Open Forum Infectious Diseases

BRIEF REPORT

Mpox Recurrence and Tecovirimat Resistance in a Patient With Advanced Human Immunodeficiency Virus Disease

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We present a case of mpox recurrence in a transgender woman with AIDS. Her recurrent lesions required several courses of antiviral therapy over a 5-month period and her monkeypox viral genome was subsequently noted to have tecovirimat resistance mutations. Interestingly, she developed a robust orthopoxvirus-specific T-cell response.

Keywords. HIV; mpox; T cells; tecovirimat; resistance

The human mpox outbreak caused by the orthopoxvirus human monkeypox virus (hMPXV) spread globally starting in May 2022, disproportionately affecting sexually active men who have sex with men [1]. The extent of immunity after infection is unknown. Additionally, there are limited data on reinfection. We present a case of a transgender woman with AIDS who had a prolonged course of mpox 3 months after recovering from an initial episode.

CASE PRESENTATION

This is a case of a 35-year-old, unhoused transgender female patient with untreated human immunodeficiency virus (HIV) infection, diagnosed in 2014 but inconsistently engaged in care, who presented with skin lesions and abdominal pain 155 days after an initial mpox diagnosis. She had previously been diagnosed with mpox in August 2022 while living in another state where she was subject to commercial sexual exploitation. At that time, day (D) 0, she presented to an emergency department (ED) with fever, abdominal pain, and skin lesions. Polymerase chain reaction (PCR) testing for orthopoxvirus was positive on D0, and she was treated with a course of oral tecovirimat (D11–D24) after difficulty connecting her to care. Per her report she had >80 skin lesions, which resolved D28. She did not receive mpox vaccination.

On D140, she presented to an ED with fever, severe lower abdominal and rectal pain, and inability to have a bowel movement. She was diagnosed with proctocolitis (seen on computed tomography [CT] scan) and was prescribed empiric antibiotics. She did not take the antibiotics. She returned to an ED on D150 with persistent rectal pain, abdominal pain, constipation, and 2 eschars on her abdomen and 2 circular lesions on her scrotum enlarging over the past week, but then left without treatment to secure housing. She was seen again on D152 for fever and abdominal lesions. CT showed proctocolitis. No additional testing was performed.

She then relocated to Maryland to be free of sexual exploitation. On D155 she was treated with ciprofloxacin and metronidazole for proctosigmoiditis in an ED. Lesions on her scrotum, abdomen, and right hand were not tested. On D157 she presented to a Johns Hopkins–affiliated ED with ongoing severe generalized abdominal and rectal pain as well as the nonhealing sores. She had ulcerated lesions to anterior abdominal wall, scrotum, and multiple fingers (Figure 1). CT showed proctocolitis. She had severe rectal pain with no outer rectal lesions. She was admitted for symptom control and additional workup. PCR of a skin lesion was positive for orthopoxvirus and she was started on oral tecovirimat 600 mg twice daily on D164. She was switched to intravenous (IV) tecovirimat on D167–D181 for ongoing fever, disease severity, and concerns of poor oral intake and malabsorption of the drug. She additionally received 2 doses of IV cidofovir on D167 and D174 and received vaccinia intravenous immunoglobulin (IVIG) on D167 and D170 based on available guidance at the time. She transitioned back to oral tecovirimat, and her rectal and abdominal pain subsided and oral intake improved. Her treatment course is summarized in Figure 2*A*.

Her HIV-1 RNA was 2.1 million copies/mL on D165, and CD4 count was 23 cells/μL (3.3%) on D159. She was started on bictegravir/tenofovir alafenamide/emtricitabine as well as trimethoprim-sulfamethoxazole prophylaxis on D167, and on D226, her viral load was 173 copies/mL and her CD4 count was 366 cells/μL (13%).

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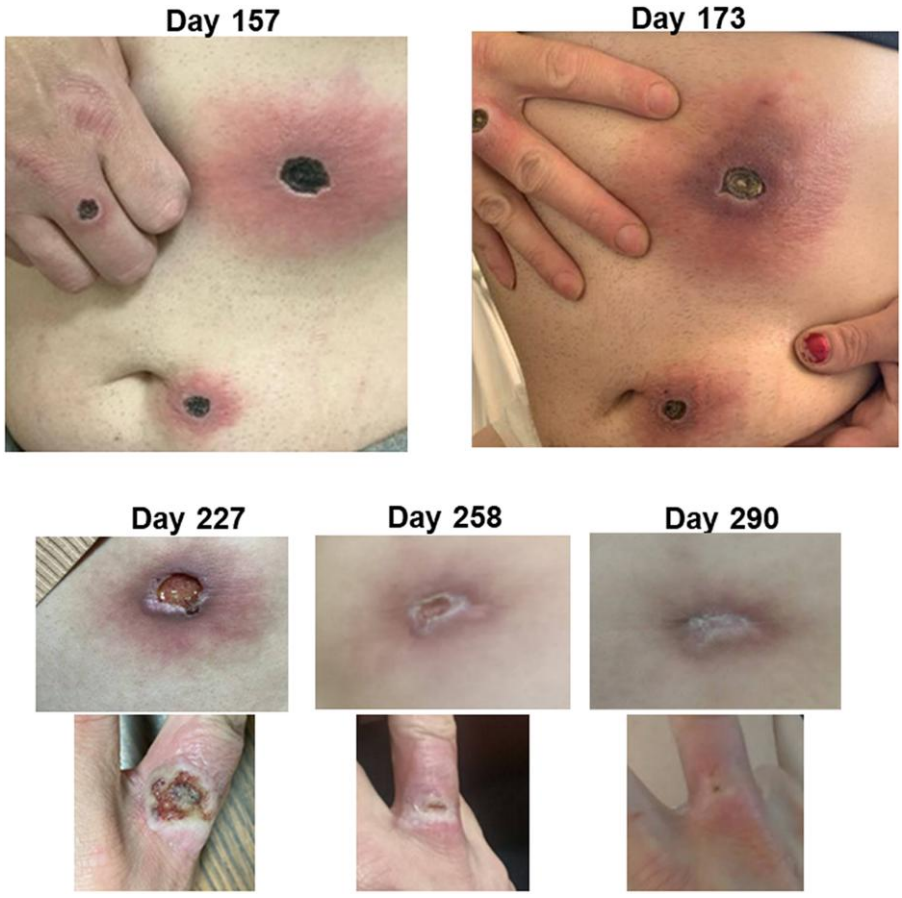

Figure 1. Progression of mpox skin lesions. Finger and 2 abdominal lesions on admission day (D) 157 and D173. Large abdominal lesion and finger lesion on D227, D258, and D290.

She was discharged after a 3-week hospitalization and remained isolated in housing sponsored by the health department. She was continued on oral tecovirimat in the setting of persistent lesions and immunosuppression. She was started on gender-affirming hormone therapy. The large abdominal, finger, and scrotal lesions were slow to heal. On D226, she was readmitted for concern of worsening wounds, given increased erythema and drainage that had not responded to oral antibiotic therapy. During that admission, the abdominal wound was retested and continued to be positive for orthopoxvirus PCR on D227 despite 9 weeks of tecovirimat. Considering the slow response to tecovirimat, she was treated with 1 dose of brincidofovir 200 mg on D230 and was also started on topical cidofovir 3% based on available guidance at the time. On discharge she continued on tecovirimat and topical cidofovir and showed improvement of the lesions.

After stopping the topical cidofovir on D240, she felt the lesions worsened again, so she subsequently restarted topical cidofovir 1% on D250, which resulted in improvement of the skin lesions. By D297, her lesions had fully healed. Topical cidofovir was stopped and tecovirimat was continued for 2 more weeks, then stopped at D310.

To determine whether she had developed an orthopoxvirus-specific immune response in the setting of prolonged infection and immunosuppression, an enzyme-linked immunosorbent spot assay was performed on D255 as previously described [2]. Her cells responded to an orthopoxvirus peptide pool and to 2 of the 5 human vaccinia virus proteins tested (Figure 2*B*). Her responses were comparable to previously described responses in people with HIV (PWH) on antiretroviral therapy (ART) with convalescent mpox [2].

To determine if she had developed resistance to tecovirimat, the sample from D227 was analyzed. Prior samples were unavailable. The whole genome amplification was conducted using 2 pools of primers in 2 PCR reactions, following previously established protocol [3]. We determined an average depth exceeding 400 with a genome coverage of 99.0%. The analysis of the consensus sequence, generated using Nextclade, indicated that the isolate belongs to clade IIB and lineage B.1.20. Comparison of the amino acid sequence of the isolate with the Nextclade reference (NC_063383.1) revealed 3 amino acid substitutions (A290V, E353K, I372N) within the OPG057 gene, which encodes the VP37 protein. The A290V

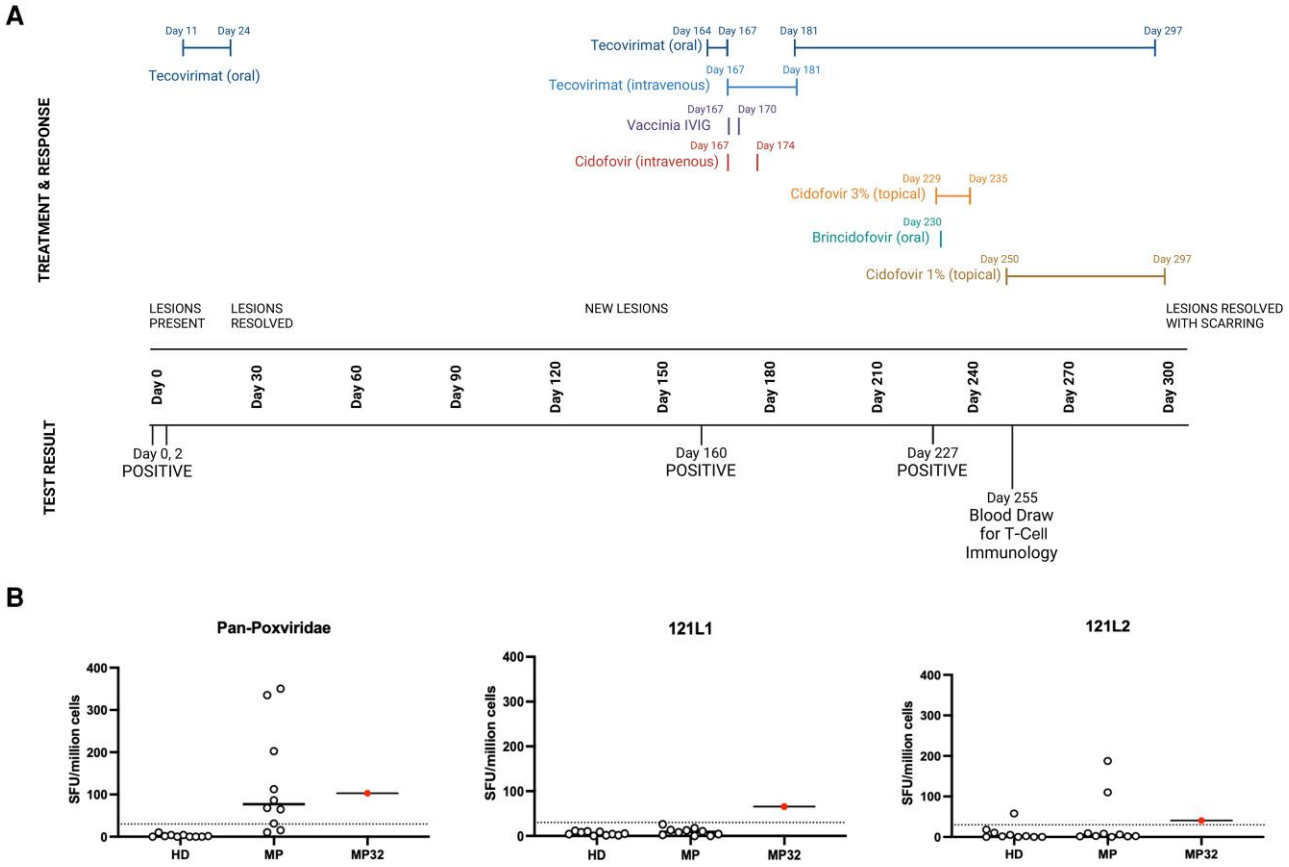

Figure 2. *A*, Overview of the antiviral therapy the patient received with timeline of appearance and resolution of skin lesions. *B*, T-cell responses to orthopoxvirus peptide pools and human vaccinia virus protein subunits 121L1 and 121L2 in our patient (MP32), compared to previously described responses from healthy donors and convalescent mpox patients. Abbreviations: HD, healthy donors; IVIG, intravenous immunoglobulin; MP, convalescent mpox patients; SFU, spot-forming units.

and I372N changes have previously been associated with tecovirimat resistance [4–6].

DISCUSSION

There have been several reports of possible hMPXV reinfection [7–14] (reviewed in Supplementary Table 1); however, only 1 was able to distinguish between reinfection and relapse by sequence analysis [14]. Interestingly, none of the prior cases required hospitalization or treatment with antivirals. A total of 8 PWH with possible hMPXV reinfection have been described [9, 11, 13], but all the patients were on ART and had CD4 counts between 296 and 1106 cells/μL, with undetectable viral loads. In contrast, our patient had profound immunosuppression prior to initiating ART. Severe complications of mpox are more likely in patients with CD4 <100 copies/mL including necrotizing skin lesions [15]. Our patient responded poorly to 14 days of parenteral tecovirimat, 2 doses of vaccinia IVIG, and 2 doses of parenteral cidofovir. She had a positive PCR response 2 months after the completion of these antivirals while being maintained on oral tecovirimat. We recently reported similar cases of prolonged disease courses in patients with advanced HIV infection including 2 patients who died [16].

In addition to her immunosuppression, resistance to tecovirimat, noted with the sample from D227, likely contributed to her poor treatment response. This resistance was not noted until after her completion of therapy and recovery. Tecovirimat resistance has been mostly noted in patients with severe immunosuppression who have had multiple courses of treatment with the drug such as our patient [6].

Her eventual recovery occurred in the setting of initiating ART while continuing oral tecovirimat and initiating topical cidofovir. Her viral genome had substitutions associated with resistance to tecovirimat on D227, and the patient felt her lesions started to improve with the initiation of the topical cidofovir. Cidofovir is a monophosphate nucleotide analog that prevents the incorporation of deoxycytidine triphosphate into viral DNA. It inhibits hMPXV replication in vitro [17] and several case reports have reported a clinical response to the topical formulation of this drug [18, 19].

There have not been studies of the hMPXV-specific immune responses in patients with possible reinfection. The fact that her second course was more prolonged than the first suggests that she did not develop immunity to the virus after her initial presentation. However, despite her profound immunosuppression, after mpox recurrence she developed a T-cell response that was like that seen in patients with nonrecurring disease. This might be due to immune reconstitution after starting ART 3 months prior to the analysis. Her prolonged exposure to viral antigens might be another explanation for her T-cell response and the antiviral agents she was on, including vaccinia immunoglobulin, are another confounding factor. Further studies are needed to better characterize the correlates of immunity to hMPXV.

The patient visited multiple healthcare facilities before her mpox diagnosis and throughout her illness. Contributing to the delay in diagnosis was her fractured care in the setting of homelessness, sexual exploitation, lack of routine HIV care, and recurrent treatment of bacterial causes of proctocolitis. Transgender women with mpox have been noted to have high rates of HIV (50%) and engage in sex work (55%), highlighting the potential increased risk of disease, delayed care, and adverse outcomes in this population [20, 21]. The inclusion of transgender women in future studies is important for prevention and public health response to future outbreaks.

In summary, we report a case of mpox recurrence with a prolonged course and identification of tecovirimat resistance mutations in a transgender woman with AIDS. This case highlights the need for further research on mpox treatment, including the risk of tecovirimat resistance with repeat and prolonged use, and the treatment response in PWH and low CD4 count. It also highlights the effects of social determinants on access and engagement in care and the need for a comprehensive approach.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Patient consent. The Johns Hopkins Medicine Institutional Review Boards approved this work, and informed consent was obtained from the patient.

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Potential conflicts of interest. All authors: No reported conflicts.

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