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Monkeypox-Induced Myocarditis: A Systematic Review

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> Abstract: Monkeypox virus has emerged in different parts of the world with varying clinical symptoms and outcomes. To date, only a few studies have reported cardiac manifestations among monkeypox-infected patients. We aim to systematically evaluate the symptoms, imaging findings, management, and outcomes among monkeypox-induced myocarditis patients. We conducted a systematic literature search in PubMed, Embase, and Scopus from inception till 5th January 2023 by using predefined MESH terms and "AND" and "OR." The following search terms were used: "monkeypox virus" AND "myocarditis." A total of 6 studies with 9 monkeypox-induced myocarditis patients were included in this analysis. The mean age of patients was 33.6 years, with all being male patients.

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The most common symptoms were fever (89%) and chest pain (100%). Electrocardiogram findings showed 44% of patients had ST-elevation, and 22% had sinus tachycardia. The echocardiographic findings show a mean ejection fraction of 52.14%, while 57% of patients had preserved ejection fraction, and 67% had normal wall motion. Cardiac magnetic resonance findings show 40% of patients had late gadolinium enhancement, and 40% had edema. Management of patients was primarily supportive (33%), and 33% of patients were administered Beta blockers and ACE inhibitors. Overall all patients survived with a good prognosis. Our study's findings show that all cases were reported among male patients with the most common symptoms of chest pain. The overall prognosis was good, with no mortality reported. Infected patients complaining of chest pain should not be ignored, and proper investigation of myocarditis must be considered. (Curr Probl Cardiol 2023;48:101611.)

Introduction

he monkeypox virus is a double-stranded DNA virus of the poxviridae family coming under the genus of orthopoxviruses.¹ The first case of this zoonotic infection in humans was reported in 1970.² This infection has been endemic in the region of Africa, although, in recent times, cases are being reported from around the world, especially from the month of April in the year 2022, with the number of cases rising to more than 1500 from 43 countries.^{1,3} The spread of monkeypox from the Democratic Republic of Congo to all over the globe is a concerning threat to public health. The pox virus infection is thought to have emerged due to the rise in international transport and travel throughout multiple countries and the loss of protection against smallpox which was previously present due to vaccines.^{1,4,5} It is classically transmitted by contact with respiratory droplets, body fluids, and the skin of an infected patient and presents with fatigue, fever, muscle ache, backache, headache, rash, and lymphadenopathy. Antiviral therapy for smallpox may help slow the spread of monkeypox, but there is currently no specific treatment for monkeypox, as confirmed by the Centre for Disease Control (CDC).^{1,6} It remains unknown whether vaccines against smallpox will be efficient for controlling monkeypox.⁵

Adding to the turmoil, various complications have been identified, including inflammatory conditions like myocarditis and pericarditis.^{6,7} A rise in cardiac biomarkers associated with the symptoms of chest pain was observed in the case reports described for monkeypox-induced myocarditis. Lymphocytic inflammation followed by myonecrosis is the most common pathophysiology in viral myocarditis, although the specifics of the pathophysiology of myocarditis by pox virus remain an area of study.⁷ Monkeypox-associated viral pericarditis presented with a pericardial effusion which was mild, and it is suggested to have a suspicion in patients who show *Electrocardiographic* changes of ST elevation associated with pain in the chest.⁶ The published case reports are of patients who were unvaccinated for orthopoxvirus and were otherwise healthy without an immunocompromised state.^{6,7} Interestingly, myopericarditis also occurs as an adverse effect of smallpox vaccinations, as seen in the nationwide surveillance in the United States in 2003.⁸ The limitation in the number of case descriptions available on the reemerging pathologies and their unusual after-effects compel further evaluation and studies for risk stratification, as acute cardiac complications are self-limiting and if subacute or undetected, they pose a challenge in diagnosis, resulting in delayed and long term manifestations especially ventricular arrhythmias which are life-threatening, ultimately affecting the morbidity and mortality.^{8,9}

Methods

This systematic review was conducted and reported in conformity with the Cochrane and PRISMA (preferred reporting items for systematic review and meta-analysis) 2020 guidelines as described previously.¹⁰⁻¹² The prespecified protocol has been registered on Prospero (CRD42023388476).

Search Strategy

We conducted a systematic literature search in PubMed, Embase, and Scopus using predefined MESH terms by using "AND" and "OR." The following search terms were used: (((((((monkeypox virus [MeSH Terms]) OR (Monkeypox[OtherTerm])) AND (myocarditis [MeSHTerms])) OR (pericarditis[MeSH Terms])) OR (Myocarditis [Other Term])) OR (Inflammation[Other Term])) OR (Heart disease [Other Term])) AND (outcomes[Other Term]).

Eligibility Criteria

Studies were included if they fulfilled the following criteria; patients (of any age) who developed a rash and symptoms with a confirmed diagnosis of Monkeypox via swab or blood test, case reports, case series, and prospective and retrospective studies. Studies that involved animal testing and review articles were excluded.

Study Selection

We queried databases from inception till January 5th, 2023 without language restriction. The studies were carefully screened and exported to the Endnote 2020 library (**X9**). Two reviewers (DM and SV) reviewed the titles and abstract. Discrepancies regarding the inclusion of studies were arbitrated by the senior author (VJ). The same reviewers also performed the full-text screening independently to decide which articles fulfilled the inclusion criteria. The senior author arbitrated discrepancies regarding the inclusion of studies.

Data Extraction and Statistical Analysis

The following data were extracted from the studies: demographic data (age and gender), study design, publication year, study location, patient comorbidities, symptoms, length of hospitalization, duration of management, the treatment used, and patient outcomes. Two authors (DM, YMN) assembled all available information in a shared Excel 2019 spreadsheet. For missing, incorrect or unreported data, the corresponding authors of the respective papers were contacted via email for clarification. Supplementary material related to the main article was also investigated in such cases. Finally, descriptive statistics were used to summarize the data in this paper. The mean and standard deviation were adopted to describe continuous variables, whereas frequencies and percentages were used for dichotomous data. All statistical analyses were conducted using the software R version 4.1.2 (available at https://cran.r-project.org/).

Results

Study Selection

The preliminary database search using the prespecified keywords yielded 65 articles, of which 25 studies were excluded after removing duplicates. Twenty-five articles were further excluded based on title and

abstract screening based on inclusion criteria among monkeypox patients. The full-text review was conducted for the remaining 15 studies identified during the search period. Further, 9 studies were removed as the patients enrolled were either not positive for monkeypox or there was no conclusive evidence for myo/pericarditis based on lab and imaging findings. Hence, a total of 6 studies^{6,7,13-16} were included in the review, of which 4 are case reports, and 2 are case series (Supplementary Fig 1).

Baseline Characteristics of Included Patients

A total of 6 studies with 9 patients were included in this systematic review. The mean age of the patients was 33.6 years, and all were male patients. All included patients tested positive on PCR for the monkeypox virus. A total of 50% of the patients were homosexual among all monkeypox-induced myocarditis patients whose data were reported (n = 4/8), while 50% of patients had a history of unprotected sex (n = 2/4) (Table 1).

Symptoms, Lab Findings, and Imaging Test

Symptoms were variably reported in different studies, thus making the total number of patients with a particular symptom different for each symptom. The proportion of most common symptoms was: 100% of patients had chest pain (n = 9/9), 89% of patients had fever (n = 8/9), 100% of patients had dyspnea (n = 4/4), 78% of patients had a genital lesion (n = 7/9) (Table 2 and Supplementary Table 1).

Electrocardiographic data were variably reported in different studies: 44% of patients had ST-elevation (n = 4/9), 22% of patients had sinus tachycardia (n = 2/9), and 33% patients were having normal sinus rhythm (n = 3/9) (Table 3 and Supplementary Table 1).

In cardiac biomarkers, Mean Troponin I = 0.19 ng/mL, HsTroponin T was 1.43 ng/mL, and the mean CRP level was 152.2 mg/L (Table 3 and Supplementary Table 1).

Author	Year	Country	Study Design	Sample Size	Male	Age	Age [Mean]
Dumont et al. ¹³	2022	France	Case series	3	3	21, 25, 32	26
Brouillard et al. ¹⁴	2022	Canada	Case report	1	1	34	34
Nava et al. ⁷	2022	USA	Case series	2	2	32, 37	34.5
Shaik et al. ⁶	2022	USA	Case report	1	1	51	51
Tan et al. ¹⁵	2022	Canada	Case report	1	1	40	40
Pinho et al. ¹⁶	2022	Portugal	Case report	1	1	31	31
Shaik et al. ⁶ Tan et al. ¹⁵ Pinho et al. ¹⁶	2022 2022 2022	USA Canada Portugal	Case report Case report Case report	1 1 1	1 1 1	51 40 31	51 40 31

Table 1. Baseline demographic, and study characteristic of included studies

Author	DCD for		Unprotoctod	Homosovuol	Fovor	Choct	Conital	Dycanoo
Author	Monkeypox	Test	Sex History	Homosexual	rever	Pain	Lesion	Dyspilea
Dumont et al. ¹³	Positive	NR	1	1	3	3	2	NR, NR, NR
Brouillard et al. ¹⁴	Positive	Negative	NR	0	1	1	1	1
Nava et al. ⁷	Positive	NR	NR, NR	1	1	2	2	2
Shaik et al. ⁶	Positive	NR	NR	NR	1	1	0	1
Tan et al. ¹⁵	Positive	NR	1	1	1	1	1	NR
Pinho et al. ¹⁶	Positive	NR	NR	1	1	1	1	NR

Table 2. Symptoms and diagnostic test of monkeypox-induced myocarditis patients

Among patients under whom an *Echocardiographic* test was done shows, 67% of patients had normal wall motion (n = 4/6), 43% of patients had reduced ejection fraction (n = 3/7), 57% of patients had preserved ejection fraction (n = 4/7), while mean ejection fraction was 52.14%, and 1 patient had mild pericardial effusion (Table 3 and Supplementary Table 1).

X-ray findings were normal among the majority of available data of patients, with only 1 patient reported to have nonspecific retrocardiac opacity (n = 1/3), and a majority do not have any data reported (Table 4 and Supplementary Table 1).

Cardiac magnetic resonance (CMR) findings showed 40% of patients had late gadolinium enhancement (n = 2/5), and 40% of patients had edema (n = 2/5). A total of 60% of patients had CMR findings suggestive of myocarditis (n = 3/5), 1 reported mild pericardial effusion, and 4 patients have not reported any data on CMR findings (Table 4 and Supplementary Table 1).

Among management of myocarditis patients, 33% of patients were administered beta-blockers (n = 3/9), 33% of patients with ACE inhibitors (n = 3/9), 44% of patients with antiviral drugs (n = 4/9), 33% of patients with supportive care (n = 3/9), and 22% patients were given antibiotics (n = 2/9). The overall prognosis was good, and all patients recovered without any mortality (n = 9/9) (Table 4 and Supplementary Table 1).

Discussion

Monkeypox or Mpox¹⁷ is a zoonotic infection caused by the monkeypox virus, which is quite similar to the smallpox infection, both belonging to the orthopoxvirus. Monkeypox was initially isolated in Denmark in the late 1950s from Singapore in a colony of laboratory monkeys that were used for poliovirus research.¹⁸ Later, additional outbreaks were seen in US laboratories and from zoo animals in

Author	ECG Findings	Trop I	Hs Trop T	CRP	Echo Findings	LVEF%	LV Hypokinesia
Dumont et al. ¹³	ST elevation: 2 No changes: 1	NR	4040 pg/mL, 700 pg/mL, 2035 pg/mL	27 mg/L, 39 mg/L, 115 mg/L	NR	56%, 45%, NR	Hypokinesia: 1 Akinesia: 1 NR: 1
Brouillard et al. ¹⁴	ST elevation, sinus tachycardia 1	NR	211.5 ng/L	154.5 mg/L	Normal left ventricle (LV) size, reduced global longitudinal strain (–14.4%)	44%	1
Nava et al. ⁷	Normal sinus rhythm: 1 T wave inversions: 1	NR, 0.35 ng/mL	165 ng/L, NR	0.5 mg/dL , NR	Normal regional wall motion: 2	1.69%2. NR	NR: 2
Shaik et al. ⁶	Sinus tachycardia and ST elevation	0.02 ng/mL	NR	65.5 mg/dL	No wall motion abnormalities and mild pericardial effusion	55%	NR
Tan et al. ¹⁵	ST-segment changes 1	NR	NR	NR	Moderate global left ventricular dysfunction	40%	NR
Pinho et al. ¹⁶	Sinus rhythm with nonspecific changes	NR	NR	70 mg/L	Preserved biventricular systolic function and no pericardial effusion	56%	NR

Table 3. Cardiac biomarker, and echocardiographic findings among monkeypox-induced myocarditis patients

able 4.	X-ray,	cardiac magnetic	resonance, management	, and outcomes amon	ng monkeypox-induced	1 myocarditis	patients
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Authors	X-ray Findings	CMR Findings	Management	Outcomes (Alive)
Dumont et al. ¹³	NR	No evidence of cardiac inflammation: 1 NR: 1 Inferolateral segmental myocarditis: 1	β blocker and ACEI: 2 β blocker, antiaggregation and antiviral: 1	3
Brouillard et al. ¹⁴	Nonspecific retro-cardiac opacities	LV EF mildly reduced with mild LV dilation: 1 No LGE present	ACEI, Antibiotic, and antiviral: 1	1
Nava et al. ⁷	NR, NR	NR: 2	Antiviral and antibiotic: 1 supportive care: 1	2
Shaik et al. ⁶	No pathology	NR	Supportive treatment and antiplatelet	1
Tan et al. ¹⁵	NR	Small pericardial effusion, LGE present, focal edema, consistent with acute myocarditis	Antiviral	1
Pinho et al. ¹⁶	Normal cardiothoracic index, and no interstitial infiltrates, pleural effusion, or masses	Myocardial edema, LGE reveal subepicardial enhancement, finding suggestive of myocardial inflammation	Supportive treatment	1

Rotterdam.¹⁹ In 1977, naturally occurring smallpox was eradicated, and the smallpox vaccination was discontinued.²⁰ It also provided protection from mpox, which led to the rise in the cases of mpox in Central and West Africa. It is still unclear if HIV infection increases the risk of mpox infection. However, the risk of progressing to severe disease has been reported to be higher in those with low CD4 counts.²¹ Animal-to-human transmission and human-to-human transmission have been noted for monkeypox. In Africa, the monkeypox virus has been noted to spread through rope squirrels, tree squirrels, Gambian pouched rats, dormice, and various species of monkeys.²² Human-to-human transmission can occur through direct contact with infectious sores, scabs, or body fluids.²³ Transmission can occur by contact with materials or fomites such as clothing or linens contaminated with infectious material from body fluids or sores.^{24,25} Other modes of transmission are through respiratory secretions, vertical transmission, percutaneous inoculation via needlestick injuries, and though other bodily fluids.

Persons with behavioral and occupational risk factors for mpox infection are considered for postexposure prophylaxis, as mentioned below. Behavioral risk factors can be men who have sex with men, gay, transgender or nonbinary people having a new diagnosis of 1 or more sexually transmitted diseases. A few other risk factors are having sex at a commercial sex venue and sex in association with a large public event within the past 6 months. Sexual partners of people with the above risks also increase their risk of getting mpox. Occupational exposure to orthopoxvirus also increased the risk in research laboratory personnel and specialized clinical laboratory personnel.³

Monkeypox-Induced Myocarditis/Pericarditis

Myocarditis can be a challenging diagnosis as it has different clinical presentations and histological findings. Etiology, disease stage, acuity of the condition, and its progression decide the prognosis of the condition. Many cases have been reported during the outbreak in nonendemic countries since May 2022, especially in those men who have sex with men with atypical anogenital and oropharyngeal lesions.²⁶ A few cases of monkeypox-induced myocarditis have been noted. They tend to have an idiopathic source or are linked to viral etiologies.^{27,28} Herpes simplex virus has been known to be associated with pericarditis. Dumont et al.,¹³ in their case series study, described only 5 cases of myocarditis attributed to monkeypox. Two cases were described out of 528 human monkeypox

infections around 16 countries in 2022. One was described in a patient with HIV with 780 CD4 cells per cubic mm, while the other had no medical history, with their symptoms lasting for less than 7 days.³

Pathophysiology

The most common histologic finding that has been associated with viral myocarditis is the lymphocytic infiltration of the myocardium.²⁶ This might indicate the possible role of the immune system in the development of inflammation. Besides, viral particles can cause direct damage to the myocardium. The viral genomes attach to the immunological cells that circulate throughout the body and lodge into the heart, where they further replicate and cause localized tissue destruction.⁷ The injury to cardiac myocytes can then be explained, which is often seen 2 weeks postinfection in the form of myocardial necrosis (Fig 1). It is important to note that viral myocarditis is often associated with pericarditis and/or endocarditis, both of which are of lymphocytic nature.^{26,29} Exudative pericarditis is not a difficult diagnosis but aseptic endocarditis, although uncommon, is very difficult to suspect clinically.

Although viral myocarditis is thought to be the most common infectious etiology of acute myocarditis,^{26,29} the pathophysiologic mechanisms responsible for myocardial injury & necrosis are not yet fully understood. Some studies have also reported ischemia without significant coronary artery disease as a possible cause which is indicative of coagulopathies.^{30,31} Endomyocardial biopsy, the gold standard modality for the diagnosis of acute myocarditis, is an invasive technique due to which limited data is available on biopsy findings. Cardiac magnetic resonance, within such circumstances, has provided physicians with a noninvasive tool for myocardial tissue characterization.

Endomyocardial biopsy has shown an evident shift in the prevalence of cardiotropic viruses over time.^{29,32} Provided the broad repertoire of causative viral pathogens, the possibility of the Mpox virus as another emerging cardiotropic virus cannot be ruled out.

Monkeypox Vaccination and Recommendations

Pre-exposure prophylaxis is recommended in individuals who have increased behavioral or occupational factors. They should be vaccinated with the live, nonreplicating, modified vaccinia Ankara (MVA) vaccine. If MVA is not available replication-competent smallpox vaccine (ACAM2000) should be considered in selected persons because of the increased risk of side effects. Even after receiving pre-exposure





prophylaxis, patients should be monitored for exposure. Additional postexposure vaccination is not indicated.³³

Postexposure prophylaxis with MVA and ACAM2000 vaccine is highly recommended. MVA is a highly attenuated, nonreplicating vaccinia virus that has an excellent safety profile even in immunocompromised. ACAM2000 is a replication-competent smallpox vaccine that is approved in the US for the prevention of smallpox. It can also be used for the prevention of mpox. The CDC recommends PEP depending on the exposure risk.²³

Strength and Limitations

To our knowledge, this is the very first systematic review of available literature to date showing the cardiovascular complications (ie, myocarditis) post monkeypox infection. The major limitations of our study are the limited number of studies, with the majority of data being available from case reports or case series. Another limitation of our study is the limited data on CMR, echocardiography, and other invasive procedures. The findings of this study cannot be generalized because of the very less sample size and hence should be interpreted cautiously.

Conclusion

Our study's findings show that most cases are noticed among male patients with the most common symptoms of chest pain. The overall prognosis was good, with no mortality reported. Infected patients complaining of chest pain should not be ignored, and proper investigation of myocarditis must be considered. In the future, more studies are needed to estimate robust estimates of and incidence of myocarditis and outcomes among monkeypox-infected patients.

Data Availability Statement

All data used for this study is available online or in the Supplementary file.

Ethical Approval

Not required.

Authors' Contribution

Conceptualization: Akash Jaiswal; Methodology: Vikash Jaiswal; Formal analysis and investigation: Vikash Jaiswal, Dattatreya Mukherjee; Writing—original draft preparation: Qamar Sultana, Dattatreya, Simmi Lahori, Vibhor Agrawal; Writing—review and editing: Akash Jaiswal, Vibhor Agrawal; Funding acquisition: None.

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Supplementary materials

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