Clinical Infectious Diseases

BRIEF REPORT

A case of mpox reinfection

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A healthy young man first diagnosed with mpox in May 2022 presented again in November 2022 with anal proctitis and a positive PCR on a rectal swab for MPX virus (MPXV) after a recent trip to Brazil, where he engaged in condomless sexual intercourse with multiple male partners.

Keywords: mpox, monkeypox, immunity, reinfection

INTRODUCTION

Mpox caused by *mpox virus* (MPXV), was considered a sporadic zoonotic disease limited to West and Central African countries until the current worldwide outbreak was declared in May 2022. MPXV belongs to the *Orthopoxvirus* genus, as do *Vaccinia-*, *Cowpox-*, and *Variola virus*, all of which are infectious to humans. MPXV infection generates humoral and cellular immunity

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DOI: 10.1093/cid/ciad147

that is expected to provide long-term protection against reinfection[1]. These assumptions are based on extensive experience with *Variola virus*, the agent of smallpox disease[2]. Smallpox infection or vaccination with the attenuated *Vaccinia virus* provided almost complete protection from infection with *Variola virus* thanks to cross-immunity[2]. Even years after the last smallpox vaccination, individuals historically vaccinated are considered less likely to be infected by MPXV than non-vaccinated and protected from severe disease [3]. MPXV reinfection has only been reported by Golden et al. [4] so far suggesting it is at most an infrequent event. After 1980, waning immunity against smallpox of historically vaccinated or naturally infected and the heightened number of susceptible individuals are considered main drivers for the mpox flares of the past decades in African endemic regions. In the DRC, between 1980 and 2007, reported infections with MPXV increased 20-fold. While these studies suggest protective, long-lasting cross-immunity through smallpox vaccination, data on elicited protection after MPXV infection is scarce. Here we report a case of mpox reinfection in an otherwise healthy adult.

CASE REPORT

A 31-year-old man in good general health presented in May 2022 with four umbilicated lesions on the penis. He was on pre-exposure prophylaxis (PrEP) for HIV and reported having had condomless sex with men, including receptive anal intercourse. He did not report previous smallpox infection or vaccination. On physical exam, no lymphadenopathy was found, and oropharyngeal and anal inspection was normal. The patient did not report fever or any other symptoms. Skin lesions and pharyngeal swabs tested positive for MPXV by real-time *orthopoxvirus* PCR[5] with a cycle threshold (Ct) of 16.5 and 35.3, respectively. He was also diagnosed with asymptomatic urinary *Chlamydia trachomatis* infection. Within two weeks, skin lesions spontaneously resolved without complications.

On 1 December 2022, the patient reported persistent perianal pain without bleeding nor discharge. Symptoms had started two weeks before, on his return from Brazil in November 2022, where he had engaged in condomless anal intercourse with multiple male partners. No other complaints or symptoms were reported. He related a last receptive anal intercourse two weeks before the presentation. The patient did not recall any signs or symptoms of mpox among his partners, nor was he aware of an MPXV infection among them. Clinical examination found no skin lesion in the perianal region or other body parts. Apart from a slightly palpable painless right inguinal lymphadenopathy, the medical examination was normal. Four weeks after symptom onset, a proctologic examination revealed a small anal fissure but no typical mpox lesion.

Sexually transmitted infectious diseases were screened using standard diagnostic tests. The anal swab done on 1 December came back positive for MPXV with a Ct of 27 and for *Chlamydia trachomatis* (non LGV). The latter was treated with a 7-day course of doxycycline. HIV serology and viremia were negative, syphilis serology negative for acute infection. On 13 December 2022,

DOI: 10.1093/cid/ciad147

rectal and pharyngeal swabs were collected again and turned out negative. *Orthopoxvirus* PCR was also negative in the blood and urine on 13 December 2022. Total mpox antibodies were tested (Custom Monkeypox Human ELISA Kit, RayVio, Georgia, USA) on sera collected prior to the first episode in May 2022 and after the second in December 2022: they came back negative and positive, respectively. Unfortunately, no serum had been collected between the two episodes.

DISCUSSION

We report a case of probable mpox reinfection. The patient's *Orthopoxvirus* PCR returned positive on an anal swab 14 days after the last receptive anal intercourse and 6 months after a previously confirmed MPXV-infection. It is not possible to determine if this second mpox episode contributed to the proctitis in the context of concomitant *Chlamydia trachomatis* infection and the presence of an anal fissure. Specific mpox mucosal lesions might have been missed as the proctologic examination was carried out 4 weeks after symptom onset. It is therefore impossible to distinguish between symptomatic and asymptomatic reinfection. Though viral culture could not be performed to confirm active infection with certainty, a trusted physician's detailed anamnesis undertaken during the second episode makes anal contamination following condomless anal intercourse with an mpox-positive partner in the days before sampling unlikely. The disease course was mild, and the patient recovered completely. No immunosuppressive condition were found and HIV could be excluded.

This case illustrates that sterilizing immunity may be limited despite prior systemic infection. Studies suggest historical smallpox infection or vaccination produces cross-immunity against mpox[3,6]. The vaccine currently used against MPXV, the Modified Vaccinia Ankara vaccine (MVA-BN), an attenuated live non-replicating vaccinia virus in human cells, was shown to elicit sufficient cross-neutralizing activity against MPXV to prevent infection and reduce disease severity [7]. After mpox infection, a study showed that 83% and 71% of historically vaccinated and non-vaccinated individuals developed MPXV-neutralizing antibodies in serum[6]. Of these, neutralization antibody titers were low irrespective of vaccination status[6]. One possible explanation given by the authors was the sampling time, which occurred early in the symptomatic phase[6]. These findings might also be explained by the not well-established neutralization assays used for MPXV, possibly leading to lower sensitivities. Nonetheless, natural mpox infection may not elicit sufficient neutralizing antibody responses in a subset of healthy individuals. However, neutralization activity most likely only partially reflects MPXV elicited immune response as cellular immunity was also determined to be important[8]. In addition, the role of mucosal immunity remains unclear; the same holds for whether the primary site of MPXV infection – here, the genitals – elicits sufficient mucosal immunity on every other mucosa, such as the gastrointestinal tract. Indeed, mucosal immunity was shown to be critical in mucosal-transmitted viral infections[9].

Reinfection in our patient most likely occurred in Brazil, which in November 2022 had one of the highest reported daily new cases of mpox. Because of the nature of MPXV, a dsDNA virus that has shown few variations since the outbreak's beginning, it seems unlikely that reinfection occurred because of a mutation-driven immune escape of a Brazilian variant. The patient's first isolate was sequenced confirming MPXV B.1., but a technical issue and lack of sufficient specimen precluded from obtaining the second sequence (Oxford Nanopore MinION), so strain comparison could not be made. With only two Brazilian MPXV sequences reported on nextstrain.org, the hypothesis of a mutation-driven immune escape cannot be excluded entirely. Yet, the large cross-immunity between different *orthopox* viruses and the large number of shared epitopes driving the immune response[10] makes the appearance of an immune escape mutation that would impede the activity of cross-reactive antibodies unlikely. Nevertheless, numerous immune evasion mechanisms have been described in poxviruses; mainly in the better-studied *Vaccinia* virus[11], but also in MPXV, which was shown to inhibit T-cell activation[12]. Yet, the clinical significance is not well understood.

In this case, the high rate of mucosal lesions associated with anal intercourse leading to high viral load exposure might have outweighed the host's local immune response and led to local and transient replication of MPXV. Asymptomatic shedding of MPXV in mpox-naïve individuals has previously been described[13]. In mpox non-naïve individuals, asymptomatic reinfection and shedding might also occur, particularly in the case of large inocula and because a subset of otherwise healthy individuals may not develop sterilizing immunity. This could have major public health implications as it could lead to a rise of a- or paucisymptomatic mpox reinfections possibly leading to a rise in symptomatic mpox in naïve individuals. This would ineluctably rise the question of extending vaccination to recovered individuals.

Furthermore, persistent MPXV-positive PCRs after infection have been reported in the literature and are suggestive for prolonged MPXV-shedding [14]. Our patient was tested positive for MPXV 6 months after his first episode and a repeated rectal swab 13 days after the second diagnosis came back negative. A mathematical modelling study, found a median time of rectal sample PCR-positivity of 8.3 days with a 95th percentile at 14.7 days[15]. To our knowledge, persistent shedding over this time frame has not been reported so far, regardless of the sampling site, making the hypothesis of persistent shedding from his first infection unlikely.

CONCLUSION

While the next few months will be decisive in determining whether this case is an exception or the first of a beginning series, it is crucial to raise awareness among clinicians that MPXV may not develop effective protection in time and that if suspicion criteria are met, patients should be tested again for MPXV. With the growing evidence for asymptomatic and/or prolonged shedding of MPXV, screening among naïve, recovered and vaccinated individuals also needs to be addressed. Meanwhile, public health authorities should be informed and prepare for the

consequences increasing mpox reinfections would imply for the management of the current mpox epidemic. Further tools may be useful, such as the development of specific mpox vaccines.

NOTES

Acknowledgement: We thank Florian Laubscher for the help on the viral sequencing process.

Author Declaration: AC reports MSD research funding, and Unrestricted Education grants from MSD, Gilead Sciences, and ViiV Healthcare. The remaining authors confirm that there are no known conflicts of interest associated with this publication and there has been no financial support for this work.

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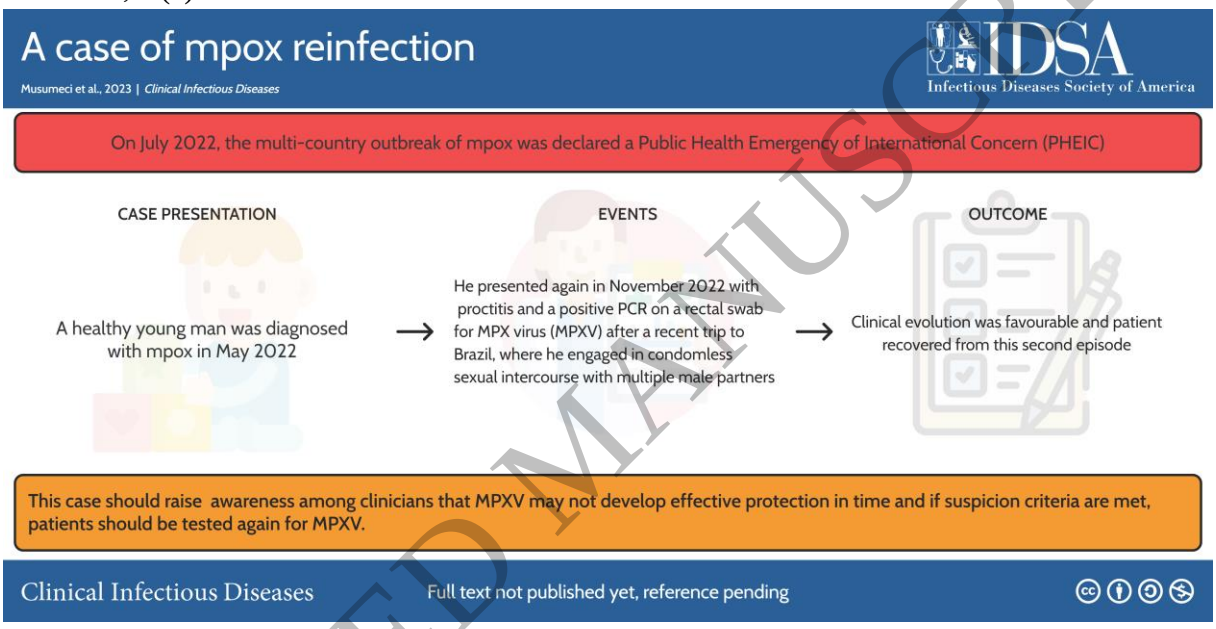

Graphical Abstract