FAST TRACK

Clinical features and novel presentations of human monkeypox in a central London centre during the 2022 outbreak: descriptive case series

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ABSTRACT

OBJECTIVE

To characterise the clinical features of monkeypox infection in humans.

DESIGN

Descriptive case series.

SETTING

A regional high consequences infectious disease centre with associated primary and secondary care referrals, and affiliated sexual health centres in south London between May and July 2022.

PARTICIPANTS

197 patients with polymerase chain reaction confirmed monkeypox infection.

RESULTS

The median age of participants was 38 years. All 197 participants were men, and 196 identified as gay, bisexual, or other men who have sex with men. All presented with mucocutaneous lesions, most commonly on the genitals (n=111 participants, 56.3%) or in the perianal area (n=82, 41.6%). 170 (86.3%) participants reported systemic illness. The most common systemic symptoms were fever (n=122, 61.9%), lymphadenopathy (114, 57.9%), and myalgia (n=62, 31.5%). 102/166 (61.5%) developed systemic features before the onset of mucocutaneous manifestations and 64 (38.5%) after (n=4 unknown). 27 (13.7%) presented exclusively with mucocutaneous manifestations without systemic features. 71 (36.0%) reported rectal pain, 33 (16.8%) sore throat, and 31 (15.7%) penile oedema. 27 (13.7%) had oral lesions and 9 (4.6%) had tonsillar signs. 70/195 (35.9%) participants had concomitant HIV infection. 56 (31.5%) of those screened for sexually transmitted infections had a concomitant sexually transmitted infection. Overall, 20 (10.2%) participants were admitted to hospital for the management of symptoms, most commonly rectal pain and penile swelling.

CONCLUSIONS

These findings confirm the ongoing unprecedented community transmission of monkeypox virus among gay, bisexual, and other men who have sex with men seen in the UK and many other non-endemic countries. A variable temporal association was observed between mucocutaneous and systemic features, suggesting a new clinical course to the disease. New clinical presentations of monkeypox infection were identified, including rectal pain and penile oedema. These presentations should be included in public health messaging to aid early diagnosis and reduce onward transmission.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Previous cases of human monkeypox infection in the UK were imported or directly related to imported cases from West Africa, with limited reported human to human transmission

The symptoms included in the current UK Health Security Agency case definitions are based on those documented in previous outbreaks

WHAT THIS STUDY ADDS

Common symptoms were identified that are not included in current public health messaging, including rectal pain and penile oedema

Features suggesting a change from the classic presentation of the disease were observed, including a variable temporal association between mucocutaneous and systemic features and a biphasic appearance of lesions

Data characterising the clinical presentations, progress, and management of these cases is urgently needed to help guide both the management of patients with monkeypox infection and the response to the outbreak

Introduction

On 6 May 2022, the UK High Consequence Infectious Diseases (HCID) network was alerted to an individual with monkeypox who had recently returned from West Africa. Six further infected individuals were identified the following week, without epidemiological linkage to West Africa. As of 12 July, 1735 people had been identified with monkeypox in the UK, most (96%) occurring in gay, bisexual, or other men who have sex with men, and 79% occurring in London.[1 2] People with monkeypox infection have also been reported in several other non-endemic countries in Europe and the Americas, with the highest reported case loads outside of the UK in Spain and Germany.[3]

Monkeypox is due to an orthopoxvirus, which rarely causes disease in humans. Although the exact reservoir of the virus is still unknown, rodents are suspected to play a part in transmission. The virus was first identified in 1958, among primates in captivity for research purposes.[4] Two genetically distinct viral clades are described: Central African (Congo Basin) and West African.[5] The first reports of humans becoming infected were recorded in 1970, when a

UK Health Security Agency case definition of possible and probable monkeypox infection as of 16 July 2022

Possible infection

- A person with a febrile prodrome* compatible with monkeypox infection where there is known prior contact with a confirmed case in the 21 days before symptom onset.
- Or
- A person with an illness where the clinician has a high suspicion of monkeypox (for example, this may include prodrome or atypical presentations with exposure histories deemed high risk by the clinician, or classical rash without risk factors).

Probable infection

- A person with an unexplained rash on any part of their body plus one or more classical symptom or symptoms of monkeypox infection*† since 15 March 2022 and either:
- has an epidemiological link to a confirmed or probable case of monkeypox in the 21 days before symptom onset
- reported a travel history to West or Central Africa in the 21 days before symptom onset
- is a gay or bisexual man or man who has sex with men

*Consists of fever ≥38°C, chills, headache, exhaustion, muscle aches (myalgia), joint pain (arthralgia), backache, and swollen lymph nodes (lymphadenopathy).
†Acute illness with fever (>38.5°C), intense headaches, myalgia, arthralgia, back pain, lymphadenopathy.

smallpox-like illness was investigated in areas of the Democratic Republic of Congo thought to be free of variola.[6 7] Monkeypox is endemic in the Congo Basin and West Africa, where outbreaks involving 23 to 88 people have been described.[8 9] Several animal species are susceptible to the infection, and animal to human transmission through handling and ingesting wild game animals has been identified as the primary route of infection in African outbreaks, followed by human to human transmission through close contact with infected individuals.[10] Spread of respiratory droplets and direct contact with skin lesions and scabs have been described as the predominant routes of transmission between humans, but transmission can also occur via fomites.[11] In 2003, the first monkeypox outbreak in the Western hemisphere was reported in 11 people in the United States who had been in close contact with infected prairie dogs. These animals had been transported alongside a Giant Gambian rat, presumed to be the primary source of the infection.[12] Since 2018, travel associated monkeypox infection has been diagnosed in four people in the UK, with onward transmission to three further people.[13] Sporadic cases of imported infections have also been reported in the US, Singapore, and Israel.[14]

The incubation period of monkeypox is currently understood to be about 12 days (range 5-24 days).[11 12] Classic descriptions of monkeypox infection depict biphasic clinical features, with a prodromal phase characterised by fever, malaise, sweats, lymphadenopathy, and headache, followed by skin eruption 2-4 days later.[11] Skin lesions follow a typical pattern of evolution, starting as macules and progressing into papules, vesicles, and pustules, which subsequently crust over and then desquamate.[13 15] Historically, lesions have appeared simultaneously and progressed sequentially.[16] Lesions have predominantly affected the face (95% of infected people), palms and soles (75%), mucous membranes (70%), and, less commonly, genitals.[5] Most infections are self-limiting and relatively mild, with symptoms lasting 2-4 weeks. Severe manifestations of infection include encephalitis, secondary skin infection, pneumonia, and ocular disease leading to loss of vision. Higher risk populations include neonates, children, and those with immunodeficiency.[17]

Monkeypox is designated as a high consequence infectious disease in the UK.[18] In the 2022 outbreak, the rapid community spread meant that most infected individuals were managed at home after risk assessment.[19] The box shows the current UK Health Security Agency case definition of possible and probable monkeypox infection.[20]

The observed clinical features of monkeypox infection in the 2022 UK outbreak differ from those in historical reports. We describe the characteristics and clinical features of monkeypox infection in people managed through a single south London centre and present a series of novel presentations.

Methods

Setting

We conducted a retrospective observational analysis of people with polymerase chain reaction (PCR) confirmed monkeypox virus, who were tested and managed through a south London HCID centre. The centre is one of five HCID centres in the UK and serves an inner city central and south London population. Swabs for diagnostic sampling were taken from the lesions at affiliated community sexual health and HIV medicine services, on admission to hospital (inpatient ward or emergency department) or on transfer of patients with suspected monkeypox from neighbouring NHS trusts (see supplementary figure 1). Samples were processed at the Rare and Imported Pathogens Laboratory at Porton Down, UK.[21] People with suspected and confirmed monkeypox infection were risk stratified according to disease severity, immune status, and their ability to self-isolate, and managed accordingly. As part of routine clinical care, individuals were clinically assessed before testing. All people with a positive PCR test result for monkeypox virus took part in a telephone consultation to be counselled about their result and to conduct a risk assessment.

Inclusion criteria and data collection

All people tested for monkeypox virus between 13 May and 1 July 2022 were identified through routine tracking of samples sent from the centre's virology laboratory to the Rare and Imported Pathogens Laboratory. Those who tested positive were included for further study.

Clinical data were collected through one of three electronic healthcare systems: Electronic Patient Record iSOFT Clinical Manager 1.6 (iSOFT Group, Falls Church, VA), eNoting Client (an in-house patient records system), and preView (IMS MAXIMS, Milton Keynes,

UK). Data were collected on personal characteristics, signs and symptoms reported at presentation, mucocutaneous manifestations (description, number, characteristics, and locations), risk factors as defined by the UK Health Security Agency (travel, contacts, and sexual history), HIV status, and sexual health screen results. Typical lesions were defined as macules, papules, vesicles, pustules, umbilication, crust, or scab.

Statistical analysis

We calculated means and medians for continuous data, and percentages for nominal data. The Clopper-Pearson exact method was used to calculate confidence intervals for symptom prevalence. Kaplan Meier for length of stay analysis was calculated using Graphpad Prism version 9.3.1. All other analysis was calculated using Microsoft Excel version 16.62.

Patient and public involvement

The research question for this study was formed through discussions with patients. Although there was no further direct patient or public involvement in this paper owing to limited resources, we have asked members of the public to read our manuscript after submission and also plan to disseminate key messages through social media and conferences.

Results

Of 295 people tested for monkeypox virus by PCR between 13 May and 1 July 2022, 197 (66.8%) tested positive. Overall, 155 (78.7%) of the participants presented via affiliated sexual health and HIV medicine services, 24 (12.2%) via an emergency department, and 18 (9.1%) after acute admission to a ward.

Description of cohort

Personal characteristics

All 197 infected individuals were men. The median age was 38 years (interquartile range 32-42 years, range 21-67 years).

Clinical presentations

All 197 participants (100%, 95% confidence interval 97.8% to 100%) presented with mucocutaneous manifestations. These had a range of documented descriptions (see supplementary figure 2) and not all lesions progressed through the traditionally recognised evolution of macule to papule to vesicle to pustule to scab. Lesions were most commonly found on the genitals (n=111, 56.4%, 49.1% to 63.4%) and anus or perianal area (n=82, 41.6%, 34.7% to 48.8%). Genital lesions or perianal lesions, or both, occurred in 174 participants (88.3%, 83.0% to 92.4%) (table 1).

The median number of lesions at presentation was 5 (interquartile range 3-11). Eight (4.1%) participants had more than 100 lesions. A numerical count of lesions was not documented for 29 participants. Twenty two (11.2%, 7.1% to 16.4%) participants presented with a solitary lesion: 12 involved the genitals and seven the perianal area. Twenty seven (13.7%, 9.2% to 19.3%) participants described mucocutaneous manifestations as being pruritic and 27 (13.7%, 9.2% to 19.3%) reported a concomitant widespread maculopapular rash.

Systemic illness was reported by 170 (86.3%) participants. The most commonly described systemic symptoms were fever (n=122, 61.9%, 54.8% to 68.7%), lymphadenopathy (n=114, 57.9%, 50.6% to 64.9%), and myalgia (n=62, 31.5%, 25.1% to 38.5%) (table 2). In contrast with existing case reports suggesting that prodromal systemic symptoms precede skin lesions, we observed a variable temporal association between mucocutaneous and systemic features. In 102/166 (61.5%, 53.6% to 68.9%) participants, symptoms developed before the onset of mucocutaneous manifestation and in 64 (38.5%, 31.1% to 46.4%) after (n=4, unknown). Twenty seven participants (13.7%, 9.2% to 19.3%) presented with mucocutaneous manifestations without systemic symptoms.

Notably, 71 (36.0%, 29.3% to 43.2%) participants reported rectal pain or pain on defecation, 33 (16.8%, 11.8% to 22.7%) sore throat, and 31 (15.7%, 11.0% to 21.6%) penile oedema. Overall, 31/111 (27.9%, 19.8% to 37.2%) participants with genital lesions had penile oedema and 60/82 (73.2%, 62.2% to 82.4%) participants with perianal lesions had rectal pain.

Exposure to infection

Of the 197 participants, 196 (99.5%) identified as gay, bisexual, or other men who have sex with men.

Forty one of 155 (26.5%) participants reported known close contact with someone who showed symptoms of or had confirmed monkeypox infection (n=42 not recorded).

Fifty four (27.4%) participants had a history of travel abroad within four weeks before symptom onset. Most common destinations were within western Europe: Spain (20), France (8), Belgium (4), Germany (4), and Greece (4). One participant had returned from an endemic area (West Africa).

Overall, 170/177 (96.0%) reported sexual contact with a male partner within 21 days of symptoms developing (n=20 unknown).

HIV and sexual health

Seventy of the 197 (35.5%) participants had HIV-1 co-infection (n=2 unknown). Sixty four (91.4%) of these participants were receiving antiretroviral therapy (n=4 unknown) (table 3). Fifty five (78.6%) had an undetectable HIV-1 viral load (<200 copies/mL) (n=13 unknown). The median CD4 count was 664 cells/µL (interquartile range 522-894 cells/µL) (n=40 unknown).

Of those tested for concomitant sexually transmitted infections, 34 (21.1%) tested positive for *Neisseria gonorrhoeae*, 18 (11.2%) for *Chlamydia trachomatis*, 11 (7.0%) for herpes simplex virus 1 or 2, and 6 (3.7%) for *Treponema pallidum* (table 4). Overall, 56/178 (31.5%) participants had a concomitant sexually

Table 1 | Characteristics and anatomical location of lesions in participants with monkeypox infection

Characteristics	No of participants (n=197)	% or % (95% CI)
Mucocutaneous manifestations		
Typical lesions	197	100.0 (97.8 to 100)
Maculopapular rash	27	13.7 (9.2 to 19.3)
Polymorphic appearance	70	35.5 (28.9 to 42.7)
No of lesions		
1	22	11.2
2-10	102	51.8
11-50	36	18.3
51-100	0	0
≥100	8	4.1
Unknown	29	14.7
No of sites		
1	76	38.6
2	30	15.2
3	40	20.3
4	27	13.7
≥5	24	12.2
Sites of typical lesions		
Face	71	36.0 (29.3 to 43.1)
Trunk	70	35.5 (28.9 to 42.7)
Arms/legs	74	37.6 (30.8 to 44.7)
Hands/feet	56	28.4 (22.2 to 35.3)
Genitals	111	56.4 (49.1 to 63.4)
Anus or perianal area	82	41.6 (34.7 to 48.8)
Oropharyngeal	27	13.7 (9.2 to 19.3)

transmitted infection, and 12 of these cases had more than one simultaneous sexually transmitted infection. Nineteen participants were not screened for any sexually transmitted infection at initial review.

Table 2 | Symptoms reported at time of presentation in participants with monkeypox infection

Symptom	No	% or % (95% CI)
UKHSA case definition for classic symptoms		
Mucocutaneous manifestations	197	100.0 (97.8 to 100)
Fever	122	61.9 (54.8 to 68.7)
Headache	49	24.8 (19.0 to 31.5)
Fatigue/lethargy	46	23.4 (17.6 to 29.9)
Myalgia	62	31.5 (25.1 to 38.4)
Arthralgia	21	10.(6.7 to 15.8)
Back pain	21	10.7 (6.7 to 15.8)
Lymphadenopathy:	114	57.9 (50.6 to 64.9)
Axillary	1	0.9
Cervical	16	14.0
Inguinal	90	79.0
Cervical and inguinal	7	6.1
No of UKHSA case definition classic symptoms, excluding cutaneous manifestations		
0	27	13.7
1	55	27.9
2	43	21.8
3	36	18.3
4	12	6.1
5	13	6.6
6	5	2.5
7	6	3.0
Other symptoms		
Rectal pain or pain on defecation	71	36.0 (29.3 to 43.2)
Sore throat	33	16.8 (11.8 to 22.7)
Penile swelling	31	15.7 (11.0 to 21.6)
Bleeding/discharge per rectum	22	11.2 (7.1 to 16.4)
Dysuria	11	5.6 (2.8 to 9.8)
Conjunctivitis	2	1.0 (0.1 to 3.6)

UKHSA=UK Health Security Agency.

People requiring hospital admission

Twenty five (12.7%) participants were admitted to hospital, of whom 20 (10.2% of the total cohort) were admitted for clinical reasons. The remainder were admitted for containment as they were unable to effectively self-isolate at home.

The most common clinical reasons for admission were perianal or rectal pain (8/20 participants) and penile swelling (5/20). Three participants had perianal or groin abscesses. Two participants had tonsillar abscesses. Two participants required ophthalmology review owing to eye involvement. Urinary retention, superimposed bacterial lower respiratory tract infection, and disseminated lesions in the context of immunocompromise occurred in one patient each. Of 20 participants admitted to hospital for clinical reasons, 15 (75.0%) had HIV co-infection. Three (15.0%) of the admitted participants were considered to have immunosuppression due to either HIV or immunosuppressive treatment.

No participants required organ support or died. One participant required patient controlled analgesia with fentanyl for severe rectal pain. Five participants had substantial proctitis confirmed on magnetic resonance imaging (MRI), one participant with rectal pain developed a rectal perforation that was managed conservatively, and one patient developed necrotising secondary bacterial infection. Participants with rectal pain were treated with oral and topical analgesia (paracetamol, ibuprofen, opioids, and lidocaine gel); rectal suppositories containing emollient, mesalazine, or steroid; and oral laxatives. To date no adverse events associated with these treatments have been observed.

Median length of stay for discharged participants was 8 days (interquartile range 3.5 to 10 days) (see supplementary figure 3). One participant remains in hospital, and one additional patient was transferred to a different hospital for capacity reasons.

Test negative participants

Of the 98/295 people who tested negative for monkeypox virus by PCR, the most common clinical presentations were rash (n=46, 47.0%), oral or genital ulcers (n=16, 16.3%), and pustules (n=24, 24.5%). Other presentations included rectal symptoms (n=8, 8.2%), sore throat (n=2, 2.0%), fever (n=1, 1.0%), and hidradenitis suppurativa (n=1, 1.0%).

An alternative diagnosis was identified in 49 participants (50.0%), including *T pallidum* (n=14, 14.3%), herpes simplex virus (n=13, 13.5%), *N gonorrhoeae* (n=12, 12.2%), varicella zoster virus (n=7, 7.1%), *C trachomatis* (n=6, 6.1%), bacterial skin infection (n=3, 3.1%), *Mycoplasma genitalium* (n=1, 1.0%), skin infestation (n=1, 1.0%), and new HIV-1 infection (n=1, 1.0%).

Novel presentations

We describe presentations of monkeypox infection in the participants that are not commonly reported. Corresponding images appear at the end of the article.

Table 3 | HIV co-infection and immune status of participants with monkeypox infection

	No with event/Total No of participants (%)
HIV status	
Positive	70/197 (35.5)
Negative	125/197 (63.5)
Unknown	2/197 (1.0)
Antiretroviral therapy	
Yes	64/70 (91.4)
No	2/70 (2.9)
Unknown	4/70 (5.7)
HIV-1 viral load <200 copies/mL	
Yes	55/70 (78.6)
No	2/70 (2.8)
Unknown	13/70 (18.6)
CD4 count	
<200 cells/µL	0
Median (interquartile range) CD4 count (n=30)	664 (522-894)
Unknown	40

Some symptoms were severe and required hospital admission. Images (refer to end of article) represent both a range of presentations and a series of progression, giving an insight into the clinical course of the disease in an outbreak largely centred on gay, bisexual, and other men and men who have sex with men.

Penile oedema

Of the 31 participants who reported penile oedema, five had documented paraphimosis or phimosis.

One participant, a 34-year-old circumcised man, presented with multiple penile lesions with clinically significant associated oedema. He had a history of Crohn's disease and was receiving adalimumab. He initially described multiple small, vesicular lesions on the penile shaft, coronal sulcus, and scrotum, which enlarged over the next two days, becoming umbilicated, flesh coloured papules (fig 1). The lesions then became more indurated, and the patient developed fever and cervical lymphadenopathy. On day 5 of symptoms, he developed erythema and swelling that extended from the mid-penile shaft to the glans. Overnight the swelling progressed rapidly, and the patient was admitted to hospital for assessment.

On examination, 14 large, umbilicated lesions were identified along the penile shaft, coronal sulcus, and scrotum. There was associated subcutaneous oedema with no evidence of necrosis, and the skin was not tense or painful. Single pustular lesions on the participant's arm, back, and hip were also noted, along with inguinal lymphadenopathy. He was able to urinate. Results of a Treponema pallidum particle assay and rectal swab for *N gonorrhoeae* and *C trachomatis* nucleic acid amplification tests were negative, respectively. The urology team advised conservative management with cold compression and massage, and analgesia including topical lidocaine gel, ibuprofen, and oral morphine sulphate. Over the next 48 hours the swelling remained unchanged, with bruising extending from the glans towards the penile base. The swelling subsequently subsided gradually, and the patient was discharged on day 13. By day 16 the swelling had largely resolved, and the penile lesions had crusted over.

Table 4 | Concomitant sexually transmitted infections in participants with monkeypox infection

Sexually transmitted infection	No (%) positive
Neisseria gonorrhoeae n=161 (n=36 unknown)	34 (21.1)
Rectum	25 (73.5)
Throat	10 (29.4)
Urethra/urine	7 (20.6)
3 in 1 sampling	1 (2.9)
Multiple site	9 (26.5)
Chlamydia trachomatis n=161 (n=36 unknown)	18 (11.2)
Rectum	13 (72.2)
Throat	3 (16.7)
Urethra/urine	3 (16.7)
3 in 1 sampling	1 (5.6)
Multiple sites	2 (11.1)
Herpes simplex virus n=157 (n=40 unknown)	11 (7.0)
Treponema pallidum (serology or polymerase chain reaction) n=163 (n=34 unknown)	6 (3.7)
People with any sexually transmitted co-infection n=178 (n=19 without any screening sent)	56 (31.5)

Secondary bacterial infection

One participant, a 47-year-old man with a history of HIV (viral load <200 copies/mL on antiretroviral therapy, CD4 count 755 cells/µL), was referred for review with extensive genital lesions, penile swelling, and purulent penile discharge.

He attended the emergency department when he first noticed spreading vesicles on his scrotum. A swab taken from the lesion confirmed monkeypox virus. The patient re-presented to the emergency department with progressive scrotal swelling, pain, and worsening penile ulceration and was subsequently admitted to hospital. On examination, extensive purulent lesions were identified on the penis and scrotum, with surrounding oedema (fig 2, also see supplementary figure 4). Vesicles were also noted on the arms and torso. No pain was elicited during digital rectal examination. Although there was no urinary retention or dysuria, the patient was catheterised because of concerns about increasing swelling of the penis. He was treated with co-amoxiclav to cover for a superadded bacterial infection but was switched to meropenem and clindamycin because of clinical suspicion of Fournier's gangrene. A swab sample taken from the penis grew *Staphylococcus aureus* and *Streptococcus dysgalactiae*. Lesions were negative for herpes simplex virus. A computed tomography scan showed extensive penile ulceration, a large hydrocele, and fluid within the scrotum. There was no collection or gas within soft tissue. The participant remains an inpatient at the time of writing.

Rectal perforation

Overall, 71 (36.0%) participants reported rectal pain or pain on defecation, and this was a common reason for admission (n=8). Five participants had proctitis confirmed on MRI, with one having a perforated rectum and one a perianal abscess.

One participant, a 46-year-old man with a history of HIV (viral load <200 copies/mL on antiretroviral therapy, CD4 count 1200 cells/µL), presented with severe rectal pain.

Symptoms started with fever, sore throat, and fatigue, followed by severe rectal pain. He was seen in the sexual health service, started on empirical doxycycline for proctitis, and tested for monkeypox virus. Over the next two days the patient developed a papular rash on his upper arms and trunk. A week after symptom onset, the rectal pain became so severe the patient required admission to hospital for pain control.

On examination, a papular rash with white exudates was identified in the oral cavity, along with right sided cervical lymphadenopathy. A cluster of tender, white perianal papules were located at the 3 o'clock position. Digital rectal examination elicited noticeable tenderness in the rectum and anal canal. The patient had ongoing fevers and continued to develop new skin lesions. He was started on tecovirimat 600 mg twice daily for 14 days. Results were negative for *N gonorrhoeae* and *C trachomatis* (triple site (throat, rectal, and urethral) sampling). No evidence of concomitant *T pallidum* infection was found.

MRI on day 12 of symptoms showed active proctitis with evidence of a localised lower rectal wall perforation and associated collection (fig 3). The patient was treated conservatively with intravenous ceftriaxone and metronidazole.

Solitary lesion

In total, 22 (11.2%) participants presented with a solitary cutaneous lesion.

One participant, a 53-year-old man with a history of HIV (viral load <200 copies/mL on antiretroviral therapy), presented with a single skin lesion on his thigh. Initially this was a small papule on the medial right thigh but developed into a painful mass with surrounding erythema. After review by a general practitioner, the patient started flucloxacillin, but with no benefit. He presented to the emergency department because the lesion had increased in size. He had no associated fever or other systemic symptoms.

On examination a 4×2 cm, tender area of induration with a central area of crusting was noted, along with bilateral inguinal lymphadenopathy (fig 4). The patient was admitted to hospital for treatment with intravenous antibiotics and further investigation. Ultrasound imaging showed inflamed subcutaneous tissues within the upper right thigh, with a tract to a further lesion in the upper right outer thigh, and reactive groin lymph nodes (see supplementary figure 5). Samples were negative for Leishmania, Rickettsiae, and *T pallidum*, and for *N gonorrhoeae* and *C trachomatis* (triple site (throat, rectal, and urethral) sampling). The patient was discharged with oral co-amoxiclav. However, because of ongoing symptoms and the increase of monkeypox infection in the UK, he was reassessed and tested for monkeypox virus, with a positive result 13 days after symptom onset. How the patient became infected is unclear and there was no known sexual or other exposure to the virus. The patient was reviewed on day 18 by virtual consultation, at which time the crust on the thigh lesion had fallen off.

Polymorphic lesions

Seventy (35.5%) participants had cutaneous manifestations at different stages of evolution at a single time point documented in the clinical notes.

One participant, a 48-year-old man, presented with polymorphic skin lesions having first noticed a single erosion on his scrotum, which spread to the penile base and foreskin. On day 3 he developed pustular lesions with an erythematous base on his arms, behind his knee, below his ear, and on the bridge of his nose (fig 5). He attended the sexual health service and emergency department with ulcerated genital lesions and was treated with flucloxacillin. On day 5 he developed systemic symptoms, including fever, myalgia, back pain, headaches, and lethargy. By day 17 the genital lesions had crusted over; however, the patient developed new pustular lesions on his hands. By day 24, the lesions on the hands, legs, and face had crusted over. The previously crusted scrotal and penile lesions became ulcerated, and the patient was treated with co-amoxiclav for a suspected secondary bacterial infection. A swab grew *Streptococcus pyogenes*. Screening results were negative for herpes simplex virus, *T pallidum*, *N gonorrhoeae*, and *C trachomatis*.

Maculopapular rash

Twenty seven (13.7%) participants reported an erythematous maculopapular rash of varying distribution and rapid onset, separate to areas of blistering or pustules. One of these participants had positive syphilis serology (n=4 unknown).

One participant, a 36-year-old man with a history of HIV (viral load <200 copies/mL on antiretroviral therapy, CD4 count >400 cells/µL), reported a rapidly progressive maculopapular rash soon after developing perianal vesicles.

The vesicles initially progressed into three pruritic, pustular, perianal lesions. On day 4 the patient presented to the sexual health service with rectal pain, tenesmus, rectal bleeding, and difficulty defecating. He was treated empirically for proctitis with doxycycline 100 mg twice daily and aciclovir 400 mg three times daily. On day 6 the patient awoke to a widespread symmetrical, pruritic maculopapular rash across his torso, back, legs, and buttocks, and reported inguinal lymphadenopathy (fig 6; also see supplementary figure 6). He denied any fever or systemic features. Results for herpes simplex virus, *N gonorrhoeae*, and *C trachomatis* (3 in 1 sampling) and *T pallidum* were negative. By day 8 the perianal lesions had begun to crust over, tenesmus had improved, and the rash had started to diminish.

Oropharyngeal manifestations

Twenty seven (13.7%) participants had oropharyngeal lesions and nine (4.6%) had tonsillar erythema, pustules, oedema, or abscess.

One participant, a 25-year-old man, presented with a right sided tonsillar abscess.

He described developing right sided neck pain, quickly followed by an erythematous, pruritic rash over his trunk. He subsequently developed fever, progressively worsening right submandibular swelling, and pain, and he reported fatigue. The swelling increased, resulting in dysphagia and difficulty breathing. The patient was referred to his local ear, nose, and throat centre where a right tonsillar abscess was observed.

A single papule was noted on the patient's right forearm. A swab taken from the papule tested positive for monkeypox virus, and the patient was transferred to the high consequence infectious diseases ward. On examination he had a widespread symmetrical erythematous maculopapular rash over his chest (sparing the midline), back, and upper arms, with areas of confluent erythema (fig 7). Smaller areas of a petechial rash were also noted. The right tonsil was enlarged, with an overlying pustular lesion and yellow-green exudate, with associated right cervical lymphadenopathy (fig 7). A small, crusted lesion was evident on each antecubital fossa. The patient had no genital or anal lesions. He was treated with benzylpenicillin and metronidazole. Tonsillar and skin swabs tested positive for monkeypox virus by PCR. Over the course of hospital admission, the rash subsided and the dysphagia improved. Two repeat throat swabs tested positive for monkeypox virus by PCR. Results for *N gonorrhoeae* and *C trachomatis* were negative. Additionally, test results for blood cultures, respiratory viral screen, herpes simplex virus, and varicella zoster virus PCR, and HIV, Epstein Barr virus, cytomegalovirus, and mumps IgM were all negative.

Abscesses

Two participants had soft tissue abscesses identified on ultrasound examination.

One of these participants, a 45-year-old man with a history of HIV (viral load <200 copies/mL on antiretroviral therapy), presented with a left sided groin abscess 10 days after he had shaved the area. The patient attended the emergency department for a left inguinal swelling, which had enlarged over three days, and the patient had associated fever and headache. The swelling had an overlying pustule, which the patient had described as an ingrown hair follicle.

On examination, the swelling, measuring 6×8 cm, was incised and drained by the surgical team. The next evening the patient developed papules and pustules over the mons pubis and face, followed by his neck, wrists, and back (eight lesions in total). Test results for *N gonorrhoeae* and *C trachomatis* (triple site (throat, rectal, and urethral) sampling) were negative. About five days later all the lesions had crusted over.

Confluent lesions

One participant, a 40-year-old man with a history of HIV (viral load <200 copies/mL on antiretroviral therapy, CD4 count >500 cells/µL), first presented with vesicular lesions at the base of his penis that he had attributed to shaving. He then developed a fever, cervical lymphadenopathy, headache, fatigue, and loss of appetite. He subsequently developed lesions on his face, hands, torso, thighs, and penile shaft (fig 8). Oral flucloxacillin was started because of the erythema around the lesions. The genital lesions progressed from vesicles to pustules, which in the next five days scabbed over. The scabbed lesions then coalesced and ulcerated, with substantial yellow purulent exudate. On day 8 of symptom onset the patient presented to the emergency department and was discharged owing to no clinical concern. He was admitted to hospital three days later for pain management, wound care, and treatment of presumed secondary bacterial infection. He received intravenous co-amoxiclav, octenisan wash, and fucidin cream, and the appearance of the lesions improved. A wound swab showed heavy mixed growth, including coliforms. Test results for *N gonorrhoea* and *C trachomatis* (triple site (throat, rectal, and urethral) testing), herpes simplex virus, and *T pallidum* were all negative. The patient was discharged after five days with prescribed oral co-amoxiclav.

Discussion

We describe the clinical characteristics of the first 197 patients with monkeypox infection diagnosed or managed within a south London HCID centre and associated sexual health and HIV services during the 2022 outbreak in London. We identified important differences in clinical manifestations between the current outbreak and previous outbreaks in endemic regions, which colleagues in the wider healthcare setting, including primary care and clinics specialising in genitourinary medicine; ear, nose, and throat conditions; and infectious diseases should be aware of to facilitate early diagnosis of monkeypox infection (table 5).

Principal findings

The characteristics of the cohort we describe differ from those of populations affected in previous outbreaks in endemic regions. In previous outbreaks where a higher proportion of the population had been vaccinated against smallpox, most infections occurred in young children.[23 24] More recently, outbreaks of the West African and Congo Basin clades have affected both adults and children, with male patients being disproportionately represented in some reports in West and Central Africa.[10 22 25 26] In contrast with previous reports, the current cohort comprised men only, and most (99.5%) identified as gay, bisexual, or other men who have sex with men. Only one participant had recently travelled to an endemic region; this study therefore further corroborates ongoing autochthonous transmission within the UK.

This cohort identifies relatively common symptoms currently excluded from public health messaging and diagnostic criteria. Fourteen per cent of this cohort did not meet the current UK Health Security Agency definition for a probable case. Although not widely

Table 5 | Summary of signs and symptoms of monkeypox infection in a London 2022 cohort compared with previous reports from the Democratic Republic of the Congo in 2007-11 and Nigeria in 2017-18

	London 2022 (n=197)	Democratic Republic of the Congo 2007-11 (n=216)[10]	Nigeria 2017-18 (n=122)[22]
Features			
Lesions (ordered by frequency)	Macular, papular, vesicular, pustular, umbilicated, scabbed, crusted, widespread maculopapular (see supplementary figure 2)	Macular, papular, vesicular, pustular, umbilicated, scabbed	Vesiculopustular
Mean count at presentation	6*	370	NA
Progression	Lesions present at different stages simultaneously. Not all lesions progressed from one phase to another in order	Progression from one phase to another occurs in order	NA
Distribution (most common)	Genitals (56.4%), perianal (41.6%)	Head, arms	Face (96% of 71), leg (91% of 69), trunk (80% of 70)
Symptoms			
Systemic (most common)	Fever (61.9%), lymphadenopathy (57.9%), myalgia (31.5%)	Malaise (85.2%), lymphadenopathy (57.4%), fever/chills (45.3%), sweats (19.9%)	Fever (88%), headache (79%), lymphadenopathy (69%), myalgia (63%)
Localised (most common)	Rectal pain (36.0%), sore throat (16.8%), penile oedema (15.7%)	Sore throat (78.2%), nasal discharge/congestion (31.0%)	Sore throat (58%)

NA=not available.
*Lesion count displayed as mean to allow comparison with previous data.

described in literature, penile swelling and rectal pain were common presentations in this cohort and the most frequent indications for hospital admission. Severity of symptoms did not, however, always correlate with a high lesion burden or typical patterns of cutaneous manifestations. Five participants presented with abscesses. These patients had a low lesion burden or atypical rashes and therefore monkeypox infection was not suspected during initial review on surgical wards.

At presentation, almost half (47.2%) of the cohort had exclusively mucocutaneous manifestations or developed systemic symptoms after rather than preceding the onset of lesions. This contradicts the current UK Health Security Agency probable case definition, which requires typical systemic symptoms to be present in addition to cutaneous lesions and epidemiological risk.[20] The predilection of lesions to genital, perianal, and perioral or tonsillar areas, and the history of recent sexual contact in 96% of our cohort suggests lesions may initially form at the site of inoculation, followed by the development of systemic symptoms and subsequent dissemination of lesions. However, some of the participants, such as those with solitary lesions, did not develop further dissemination. More than a third (35.5%) of this cohort described a polymorphic rash, a finding that has been recognised in other emerging evidence from this outbreak.[27] Lesions appearing at different stages and timepoints could be a consequence of autoinoculation. Widespread maculopapular rashes were also observed that did not become pustular or ulcerated. These patterns represent a change in the clinical presentation of the disease.

Solitary lesions and tonsillar signs were not previously known to be typical features of monkeypox infection. On initial presentation, single lesions could be mistaken for other conditions such as syphilis, lymphogranuloma venereum, and ingrown hair follicles. Throat features included ulcers, pain, secondary bacterial superinfection, and quinsy, which could all be mistaken for bacterial tonsillitis. Infection in patients presenting in such ways may have gone undiagnosed in the community for some time. This could help to explain why the outbreak had become so widespread at the point of detection.

Just under a third (31.5%) of the cohort screened for a sexually transmitted infection had a co-infection. The most common co-infections were *N gonorrhoeae* and *C trachomatis* on rectal sampling, which might have increased the severity of rectal symptoms at presentation. In those who tested negative for monkeypox virus, the most common alternative diagnoses were syphilis, herpes simplex virus, varicella zoster virus, *N gonorrhoeae*, and *C trachomatis*. It is imperative to screen all people for sexually transmitted infections who present to healthcare settings with suspected monkeypox infection to ensure prompt diagnosis and treatment of co-infections.

Policy implications

This study supports previous findings that monkeypox infection is generally a self-limiting disease with a low fatality rate.[17] No deaths were reported in the cohort and no patients required level 2 or 3 care. Many patients do, however, seem to require admission for symptom control, which during a growing outbreak has important implications for the allocation of healthcare resources. Additionally, we have recognised some serious complications of monkeypox infection, including severe penile oedema, tonsillar abscess requiring monitoring for airway patency, imaging confirmed proctitis, and rectal perforation.

Only a quarter of this cohort had known contact with someone with confirmed monkeypox infection, raising the possibility of either asymptomatic or paucisymptomatic transmission. Understanding these findings will have major implications for contact tracing, public health advice, and ongoing infection control and isolation measures.

Strengths and limitations of this study

This cohort captures a spectrum of disease severity, encompassing those presenting to sexual health services, attending emergency departments, and requiring hospital admission, including transfers

between hospitals. Limitations of this study, however, are the retrospective design, observational nature, potential variability of clinical record keeping, and single centre geographically limited data. The lack of prospective, prespecified data collection criteria means that some findings might be underestimated if not documented at the time.

Conclusions

These findings confirm the ongoing unprecedented community transmission among gay, bisexual, and other men who have sex with men seen in the UK and many other non-endemic countries. Urgent research is needed to further understand the modes of transmission of monkeypox virus, particularly around sexual contact, and also the possibility of asymptomatic spread. We have highlighted new clinical presentations and shown photographs to assist clinicians in the diagnosis of monkeypox infection.

Rectal pain and penile oedema were the most common presentations requiring hospital admission in this cohort, yet these symptoms are not currently included in public health messaging. We recommend clinicians consider monkeypox infection in those presenting with these symptoms. Those with confirmed monkeypox infection with extensive penile lesions or severe rectal pain should be considered for ongoing review or inpatient management. The variable temporal association between mucocutaneous and systemic features, presence of solitary lesions, and biphasic appearance of lesions represent a variation from the classic features.

The continued growth of this outbreak means that spread to vulnerable populations is possible, including immunocompromised individuals and children, and the implications of this are not yet understood. Nosocomial transmission is an infrequent but avoidable consequence of unrecognised monkeypox infection in patients admitted to hospital.[13 28] Disseminating awareness of atypical presentations is of vital clinical importance as failure to recognise monkeypox infection as a possible differential could pose a major risk to healthcare professionals and other contacts. Continued research will impact local and national infection control and isolation policies and guide the development of new diagnostics, treatments, and preventive measures. It is vital that as these research efforts continue, the populations that are already affected in endemic regions with higher reported mortality secondary to monkeypox infections are not excluded from the development and implementation of these interventions.

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Contributors: AP, JB, and DDSF conceived this project. AP, JB, JCHT, DDSF, AD, CYM, LBS, JM, JP, CT, RS, MA, CP, and VN collected the data. AP, JB, JCHT, AD, CYM, and LBS were responsible for statistical analyses. AP, JB, JCHT, and DDSF wrote the first draft of the manuscript. AP, JB, JCHT, DDSF, AD, CYM, LBS, JM, JP, CT, RS, MA, CP, VN, and AB edited the manuscript. AN, DC, AB, HW, CVNTP, AB, EA, GN, and SD provided support and advice throughout the process of writing and analysing this study. All authors approved the final version of the manuscript. AN is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at https://www.icmje.org/disclosure-of-interest/ and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Data and clinical images were collected as part of routine care by the responsible clinical team and anonymised at the point of extraction. Written informed consent was given for the use of all clinical images and details of disease progression. The data collection was approved by Guy's and St Thomas' NHS Foundation Trust clinical governance committee as a service evaluation.

Patient consent: Obtained.

Data sharing: Anonymised data is available on reasonable request.

The lead author (AN) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported and that no important aspects of the study have been omitted.

Dissemination to participants and related patient and public communities: To disseminate our results, we will share this information within our professional societies and networks at conferences and webinars. We will use social media to share the key messages and produce a plain language summary to be used for wider dissemination to patient advocacy groups, and patient organisations.

Provenance and peer review: Commissioned; externally peer reviewed.

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Supplementary material: additional figures and photographs

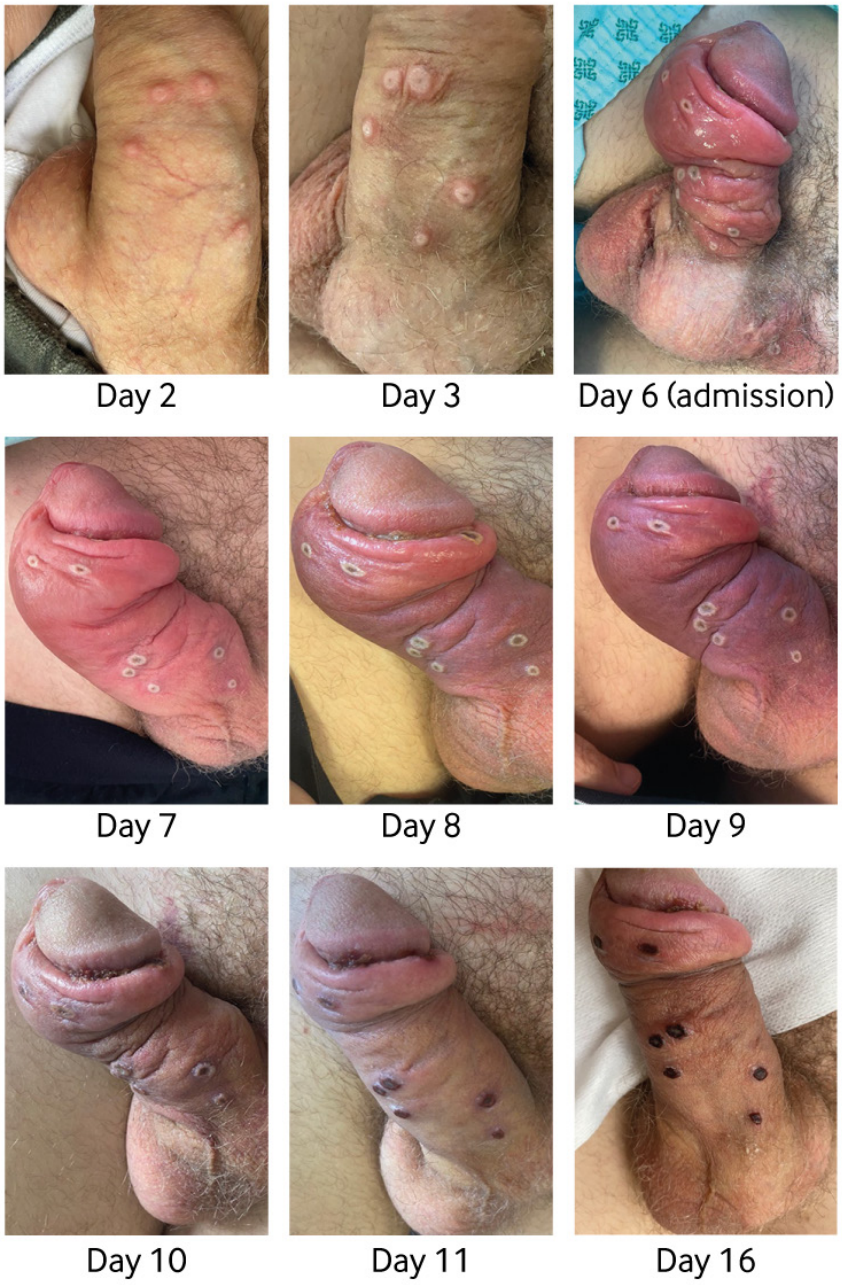

Fig 1 | Progression of penile lesions and penile oedema

Fig 2 | Secondary bacterial infection of penis due to *Staphylococcus aureus* and *Streptococcus dysgalactiae*. Also see supplementary figure 4

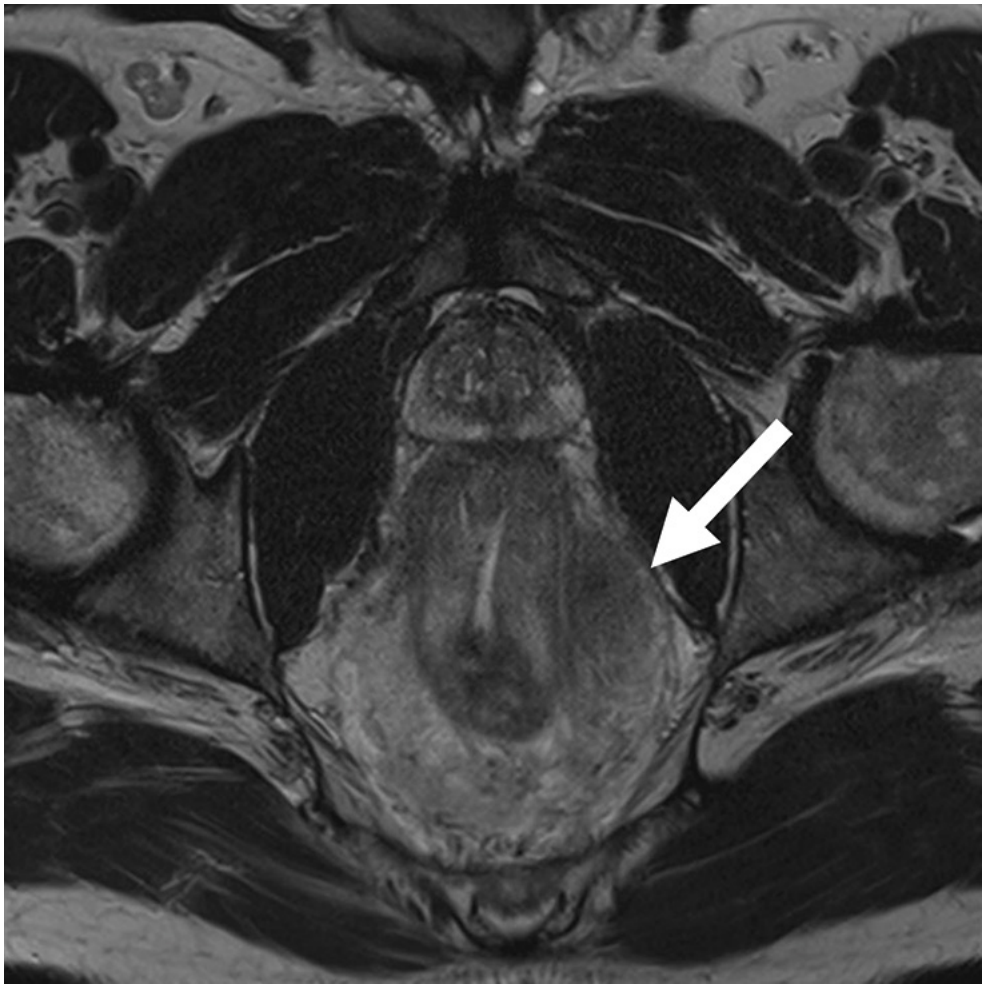

Fig 3 | T2 weighted magnetic resonance imaging scan of pelvis showing a 3.5 cm cavity in left mesorectum, adjacent to the rectal wall representing an area of localised perforation (arrow)

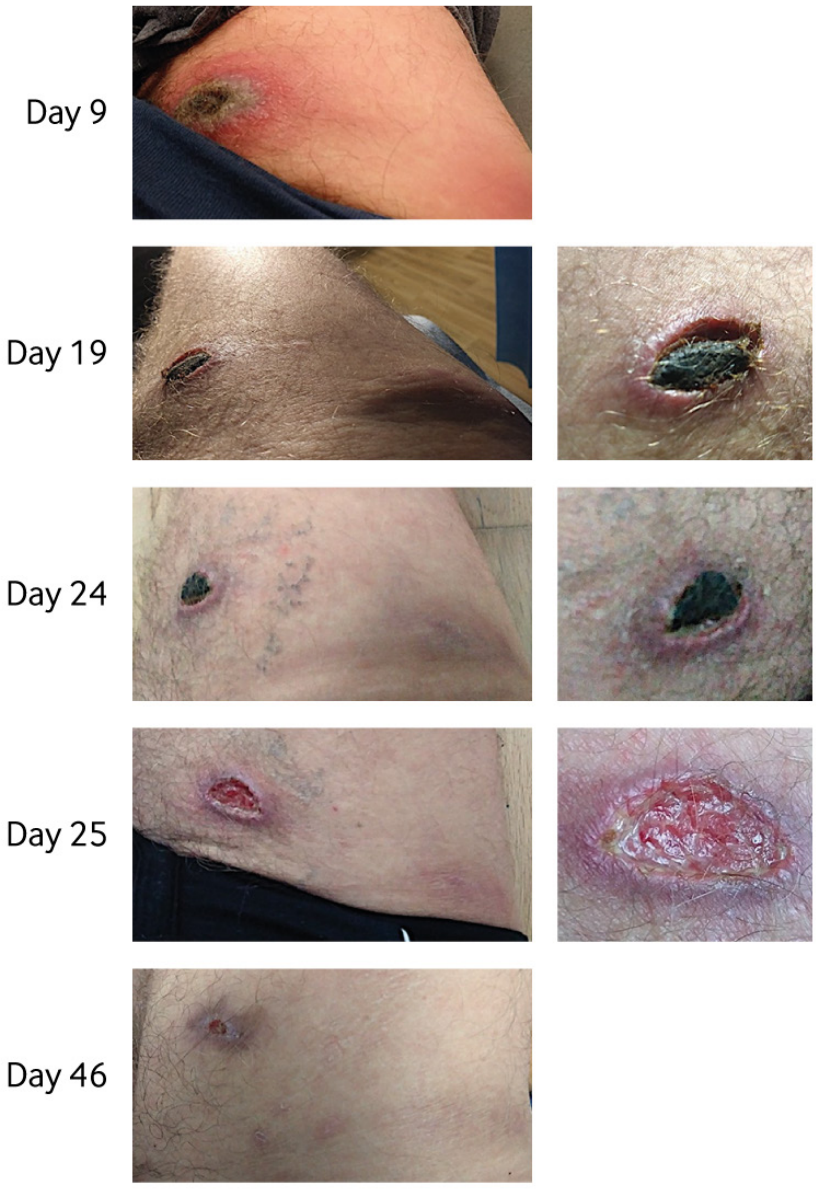

Fig 4 | Development of solitary lesion on right upper inner thigh, tracking laterally to outer thigh. Also see supplementary figure 5

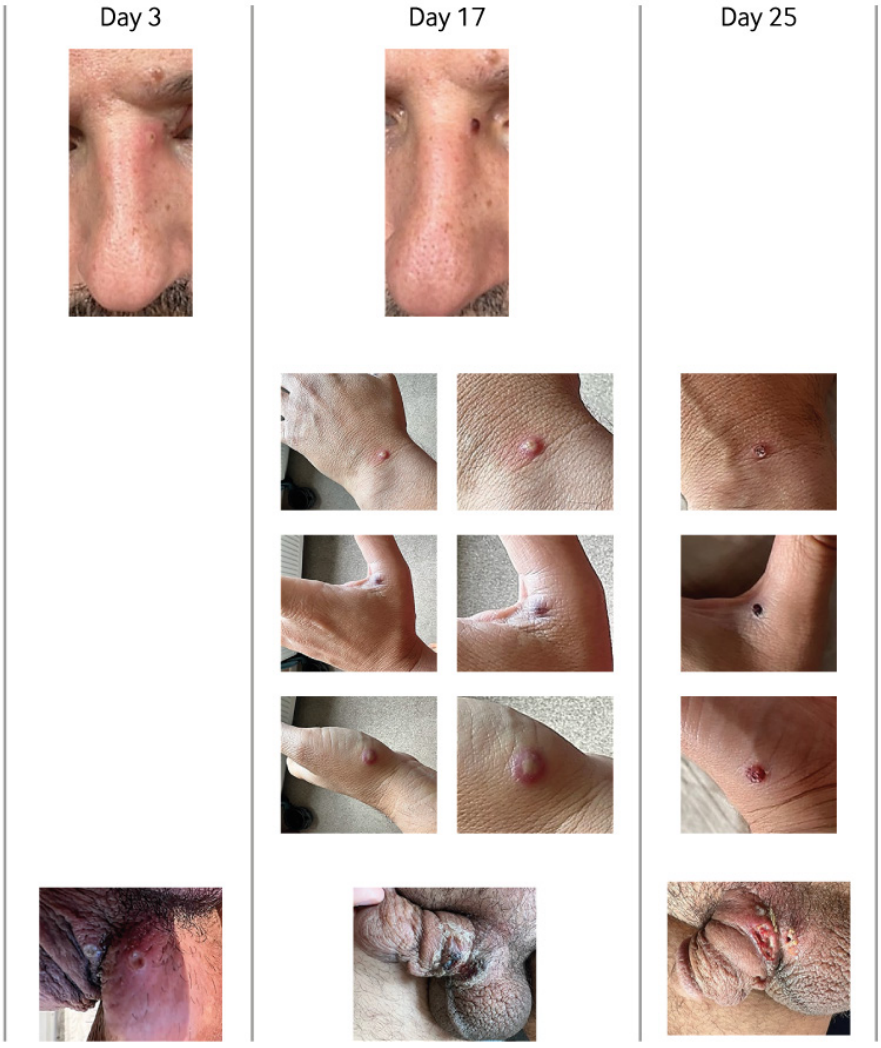

Fig 5 | Cutaneous lesions on the nose, hand, and penis over time. On day 17 there were fresh pustular lesions on the hand, a partly scabbed lesion on the face, and fully scabbed lesions on the penis

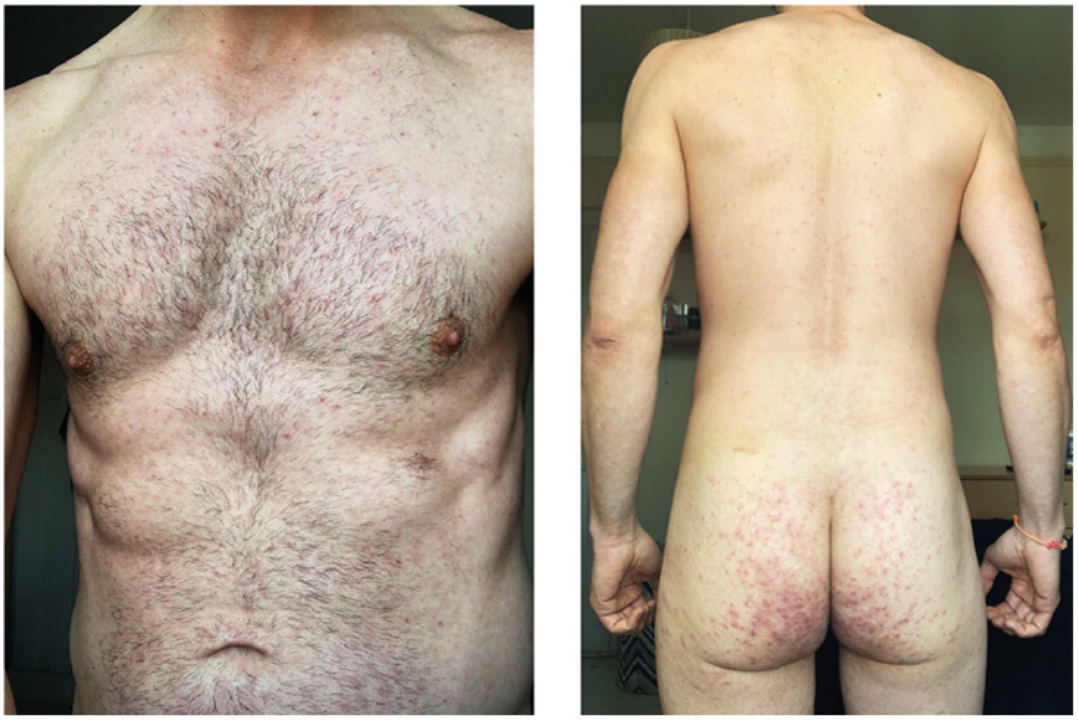

Fig 6 | Symmetrical maculopapular rash of the torso, back, and buttocks. Also see supplementary figure 6

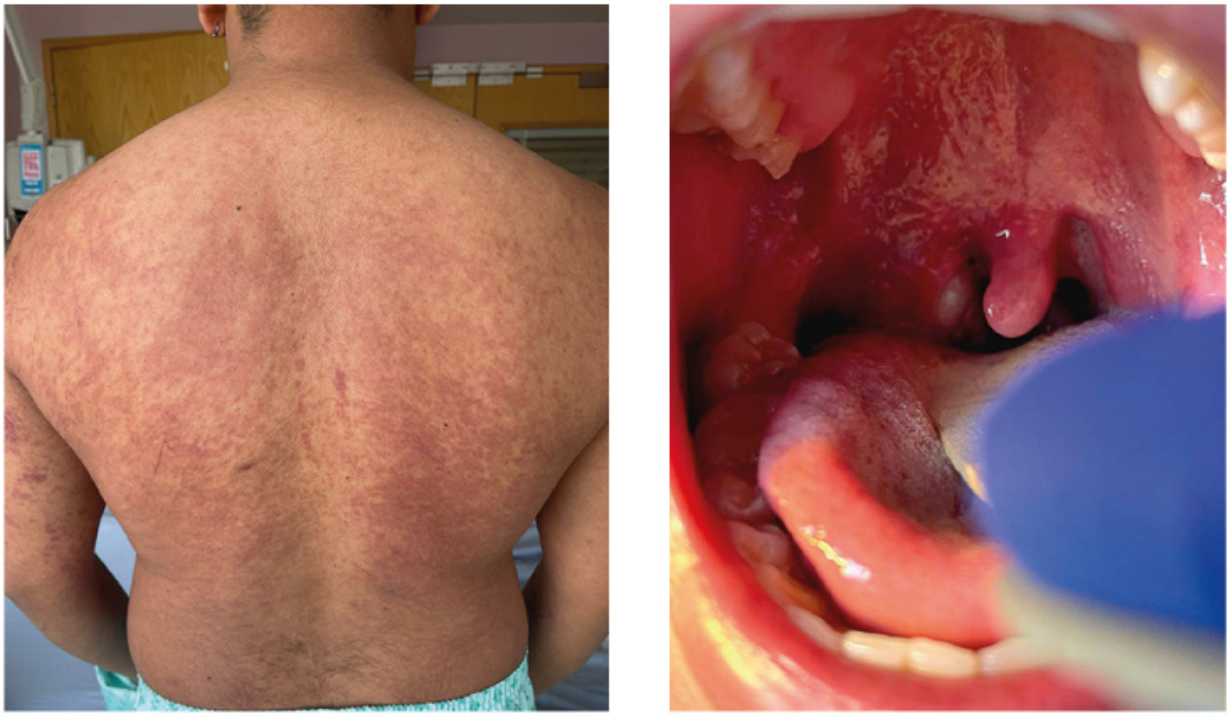

Fig 7 | (Left) Symmetrical erythematous maculopapular rash on back and upper arms, with areas of confluent erythema. (Right) Right tonsillar enlargement with an overlying pustular lesion and yellow-green exudate with slight deviation of the uvula

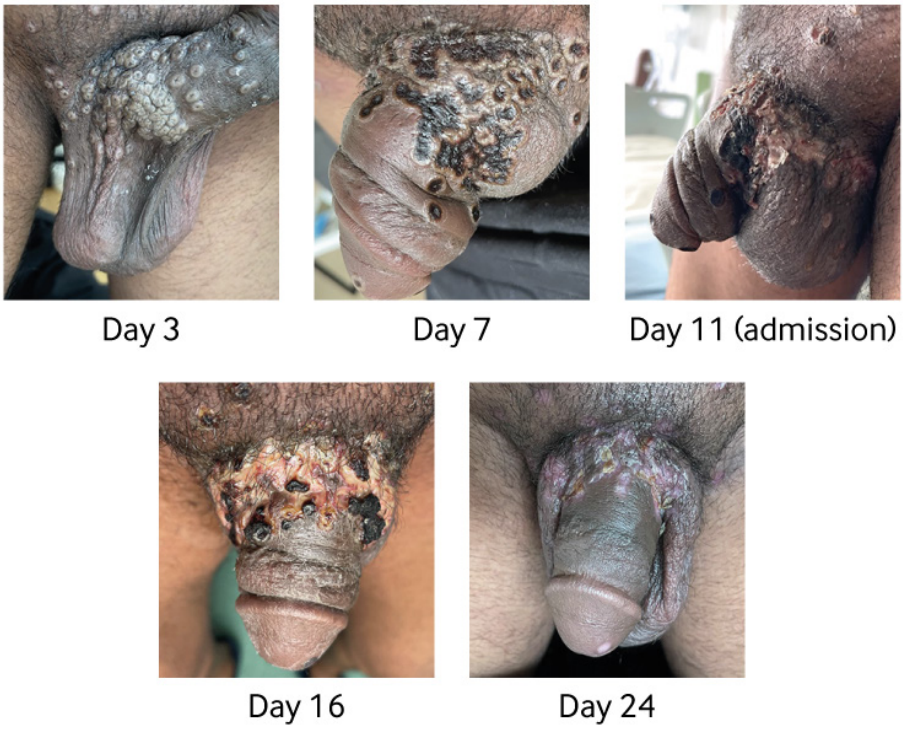

Fig 8 | Progression of penile lesions. Multiple lesions progressed to become confluent, subsequently forming a large ulcer