

Original article

Clinical characteristics of ambulatory and hospitalized patients with monkeypox virus infection: an observational cohort study

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ARTICLE INFO

Article history:

Received 27 July 2022

Received in revised form

13 August 2022

Accepted 14 August 2022

Available online 23 August 2022

Editor: L. Leibovici

Keywords:

Complications

Disease attributes

Emerging communicable diseases

Monkeypox

Skin diseases

ABSTRACT

Objectives: A global outbreak of monkeypox virus infections in human beings has been described since April 2022. The objectives of this study were to describe the clinical characteristics and complications of patients with a monkeypox infection.

Methods: All consecutive patients with a polymerase chain reaction (PCR)–confirmed monkeypox infection seen in a French referral centre were included.

Results: Between 21 May and 5 July 2022, 264 patients had a PCR-confirmed monkeypox infection. Among them, 262 (262/264, 99%) were men, 245 (245/259, 95%) were men who have sex with men, and 90 (90/216, 42%) practiced chemsex in the last 3 months. Seventy-three (73/256, 29%) patients were living with human immunodeficiency virus infection, and 120 (120/169, 71%) patients were taking pre-exposure prophylaxis against human immunodeficiency virus infection. Overall, 112 (112/236, 47%) patients had contact with a confirmed monkeypox case; it was of sexual nature for 95% of the contacts (86/91). Monkeypox virus PCR was positive on the skin in 252 patients, on the oropharyngeal sample in 150 patients, and on blood in eight patients. The majority of patients presented with fever (171/253, 68%) and adenopathy (174/251, 69%). Skin lesions mostly affected the genital (135/252, 54%) and perianal (100/251, 40%) areas. Overall, 17 (17/264, 6%) patients were hospitalized; none of them were immunocompromised. Complications requiring hospitalization included cellulitis ($n = 4$), paronychia ($n = 3$), severe anal and digestive involvement ($n = 4$), non-cardia angina with dysphagia ($n = 4$), blepharitis ($n = 1$), and keratitis ($n = 1$). Surgical management was required in four patients.

Conclusion: The current outbreak of monkeypox infections has specific characteristics: it occurs in the men who have sex with men community; known contact is mostly sexual; perineal and anal areas are frequently affected; and severe complications include superinfected skin lesions, paronychia, cellulitis, anal and digestive involvement, angina with dysphagia, and ocular involvement. **Morgane Mailhe, Clin Microbiol Infect 2023;29:233**

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Introduction

Monkeypox is a zoonotic disease caused by an *Orthopoxvirus*. The first human case was described in 1970 in the Democratic Republic of Congo. Since then, endemic circulation has been reported in West and Central Africa [1]. However, the respective role of animal-to-human transmission or human-to-human transmission is still poorly understood [2]. The number of cases and outbreaks is increasing in endemic areas. This may partly be due to the worldwide decline in *Orthopoxvirus* herd immunity, following the cessation of smallpox vaccination when smallpox was declared eradicated in 1980 [3]. It had been foreseen that monkeypox was likely to emerge as the most important *Orthopoxvirus* infection in human beings [4].

Outbreaks occurring in imported cases outside endemic areas were initially considered rare and self-limiting [5,6]. The first human-to-human transmission of monkeypox outside an endemic area has been reported in the United Kingdom in 2018, in a nosocomial context [7] and a household cluster [8]. On 7 May 2022, a human monkeypox infection was diagnosed in a person who was traveling from Nigeria to the United Kingdom. Since then, an unprecedented outbreak has spread across several non-endemic countries worldwide such as Europe and North America.

Data on the clinical characteristics of patients affected during the current outbreak are scarce [9,10]. Men who have sex with men (MSM) seem to be particularly affected, suggesting a probable human-to-human sexual transmission [11]. Considering this modification of transmission pattern, the clinical presentation is likely to be modified as well, compared with the smallpox-like disease reported during African clusters [12].

Here, we describe the demographic and clinical features of 264 individuals with a confirmed monkeypox virus (MPXV) infection in a French referral hospital.

Methods

Study design and population

This observational study was conducted at Bichat Claude Bernard university hospital in Paris. All consecutive patients diagnosed with MPXV infection between 21 May and 5 July 2022 were included. Bichat Claude Bernard university hospital was one of the referral centres in the Paris Metropolitan area for MPXV infection.

Ethics

Participants gave consent for the use of their anonymized medical data. Written consent was sought for the anonymous publication of images. The Research Ethics Committee of the North Parisian Academic Hospital Group approved the study.

Procedures

All patients underwent a standard medical examination. Patients had at least one and up to three samples collected: throat swab, skin swab, and EDTA blood sample. The skin swab was rubbed against all detected skin lesions and a pustule was popped if possible to increase sample sensitivity. After a heat inactivation step (12 minutes at 70°C), nucleic acids were extracted using MagNA Pure LC 2.0 Instrument (Roche, Meylan, France). MPXV-specific real-time polymerase chain reaction (PCR) assay validated by both Centers for Disease Control and Prevention and the French *Orthopoxvirus* national reference centre (IRBA: Institut de Recherche Biologique des Armées) was performed [13]. An exogenous internal extraction and amplification control was added to each

sample before extraction (Simplex Extraction and Amplification Control Set, DiaSorin, Saluggia, Italy) [14]. Negative controls were added to each extraction batch, and a positive control provided by the French *Orthopoxvirus* national reference centre was tested in each PCR run. Confirmed MPXV cases were defined as individuals with positive PCR assay results on any kind of sample. A standard sexual health screen was not performed to limit the number of samples analysed by the level 3 laboratory, according to local infection control policies [15,16].

Data collection and analysis

Routinely collected data were anonymously extracted from the patient's electronic medical records into a secured database. Median and interquartile ranges (IQRs) represented continuous variables, whereas numbers and percentages represented categorical variables.

Results

Between 21 May and 5 July 2022, 420 patients were tested for MPXV infection at Bichat - Claude Bernard Hospital, of whom 264 (264/420, 63%) had at least one positive PCR test result.

Among the 264 patients, the vast majority were men (262/264, 99%), except for one woman and one transgender woman (Table 1). Patients were relatively young, with a median age of 35 (30–41) years, and most of them were born in France (178/245, 73%). Seventy-six (76/227, 33%) patients travelled during the previous month but none to Central Africa. Thirty-eight (38/206, 18%) patients had a pet, most commonly cats or dogs. The most frequent medical condition was human immunodeficiency virus (HIV) infection (73/256, 29%). Few patients (7/253, 3%) were immunocompromised.

A history of smallpox vaccination was present for 29 (29/238, 12%) patients, of whom 4 had an early post-exposure ring vaccination with a third generation smallpox vaccine (IMVANEX(c)) during the current outbreak.

Among the 264 patients, 245 were MSM (245/259, 95%), and 120 among the patients without HIV infection were taking pre-exposure prophylaxis against HIV infection (120/169, 71%). In terms of sexual behaviour, current chemsex was frequent (90/216, 42%), such as condomless sex (106/264, 40%). The median (IQR) number of sexual partners over the last month was 5 (2–10). A history of sexually transmitted infection was present in 209 (209/235, 89%) patients, 139 of whom had it in the last year (139/187, 74%).

Less than half of the patients (112/236, 47%) were aware of being in contact with a confirmed case of MPXV, of whom 86 declared sexual contact (86/91, 95%). In these patients, the median (IQR) time between contact and symptoms start was 6 (3–8) days, which is consistent with the incubation period.

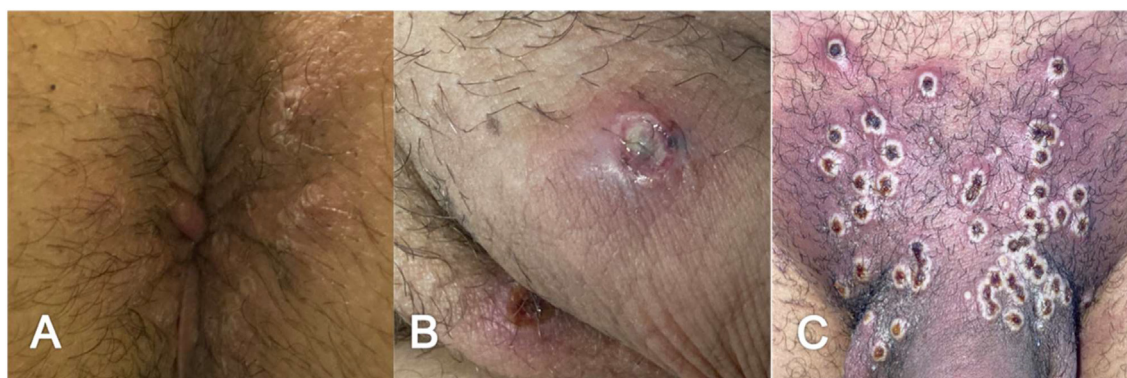
For more than half of our patients (136/258, 53%), no prodromal phase before skin lesions appearance was observed. The median time between the onset of symptoms and skin lesions' appearance was 3 (2–4) days.

The majority of patients presented with fever (171/253, 68%) and adenopathy (174/251, 69%). The median number of skin lesions was 5 (3–10), mainly affecting the genital (135/252, 54%) and the perianal (100/251, 40%) areas (Fig. 1). Typical lesions included observed papules (82/244, 34%), vesicles (138/243, 57%), pustular papules (80/243, 33%), ulcerations (84/244, 34%), and scabs (59/243, 24%) (Fig. 2). A rash was present in 20 patients (20/248, 8%). Of note, 45 patients reported multiple flare-ups (45/264, 17%). The time before scabs' fall was notified for 17 patients, with a median of 15 (12–18) days since the onset of skin lesions (Fig. 3).

Table 1
Demographic and clinical characteristics of the study population

| Characteristic | Patients (N = 264), n (%) or median (IQR) | NA |
|---|---|----|
| Age (y), median (IQR) | 35 (30–41) | — |
| Male sex | 262 (99%) | — |
| Born in France | 178 (73%) | 19 |
| MSM | 245 (95%) | 5 |
| Number of sexual partners during the last month, median (IQR) | 5 (2–10) | — |
| Condomless sex during the last month | 106 (40%) | — |
| HIV | 73 (29%) | 8 |
| Immunocompromised state | 7 (3%) | 11 |
| Cancer | 5 (2%) | 8 |
| History of STI | 209 (89%) | 29 |
| STI during the last year | 139 (74%) | 22 |
| Current pre-exposure prophylaxis treatment (among patients not infected with HIV) | 120 (71%) | 14 |
| Use of chemsex | 90 (42%) | 48 |
| History of smallpox vaccination | 29 (12%) | 26 |
| Known contact with a confirmed case | 112 (47%) | 28 |
| Time between contact and beginning of symptoms (d), median (IQR) | 6 (3–8) | — |
| General symptoms | — | — |
| Fever | 171 (68%) | 11 |
| Adenopathy | 174 (69%) | 13 |
| Pharyngitis | 51 (20%) | 12 |
| Angina | 41 (16%) | 12 |
| Respiratory signs | 31 (12%) | 9 |
| Headaches | 89 (35%) | 9 |
| Skin lesions | — | — |
| No symptoms before skin lesions appearance | 136 (53%) | 8 |
| Time between beginning of symptoms and skin lesions (d), median (IQR) | 3 (2–4) | — |
| Time between beginning of symptoms and medical examination (d), median (IQR) | 6 (4–8) | — |
| Number of skin lesions, median (IQR) | 5 (3–10) | — |
| Lesion type | — | — |
| Skin rash | 22 (9%) | 11 |
| Papules | 82 (34%) | 20 |
| Vesicles | 138 (57%) | 21 |
| Pustular papules | 80 (33%) | 21 |
| Ulcerations | 84 (34%) | 20 |
| Scabs | 59 (24%) | 21 |
| Affected areas | — | — |
| Genital area | 135 (54%) | 12 |
| Limbs | 121 (48%) | 12 |
| Torso | 105 (42%) | 12 |
| Perianal area | 100 (40%) | 13 |
| Face | 88 (35%) | 12 |
| Palmoplantar area | 36 (14%) | 14 |
| Complications | 92 (36%) | 7 |
| Anal pain | 45 (18%) | 7 |
| Cellulitis | 25 (10%) | 7 |
| Urinary signs | 11 (4%) | 7 |
| Ocular disease | 10 (4%) | 7 |
| Abscess | 7 (3%) | 7 |
| Lymphangitis | 5 (2%) | 7 |
| Paronychia | 3 (2%) | 7 |

HIV, human immunodeficiency virus; IQR, interquartile range; MSM, men who have sex with men; NA, not available; STI, sexually transmitted infection.

**Fig. 1.** Genital lesions. (A) Anal margin, (B) early penile ulcerations, and (C) late penile lesions.

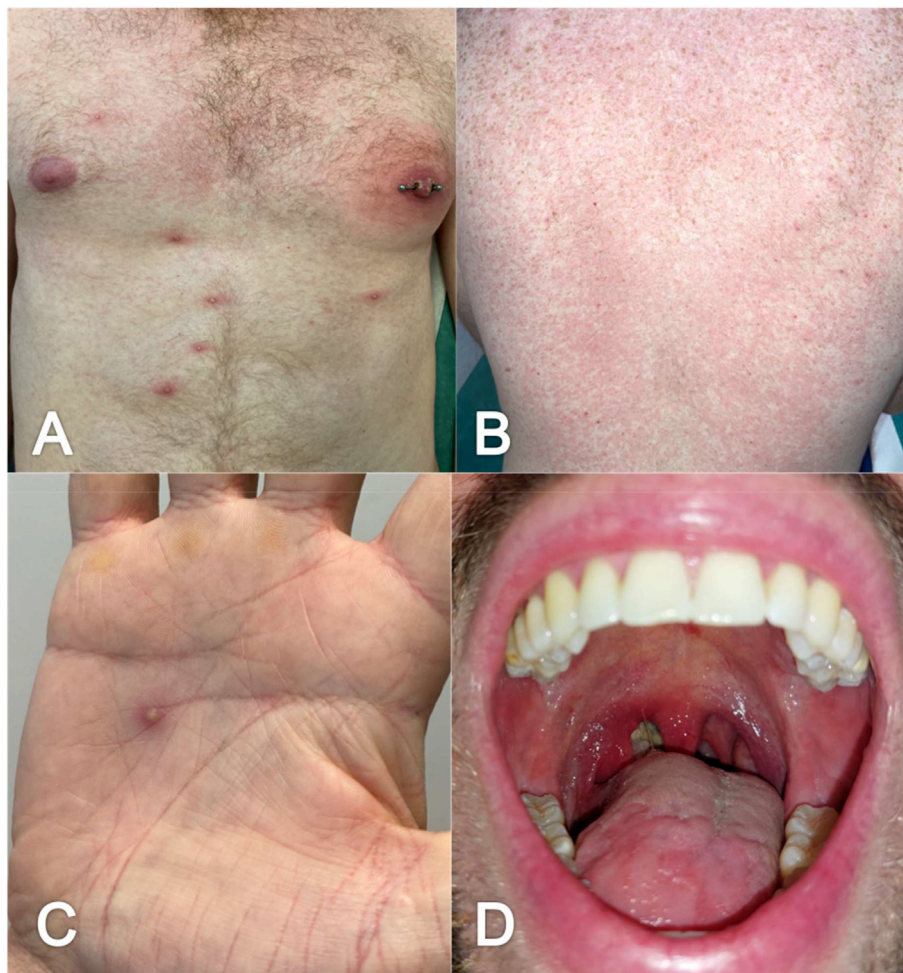


Fig. 2. Skin lesions. (A) Chest vesicles, (B) back rash, (C) palmar pustule, and (D) oropharyngeal lesions.

Complications affected more than a third of the patients (92/257, 36%). The most frequent complications were anal pain (45/257, 18%) and secondary bacterial skin infections such as cellulitis (25/257, 10%). Headaches were frequently associated (89/255, 35%), and one case of Bell's palsy was diagnosed 3 weeks after the MPXV infection. No case of encephalitis or neurologic involvement was described in this cohort. No deaths were reported.

Skin PCR test was conducted for 258 patients: 252 positive (98%) and six negative (2%), with a median (IQR) cycle threshold (Ct) of 23 (21–26). Oropharyngeal PCR test was conducted for 197 patients: 150 positive (76%) and 47 negative (24%), with a median (IQR) Ct of 32 (27–35). Blood PCR test was performed for 26 patients: 8 positive and 18 negative, with a median [IQR] Ct of 36 (35–37). Among 192 patients who had both skin and throat samples, 139 had positive PCR results on both samples (72%). Ct was significantly higher for the throat sample (median, 32; IQR, 27–35) compared with the skin sample (median, 23; IQR, 21–26; $p < 0.01$).

Hospitalized patients

Among 264 patients, 17 (6%) were hospitalized and all were men (Table 2). The median age of hospitalized patients was 30 years. They presented with few comorbidities and no immunosuppression. The four hospitalized patients infected with HIV had a CD4 cell count of $>500/\text{mm}^3$. One patient had a history of smallpox vaccination during childhood.

The median (IQR) delay between the onset of symptoms and hospitalization was 7 (5–9) days. Hospitalizations were related to skin infections in six cases, gastrointestinal symptoms in four cases, severe non-cardiac angina in four cases, ocular impairment in two cases, and respiratory tract impairment in one case. One patient with an ocular involvement also had paronychia. Overall, all but one patient had a suspicion of bacterial superinfection, and 16 patients received antibiotics. Severe pain was frequent, and all patients required painkillers, including acetaminophen (17/17) and opioids (7/17).

Skin infections were bacterial superinfections of either hand lesions leading to paronychia and lymphangitis or of genital lesions leading to cellulitis. The management was medical in three cases and included surgery in three cases (2 paronychia and one thigh cellulitis). The surgical management consisted of drainage and samples found *Staphylococcus aureus* in all cases. Genital and perineum cellulitis mimicked Fournier gangrene with extensive necrotizing lesions; however, the full resolution was achieved without surgical debridement. Urethritis and penile oedema secondary to cellulitis were observed; however, the patients did not require urinary catheterization. In terms of digestive impairment, two patients presented with abdominal pain, fever, and profuse diarrhoea. They both had extensive colonic and rectal lesions confirmed by abdominal computed tomography scan. One patient underwent a recto sigmoidoscopy, showing ulcerative lesions. A biopsy was performed and showed a rectal mucosa of preserved



Fig. 3. Complications. (A) Paronychia with lymphangitis, (B) genital necrotizing cellulitis, and (C) cheilitis.

architecture, with a moderate non-specific acute inflammatory reaction. They both had an empiric antibiotic treatment for bacterial colitis, and the symptoms finally resolved. The other two patients hospitalized for gastrointestinal symptoms presented with symptoms of painful proctitis.

Dysphagia was the main reason for hospitalization in the four patients experiencing angina, which was consistently associated with bulky cervical lymph nodes. Of note, none of these patients experienced dyspnea. Three patients underwent a computed tomography scan, which showed a peritonsillar abscess in two cases. One patient was treated medically because of its small size and one had two-needle surgical drainages at the bedside with a favourable evolution.

Two patients had ocular involvement: one was relatively minor, involving palpebral lesions only, and the other was severe with the association of blepharitis, conjunctivitis, and keratitis. The diagnosis of MPXV infection was delayed because of this atypical presentation, and the patient received several treatments (oral valaciclovir, ocular tobramycin, ocular dexamethasone, ocular ganciclovir) beforehand. Two injections of intravenous antiviral treatment (cidofovir 5 mg/kg) were administered; however, the evolution is still ongoing.

The median (IQR) length of hospital stay was 3 (3–4) days, notably because of the young age of the patients, who preferred outpatient care. The management was often multidisciplinary involving other specialists in 13 cases (13/17, 76%). All patients but the one with the keratitis achieved full resolution of symptoms.

Discussion

This study describes 264 patients with MPXV infection in the context of the current western epidemic. During the same period, 577 cases were confirmed in France [17], including 387 in the Ile-de-France area.

As reported in other European countries, the transmission occurred almost exclusively within the community of MSM, often

with multiple partners. In this study, a significant percentage (71%) of affected patients was taking pre-exposure prophylaxis and 42% practiced chemsex. This encourages public health authorities to target prevention and vaccination messages to these populations that are at a high risk. Several countries including Canada, the United Kingdom, and France have already recommended preventive smallpox vaccine to MSM and particularly those with multiple partners.

The clinical pattern observed differs from that in the previous African outbreaks, with less frequent systemic signs and fewer skin lesions, than was reported during the 2003 outbreak in the United States [18]. However, a characteristic feature of this outbreak is the predominant genital and anal localization of skin lesions [19] leading to severe pain. These results argue for a current transmission of monkeypox during sexual intercourse.

Few studies have reported the proportion and the nature of hospitalized patients in the current outbreak, and MPXV is mistakenly often regarded as a benign disease. However, among the 264 patients in this study, 17 patients required hospitalization with different types of severe MPXV infection: 6 had skin superinfections such as necrotizing cellulitis or subcutaneous abscesses, requiring surgery for four of them; four had angina with dysphagia, one of whom required surgical drainage; four had severe anal or colorectal involvement; and two had ophthalmic involvement.

Unlike previous epidemics, the hospitalized patients neither were immunocompromised nor had conditions, particularly at risk of a severe form. It seems necessary to better study and communicate about the risk of severe local complications of MPXV infection, in particular local complications including genital, digestive and anal, oropharyngeal, or ophthalmological involvement. Physicians from different fields will take care of patients with MPXV infection and need to be able to diagnose early and appropriately manage this emerging disease.

Pain relief appears as one of the main challenges in the medical management of patients with MPXV infection, with patients experiencing headaches, sore throat, back pain, and mouth sores, as

Table 2
Description of hospitalized patients

| Patient | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 |
|-----------------------------------|-------|------|------|------|------|-------------------|--------------------|-----------|-------------|------|------|--------------------|------|-------|-------|-----|------|
| Age (y) | 34 | 35 | 30 | 31 | 44 | 47 | 25 | 28 | 36 | 30 | 34 | 33 | 28 | 37 | 24 | 48 | 28 |
| Medical history | HIV | HIV | None | None | None | Venous thrombosis | None | Cured ALL | HIV/Chemsex | None | None | None | None | None | None | HIV | None |
| Symptoms | | | | | | | | | | | | | | | | | |
| Fever | X | X | X | | X | X | X | X | X | X | X | | X | | | X | X |
| Total number of skin lesions | 30–50 | 6–15 | 6–15 | 6–15 | 6–15 | 6–15 | 6–15 | 15–30 | 6–15 | ≤5 | 6–15 | 6–15 | 6–15 | 15–30 | 15–30 | 0 | 6–15 |
| Lymph nodes | X | | | X | X | X | X | X | X | X | X | NA | X | X | X | X | X |
| Necrotic cellulitis | | | | | | | Genital + perineal | | | | | Genital + perineal | | | | | |
| Reason for hospitalization | | | | | | | | | | | | | | | | | |
| Paronychia | | | X | X | | X | | | | | | | | | | | |
| Lymphangitis | | | X | X | | X | | | | | | | | | | | |
| Dysphagia | | X | | | X | | | | | | | | | | | | |
| Colitis | | | | | | | | X | | | | | | | | | |
| Rectitis | X | | | | | | | X | | | | | | | | | |
| Ocular signs | | | X | | | | | | | | | | | | | | |
| Urologic | | | | | | | | | | | | | | | | | |
| Respiratory | | | | | | | | | | | | | | | | | |
| Urethritis | | | | | | | | | | | | | | | | | |
| Surgical management | | | | | | | | | | | | | | | | | |
| Antibiotics | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Anal treatment | | | | | | | | | | | | | | | | | |
| Cidofovir | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Acetaminophen | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Ortho-pedist | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Ophthalmologist | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Pain killers | | | | | | | | | | | | | | | | | |
| Opioids | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Other specialists involved | | | | | | | | | | | | | | | | | |
| Acetaminophen | | | | | | | | | | | | | | | | | |
| Ortho-pedist | | | | | | | | | | | | | | | | | |
| Ophthalmologist | | | | | | | | | | | | | | | | | |
| ENT surgeon | | | | | | | | | | | | | | | | | |
| Gastro-entéro-logist | | | | | | | | | | | | | | | | | |
| Procto-logist | | | | | | | | | | | | | | | | | |
| Acetaminophen | | | | | | | | | | | | | | | | | |
| Uro-logist | | | | | | | | | | | | | | | | | |
| Dermatologist | | | | | | | | | | | | | | | | | |
| Length of hospital stay (d) | 2 | 2 | 2 | 4 | 5 | 3 | 3 | 15 | 3 | 2 | 3 | 3 | 4 | 3 | 3 | 3 | 3 |

ALL, acute lymphocytic leukemia; HIV, human immunodeficiency virus.

previously reported [20]. Probably because of the change of transmission mode, anal pain was also very frequently observed (18%) in our patients and debilitating. The opioid prescription was often required in hospitalized patients but also for outpatients. There is currently no validated antiviral therapy for MPXV infection. Antivirals that appear effective *in vitro* include brincidofovir, cidofovir, tecovirimat, and hypervalent immunoglobulins. Given the unavailability of tecovirimat at the time of patient management, only one patient in this study received an intravenous antiviral treatment, cidofovir, for a severe ophthalmologic form with keratitis. Ocular complications, including keratitis and corneal melt, have been described with other poxviruses such as cowpox or smallpox [21,22].

The main limitation of the study is its monocentric nature with a possible patient recruitment bias related to the location and the specificities of the hospital. As a referral centre, the rate of complications and hospitalization rate may be overestimated. Owing to the hygiene protocols specificities in France regarding the analysis of body fluids in patients with MPXV infection, we were not able to test patients for associated sexually transmitted infections, although they appear to be frequent [9]. The follow-up of the patients was limited in this study and the evolution of the lesions, in particular concerning the risk of scarring, must be specified.

These results confirm the transmission of MPXV within the MSM community and provide data on the clinical characteristics of the disease and particularly on the severe infections found during the current epidemic. Four patterns of severe infections were observed: superinfected skin lesions including paronychia and genital cellulitis, severe anal and gastrointestinal symptoms, angina with dysphagia, and ocular involvement. Prospective national and international cohorts should refine the clinical description of patients including severe forms.

Author contributions

M.M. and A.L.B. are co-first authors and drafted the manuscript. N.P.S., M.T., D.L.P., and L.D. revised the manuscript. M.M., A.L.B., M.T., D.L.P., L.D., C.B., S.P., M.C., C.D.L.P.D.V., B.P., and B.M. were involved in the clinical management of outpatients and participated in the creation of the database. M.C. and V.J. were involved in the clinical management of hospitalized patients. F.B. gave his expert opinion in dermatology. C.C. was involved in the clinical management of patients in the emergency unit. V.F., N.F., and D.D. conducted the monkeypox virus polymerase chain reactions of the patients. All authors read, revised, and approved the final manuscript.

Transparency declaration

DD received payment from Viiv Health Care, Glaxo-Smith-Kline, Gilead Sciences, and Janssen Cilag for participating in meetings and/or on a Data Safety Monitoring Board or Advisory Board. The other authors declare that they have no conflicts of interest.

Acknowledgements

We thank the patients and the entire team of the Infectious and Tropical Diseases Department at Bichat for the care of patients during this epidemic period, especially Sylvie Lariven and Christophe Rioux.

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