	First	10 days	F	22	Hypothyroidism	Extensor surfaces including hands and feet	Short pulse of prednisolone 1 mg/kg bodyweight in combination with ibuprofen and topical corticosteroids

EM, erythema multiforme; F, female; M, male; NR, not reported.

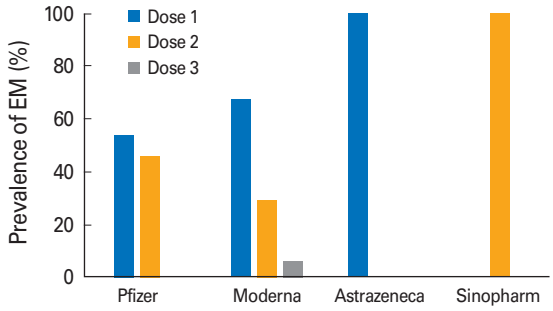

Fig. 1. Occurrence of erythema multiforme (EM) based on the dose of Pfizer, Moderna, AstraZeneca, and Sinopharm vaccines.

to two groups of ≥50 years and <50 years. Accordingly, 40% of patients with EM were <50 years and 60% were ≥50 years. Jimenez-Cauhe et al. [47] reported that all four patients who developed EM following COVID-19 infection were females with a mean age of 66.75 years. Although EM may occur at any age, it has the highest prevalence rate in young adults between 20 to 40 years [10]. This statement is different from the present findings, which may be due to the higher prevalence and priority of COVID-19 vaccination in the elderly.

The present study showed that the prevalence of EM following COVID-19 vaccination in females was twice that in males. Previous studies have also demonstrated that females have stronger immune responses to external antigens such as vaccines than males, and thus, they more commonly experience side effects such as EM [48-52].

EM due to COVID-19 vaccination appeared after the first dose of vaccine in 44%, after the second dose in 30%, and after the third dose in 1%. Information regarding the dose of vaccine was not disclosed for 25% of the cases. In the reported cases, the prevalence of EM was 54% after the first dose and 46% after the second dose of Pfizer, and 67% after the first dose, 29% after the second dose, and 4% after the third dose of Moderna. In cases who received AstraZeneca vaccine whose vaccine dose had been disclosed, all cases of EM occurred after the first dose of vaccine. One case of EM was reported after Sinopharm vaccine, which occurred after receiving the second dose (Fig. 1).

In a cohort study by Robinson et al. [53], only 13% of individuals who experienced cutaneous symptoms after the first dose of COVID-19 mRNA vaccination developed cutaneous reactions again after the second dose. McMahon et al. [39] in their registry-based study aimed to assess the development of skin reactions following receiving Pfizer and Moderna COVID-19 vaccines. They reported that injection site reactions were the most common cutaneous side effect, which were

Table 2. Number of patients who developed erythema multiforme following the first or second dose of coronavirus disease 2019 vaccination as reported in the studies

No.	Author	Study design	Pfizer		Moderna		Johnson & Johnson		Astra Zeneca		Sinopharm		Baharat		Unknown	
			D1	D2	D1	D2	D1	D2	D1	D2	D1	D2	D1	D2	D1	D2
26	Tan et al. [40]	Review	7	2	0	1	0	0	0	0	0	0	0	0	0	0
27	Freeman et al. [41]	Registry-based	1	4	13	3	0	0	1	0	0	0	0	0	1	1
28	McMahon et al. [39]	Registry-based	0	0	3	0	0	0	0	0	0	0	0	0	0	0
29	Pourani et al. [42]	Cross-sectional questionnaire-based	0	0	0	0	0	0	1 (dose NR)		1 (dose NR)		0	0	0	0
30	Lee et al. [43]	Nationwide observational study	2 (dose NR)		0	0	0	0	13 (dose NR)		0	0	0	0	0	0
31	McMahon et al. [44]	Registry-based	0	0	1 (dose NR)		0	0	0	0	0	0	0	0	0	0

D, dose; NR, not reported.

more common by approximately 2.7 times after receiving the first dose compared with the second dose. Also, vaccinated individuals reported experiencing less cutaneous side effects after the second dose.

Lower percentage of complications after the second dose can be due to the fact that those who developed complications after the first dose did not receive the second dose. Time of conduction of studies is also important, since some studies were conducted before the widespread administration of second dose. Moreover, another study showed that the immune response elicited by the injection of first dose can modify and balance the subsequent reactions after receiving the second dose [40]. Nonetheless, Studdiford et al. [54] discussed that patients who developed EM following vaccination had better not receive any additional dose due to the possibility of development of more severe skin reactions upon re-exposure. Therefore, although occurrence of EM after vaccination is not a contraindication for re-vaccination, such patients are recommended to undergo precise monitoring after re-vaccination since they may be at higher risk of developing more severe side effects such as EM major, Stevens-Johnson syndrome, or toxic epidermal necrolysis [55].

Of 96 doses of COVID-19 vaccines that led to development of EM, 79% were mRNA vaccines (32% Moderna and 47% Pfizer), 17% were adenoviral vector vaccines (AstraZeneca), 2% were inactivated whole-virus vaccines (Sinopharm), and 2% were unknown (Fig. 2). Other studies also reported allergic reactions following COVID-19 vaccination, especially mRNA vaccines [56-61].

The spike protein of coronavirus has been coded in mRNA COVID-19 vaccines. Immunohistochemical assessment of cases who received such vaccines and developed EM revealed this hallmark in their endothelial cells and epithelial

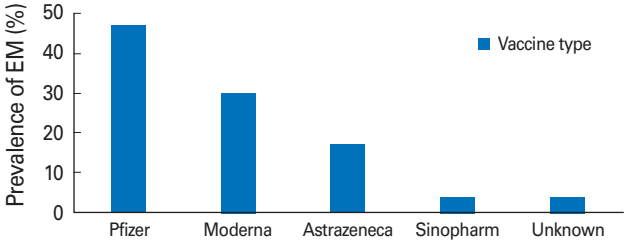

Fig. 2. Occurrence of erythema multiforme (EM) based on the type of received vaccine.

cells of their endocrine ducts. Thus, EM secondary to COVID-19 vaccination with mRNA vaccines is an expected complication [14]. Also, with respect to Pfizer and Moderna viruses, it has been reported that their components such as polyethylene glycol may cause systemic hypersensitivity reactions in patients [59]. In addition to polyethylene glycol, Moderna vaccines contain tromethamine, which can also cause allergic reactions to the gadolinium-based contrast agents [62]. Therefore, EM is probably more common after the injection of mRNA COVID-19 vaccines.

On the other hand, adjuvants such as aluminum salt present in AstraZeneca vaccine can also cause type IV hypersensitivity reaction [63]. AstraZeneca vaccine also contains polysorbate 80 which may be responsible for allergic reactions. To date, only one case of anaphylaxis due to AstraZeneca vaccine has been reported in the literature [64].

In general, inactive vaccines are safer in terms of possible allergic reactions [65]. Nonetheless, it should be noted that these vaccines also cause milder immune responses to SARS-CoV-2 compared with other vaccines [66].

Of the 90 cases of EM reported in this review, 20% of patients had a history of an underlying condition or medication intake while 12% had an unremarkable medical history. The

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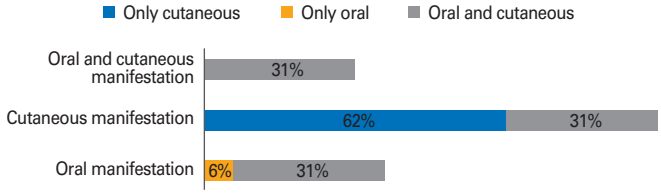

Fig. 3. Frequency of oral and cutaneous manifestations of erythema multiforme after coronavirus disease 2019 vaccination.

medical history of the remaining patients had not been disclosed. Of patients whose medical history had been reported, approximately one-fourth had auto-immune diseases. Evidence shows that EM may occur following some autoimmune diseases such as the inflammatory bowel disease or rheumatoid arthritis [67]. Although the etiology of rheumatoid arthritis is still unknown, it is believed to have an autoimmune origin. Infectious agents may serve as a trigger in genetically susceptible patients, which are determined by human leucocyte antigen (HLA) genes, and cause immune system dysregulation [68]. The major histocompatibility complex (which is a specific gene complex located on the short arm of chromosome 6 in humans, known as the HLA system) determines the host response to antigens, at least to some extent. Thus, various HLA associations reported in EM are not far from expectation [69-74].

Further assessments in the present study revealed that patients with a history of autoimmune disease received Pfizer vaccine in 75% and Moderna vaccine in 25% of the cases. Considering the possibility of development of EM as the result of presence of an autoimmune condition combined with mRNA vaccination, such patients should preferably receive another vaccine type as a precautionary measure.

Of all patients who developed EM after COVID-19 vaccination, 37% had oral, 93% had cutaneous, and 31% had both oral and cutaneous manifestations (Fig. 3). It appears that cutaneous hypersensitivity reactions due to vaccination occur as the result of expression of vaccine antigens on the surface of keratinocytes. This can lead to T lymphocyte immune responses against epidermal cells, which eventually result in cell death and dermo-epidermal separation [75]. Moreover, a previous study reported that EM may manifest in the form of oral mucosal ulcers without cutaneous involvement. Involvement of oral mucosa, especially the labial mucosa, buccal mucosa, non-attached gingiva, and lip vermilion occurs in over 70% of the cases of EM [76]. Oral EM is characterized by periodic development of intraoral vesicles and erosions, with significant adverse effects on speech, mastication, and deglutition. Diagnosis is difficult in most cases, because the clinical manifestations of EM mimic those of other oral inflammatory and vesiculobullous diseases [77]. Oral EM more commonly occurs in adolescents and young adults; however, it may occur at any age [78]. It may occur periodically ranging from every 3 weeks to once a year [79].

Regarding the latency period until development of symptoms, patients were divided into two groups of ≥3 days and <3 days in the present study. Accordingly, 45% of patients developed EM in less than 3 days after vaccination while 55% showed the first symptoms after 3 days. Other studies reported insignificant reactions such as fever, and swelling, redness and pain of the injection site within 3 days after vaccination, and significant local or delayed reactions within 4 days or longer after the first dose of vaccines (hepatitis, rubella, etc.) [80]. Chahal et al. [75] reported an average latency period of 6 days after vaccination (smallpox, hepatitis B, etc.) until development of EM.

Although there is no specific treatment for EM, corticosteroids are most commonly administered for management of acute cases. Corticosteroids are prescribed topically, orally (30–90 mg prednisolone daily) or intravenously (0.5–1 mg/kg body weight methyl prednisolone every 8 hours) for more severe cases [81]. Management of oral EM is mainly palliative, and includes oral analgesics and lidocaine viscous mouthwash. Adequate nutrition and fluid intake are also emphasized [78].

Conclusion

EM is a rare occurrence after vaccination, and should not hinder vaccination. Due to its rarity, finding a causal relationship is difficult. Nonetheless, EM following COVID-19 vaccination has been reported in the literature specially in women and for mRNA vaccines. Considering the extensive administration of COVID-19 vaccines due to COVID-19 pandemic, knowledge enhancement regarding cutaneous and mucosal reactions related to COVID-19 vaccination over time is imperative.

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