An atypical presentation of human monkeypox infection with clinicopathologic correlation

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Abstract

There is growing evidence to support new modes of transmission for human monkeypox infection. As these methods are being explored, this report delineates the day-to-day clinical sequelae following the initial exposure in an HIV-positive man who had sexual intercourse with another man days preceding his infection. We describe atypical cutaneous manifestations involving widespread erythematous pustules with preceding anogenital ulcerations and concomitant bilateral inguinal lymphadenopathy. Clinicopathologic correlation is used to assist in the workup and establishing the diagnosis. Our case supports others reported in the literature that suggest sexual contact as a means of transmission. More research is needed that investigates the presence of infection in both men and women, including those who could act as carriers, to elucidate other pathways in this evolving yet evasive viral disease.

Keywords: atypical, genital ulcers, HIV, lymphadenopathy, monkeypox, Mpox, perianal ulcers, sexual transmission

Introduction

First discovered in 1958, the monkeypox (Mpox) virus is endemic to Central and Western Africa, but has recently started to propagate in countries across the world [1]. The virus was first reported outside Africa in 2003 during an outbreak that arose after transportation of exotic animals from Ghana to the United States, leading to infection of pet prairie dogs [2]. Thereafter, scattered incidents occurred involving travel to Nigeria [2]. As of June 8, 2022, however, 1,285 laboratory-confirmed cases have been reported to the World Health Organization from 28 different countries, where Mpox is not endemic [3]. During the initial writing of this manuscript, 49 cases were reported in the USA, 5 of which originated in Florida. Currently, there are over 30,000 reported cases in the USA alone and over 89,000 worldwide with 2,898 originating from Florida. Herein, we report a case of human Mpox infection diagnosed in Fort Lauderdale, Florida.

Case Synopsis

A 45-year-old man with a past medical history of HIV (well-controlled on dolutegravir/abacavir/lamivudine with a CD4 count >600/mm^3; normal range 500-1500/mm^3,), hepatitis C status-post treatment, and intravenous drug use, presented to a Broward County hospital in Fort Lauderdale, Florida, with a new-onset, widespread pustular eruption. Of note, he reported a history of work-associated travel in the month preceding this new onset illness involving the following countries: United States, Spain, Italy, England, Turkey, and the Bahamas. He denied any contact with exotic animals during this time. However, while in London, he had unprotected anal and oral sexual intercourse with a male partner. Five

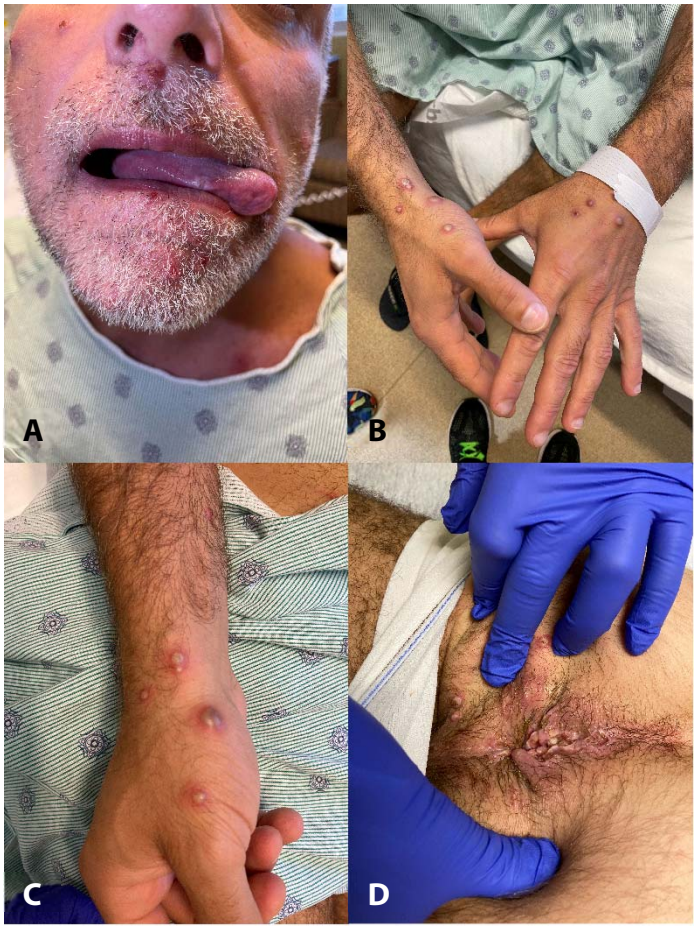

Figure 1. ***A)*** *Oral leukoplakia involving the lateral tongue.* ***B)*** *Widespread pustules with surrounding erythema were noted throughout the body,* ***C)*** *including the acral surfaces of the hands.* ***D)*** *Anogenital ulcerations in an HIV-positive man and PCR-confirmed human monkeypox infection following sexual intercourse*

days later, he developed wart-like, pruritic papules on the perianal skin, and 7-8 days after sexual intercourse, he developed fever, shortness of breath, and fatigue. The symptoms persisted for about four days and when he started to clinically improve he traveled to the Bahamas. Soon after arrival, erythematous papules and large pustules with surrounding erythema began forming on his face and spread rapidly in a caudal distribution, involving his trunk and extremities. The patient reported having rapidly progressing widespread cutaneous and mucosal involvement within twenty-four hours of the first lesion appearing on his face. At this time, he was evaluated by a local healthcare professional who had a high suspicion for Mpox, leading to his transfer to our facility for further evaluation and management. The patient denied a history of smallpox vaccination.

Physical examination revealed numerous 2-9mm tense, umbilicated pustules with an erythematous base involving the head, neck, trunk, and extremities, including hands and feet (**Figures 1, 2**). The gluteal fold had ulcerated, erythematous papules coalescing into plaques with a yellow fibrinous base (**Figure 1B**). Oral mucosa, though initially spared, had an eroded leukoplakia with surrounding erythema on the right lateral surface of the tongue (**Figure 1A**). Other physical findings included bilateral, non-tender inguinal lymphadenopathy. Head and neck lymphadenopathy was not present, and the patient was afebrile at presentation and remained so throughout his disease course. Laboratory analysis revealed normal levels of white blood cells, platelets,

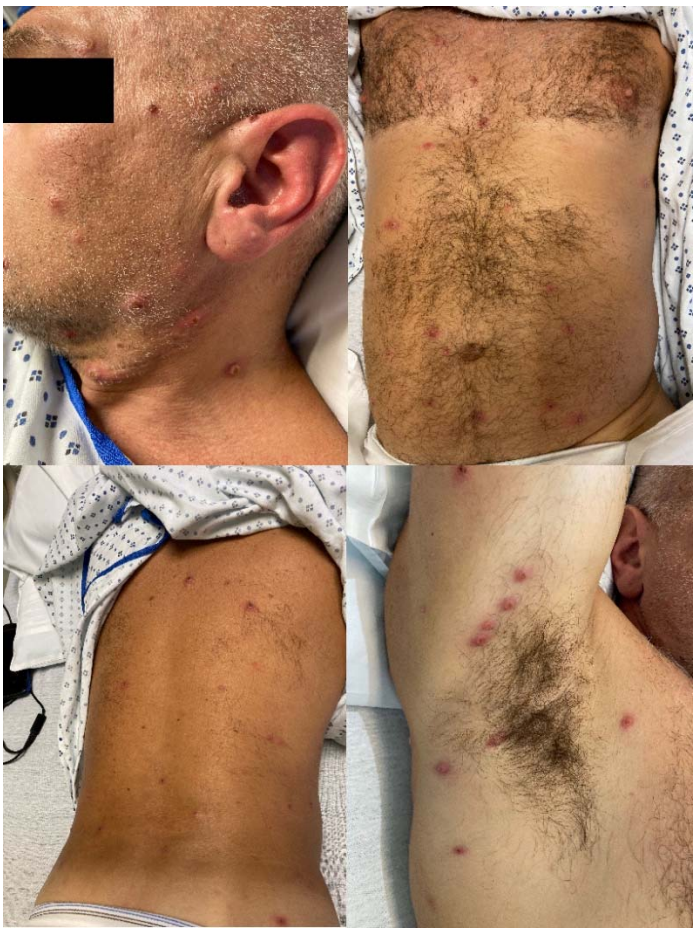

Figure 2. *Widespread large pustules with surrounding erythema and few erythematous papules were noted on the head and neck area, trunk, and extremities in an HIV-positive man with PCR-confirmed human Mpox infection 12 days after sexual intercourse with a man who developed similar symptoms.*

and hemoglobin with a mildly decreased red blood cell count and elevated absolute lymphocytes at 5,660/μl, (normal range: 1000-4800/μl). Other tests for sexually transmitted infections including gonorrhea, chlamydia, herpes simplex virus, and syphilis were negative.

Two lesions from the left flank and scapula were swabbed and sent to the CDC for analysis, which resulted in a positive orthopox real-time polymerase chain reaction, specifically of the West African clade. Punch biopsies were obtained from the left arm, back, and abdomen, revealing findings consistent with a Poxviridae infection. These histologic attributes consisted of focal superficial central ulceronecrotic area associated with a superficial, and to a lesser extent, deep dermal perivascular and periadnexal lymphohistiocytic predominant (**Figure 3A**, **B**) mixed infiltrate with conspicuous neutrophils and fewer eosinophils (**Figure 3C**, **D**). Epidermal neutrophilic exocytosis, variable degree of sebocyte necrosis, and sparing of eccrine apparatus were noted. Additionally, and adjacent to the aforementioned focal superficial central ulceronecrotic area, the epidermis revealed spongiosis, irregular acanthosis, focal areas of keratinocyte ballooning degeneration (**Figure 3C**), keratinocytes with pyknotic nuclei with occasional chromatin margination as well as multinucleated and necroptotic keratinocytes (**Figure 3D**), and eosinophilic intracytoplasmic inclusion (Guarnieri) bodies (**Figure 3D**). These histologic results corroborate those from a previous isolated report in Italy, in which the authors observed similar findings in cutaneous Mpox [4].

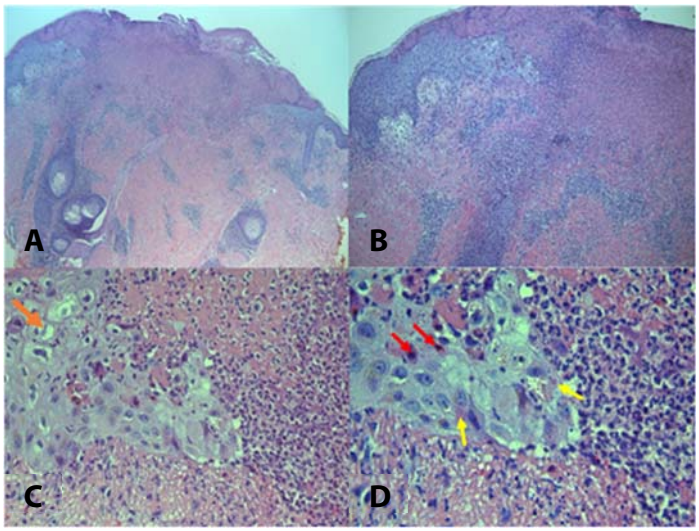

Figure 3. *Histopathology with H&E staining shows focal superficial central ulceronecrosis associated with **A, B)** a superficial and to a lesser extent deep dermal perivascular and periadnexal lymphohistiocytic predominant mixed infiltrate; **C, D)** with conspicuous neutrophils and fewer eosinophils. **C)** Additionally, and adjacent to the aforementioned focal superficial central ulceronecrotic area, the epidermis revealed spongiosis, irregular acanthosis, neutrophilic epidermal exocytosis, focal areas of keratinocyte ballooning degeneration (orange arrows). **D)** Keratinocytes with pyknotic nuclei as well as multinucleated and necroptotic keratinocytes (red arrows), and eosinophilic intracytoplasmic inclusion (Guarnieri) bodies (yellow arrows). **A)** 5×; **B)** 10×; **C)** 40×; **D)** 63×.*

Our patient improved after one week of supportive care, lidocaine gel for the painful anogenital ulcerations, and mupirocin application to some of the wounds. The disease was self-limiting requiring no additional treatment and he was discharged two weeks after admission once his lesions crusted over.

Case Discussion

The Mpox virus belongs to the genus, *Orthopoxvirus*, which contains linear double-stranded DNA within a lipoprotein envelope [1]. The virus uses African rodents as its natural reservoir and may infect squirrels, rats, mice, and prairie dogs, in addition to monkeys and humans [1]. Monkeypox virus may be transmitted through contact with contaminated surfaces, including the cutaneous lesions themselves, or large respiratory droplets [5,6]. Following an incubation period of 5 to 21 days, prodromal symptoms including fever, myalgias, headache, and lymphadenopathy may occur one to 5 days prior to rash onset [6]. Cutaneous manifestations usually begin on the head and neck, progressing caudally to involve the remainder of the body [6]. Although the rash undergoes several stages of evolution from macules to papules to vesicles and pustules with eventual crusting, lesions in different stages may be observed simultaneously [6]. Previously, cervical lymphadenopathy was commonly observed in Mpox patients. However, since the 2022 outbreak, fewer than 20% of cases have presented with cervical lymphadenopathy and instead, there is a predilection for inguinal lymph

node involvement (35-48%), in the setting of anogenital ulcers (18-57%), as has been observed in this current case [7].

There are numerous recent reports from the CDC illustrating an acute onset of anogenital ulcerations as the initial manifestation of the disease. Hornuss et al., reported four patients that presented to clinics with vesicular eruptions in the genital and perianal region. In this case series, one patient was treated for condylomata acuminata but when his vesicular papules progressed into ulcerative plaques, testing for Mpox was performed yielding a positive result [8]. In the Thornhill case series, 500 individuals out of 528 presented with a rash or skin lesions with 328 (73%) of those lesions occurring in the anogenital area. Solitary genital lesions may be misdiagnosed as common sexually transmitted infections which can delay treatment and further the spread of the disease. Moreover, sexual activity preceding Mpox infection has been reported for many of the recent cases affecting men who have sex with men [9], leading to the theory that direct, intimate contact and/or exchange of body fluids are possible means of transmission. Moreover, the global spread of Mpox appears to be linked to individuals traveling abroad or attending large gatherings since these actions have been reported to precede their symptom onset [9,10].

Our patient case supports the growing number of reports in the literature that describe oral and anogenital ulcerations presenting either in isolation or preceding the classic widespread, vesiculopustular eruption and thus, serving as possible inoculation sites [9]. Monkeypox virus has not only been identified in anorectal mucosa via swabbing in asymptomatic carriers [11], but the DNA itself has also been isolated in semen by PCR [9]. Whether the virus isolated in body fluids is capable of replicating upon transmission is not confirmed [9].

Given the rising incidence also observed in young pediatric patients without an identifiable source [12,13], there are likely other driving forces behind the global outbreak which remain to be elucidated. Mutational alterations, specifically arising from apolipoprotein B editing complex, are being explored as potential factors facilitating viral transmission [14]. Additionally, cross-protective immunity has waned since the discontinuation of smallpox vaccinations in 1978, which coincides with the rising cases of human Mpox globally even preceding the recent outbreak [15].

Conclusion

In summary, because of the atypical constellation of findings that human Mpox infection has adopted recently, there have been numerous cases of misdiagnoses in patients with confirmed disease, delaying the appropriate treatment. Thus, it is important for healthcare professionals to include Mpox in their differential diagnosis when evaluating cutaneous manifestations in the genital and perianal region. Further research is necessary to elucidate specific modes of transmission for human Mpox infection.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. Moore MJ, Rathish B, Zahra F. Mpox (Monkeypox). *StatPearls*. StatPearls Publishing, 2023
2. Bunge EM, Hoet B, Chen L, et al. The changing epidemiology of human monkeypox-a potential threat? a systematic review. *PLoS Negl Trop Dis*. 2022;16:e0010141. [PMID: 35148313].
3. Multi-country monkeypox outbreak: situation update. World Health Organization. https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON390
4. Maronese CA, Beretta A, Avallone G, et al. Clinical, dermoscopic and histopathological findings in localized human monkeypox: a case from northern italy. *Br J Dermatol*. 2022;187:822-823. [PMID: 35822390].
5. Kozlov M. Monkeypox goes global: why scientists are on alert. *Nature*. 2022;606:15-16. [PMID: 35595996].
6. Petersen E, Kantele A, Koopmans M, et al. Human monkeypox: epidemiologic and clinical characteristics, diagnosis, and prevention. *Infect Dis Clin North Am*. 2019;33:1027-1043. [PMID: 30981594].
7. Riccò M. When a neglected tropical disease goes global: early estimates from the monkeypox outbreak, the first 1,054 cases. *Acta Biomed*. 2022;93:e2022330. [PMID: 36533765].
8. Hornuss D, Daehne T, Goetz V, et al. Transmission characteristics,

replication patterns and clinical manifestations of human monkeypox virus—an in-depth analysis of four cases from germany. *Clin Microbiol Infect*. 2023;29:112.e5-112.e9. [PMID: 36155255].

9. Thornhill JP, Barkati S, Walmsley S, et al. Monkeypox virus infection in humans across 16 countries - april-june 2022. *N Engl J Med*. 2022;387:679-691. [PMID: 35866746].
10. Wong L, Gonzales-Zamora JA, Beauchamps L, Henry Z, Lichtenberger P. Clinical presentation of Monkeypox among people living with HIV in south florida: a case series. *Infez Med*. 2022;30:610-618. [PMID: 36482948].
11. Ferré VM, Bachelard A, Zaidi M, et al. Detection of monkeypox virus in anorectal swabs from asymptomatic men who have sex with men in a sexually transmitted infection screening program in paris, france. *Ann Intern Med*. 2022;175:1491-1492. [PMID: 35969863].
12. Hobson G, Adamson J, Adler H, et al. Family cluster of three cases of monkeypox imported from nigeria to the United Kingdom, May2021. *Euro Surveill*. 2021;26. [PMID: 34387184].
13. Tutu van Furth AM, van der Kuip M, van Els AL, et al. Paediatric monkeypox patient with unknown source of infection, the netherlands, June 2022. *Euro Surveill*. 2022;27. [PMID: 35866435].
14. Marty AM. Why is there expanding community transmission of monkeypox in 2022? *Lancet Microbe*. 2022;3:e810-e811. [PMID: 35940185].
15. Islam MM, Dutta P, Rashid R, et al. Monkeypox at the human-animal-ecology interface: a comprehensive review of viral characteristics, transmission, pathobiology, prevention, and control strategies. *Virulence*. 2023; 14 :2186357. [PMID: 36864002].