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Short Communication

Mpox reinfection: A rapid systematic review of case reports

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ABSTRACT

Background: Mpox re-emerged worldwide with the multi-country outbreaks that occurred in May 2022, threatening the public health of human beings.

Methods: This rapid systematic review summarized mpox reinfection cases documented. Electronic databases (PubMed, MedRxiv, and Social Science Research Network) were searched without time limitation, using the keywords "mpox," "monkeypox," & "reinfection," "reoccur," "reoccurrence," "episode," and "relapse". All laboratory-confirmed cases of mpox reinfection published in the literature were included in this study.

Results: A total of seven publications (nine cases) from Africa, Europe, and South America were included. All mpox reinfection cases were male, with a median age of 36; 88.89% of cases had unprotected sexual behaviors with other males before each illness episode. The average onset interval between the two episodes was about 4 months. Perianal lesions and lymphadenopathy were major symptoms in both episodes, and no differences in clinical severity were reported between the two episodes. The mean duration of the two episodes was approximately 22 days and 13 days, respectively; which the mean duration of the second episode was shorter than the first infection ($t = 2.17$, $p = 0.0487$). Sexually transmitted infections were commonly concurrent among most cases, accounting for 55.6% and 77.8% in the two episodes, respectively. Full vaccination against mpox was rare among reinfection cases.

Conclusion: A second infection is possible even in a short period. Reinforcing monitoring, reducing high-risk behaviors, and heightening health education regarding mpox for high-risk populations are crucial to limit mpox spread, including persons with a history of mpox infection.

1. Introduction

Mpox, as a re-emerging zoonotic disease, threatens the public health of human beings globally. It typically presents as a self-limiting disease characterized by fever (≥37.4°C), an extensive characteristic rash, and lymphadenopathy [1,2]. Transmission occurs primarily through contact with bodily fluids or lesions on the skin or internal mucosal surfaces [1]. Human-to-human transmission is limited. A survey across 16 countries stated that approximately 95% of transmissions were suspected to have occurred through sexual activity [3]. As of 30 September 2023, a total of 91,123 laboratory-confirmed cases from 115 countries were reported, along with 663 probable cases and 157 deaths [4]. To our knowledge, smallpox or cowpox reinfection human cases were documented rarely, but mpox reinfection cases were reported from many countries [5–11]. With the re-emergence of mpox in African countries [12] and increasing cases reported from non-endemic epidemic areas [4], the uncertainty of mpox reinfection has become a public health concern that cannot be ignored.

Individuals who experienced smallpox or received vaccination were generally thought to generate a robust immune response. Likely, it was initially believed that infection or vaccination against mpox would be the same.

Abbreviations: WHO, World Health Organization; MPXV, Monkeypox Virus; MSM, men who have sex with men; STIs, sexually transmitted infections; PHEIC, public health emergency of international concern.

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However, studies on mpox reinfection were reported in 2023 across various countries, despite a significant decline in reported cases worldwide following the multi-country outbreaks that occurred in May 2022 [4]. This indicated that humans can also be at a risk of reinfection. The high-risk groups of mpox reinfection, the onset of the interval between the two episodes and the characteristics of the two episodes were unclear, which need to be elucidated. Here, we summarized the mpox reinfection cases reported up to now and provided scientific references for the control and prevention of mpox reinfection.

2. Methods

Electronic databases (PubMed, MedRxiv, and Social Science Research Network) were searched without time limitation, using the keywords “mpox,” “monkeypox,” & “reinfection,” “reoccur,” “reoccurrence,” “episode,” and “relapse”. All laboratory-confirmed cases of mpox reinfection published in the literature were included in this study.

3. Results

Seven studies from Switzerland, the United Kindom, France, Brazil, Spain, Italy, and Nigeria were included in our study. A total of nine confirmed mpox reinfection cases have been reported in these publications, with no death. Nine Mpox reinfection cases are male, and most of them (8 cases) are men who have sex with men (MSM). The median age was 36 years old (ranging between the early 30s and 51 years old). 88.89% of cases (8 cases) had unprotected sexual behaviors (all had anal intercourse and two also had oral intercourse) with other MSM before each illness episode. The average onset interval between the two episodes was approximately 4 months, with a range of 1.5 months to 9 months. No cases reported severe symptoms during both illness courses, and no differences in clinical severity were observed between the two episodes among cases. Perianal lesions were reported in most cases in both episodes, followed by lymphadenopathy. The mean duration of the two episodes was approximately 22 days and 13 days, respectively. The mean duration of the second episode was shorter than the first infection ($t = 2.17$, $p = 0.0487$). 55.6% (5/9) and 77.8% (7/9) of cases experienced co-occurrence with sexually transmitted infections (STIs) in the two episodes, respectively. Most cases did not report treatments for both episodes. Specifically, only one case reported treatment of the two episodes, and three cases only reported treatment of the first episode.

Except for one healthcare worker (Number 9 in Table 1), other reinfection cases were MSM. The healthcare worker had close contact with a confirmed mpox case one week before his first onset of symptoms, and he was exposed to the room of a confirmed case without donning personal protective equipment five days prior to his second episode. His symptoms for both episodes are different from those symptoms from other cases. More details of these cases are provided in Table 1.

Among the nine mpox reinfection cases, two cases were vaccinated against smallpox. One case was vaccinated with a complete two-dose course of smallpox vaccination between the two episodes, and another one was vaccinated before the primary infection when he was a child. Nine reinfection cases were reported in 2022. Genetic sequencing was successfully performed in only one case with both episodes, revealing the presence of human Monkeypox virus (MPXV) subtype IIb, lineage B.1. Detailed information on these cases was provided in Table 1.

4. Discussion

Our study found two cases who received smallpox vaccines before or after their initial mpox episode still experienced mpox reinfection. Potential reasons for this phenomenon include immune escape, waning vaccine protection over time, offsetting of immunity from post-exposure vaccination, and natural infections. It needs to be verified in further studies. Additionally, due to sequencing failures, the MPXV clades of the two episodes cannot be distinguished, which can not rule out the possibility that a case can be infected with different MPXV clades in two episodes. A finding reported 85% protective efficacy of smallpox vaccination in protecting against mpox [13], however, it was not observed in our study because limited mpox reinfection cases were documented yet and most cases were not vaccinated against smallpox. The coverage of mpox vaccination was low worldwide before this global outbreak occurred in May 2023. The vaccine is available against MPXV [14], but additional critical information regarding mpox vaccination, including vaccine development, vaccination dosage, and vaccination frequency warrants future studies.

There is a high proportion of mpox reinfection cases with concurrent STIs in both episodes, highlighting the importance of the co-prevention of mpox and STIs. Furthermore, most mpox reinfection cases were MSM, which underscored the need to strengthen mpox surveillance among the MSM population, including health education, vaccination, and the availability of rapid molecular point-of-care tests [15]. Previous studies indicated knowledge gaps regarding mpox among healthcare workers [16,17], MSM [18], and the general public [19], highlighting the importance of targeted health education initiatives [20].

Additionally, no cases reported severe symptoms during both illness courses, and no differences in clinical severity were observed between the two episodes among cases. The mean duration of the second episode was shorter than the prior infection.

Table 1
Characteristics of nine mpox reinfection cases.

Number	1[†] [5]	2[‡] [6]	3[*] [7]	4[&] [8]	5 [8]	6[❋] [9]	7 [10]	8 [10]	9[a] [11]
Country	Switzerland	United Kindom	France	Brazil	Brazil	Spain	Italy	Italy	Nigeria
Age	34	early 30s	36	39	40	51	36	33	36
Initial episode									
Onset date	May 2022	Jul 2022	not reported	Jul 7, 2022	Jul 13, 2022	Jul 23, 2022	May 17, 2022	Jul 7, 2022	Nov 14, 2017
Clinical features	lesions on the penis	rectal pain, rectal discharge, inguinal lymphadenopathy	lesions on penis, trunk, and limbs	fever, odynophagia, myalgia, lesions on anus, perianal lesion	perianal vesicular lesion, myalgia	pseudopustules on the pubis and penis, groin lymphadenopathy	asthenia, pharyngodynia, fever with tenesmus, mucorrhea, perianal ulceration, lymphadenopathy	proctitis, lesion on lip, lymphadenopathy	ILI, systemic lesions, submental and inguinal lymphadenopathy
Duration	2 weeks	2 weeks	30 days	35 days	30 days	3 weeks	16 days	20 days	14 days
Concurrent disease	chlamydia trachomatis	–	–	proctitis, HIV	HIV	–	chlamydia proctitis, HIV	chlamydia proctitis	–
Second episode									
Onset date	Nov 2022	Nov 2022	not report	Sept 7, 2022	Sept 8, 2022	Nov 2022	Sept 27, 2022	Aug 22, 2022	Aug 14, 2018
Clinical features	perianal pain, inguinal lymphadenopathy	headache, back pain, neck pain, anal sore, apthous mouth ulcer	lesions on penis, inguinal lymphadenopathy, influenza-like illness	lesion on penis	lesion on penis	lesion on penis, groin lymphadenopathy	lesion on the glans penis	proctitis	ILI, systemic lesions,no rash developed on the penile skin
Duration	not reported	2 weeks	not reported	10 days	10 days	4 weeks	5 days	5 days	17 days
Concurrent disease	Chlamydia trachomatis	–	HA, HB, EBV, cytomegalovirus	HIV	HIV	syphilis	chlamydia proctitis, HIV	gonorrhoea proctitis, SARS-CoV-2	–
Onset interval	6 months	4 months	3 months	2 months	2 months	3.5 months	4.5 months	1.5 months	9 months
First author	Musumeci, S.	Golden, J.	Zeggagh, J.	Rocha, S.Q.	Rocha, S.Q.	Alvarez-Lopez, P.	Raccagni, A.R.	Raccagni, A.R.	Ogoina, D.

[†] the first infection strain was MPXV lineage B.1;
[‡] received a complete two-dose course of smallpox vaccination and was treated empirically for proctitis with 2 weeks of doxycycline and 1 week of aciclovir in the first episode;
[*] both episodes were with human MPXV clade IIb, lineage B.1 and prescribed symptomatic treatment for pain in the first episode;
[&] prescribed symptomatic drugs in his first episode;
[❋] vaccinated against smallpox in his childhood, HA, hepatitis A; HB, hepatitis B; EBV, Epstein-Barr virus;
[a] the second infection strain was MPXV clade IIb, in the first episode, he received analgesics, antimalarials,amoxyl/clavulinic acid, and antipruritic drugs and did not receive any antiviral, in the second episode, he was treated with analgesics, antibiotics, and antipruritic drugs and did not receive any antiviral.

This study has a few limitations. Firstly, due to the limited number of studies reporting mpox reinfections cases and variations in reporting standards among countries and regions, there is a potential for information bias. With the increased number of mpox reinfection cases, the establishment of a standard definition of mpox reinfection is imperative. Secondly, most reinfection cases in this study lacked genomic data, therefore there might be some relapse cases instead of being counted as reinfection. Finally, information bias about reinfection without female cases might exist.

5. Conclusions

This rapid systematic review summarized the reported mpox reinfection cases and indicated that a second infection is possible even in a short period. The finding suggested that mpox reinfection is an emerging global public health, emphasizing the importance of active surveillance and targeted health education measures, particularly among the MSM population, including persons with a history of mpox infection.

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Author contributions

T.T.L.: Investigation, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. Z.J.L.: Investigation, Data curation, Visualization, Writing – review & editing. Y.X.: Formal analysis, Project administration, Validation, Visualization, Writing – review & editing. J.L.: Conceptualization, Formal analysis, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing. L.Q.: Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Writing – review & editing.

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Declaration of competing interest

All co-authors declared no conflicts of interest exist.

Data available statement

The data that support the findings of this study are openly available in reference number [5–11].

Ethics statement

Not applicable.

Informed consent

Not applicable.

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