

LETTER TO THE EDITOR**Persistent lesions in oral cavity after SARS-CoV-2 infection**

Dear Editor,

In September 2020, a 78-year-old patient was referred to the Oral Medicine Unit of the University of Bologna, because of longstanding, painful, and widespread oral ulcerative lesions and erosive plaques (Figure 1a).

In March 2020, the patient had been hospitalized because of SARS-COV-2-related severe pneumonia and acute respiratory distress. Diagnosis of SARS-COV-2 infection was confirmed by positive RT-PCR on nasopharyngeal swab. Patient's medical history also included a previous diagnosis of follicular Lymphoma, in remission.

Oral lesions appeared few days after the onset of respiratory symptoms and worsened during hospitalization. However, since priority was given to therapy for SARS-COV-2-related pneumonia, oral care was delayed.

Pneumonia was treated with hydroxychloroquine, steroids, ciprofloxacin, and tocilizumab.

In April 2020, the patient was discharged from hospital but, despite apparent COVID-19 remission, he still required home oxygen therapy and no improvements of oral ulcers were experienced.

In September, a biopsy for histopathological examination was performed. Oral mucosa was ulcerated, with granulation tissue and fibrino-leukocytic material including bacterial colonies. Neither dysplasia nor fungal invasion was observed (Figure 1b). Direct Immunofluorescence showed a non-specific deposit of fibrinogen. Immunohistochemical search for HSV 1, HSV 2, and CMV-related proteins was negative. Sub-mucosal vessels were normal without features of vasculitis or thrombosis.

Laboratory screening tests for systemic HSV, CMV, EBV viral infections or for oral manifestations of gastrointestinal disorders were inconclusive. A marked lymphopenia (5% , $0.77 \times 10^9/L$),

excessive neutrophil count (88% , $11.3 \times 10^9/L$), and high ferritin values ($1,485 \text{ ng/ml}$) were recorded.

Therapeutic attempts to relief patient's painful condition with topical betamethasone, Chlorhexidine gel, and topical lidocaine were unable to achieve improvements in pain reduction.

Finally, in October acute respiratory conditions worsened, patient refused a new hospitalization and in November 2020 died of respiratory failure.

The suspicion that oral lesions could be related to SARS-COV-2 infection was raised.

SARS-COV-2 virus invades human cells via the ACE2 receptor which is abundant in mucosa cells of the oral cavity (Xu et al., 2020). It has been speculated that oral tissues might thus provide not only a possible route of entry for the SARS-COV-2 but also an extrapulmonary target.

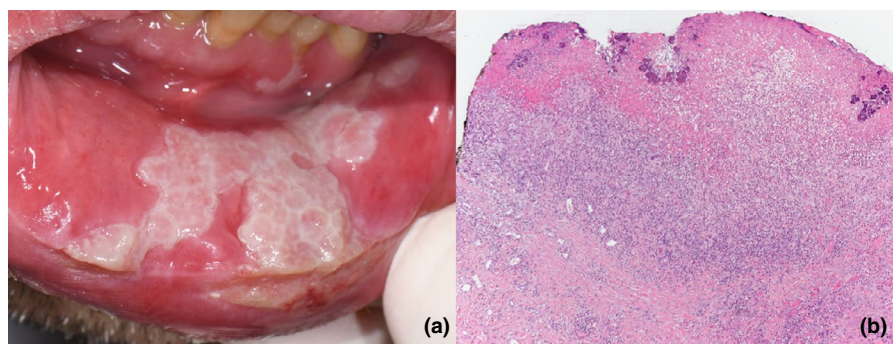
It is still unclear whether oral lesions in COVID-19 patients reflect a direct viral cytopathic damage or represent a consequence of systemic deterioration (Amorim Dos Santos et al., 2020; Mo et al., 2020; Ye et al., 2020).

Unlike previous cases, in our patient, ulcerative lesions were associated with persistent immunological impairment and did not heal after SARS-COV-2 eradication. Noteworthy, lymphopenia and neutrophilia have been described by many authors as a predictor of severity and poor prognosis in COVID-19 older patients (Mo et al., 2020; Wang et al., 2020; Ye et al., 2020).

It may be speculated that non-healing oral ulcerations may represent a sign of a persisting immunological storm-related damage after SARS-COV-2 eradication.

The present case, in agreement with emerging research, highlights the relevance of oral examination in proved or suspected

FIGURE 1 (a) Painful ulcerated plaque of the mucosal side of the inferior lip. Similar lesions affected both margins of the tongue, both lips, and soft palate. (b) At low power, the oral mucosa was ulcerated with granulation tissue and fibrino-leukocytic material including bacterial colonies. Dense inflammatory infiltrate was present in the submucosa



COVID-19 patients in order to relate oral health conditions with general prognosis.

CONFLICT OF INTEREST

All authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

Andrea Gabusi: Conceptualization; Data curation; Investigation; Writing-original draft; Writing-review & editing. **Davide Bartolomeo Gissi:** Conceptualization; Investigation; Supervision; Writing-review & editing. **Roberto Rossi:** Investigation; Writing-review & editing. **Maria P Foschini:** Methodology; Supervision; Validation; Writing-review & editing. **Lucio Montebugnoli:** Conceptualization; Methodology; Supervision; Validation; Writing-review & editing.

PEER REVIEW

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Andrea Gabusi¹ 

Davide Bartolomeo Gissi¹ 

Roberto Rossi¹ 

Maria Pia Foschini² 

Lucio Montebugnoli¹

¹Section of Oral Sciences, Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy

²Section of Anatomic Pathology at Bellaria Hospital, Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy

Correspondence

Andrea Gabusi, Section of Oral Sciences, Department of Biomedical and Neuromotor Sciences, University of Bologna, 40159 Bologna, Italy.
Email: andrea.gabusi3@unibo.it

ORCID

Andrea Gabusi  <https://orcid.org/0000-0002-7247-8615>

Davide Bartolomeo Gissi  <https://orcid.org/0000-0002-0195-7694>

Roberto Rossi  <https://orcid.org/0000-0002-6228-2934>

Maria Pia Foschini  <https://orcid.org/0000-0001-7079-7260>

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