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LETTER TO THE EDITOR

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Monkeypox-related oral manifestations and implications: Should dentists keep an eye out?

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To the Editor,

The outbreak of monkeypox in multiple nonendemic countries in North America and Europe that started in May 2022 has led to an intensive investigation at both international and national levels for a better understanding of its infection sources and transmission pathways.[1] The classic zoonosis that causes smallpox-like symptoms has experienced substantial epidemiological transformations as inter-human transmission became a leading pattern through various pathways including nosocomial infections.[2] Therefore, healthcare workers with high-risk exposure are among the recommended groups to receive vaccination by the centers for disease control in the European Union (EU) and the United States.[1,3]

Given the nature of the clinical dental practice that requires prolonged face-to-face contact with patients facilitating large respiratory droplet dispersion, the risk of inter-human transmission within dental settings should not be underestimated.[4] On top of that, dentists are well-positioned to aid national surveillance efforts in their respective countries as oral manifestations of infectious diseases, including smallpox and monkeypox, are of practical value for detection algorithms.[5] As reported in the 1972 outbreak of smallpox in Yugoslavia, tongue swelling, oral mucosal ulceration, and bleeding occurred at least 24 h before fever.[5]

We performed a rapid literature review in Ovid MEDLINE®, Embase, and Google Scholar using a combination of keywords ("monkeypox OR smallpox OR *orthopoxvirus*" AND "oral manifestations OR enanthem* OR oral mucosa") to explore the body of evidence on monkeypox-related oral manifestations. Given the similarity of the clinical presentation, smallpox, monkeypox, and chickenpox were compared in Table 1. Chickenpox is a highly contagious airborne disease that might be confused with monkeypox due to the similarity of some clinical features; and fortunately, mass vaccination leads to a massive reduction of new infections incidence.[6,7]

The clinical course of human monkeypox starts with a prodromal period lasting up to 4 days, similar to smallpox, and is characterized by fever, malaise, and headache, which are typically milder than those that occur in smallpox cases.[8] Unlike smallpox, lymphadenopathy is the characteristic symptom of human monkeypox, and it occurs during the prodromal period in submandibular, maxillary, cervical, and inguinal lymph nodes, where the nodes become enlarged, firm, and painful.[9,10] The eruptive stage usually begins within 1–3 days of fever, and it predominantly starts from the face, with a few exceptions where skin eruptions start on the forearms.[11] Skin exanthema spread in a centrifugal pattern and evolve from macules to papules, vesicles, and pustules and end as crusts.[8] In a recent review of the monkeypox outbreak of 2022, all reported cases (100%) were of the male gender with the vast majority (97.14%) having sexual relations with people of the same gender (MSM).[12] An uncommon clinical manifestation associated with the ongoing outbreak is the anogenital lesions and rashes that primarily spare the face and extremities.[12]

Oral mucosal enanthema can occur in more than 70% of the cases, and they were more significantly reported among unvaccinated than vaccinated patients (73% vs. 37%, respectively; $p < 0.001$) and among primary cases infected by animals than secondary cases infected by humans (74.8% vs. 56.2%, respectively; $p < 0.001$).[9,11] According to the US CDC, enanthem is depicted as the first stage of monkeypox lesions, and they develop intraorally usually on the tongue.[13]

In a recent case series ($n = 197$) from the UK for monkeypox diagnosed during the ongoing outbreak, Patel et al. 2022 found that oropharyngeal lesions, mainly ulcers, were reported in 27 (13.7%) cases.[14] Another recent case series ($n = 528$) from the US demonstrated that oropharyngeal manifestations were the initial symptoms of 26 cases including pharyngitis and oral and tonsillar lesions, and the second most common site for mucosal lesions after genitalia (68%) was the oropharyngeal region (23%).[15] Additionally, Peters

TABLE 1 Clinical characteristics and oral manifestations of monkeypox, smallpox, and chickenpox

Characteristic	Monkeypox	Smallpox	Chickenpox
Incubation period (days)	7–17	7–17	12–14
Prodromal period (days)	1–4	1–4	0–2
Eruptive period (days)	14–28	14–28	10–21
Fever	Mild to severe	Severe	Mild or none
Malaise	Moderate	Moderate	Mild
Headache	Moderate	Severe	Mild
Lymphadenopathy	Submandibular, maxillary, cervical, or inguinal lymphadenopathy (1–4 cm in diameter). Enlarged lymph nodes are firm, tender, and sometimes painful.	No	No
Palmar-plantar lesions	Yes	Yes	Rare
Lesions distribution	Centrifugal	Centrifugal	Centripetal
Lesions depth (diameter in mm)	Superficial to deep (4–6)	Deep (4–6)	Superficial (2–2)
Lesions appearance	Homogenous, umbilicated	Homogenous, umbilicated	Heterogenous
Time to desquamation (days)	14–21	14–21	6–14
Oral cavity lesions	Enanthema evolved rapidly to produce painful lesions and sore throat. Oral Lesions on the oral mucosa and the tongue cause difficulties with drinking and eating (dysphagia). Symptoms of an attack of acute tonsillitis with or without signs of pharyngitis were reported. Sore throat.	Enanthema over the tongue, mouth, and oropharynx.	Flat-based ulcers and oral mucosal vesicles and blisters; either painful or painless.

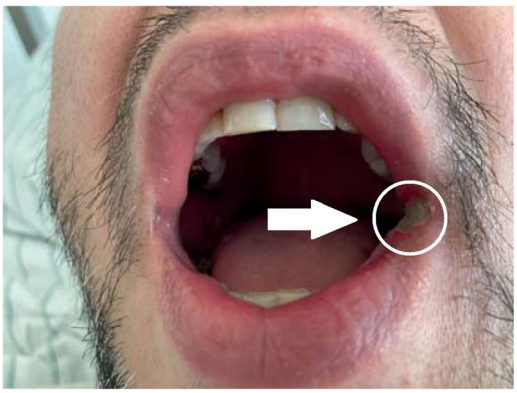

FIGURE 1 Vesicle in the left corner of the mouth documented in a monkeypox case in Germany. The photo is used after the authors' permission.

et al. 2022 reported two monkeypox cases from the US who sought medical care because of painful tongue ulcers preceding their other skin lesions and of which the swabs were positive for monkeypox virus.[16] In Germany, Schlabe et al.[17] reported that angular cheilitis was the first clinical manifestation of monkeypox in a 51-year-old male patient (Figure 1).

Dehydration is one of the monkeypox complications which can be triggered by painful oral enanthema (mouth sores) that lead to dysphagia and reduced oral intake.[18,19] In a recently published retrospective study from the United Kingdom for monkeypox patients diagnosed between August 2018 and September 2021, oral lesions were not reported; however, 28.6% of the patients complained of sore throat.[20]

To conclude, dentists need to be aware of and prepared for inter-human transmission risk through respiratory droplets and the post-exposure procedures they have to follow, ranging from self-isolation and case reporting to immediate ring vaccination. Considering the low herd-immunity of young generations against orthopoxviruses since the cessation of mass vaccination in the 1980s and the cross-reactivity between the orthopoxviruses that make smallpox vaccines, for example, Jynneos recommended for monkeypox cases; now the emerging question is whether dentists will need to re-add smallpox vaccines to their vaccination schedule in the near future. Given the limited availability of vaccines, dentists and dental team members should pay attention to the patient's history and infection control protocols, and protective measures.[21]

AUTHOR CONTRIBUTIONS

Abanoub Riad and Sameh Attia collected the data and wrote the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. ECDC. Factsheet for health professionals. Monkeypox. December 10, 2019. Accessed May 22, 2022. https://www.ecdc.europa.eu/en/all-topics-z/monkeypox/factsheet-health-professionals
2. Bunge EM, Hoet B, Chen L, et al. The changing epidemiology of human monkeypox—a potential threat? A systematic review. *PLoS Neglected Trop Dis*. 2022;16(2):e0010141. doi:10.1371/JOURNAL.PNTD.0010141
3. Centers for Disease Control and Prevention (CDC). Monkeypox | Poxvirus | CDC. Vaccines. August 5, 2022. Accessed August 15, 2022. https://www.cdc.gov/poxvirus/monkeypox/vaccines.html
4. CDC. Transmission. Monkeypox. July 16, 2021. Accessed May 22, 2022. https://www.cdc.gov/poxvirus/monkeypox/transmission.html
5. Torres-Urquidy MH. Biosurveillance and Dentistry BT. In: Acharya A, Powell V, Torres-Urquidy MH, Posteraro RH, Thyvalikakath TP, eds. *Integration of Medical and Dental Care and Patient Data*. Springer International Publishing; 2019:207-219. doi:10.1007/978-3-319-98298-4_12
6. Lo Presti C, Curti C, Montana M, Bornet C, Vanelle P. Chickenpox: an update. *Médecine et Maladies Infectieuses*. 2019;49(1):1-8. doi:10.1016/J.MEDMAL.2018.04.395
7. Jezek Z, Szczeniowski M, Paluku KM, Mutombo M, Grab B. Human monkeypox: confusion with chickenpox. *Acta Trop*. 1988;45(4):297-307.
8. McCollum AM, Damon IK. Human monkeypox. *Clin Infect Dis*. 2014;58(2):260-267. doi:10.1093/cid/cit703
9. Ježek Z, Grab B, Szczeniowski M, Paluku KM, Mutombo M. Clinico-epidemiological features of monkeypox patients with an animal or human source of infection. *Bull World Health Organ*. 1988;66(4):459-464.
10. Formenty P, Muntasir MO, Damon I, et al. Human monkeypox outbreak caused by novel virus belonging to Congo Basin Clade, Sudan, 2005. *Emerging Infect Dis*. 2010;16(10):1539-1545. doi:10.3201/EID1610.100713
11. Ježek Z, Szczeniowski M, Paluku KM, Mutombo M. Human monkeypox: clinical features of 282 patients. *J Infect Dis*. 1987;156(2):293-298. doi:10.1093/INFDIS/156.2.293
12. Bragazzi NL, Kong JD, Mahroum N, et al. Epidemiological trends and clinical features of the ongoing monkeypox epidemic: a preliminary pooled data analysis and literature review. *J Med Virol*. Published online 2022. doi:10.1002/JMV.27931
13. CDC Centers for Disease Control and Prevention. Clinical recognition. Monkeypox. August 5, 2022. Accessed August 13, 2022. https://www.cdc.gov/poxvirus/monkeypox/clinicians/clinical-recognition.html
14. Patel A, Bilinska J, Tam JCH, et al. Clinical features and novel presentations of human monkeypox in a central London centre during the 2022 outbreak: descriptive case series. *BMJ*. 2022;378:e072410. doi:10.1136/BMJ-2022-072410
15. Thornhill JP, Barkati S, Walmsley S, et al. Monkeypox virus infection in Humanshumans across 16 countries—April-June 2022. *N Engl J Med*. Published online July 21, 2022. doi:10.1056/NEJMOA2207323/SUPPL_FILE/NEJMOA2207323_DATA-SHARING.PDF
16. Peters SM, Hill NB, Halepas S. Oral manifestations of monkeypox: a report of two cases. *J Oral Maxillofac Surg*. Published online August 6, 2022. doi:10.1016/J.JOMS.2022.07.147
17. Schlabe S, Boesecke C, Isselstein J. Ulcer at corner of mouth as first sign of infection with monkeypox virus. *Dtsch Arztebl Int*. Published online July 25, 2022. doi:10.3238/ARZTEBL.M2022.0274
18. Moore M, Zahra F. Monkeypox. *StatPearls*. Published online February 28, 2022. https://www.ncbi.nlm.nih.gov/books/NBK574519/
19. Huhn GD, Bauer AM, Yorita K, et al. Clinical characteristics of human monkeypox, and risk factors for severe disease. *Clin Infect Dis*. 2005;41(12):1742-1751. doi:10.1086/498115
20. Adler H, Gould S, Hine P, et al. Clinical features and management of human monkeypox: a retrospective observational study in the UK. *Lancet Infect Dis*. 2022;22(8):1153-1162. doi:10.1016/S1473-3099(22)00228-6/ATTACHMENT/D32AAC49-E98D-4F28-89B5-BBEA95D3FCB8/MMC1.PDF
21. Patil S, Moafa IH, Bhandi S, et al. Dental care and personal protective measures for dentists and non-dental health care workers. *Dis Mon*. 2020;66(9):101056. doi:10.1016/J.DISAMONTH.2020.101056