New Microbes and New Infections 53 (2023) 101154

Contents lists available at ScienceDirect

New Microbes and New Infections

journal homepage: www.journals.elsevier.com/new-microbes-and-new-infections

Original Article

Features of Mpox infection: The analysis of the data submitted to the ID-IRI network

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https://doi.org/10.1016/j.nmni.2023.101154
Received 18 March 2023; Received in revised form 10 May 2023; Accepted 12 May 2023
Article published online: 20 May 2023
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ARTICLE INFO

Handling Editor: Patricia Schlagenhauf

Keywords:
Mpox
Outbreak
Smallpox vaccine
HIV-Infected mpox

ABSTRACT

Background: Mpox is a rare zoonotic disease caused by the Mpox virus. On May 21, 2022, WHO announced the emergence of confirmed Mpox cases in countries outside the endemic areas in Central and West Africa.
Methods: This multicentre study was performed through the Infectious Diseases International Research Initiative network. Nineteen collaborating centres in 16 countries participated in the study. Consecutive cases with positive Mpoxv-DNA results by the polymerase chain reaction test were included in the study.
Results: The mean age of 647 patients included in the study was 34.5.98.6% of cases were males, 95.3% were homosexual-bisexual, and 92.2% had a history of sexual contact. History of smallpox vaccination was present in 3.4% of cases. The median incubation period was 7.0 days. The most common symptoms and signs were rashes in 99.5%, lymphadenopathy in 65.1%, and fever in 54.9%. HIV infection was present in 93.8% of cases, and 17.8% were followed up in the hospital for further treatment. In the two weeks before the rash, prodromal symptoms occurred in 52.8% of cases. The incubation period was 3.5 days shorter in HIV-infected Mpox cases with CD4 count $<200/\mu L$, we disclosed the presence of lymphadenopathy, a characteristic finding for Mpox, accompanied the disease to a lesser extent in cases with smallpox vaccination.
Conclusions: Mpox disseminates globally, not just in the endemic areas. Knowledge of clinical features, disease transmission kinetics, and rapid and effective implementation of public health measures are paramount, as reflected by our findings in this study.

1. Introduction

Mpox is a rare zoonotic disease. The disease is caused by the Mpox virus (Mpoxv), which belongs to the Poxviridae family and the Orthopoxvirus genus. This virus is closely related to variola (smallpox) and has a clinical presentation similar to smallpox [1,2]. Data from previous studies have shown that the smallpox vaccine is approximately 85% protective against Mpoxv [3]. Smallpox was eradicated in 1980, and there has been no routine vaccination program against an Orthopoxvirus for nearly 40 years [4]. The first human case of Mpox was reported from the Democratic Republic of Congo in 1970 [5]. From 1970 to 1979, Mpox also occurred in other African countries, mainly Central and West Africa. During this period, 47 cases of Mpox were reported, 38 of which were from Congo [6]. A gradual increase in Mpox cases was observed between 1980 and 2013 [7,8].

The current outbreak in 2022 began in the United Kingdom in a patient who had travelled to Nigeria in April 2022. On May 21, 2022, the World Health Organization (WHO) announced that 92 confirmed cases of Mpox had occurred in 12 countries outside the endemic areas in Central and West Africa [9]. On July 23, 2022, the WHO Director-General declared the current Mpox outbreak a Public Health Emergency of International Concern [10]. As of March 1, 2023, 86,231 confirmed Mpox cases had been reported from 110 locations worldwide, with 84,858 cases from 103 countries or territories that have not reported cases in the past [11].

The clinical course of the disease varies from mild to severe and fatal. A one-to four-day prodrome stage phase with fever, headache, and lymphadenopathy fatigue is followed by multiple facial and body rashes [12]. The incubation period is approximately 7–14 days. Patients are thought to be contagious from the onset of the rash until desquamation four weeks later. Person-to-person transmission can occur via respiratory droplets, the placenta, skin abrasions, or contact with contaminated objects [13].

The unexpected emergence of Mpox cases with no epidemiologic link to West and Central Africa areas suggests undetected transmission and reportedly affects men who have sex with men (MSM) [14–17]. Current outbreaks among MSM suggest that transmission occurs through close and intimate physical contact and probably also sexually through seminal or vaginal fluids.

The number of international studies in the literature is small. Therefore, this multicentre and international study aimed to determine the characteristic features of Mpox disease.

2. Patients and methods

2.1. Case definition

Consecutive cases with a positive result for Mpoxv-DNA by polymerase chain reaction (PCR) in any clinical sample between January 1, 2015, and November 31, 2022, were included in the study regardless of age group.

2.2. Setting

The centres participating in the study were centres collaborating with the Infectious Diseases International Research Initiative (ID-IRI), and the study was organized through the ID-IRI network. Nineteen centres in 16 countries (Mexico, Bolivia, Puerto Rico, Italy, Hungary, Bulgaria, Portugal, Romania, Czech Republic, Egypt, Brazil, Bosnia and Herzegovina, Nigeria, Spain, Sierra Leone, and France) participated in the study.

2.3. Data collection

A questionnaire and a supplemental Microsoft® for Windows Excel® file were distributed to participating centres. Case demographics, including age, sex, comorbidities, smallpox vaccination status, contact history within 1 month before rash onset, presence of one or more PCR-positive cases in the patient's close environment (such as home, sexual partner, skin-to-skin contact), sexual orientation, number of sexual partners in the past month, travel abroad (to another country) in the previous month and status of attendance at shows or similar (festival-like) events, clinical findings, including presence of symptoms in the 15 days before the rash and the time between those symptoms and the onset of the rash (prodromal period), morphology, location, and number of rashes (lesion density), symptoms occurring along with the rash like fever, headache, sore throat, fatigue, itching, cough, mental deterioration, muscle pain, abdominal pain, nausea-vomiting, rectal pain, rectal bleeding, ulcers in the mouth, genital ulcers, lymphadenopathy, and the region of lymphadenopathy, HIV-RNA CD4 analysis results of HIV-infected persons in the past 6 months, Mpoxv DNA-positive samples (rash, nasopharyngeal, blood, urine, anal swab, semen), Mpox antiviral treatment, and complications that developed during the course of the disease were recorded by scanning patient records or automated hospital systems. At the end of the study period, participating centres submitted their data in the form of an Excel document. These datasets were then merged into a final database.

2.4. Statistical analysis

Data analysis was performed using SPSS 22.0 software (IBM SPSS). Descriptive statistics are reported as frequencies and percentages for categorical variables and as means ± standard deviations and medians (interquartile range (IQR)) for continuous variables according to the results of a normality test. Groups comparisons, used the chi-square test and Fisher's exact test for the categorical variables, for numerical variables, used Student's *t*-test for parametric data and the Mann Whitney-U test for nonparametric data. And assigned statistical significance to p-values less than 0.05.

2.5. Ethical approval

The Clinical Research Ethics Committee of the Ministry of Health, Göztepe Training and Research Hospital of Medeniyet University, Istanbul, approved an international, multicentre, retrospective study (2022/0618). The study was conducted following the ethical principles of the Declaration of Helsinki.

3. Results

The mean ± standard deviation age of the 647 cases included in the study was 34.54 ± 8.07 years; 638 (98.6%) were males, 9 (1.4%) were female, and 3 cases were children. Four hundred thirty-six (67.4%) of the 647 cases had comorbidities. Of the comorbidities, 409/436 (93.8%) were HIV infected. Sexual orientation was homosexual in 601 (93.3%) of the 644 adult cases. In addition, 217 (33.7%) of 644 adult patients provided information on the number of sexual partners in the past month. Of these, 17 (7.8%) reported no sexual activity, while 62 (28.6%) had a single partner (Table-1).

3.1. Origins of mpox cases

558 (86.2%) Mexico, 15 (2.3%) Bolivia, 14 (2.2%) Italy, 13 (2%) Puerto Rico, 9 (1.4%) Hungary, 6 (0.9%) Bulgaria, 6 (0.9%) Portugal, 6 (0.9%) Romania, 5 (0.8%) Czech Republic, 4 (0.6%) Egypt, 4 (0.6%) Brazil, 2 (0.3%) Bosnia and Herzegovina, 2 (0.3%) Nigeria, 1 (0.2%) Barcelona, 1 (0.2%) Sierra Leone, 1 (0.2%) France.

3.2. Contact history

Smallpox vaccination history was positive in 22 cases (3.4%). It was found that only 58 (9%) patients had one or more Mpoxv PCR-positive cases in their close environment. One hundred twenty-three cases (19%) reported no contact, while 524 cases did. Of those 524 cases, 483 (92.2%) reported sexual contact, 18 (3.4%) reported status of attendance at shows or similar (festival-like) events, 9 (1.7%) reported household contact, 2 (0.4%) reported healthcare contact, 3 (0.6%) reported other events (1 case reported flying more than 10 h, one patient reported it could be because he was a flight a2ttendant, 1 case reported being in the sauna nine days ago) (Table-1).

3.3. Course of the disease

The duration between exposure and onset of symptoms (incubation period) [median (IQR)] was 7.0 (2–25) days. In 97.4% (n = 630) of cases, the Mpoxv-DNA (PCR-positivity) was isolated from the rash lesion. One hundred fifteen (17.8%) cases were followed up in the hospital for further treatment. Antiviral treatment against Mpox was initiated in 2 patients; 2 patients (0.3%) received cidofovir treatment, and no patient was treated with tecovirimat. No patient has died of Mpox in this study.

3.4. Symptomatology

Rash was not detected in 3 cases. In 340/644 (52.8%) cases, prodromal symptoms were described in the two weeks preceding the rash. The symptoms observed during this period were fever (n = 275, 80.9%), fatigue (n = 210, 61.7%), headache (n = 152, 44.7%), and sore throat (n = 89, 26.2%). The most common symptoms and signs among cases were rashes (n = 644, 99.5%), lymphadenopathy (n = 419, 65.1%), and fever (n = 337, 54.9%). The morphology of the rashes was mixed in 340 (52.8%) patients. Lesions were detected in more than one region in 502 (92.3%) cases. The lesions were located in the genital region in 382 (59.3%) cases and on the body in 378 (58.7%) cases. There were 10–49 lesions in 574 (89.1%) cases. Lymphadenopathy was detected in 419 (65.1%) cases, and the most common location was the inguinal region (n = 327, 78%). In 75 patients (17.9%), lymphadenopathy was present in multiple regions (Table-2).

Table-1
Demographic data of patients with Mpox.

Variables	n	(%)
	647	100
Comorbidity	436	67.4
HIV	409	93.8
Syphilis	44	10.1
HCV	20	4.6
HBV	7	1.6
Others	14	3.2
Exposure		
Reported exposure	524	100
Sexual contact	483	92.2
Household contact	9	1.7
Show festival-like event	18	3.4
Healthcare	2	0.4
Other events	3	0.6
Incubation period (days) (median (IQR)	7.0 (2–25)	
History of smallpox vaccination		
Yes	22	3.4
No	577	89.2
Unknown	48	7.4
Travel abroad (to another country) in the last month	45	7
Sexual orientation	644	100
Homosexual	601	93.3
Heterosexual	30	4.7
Bisexual	13	2
Number of sexual partners in the past month		
Reported sexual partners	217	33.7
0	17	7.8
1	62	28.6
2-5	95	43.8
6-10	35	16.1
More than 10	11	5.1
Presence of positive case/s close environment the patient	58	9
Mpoxv DNA-positive samples	647	100
Rash	630	97.4
Nasopharyngeal	39	6
Blood	23	3.6
Urine	14	2.2
Anal swab	11	1.7
Semen	4	0.6
Complications	47	7.3
Proctitis	20	42.6
Soft-tissue superinfection	13	27.7
Balanitis	9	19.1
Others	9	19.1
Sequelae	4	0.6
Phimosis	3	75
Anal prolapse	1	25

3.5. Features of HIV-infected patients

In 310 (75.8%) of 409 HIV-infected patients, CD4 cell count and HIV-RNA value were determined in the past six months, and the median CD4 cell count (IQR) was 516.5 (24–973)/μL. Thirty (9.7%) had a CD4 cell count of <200/μL. The HIV-RNA value was negative in 267 (86.1%) cases, a positive value was found in 43 cases (13.6%), and the median (IQR) of the HIV-RNA value was 3139 (51–274,962) IU/mL.

Table-2
Symptoms occurring along with the rash.

Variables	n	%
Rash	644	100
Lesion density		
<10	49	7.6
10-49	574	89.1
50-100	20	3.1
More than 100	1	0.2
Lesion morphology		
Vesicular	166	25.8
Papular	123	19.1
Macular	15	2.3
Mixed	340	52.8
Location of lesions		
Face	183	28.4
Neck	90	14
Scalp	50	7.8
Body	378	58.7
Legs	232	36
Arms	262	40.6
Genital	382	59.3
Perianal	222	34.5
Oral	80	12.4
Perioral	16	2.5
Hands and feet	90	14
Palms of hands	84	13
Mixed location	502	78
Symptom/s	**614**	95.3
Fever	337	54.9
Headache	190	30.9
Sore throat	130	21.2
Fatigue	246	40.1
Itching	203	33.1
Cough	16	2.6
Mental deterioration	4	0.7
Muscle pain	224	36.4
Abdominal pain	6	0.9
Nausea-vomiting	17	2.8
Rectal pain	67	10.9
Rectal bleeding	12	1.9
Ulcers in the mouth	38	6.2
Genital ulcers	220	35.8
Lymphadenopathy	419	65.1
Region of lymphadenopathy		
Inguinal	327	78
Cervical	144	34.4
Axillary	23	5.5
Mixed	75	17.9

3.6. Impact of HIV on mpox disease

HIV-infected individuals were divided into two groups with CD4 counts below 200 and above 200. The median in these two groups, the median (IQR) duration between exposure and onset of symptoms was 6.5 (2–21) days in those with CD4 > 200, and the median (IQR) duration between exposure and onset of symptoms was 3 (2–6) days in those with CD4 < 200, and this difference between groups was statistically significant ($p < 0.001$). No significant difference was found between other demographic characteristics and findings (Table-3).

3.7. Smallpox vaccination

Study subjects were divided into two groups: those with smallpox vaccination (smallpox-vaccinated cases) and those without (unvaccinated cases). Lymphadenopathy was present in 6 (27.3%) of 22 smallpox-vaccinated cases and 389 (67.4%) of 577 unvaccinated cases. This difference between groups was statistically significant ($p = 0.001$), and no significant difference was found between other demographic characteristics and findings (Table-3).

Table 3
Demographics and symptoms in patients with Mpox.

Variables	CD4≥200/μl HIV infected patients	CD4<200/μl HIV infected patients	Smallpox vaccinated	Smallpox unvaccinated
Age (mean ± SD)	35.11 ± 7.26	37.36 ± 8.99	45.68 ± 7.37	33.56 ± 7.89
Incubation period (days) (median (IQR)	n 118 6.5 (2–21)	n 19 3 (2–6)	n 15 9.5 (2–16)	n 287 6.5 (2–25)
	n (%)	n (%)	n (%)	n (%)
	280	30	22	577
Rash	280 (100)	30 (100)	22 (100)	574 (99.5)
Lymphadenopathy	182 (64.5)	21 (70)	6 (27.3)	389 (67.4)
Fever	153 (54.6)	12 (40)	10 (45.5)	285 (49.4)
Headache	90 (32.1)	6 (20)	9 (40.9)	167 (28.9)
Sore throat	60 (21.4)	8 (26.7)	10 (45.5)	96 (16.6)
Fatigue	112 (40)	13 (43.3)	9 (40.9)	211 (36.6)
Itching	87 (31.1)	9 (30)	6 (27.3)	166 (28.8)
Cough	5 (1.8)	2 (6.7)	1 (4.5)	9 (1.6)
Mental deterioration	2 (0.7)	0	0	3 (0.5)
Muscle pain	104 (37.1)	10 (33.3)	10 (45.5)	201 (34.8)
Abdominal pain	1 (0.4)	0	2 (9.1)	4 (0.7)
Nausea-vomiting	9 (3.2)	0	1 (4.5)	12 (2.1)
Rectal pain	10 (3.6)	2 (6.7)	1 (4.5)	57 (9.9)
Rectal bleeding	7 (2.5)	1 (3.3)	0	10 (1.7)
Oral ulcers	11 (3.9)	3 (10)	2 (9.1)	28 (4.9)
Genital ulcers	88 (31.4)	6 (20)	4 (18.2)	187 (32.4)

4. Discussion

Our study presents 647 Mpox cases reported from 16 countries. The patients are middle-aged men with homosexual-bisexual patterns and a high rate of HIV infection, and sexual contact is the most important Mpox transmission method. We found that lymphadenopathy was significantly lower in smallpox-vaccinated cases compared to unvaccinated cases. In addition, the median duration between exposure and onset of symptoms was significantly shorter in HIV-infected patients with CD4 counts below 200 than in those with higher levels.

The age distribution of our cases was similar to the cases reported in the 2022 outbreak [16,18,19]. In previous outbreaks, the mean age of patients was 20 years, but in the current outbreak, infections occurred more frequently in the adult population [15]. The increase in age in this outbreak may be due to clustering in a particular age group, with MSM individuals accounting for almost all cases. Only 7% of our cases had travelled abroad (to another country) in the past month. Nearly all of them had acquired the virus locally. In the population that did not travel to endemic areas, the most common transmission route was direct person-to-person contact in our study and other published series.

Smallpox vaccination has been shown to provide cross-protection against other infections caused by Orthopoxviruses, including Mpox. Based on the available data, approximately 90% of the detected cases were born after the end of the smallpox eradication program [3,7,20]. In our study, there was a small group of cases with a history of smallpox immunization. After the cessation of smallpox vaccination in the early 1980s, the decline in vaccine-induced herd immunity and the lack of protection in younger age groups may have contributed to widespread infection with Mpoxv.

Confirmation of Mpox infection requires laboratory detection, although clinical and epidemiologic criteria are currently being re-evaluated, and may vary by condition and geographic location. Mpox infection can be confirmed by isolation in a viral culture or by positive PCR for Mpoxv-DNA from a patient sample [21]. Mpoxv-DNA was tested positive at least once in all our cases. Because 99.5% of our subjects had rashes, the most frequent sample was collected from the rash lesion, and

therefore the most frequent sample positivity was detected from the rash lesion. We recommend testing semen and vaginal secretion samples, as well as other samples, as this will shed light on the cause of transmission in cases with a history of sexual contact.

The incubation period for Mpoxv in humans is usually between 7 and 14 days [21]. The duration between exposure and onset of symptoms reported in our cases was similar to that reported in the literature, with a median of 7 days. In 18 HIV-infected patients with a CD4 count below 200, this period was a median of 3 days, whereas it was 6.5 days in patients with a CD4 count above 200. This finding may be related to more rapid Mpoxv replication due to HIV-related immunosuppression. It has been reported that Mpox patients are not infectious until the onset of symptoms [22]. Moreover, because of the short incubation period, these patients may be infectious earlier, spreading the disease rapidly.

Typically, Mpox starts with the febrile prodromal stage that may be accompanied by weakness, headache, and sore throat, followed by an extensive rash that usually affects the palms and soles [22]. However, in half of our cases, no prodromal symptoms were noticed before the rash, and one-fifth of those who reported prodromal symptoms did not have fever. Therefore, regardless of whether prodromal symptoms preceded the rash, caution is needed in patients with a contact history of rash consistent with Mpox. A sample should be obtained for testing.

Rash was detected in the genital area in more than half of our cases. Clustering skin rashes, in the genital region in particular, were among the most common features reported in 2022 in other papers [15–17]. The most common clinical features of Mpox before the current outbreak were fever, rash, lymphadenopathy, and fatigue [23]. In our series, the most common symptoms associated with rash was lymphadenopathy, most commonly seen in the inguinal area, and fever in more than half, followed by fatigue. The inguinal/genital lymphadenopathy was also reported to be common in cases that were mostly infected by sexual contact [15–17].

The presence of lymphadenopathy is the distinguishing feature between Mpox and smallpox [20,21]. In our study subjects, the most striking difference between vaccinated and unvaccinated smallpox cases was that lymphadenopathy was significantly lower compared to unvaccinated cases. The severity of disease and lymphadenopathy formation may have decreased due to vaccination protection. This finding is important because it reduces suspicion for the disease in vaccinated individuals, and may reduce sampling, thus, potentially delays diagnosis. Even if vaccinated individuals do not have lymphadenopathy, we recommend sampling for Mpoxv testing if there are epidemiologic linkages or compatible clinical findings.

Although the clinical symptoms of Mpox are milder than those of smallpox, the disease can be more severe in children and immunocompromised individuals. The mortality rate ranges from 1% to 10% [23,24]. HIV infection and the degree of control may alter the severity and duration of clinical symptoms [13]. Although there are case series of HIV-infected patients in recent studies, no deaths have been reported [16–19,25]. Although there were 409 HIV-infected patients in our study, the cases were mild and self-limiting, and there were no severe complications or deaths. We suspected that the reason for the mild course, particularly among the HIV-infected cases, might be that median CD4 cell count was rather high with 516.5/μL. When the HIV-infected cases were divided into groups with CD4 counts below and above 200/μL, we could not show any difference in clinical findings and disease severity between these groups. The reason might be the low mortality rate of the circulating strain, and the low number of patients with CD4 count below 200 (30 cases). One hundred fifteen cases were followed up in the hospitals for further support. However, this was not related to the clinical severity of the patients, but for the isolation purposes and the follow-up recommendations released in each country and region.

Currently, there is no clinically proven specific treatment for Mpox infection. As with most viral diseases, treatment consists of supportive symptom control. Studies report the efficacy of tecovirimat, cidofovir, brincidofovir and other antiviral drugs against poxvirus [26]. In our cases, cidofovir was used in only two patients. The first case was a 30-year-old man with comorbidities related to HCV, HIV, and Kaposi's sarcoma, a CD4 count of 56//μL, and an HIV viral load of 212,000 copies/mL. A soft-tissue superinfection developed on day 6 of the rash. It was predicted that this case might have a severe course due to comorbidities and immunosuppression, and treatment was started. The second case was a 28-year-old healthcare worker who had no comorbidities. In this case, there were no conditions suggestive in being responsible for a severe course of the disease. It was reported that treatment was started because he was a healthcare worker.

Among the limitations of the study, the reported cases are people who applied to the health institution with symptoms and had tests done, so we do not have data on asymptomatic cases. Another limitation is the difficulty in accurately determining the disease incubation period in cases. Because in most cases, the number of sexual intercourse and partners is high in sexual contact, which is reported as a means of transmission. Considering the partner's incubation period, it is almost impossible to distinguish from which contact the infection thought to be Mpox originated, especially with the same partner.

As a result, we found that the incubation period of HIV-infected Mpox cases with a CD4 count <200/μL is median (IQR) 3.5 (2–6) days shorter, and we found that the presence of lymphadenopathy, which is a characteristic finding of Mpox, accompanies the disease to a lesser extent in cases with smallpox vaccination. It should not be ignored that this disease can affect the entire society, not just the endemic areas or particular group. Therefore, knowledge of clinical findings, disease transmission, prevention, control, and rapid and effective implementation of public health measures are of paramount importance.

Ethical consent

Ethical consent was obtained from Istanbul Medeniyet University School of Medicine (2022/0618).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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