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Research letter

A retrospective and comparative analysis of suspected and confirmed Monkeypox virus-infected patients

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1. Introduction

Monkeypox virus (currently known as "mpox") is a species of the genus Orthopoxvirus that causes human smallpox. It was first described in 1970 in the Democratic Republic of Congo. Mpox has been described as endemic only in parts of Africa (in eleven countries on that continent), often after contact with a natural reservoir of the virus, usually rodents. However, sporadic outbreaks have been reported in the United States associated with imported wildlife from Ghana [1–3]. In May 2022, following an international health alert originating in the United Kingdom, cases of mpox infection began to be reported in many regions other than those described above. The total number of mpox cases increased dramatically overall. This led the World Health Organization to declare the global outbreak of mpox "a public health emergency of international concern (PHEIC)" on July 23, 2022 [4,5]. The clinical presentation of mpox infection is similar to that of human smallpox, with some notable differences. The incubation period is usually 7 to 14 days (range 4 and 21 days). A febrile prodrome (between 1 and 4 days) consisting of headache, myalgia, asthenia and sweating may occur. Then, usually between 1 and 3 days later, skin lesions may appear, the number and location of which are highly variable. They usually progress from macules to papules, pustules, and crusts (in that order) before desquamation. In addition, a large majority of cases may present with lymphadenopathies [2,6]. Subsequently, comparative analysis of baseline clinical and demographic characteristics of patients with suspected or confirmed mpox infection may help clinicians differentiate mpox infection from alternative diagnoses. Our study aimed to identify epidemiologic and clinical factors predictive of confirmed mpox-infected patients.

2. Methods

This was a retrospective observational study of adult patients with suspected mpox infection (i.e., patients meeting the World Health Organization's case definition of probable or suspected mpox issued as of August 25, 2022) who were seen at the Infectious Diseases Unit, Hospital Clínico Universitario San Juan, Alicante, Spain, between May 2, 2022, and February 2, 2023. The study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of the Hospital Clínico Universitario San Juan (IRB protocol No. 23/035). Given the retrospective nature of the study, the IRB considered it unnecessary to obtain written informed consent from the patients.

The population base of our academic hospital was 237,467 inhabitants (394 hospital beds) in Alicante, Spain. Patients were referred to our sexually transmitted disease clinic from primary care or the emergency room. The incidence rate was calculated by dividing the number of confirmed cases by the number of residents registered in the department on the day of the outbreak.

For all suspected mpox-infected patients, epidemiologic data such as age, sex, type of sexual practices (men who have had sex with men (MSM), women (MSW), or with both men and women (MSMW)), and source of infection were recorded in the medical records. Patients' mpox vaccination status was recorded in the medical history as part of the study variables.

Patient outcomes, complications (immediate or sequelae), previous or concomitant HIV diagnosis, and other coexisting sexually transmitted infections (STIs) were also recorded in the medical records. Skin lesion swabs and anorectal swabs were routinely collected as part of the initial patient evaluation at our STI clinic or emergency department. Eight additional specimens, including urine, blood, saliva, and throat/urethral swabs, were collected according to the physician's criteria based on the patient's symptoms. The Alinity MPXV Assay®, a real-time polymerase chain

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reaction (PCR) test for the qualitative detection of Monkeypox virus DNA in human skin lesion specimens, was used as the microbiology-confirmed diagnostic method.

We calculated proportions for categorical variables and medians with interquartile ranges (IQR) for continuous variables. Qualitative variables were compared using Pearson's chi-squared test or Fisher's exact test, whereas the Kruskal-Wallis test was used for quantitative variables. The incidence rate was calculated by dividing the number of confirmed cases by the population registered with the health department at the time of the outbreak. Using a logistic regression model, we compared confirmed mpox cases (*i.e.* those with positive PCR on any sample) with negative cases. The selection of variables for multivariate analysis was based on their clinical significance and the results of the univariate analysis. A p-value of <0.05 was considered statistically significant. Data were analyzed using IBM SPSS Statistics, version 22.

3. Results

Between May 2, 2022, and February 2, 2023, 89 patients with suspected mpox infection were evaluated. The diagnosis was microbiologically confirmed in 54 (60.7%) cases. The incidence rate of mpox infection was 22.7 cases per 100,000 population during the study period. Most cases (95.7%) occurred between 2nd June and 26 September 2022 (16 weeks). The highest incidence was between 21st July and 29th August 2023 (51.2%, 5 weeks). All but three cases were unvaccinated. In Spain, mpox vaccination began at the end of August 2022. As most of the infected patients presented during this summer period, there were no incident cases that were fully vaccinated.

Most patients self-identified as cisgender males (n = 80; 89.9%), followed by cisgender females (n = 8; 9%), and transgender males (n = 1; 1%). The mean age of the patients was 40.3 ± 12.2 years (range 19–77). Of the 80 cisgender male patients enrolled, 66 patients were MSM (81.5%). Sixty-four of 89 patients (71.9%) recognized that they were at significant risk for contact with other mpox-infected patients (sexual or close contact). The median number of days from symptom onset to specimen collection for PCR was 11 days (IQR 7–14). Six patients required hospitalization (6.7%). Of the 89 patients with suspected mpox in the specimen, 54 were microbiologically confirmed and considered cases. The remaining 35 patients had negative microbiological results. In 3/35 patients, no alternative diagnosis was considered and they were excluded from the comparative analysis to avoid selection bias. The remaining 32 patients had a confirmed alternative diagnosis of either viral, bacterial or fungal infection or inflammatory disease. Viral infections included COVID-19 (n = 2), herpes simplex virus (n = 4), Zika virus (n = 1), human papillomavirus (n = 1), or human immunodeficiency virus (HIV, n = 1). No cases of varicella were recorded, as human varicella is very rare in Spain. Bacterial infections included infections with *Chlamydia* (n = 3), *N. gonorrhoea* (n = 2), syphilis (n = 2), bacterial balanitis (n = 1), impetigo (n = 1), methicillin-resistant *Staphylococcus aureus* (MRSA) infection (n = 1), or *Shigella* (n = 1). Four fungal infections initially suspected to be mpox infections were diagnosed: tinea corporis (n = 2), tinea cruris (n = 1), and *Candida* balanitis (n = 1). Four inflammatory conditions were diagnosed: psoriasis (n = 2), insect stings (n = 1), and oral sores (n = 1).

Table 1
Clinical manifestations presented by the eighty-nine patients with suspected mpox infection. CNS: Central Nervous System.

Cutaneous (macular, papular, vesicular, or pustular)	n = 76 (85.4%)
Systemic	n = 47 (52.8%)
Genital	n = 43 (48.3%)
Lymphadenopathy	n = 33 (37.1%)
Proctitis	n = 14 (15.7%)
Pharyngitis	n = 11 (12.4%)
CNS	n = 11 (12.4%)
Abdominal	n = 8 (11.1%)
Respiratory	n = 2 (2.2%)
Urinary	n = 1 (1.1%)

The clinical manifestations of the 89 patients with suspected mpox infection enrolled in the study are summarized in Table 1.

Of the confirmed mpox-infected patients, 53 were male (98.1%). Of these, 50 were MSM (94.33% of males and 92.6% of all confirmed cases). Most patients were born in Spain (51.9%), while others were from South America (29.7%), Europe (9.7%), or Central America (9.3%). Differences in epidemiologic and clinical characteristics between patients with and without confirmed mpox infection are shown in Table 2. Some epidemiologic characteristics were associated with mpox infection in univariate analysis (sex, MSM, previous contact), but only MSM sexual practices remained significantly associated with mpox infection in multivariate analysis (odd ratio (OR) 26.38, 95% confidence interval (CI) 3.50–198.4; p = 0.001).

Some clinical features (systemic symptoms, lymphadenopathy, genital lesions) were associated with mpox diagnosis in the univariate analysis, but only systemic symptoms (fever, fatigue, arthralgia) were significantly associated with mpox infection in the multivariable logistic regression model (OR 10.52, 95% CI 2.56–43.14; p = 0.001). In the univariate and multivariate models, the presence of abdominal symptoms (nausea, vomiting, or diarrhea) was significantly associated with an infectious or inflammatory process other than mpox infection (OR 0.042, 95% CI 0.004–0.41; p = 0.007). HIV infection prior to diagnosis of pox infection was not significantly associated with increased incidence of infection or its complications. A history of sexual contact or exposure to a patient with mpox infection was significantly associated with the presence of a concomitant STI in the univariate regression model (28.1% vs. 4%; p = 0.013), but not in the multivariate model.

Most mpox infections were mildly symptomatic. However, 6/54 (11.1%) patients had severe disease and were hospitalized. Complications included bacterial superinfection (n = 3), penile edema without paraphimosis (n = 2), and proctitis requiring analgesics (n = 2). One patient developed a severe encephalitis. He was treated with supportive care and tecovirimat. Unfortunately, he died 6 days after admission. Hospital stays ranged from 1 to 8 days.

4. Discussion

Our study analyzes a monocentric cohort of patients with suspected mpox infection in the context of the global outbreak that began in the United Kingdom in May 2022. Spain was the third most affected country, providing evidence of community spread. In our series, most of the patients (51.2%) were diagnosed in July and August 2022, as previously reported in other series [7]. All but three cases were unvaccinated. Our mpox infection rate was 22.7 cases per 100,000 population, compared with the lowest in Brazil (3.8 cases/100,000) and the highest in the U.S. (150 cases/100,000) [8,9]. Our epidemiological characteristics are close to those previously reported (males, between 35 and 45 years of age) [10,11]. Most cases were identified as MSM, leading to the hypothesis that mpox may be spread through close contact during sexual activity. In a report of 528 cases of confirmed human mpox infection in sixteen countries, 98% of patients were MSM.[1]. Candela et al. found that 96% of patients infected with mpox were MSM, compared with 92.6% in our series [11]. In contrast, only 1.9% of MSM patients were diagnosed with pathologies other than mpox infection. In addition, MSM was significantly associated with mpox infection in multivariate analysis. In our series, 71.9% admitted sexual or close contact

Table 2
Risk factors and symptoms associated with a diagnosis of mpox: differences between confirmed and unconfirmed cases of mpox infection.*MSM: men having sex with men; CNS: central nervous system; HIV: human immunodeficiency virus; STI: sexually transmitted infection.

	Mpox positive $n = 54$	Mpox negative $n = 32$	Univariate model	p-value	Multivariate model	p-value
Age	40.5 ± 10.5	40.1 ± 14.5	OR 0.99 (0.96–1.03)	$p = 0.890$	–	–
Origin (Spanish)	51.9%	62.9%	OR 0.91 (0.80–1.03)	$p = 0.145$	–	–
Male sex	98.1%	80%	OR 10.96 (1.25–95.5)	$p = 0.030$	OR 1.04 (0.6–––19.55)	$p = 0.975$
MSM	**92.6%**	**1.9%**	**OR 14.54 (4.39–50.09)**	**$p < 0.001$**	**OR 26.38 (3.50–198.4)**	**$p = 0.001$**
Prior contact	70.3%	29.7%	OR 4.21 (1.58–11.18)	$p = 0.004$	OR 1.314 (0.34–5.63)	$p = 0.715$
Skin lesions	87.6%	82.9%	OR 1.38 (0.42–4.54)	$p = 0.587$	–	–
Systemic symptoms	**68.5%**	**28.6%**	**OR 5.441 (2.14–13.81)**	**$p < 0.001$**	**OR 10.52 (2.56–43.14)**	**$p = 0.005$**
Pharyngitis	16.77%	5.77%	OR 3.30 (0.66–16.29)	$p = 0.143$	–	–
Gastrointestinal symptoms	**3.7%**	**17.1%**	**OR 0.18 (0.03–0.98)**	**$p = 0.047$**	**OR 0.04 (0.004–0.41)**	**$p = 0.007$**
Proctitis	20.4%	8.6%	OR 2.72 (0.70–10.29)	$p = 0.147$	–	–
Lymphadenopathy	44.4%	25.7%	OR 2.31 (0.91–5.85)	$p = 0.047$	OR 1.51 (0.42–5.37)	$p = 0.520$
Genital lesions	59.3%	31.4%	OR 3.17 (1.29–7.77)	$p = 0.012$	OR 2.56 (0.71–9.12)	$p = 0.147$
Urinary symptoms	1.9%	0%	OR 1	$p = 1$	–	–
CNS symptoms	14.8%	8.6%	OR 1.85 (0.45–7.53)	$p = 0.388$	–	–
Respiratory symptoms	1.9%	2.9%	OR 0.64 (0.03–10.60)	$p = 0.756$	–	–
Previous HIV	44.4%	28.6%	OR 1.92 (0.77–4.78)	$p = 0.161$	–	–
Previous STI	63%	42.9%	OR 2.26 (0.95–5.39)	$p = 0.065$	OR 0.81 (0.14–4.51)	$p = 0.813$
Concomitant STI	18.5%	25.7%	OR 0.65 (0.23–1.82)	$p = 0.420$	–	–

with previously mpox-infected patients (mean 11.2 ± 4.3 days). Tarin-Vicente et al. described an incubation period of 7 days and prior contact in 79% of cases [10]. In our cohort, 44.4% of patients had a prior diagnosis of HIV, as previously described in published cohorts during the 2022 outbreak, ranging from 36% to 42% among cases diagnosed with mpox infection [1,12]. It is not known whether HIV infection affects a person's risk of mpox infection. However, a higher risk of progression to severe disease has been reported in patients with low CD4 lymphocyte counts [13].

There are few comparative studies between mpox infection and other processes (infectious or not) with similar clinical presentations. Hussain et al. recently reviewed the major differential diagnoses, as early and correct diagnosis allows for appropriate treatment [12]. Conditions that may mimic mpox infection include smallpox, chickenpox, primary and secondary syphilis, acute retroviral syndrome, and genital HSV [14].

Our study analyzed not only confirmed cases of mpox infection, but also, in a novel way, suspected cases with alternative diagnoses. Overall, there were 32 patients (36%) in whom an alternative diagnosis was confirmed, with many cases being viral (COVID-19, HSV, HIV, HPV) or bacterial (other STIs such as *Chlamydia*, *N. gonorrhoeae*, or syphilis). We then performed a comparative study of the epidemiologic and clinical characteristics of the two groups of patients. The main difference in the univariate study was male sex, MSM, previous exposure, the presence of systemic symptoms (fever, chills, and malaise) and genital symptoms (skin lesions) in confirmed cases of mpox virus. On the other hand, in the group of patients with alternative diagnoses, abdominal symptoms (diarrhea, nausea, vomiting, or abdominal pain) were significantly more common (17.1%) than in patients with mpox infection (3.7%). No other variables analyzed, such as age, origin, presence of other symptoms (cutaneous, proctitis, pharyngeal, lymphadenopathy, or CNS), the presence of HIV, or previous or concomitant STIs, were statistically significantly different.

On multivariate analysis, only the MSM status and systemic symptoms such as fever, chills, and malaise were significantly associated with mpox infection. Systemic symptoms are common and may occur before the rash appears (prodromal stage) or shortly after (early clinical stage). These symptoms are due to a viremic phase of the disease. Tarin-Vicente et al. reported systemic symptoms during the disease in 88% of cases (48% before rash onset and 59% after) [10]. In a Belgian sexual health clinic, Hens et al. found other significant characteristic symptoms such as lymphadenopathy, skin lesions and proctitis, that were significantly associated with mpox [15]. Surprisingly, their study found a negative association between reported contact with a confirmed or suspected mpox index case and mpox diagnosis. In contrast, our study found a negative association between abdominal symptoms and mpox infection. Rimmer et al. showed that being *cis*-male and self-identifying as gay, MSM, MSMW, having lymphadenopathy at presentation, and having genital or buttock/perianal skin lesions were associated with mpox infection [16]. In a recently published cohort, Moretti et al. found MSM, living with HIV, having multiple sexual partners in the past 3 weeks, and having skin lesions in the anogenital area as predictive factors for mpox diagnosis [17]. Conversely, in our cohort, gastrointestinal symptoms (such as diarrhea, nausea, vomiting, or abdominal pain) were not associated with mpox infection, which was not previously reported in the above literature [6].

This study has several limitations. Due to its retrospective, multi-investigator design, some disease manifestations, epidemiologic data, or baseline characteristics (HIV serostatus) may have been underreported. However, the incubation period was not systematically recorded and may be longer than previously described. Because this study was monocentric, the sample size is small; however, the data found in the literature support our main findings.

In conclusion, although cutaneous manifestations are hallmarks of mpox, they may also be seen with chickenpox, measles, COVID-19, syphilis, HIV, or HSV primary infections. More definitive clinical signs of mpox infection are needed. In our series, MSM and systemic symptoms (fever, chills, and malaise) were significantly associated with the risk of mpox infection. In addition, gastrointestinal symptoms such as diarrhea, nausea, vomiting, or abdominal pain were not associated with mpox infection. We did not find significant differences in our study that would indicate that the presence of an HIV diagnosis might be associated with a higher rate of mpox infection. However, other research has shown an increased risk of progression to more severe disease in individuals with low CD4 cell counts.

Conflict of interest

None.

References

[1] Thornhill JP, Antinori A, Orkin CM. Monkeypox virus infection across 16 countries – April–June 2022. Reply N Engl J Med 2022;387:e69.
[2] Ghazanfar A. Epidemiology, clinical features, diagnosis, and management of Monkeypox virus: a clinical review article. Cureus 2022;14:e28598.

[3] Angelo KM, Smith T, Camprubí-Ferrer D, et al. Epidemiological and clinical characteristics of patients with Monkeypox in the GeoSentinel Network: a cross-sectional study. Lancet Infect Dis 2023;23:196–206.
[4] Suárez Rodríguez B, Guzmán Herrador BR, Díaz Franco A, et al. Epidemiologic features, and control measures during Monkeypox outbreak, Spain, June 2022. Emerg Infect Dis 2022;28:1847–51.
[5] Patauner F, Gallo R, Durante-Mangoni E. Monkeypox infection: An update for the practising physician. Eur J Intern Med 2022;104:1–6.
[6] Altindis M, Puca E, Shapo L. Diagnosis of Monkeypox virus – an overview. Travel Med Infect Dis 2022;50:102459.
[7] Núñez I, Ceballos-Liceaga SE, de la Torre A, et al. Predictors of laboratory-confirmed mpox in people with a pox-like illness. Clin Microbiol Infect 2023:1567–72.
[8] Pascom ARP, Souza IN, Krummenauer A, et al. Epidemiological and clinical characteristics of Monkeypox cases in Brazil in 2022: a cross-sectional study. Epidemiol Serv Saude 2022;31:e2022851.
[9] Payne AB, Ray LC, Kugeler KJ, et al. Incidence of Monkeypox among unvaccinated persons compared with persons receiving ≥1 JYNNEOS vaccine dose — 32 U.S. Jurisdictions. July 31– September 3. 2022. Morb Mortal Wkly Rep 2022;71:1278–82.
[10] Tarin-Vicente EJ, Alemany A, Agudo-Dios M, et al. Clinical presentation, and virological assessment of confirmed human Monkeypox virus cases in Spain: a prospective observational cohort study. Lancet 2022;400:661–9.
[11] Candela C, Raccagni AR, Bruzzesi E, et al. Human Monkeypox experience in a Tertiary Level Hospital in Milan, Italy, between May and October 2022: epidemiological features and clinical characteristics. Viruses 2023;15:667.
[12] Hussain A, Kaler J, Lau G, et al. Clinical conundrums: differentiating Monkeypox from similarly presenting infections. Cureus 2022;14:e29929.
[13] Cholli PA, Miller MJ, Paromita P, et al. Characteristics of patients hospitalized with mpox during the 2022 U.S. outbreak. Presented at: Conference on Retroviruses and Opportunistic Infections 2023; 2023. Seattle, WA. Available at: https://www.croiconference.org/wp-content/uploads/sites/2/posters/2023/CROI_Poster_-_Mpox_in_Hospitalized_Patien_(1)-133199180923744122.pdf.
[14] Long B, Liang SY, Carius BM, et al. Mimics of Monkeypox: considerations for the emergency medicine clinicians. Am J Emerg Med 2023;65:172–8.
[15] Hens M, Brosius I, Berens-Riha N, et al. Characteristics of confirmed mpox cases among clinical suspects: a prospective single-centre study in Belgium during 2022 outbreak. New Microbes New Infect 2023;52:101093.
[16] Rimmer S, Barnacle J, Gibani MM, et al. The clinical presentation of Monkeypox: a retrospective case-control study of patients with possible or probable Monkeypox in a West London cohort. Int J Infect Dis 2023;126:48–53.
[17] Moretti M, Heymans B, Yin N, et al. Diagnostic approach to Monkeypox outbreak, a case-control study. Int J STD & AIDS 2023;34:338–45.