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Morphological and tissue-based molecular characterization of oral lesions in patients with COVID-19: A living systematic review

Felipe Martins Silveira a,b, André Luiz Rodrigues Mello c, Laura da Silva Fonseca c, Luís dos Santos Ferreira c, Laura Borges Kirschnick d, Manoela Domingues Martins b,d, Lauren Frenzel Schuch d, José Alcides Almeida de Arruda d, Ciro Dantas Soares d,f, Alexandre de Oliveira Sales b, Ronell Bologna-Molina a,b, Alan Roger Santos-Silva d, Ana Carolina Uchoa Vasconcelos c,*

a Molecular Pathology Department, School of Dentistry, Universidade da República, Montevideo, Uruguay
b Department of Oral Pathology, School of Dentistry, Universidade Federal do Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil
c Diagnostic Center for Oral Diseases, School of Dentistry, Universidade Federal de Pelotas, Pelotas, Rio Grande do Sul, Brasil
d Department of Oral Diagnosis, Piracicaba Dental School, Universidade Estadual de Campinas, Piracicaba, São Paulo, Brazil
e Department of Oral Surgery, Pathology and Clinical Dentistry, School of Dentistry, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil
f Division of Anatomic Pathology, Getulio Sales Diagnósticos, Private Pathology Service, Natal, Rio Grande do Norte, Brazil

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ABSTRACT

Objective: This living systematic review aims to integrate the morphological and tissue-based molecular characterization of oral lesions occurring in individuals infected by COVID-19 (OLICs).

Materials and Design: This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. PubMed, Web of Science, Scopus, Ovid, Embase, and LILACS were searched to identify reports on OLICs with morphological and/or tissue-based molecular data.

Results: Four studies reporting five cases were included. Three patients were male, and the mean age of the individuals was 47.6 years. The most reported anatomical location was the palate (n = 4), whereas ulcers were the most frequent clinical presentation (n = 3). Histopathologically, all cases revealed cell vacuolization and exocytosis in the epithelial layer. In the mesenchymal layer, inflammatory cell infiltrate and thrombi/microvascular thrombosis were observed in three cases. Immunohistochemical reactions were performed in two cases. Both cases were negative for HHV-1, HHV-2, and CMV. One case revealed positivity for SARS-CoV-2 spike protein. No other molecular tests were found for the characterization of OLIC.

Conclusions: The pathological characteristics of OLICs are still unspecific. However, with the ongoing COVID-19 pandemic and well-documented new cases, whether OLICs are due to coinfections or has a primary origin can be determined.

1. Introduction

Severe acute respiratory syndrome (SARS) coronavirus 2 (CoV-2) was first detected in Wuhan, China, in December 2019, and soon after a global pandemic, as labeled by the World Health Organization (WHO), began (World Health Organization, 2022). As of July 2021, there were 190,169,833 confirmed cases of coronavirus disease 19 (COVID-19), and the disease had caused approximately 4086,000 deaths worldwide (World Health Organization, 2022). The SARS-CoV-2 virus leads to severe respiratory disturbance that may develop into acute respiratory syndrome. Symptoms are characterized by a wide range of clinical presentations, varying from headache, fever, and dry cough to severe pneumonia in more severe cases. The respiratory system seems to be the most affected, although some of the infected individuals present symptoms and signs at other distant places in the body, such as the oral and perioral regions (Tang et al., 2020). Thrombotic complications seem to be frequent in COVID-19 (Hanff, Mohareb, Giri, Cohen, & Chirinos, 2020).

Abbreviations: OLICs, oral lesions occurring in individuals infected by COVID-19.

* Correspondence to: Centro de Diagnóstico das Doenças da Boca – CDDB – Faculdade de Odontologia, Universidade Federal de Pelotas, R. Gonçalves Chaves, 457, room 607, Pelotas, Rio Grande do Sul 96015-560, Brazil.
E-mail address: carolinavau@gmail.com (A.C.U. Vasconcelos).

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The prevalence of oral manifestations in individuals infected by SARS-CoV-2 is virtually unknown. Concerns have been raised about whether the oral manifestations are caused by SARS-CoV-2, a pattern of different viruses that take advantage of systemic weaknesses during COVID-19, or even an adverse reaction to therapies used to control the disease. Recent literature has reported that oral lesions are usually symptomatic, presenting as ulcers, erosions or macules (Santos, Nordon, Carvalho da Silva, Acevedo, De Luca Canto & Sugaya, 2021a; Santos et al., 2021b). The tongue and labial mucosa are the most common locations, and there is no sex predilection (Irani, Amiri, Zartab, & Aflatoonian, 2021). Clinically, the oral manifestations of COVID-19 can make a differential diagnosis with aphthous stomatitis, herpetiform lesions, necrotizing periodontal disease, angina bullosa-like, angular cheilitis, and Melkerson-Rosenthal syndrome.

To date, there is no definitive evidence in the specific microscopic findings of oral lesions occurring in individuals infected with COVID-19 (OLICs) that suggest etiopathogenesis. In turn, only a few histopathological studies of OLIC have been published elsewhere. Studies have generally shown unspecific histopathological properties such as vascular ectasia and perivascular lymphocytic infiltrate in biopsies from oral lesions of COVID-19 patients. Additionally, the SARS-CoV-2 spike protein was positive by immunohistochemistry in inflammatory endothelial cells and keratinocytes, and acinar and ductal cells of the minor salivary glands in one study (Cruz Tapia, Peraza Labrador, Guimaraes, & Matos Valdez, 2020; Soares, Carvalho, Carvalho, Carvalho, & Almeida, 2020; Soares, Mosqueda-Taylor, de Carvalho, & de Almeida, 2020). Recent studies have established angiotensin-converting enzyme 2 (ACE2) as the functional host receptor for SARS-CoV-2 (Bourgonje et al., 2020). The OLICs have become an important field of research once their morphological and molecular characterizations are not well defined. In this sense, a living systematic review (LSR) is the recommended methodology to incorporate scientific evidence that is continuously emerging (Elliott, Synnot, Turner, Simmonds, Akl & McDonald, 2017). From this perspective, this LSR aims to incorporate the available data on the demographic, clinical, morphological and tissue-based molecular characterization of OLICs.

2. Materials and methods

2.1. Eligibility criteria

Case reports and case series on OLICs confirmed by polymerase chain reaction (PCR) tests and presenting the histopathological report and/or tissue-based molecular characterization (i.e., immunohistochemistry, electron microscopy, immunofluorescence, or PCR) of the lesion were included in this LSR. No restrictions were imposed on the date of publication, language or geographic region where the study was conducted. Bibliographic reviews, systematic reviews, editorial reviews, meeting/congress abstracts, experimental studies, in vitro or ex vivo studies, and articles in which it was not possible to access the full text were excluded.

2.2. Information sources and search strategies

Electronic searches were undertaken in August 2021 in PubMed (National Library of Medicine, Web of Science (Clarivate Analytics), Scopus (Elsevier), Ovid (Wolters Kluwer), Embase (Elsevier), and LLACS (Virtual Health Library). The complete scheme for the search strategy in the PubMed database is provided in Supplementary Table 1. Specific searches were tailored to each database. The retrieved references were exported to EndNote software (Clarivate Analytics, Philadelphia, USA), and duplicates were removed upon identification. To identify any eligible articles that may not have been retrieved by the search strategy, hand searches were conducted to check all references of the included articles. The same search strategy will be updated every 12 months for two years, and we will take at least one month to apply the review process for study selection, data collection, risk of bias, and synthesis of results.

2.3. Selection process

The selection was performed in two phases by two authors (L.S.F. and A.L.R.M.). In phase 1, the two authors independently reviewed the titles and abstracts of all references according to the eligibility criteria. If the title or abstract fulfilled the eligibility criteria, the study was incorporated into phase 2. In this phase, the same eligibility criteria were applied to the full text of the articles. Possible disagreements between the two authors were resolved by a third author (A.C.U.V.) – a senior lecturer in Oral Pathology & Oral Medicine. The final selection was made based on the full text of the publication, ensuring that only studies that did not meet the eligibility criteria were excluded. The calibration of the reviewers was verified by assessing the agreement among the three reviewers (L.S.F., A.L.R.M., and A.C.U.V.) regarding the evaluation of titles/abstracts of the first 50 references retrieved during the searches. A kappa value of 0.93 was achieved, i.e., excellent agreement between reviewers.

2.4. Data extraction and data items

The following data, when available, were obtained from each reference and recorded on a standardized form: continent of publication, sex, age, skin color, systemic condition, general systemic conditions, serological tests, pharmacological management for COVID-19, and status, and number of OLICs/patients, anatomical location, concomitant skin lesions, fundamental lesion, symptomatology, time of progression, histopathological features, immunohistochemistry, electron microscopy, immunofluorescence, PCR, follow-up, and lesion treatment. In cases where the information was lacking, unclear, incomplete or not described in the studies, contact was made with the authors of the respective studies. If the contact was not effective, the data were disregarded or indicated as not informed. Doubts during the data extraction process were resolved through discussion among the authors.

2.5. Critical appraisal of the included studies

The methodological quality of the included articles was assessed using the Joanna Briggs Institute – University of Adelaide tool for case reports or case series (Gagnier et al., 2013). The case reports included were assessed according to the following parameters: clear description of the patient’s demographic characteristics, medical history and presentation as a timeline, clear description or presentation of the patient’s current clinical condition, clear description of the diagnostic tests and assessment methods, clear description of the treatment provided, information on the postintervention clinical condition, identification or report of adverse events, and lessons provided by the case report. The case series articles included were assessed according to the following parameters: clear statement of the criteria for inclusion, condition measured in a standard and reliable way, use of valid methods for identification of the condition, consecutive and complete inclusion of participants, clear reporting of the demographics and clinical information of the participants, clear reporting of the outcomes and of the demographic information regarding study site(s)/clinic(s), and use of appropriate statistical analysis. In each article included, the parameters could be rated as “yes” (low risk of bias), “no” (high risk of bias) or “not applicable”.

2.6. Other information

This systematic review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Page, McKenzie, Bossuyt, Boutron, Hoffmann & Mulrow, 2021). A protocol was drafted and registered with the International Prospective Register of Systematic Reviews (PROSPERO), protocol number:
2.7. Synthesis methods

Descriptive statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS, version 25.0, Armonk, US).

3. Results

3.1. Study selection

The electronic searches yielded 1188 references. After the removal of 55 duplicates, the inclusion and exclusion criteria were applied to 1133 references. After the exclusion of 1110 references according to the eligibility criteria, a total of 23 articles were selected for full-text assessment. Of these, 21 articles were excluded for the following reasons: the study did not present the histopathological characteristics of the oral lesions and the oral lesion developed before the COVID-19 infection. Finally, two articles fulfilled the eligibility criteria, and two articles were identified in the manual search process. Therefore, a total of four studies reporting five cases of OLICs with histopathological records were included in this systematic review (Ansari, Gheitani, Heidari, & Heidari, 2021; Cruz Tapia et al., 2020; Soares et al., 2020, 2021). A flowchart of the selection process of the studies is illustrated in Fig. 1.

Fig. 1. Flowchart of the selection process.
3.2. Demographic and clinicopathological features and treatment of the affected individuals

Considering the few included studies in this LSR in this first approach, the results were presented based in a descriptive statistics. In this sense, the data is qualitative described for each result. The demographic and clinical data of the affected patients are displayed in Table 1. Articles from three countries were included. Cases were reported from Iran (n = 2/40%), Brazil (n = 2/40%), and Mexico (n = 1/20%). Three patients were male (60%), and two were female (40%). The mean age of the individuals was 47.6 years (range: 23–75 years). All individuals (n = 5/100.0%) were white. The following associated systemic conditions were fever (n = 2/40%), hypertension (n = 2/40%), and coronary heart disease (n = 1/20%). Of the informed cases, the general systemic conditions were fever (n = 3/23%), shortness of breath (n = 2/15.4%), cough (n = 2/15.4%), hypoxia (n = 1/7.7%), vesiculobullous lesions on the skin (n = 1/7.7%), myalgia (n = 1/7.7%), dysegesia (n = 1/7.7%), headache (n = 1/7.7%), and burning mouth (n = 1/7.7%). Serological tests were performed in two patients: HSV was negative in both cases (n = 2/100%). The drugs used for COVID-19 management were supportive treatment [analgesic and anti-thermal drugs] (n = 3/50%), antibiotic therapy (n = 2/33.3%), and antivirals (n = 1/16.7%). Regarding the status of the patients, all of them (n = 5/100%) were alive.

3.3. Clinical, morphological and molecular characterization, and treatment of oral lesions

The features and molecular characterization of the OLICs are displayed in Table 2. All OLICs involved multiple lesions, and the anatomical location most commonly affected was the palate, with 3 cases (37.5%), followed by the lips and tongue, with two cases (25%). Considering the few included studies in this LSR in this first approach, the results were presented based in a descriptive statistics. In this sense, the data is qualitative described for each result. The demographic and clinical data of the affected patients are displayed in Table 1. Articles from three countries were included. Cases were reported from Iran (n = 2/40%), Brazil (n = 2/40%), and Mexico (n = 1/20%). Three patients were male (60%), and two were female (40%). The mean age of the individuals was 47.6 years (range: 23–75 years). All individuals (n = 5/100.0%) were white. The following associated systemic conditions were fever (n = 2/40%), hypertension (n = 2/40%), and coronary heart disease (n = 1/20%). Of the informed cases, the general systemic conditions were fever (n = 3/23%), shortness of breath (n = 2/15.4%), cough (n = 2/15.4%), hypoxia (n = 1/7.7%), vesiculobullous lesions on the skin (n = 1/7.7%), myalgia (n = 1/7.7%), dysegesia (n = 1/7.7%), headache (n = 1/7.7%), and burning mouth (n = 1/7.7%). Serological tests were performed in two patients: HSV was negative in both cases (n = 2/100%). The drugs used for COVID-19 management were supportive treatment [analgesic and anti-thermal drugs] (n = 3/50%), antibiotic therapy (n = 2/33.3%), and antivirals (n = 1/16.7%). Regarding the status of the patients, all of them (n = 5/100%) were alive.

Table 1
Demographic, clinicopathological features, and treatment of the individuals.

| Variable                                      | n (%)       |
|-----------------------------------------------|-------------|
| Continent (n = 5)                             |             |
| Americas                                      | 3 (60.0)    |
| Asia                                          | 2 (40.0)    |
| Sex (n = 5)                                   |             |
| Male                                          | 3 (60.0)    |
| Female                                        | 2 (40.0)    |
| Age (years)                                   |             |
| Mean DS                                       | 47.6 (± 19.3)|
| Range                                         | 23–75 years |
| Skin color (n = 5)                            |             |
| White                                         | 5 (100.0)   |
| Systemic condition (n = 5)                    |             |
| Diabetes                                      | 2 (40.0)    |
| Hypertension                                  | 2 (40.0)    |
| Coronary heart disease                        | 1 (20.0)    |
| General systemic conditions (n = 13)          |             |
| Fever                                         | 3 (23.0)    |
| Shortness Of Breath                           | 2 (15.4)    |
| Cough                                         | 2 (15.4)    |
| Hypoxia                                       | 1 (7.7)     |
| Vesiculobullous lesions on skin               | 1 (7.7)     |
| Myalgia                                       | 1 (7.7)     |
| Dysegesia                                     | 1 (7.7)     |
| Headache                                      | 1 (7.7)     |
| Burning mouth                                 | 1 (7.7)     |
| Serological tests (n = 2)                     |             |
| HSV Negative                                  | 2 (100.0)   |
| Pharmacological management to COVID-19 (n = 6) |             |
| Supportive treatment                          | 3 (50.0)    |
| Antibiotic therapy                            | 2 (33.3)    |
| Antiviral                                     | 1 (16.7)    |
| Status (n = 5)                                |             |
| Alive                                         | 5 (100.0)   |

* Some cases presented more than one feature.

Table 2
Clinical, morphological and molecular characterization, and treatment of the oral lesions.

| Variable                                      | n (%)       |
|-----------------------------------------------|-------------|
| Number of OLICs / patient                     |             |
| Single                                        | –           |
| Multiple                                      | 5 (100.0)   |
| Anatomical location (n = 8)                   |             |
| Palate                                        | 3 (37.5)    |
| Lips                                          | 2 (25.0)    |
| Tongue                                        | 2 (25.0)    |
| Buccal mucosa                                 | 1 (25.0)    |
| Concomitant skin lesions (n = 5)              |             |
| Yes                                           | 2 (40.0)    |
| N.I.                                          | 3 (60.0)    |
| Fundamental lesion (n = 6)                    |             |
| Ulcer                                         | 3 (50.0)    |
| Macule                                        | 2 (33.3)    |
| Blisters                                      | 1 (16.7)    |
| Symptomatology (n = 4)                       |             |
| Burning mouth                                 | 1 (25.0)    |
| Pain                                          | 2 (50.0)    |
| Dysphagia                                     | 1 (25.0)    |
| Evolution time (days)                         |             |
| Mean (DS)                                     | 5.0 (± 2.0) |
| Range                                         | 3–7 days    |
| Histopathological features                    |             |
| Epithelial Layer                              |             |
| Vascularization                               | 5 (100.0)   |
| Exocytosis                                    | 5 (100.0)   |
| Ulcer                                         | 2 (40.0)    |
| Mesenchymal Layer                             |             |
| Inflammation                                  | 3 (60.0)    |
| Thrombi/microvascular thrombosis              | 3 (60.0)    |
| Hemorrhage                                    | 2 (40.0)    |
| Necrosis                                      | 1 (20.0)    |
| Immunohistochemistry                          |             |
| Soares et al. (2020)                          |             |
| HHV-1                                         | –           |
| HHV-2                                         | –           |
| CMV                                           | –           |
| Treponema pallidum                            | –           |
| CD20                                          | –           |
| CD68                                         | +           |
| CD163c                                        | +           |
| CD138c                                        | +           |
| CD4                                          | +           |
| CD34                                         | +           |
| CD3t                                         | +           |
| CD8                                          | +           |
| Soares et al. (2021)                          |             |
| HSV-1                                         | –           |
| HHV-2                                         | –           |
| HHV-3                                         | –           |
| CMV                                           | –           |
| SARS-CoV-2                                    | +           |
| Electron microscopy                           | –           |
| Immunofluorescence                            | –           |
| Polymerase chain reaction                     | –           |
| Follow up (days) (n = 5)                      |             |
| Mean (DS)                                     | 12.8 (± 7.4)|
| Range                                         | 7–21 days   |
| Lesion treatment (n = 6)                      |             |
| Topical analgesic, antibiotic and corticotherapy | 3 (50.0)    |
| Systemic corticotherapy                       | 2 (33.3)    |
| Supportive treatment                          | 1 (16.7)    |

N.I., not informed

a Some cases presented more than one characteristic
b Described according to presence or absence reported in the histopathological records or observed in the provided figures of the cases

c Positivity in inflammatory cells or endothelial cells
each. One case (12.5%) occurred in the buccal mucosa. Two cases reported concomitant skin lesions. Ulcer was the fundamental lesion present in three cases (50%), macule in two cases (33.3%) and bullous in one case (16.7%). Four individuals had symptomatology, such as pain (n = 2), burning mouth (n = 1), and dysphagia (n = 1). The mean time of progression was 5 (± 2.0) days. Regarding the treatment for OLICs, topical agents were used in three cases (30%), systemic corticotherapy was employed in two cases (33.33%) and supportive treatment was employed in one case (16.7%).

3.4. Morphological analysis

Regarding the histopathological findings of the OLICs, in the epithelial layer all cases (n = 5/100%) presented vacuolization and exocytosis. The presence of ulcer was described in two (40%) cases. In the mesenchymal layer, inflammatory cell infiltration was observed in three cases (60%), presence of thrombi/microvascular thrombosis in three cases (60%), and presence of hemorrhage in two cases (40%). Focal areas of necrosis were reported in one case (20%). The complete histopathological description of each of the cases included in this systematic review is summarized in Supplementary Table 2.

3.5. Immunohistochemical analysis

Immunohistochemical reactions were performed in two cases. A study (Soares et al., 2020) reported focal positivity to CD20, CD68, CD163, CD138, and CD4 (inflammatory cells). The same authors also showed positivity for CD34 (endothelial cells), CD3 (lymphocytic infiltrate) and CD8 (lymphocytic infiltrate). In addition, HHV-1, HHV-2, CMV, Treponema pallidum, and EBV determined by in situ hybridization were negative. Another study (Soares et al., 2021) reported positivity for SARS-CoV-2 spike protein. HSV-1, HSV-2, human herpesvirus-3, and CMV were negative. The complete immunohistochemical description of each of the cases included in this systematic review is summarized in Supplementary Table 2.

In Fig. 2, we illustrated some histopathological findings in a 47-year-old male patient with an ulcer in the palate (from the authors’ files). In the lamina propria, an intense inflammatory infiltrate admixed with some microvessel thrombi was observed. Also, the spike protein of the SARS-CoV-2 was positive in the lymphocytes, macrophages and other mononuclear inflammatory cells and in the endothelium.

3.6. Critical appraisal of the included studies

A critical appraisal of the reported cases demonstrated that all articles provided a clear description of the patient’s demographic characteristics and details of their current clinical conditions. The diagnostic tests or assessment methods employed, the interventions and treatment procedure, the postintervention clinical condition and clear information about the patient’s medical history and timeline were clearly described in all articles. Only one article identified or described adverse events or unanticipated events. All articles provided lessons. The critical appraisal of the studies is presented in Supplementary Table 3.

4. Discussion

Since the onset of the COVID-19 pandemic, case reports and letters to the editor have been published documenting individuals with oral manifestations after SARS-CoV-2 infection. However, only a few of them have explored their morphological features (Ansari et al., 2021; Cruz Tapia et al., 2020; Soares et al., 2020, 2021). The present LSR evaluated the available evidence related to the molecular characterization of
Although variable - especially with the patient Martin-Carrillo, Magaletsky, Martin Rios, Herranz Mañas, and Artigas Almazan (2021) also found a slight female preference. In contrast, some epidemiological studies reported that males had significantly higher disease severity than females (Gebhard, Regitz-Zagrosek, Neuhauer, Morgan, & Klein, 2020; Wu & McGoogan, 2020). Recent studies suggest that sex hormones may influence the viral infectivity process (Mohamed, Moulin, & Schiöth, 2021). However, the pathophysiology of this difference has not yet been established and it was observed that genes encoding entry factors for SARS-CoV-2 appeared similar in epithelial cells from males and females (Huang, Pêrez, Kato, Mikami, Okuda & Gilmore, 2021; Marchesan, Warner, & Byrd, 2021).

The most common general clinical features observed in cases analyzed in this LSR were fever, dry cough, and shortness of breath. Although variable - especially with the patient’s immune system and age, these features are also reported as main general clinical manifestations in recent epidemiological studies of individuals infected by COVID-19 (Gu, Ni, Hu, Liang, Ou & He, 2020; Hu, Guo, Zhou, & Shi, 2021; Tu, Tu, Gao, Shao, & Sheng, 2020). The current gold standard for diagnosing COVID-19 is based on a molecular test using real time (RT)-PCR, aiming to detect the RNA of the virus in respiratory samples, such as nasopharyngeal swabs or bronchial aspirate (Böger et al., 2021).

However, in some cases, serological tests are useful to discern opportunistic infections, such as HSV infection. Currently, there is no specific antiviral treatment recommended for COVID-19, but some vaccines are already available. For mildly to moderately ill patients, active symptomatic support remains the key for management, such as maintaining hydration and nutrition and controlling fever and cough, as observed in most of the present cases. Nonetheless, for patients with severe infection or those with respiratory failure, oxygen inhalation through a mask, high nasal oxygen flow inhalation, noninvasive ventilation, or mechanical ventilation is needed (Hu et al., 2021).

Regarding the oral lesions manifested in the patients included in this study, palate was the most common site, and ulcer was the most common manifestation. Interestingly, other viral infections also generally occur more often in the hard palate (i.e., keratinized mucosa) (Reichart, 2003; Arduino, Campolongo, Scinnameo, Conrotto, Gambino & Cabras, 2018). In recent systematic reviews (Santos et al., 2021a, 2021b) of oral manifestations in COVID-19 patients, authors reported that oral lesions exhibited miscellaneous clinical aspects, such as ulcers, blisters, macules, and plaques, varying in quantity, color appearance, and anatomical localization. Most patients had oral mucosal injury during the hospitalization period, supporting the hypothesis of coinfections, immunity dysregulation period, supporting the hypothesis of coinfections, immunity dysregulation period, supporting the hypothesis of coinfections, immunity dysregulation.
Menter, Haslbauer, Nienhold, Savic, Hopfer, and Deigendesch (2020) reported that the predominant histopathological findings in the lungs of autopsied patients who died from COVID-19 were capillary congestion, microthrombi and moderate intra-alveolar fibrin exudation, and Varga et al. (2020) observed endothelial damage in the kidneys and intestines of patients with COVID-19. Therefore, although the pathophysiology of COVID-19 has not yet been well elucidated, there is evidence of virus-induced vascular dysfunction in infected individuals.

The results of the present systematic review have limitations that should be addressed. First, only a few cases of OLICs with associated histopathological reports have been reported to date, and most of them are letters to the editor that provide mostly objective information. Currently, most of the manifestations of COVID-19 have been studied in organs that present more severe complications, and studies on oral lesions are still sparse. In addition, some authors have described an alarming impact of the COVID-19 pandemic on overall general outpatient visits in oral medicine centers and on the rate of oral biopsies (Alves et al., 2021; Gomes, Schuch, Tarquínio, Etges, & Vasconcelos, 2020; Marques et al., 2020). It is possible that this situation could contribute to the underestimation of the real frequency of these lesions. Finally, it is becoming increasingly difficult to publish case reports – even those related to pandemic scenarios.

5. Conclusion

In summary, as few cases thus far have had the histopathological features of OLICs and all of them had mostly nonspecific characteristics, it is unfeasible to determine the pathophysiology of these lesions. It is suggested that histopathology alone might not answer the relevant clinical question about the etiology of OLICs. Future studies evaluating the molecular profile of OLICs are needed to better characterize these lesions. It is important that oral medicine providers share OLIC cases with different medical specialties and oral and maxillofacial pathologists to establish a better understanding of this new condition. Finally, the clinicians should be aware of intra and extraoral manifestations of COVID-19 – especially in scenario with new variants.

Ethics approval statement

Not applicable.

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CRediT authorship contribution statement

Felipe Silveira: Conceptualization, Methodology, Investigation, Data curation, Writing – original draft. Ana Carolina Vasconcelos: Conceptualization, Methodology, Investigation, Data curation, Writing – original draft, Supervision. Andre Mello: Conceptualization, Investigation, Writing – review & editing. Laura Fonseca: Conceptualization, Investigation, Writing – review & editing. Luise Ferreira: Conceptualization, Investigation, Writing – review & editing. Ciro Soares: Data curation, Investigation, Resources, Writing – review & editing. Alan Santos-Silva: Data curation, Investigation, Resources, Writing – review & editing. Alexandre Sales: Resources, Visualization, Writing – review & editing. Laura Kirschnick: Investigation, Visualization, Writing – review & editing. Manoela Martins: Investigation, Visualization, Writing – review & writing. Lauren Schuch: Investigation, Visualization, Writing – review & writing. Alcides Arruda: Investigation, Visualization, Writing – review & writing. Ronell Bologna-Molina: Investigation, Visualization, Writing – review & writing.

Declarations of interest

None.

Author agreement

All authors have seen and approved the final version of the manuscript.

Data sharing

Data available in article supplementary material.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.archoralbio.2022.105374.

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