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LETTER

Aphthous stomatitis in COVID-19 patients: Case-series and literature review

Dear Editor

We have read with great interest the review of Iranmanesh et al. (2020) on oral manifestations of coronavirus diseases (COVID-19) which demonstrated the emergence of aphthous-like lesions in 16 cases thus suggesting that neutrophil chemotaxis, stress, and immunosuppression could be causal pathways for this condition to appear in COVID-19 patients.[1] As a result of this, we aim to report according to the CARE guidelines, the characteristics of 21 laboratory-confirmed COVID-19 patients with aphthous stomatitis.[2] We have also performed an updated literature search in Ovid MEDLINE, EMBASE, Cochrane Library, Epistemonikos from inception until November 26th, 2020 with a combination of keywords (COVID-19 or SARS-CoV-2) and aphthous.

A retrospective analysis of our hospital records for COVID-19 patients during the period of April-September 2020 revealed that out of 1237 patients tested positive by our screening clinic, 21 patients (1.7%) complained of intra-oral pain related to aphthous stomatitis. The patients had undertaken polymerase chain reaction (PCR) testing of SARS-COV-2 due to various purposes including pre-travel (14.3%) and post-travel (9.5%) screening, direct (9.5%) and indirect (4.8%) contact with an infected case, presenting with mild (42.9%), and moderate (19%) respiratory symptoms (Table 1).

Their mean age was 31.57 ± 11.01 (16-56) years old, and 17 patients (81%) were females. While the vast majority were non-smokers, only two patients (9.5%) were smokers. The PCR test confirmed their infection with a mean cycle threshold (Ct) value of 25.76 ± 6.21 (12-32). Regarding their characteristic symptoms of COVID-19, three patients (14.3%) had persistent fever, five patients (23.8%) had a dry cough, five patients (23.8%) had anosmia, and two patients (9.5%) had ageusia. According to the Australian classification for COVID-19, 18 patients (85.7%) experienced a mild course of the disease, whereas 3 patients (14.3%) had a moderate course.[3]

On intraoral examination, solitary ulcerative white halos with well-defined erythematous margins were observed in the buccal mucosa (33.3%), upper lip (14.3%), lower lip (14.3%), tongue (14.3%), palate (9.5%), gingiva (9.5%) and both of palate and gingiva (4.8%). The mean size of the ulcers was 2 ± 0.86 (1–4) mm, and they caused pain with a mean intensity of 5.38 ± 1.5 (3–8) which was measured by means of an 11-item numerical rating scale (NRS) when with "0" denoting "no pain" and "10" denoting "pain as bad as you can imagine".[4] The patients were asked whether they had experienced similar ulcerative lesions previously and based on their negative answer, the recurrent aphthous stomatitis (RAS) was ruled out. To manage their pain, 18 patients (85.7%) were prescribed chlorhexidine gluconate 0.12% (CHX) mouthwash, and 3 patients (14.3%) were prescribed paracetamol (PCM). The pain duration was reported by 19 patients with a mean of 2.68 ± 0.67 (2–4) days; however, 2 patients were missed from the follow up. It is worthy to note that prevalence of aphthous stomatitis among COVID-19 patients could have been underestimated because we had not performed an intra-oral examination for all positive COVID-19 cases in order to confirm whether they had aphthous or not; nevertheless, our records are based on subjective reporting by the patients.

Inferential statistics revealed that pain duration was significantly lower in patients treated with CHX (2.50 ± 0.52 days) than patients treated with PCM (3.67 ± 0.58 days); $t(17) = -3.54$, $P = .003$. This difference could be attributed to the severity of the aphthous condition, not to the drugs themselves. In case of CHX, patients had higher mean pain intensity (5 ± 1.24 vs 7.67 ± 0.58) and ulcer size (1.83 ± 0.79 vs 2.67 ± 1.15) than in case of PCM; $t(19, 19) = -3.61, -1.61$; $P = .002, .125$, respectively. Gender and age were not associated with any of the aphthous characteristics; however, tobacco smoking was the only risk factor significantly associated with pain intensity, the onset of aphthous stomatitis, anosmia, and ageusia $P = .032$, 0.042, .006, and ≤.001, respectively.

On reviewing the currently growing evidence on aphthous stomatitis of COVID-19 patients, we have found 22 cases reported in 8 publications (7 case reports, 1 prevalence study).[5-12] Fourteen cases (63.6%) were from Americas, five (22.7%) from Europe, two (9%) from the Middle East, and one (4.5%) from Asia-Pacific (Table 2). The aphthous lesions were equally distributed across gender; however, female predominance was noticed in the prevalence study of Florida, which is similar to our series.[11] Seventeen patients (77.3%) were below 40 years old; similarly, the majority of our series (80.1%) was below 40 years old. The onset of aphthous lesions was reported in 10 patients only; it was estimated using the latency period since COVID-19 symptoms emergence which ranged between 0 and 10 days with two patients experienced aphthous stomatitis concurrently with COVID-19 symptoms onset. The most common sites were tongue, lower and upper lip; this pattern was in agreement with what we had found in our patients except for buccal mucosa which was affected only in one patient although it was the first site in our series.

To conclude, the current epidemiologic evidence does not seem to be different from the typical characteristics of aphthous stomatitis in terms of female predominance and young age affinity.[13] This series supports the demand for larger studies to shed light on

TABLE 1 Demographic, clinical and laboratory characteristics of COVID-19 patients with aphthous stomatitis, April-September 2020

ID	Gender	Age	Smoking	Testing reason	Ct[a]	Severity[b]	Cough	Fever	Anosmia	Ageusia	Location	Pain	Size	Duration	Onset	TTT[c]
1	Male	19	Non-smoker	Before travel	31	Mild	No	No	No	No	Buccal mucosa	4	1	2	0	CHX
2	Female	38	Non-smoker	Direct contact	15	Mild	No	No	No	No	Tongue	5	1	3	0	CHX
3	Female	42	Non-smoker	Indirect contact	28	Mild	No	No	No	No	Lower lip	4	3	2	0	CHX
4	Male	31	Non-smoker	After travel	18	Mild	No	No	No	No	Lower lip	3	2	2	0	CHX
5	Female	56	Non-smoker	Mild symptoms	26	Mild	Yes	No	No	No	Buccal mucosa	4	2	3	0	CHX
6	Female	27	Non-smoker	Moderate symptoms	20	Mild	Yes	No	No	No	Upper lip	5	2	3	0	CHX
7	Female	46	Non-smoker	Mild symptoms	27	Moderate	No	Yes	No	No	Upper gingiva	7	2	3	1	CHX
8	Female	20	Non-smoker	Mild symptoms	29	Mild	No	No	Yes	No	Buccal mucosa	7	2	3	0	CHX
9	Female	31	Non-smoker	Mild symptoms	31	Mild	No	No	No	No	Tongue	4	2	3	0	CHX
10	Male	20	Non-smoker	Mild symptoms	32	Mild	No	No	Yes	No	Palate	6	2	3	0	CHX
11	Female	36	Smoker	Moderate symptoms	12	Moderate	Yes	Yes	Yes	Yes	Palate and upper and lower gingiva	8	4	4	0	PCM
12	Female	27	Non-smoker	Moderate symptoms	18	Mild	No	No	No	No	Palate	8	2	4	0	PCM
13	Female	17	Non-smoker	After travel	31	Mild	No	No	No	No	Buccal mucosa	4	1	2	0	CHX
14	Female	24	Non-smoker	Before travel	32	Mild	No	No	No	No	Tongue	4	1	2	0	CHX
15	Female	38	Non-smoker	Mild symptoms	27	Moderate	No	Yes	No	No	Buccal mucosa	5	1	2	0	CHX
16	Female	25	Non-smoker	Mild symptoms	24	Mild	No	No	Yes	No	Upper gingiva	6	2	Missed	0	CHX
17	Female	16	Non-smoker	Moderate symptoms	19	Mild	Yes	No	No	No	Upper lip	6	1	Missed	0	CHX
18	Female	26	Non-smoker	Direct contact	30	Mild	No	No	No	No	Buccal mucosa	7	2	3	0	CHX
19	Male	37	Smoker	Mild symptoms	32	Mild	No	No	Yes	Yes	Buccal mucosa	7	2	3	1	PCM
20	Female	39	Non-smoker	Mild symptoms	29	Mild	Yes	No	No	No	Upper lip	5	4	2	0	CHX
21	Female	48	Non-smoker	Before travel	30	Mild	No	No	No	No	Lower lip	4	2	2	0	CHX

[a]Ct: cycle threshold value.
[b]Severity: COVID-19 clinical course severity according to NHMRC, Australia.
[c]TTT: treatment used was either chlorhexidine gluconate 0.12% mouthwash (CHX) or paracetamol (PCM).

TABLE 2 COVID-19 patients with aphthous lesions

Study, location	Number	Gender	Age	Confirmation [a]	Type	Location [b]	Onset [b]	Description
Dominguez-Santas et al[5], Madrid (Spain)	4	1 Female; 3 Males	43; 33; 37; 19	Confirmed	Minor aphthous ulcers	Buccal mucosa; opper gingiva; tongue; lower lip	Latency from COVID-19 symptoms: 4, 3, 5, 0 days, respectively.	All lesions measured less than 1 cm. They mainly affected the nonkeratinized mucosa. The majority of them had a creamy-colored fibrin surface with an erythematous peripheral ring.
Malih et al[6], Tehran (Iran)	1	Male	38	Confirmed	Aphthous lesion	Tonsil	N/A	Erythema and aphthous ulcer developed on left tonsil, which was found on laryngeal exam.
Corchuelo et al[7], Cali (Colombia)	1	Female	40	Confirmed	Aphthous lesion	Lower gingiva	N/A	Painful aphthous ulcerative lesion developed on the attached gingiva of the first lower premolar.
Brandão et al[8], Sao Paulo (Brazil)	7	2 Females; 5 Males	81; 83; 72; 32; 35; 29; 28	Confirmed	Aphthous-like stomatitis	Upper, lower lip and tongue; tongue; upper and lower lip; tongue; tonsil; tongue; upper and lower lip	Latency from COVID-19 symptoms: N/A, N/A, N/A, 10, 6, 2, 8 days, respectively.	Multiple shallow aphthous-like painful lesions of varying sizes.
Díaz Rodríguez et al[9], Madrid (Spain)	1	Female	43	Confirmed	Aphthous-like stomatitis	Tongue	N/A	In addition to the aphthous-like ulceration, the patient reported burning tongue sensation and tongue depapillation.
Al-Khanati et al[10], Damascus (Syria)	1	Male	24	Suspected	Aphthous-like stomatitis	Lower lip	The same day of COVID-19 symptoms (fever, headache)	Two aphthous-like ulcers on the mucosa of the lower lip, which enlarged and became painful in 3 days. The patient suffered from burning sensation related to the tongue associated with halitosis.
Katz et al[11], Florida (USA)	6	6 Female	2 patients (10-17 y); 4 patients (18-34 y)	Confirmed	Recurrent oral aphthae	N/A	N/A	The diagnosis of recurrent aphthous stomatitis (RAS) was made by physicians who might not be familiar with oral diagnosis.
Putra et al[12], Jakarta (Indonesia)	1	Male	29	Confirmed	Aphthous lesion	N/A	Latency from COVID-19 symptoms: 7 days.	Aphthous stomatitis was noticed after 7 days of symptoms emergence and treated by typical oral hygiene.

[a]Laboratory confirmation of the SARS-COV-2 infection by means of polymerase chain reaction (PCR) testing.
[b]N/A: not reported by the investigators.

pathophysiology and prevalence of this lesion positively associated with immuno-compromised population.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Abanoub Riad: Writing-original draft. **Islam Kassem**: Data curation; Investigation. **Jan Stanek**: Writing-original draft; Investigation. **Mai Badrah**: Formal analysis. **Jitka Klugarova**: Writing-review & editing. **Miloslav Klugar**: Supervision; Writing-review & editing.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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