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Original article

EPIDEMIOLOGICAL, CLINICAL AND VIROLOGICAL CHARACTERISTICS OF PATIENTS WITH MONKEYPOX. A RETROSPECTIVE STUDY

PATRICIA A. FERNÁNDEZ PARDAL[1], LUCILA MARCHETTA[1], MARÍA GRACIA FUNES GHIGI[1], MARÍA BELÉN BOUZAS[2], LILIA MAMMANA[3], MARÍA JAVIERA PERELLÓ[3], JOSÉ LUIS FRANCOS[4], IGNACIO BRAGA[4], DANIELA MASINI[4], PABLO A. SAÚL[5], VIVIANA LEIRO[1]

[1]Unidad de Dermatología, [2]División Análisis Clínicos, [3]Unidad de Virología, [4]Departamento de Urgencias, [5]Unidad de Inmunocomprometidos, Sala 3 ID Terapia Intensiva, Hospital F. J. Muñiz, Buenos Aires, Argentina

Postal address Patricia Fernández Pardal, Hospital F. J. Muñiz, Uspallata 2272, 1282 Buenos Aires, Argentina
E-mail: patriciafernandezpardal@yahoo.com.ar
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Abstract

Introduction: The outbreak of monkeypox occurred in 2022 and led to a fast spread of the disease worldwide. The goal of this study is to describe the epidemiological, clinical, virological and evolving characteristics of the disorder.

Methods: We conducted a retrospective, observational and analytical study between July and October, 2022, in a Dermatology Unit.

Results: 124 subjects were included. Mean age was 31.5 years, 123 (99.2%) were men and 75 (60.5%) were HIV positive. The main transmission route was sexual and the incubation period was 7 days. The onset of the rash were the genitalia and perianal region in 74.2% of cases, and median time elapsed until the last scab fell off was 16 days. All patients developed a vesicular rash and 86.3% of them had systemic symptoms. Disease was moderate in 68.5% of patients and complications occurred most often when systemic symptoms and/or disseminated skin disease were present. Proctitis was the most frequent complication (59.4%) and its greater incidence was seen in the population with HIV. No significant difference was observed in real-time PCR cycle threshold values with regards to type of sample or duration of disease. Survival rate was 99.2% and other concomitant sexually transmitted infections were detected in 33.8% of patients.

Discussion: It is important to suspect the disease in subjects with high-risk sexual practices and a consistent clinical presentation. Swab samples of lesions as well as of scabs have proven useful for the diagnosis.

Key words: monkeypox, HIV, virosis, skin, rash

Resumen

Características epidemiológicas, clínicas y virológicas de pacientes con viruela símica. Estudio retrospectivo

Introducción: El brote de viruela símica 2022 se extendió rápidamente por todo el mundo. El objetivo del presente trabajo es describir las características epidemiológicas, clínicas, evolutivas y virológicas.

Métodos: Estudio retrospectivo, observacional y analítico entre julio-octubre del 2022 en pacientes atendidos en una Unidad de Dermatología.

Resultados: Se incluyeron 124 individuos. La mediana de edad fue de 31.5 años, siendo 123 (99.2%) hombres y 70 (60.5%) HIV positivos. La vía principal de contagio fue la transmisión sexual y el período de incubación de 7 días. Las lesiones se iniciaron en la región genital y perianal en el 74.2% de los casos y el tiempo hasta la caída de la última costra presentó una mediana de 16 días. Todos desarrollaron exantema vesiculoso, el 86.3% de los individuos presentó síntomas sistémicos. La enfermedad fue moderada en el 68.5% de los pacientes y las complicaciones se observaron con mayor frecuencia en aquellos con síntomas sistémicos y/o enfermedad

diseminada. Proctitis fue la complicación más destacada (59.4%) y su mayor incidencia se observó en la población con HIV. No hubo diferencias significativas en los valores de Ct de la qPCR al evaluar tipo de muestra procesada o tiempo de evolución de la enfermedad. La sobrevida fue del 99.2% y en el 33.8% de los pacientes se detectaron otras infecciones concomitantes de transmisión sexual.

Discusión: Se debe sospechar la enfermedad en individuos con cuadro compatible y prácticas sexuales de riesgo. Las muestras de hisopado de lesiones y de costra resultaron útiles para el diagnóstico.

Palabras clave: viruela símica, HIV, virosis, piel, exantema

KEY POINTS

- The outbreak of monkeypox occurred in 2022, lesions were mainly located in the genitalia and perianal region, while prodromal symptoms were either mild or absent.
- In our study, sexual transmission was the main route of contagion. Almost all patients were young men, homosexual, and engaged in high-risk sexual practices. In 86.3% of 124 patients, systemic symptoms were present, and in 64.5% they occurred before the appearance of skin lesions. Most patients had regional lymphadenopathies and a moderate form of the disease. Complications were seen in 55.6% of cases, and proctitis was the most frequent. The qPCR Ct was similar in samples of vesicles, pustules and scabs, regardless of duration of the disease.

Monkeypox (mpox) was first described in 1958 in Denmark in laboratory monkeys brought from Singapore, and the first case in humans was reported in 1970 in the Democratic Republic of Congo. Since then, epidemic outbreaks have occurred, especially in African countries, and since 2017, other countries have also reported cases. On July 23, 2022, the World Health Organization (WHO) declared a public health emergency due to a new outbreak originated in May in Great Britain that spread quickly to the rest of the world. In November 2022, the WHO renamed the disease as mpox[1,2].

The mpox virus (MPXV) belongs to the Poxviridae family (double-stranded DNA virus), Chordopoxvirinae subfamily and Orthopoxvirus genus. There are two clades in Africa: one in Central Africa and one in Western Africa, with different epidemiological characteristics. The clade of Central Africa is prevalent in the Democratic Republic of Congo and other countries; it is clinically associated with a more severe disease and mortality may reach 11%. The clade of Western Africa is detected in Nigeria, Ivory Coast and Sierra Leone; it exhibits less human to human transmission and less clinical severity, with a mortality rate of up to 6%. A third variant appears to be responsible for the current outbreak; it is linked to the second variant, but is less virulent[2,3].

The virus spreads from person to person through direct contact with the lesions in the skin, mucosae, body fluids, fomites and respiratory secretions, as well as via the placenta. Following the infection, the incubation period lasts between 5 and 21 days. Prodromal symptoms are fever, headache, asthenia and lymphadenopathy, followed by a rash that progresses through the stages of macules, papules, vesicles, pustules and scabs. The disease usually lasts 2 to 4 weeks[2].

Historically, the clinical manifestation of mpox was a rash affecting multiple body regions. In the current outbreak, lesions were mainly located in the genitalia and perianal region, while prodromal symptoms were either mild or absent[2,4-6].

The goal of this study is to describe the epidemiological, clinical and virological characteristics observed in the group of patients included. Among our specific goals, we sought to compare the incubation period in patients with confirmed and probable epidemiological link, analyze the relation between the type of sexual contact and the site of initial lesions, evaluate potential factors associated with complications and the severity of the disease, and to analyze the relation of real-time PCR cycle threshold (qPCR Ct) with sample type and the time elapsed since the onset of the rash.

Materials and methods

Study design and participants

We performed a retrospective, observational and analytical study in patients seen at the Dermatology Unit of a public Infectious Disease Hospital from the Government of Buenos Aires city. Outpatients were evaluated at the Sexually Transmitted Diseases (STDs) Clinic or the Dermatology Urgency Room, while inpatients were seen in the hospitalization room, due to consultations requested by other Departments. Patients included were assessed during the study period, from July 1st to October 31st, 2022.

The study was approved by the Ethics Committee of the hospital. Data were collected and analyzed anonymously and were not associated to patients' identity. Patient consent was obtained for publication of images.

Procedures

Patients were evaluated by 4 dermatologists. Subjects of any sex and age were included, with a confirmed diagnosis of mpox by viral detection with real-time PCR (qPCR) in swab samples of lesions and/or scabs.

Data were obtained from the medical records and the detailed clinical data were entered into a spreadsheet. Outpatients were initially evaluated and followed with a weekly telephone call; at the end of the isolation period they were re-evaluated or before, if they presented intense pain, complications or at the request of the patients.

Samples were obtained from at least two different sites by swabbing vesicles or pustules or by scabs collected in sterile vials.

When more than one sample was obtained from the same patient, the sample with lower Ct value was selected for analysis.

Real time PCR for MPVX

Molecular diagnosis of MPXV was performed at the National Reference Institute for Infectious Diseases *INEI-ANLIS Dr. Carlos Malbrán* between May and August of 2022. Afterwards it was decentralized and the Virology Unit at our Hospital centralized the molecular diagnosis from the public health system of Buenos Aires city. The Ct values were only evaluated in the samples studied at our Hospital.

Extraction of nucleic acids was performed with automated equipment (MagnaBio plus Virus DNA/RNA purification kit III, Bioer), and the swabs were re-suspended in 600 µl of sterile saline solution; 300 µl were used for the extraction and a 300 µl aliquot was stored. Scabs were treated with tissue lysis buffer (DS BIO Quick Tissue/Culture cells Genomic DNA extraction kit, Dongsheng Biotech), and 300 µl were used for extraction.

The qPCR assay recommended by PAHO was employed which allows the detection of all MPXV strains form the G2R_G gene[7,8], and the detection of the RNase P gene as sample's cell control[9]. All swab samples with Ct values ≥34, and those with discordant results were re-analyzed from the nucleic acid extraction step on. In the case of scab samples with Ct values ≥34, the qPCR reaction was repeated before reporting the final result.

All patients were offered work-up studies to rule out other STDs (syphilis, HIV and hepatitis B and C).

Variables

Variables assessed are described in Tables 1 and 2.

Sexual orientation and gender identity: sexual orientation was classified as heterosexual, homosexual and bisexual, and gender identity as cis, trans and non-binary[10].

Vaccines: the smallpox vaccine was administered in our country until 1978, and individuals born until 1977 received at least one dose. The vaccine against mpox was not available in our country during the study period.

High-risk sexual practices: these comprised: lack of barrier methods during genital, anal or oral sexual relations during the past month, a history of STD during the past year, or the practice of chemsex.

Epidemiological link: it was considered confirmed when any of the following had a confirmed diagnosis of the disease: a sexual partner, a non-sexual contact living with the patient, or a non-sexual contact not living with the patient. It was considered probable when there was no confirmed epidemiological link, but the patient had engaged in sexual intercourse during the previous 21 days, in an anatomical site

Table 1 | Demographic and epidemiological features

	Participants (n = 124)
Age, in years	31.5 (28-38)
Biological Sex N (%)	
Male	123 (99.2)
Female	1 (0.8)
Gender identity N (%)	
CIS man	122 (98.4)
CIS woman	1 (0.8)
TRANS woman	1 (0.8)
Nonbinary	0 (0.0)
Unknown	0 (0.0)
Sexual orientation N (%)	
Homosexual	107 (86.3)
Heterosexual	5 (4.0)
Bisexual	5 (4.0)
Unknown	5 (4.0)
HIV N (%)	75 (60.5)
CD4 T lymphocytes ≥ 350 cells/ul	50/75 (66.7)
CD4 T lymphocytes < 350 cells/ul	10/75 (13.3)
Unknown	15/75 (20.0)
Antiretroviral therapy	64/75 (85.3)
PREP consumption N (%)	6 (4.8)
High-risk sexual practices N (%)	102 (82.2)
No use of barrier method in the last month N (%)	97/102 (95)
STD in past 12 months N (%)	29/102 (28.4)
Chemsex N (%)	24 /102 (23.5)
Epidemiological link N (%)	
*Confirmed epidemiological link	32 (25.8)
Sexual contact	28/32 (87.5)
Sexual partner residing in Argentina	27/28 (96.4)
Sexual partner residing in another country	1/28 (3.6)
Non-sexual partner cohabitant	2/32 (6.2)
Non-sexual contact outside the home environment	2/32 (6.2)
*Probable epidemiological link	62 (50.0)
Resident in Argentina	49/62 (79.0)
Resident in another country	15/62 (24.2)
*Without epidemiological link	26 (21.0)
*Unknown	4 (3.2)
Referred sexual intercourse N (%)	
Genital sex	81 (65.3)
Oral sex	61 (49.2)
Anal-receptive sex	60 (48.4)
Incubation period, in days	7 (5-11)
Smallpox vaccine in childhood N (%)	15 (12.1)
Mpox vaccine N (%)	0 (0.0)

STD: sexually transmitted disease

Data are expressed as median (IQR) or n (%)

Table 2 | Summary of clinical characteristics of individuals with monkeypox

	Participants (n = 124)
Inicial clinical manifestation N (%)	
Systemic symptoms	69 (55.6)
Rash	52 (41.9)
Unknown	3 (2.4)
Time elapsed of the disease until the first consultation, in days	5 (4-8)
Clinical features N (%)	
*Systemic symptoms	107 (86.3)
fever	102/107 (95.3)
myalgia-asthenia-arthralgia	79/107 (73.8)
headache	66/107 (61.7)
sore thoat	44/107 (41.1)
diarrhea and vomiting	4/107 (3.7)
*Lymphadenopathies	112 (90.3)
regional	85/112 (75.9)
generalized (3 or more lymph node groups)	27/112 (24.1)
*Oral lesions	39 (31.4)
erithematous enanthema of the fauces	31/39 (79.5)
erosions/ulcerations	20/39 (51.28)
petechiae	3/39 (7.7)
*Clinical features of the rash	124 (100.0)
vesicopustular rash	124 (100.0)
maculopapular rash	8 (6.5)
Type of skin lesions at the time of the first consultation	
Vesicles and pustules	113 (91.1)
Erosions	74 (59.7)
Scabs	66 (25)
Papules	31 (25)
Ulcers	19 (15.3)
Lesion polymorphism	96 (77.4)
Number of lesions N (%)	
1-2	3 (2.4)
3-20	78 (62.9)
Over 20	41 (33.1)
No data	2 (1.6)
Body areas affected	3 (2-4)
Limbs N (%)	96 (77.4)
* upper limbs	69/96 (71.9)
* lower limbs	65/96 (67.7)
* hands and feet	70/96 (72.3)
Genital region (including pubis) N (%)	91 (73.4)
Trunk (including buttocks) N (%)	86 (69.3)
Head N (%)	76 (61.3)
Perianal region (including anal region) N (%)	54 (43.5)
Site of onset of the rash N (%)	
Genital	58 (46.8)
Anal/perianal	34 (27.4)
Oral	7 (5.6)
Others	28 (22.6)
Complications N (%)	69 (55.6)
Proctitis	41/69 (59.4)
Tonsillitis	14/69 (20.3)
Bacterial superinfection	10/69 (14.5)
Penile edema with phimosis/paraphimosis	8/69 (11.6)
Purpura/necrosis	8/69 (11.6)
Ocular involvement	3/69 (4.3)
Coinfection with another STI N (%)	42 (33.9)
Syphilis	22/42 (52.4)
Hepatitis C	6/42 (14.3)
Genital Warts	6/42 (14.3)
Gonorrhea	5/42 (11.9)
Hepatitis B	4/42 (9.5)
HIV	4/42 (9.5)
Genital herpes	3/42 (7.1)
Chlamydia infection	2/42 (4.8)
Number of patients studied in the Virology Unit N (%)	98 (79.0)
Type of sample obtained N (%)	
Lesion swab	85/98 (86.7)
Scabs	6/98 (6.1)
Lesion swab and scabs	7/98 (7.1)

STDs: sexually transmitted disease
Data are expressed as median (IQR) or n (%)

coinciding with the site of the initial lesions. When none of the previous criteria were present, the epidemiological link was considered to be absent.

Incubation period: interval between contact with the confirmed or suspicious case and the beginning of symptoms.

Initial symptoms: they were categorized as systemic and cutaneous, and when both symptoms appeared concomitantly, they were included in the first group.

Time elapsed until scabs fall-off: interval between the appearance of the cutaneous and mucosal lesions and fall-off of the last scab.

Body areas affected: they were divided into trunk (including the gluteal region), limbs (upper and lower limbs, palms and soles), genital region (including the pubis), perianal region (including the anal region) and cephalic pole (including the mouth). The disease was considered disseminated when 3 or more areas were affected.

Treatment with opioid pain relievers or corticosteroids: due to pain and inflammation caused by mpox.

Disease severity: it was categorized as mild (less than 20 lesions, without complications or disseminated disease, not requiring treatment with systemic corticosteroids or opioid painkillers), moderate (more than 20 lesions or with complications not requiring treatment with systemic corticosteroids or opioid painkillers) and severe (at least one condition present: hospitalization -except for social reasons-, death due to mpox-related causes, complications requiring treatment with systemic corticosteroids and/or opioid pain relievers).

Time elapsed from skin involvement until virological testing: interval between the first sign of skin involvement and the moment in which the sample was obtained.

Statistical analysis

Quantitative variables were reported as mean and standard deviation (SD) or median and inter-quartile range (IQR), according to their distribution (Shapiro-Wilk test). Categorical variables were described as absolute and relative frequencies. To compare quantitative variables, we used the t-test o Mann-Whitney-Wilcoxon test, according to their distribution. For comparison of categorical variables, the Chi square or Fisher's test were used. When p values were < 0.05 they were considered statistically significant. All statistical analyses were performed with R® software, version 4.2.2, and its RStudio® interface, version 2022.07.1.

Results

A total of 126 patients with mpox were evaluated during the study period; 124 were included and 2 were excluded because of missing data.

Demographic and epidemiological characteristics

Patients' demographic and epidemiological characteristics are detailed in Table 1. Median age was 31.5 years (IQR: 28-38), 123 (99.2%) were men, of whom 107 (86.3%) were homosexual. High- risk sexual practices were recorded in 102 patients (82.3%), and the most frequent one was not using a barrier method in 97 (95%). Seventy-five patients were HIV positive (60.5%) and only 10 (13.3%) had a CD4 T lymphocyte count (CD4TL) of less than 350/mm^3.

Fifteen patients (12.1%) had received a smallpox vaccine during childhood. No difference in disseminated disease was found between patients of this group and non-vaccinated patients [13 (86.7%) vs. 74 (67.9%), $p = 0.23$].

Among the 124 patients, 32 (25.6%) had a confirmed epidemiological link (87.5% referred a sexual contact with the source), 62 (50%) had a probable epidemiological link, and in 26 (20.9%) no link was found. In 4 cases (3.2%), this information was not available.

Median duration of the global incubation period was 7 days (IQR: 5-11), and no difference was found between patients with a confirmed versus probable epidemiological link [median (IQR) 7 (4.0-9.5) vs. 7 (6.5-12.5), $p = 0.14$].

Infection features

Mpox infection features are described in Table 2. All patients exhibited skin involvement and 107 (86.3%) also had systemic symptoms, which were present since the beginning of the disease in 55.6% of cases (prodromal symptoms). The most frequent systemic symptom was fever (80.3%) and 112 patients (90.3%) had lymphadenopathy, which was generally regional (75.9%).

All patients had vesiculopustular rash (Fig. 1). Lesions began as papules, evolved to vesicles and then to pustules, many of them had a central umbilication and were surrounded by an erythematous halo. Subsequently, the lesions became unroofed, leaving an erosion or ulceration and finally were covered by scabs. Vesicles and pustules were the most frequently found lesions on initial consultation (91.1%). Ninety-six patients (77.4%) presented with polymorphic skin lesions, i.e., appearance of more than one type of elementary lesion simultaneously.

The lesions first appeared in the genital and perianal regions in 74.2% of patients. Initial lesions in the genital region were seen more frequently in patients who reported having genital intercourse compared to those who didn't [47 (60%) vs. 0 (0%), $p = 0.00007$]. Likewise, lesions that appeared initially in the perianal region were seen most often in patients who reported having receptive anal intercourse vs. patients who didn't [28 (48.3%) vs. 3 (11.1%), $p = 0.0002$]. In contrast, mouth lesions were not more frequent in patients who had engaged in oral sex ($p = 0.4221$) (Table 3).

During the whole period of disease, 65.3% of patients had less than 20 lesions. The median number of affected body areas was 3 (IQR: 2-4): the limbs (77.4%) and genital area (73.4%) were the most affected regions. Most of cases (70.1%) were classified as disseminated skin disease, affecting at least 3 body areas. Oral involvement was present in 39 patients (31.5%); erythematous enanthema of the fauces (79.5%), erosions (51.3%) and petechiae (7.7%) were observed. Among those 39 patients, 14 had tonsillitis as a complication.

The last scab fell off after a median of 16 days (IQR: 13-18). In addition to the vesiculopustular rash, a small number of patients (6.5%) exhibited a concomitant maculopapular (morbilliform) rash involving the trunk.

Complications

Half of the patients (55.6%) had complications (Table 2, Fig. 2); among them, proctitis was the most common (59.4%) and in 68.2% of these patients, initial lesions appeared in the anal/perianal region (Table 3).

As to the overall frequency of complications, a significant difference was seen in patients with disseminated disease vs. those with localized disease [56 (64.4%) vs. 13 (36.1%), $p = 0.007$]. Also, complications were greater in patients who

Figure 1 | Rash features of mpox: erythematous papules (A), pustules with central umbilication (B and C), erythematous halo (D), scabs (E) and lesion polymorphism (F)

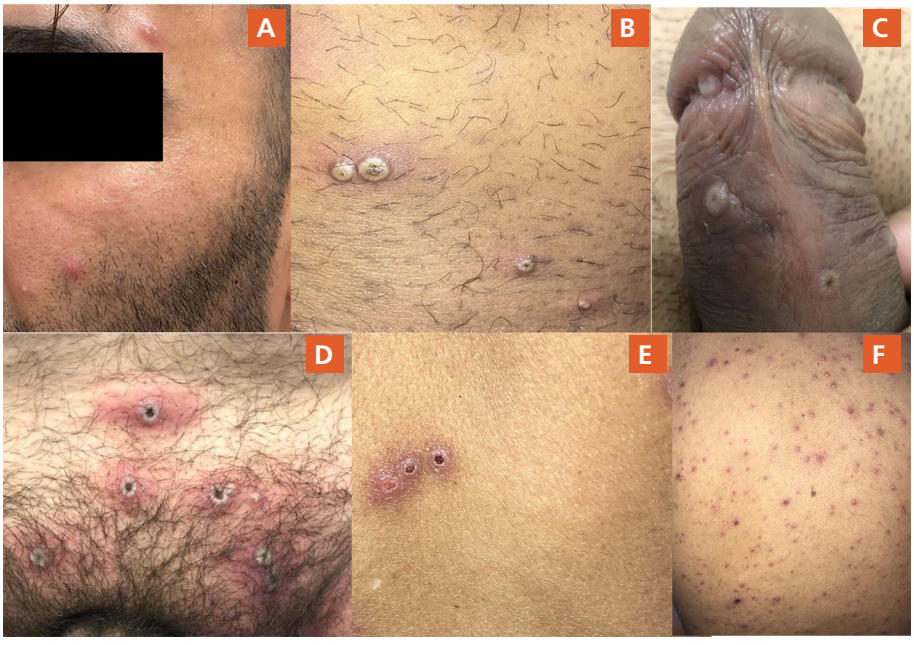


Figure 2 | Complications in individuals with mpox. Perianal lesions with proctitis (A), penile edema causing phimosis (B), purpuric plaque (C), ulcers with necrotic scabs (D), ulcers surrounded by pustules with an erythematous halo (E), and tonsillitis (F)

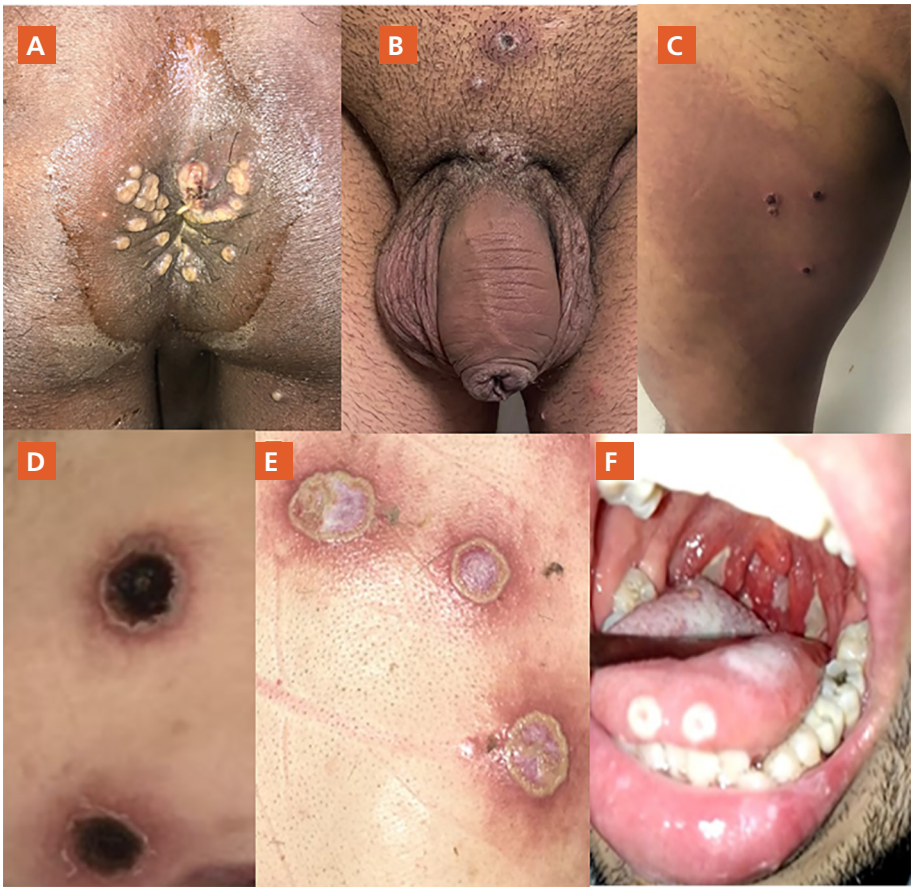


Table 3 | Site of onset of the rash according the referred sexual intercourse

	Referred sexual intercourse		
Site of onset of the rash	**Genital**	**Anal receptive**	**Oral**
Genital	47 (60.3)	21 (36.2)	30 (51.7)
Perianal / anal	21 (27.0)	28 (48.3)	22 (37.9)
Mouth	2 (2.5)	1 (1.7)	2 (3.5)
Other	8 (10.2)	8 (13.8)	4 (6.9)
Total	78 (100)	58 (100)	58 (100)

presented initially with systemic symptoms vs. those with skin lesions [46 (66.6%) vs. 21 (41.2%), $p = 0.009$]; and the main complication was proctitis [31 (45.6%) vs. 8 (15.7%), $p = 0.002$]. By contrast, in patients with systemic symptoms no difference was seen between those with and without proctitis [38 (95.0%) vs. 68 (84.0%, $p = 0.14$]. Among the HIV population, proctitis was more frequent [33 (44.6%) vs. 8 (17.0%), $p = 0.003$], although they hadn't an overall increased risk of complications [47 (63.5%) vs. 22 (45.8%), $p = 0.08$]. Also, no difference in the overall frequency of complications was found in patients with HIV and less than 350 CD4TL when compared to those with higher

counts [29 (58.0%) vs. 8 (80.0%), $p = 0.29$]. Patients who had been vaccinated against smallpox during childhood had a lower overall frequency of complications than non-vaccinated patients [4 (26.7%) vs. 65 (60.2%) respectively, $p = 0.03$]. However, and probably related to the small sample size, no difference was found when complications were analyzed individually (Fig. 3).

Disease severity

In 21 patients (16.9%) the disease was mild, while it was moderate in 85 (68.5%) and severe in 17 (13.7%); in one patient this information was not available (Table 2). Severity of the disease differed according to the site of initial lesions ($p = 0.00004$) (Fig. 4). In all patients with onset of the rash in the anal/perianal region, the disease was moderate or severe, in 82.3% due to proctitis. In contrast, severity of the disease was not different between patients with or without systemic symptoms ($p = 0.16$), between those who started the disease with systemic symptoms vs. with rash ($p = 0.44$), between patients with and without HIV ($p = 0.82$), nor between patients with HIV and CD4TL higher or lower than 350/mm^3 ($p = 0.13$). All patients vaccinated against smallpox during childhood had moderate disease.

Virological diagnosis of MPXV

The diagnosis of MPXV was made with a swab of a lesion in 102 cases (82.3%), with scab samples in 6 cases (4.8%), and in 16 cases (12.9%) using both types of samples. A qPCR Ct analysis was performed in the samples of the 98 patients assessed at the Virology Unit (Table 2).

A median of 2 samples (IQR: 2-2) was analyzed for each patient. No difference was found in qPCR Ct between the samples of swabs vs. those of scabs [median (IQR) 18.8 (17.4-20.1) vs. 17.2 (12.75-26.9), $p = 0.26$], nor between samples from patients with evolution time of skin lesions of up to 5 days vs. more than 5 days [median (IQR) 18.9 (17.4-20.4) vs. 18.5 (17.2-20.1), $p = 0.35$] (Fig. 5).

Clinical course and treatment

Eight patients (6.4%) were hospitalized to provide pain management and treatment of complications, and in two cases for contact isola-

Figure 3 | Factors associated with the development of complications

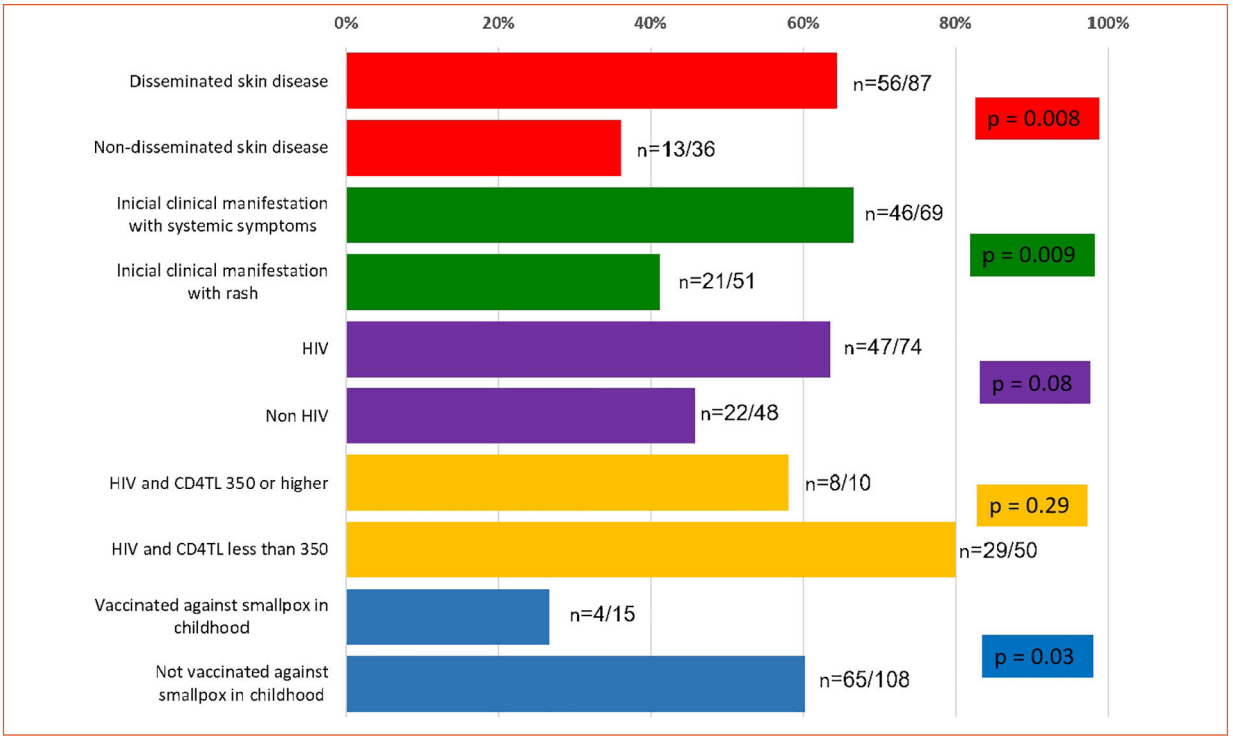


Figure 4 | Disease severity according to the site of onset of the rash

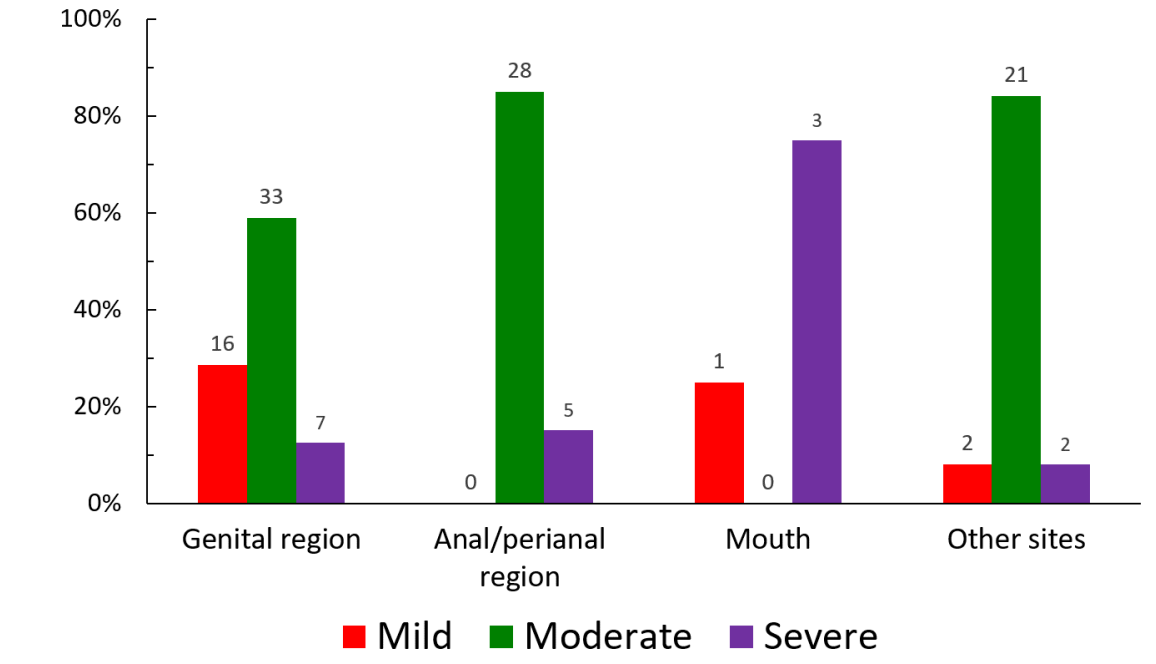
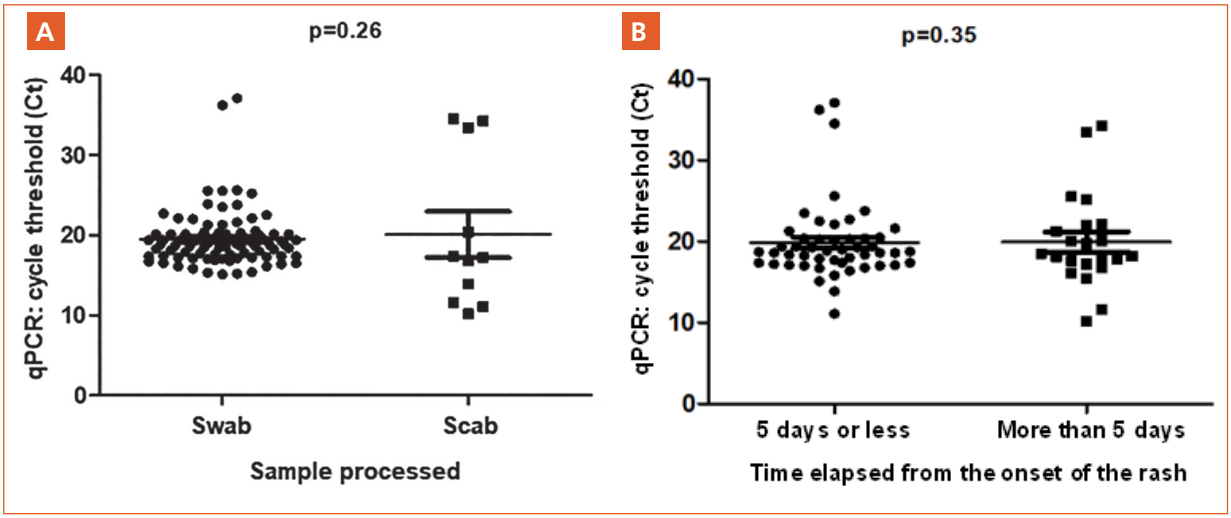


Figure 5 | Cycle threshold (Ct) according to the type of sample processed (A) and the time elapsed from de onset of the rash (B). On the figures, each sample is represented by a point, the median by the long horizontal line, and the first and third quartiles by short horizontal lines



tion. In our series, 18 patients (14.5%) required treatment with systemic corticosteroids and/or opioid painkillers to reduce inflammation and pain. Two cases (1.6%) with HIV (CD4TL < 350/mm^3) had severe disease with extensive skin necrosis, and required admission to the intensive care unit. Both patients were treated with tecovirimat at a dose of 600 mg BID, orally or by nasogastric tube; one during 4 days until his death due to ventilator-associated pneumonia[11], and the other patient during 9 days with good clinical response.

Almost all patients recovered (99.2%). Concomitant STDs were detected in 42 patients (33.8%), syphilis being the most frequent.

Discussion

Since the beginning of the mpox outbreak in 2022, 87 113 cases have been reported worldwide; affected countries are 111 and a 130 deaths were reported by the WHO. The highest number of cases was reported in the region of the Americas, and a per-country analysis shows that 84.4% of cases are concentrated in the U.S., Brazil, Spain, France, Colombia, México, Peru, the United Kingdom, Germany and Canada. Among affected patients, 96.2% were male, with a median age of 34 years[12].

In Argentina, since epidemiological week 21, 2022, until week 16, 2023, confirmed cases were 1129, with 2 deaths. The highest number of cases was reported between weeks 31 and 51, 2022. A 95% of the diagnoses was concentrated in the large urban conglomerates, i.e., Buenos Aires City, the Province of Buenos Aires and Córdoba. In Buenos Aires City, up to week 19, 2023, the total number of confirmed cases was 713, of which 215 have been studied at our institution[12].

In our study we have included 124 patients evaluated at the Dermatology Department. Age, biological sex, sexual identity and sexual orientation agree with the published data, with marked predominance of young men, cis and homosexual.

The following 4 findings of this study support the premise of sexual transmission as main route of contagion: 1) most patients (82%) referred high-risk sexual practices, in agreement with the literature[13-15]; 2) 87.5% of patients with confirmed epidemiological link had engaged in sexual contact with the source; 3) initial lesions in the genital and perianal regions were associated with a history of sexual genital and/or anal receptive intercourse respectively, and 4) in 74.2% the onset of the rash was in the genital and perianal regions. Among these patients it is essential to rule out other STDs; in our series they were present in 33.8% of them.

The overall incubation period was 7 days, coinciding with observations of other authors[2,4,13]. No difference in incubation period was seen in patients with vs. those without a confirmed epidemiological link.

Systemic symptoms were frequent (86.3%) and they were present since the beginning of the disease in more than half of cases as prodromal symptoms; fever was seen most often, as described by other authors[2,4,13,16,17].

Regional lymphadenopathies were observed in the majority of cases and were generalized in 24%; this finding was not cited frequently in the literature.

All our patients exhibited skin involvement with a vesiculopustular rash and a median of 3 regions involved. Although this was similar to the findings published by Tarin-Vicente et al[4], both studies classified body regions differently. Most of our cases (70.2%) were categorized as disseminated disease, which differs from what has been described for this outbreak, with lesions that tend to be located in the site of inoculation. As previously reported[4,13,18], we found that the 2 most affected regions were the limbs and genital area, although in our series the limbs were involved more often. This may be explained by the fact that in our study the hands and feet were included in the limbs region, while other authors did not group both areas. Macular exanthema was observed with similar frequency (6%) to that of previous reports[4,17].

The mouth was affected in 31% of patients, a higher rate (7-25%) than that of other publications, and consisted in erythematous enanthema of the fauces, erosions, ulcerations and petechiae[4,16-18].

In accordance with previous publications, proctitis was the most frequent complication (33%)[2,4]. We found a greater risk of complications among patients whose initial symptoms were systemic and/or who presented with disseminated lesions.

To classify severity we considered the number of lesions, areas involved, complications, requirement of opioid pain relievers or systemic corticosteroids for pain management, hospitalization or progression with death; this differed from other studies that only considered the number of lesions for that purpose[4]. This classification would allow a better selection of patients requiring closer monitoring and/or antiviral treatment. Regarding severity of the clinical presentation, we found no difference between patients with and without HIV, which coincides with previous reports. Among patients

with HIV, we found no difference between those with CD4TL titers higher or lower than 350/mm^3. However, 2 patients with HIV (and less than 100 CD4TL) had severe disease associated with extensive skin necrosis. Oriol, Mitjà et al[19], described this clinical presentation in a subgroup of patients with a CD4TL count of less than 200/mm^3, associated with a 15% mortality.

The Ct value indicates the number of cycles required for amplification and detection of the viral genetic material in a certain sample, and is inversely proportional to the amount of virus present in that sample. In our study, median Ct value was 18, similar in swab and scab samples ($p = 0.26$). Although the number of the latter was small, it allows to infer that scabs are useful samples, despite their processing is more complex. Since Ct did not differ in samples from patients with skin affected for less or more than 5 days ($p = 0.35$), samples seem to be adequate for diagnosis and also a possible source of contagion.

During the 2022 outbreak, worldwide mortality was 0.1%, related to encephalitis and in immunosuppressed hosts. In Argentina, the rate is similar and, of the two deaths reported, one was a patient with HIV who developed the severe form of mpox and is included in this series[2,11].

A literature review showed that during the current outbreak, about half of the patients required treatment for pain relief[2]. In our series the percentage is lower, since we only considered opioid pain relievers and systemic corticosteroids. In our country, specific treatment for mpox is not available, however, two patients received tecovirimat as compassionate use.

Few cases of re-infection have been reported until present[20-22]. One patient of our series presented reinfection after the study period. We believe that studies assessing the duration of immunity and long-term impact on re-infections, as well as the protective role of the smallpox vaccine administered during childhood are necessary. Importantly, all countries should have access to specific treatment for mpox.

Among the study limitations, its retrospective nature could have led to omission of certain data, and the fact that only patients seen by the Dermatology Department were included. However, a substantial number of patients were assessed in detail and all had a confirmed virological diagnosis.

In conclusion, this study allows to better understand the clinical manifestations of mpox in our country. It is important to suspect the disease in subjects with high-risk sexual practices and a consistent clinical presentation, with or without systemic symptoms. Even if there is no history of travel or contact with foreigners, the diagnosis should be suspected. Because of the sexual transmission of the disease, concomitant STDs should be ruled out. Swab samples of lesions as well as of scabs have proven useful for the diagnosis.

Additionally, the study contributes to expand the information and adopt prevention measures regarding this disease and to establish priorities for vaccination.

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References

1. Nuzzo JB, Borio LL, Gostin LO. The WHO Declaration of Monkeypox as a Global Public Health Emergency. *JAMA* 2022; 328: 615-17.
2. Mitjà O, Ogoina D, Titanji BK, et al. Monkeypox. *Lancet* 2023; 401: 60-74.
3. Biscayart C, Ferrer MF, Otreras A, et al. Viruela símica: zoonosis emergente con impacto global. *ASEI* 2022; 109: 1-47.
4. Tarín-Vicente EJ, Alemany A, Agud-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.
5. Palich R, Burrel S, Monsel G, et al. Viral loads in clinical samples of men with monkeypox virus infection: a French case series. Lancet Infect Dis 2023; 23: 74-80.
6. Kozlov M. How does monkeypox spread? What scientists know. *Nature* 2022; 608: 655-6.

7. Li Y, Zhao H, Wilkins K, et al. Real-time PCR assays for the specific detection of monkeypox virus West African and Congo Basin strain DNA. *J Virol Methods* 2010; 169: 223-7.
8. Organización Mundial de la Salud. Pruebas de laboratorio para el virus de la viruela del mono. Ginebra: OMS; 2022. In https://www.who.int/publications/i/item/WHO-MPX-laboratory-2022; accessed July 2023.
9. Centers for Disease Control & Prevention. Test Procedure: Monkeypox virus Generic Real- Time PCR Test. In https://www.cdc.gov/poxvirus/monkeypox/pdf/pcr-diagnostic-protocol-508.pdf; accessed July 2023.
10. Guía para la atención respetuosa de la diversidad de género de las personas. Sociedad Argentina de Dermatología. 2022. In https://sad.org.ar/wp-content/uploads/2022/12/Guia-para-una-atencion-respetuosa-de-la-diversidad-de-genero-de-las-personas-adaptada-a-la-consulta-dermatologica.docx.pdf ; accessed July 2023.
11. Lamberto Y, Domínguez C, Montaldo F, Saúl P, Chediack V, Cunto E. A case of monkeypox in intensive care in Argentina. *Medicina (B Aires)* 2023; 83: 324-8.
12. Boletín Epidemiológico Nacional semana epidemiológica 16, número 650, año 2023. Ministerio de Salud Argentina. In https://bancos.salud.gob.ar/sites/default/files/2023-05/BEN_650_SE_16_tendencias_1.pdf ; accesed July 2023.
13. Villaverde MC, Alfano MS, et al. Viruela símica humana: características epidemiológicas y clínicas de una serie de casos. *Medicina (B Aires)* 2023; 2023; 83: 569-78.
14. Duarte A, Iannantuono MV, Perez M, et al. Viruela símica y faringitis exudativa en Argentina. *Medicina (B Aires)* 2022; 82: 770-3.
15. Sánchez Doncell J, Sotelo CA, Braga I, et al. Viruela símica: Vigilancia epidemiológica en la Unidad de Monitoreo Ambulatorio Muñiz, Buenos Aires. *Medicina (B Aires)* 2022; 82: 816-21.
16. Girometti N, Byrne R, Bracchi M, et al. Demographic and clinical characteristics of confirmed human monkeypox virus cases in individuals attending a sexual health centre in London, UK: an observational analysis. *Lancet Infect Dis* 2022; 22: 1321-8.
17. Català A, Clavo-Escribano P, Riera-Monroig J, et al. Monkeypox outbreak in Spain: clinical and epidemiological findings in a prospective cross-sectional study of 185 cases. *Br J Dermatol* 2022; 187: 765-72.
18. 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: 679-91.
19. Mitjà O, Alemany A, Marks M, et al. Mpox in people with advanced HIV infection: a global case series. *Lancet* 2023;401: 939-49.
20. Álvarez-López P, Borras-Bermejo B, López Pérez L, et al. Suspected case of monkeypox reinfection versus reactivation in a immunocompetent patient, Barcelona, 2022. *Int J STD AIDS* 2023; 34: 649-52.
21. Raccagni AR, Canetti D, Mileto D, et al. Two individuals with potential monkeypox virus reinfection. *Lancet Infect Dis* 2023; 23: 522-4.
22. Musumeci S, Najjar I, Boffi El Amari E, et al. A case of mpox reinfection. *Clin Infect Dis* 2023; 77: 135-7.