

Research Letter

## Oral lesions are frequent in patients with Chikungunya infection

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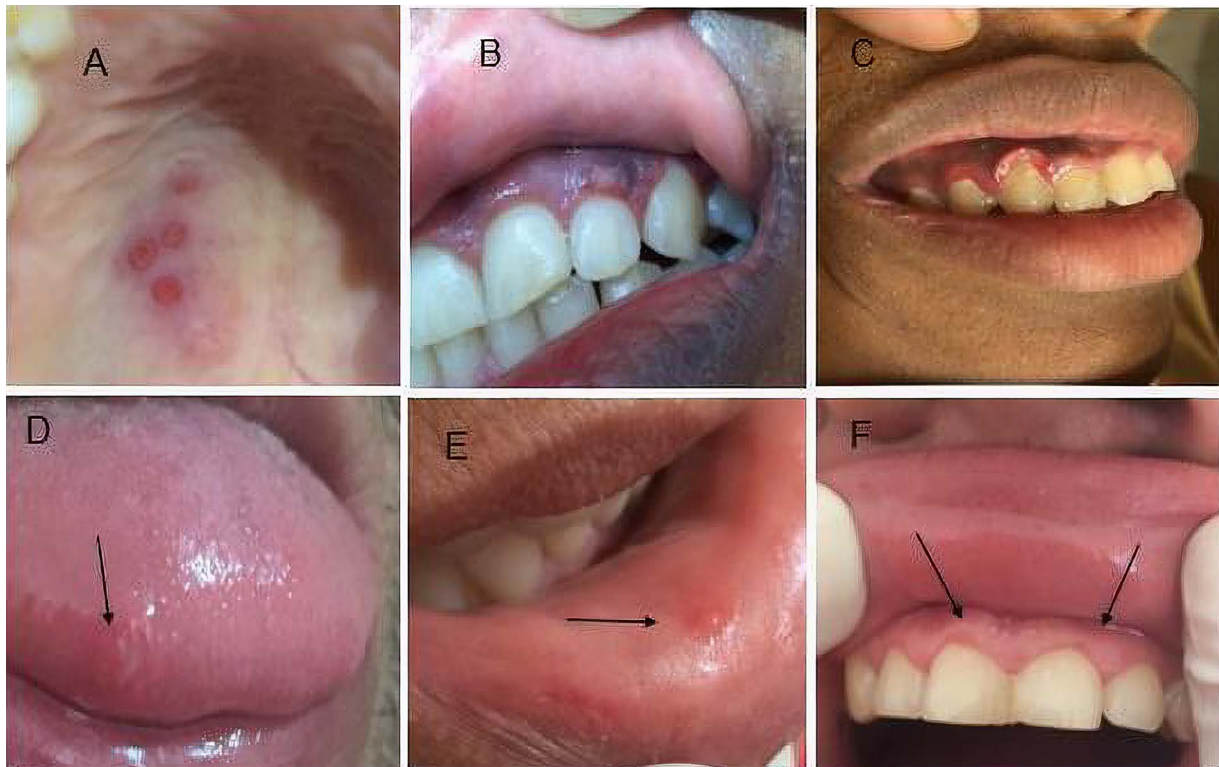
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After 50 years of restriction to areas of Asia and Africa, Chikungunya outbreaks emerged in all continents in the past 20 years becoming part of the Centers for Disease Control and Prevention (CDC) list of traveller-related infections. As Chikungunya outbreaks increase in frequency, a wide variety of clinical manifestations related to this infection have been reported. This study aimed to characterize the oral lesions related to Chikungunya infection in a multicentre cohort in northeastern Brazil. The study was approved by the Research Ethics Committee of the Faculdade de Medicina da Bahia, Universidade Federal da Bahia (approval number: 1.657.324). Written informed consent was obtained from all participants or legal guardians.

In total, 105 individuals with acute (<10 days of disease onset) mono-chikungunya virus (CHIKV) infection were evaluated by an otolaryngologist and dentist. Chikungunya infection was confirmed by polymerase chain reaction (PCR) ( $n=61$ ) and/or specific IgM ( $n=63$ ). Approximately 59 individuals tested positive for CHIKV by real-time PCR (RT-PCR) in serum specimens, 14 in saliva and 12 in urine specimens.

Oral lesions were detected in 21 out of 105 cases (20%) with acute CHIKV infection. Five of these individuals tested positive for CHIKV in saliva samples. Oral lesions occurred 2–6 days after disease onset. Odynophagia and/or dysphagia were reported by 20 patients. Most cases ( $n=15$ , 71.4%) presented isolated painful ulcers with well-circumscribed margins and erythematous halo (Figure 1). Gingival bleeding ( $n=7$ , 33.3%) and vesicles ( $n=3$ , 14.3%) were also observed, as well as edema ( $n=1$ , 4.8%) in marginal vestibular gum in the absence of plaque and dental caries (Figure 1). Lesions mainly affected the following locations: gingiva (43%), lips (52.4%), tongue (43%) and jugal mucosa (28.6%).

During acute infection, presence of an oral lesion was strongly associated with maculopapular rash and retroocular pain (85.7%,  $P=0.025$  and 81%,  $P=0.036$ , respectively), suggesting a polysymptomatic profile associated with oral involvement. However, presence of oral lesion in the acute stage of infection was not related to persistent arthralgia in a follow-up period of 12 months.



**Figure 1.** Clinical aspect and localization of oral lesions in patients with CHIKV infection. (a–d) Rounded ulcerated lesions, with circumscribed margins and halo-erythematous, in regions of hard palate (a), at the vestibular mucosa of the marginal gingiva (b and c) and at the tip of the tongue (d). (e) Vesicular-bullous lesion on the lower lip. (f) Edematous and bleeding regions in vestibular mucosa of gingiva margin of the upper central incisors.

In our study, 20% of the CHIKV-infected individuals presented with oral lesions early after disease onset, comparable with the 2.3–54.3% rate previously reported for oral lesions during acute CHIKV infection.<sup>1–4</sup> Due to intense arthralgia and myalgia, patients may not spontaneously report oral complaints. The relative high incidence of painful oral lesions adversely affecting eating and drinking underpins the need for routine intrabuccal exam in patients with acute CHIKV illness.<sup>5</sup> Symptomatic relief medications may help mitigate morbidity during acute CHIKV infection.

Among the oral lesions found in the present series ( $n = 21$ ), 86% were characterized as ulcers and vesicles. Painful oral ulcers in the form of aphthae-like erosions seems to be the most common oral manifestation, observed in 13.6–16% of CHIKV-infected patients and lasting 3–10 days without any sequelae.<sup>6–8</sup> Detection of oral ulcer in the context of an arbovirus infection, while not a specific sign, may be suggestive of Chikungunya etiology.

Gingivorragia associated with gingivitis was previously described in a range of 1.4–54.4% of Chikungunya cases,<sup>1,3</sup> even despite normal platelet counts.<sup>9</sup> Of note, others haemorrhagic manifestations, such as skin and mucosal bleeding, were considered positive predictor of Chikungunya infection among patients with suspected arbovirus infection.<sup>10</sup>

We detected CHIKV in saliva of 27% of patients with oral involvement suggesting that lesions may result from direct viral activity. Further studies are needed to confirm this hypothesis. Additional research exploring pathological and immunological features of oral lesion may also provide

insights into the pathogenesis of Chikungunya-mediated tissue damage.

In conclusion, the presence of oral ulcers was found to be relatively common during acute CHIKV infection, resulting in pain and dysphagia that potentially increases the morbidity of this arbovirus infection.

### Authors' Contributions

P.M.M.C., K.A., V.S.B., V.N. and E.S.N. performed clinical evaluation. P.M.M.C., L.P.M., C.M.O., L.P.C., L.A.S. A.P.B. and R.K. were responsible for diagnostic tests. P.M.M.C., K.A. and V.S.B. wrote the manuscript with contributions of L.P.C., A.P.B. and M.B. T.C.S. performed statistical analysis M.B., A.P.B., V.S.B. and R.K. supervised the Project. All authors provided critical feedback and helped shape the manuscript.

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### Conflict of Interest Statement

The authors declare no financial interests or connections, direct or indirect, or other situations that might raise the question of bias in the work reported or the conclusions, implications or opinions stated—including pertinent commercial or other sources of funding for the individual author(s) or for the associated department(s) or organization(s), personal relationships or direct academic competition.

### References

1. Kannan M, Rajendran R, Sunish IP, Balasubramaniam R *et al.* A study on chikungunya outbreak during 2007 in Kerala, South India. *Indian J Med Res* [Internet] 2009; 129:311–5. <https://www.ncbi.nlm.nih.gov/pubmed/19491425>.
2. Staikowsky F, Talarmin F, Grivard P *et al.* Prospective study of Chikungunya virus acute infection in the Island of La Réunion during the 2005–2006 outbreak. *PLoS One* [Internet] 2009; 4. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2764049/>.
3. Katti R, Shahapur PR, Udupudi KL. Impact of chikungunya virus infection on oral health status: an observational study. *Indian J Dent Res* [Internet] 2011; 22:613. <https://www.ncbi.nlm.nih.gov/pubmed/22124070>.
4. Kumar R, Sharma MK, Jain SK, Yadav SK, Singhal AK. Cutaneous manifestations of chikungunya fever: observations from an outbreak at a Tertiary Care Hospital in Southeast Rajasthan, India. *Indian Dermatol Online J* [Internet] 2017; 8:336–42. <https://www.ncbi.nlm.nih.gov/pubmed/28979866>.
5. Simarmata D, Ng DCE, Kam Y-W *et al.* Early clearance of Chikungunya virus in children is associated with a strong innate immune response. *Sci Rep* [Internet] 2016; 6. <https://www.nature.com/articles/srep26097>.
6. Riyaz N, Riyaz A, Rahima *et al.* Cutaneous manifestations of chikungunya during a recent epidemic in Calicut, North Kerala, South India. *Indian J Dermatol Venereol Leprol* [Internet]. 2010;76: 671–6. <http://www.ijdv.com/article.asp?issn=0378-6323;year=2010;volume=76;issue=6;spage=671;epage=676;aulast=Riyaz>.
7. Singaraju GS, Vanaja E, Sathe PS. Oral manifestations of Chikungunya fever in clinically diagnosed Chikungunya cases (CDCG)-a purposive study. *Annals Essences Dent* [Internet] 2010; 2:25–9. <https://www.longdom.org/abstract/oral-manifestations-of-chikungunya-fever-in-clinically-diagnosed-chikungunyarncases-cdcga-purposive-study-764.html>.
8. Anderson KB, Pureza V, Walker PF. Chikungunya: acute fever, rash and debilitating arthralgias in a returning traveler from Haiti. *J Travel Med* [Internet]. 2014; 21: 418–20. <https://academic.oup.com/jtm/article/21/6/418/1843067>.
9. Nkoghe D, Kassa RF, Caron M *et al.* Clinical forms of Chikungunya in Gabon, 2010. *PLoS Negl Trop Dis* [Internet] 2012; 6:e1517. <https://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0001517>.
10. Alvarado LI, Lorenzi OD, Torres-Velásquez BC *et al.* Distinguishing patients with laboratory-confirmed chikungunya from dengue and other acute febrile illnesses, Puerto Rico, 2012–2015. *PLoS Negl Trop Dis*. [Internet] 2019; 13:e0007562. <http://dx.plos.org/10.1371/journal.pntd.0007562>.