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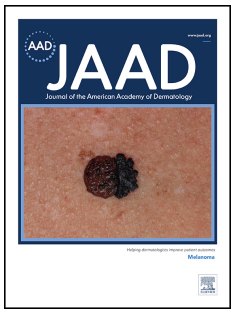

A dermatologic assessment of 101 mpox (monkeypox) cases from 13 countries during the 2022 outbreak: skin lesion morphology, clinical course, and scarring

Sonya Prasad, MSc, Cristina Galvan Casas, MD, Alexis G. Strahan, MSN, L. Claire Fuller, MD, Klint Peebles, MD, Andrea Carugno, MD, Kieron S. Leslie, FRCP, DTM&H, Joanna L. Harp, MD, Teodora Pumnea, MD, Devon E. McMahon, MD, Misha Rosenbach, MD, Janet E. Lubov, BSN, Geoffrey Chen, BA, Lindy P. Fox, MD, Allen McMillen, MS, Henry W. Lim, MD, Alexander J. Stratigos, MD, Terrence A. Cronin, MD, Mark D. Kaufmann, MD, George J. Hruza, MD, MBA, Lars French, MD, Esther E. Freeman, MD, PhD

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Sonya Prasad MSc[1,2], Cristina Galvan Casas MD,[3,4] Alexis G. Strahan MSN[1,5],L. Claire Fuller MD[6,7], Klint Peebles MD[8], Andrea Carugno MD[9,10], Kieron S. Leslie FRCP, DTM&H[11], Joanna L. Harp MD[12], Teodora Pumnea MD[13], Devon E. McMahon MD[14], Misha Rosenbach MD[14,15], Janet E. Lubov BSN[1,16], Geoffrey Chen BA[17], Lindy P. Fox MD[11], Allen McMillen MS[18], Henry W. Lim MD[19], Alexander J. Stratigos MD[20], Terrence A Cronin, MD[21], Mark D. Kaufmann MD[22], George J. Hruza MD, MBA [23], Lars French MD[13,24], Esther E. Freeman MD, PhD[1,17]

[1]Department of Dermatology, Massachusetts General Hospital, Boston, MA; [2]Icahn School of Medicine, The Mount Sinai Hospital, New York, NY; [3]University Hospital Mostoles, Madrid, Spain; [4] Fundación Lluita contra les infeccions, Hospital Germans Trias i Puyol, Badalona, Barcelona, Spain; [5]Mercer University School of Medicine, Savannah, GA; [6]Chelsea and Westminster NHS Foundation Trust, London, UK; [7]International Foundation for Dermatology, London, UK; [8]Department of Dermatology, Kaiser Permanente Mid-Atlantic Permanente Medical Group, Rockville, MD; [9]Dermatology Unit, ASST Papa Giovanni XXIII Hospital, Bergamo, Italy; [10]Ph.D. Program in Molecular and Translational Medicine (DIMET), University of Milan-Bicocca, Milan, Italy; [11]Department of Dermatology, University of California San Francisco, San Francisco, CA; [12] Department of Dermatology, Weill Cornell Medicine, New York, NY;[13] Department of Dermatology, University Hospital, Munich University of Ludwig Maximilian, Munich, Germany; [14]Department of Dermatology, University of Pennsylvania, Philadelphia, PA; [15]Department of Internal Medicine, University of Pennsylvania, Philadelphia, PA; [16] Wright State University Boonshoft School of Medicine, Dayton, OH; [17]Medical Practice Evaluation Foundation, Massachusetts General Hospital, Boston, MA; [18] American Academy of Dermatology, Rosemont, IL; [19] Department of Dermatology, Henry Ford Health, Detroit, MI; [20] First Department of Dermatology-Venereology, National and Kapodistrian University of Athens, Andreas Sygros Hospital, Athens, Greece;[21] University of Miami Department of Dermatology and Cutaneous Surgery, Melbourne, FL; [22]Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, NY; [23]Department of Dermatology, Saint Louis University, Saint Louis, MO; [24]Dr. Philip Frost, Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL.

*Twitter handle: @DrEstherFreeman

Corresponding author:

Esther Freeman, MD PhD
55 Fruit St, Bartlett Hall 6R
Boston, Massachusetts 02114
Email: efreeman@mgh.harvard.edu

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Conflicts of Interest*:* Esther Freeman, Klint Peebles, Misha Rosenbach, Terrence Cronin and George Hruza are members of the AAD Ad Hoc Task Force to Create Monkeypox Content. Esther Freeman is the Principal Investigator of the AAD/ILDS Dermatology Registry for COVID-19, Monkeypox, and Emerging Infections, and serves on the WHO Living Monkeypox Atlas and the WHO Monkeypox Guidelines Committee. Kieron Leslie is a dermatology consultant for the ACTG Study: Tecovirimat For Human Monkeypox Virus (STOMP) and is the Lead Dermatologist on the WHO Living Monkeypox Atlas. Alexander Stratigos is the immediate past President of the EADV. Mark Kaufmann is the President of the

AAD. Terrence Cronin is President-elect of the AAD. Lars French is the President of the ILDS. Henry W. Lim and Claire Fuller are Board members of the ILDS. Lindy Fox is a Board member of the AAD.

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1

Abstract

Background:
In the 2022 monkeypox (mpox) outbreak, 79,000 global cases have been reported. Yet, limited dermatologic data have been published regarding lesion morphology and progression.

Objective:
To characterize skin lesion morphology, symptomatology, and outcomes of mpox infection over time.

Methods:
The AAD/ILDS Dermatology COVID-19, Monkeypox, and Emerging Infections Registry captured de-identified patient cases of mpox entered by healthcare professionals.

Results
From August 4-November 13 2022, 101 cases from 13 countries were entered, primarily by dermatologists (92%). Thirty-nine percent had fewer than five lesions. In 54% of cases skin lesions were the first sign of infection. In the first 1-5 days of infection, papules (36%), vesicles (17%) and pustules (20%) predominated. By days 6-10, pustules (36%) were most common, followed by erosions/ulcers (27%) and crusts/scabs (24%). Crusts/scabs were the predominant morphology after Day 11. Ten cases of morbilliform rash were reported. Scarring occurred in 13% of cases.

Limitations
Registry-reported data cannot address incidence. There is potential reporting bias from the predilection to report cases with greater clinical severity.

Discussion
These findings highlight differences in skin findings compared to historical outbreaks, notably the presence of skin lesions prior to systemic symptoms and low overall lesion-counts. Scarring emerged as a major possible sequela.

Capsule summary

- This international, registry-based study highlights variations in clinical course and morphologic lesion progression during the 2022 monkeypox (mpox) outbreak in contrast to prior outbreaks.
- Early detection and treatment are crucial for minimizing disease burden. Dermatologists play key roles in detection, especially given novel morphology and progression noted during this outbreak.

Introduction:

Monkeypox virus (mpox) is a zoonotic, double-stranded DNA virus of the *Orthopoxvirus* genus. Mpox infection has similar skin manifestations to smallpox, but is less severe, self-limited with lower case-fatality rates (1). Prior to May 2022, mpox was described as a zoonotic and traveler-associated infection, with few cases reported outside endemic countries (2). Over 79,000 cases of mpox infections in 103 non-endemic countries have been reported since May 2022 (3, 4). In July 2022, the World Health Organization declared the ongoing outbreak a "Public Health Emergency of International Concern" (5).

Human-to-human transmission occurs via direct contact with skin lesions, respiratory droplets, and, less commonly, through fomites (6). Mpox viral DNA has been detected in a replication-competent form that may support sexual transmission, though not yet confirmed (7, 8). The incubation period of mpox ranges from 5-24 days (7). Additional evidence of possible pre-symptomatic transmission has also emerged (9, 10).

Classic mpox begins with a prodrome of fever, fatigue, and lymphadenopathy, followed by skin lesions, predominantly on the face (7). Lesions typically progress from umbilicated papule to pustule to crusted scab prior to re-epithelialization and resolution (11). Abscesses and mucocutaneous lesions were rarely reported prior to the current outbreak.

Studies from the 2022 mpox outbreak have reported notable distinctions in transmission dynamics and clinical presentation in nonendemic countries (9, 10). The previously reported prodrome of fever/lymphadenopathy/myalgia has not always followed the expected timeline and may appear simultaneously or after cutaneous symptoms (6, 12, 13). Skin lesions have been noted commonly in the anogenital region, as frequently as 73% (6). Instead of lesions traveling in uniform crops, new lesions developed well into the disease course (12). Novel symptoms during this outbreak included rectal pain, sore throat, penile edema, and high frequency of mucocutaneous lesions (6, 12, 14). In immunosuppressed patients, more severe and atypical, necrotic skin lesions have occurred (15).

Many affected patients in 2022 are living with human immunodeficiency virus (HIV, 41%) and/or had a concomitant sexually transmitted infection (STI, 29%). Nearly all mpox infections (98%) occurred among gay or bisexual men who reported recent sexual activity (95%) (6).

While case reports and clinical studies continue to emerge, few have reported more specifically on the dermatologic features of mpox infection, including morphologic progression and associated symptomatology. Efforts to increase early recognition are important for timely treatment and stigma reduction.

Our objective was to characterize clinical mpox symptoms, timeline, skin lesion morphology over time, affected population, hospitalization, treatment, and outcome of patients reported to the American Academy of Dermatology (AAD) and International League of Dermatological Societies (ILDS) Dermatology COVID-19, Monkeypox, and Emerging Infections Registry.

Methods:

Data Collection

The registry was established in March 2020 to collect information on the cutaneous manifestations of COVID-19 and COVID-19 vaccine reactions, as a collaboration between the American Academy of Dermatology and the International League of Dermatological Societies. The registry was expanded on August 4th, 2022, to become the "AAD/ILDS Dermatology COVID-19, Monkeypox (mpox), and Emerging Infections Registry," the same day that the United States declared mpox to be a public health emergency. The expanded registry accepts cases of mpox and mpox/smallpox vaccine reactions.

Case entry is open to healthcare workers only, including nurses, residents, and other medical providers. All data inputted to the registry via REDCap® online survey platform. De-identified cases are accepted globally, and data entry is not restricted to AAD/ILDS members. The Massachusetts General

Brigham Institutional Review Board exempted this study as not human subject research. All data were analyzed using Stata version 16 (StataCorp, LLC).

Survey Development

The mpox infection module of the registry collects data on patient demographics, exposure to mpox, symptomatology, morphology of cutaneous reaction(s), timing, duration of symptoms, diagnosis, and treatments. "Unknown" was an available option when applicable. The survey questionnaire was developed by a panel of experts in dermatology and infectious disease.

Detailed skin lesion morphology

Skin lesions were classified into papule(s), vesicle(s) or blister(s), pustules, erosion(s), ulcer(s), crust, abscess, or morbilliform rash. Registrants were asked for timing of initial onset of each type of lesion, as well as the time periods over which each type of lesion continued to be present.

Results:

Patient and Reporter Population

101 cases of mpox infection across 13 non-endemic countries were reported to the AAD/ILDS registry between August 4 and November 13, 2022, of which 97% were male with a median age of 35 (IQR 31,44) (**Table 1**). 92% were reported by dermatologists and were submitted by health professionals from Italy (19%), Germany (16%), Spain (16%) and the United States (32%). Most patients reported to the registry were White (62%), followed by Hispanic/Latino (20%) and Black/African American (11%).

Exposure & Diagnosis

Thirty-two respondents (32%) reported a known mpox exposure. Most respondents described their exposure as a sexual contact (26/32, 26% of total). The majority engaged in same sex sexual

behavior (87%) and group sex activity (27%), defined as sexual activity between greater than two people, at a festival, group sex event, or sex party.

The median time from exposure to onset of symptoms among patients for which an exposure was identifiable was 7 days (IQR 7,10). The median time from first symptom (Day 0) to day of diagnosis, was 5 days (IQR 4,9). All but 2 patients had PCR-confirmed diagnoses; one patient was diagnosed on biopsy while the other was based on clinical suspicion.

Clinical Presentation at Sign/Symptom Onset

Over half (54%) the cases submitted to the registry reported skin lesions or rash as the very first sign/symptom of infection, with others reporting fever (16%), general malaise (9%), sore throat (8%), or rectal pain (7%) **(Table 2).** Onset of skin lesions or rash most often occurred in the initial phases of infection. For patients presenting with skin lesions as their first sign/symptom, most (43/61 patients) had exclusively skin lesions. 85% reported skin lesions within the first 3 days of sign/symptom onset.

On the day of skin lesion appearance, 20% had a single lesion, whereas 52% had 2-5 lesions and 20% had 6-20 lesions. Seventy patients developed initial skin lesions either in the genito-inguinal area (44%) or the peri-anal/anal area (26%). Of the remaining cases (n=29), most frequently reported areas included the face (16%), lips (5%) or arms/hands (4%). Two patients in the registry were reported to present *initially* with a generalized, morbilliform rash, nonspecific to one anatomical area.

General Clinical Presentation

All patients developed mucocutaneous lesions, and nearly all patients (98%) had skin manifestations (**Table 2)**. Common systemic symptoms reported throughout the course of illness included fever (64%), lymphadenopathy (52%), fatigue (39%), proctitis (17%), sore throat (21%), headache (19%) and rectal pain (16%). Edema was reported in 25 (25%) of cases, most commonly of the

face (8/23) and the scrotal or penile areas (12/23). Anatomically, symptoms most often progressed throughout the course of infection to involve the genitals, anus/peri-anal area, face, and extremities.

Lesion Morphology

The most common skin lesion morphologies and secondary characteristics reported included papules, vesicles/blisters, pustules, erosions/ulcers and crust/scabs (**Figure 1 & Supplement 1)**. On Day 0, the most common skin morphologies were papules (25%), vesicles (17%) or pustules (20%). On Days 1-5, lesions were papules (36%), vesicles (36%), pustules (39%), or erosions/ ulcers (21%). By Days 6-10, pustules (36%) were most common, followed by erosions/ulcers (27%) and crusts/scab (24%). After Day 11, crust and scabs were predominant. Overall, pustules were the most common morphology (24%).

While morphologic transitions observed herein mirror historical reports overall, on the individual patient level, lesion progression did not always follow this sequence. For instance, some patients experienced multiple morphologies at the same time or skipped from initial morphologies such as a papule to a later stage morphology such as an ulcer, without a vesicle or pustules in between (**Figure 2 & 3**).

Other less frequent morphologies included abscesses (n=4) and morbilliform rash (n=10). Morbilliform rash occurred in the range of Days 0 – 15 (frequently on Days 1-5).

Medical History & Hospitalization

Seven patients had been vaccinated for smallpox/mpox; 4 were known to have received the vaccine prior to mpox exposure/infection and the remaining 3 were vaccinated either after exposure or after infection.

Many cases (38%) had a concurrent sexually transmissible infection at the time of mpox infection including gonorrhea (17%), syphilis (14%) and chlamydia (7%) **(Supplement 2)**. Seven patients (7%) had

herpes simplex virus active infection. 38% of the registry cohort was documented as having a history of HIV. No other causes of immunosuppression were reported.

Twenty-one patients required hospitalization (21%). Patients were hospitalized for skin rash/lesions (n=6), health system isolation protocol (n=5), sore throat/oral lesions (n=4), rectal pain (n=3), sepsis (n=1), malaise (n=1), and other (n=1).

Treatment & ***Resolution***

Resolution of infection was defined as the time at which complete re-epithelialization of the lesion-affected area has occurred. Of the total registry cases, 86 patients were reported to have reached resolution of skin infection at the time of entry. The median time to resolution was 20 days (IQR 14,22). Of those who had resolved infection, 13% (11/86) had visible scarring after resolution, reported between 1-4 months after infection.

A quarter (25%) of the patients reported to the registry received tecovirimat (TPOXX) for mpox infection, all from the U.S **(Supplement 2)**. Other frequently reported treatments included IV or oral antibiotics (9%), topical medications including antiseptics, topical antibiotics, and topical analgesics (11%) and/or oral pain medications (7%). No patients received Cidofovir, Brincidofovir, IV pain medication, or vaccinia globulin.

Discussion:

In this registry-based study, we report clinical symptoms and morphologic evolution of 101 mpox cases across 13 non-endemic countries from the AAD/ILDS Dermatology COVID-19, Monkeypox (mpox), and Emerging Infections Registry. This multinational study highlights the importance of dermatologic assessment in early recognition and treatment of mpox infection as skin or mucocutaneous lesions were the initial clinical sign in the majority of cases. Additionally, low lesion counts and involvement of the

peri-anal or genito-inguinal regions create potential for under recognition or misdiagnosis. A unique feature of this work was case entry by dermatologists (92%), which adds specificity to morphologic reporting. Scarring, a finding in 13% of registry cases, highlights both the need for further investigation on this potential long-term sequela and the continued role of dermatologists in care of affected patients.

Studies conducted during the 2022 outbreak of mpox have highlighted key differences in clinical presentation of skin lesions compared to prior outbreaks and endemic mpox (14, 16). In concert with other studies in the current epidemic, most registry cases presented with initial skin lesions in the genito-inguinal (44%) or peri-anal (26%) region. However, this study's inclusion of the progression of skin lesions provides novel evidence of morphologic changes differing from previously reported lesion progression: in some cases, skin lesions skipped morphologic phases, for example progression from papule to ulcer, and included multiple lesion types at any one point during the illness. Skin lesions also appeared prior to onset of typical prodromic signs and symptoms in 54% of reported cases and, upon initial presentation, 82% had fewer than 20 total lesions. In 20% of cases, a single lesion was the initial presenting skin sign and 72% had fewer than 5 lesions, emphasizing a need for high clinical suspicion in those presenting with isolated lesions who are part of high-risk groups. Total lesion count over the disease course similarly demonstrated relatively low lesion counts, with 77% of reported cases with 20 or fewer lesions. Despite reports of fewer lesions during the illness course as compared to prior studies, the frequency of hospitalization was higher, with 21% of reported cases requiring hospitalization (12, 17).

In patients who reached clinical resolution, a significant proportion (13%) experienced residual scarring in areas of lesion development- an outcome underemphasized in the current literature (18). Scarring has potential implications when considering the stigmatization and discrimination associated with mpox infections and the effects on physical and mental health in this patient population. In

collaboration with the CDC, the AAD has released provider and patient-facing recommendations on caring for skin lesions and how to reduce the risk of scarring (19).

The largest burden of mpox in the 2022 outbreak has been reported in gay, bisexual, and other men who have sex with men, reflected similarly in our registry data (87%) (4, 20). It is important for clinicians treating sexual and gender diverse patients with mpox infections to recognize the potential for compounded stigma and work alongside patients to minimize the risk of scarring. Further investigations are needed to identify methods of reducing scarring in lesions of varying morphology and anatomical location as seen in the current outbreak.

An additional morphology noted in this study that has been only rarely reported in prior studies is morbilliform rash (6, 14). Several possible explanations exist. This may be an immune response to viral infection, a result of virally infected skin, or a combination of both. Morbilliform eruptions are seen in other viral eruptions such as measles or parvovirus, though generally less typical of pox viruses. Less likely would be a morbilliform drug eruption since several patients had not yet been exposed to oral medications at the time of rash development.

This study is limited by the constraints of registry-reported data, which cannot estimate the prevalence or incidence, nor can it ensure accuracy or uniformity of healthcare-provider input. Additionally, as reflected in a higher frequency of hospitalization, there is potential for preferential reporting of more severe or clinically evident mpox cases, especially those with cutaneous manifestations. In terms of lesion characterization, the registry did not capture presence or absence of umbilication. Also, 'pseudopustule' was not included as a possible lesion morphology.

The largest global burden of mpox reported cases in the current outbreak lies in the United States, representing over 1/3rd of cases worldwide (21); this distribution is mirrored in the registry-reported data (32%,U.S.). In the U.S. population, race and ethnicity data indicates that black or African American patients are disproportionally affected (20). Registry-reported cases were primarily in white

patients (62%). Concerted efforts to capture cases in black or African American patients would more accurately reflect the clinical course and associated outcomes during the current outbreak.

These findings reinforce deviations in skin findings in the current mpox outbreak compared to prior mpox outbreaks– notably the presence of skin lesions prior to the onset of systemic illness and the presence of fewer than 20 skin or mucocutaneous lesions overall. Our study adds detail regarding the morphology of skin lesions during the 2022 outbreak, quantifying patients experiencing atypical progression of lesions and/or the involvement of multiple morphologies simultaneously. Case entry was completed primarily by dermatologists, supporting lesion evaluation and reporting. Scarring after mpox infection affects a large proportion of reported cases and warrants further investigation to reduce negative long-term outcomes.

While the current outbreak trends downward, transmission continues. Vaccine coverage remains sub-optimal, especially in racial/ethnic minority populations and in low- and middle-income countries (10). Previously endemic countries in central and west Africa have, at time of writing, no access to Jynneos/Imvanex vaccine. As the virus continues to circulate and we prepare for possible future surges, we must remain vigilant in evaluating patients for subtle and atypical presentations to interrupt mpox virus transmission.

Table 1. Characteristics of cases reported for mpox infection to the AAD/ILDS Registry

Characteristic	Total (N = 101)
Reporter	
Dermatologist	93 (92.1%)
Other Physician	2 (2.0%)
Podiatrist	1 (1.0%)
Other Medical Professional	5 (4.9%)
Patient age, y, median (IQR)	35 (31,44)
Patient sex, male, n (%)	98 (97.0%)
Patient race/ethnicity, n (%)*	
White	63 (62.4%)
Black/African American	11 (10.9%)
Hispanic/Latino	20 (19.8%)
Asian	3 (3.0%)
Other	2 (2.0%)
Missing	3 (3.0%)
Patient Geographic Region	
North America	32 (31.7%)
Europe	60 (59.4%)
Spain	17 (16.8%)
Italy	18 (24.0%)
Germany	17 (16.8%)
Asia	5 (5.0%)
Latin America and the Caribbean	2 (2.0%)
Africa	2 (2.0%)

IQR, Interquartile Range

*Question not asked of all participants

Table 2. Cutaneous and systemic symptoms of mpox infection at symptom onset and total duration of illness

Symptoms	Total (N = 101)
Initial Symptoms (Day 0)	
Skin lesions or rash*	55 (54.5%)
Intra-oral or throat lesions†	1 (1.0%)
Lymphadenopathy	3 (3.0%)
Fever	16 (15.8%)
General malaise (fatigue, chills, myalgia)	9 (8.9%)
Sore throat	8 (7.9%)
Rectal pain	7 (6.9%)
Ocular/Ophthalmic Symptoms	1 (1.0%)
Edema	1 (1.0%)
Number of Lesions at Symptom Onset	
1	20 (19.8%)
2-5	52 (51.5%)
6-20	20 (19.8%)
21-50	5 (5.0%)
Unknown	4 (4.0%)
Anatomical Site of Mucocutaneous Lesions	
Oral cavity	11 (10.9%)
Tonsils	3 (3.0%)
Throat	0 (0%)
Soft palate	1 (1.0%)
Total Number of Lesions – Throughout Duration of Infection	
1	10 (9.9%)
2-5	29 (28.7%)
6-25	38 (37.6%)
26-50	17 (16.8%)
51-100	3 (3.0%)
101+	1 (1.0%)
Edema Location	
Peri-orbital	2 (2.0%)
Face§	8 (7.9%)
Peri-rectal/peri-anal	4 (4.0%)
Scrotal/penile	12 (11.9%)
Extremities	4 (4.0%)
Symptoms During Course of Illness	
Skin lesions or rash	99 (98.0%)
Intra-oral or throat lesions	15 (14.9%)
Fever	65 (64.4%)
Chills	21 (20.8%)
Myalgia	18 (17.8%)
Arthralgia	10 (9.9%)
Fatigue	39 (38.6%)
Sore Throat	21 (20.8%)
Cough	5 (5.0%)
Headache	19 (18.8%)
Lymphadenopathy	52 (51.5%)
Proctitis	17 (16.8%)
Rectal Pain	16 (15.8%)
Penile Edema	5 (5.0%)
Other ¶	8 (7.9%)

*Any location on the body including groin, anal/peri-anal or lips

†Specified as lesions inside mouth or in the throat

§Includes the lips, excludes eyes

Patients also reported to have eye pain, abdominal pain and vomiting, conjunctivitis, penile pain, limb edema

Figure 1. Cutaneous morphologies of skin lesions from patients reported with mpox infection to the AAD/ILDS Registry

*Color intensity indicates frequency of skin morphology at designated time period

Figure 2. Exemplar individual patient skin morphologies over time among select registry cases

*All cases included in *Figure 2* were resolved at time of reporting

Figure 3. Morphology of pseudopustular mpox skin lesions “pseudopustular donuts” (For additional images, see Supplement 1)

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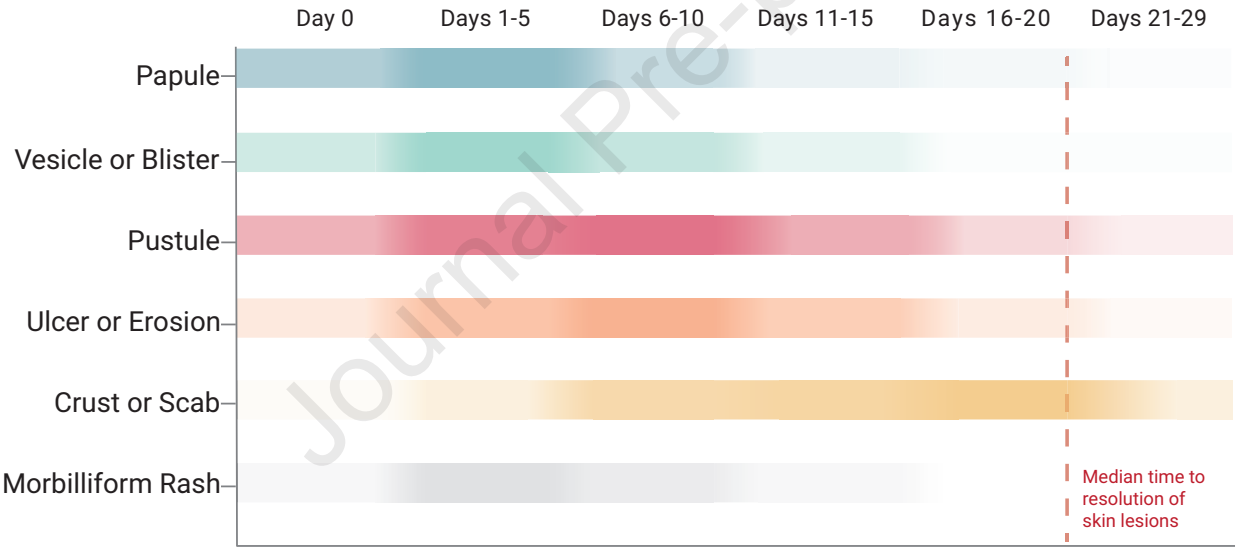

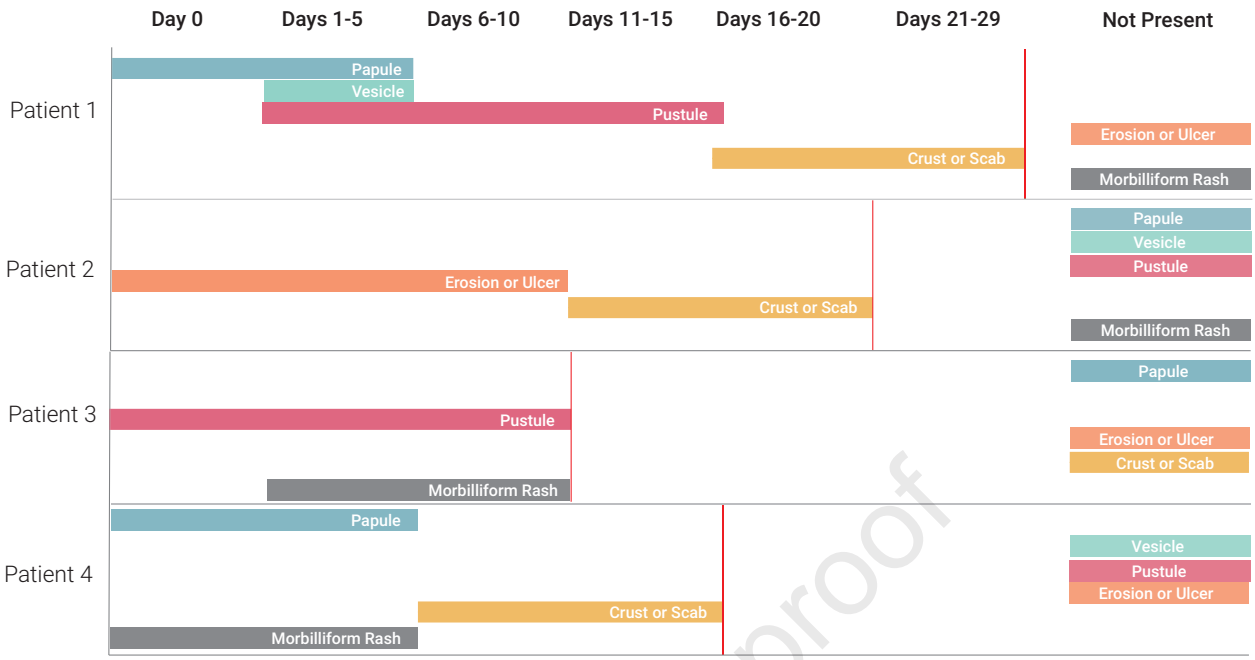

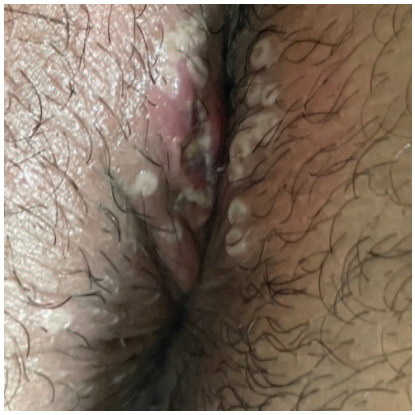

Capsule summary

- This international, registry-based study highlights variations in clinical course and morphologic lesion progression during the 2022 monkeypox (mpox) outbreak in contrast to prior outbreaks.
- Early detection and treatment are crucial for minimizing disease burden. Dermatologists play key roles in detection, especially given novel morphology and progression noted during this outbreak.