

# Atypical Clinical Presentation of Monkeypox Complicated by Myopericarditis

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We present a case of monkeypox infection in a man presenting with genital and labial ulcers, followed by submandibular lymphadenopathy, fever, and constitutional symptoms. His course was complicated by myopericarditis and an ongoing pleomorphic skin eruption. Viral deoxyribonucleic acid was detected by polymerase chain reaction in skin swabs, nasopharyngeal swab, saliva, and semen.

**Keywords.** case report; monkeypox; myopericarditis; viral shedding.

Monkeypox is a systemic illness caused by an orthopoxvirus, featuring cutaneous manifestations that evolve from maculopapular to vesiculopustular and finally crusted ulcerative lesions [1]. It is primarily a zoonotic infection endemic to West and Central Africa, with rare exported cases elsewhere including a 2003 outbreak in the United States linked to prairie dogs [2]. As of June 27, 2022, however, there have been 3413 cases in 50 countries, most among men who have sex with men [3]. We report a case of monkeypox with distinct clinical features including myopericarditis.

## CASE PRESENTATION

A man in his 40s with stable human immunodeficiency virus (CD4 count = 609 cells/mm<sup>3</sup>, viral load undetectable on

antiretroviral therapy) presented to primary care with a 7-day history of skin lesions and a 3-day history of constitutional symptoms. He had first noticed painless “bumps” on his penis and pubic region, followed by a similar lesion just above his upper lip the next day. Over the ensuing week, these lesions gradually enlarged, filled with clear whitish fluid, and became surrounded with erythema, before crusting. He subsequently developed fever, chills, myalgias, headache, and tender right submandibular lymphadenopathy.

Within the 3 weeks before symptom onset, he had had 1 male sexual partner, with whom he had engaged in oral sex (giving and receiving), rimming (performing oroanal sex), and condomless insertive anal sex, both 12 and 4 days before symptom onset. He lived in an apartment with 1 person who remained healthy (and subsequently tested monkeypox polymerase chain reaction [PCR] negative in blood, pharyngeal, and urine samples), and he denied sick contacts, travel, or animal exposures. He had never received varicella or smallpox vaccines, and had no history of varicella or zoster. Initial diagnostic considerations included primary infection with herpes simplex virus (HSV) type 1 or 2, for which he was prescribed valacyclovir, and syphilis.

His infectious diseases physician was consulted, who suspected monkeypox infection and assessed him the following day. By then, fever had resolved, but myalgias and headache persisted. He had also developed new umbilicated maculopapular and vesicular skin lesions over his chest and arms. He further complained of central, nonradiating, pressure-like chest pain but denied cough, palpitations, or shortness of breath.

On examination he appeared uncomfortable, with blood pressure = 128/83, heart rate = 80, oxygen saturation = 100% on room air, and temperature = 36.4°C. There was mild pharyngeal erythema but no oropharyngeal lesions. There was a mildly tender, 3-cm right submandibular lymph node (Figure 1A) but no axillary or inguinal lymphadenopathy. Cardiac, respiratory, and abdominal examinations were normal. There were 0.5- to 1.5-cm crusted ulcers with central depression at the upper lip, penis, and pubic area (Figure 1B). There were faint 2- to 4-mm papules (Figure 1C) and small vesiculopustular lesions over his trunk (Figure 1D), measuring up to 1.5 mm (Figure 1E).

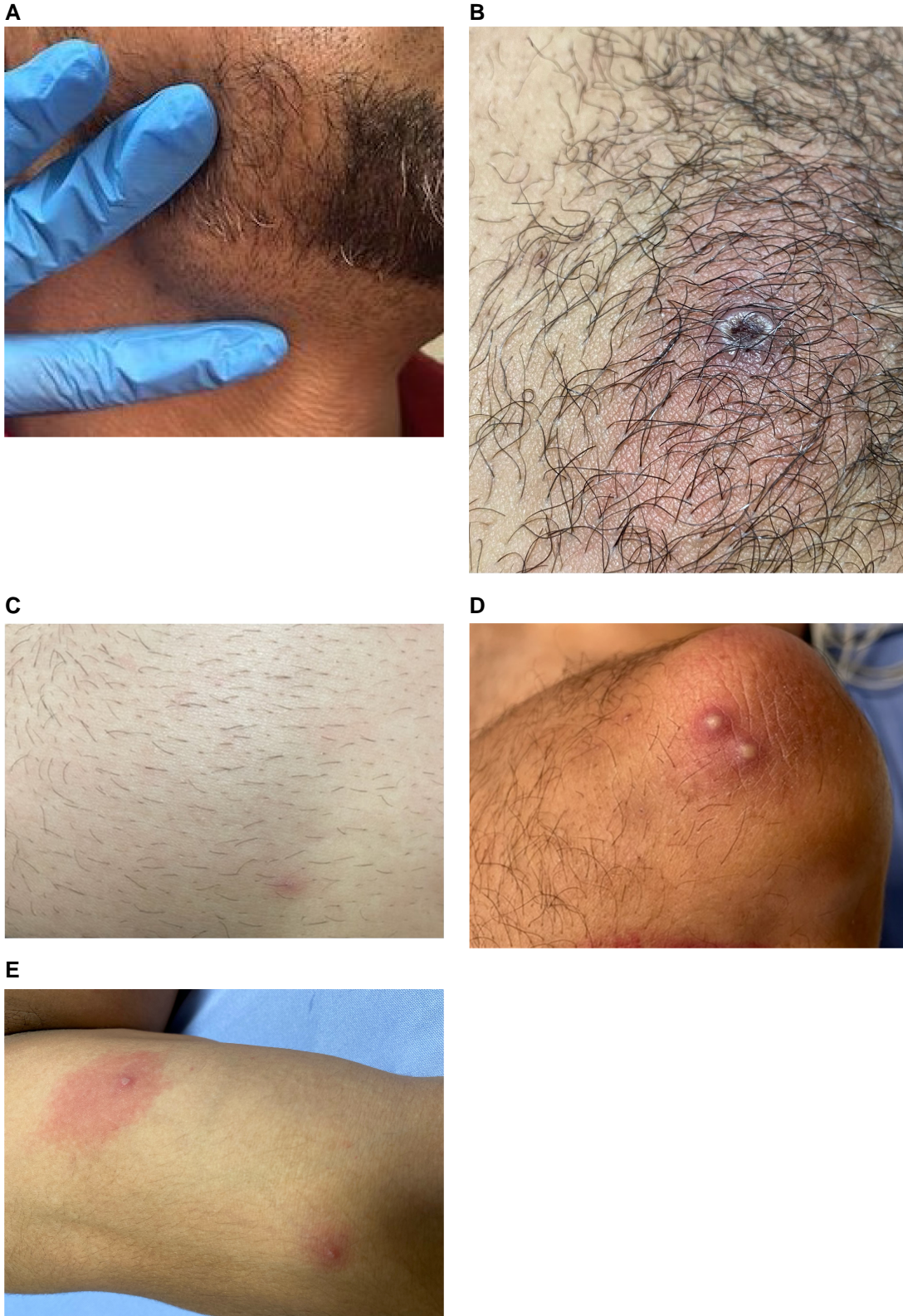
Routine chemistries and complete blood count were normal, but troponin was 11 436 ng/L initially and peaked at 14 350 ng/L. Creatine kinase peaked at 740 U/L. Serial electrocardiograms showed the evolution of ST-segment changes consistent with myopericarditis; he was admitted to hospital with a presumptive diagnosis of myopericarditis complicating acute monkeypox infection and managed supportively. Echocardiography

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**Figure 1.** Lymphadenopathy and cutaneous manifestations of monkeypox infection. (A) Right submandibular lymphadenopathy arising on day four of illness. (B) Crusted ulcer in the pubic area on day eight. (C) Maculopapular rash on day eight. (D) Pustules on the elbow noted on day twelve. (E) Vesicular lesions on the right arm arising on day eight.

revealed moderate global left ventricular dysfunction with an ejection fraction of 40% initially, but it was normal 5 days later. Cardiac catheterization revealed normal coronary arteries. Cardiac magnetic resonance imaging showed normal left ventricular systolic function (ejection fraction = 61%), small pericardial effusion, and foci of late gadolinium enhancement in the basal/apical lateral segments corresponding with focal edema, consistent with acute myocarditis (Figure 2) [4]. New maculopapular skin lesions continued to erupt daily, evolving into 1- to 2-mm vesicles, pustules, and scabs.

Monkeypox infection was confirmed by real-time PCR in skin lesions (from days 9 to 17 from symptom onset), a nasopharyngeal swab, saliva, and semen (all day 10). A pharyngeal swab (day 9) and blood (day 10) were negative. Swab of the lip ulcer was negative for HSV-1/2 and for varicella-zoster virus by PCR. Syphilis serology and blood for cryptococcal antigen were negative. Serologies for Epstein-Barr virus, cytomegalovirus, parvovirus B19, and Chagas disease were requested, but testing was rejected by the laboratory due to biosafety concerns given that monkeypox virus was a category A pathogen at that time.

Evaluation of the patient's partner revealed 11 days of mild symptoms consistent with monkeypox that overlapped with both dates on which they had had sex; a rectal swab collected 12 days after resolution of the partner's symptoms was weakly positive for orthopoxviral deoxyribonucleic acid (DNA) by PCR. Further history revealed that the patient had socialized on the 2 evenings after the lip lesion developed, including briefly kissing friends and mutual masturbation with 2 untraceable individuals. When reassessed on day 25, our patient had made a full recovery.

## DISCUSSION

Amidst an emerging global monkeypox epidemic, we report a case of monkeypox infection in a healthy man in Canada, with distinct clinical features. First, the emergence of cutaneous lesions before systemic symptoms contrasts with the traditional natural history of monkeypox, wherein systemic features present first, and could be consistent with primary inoculation of the pathogen during sexual contact. That the anatomic sites of initial symptoms match the reported sexual activities (rectal for the receptive anal sex partner; oral/genital for our patient after oroanal and insertive anal sex) suggests transmission via direct contact. Notably, our patient felt well at first, and he was in close contact with others initially; the risk of onward transmission for casual social contacts requires further study. Finally, our patient continued to develop small numbers of new lesions on the trunk and extremities during his illness, contrasting with the traditional notion that monkeypox lesions evolve through different stages simultaneously.

That our patient's semen sample was positive for monkeypox DNA is noteworthy, similar to other recent cases [5], but

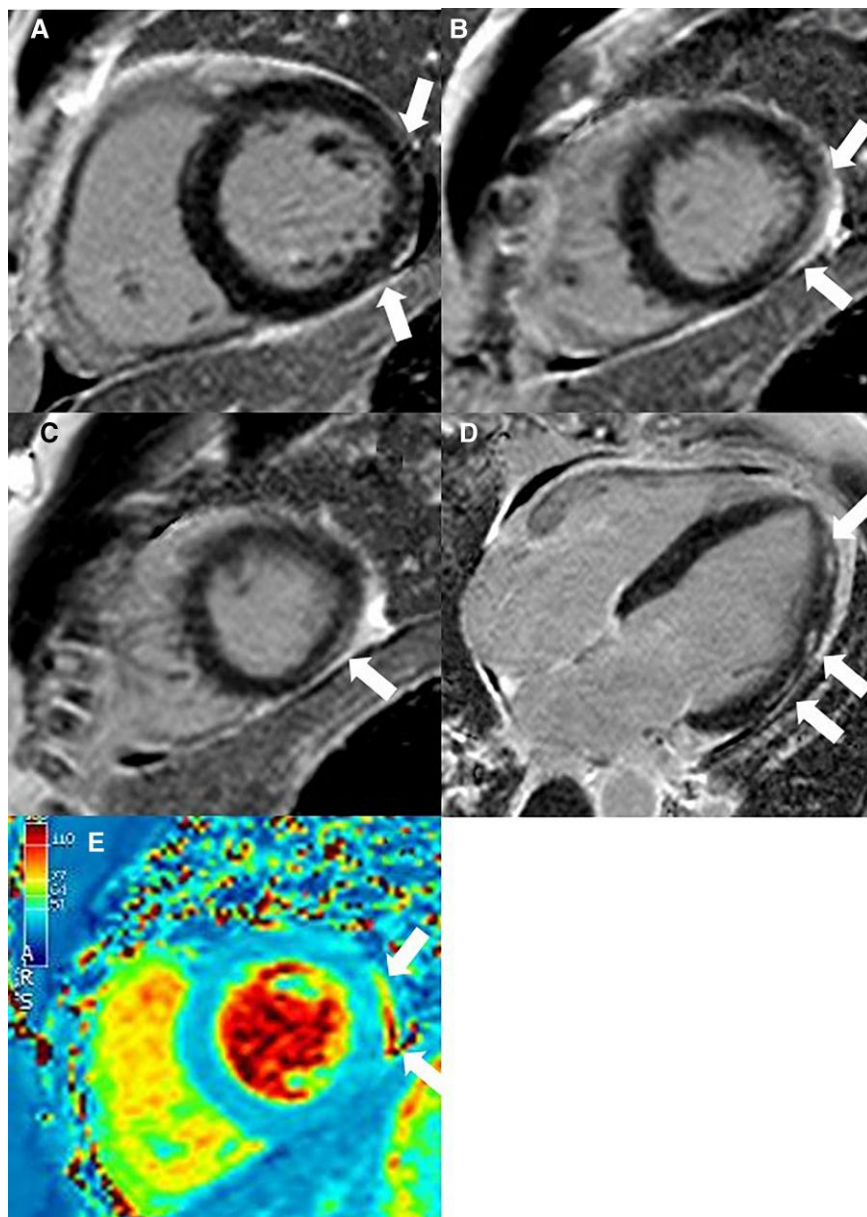
remains of uncertain significance. In a recent report of an imported case of monkeypox infection in the United Kingdom, sexual activity shortly after recovery from the acute phase of illness was associated with inguinal lymphadenopathy and recurrence of rash, leading the authors to postulate a genital reservoir of infection [6]. Given the profound potential implications of such a phenomenon for an infection spreading through sexual networks, further research on anogenital viral shedding and the duration of transmissibility must be prioritized.

Our patient also developed myopericarditis. Myocarditis, pericarditis, and myopericarditis are inflammatory conditions involving the myocardium, pericardium, or both and can be related to many underlying conditions including infections, medications, toxins, and systemic diseases. In our patient, we considered alternative infectious etiologies including severe acute respiratory syndrome coronavirus 2, viral and bacterial sexually transmitted pathogens, and common causes of myocarditis; he reported no new medications besides valacyclovir, and he was in good health overall. Monkeypox was the most likely unifying diagnosis given the temporal association with his cardiac manifestations and the negative microbiologic workup.

To our knowledge, cardiac manifestations of monkeypox infection have not been previously described. Myocarditis and pericarditis are rare complications of vaccination against the related orthopoxvirus, smallpox. In a prospective study of >1000 healthy adults in the United States who received live-attenuated vaccinia vaccine between 2004 and 2010, the incidence of myocarditis was 463 (95% confidence interval [CI] = 150–1079)/100 000 population or 214 (95% CI = 65–558) times higher than the background rate in healthy controls [7]. Another study found an increased risk of hospitalization for myocarditis for 1 year after smallpox vaccination compared to a follow-up period before vaccination, with a hazard ratio of 2.33 (95% CI = .85–6.43) [8]. A surveillance study among 37 901 civilian smallpox vaccinees identified 21 cases of myocarditis, pericarditis, or myopericarditis, resulting in 9 hospitalizations but no fatalities, yielding an estimated rate of 55/100 000 population; no comparison with background incidence was provided [9].

Two potential mechanisms of smallpox vaccine-related myopericarditis have been proposed and may have relevance to our case. Injury may be directly attributable to the virus, as myocarditis has been observed with smallpox infection [10, 11], and given that smallpox vaccine is a live-attenuated virus. Immune-mediated injury also seems likely, with several studies observing a Th1-predominant cytokine profile associated with cardiac inflammation after smallpox vaccination [12]. It is notable that immune activation after smallpox vaccine peaks on days 8–9 (range, 4–27) [12], and our patient developed chest pain 8 days after symptom onset.





**Figure 2.** Cardiac magnetic resonance imaging demonstrating myocarditis in the context of acute monkeypox infection. Late gadolinium enhancement images in short-axis (Basal *A*, mid cavity *B* and apical *C*) and 4 chamber (*D*) views. There is subepicardial late gadolinium enhancement predominantly at the basal to mid inferolateral segments, and in the apical inferior and lateral segments (arrows). Short-axis mid cavity T2 map image (*E*) demonstrates elevated regional T2 values in the mid inferolateral segment up to 93 ms (upper reference value 57 ms) (arrows), corresponding to the late gadolinium enhancement.

This case report has limitations. The results of some diagnostic tests that were ordered are not available, because biosafety concerns led to specimen transport delays and order cancellations. Revised categorization of monkeypox as a category B pathogen may alleviate such barriers in future. Pathological confirmation of monkeypox as the etiology of myopericarditis was not pursued, because a biopsy was not in the patient's best interest. We also did not administer antiviral agents because his clinical status improved rapidly. Local brincidofovir and tecovirimat availability, both oral

agents with potential activity against orthopoxviruses, was unclear at the time of this patient's presentation. Antiviral drug trials are urgently needed.

## CONCLUSIONS

Our case illustrates how the sequence of symptom development in acute monkeypox infection may differ from traditional reports, and together with our observation of viral DNA in semen, raise important questions about transmission. The



potential for serious manifestations such as myopericarditis may warrant enhanced consideration for preventative vaccines. Given the concentration of current cases among gay, bisexual, and other men who have sex with men, the meaningful engagement of community partners will be critical to ensuring an evidence-informed, equity-based response.

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