



Review

## ORAL MANIFESTATIONS OF ERYTHEMA MULTIFORME AND COVID-19: A MINIREVIEW

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### ABSTRACT

**Introduction:** Dermatological findings due to Coronavirus disease 2019 (COVID-19) have been reported in the last two years. This review aims to analyse the oral manifestations of Erythema multiforme (EM) in patients with COVID-19.

**Methods:** On the 28th of June 2022, the search was performed in PubMed by including all English studies that reported oral injuries associated with EM and COVID-19.

**Results:** The search yielded 117, but only 12 studies were eligible. The main sites affected by EM are the tongue, buccal mucosa, palate, and lips. In most cases, oral and cutaneous lesions of EM appear at the same time.

**Conclusion:** Autoreactive T-cells and massive production of cytokines are pathogenetic stages shared by either EM or COVID-19. Further studies are needed to evaluate the possible correlation between the onset of oral lesions linked to EM and COVID-19 due to the expression of the ACE2 receptor on keratinocytes.

**KEYWORDS:** COVID-19, erythema, cytokine, interleukin, angiotensin

### INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a zoonosis caused by a novel *Betacoronavirus* (SARS-CoV-2) which was first described in Wuhan, China (1). From March 2020 to nowadays World Health Organization (WHO) declared the COVID-19 pandemic (2).

Flu-like symptoms, such as myalgia, asthenia, fever, sneezing, and cough, are a spectrum linked to SARS-CoV-2 infection, and the most important complications are pneumonitis and sepsis because this virus has an elective tropism for epithelial cells of the airways and pneumocytes (3).

SARS-CoV-2, like other viruses, can represent stimuli to the innate and adaptative immune system whose consequences are cutaneous and mucosal implications (4). With the worldwide spread of SARS-CoV-2 infection, many authors reported

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cases of erythema multiforme (EM) linked to COVID-19 (5, 6).

EM is a dermatologic immune-mediated disorder, with or without mucosal involvement, triggered by viral and bacterial infections either or drugs (7). According to diagnostic criteria of Hebra, papules are the first manifestations of the disease, with a typical aspect of double concentric ring lesions and blisters: firstly, they appear symmetrically on the extremities of the body; then spontaneous healing occurs between one and four weeks, with desquamation or hyperpigmentation (8).

Mucosal injuries can precede or arise simultaneously or after the onset of cutaneous lesions, and they frequently affect the oral cavity and the oesophagus, pharynx and upper respiratory airways (8, 9).

Infections by Herpes simplex virus, Epstein-Barr virus, Cytomegalovirus, Hepatitis C virus, and influenza virus associated with EM have been described (10, 11). This review aims to describe the clinical aspects of oral manifestations of EM in patients with COVID-19.

## MATERIALS AND METHODS

PubMed was selected as the database to search articles that reported oral findings of EM related to COVID-19. The search strategy included the following terms joined with Boolean operators: “COVID-19” [Mesh] OR SARS-CoV-2 [tiab] AND (“Erythema Multiforme” [Mesh] OR “erythema multiforme” [tiab]). The studies selected were all in English. Review articles and commentary were excluded. The selection of eligible studies was first performed after a screening based on the title and abstract, then reading the full text.

## RESULTS

On the 28th of June 2022, the search yielded 117 results, and one record was identified from a review article. After an accurate screening, 95 references were excluded. Twenty-two articles were evaluated to be included in this review. Finally, 12 studies were analysed for the qualitative synthesis (Fig. 1).

As reported in Table I, many people experienced widespread oral mucosa ulceration accompanied by intense pain. Oral and cutaneous lesions of EM appear simultaneously in most cases (12–15). Oral outcomes precede the onset of dermatological signs of EM and common symptoms of COVID-19 only in one case (16).

In these studies, cutaneous lesions associated with EM were acral target lesions that sometimes extended to the chest, upper back, legs, arms, and elbows. Rashes and irregular maculopapular lesions were also described. In two cases, the skin was spared (17, 18).

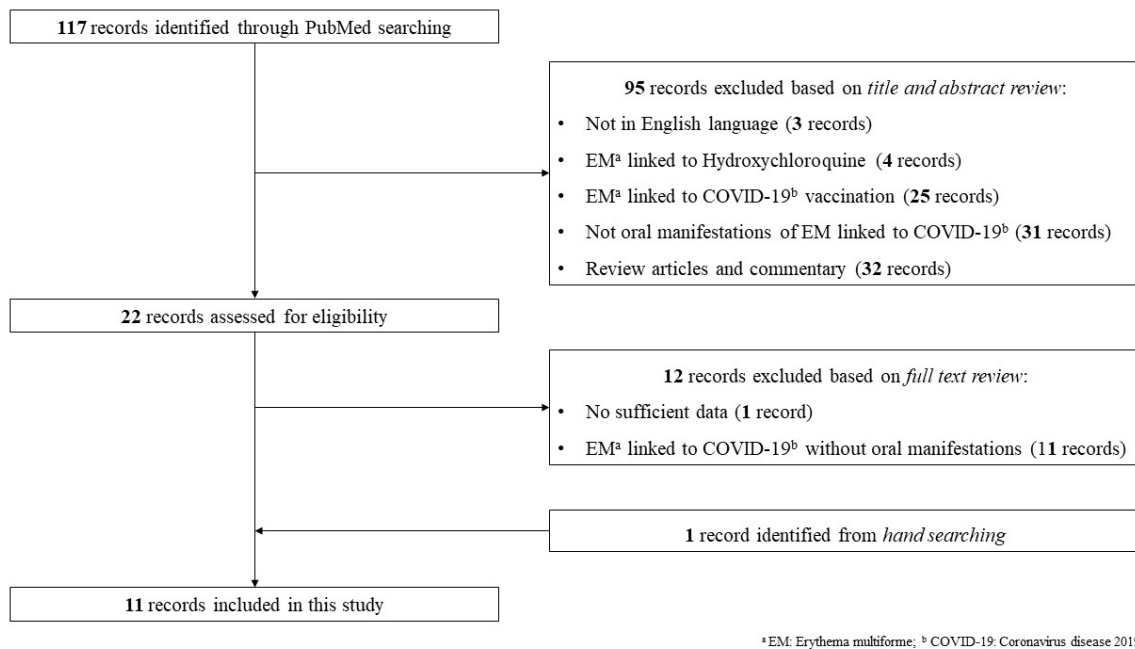
Other mucosal districts affected by ulcers akin to those found in the oral cavity were the conjunctiva, pharynx, and genitals. However, in four studies, the oral mucosa was the only mucosal site involved (12, 15, 16, 19).

## DISCUSSION

EM is a spectrum of mucocutaneous disease with or without spots, variable epidermal detachment rate, and typical either or atypical target lesions (20). Bastuji-Garin et al. identified five variants of EM: bullous EM, Stevens-Johnson syndrome (SJS), overlap SJS-Toxic epidermal necrolysis, Toxic epidermal necrolysis (TEN), the latter with or without spots (20). A new classification performed by Ayangco et al. distinguished two forms of EM (minor and major), SJS, TEN and oral EM: they can potentially have oral involvement, but the cutaneous injury is different (21).

The most important features of oral lesions linked to EM, also found in patients with COVID-19, are erosive vesicles, ulcerations with a fibrinous substrate that mimics aphthae, and target and crusty lesions associated with copious bleeding. The tongue, buccal mucosa, palate and lips are the primary sites affected by this condition. Hypersalivation and satellite lymphadenopathy completed the framework.

According to Eghbali Zarch et al., SARS-CoV-2 infection associated with a previous state of immunosuppression could lead to herpetic stomatitis, oral EM and enanthema (22). EM results from an immune system impairment elicited by antigens presented on keratinocytes (21). Aurelian et al. emphasised the role of INF- $\gamma$  in Herpes simplex virus (HSV)-



**Fig. 1.** Oral manifestations in patients with COVID-19

**Table I.** Oral erythema multiforme in patients with COVID-19

Study ID	Publication year	Sample size	Age	M (%)	Erosions	Ulcerations	Blisters	Haemorrhagic crusting lesions	Target lesions	Diagnosis
Palaia, 2022	2022	1	30	0	-	Hard palate Lips	Buccal mucosa	-	-	EM <sup>a</sup> major (SJS <sup>b</sup> )
Erbaş, 2022	2022	4	50,00*	25	Tongue	Buccal mucosa Tongue	-	Lips	-	EM <sup>a</sup>
Narang, 2021	2021	1	53	0	Oral cavity	-	-	Oral cavity	-	TEN <sup>c</sup>
Maden, 2021	2021	1	18	100	-	Buccal mucosa	-	-	-	EM <sup>a</sup> major (SJS <sup>b</sup> )
Emadi, 2021	2021	1	30	0	-	-	-	Lips	-	TEN <sup>c</sup>
Dalipi, 2021	2021	1	17	100	Lips	Left labial mucosa	Tongue	-	Left labial mucosa	EM <sup>a</sup>
Binois, 2021	2021	1	57	100	-	Buccal mucosa	-	-	-	EM <sup>a</sup> major (SJS <sup>b</sup> )
Abdelgabar, 2021	2021	1	23	100	-	Buccal mucosa	-	Lips	Tongue	EM <sup>a</sup> /EM <sup>a</sup> major (SJS <sup>b</sup> )
Rolfo, 2020	2020	1	58	0	-	Buccal mucosa	-	-	-	EM <sup>a</sup>
Labé, 2020	2020	1	6	100	Lip angles Gingiva	-	-	Lips	-	EM <sup>a</sup>
Demirbaş, 2020	2020	1	37	0	Lips Palate Tongue	-	-	-	-	EM <sup>a</sup>

\* Data are reported as mean; (-) Not stated, unclear, or unable to ascertain; a EM: Erythema multiforme; b SJS: Stevens-Johnson syndrome; c TEN: Toxic epidermal necrolysis

associated erythema multiforme (HAEM): it promotes a huge production of cytokines to induce chemotaxis of leukocytes, monocytes, NK cells, and autoreactive T-cells lead keratinocytes to lysis (23). COVID-19 share the same increase of several proinflammatory cytokines, a condition known as a “cytokine storm” (24) and activation of local autoreactive B and T cells (4). It is known that SARS-CoV-2 binds angiotensin-converting enzyme 2 receptor (ACE2 receptor) to infect pneumocytes (3) due to the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, but this receptor is also localised and overexpressed in keratinocytes during Atopic Dermatitis (25). Studies to evaluate a possible correlation between the onset of EM oral manifestations and COVID-19 due to the expression of the ACE2 receptor on keratinocytes should be considered.

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