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Original Article

Sexually Transmitted Infections

Prospective observational study on scar sequelae after MPOX infection: an analysis of 40 patients

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Abstract

Background Monkeypox (MPOX) caused a public health emergency of international concern (PHEIC) outbreak between 2022 and 2023, with a recent rise in cases that prompted the World Health Organization (WHO) to declare the disease a PHEIC once again. There is little information on its long-term scarring sequelae.

Objectives The objective of this study was to assess the risk and characteristics of scarring in patients with MPOX in a tertiary hospital.

Methods This is a prospective cohort study including patients diagnosed using polymerase chain reaction (PCR) tests. Clinical data were collected and followed up at 12–15 months to assess scarring and its impact on quality of life.

Results Of the 40 patients, 19 (47.5%) developed scars, which were more common in those with initial cutaneous manifestations. Scars significantly affected the quality of life, especially in the genital and mucosal areas. The limited sample and loss to follow-up may affect the validity of the results.

Conclusion Scarring is a frequent and disfiguring sequela of MPOX, particularly in patients with early skin symptoms. Prevention and close follow-up are crucial in mitigating these complications.

Introduction

MPOX, formerly known as monkeypox, is a viral infection caused by its namesake poxvirus that caused a public health emergency of international concern (PHEIC) between 2022 and 2023, with cases still being reported daily in 2024. On August 14, 2024, the World Health Organization (WHO) declared the disease a PHEIC for the second time due to a worrying increase in cases in non-endemic areas of Africa and in Europe.[1–3] This is particularly interesting to dermatologists, who are generally involved in the diagnosis, given the variety of mucocutaneous manifestations of the disease that usually constitute the most distinctive clinical presentation.

Clinical presentation occurs after a prodromal period of 2–4 days, including cutaneous and systemic manifestations that may or may not be concurrent. Patients develop whitish papules

on the skin on an erythematous base, also called pseudopustules, which evolve in 1–2 weeks to central umbilication with subsequent centrifugally progressing necrosis. The most frequent systemic manifestations include fever, malaise, lymphadenopathy, headache, and arthromyalgia.[4,5]

Cicatricial sequelae, including hypertrophic, keloid, atrophic scars, or pigmentary changes, have been reported anecdotally, both in the current outbreak[6–8] and in endemic cases in Africa.[9,10] However, the risk of scarring after lesions is unknown, and little objective information has been published due to the lack of long-term follow-up.[11–13] Some authors have estimated this risk at 13%–20%.[14,15] This is the first study, to the best of our knowledge, to examine the risk of scarring in these patients. This work aims to analyze the factors associated with the presence of scarring and the characteristics of scarring in patients with MPOX in the sexually transmitted infection (STI) unit of a tertiary hospital.

Materials and methods

Data collection and analysis

This study included cases with a confirmed diagnosis of MPOX in a tertiary referral hospital in Valencia, Spain. Confirmation was performed by polymerase chain reaction (PCR) testing of skin, oropharyngeal, urethral, and/or anal samples using the VIASURE Monkeypox Virus reverse transcription (RT)-PCR kit. Epidemiological, clinical, and microbiological data were collected from electronic medical records, patient history, and physical examinations at the initial and follow-up visits. At 12–15 months after the initial diagnosis, a follow-up consultation was performed to collect information on the presence of scarring and, if applicable, the clinical characteristics of the lesions. Patients without a follow-up consultation were excluded from the study. Patients with scars were asked to evaluate the impact on their quality of life using a scale from 0 to 10, where 0 represented no impact, and 7 to 10 had a substantial impact.

Ethical aspects

The research was conducted in compliance with the ethical principles of the Declaration of Helsinki, maintaining integrity, transparency, and respect for the human dignity and privacy of all patients. Informed consent was obtained for the use of clinical images.

Statistical analysis

A preliminary analysis of the numerical variables was performed with the Shapiro–Wilk test, with the student's *t*-test chosen for variables with normal distribution and the Mann–Whitney *U* test for those without normal distribution. Pearson's chi-squared and Fisher's exact tests were used for categorical variables to determine the differences between patients with and without scars. A *P*-value of less than 0.05 was considered significant. The analyses were performed with SPSS version 28 (IBM, Armonk, NY, USA).

Results

Seventy-two individuals with a confirmed monkeypox (MPOX) diagnosis by PCR tests were included in the analysis. Thirty-two patients were excluded due to the lack of at least one follow-up visit between 12 and 15 months after initial diagnosis. Of the 40 patients selected, 19 (47.5%) developed scarring as a complication, whereas 21 (52.5%) were free of this sequela. Table 1 summarizes the clinical and demographic data of the patients stratified according to the presence or absence of scarring.

The mean age of the patients was 42.5 years among patients without scars and 36.2 years among those with scars, showing statistically significant differences between the two groups. All 19 patients with scars were male, whereas 20 of the 21 (95%) patients without scars were female. Six patients in the group without scars had HIV infection (28.6%), whereas four in the scarred group were seropositive (21.1%). Regarding the smallpox vaccination status of the patients, 8 (38.1%) were vaccinated among those without scarring, and 2 (10.5%) were vaccinated among those who developed this complication with no statistically significant differences ($P = 0.1$).

Systemic symptoms accompanying the cutaneous manifestations were observed in 14 patients (67%) in the group without scars and 14 (74%) in the group with scars, with no statistically significant differences between groups. Details on the manifestations of these systemic symptoms can be found in Table 1. There were statistically significant differences between groups regarding the initial presentation of the infection: systemic or cutaneous. Twelve patients (57%) without scars initially showed systemic symptoms, whereas 2 (10%) had cutaneous manifestations initially. In patients with scars, 5 (26%) initially experienced systemic symptoms, and 9 (47%) had skin lesions as first signs.

All 19 patients had between 1 and 300 scars. Ten (52.6%) had 1 scar lesion, whereas one patient developed 300 scars. The mean number of scars per patient was 19.7 and 4.1 if the one with 300 was excluded. The median was one lesion.

Table S1 shows the distribution of active lesions and the distribution of scars in patients with these lesions. The areas presenting lesions most frequently during the active phase of the disease were the upper limbs (28) and lower limbs (21), genital area (21), trunk (18), and perianal area (13). The most frequently scarred area was the genital area (9). The areas with active lesions where the highest percentage of patients developed scarring were the nose (50%) and genital area (43%). Five (26.3%) patients had mucosal scarring. Two were on the genital mucosa, two on the perianal mucosa, and one on the tongue.

Bacterial superinfection was present in 3 (15.7%) of the 19 patients with scarring. Severe pain in the acute phase of the disease occurred in 4 (21%), whereas perilesional edema was documented in 8 (42.1%) of these patients. No such complications were recorded in patients without scarring.

Table 1 Epidemiological and clinical characteristics of patients with and without scars and associated statistical significance

Patient information	Patients without scars	Patients with scars	Test	Statistical significance
Age (range)	42.5 (22–69)	36.2 (23–49)	Student's *t*-test	0.042
Male	20 (95)	19 (100)	Chi-square	1
Female	1 (5)	0 (0)		
Sexual orientation				
Homosexual	14 (66.7)	17 (89.5)	Chi-square	0.202
Bisexual	5 (23.8)	1 (5.2)		
Heterosexual	2 (9.5)	1 (5.2)		
Vaccination	8 (38.1)	2 (10.5)	Chi-square	0.100
Non-vaccination	13 (61.9)	17 (89.5)		
HIV positive	6 (28.6)	4 (21.1)	Chi-square	0.855
HIV negative	15 (71.4)	15 (78.9)		
Nationality				
Spain	16 (76.2)	11 (57.9)	Chi-square	0.176
South America	5 (23.8)	4 (21.1)		
Europe	0 (0)	3 (15.8)		
Asia	0 (0)	1 (5.3)		
Total number of lesions (range)	8.5 (1–22)	33.4 (1–458) 9.8 (1–28)*	Mann–Whitney U test	0.654
Systemic symptoms				
Yes	14 (66.7)	14 (74)	Chi-square	0.648
No	7 (33.3)	5 (26)		
Fever				
Yes	8 (38)	12 (63)	Chi-square	0.205
No	13 (62)	7 (37)		
Arthromyalgia				
Yes	8 (38)	8 (42)	Chi-square	1
No	13 (62)	11 (58)		
Asthenia				
Yes	9 (43)	11 (58)	Chi-square	0.527
No	12 (57)	8 (42)		
Headache				
Yes	6 (29)	6 (32)	Chi-square	1
No	15 (71)	13 (68)		
Adenopathies				
Yes	12 (57)	13 (68)	Chi-square	0.683
No	9 (43)	6 (32)		
Pharyngitis				
Yes	6 (29)	4 (21)	Chi-square	0.855
No	15 (71)	15 (79)		
Urethritis				
Yes	4 (19)	2 (11)	Chi-square	0.756
No	17 (81)	17 (89)		
Proctitis				
Yes	5 (24)	3 (16)	Chi-square	0.812
No	16 (76)	16 (84)		
Clinical debut:				
Systemic	12 (57)	5 (26)	Chi-square	Chi-square: 0.022
Cutaneous	2 (10)	9 (47)		Fischer's test: 0.018
Cutaneous only	7 (33)	5 (26)		

*Excluding the subject with 458 lesions.

Thirteen of the 19 patients (68.4%) had lesions with a depressed appearance. In terms of color, 8 (42%) had lesions with hypopigmentation, many of them pearly white in appearance; 6 (31.5%) had some degree of associated erythema, 3 (15.8%) had associated hyperpigmentation, and 5 (26.3%) had skin-colored scars. Fourteen (73.7%) of the 19 patients had oval or round-looking scars, three (15.8%) of them had stellate-looking lesions, two on the nose and one on the penis, and 3 (15.8%) had fusiform or linear lesions. Table S2 summarizes the clinical appearance of the scars.

The range in scar diameter was 2–31 mm for all lesions. The mean minimum diameter of the smallest scar among all patients was 4.1 mm, and the maximum diameter was 10.6 mm. Eight of the 10 patients with scars in hairy areas (beard and genital area most frequently) had scarring alopecia as a sequela of their lesions.

The quality of life impairment of patients with scars showed a mean of 5.2 and a median of 5 out of 10 on the visual numerical scale. The mode was 3 of 10 points. Seven patients (36.8%) had a score with substantial impairment of quality of life. Three had scars in the nasal and perioral areas, and four in the genital area.

Discussion

Scarring in almost half of our cohort's patients contrasts with previous estimates that placed the risk as low as 20%. This may be because it is a complication that can often be overlooked or because many of the studies performed did not include long-term follow-up.

The age difference between groups may be due to younger patients' tendency to develop more unaesthetic or hypertrophic scars.[16] Younger patients may be a population group to monitor more closely during the course of the disease and in whom scar treatments such as fractional CO_2 laser could even be considered early.[17]

Vaccination against smallpox has been shown to provide cross-protection against MPOX even in the long term.[18] Some studies show a lower clinical severity of disease among smallpox-vaccinated patients who become infected with MPOX.[19] In our cohort, there is a lower proportion of vaccinated patients among those who developed scarring, although we did not find statistically significant differences. Vaccines developed against MPOX have been shown to reduce the risk of infection,[20,21] as well as the severity of the disease.[22] It seems reasonable to assume that vaccination will reduce the risk of scarring because it is associated with a less severe clinical picture and probably less extensive and destructive lesions, although further studies are needed to support this hypothesis.

HIV infection has been associated with much more profound and necrotic ulcers with a very high associated mortality rate.[23–25] Some authors have even proposed considering ulceronecrotic MPOX as a diagnostic criterion for acquired immunodeficiency syndrome (AIDS) due to its characteristic clinical presentation.[26] Large lesions with greater associated necrosis are likely to have a higher risk of scarring as a sequela.[27] Nevertheless, in our patients, we have not found HIV to be a risk factor for this complication. This is probably because HIV-positive patients in our cohort had an undetectable or very close to undetectable viral load, and the disease did not manifest itself in them as it does in the majority of immunocompromised patients in whom ulceronecrotic MPOX is described. One of the HIV-positive patients had atypical MPOX with many lesions of widespread distribution, affecting the entire integument. When the lesions healed, they left biopsy-confirmed anetoderma lesions. We noted the presence of highly necrotic lesions with large, deep ulcers leading to extensive scarring in the genital area in a patient with iatrogenic immunosuppression who was being treated with infliximab for Crohn's disease (Figure 1, further images depicting the case are found in Appendix S1).

During the current outbreak in 2024, two distinct routes of transmission have been described in patients with MPOX. The respiratory route is the first and most frequent in endemic cases in Africa. It is associated with higher viremia and generalized skin lesions. The second route of infection, which was the predominant one during the PHEIC, was the cutaneous route. In these cases, the skin lesions appear first and they are more localized in contact areas with the infected patient. The perioral, perianal, and genital areas have been frequently affected. Locoregional inflammatory lymphadenopathies are very often associated, and viremia has been delayed in time and at lower titers. This may explain the lower infectivity of these patients through the respiratory tract and the lower number of generalized lesions.[28,29] In patients with occupational disease transmission, more inflammatory and scarring lesions have been observed at the inoculation site.[30,31] In a 2003 outbreak in the USA involving 47 patients, Reynolds et al.[32] described the differences depending on how the infection was transmitted. They noted that patients infected through more invasive exposure (bitten or scratched by infected animals) had more pronounced systemic symptoms and risk of hospitalization. They also found that these patients had a shorter incubation period and often had an earlier onset of skin symptoms than fever. These similarities to the typical picture during the current outbreak may be due to a superimposable pathogenesis.

In our patients, the presence or absence of systemic manifestations does not seem to confer a greater or lesser risk of scarring. On the other hand, the clinical onset of MPOX by cutaneous manifestations seems to be associated with a higher

Figure 1 Extensive and multiple pearly white cicatricial plaques on the dorsum of the penis

risk of subsequent scarring. This may be due to more extensive initial lesions at the site of inoculation in the subgroup of patients infected by cutaneous inoculation. Lesions secondary to viremia, which are more disseminated but generally smaller, less necrotic, and less inflammatory, usually heal without scarring.

The number of scars is usually small, but in many cases, it is limited to a single lesion. Usually, it is in relation to the larger, more inflammatory lesion(s) during the active phase. An exception was one HIV-positive patient with numerous lesions in the active phase and 300 anetoderma lesions as sequelae.

The distribution of lesions in our patients was similar to that reported in the literature, with lesions predominating in the genital and perianal area associated with several secondary lesions that were not very numerous and widespread, with greater involvement of the trunk and limbs.[33] On the other hand, scars were predominantly distributed in the genital area as well as the nasal and perioral areas. The perioral and nasal areas were high-risk locations as few patients had lesions in the active phase, but those who did often experienced scarring. These findings are consistent with isolated reports describing intensely inflammatory lesions in these regions with significant scarring sequelae.[8,27,34] The trunk and limbs appear to be low-risk areas as lesions are very often seen to heal without scarring. The mucous membranes presented scarring lesions, including one case of lingual depapillation and two perianal polypoid lesions. Early vaccination as post-exposure prophylaxis could be particularly important in patients with lesions in at-risk areas.

Bacterial superinfection and edema affected a similar percentage of patients to those described previously.[35] They have been associated with longer disease recovery time. Patients in whom they were present had nasal, perioral, and genital lesions, increasing the degree of inflammation and possibly contributing to a larger scar after disease resolution (Figure 2; further images depicting these cases are found in Appendix S1). Active surveillance of these patients, especially those with lesions in high-risk areas, may be key to early treatment of superinfection and reduction of the aesthetic sequelae. Some authors have proposed the use of topical or intralesional cidofovir in these areas when there is a significant inflammatory component.[36,37]

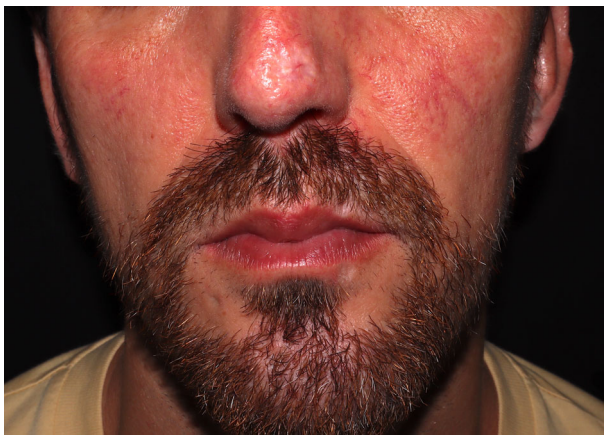

Figure 2 Facial scar lesions distributed in the nasal and perioral areas

The depressed appearance of the lesions, similar to smallpox scars, was frequent and has already been reported.[38,39] Hypopigmentation was the most common alteration in the color of the scars, followed by erythema and skin-colored scars. Hyperpigmentation was less frequent than in African patients;[40] it was more common in dark phototypes and hypopigmented lesions in light phototypes. Erythema appears to be an intermediate stage that disappears with time.[41] The size of scars and lesions varied, with larger lesions causing larger scars.

MPOX scars have received little attention during the current PHEIC but can be highly disfiguring. This study shows that some lesions significantly impact quality of life, leading to problems with self-esteem, anxiety, and depression. A total of 36.8% of patients had quality of life impairment scores of 7–10, with large scars in the central facial or genital areas. Therefore, patients with nasal, perioral, or genital lesions with a significant associated inflammatory component deserve close follow-up and even adjuvant psychological treatment.

Limitations

The most important limitation of this work is the sample size, which limits the external validity of the findings. A significant percentage of patients have not been included due to the need for a follow-up visit after 12–15 months.

Conclusions

We present a prospective study with the greatest long-term follow-up, to the best of our knowledge, in MPOX patients, focusing on the risk of scarring after infection. Scarring as a sequela of MPOX is a more frequent complication than previously estimated that can be highly disfiguring and have a major impact on patients' quality of life and psychological wellbeing. Young patients with risk factors for this infection are a group at high risk of significant sequelae, where primary prevention through vaccination is of particular importance. Central facial and genital lesions, especially if they are the initial manifestation of the disease, require close follow-up and early treatment of complications to avoid these sequelae.

Patient consent

Patients provided informed consent to participate in the study. All procedures, examinations, and data handling were performed considering patients' privacy and following ethical standards for medical research.

Data availability statement

The data supporting this study's findings are available from the corresponding author upon reasonable request.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Deep facial ulcers in the perioral and nasal area with large perilesional inflammation after the crust has been removed.

Figure S2. Scars of depressed and atrophic appearance on the nasal tip.

Figure S3. (A) Inflammatory ulcer with a fibrinous background on the dorsum of the tongue. (B) After healing of the lesion, lingual depapillation can be seen in the area of the stellate scar.

Figure S4. (A) Multiple perianal ulcers with radial distribution and endoanal involvement. (B) Nacreous perianal scarring in the areas of previous ulceration and polypoid lesion at the anal margin.

Figure S5. (A) Clustered ulcers of linear arrangement at the root of the penis. (B) Linear spindle-shaped scar as sequelae of the lesions.

Figure S6. (A) Pseudopustule with central necrosis in the proximal foreskin. (B) The resulting scar has a linear and hypopigmented appearance.

Figure S7. (A) Oval scar with a varioliform appearance in the dorsum of the penis. (B) Smaller fusiform scar.

Figure S8. Multiple hyperpigmented papules with a parchment-like appearance with histology compatible with anetoderma.

Table S1. Number of active lesions and scars in patients according to location.

Table S2. Characteristics of the scars in the patients in our sample.