## Title

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## Journal

American Journal of Tropical Medicine and Hygiene, 107(6)

## ISSN

0002-9637

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## Publication Date

2022-12-14

## DOI

10.4269/ajtmh.22-0499

Peer reviewed

*Am. J. Trop. Med. Hyg.*, 00(00), 2022, pp. 1–3
doi:10.4269/ajtmh.22-0499




# Case Report: Symptomatic Herpes Simplex Virus Type 2 and Monkeypox Coinfection in an Adult Male

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*Abstract.* A 39-year-old man presented with a history of fatigue, malaise, and rash with varied morphology on his perianal region. Polymerase chain reaction testing of the lesions confirmed coinfection with monkeypox and herpes simplex virus type 2. We emphasize the difficulty in distinguishing between monkeypox virus and herpes simplex virus type 2 based on history and examination alone.

Monkeypox virus (MPXV) is an orthopox virus (OPXV) endemic to West and Central Africa that is typically transmitted through contact with wild mammals.[1] As of October 2022, a multicontinent outbreak largely in nonendemic regions has grown to more than 28,000 cases in the United States and more than 77,000 cases globally.[2] Genomic analysis has shown that the current viral strains all belong to clade II monkeypox virus (C2-MPXV) and have evolved with substantial genetic changes compared with 2018 and 2019 C2-MPXV viruses.[3] Clinically, infections resulting from the current C2-MPXV strains cause milder disease, with fewer skin lesions and decreased mortality compared with previous C2-MPXV strains.[1,4] One notable characteristic of the current outbreak is its transmission primarily through sexual contact.[4] The presence of lesions limited to the genital area and the atypical appearance of the lesions have led to misdiagnosis with other sexually transmitted infections (STIs).[5] Coinfection of monkeypox and other infectious diseases, including Varicella zoster virus (VZV), syphilis, gonorrhea, *Chlamydia*, and HIV, have been reported previously.[4,6–9] We describe a case of coinfection with herpes simplex virus type 2 (HSV-2) and C2-MPXV and discuss its clinical implications.

## CASE DESCRIPTION

A 39-year-old man with known HIV infection presented to urgent care in July 2022 with a 2-day history of rash on the abdominal wall and perianal area. He reported several days of malaise, fatigue, and body aches preceding the development of the rash. The patient's HIV infection was well controlled, with an undetectable viral load and a CD4 count of $> 500/mm^3$ on antiretrovirals. He had rectal *Chlamydia* diagnosed 5 days earlier, for which he was taking doxycycline, and a remote history of treatment of syphilis 10 years ago. He had no known history of HSV-2 infection. Upon further questioning, he reported having unprotected insertive and receptive anal intercourse with multiple men at a sex party 6 days earlier, and travel to New York and San Francisco a few weeks ago.

On examination, the patient was afebrile and had normal vital signs. He had one umbilicated pruritic pustule surrounded by erythema on his left abdominal wall (Figure 1). He had four lesions in the perianal area: two small ulcers at the six-o'clock position and two papules with surrounding erythema just distal to these lesions on the right buttock.

Two dry Dacron swabs were collected from lesions of the abdominal and perianal regions and sent to the Los Angeles County Public Health Laboratory for Non-variola OPXV polymerase chain reaction (PCR). An additional swab, in Universal Viral Transport (UVT) medium (Becton, Dickinson and Co., Franklin Lakes, NJ), was collected from the perianal region and sent to the UCLA Clinical Microbiology Laboratory for routine HSV-1/2 PCR testing, as well as testing by a laboratory-developed multiplex PCR assay targeting both Non-variola OPXV and C2-MPXV modified from published CDC protocols.[10,11] Briefly, DNA was extracted from 400 μL of UVT medium using the MagMAX Viral/Pathogen II Nucleic Acid Isolation Kit on the KingFisher Flex Purification System (Thermo Scientific, Waltham, MA). Real-time PCR was performed using IDT PrimeTime Gene Expression Master Mix and custom IDT PrimeTime qPCR Probe Assays (Integrated DNA Technologies, Coralville, IA) on the ABI 7500 Fast Dx Real-Time PCR System (Thermo Scientific). The MPXV viral load was estimated using the Quantitative Synthetic Monkeypox Virus DNA (ATCC VR-3270SD).

Both dry swabs collected from the patient's lesions on the abdominal wall and the perianal regions tested positive for the Non-variola OPXV by the Los Angeles County Public Health Laboratory. The UVT swab of the perianal ulcer tested positive for both HSV-2 and C2-MPXV, with a OPXV target cycler threshold (Ct) of 22.6 and a C2-MPXV target Ct of 23.3. The C2-MPXV viral load was estimated to be $1.7 \times 10^5$ to $1.7 \times 10^6$ copies/mL. The patient received acyclovir treatment of HSV-2 and did not receive antivirals for MPXV.

## DISCUSSION

This case highlights the importance of considering coinfection with STIs, including MPXV. Our patient had a nonspecific perianal rash with ulcers and papules that could be consistent with multiple STIs. He lacked the classic features of deep-seated, firm, umbilicated skin lesions resulting from MPXV, which in our experience is less common in mucosal sites compared with skin sites. Furthermore, the presence of lesions in different stages at the same anatomic site is uncommon in MPXV infection.[12] Although coinfection with MPXV in endemic regions is uncommon and primarily a result of VZV,[7,8] the 2022 outbreak of monkeypox has been spread predominantly

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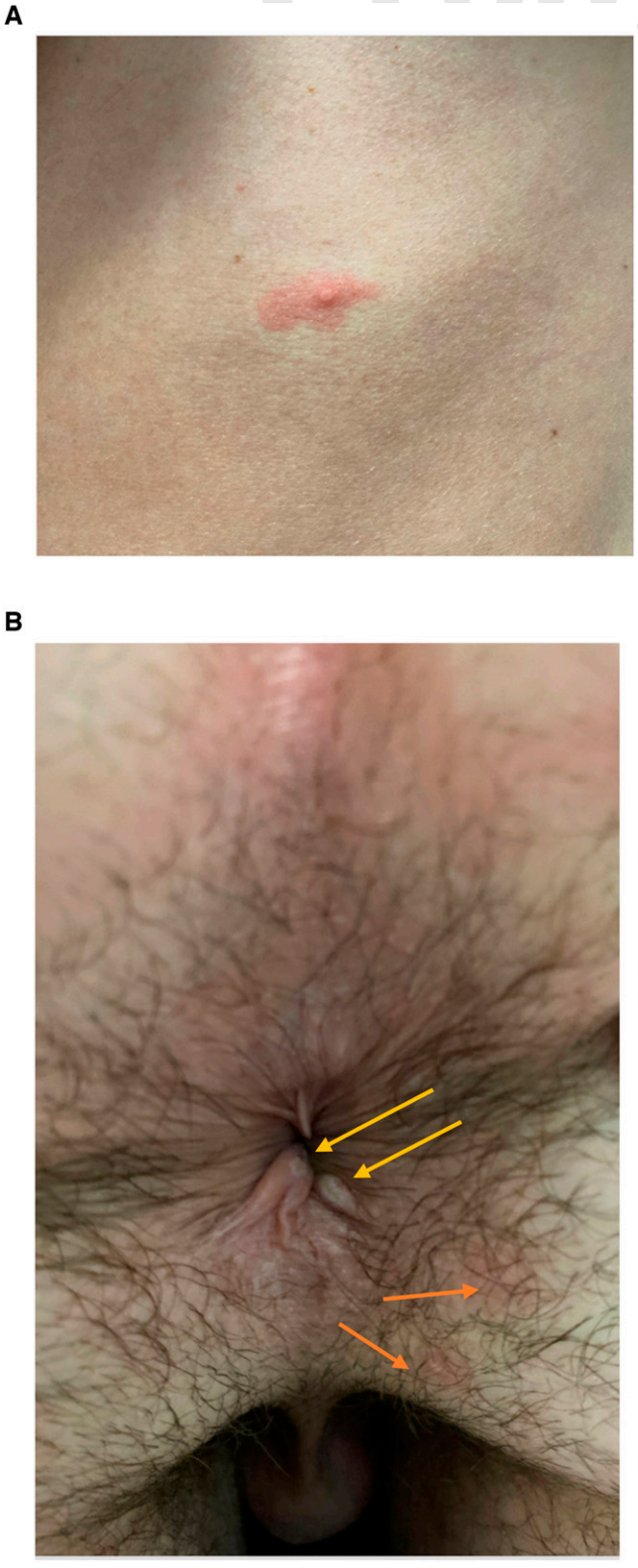


FIGURE 1. (**A**) Rash on the abdominal wall. (**B**) Two ulcers (yellow arrows) and two papules (orange arrows) in the perianal area.

through sexual contact, and 29% to 31.5% of patients have been reported to have a concomitant STI.[4,13] Gonorrhea and *Chlamydia* are the most common type of concomitant infection with MPXV, and coinfection with HSV occurs in 1% to 7% of cases.[4,13] Similar to other STIs, MPXV has been associated with high-risk sexual behavior, including multiple sex partners and anonymous sex. Our report describes a case of MPXV and HSV-2 coinfection at the same anatomic site, and we emphasize the difficulty in distinguishing between MPXV and HSV based on history and examination alone. In the presence of a rash with varied morphology, we recommend testing multiple skin lesions for multiple etiologies.

Considering coinfection for sexually transmitted diseases is particularly important given the pathogenesis and transmission of these infections. Similar to HIV,[14] MPXV may be transmitted more efficiently in the presence of ulcers resulting from HSV or syphilis. Conversely, illness resulting from MPXV may trigger HSV reactivation, as was speculated in some patients with MPXV and VZV coinfections.[7] In our patient's case, he developed all of his rashes on the same day, and he had no prior history of HSV, so he likely had cotransmission of HSV-2 and MPXV. This patient was treated with acyclovir for HSV-2 infection. Treatment of concomitant STIs is important for symptom resolution, particularly because effective antiviral therapies for C2-MPXV are still under investigation.

Increasing availability and improving the ease of MPXV testing is important. Sample collection can be painful, and having patients return for a second sample collection may be difficult. We recommend that clinical laboratories validate the standard swab in viral transport medium for their MPXV PCR test to be compatible with other common PCR tests, including HSV, VZV, gonorrhea, and *Chlamydia*. Offering multiplex testing from a single swab would save time, increase patient satisfaction, and improve diagnostic accuracy.

In conclusion, patients may present with concomitant infection resulting from MPXV and HSV with lesions in the same anatomic site that are challenging to distinguish based on appearance alone. Clinicians should consider testing for both when patients with epidemiological risk factors present with acute illness and rash.

Received August 5, 2022. Accepted for publication August 30, 2022.

Published online November 14, 2022.

Acknowledgments: We thank the UCLA Clinical Microbiology Laboratory and the Los Angeles County Public Health Laboratory for their technical assistance.

Financial support: This study was funded by the UCLA Department of Pathology and Laboratory Medicine.

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