Clinical Infectious Diseases

BRIEF REPORT

Clinical Course and Outcome of Human Monkeypox in Nigeria

Dimie Ogoina,[1] Michael Iroezindu,[2] Hendris Izibewule James,[1] Regina Oladokun,[3] Adesola Yinka-Ogunleye,[4] Paul Wakama,[5] Bolaji Otike-odibi,[6] Liman Muhammed Usman,[7] Emmanuel Obazee,[6] Olusola Aruna,[8] and Chikwe Ihekweazu[4]

[1]Infectious Disease Unit, Niger Delta University Teaching Hospital, Okolobiri, Bayelsa, Nigeria, [2]Infectious Disease Unit, Federal Medical Centre Owerri/University of Nigeria Teaching Hospital, Enugu, Nigeria, [3]Paediatric Infectious Disease Unit, University College Hospital, Ibadan, Oyo State, Nigeria, [4]Nigerian Centre for Disease Control, Abuja, Federal Capital Territory, Nigeria, [5]Nigerian Prison Services, Port Harcourt, Rivers State, Nigeria, [6]Department of Medicine, University of Port Harcourt Teaching Hospital, Port Harcourt, Rivers State, Nigeria, [7]Ministry of Health, Nasarawa, Nasarawa State, Nigeria, and [8]Global Public Health Department, Public Health England, London, United Kingdom

In a retrospective review of hospital records of 40 human monkeypox cases from Nigeria, the majority developed fever and self-limiting vesiculopustular skin eruptions. Five deaths were reported. Compared to human immunodeficiency virus (HIV)–negative cases, HIV type 1–coinfected cases had more prolonged illness, larger lesions, and higher rates of both secondary bacterial skin infections and genital ulcers.

Keywords. human monkeypox; clinical course; HIV/AIDS; outcome; Nigeria.

Although prior studies have described the epidemiology of the 2017–2018 human monkeypox (HMPX) outbreak in Nigeria [1–4], studies describing the clinical course and management of HMPX cases during the Nigeria outbreak are lacking.

In this study, we describe the clinical course, management, and outcome of patients with HMPX hospitalized during the Nigeria outbreak.

METHODS

Using a standardized checklist developed from reviewing prior studies [5–9], we conducted a retrospective review of case records of 40 HMPX patients hospitalized in various states in Nigeria between September 2017 and December 2018. The case definition and laboratory diagnosis of HMPX cases from Nigeria have been previously described [1, 10, 11].

We documented constitutional signs and symptoms at presentation, characteristics of skin rash, systemic symptoms and signs, clinical course, and complications, as well as the treatment received and sequelae at discharge or on follow-up. The human immunodeficiency virus (HIV) status of each case was documented.

Differences in study variables in relation to HIV status were determined. P value < .05 was taken as statistically significant (2-tailed). Ethical approval was obtained from the National Health Research Ethics Committee, Nigeria.

RESULTS

Study Participants

Of 51 hospitalized patients identified in the study period, 40 were included in this review. Eleven cases were excluded due to absence of details on skin characteristics (n = 7) and HIV status (n = 4).

Demographic and Clinical Characteristics

The demographic and clinical characteristics of the 40 cases in relation to their HIV status are summarized in Table 1. The cases were 28 days to 54 years of age (median, 32 years) and the majority (77.5%) were male.

The following clinical features were observed: skin rash (n = 40), fever (n = 36), lymphadenopathy (n = 35), genital ulcer (n = 25), body aches (n = 25), headache (n = 19), sore throat (n = 18), pruritus (n = 15), and conjunctivitis and photophobia (n = 9). Nasal congestion, cough, skin ulcers, and hemorrhagic skin lesions were observed in 5 cases each. Other less common features were nausea and vomiting (n = 3), hepatomegaly (n = 3), and scrotal edema (n = 2).

Of 35 cases who gave details of their first symptom, 23 (65.7%) had rash as the first symptom, while 12 (34.3%) had fever as first symptom. In 2 patients, genital rash associated with ulcer was the first symptom. Skin rashes were observed on the following sites: face (97.5%), trunk (92.5%), arms (87.5%), legs (85%), genitalia (67.5%), scalp (62.5%), palms (55%), soles (50%), mouth (37.5%), and eyes (25%). Generally, skin rashes were more apparent on the limbs and face than on the trunk. There was no reliable data on smallpox vaccination. A 21-year-old man had concomitant chickenpox diagnosed by polymerase chain reaction. Cases with genital ulcers were not screened for sexually transmitted diseases.

Lymphadenopathy was observed in the following sites: cervical (n = 11), submental (n = 5), inguinal (n = 12), axillary (n = 10), and generalized (n = 12). Twenty-one of 40 (52.5%) cases developed 1 or more complications, including secondary bacterial skin infection (n = 19), gastroenteritis (n = 5), sepsis

Received 10 October 2019; editorial decision 4 February 2020; accepted 10 February 2020; published online February 13, 2020.

Correspondence: D. Ogoina, Infectious Disease Unit, Department of Internal Medicine, Niger Delta University Teaching Hospital, Okolobiri, Bayelsa State, Nigeria (dimieogoina@gmail.com).

Clinical Infectious Diseases® 2020;71(8):e210–4

DOI: 10.1093/cid/ciaa143

Table 1. Demographics and Clinical Characteristics of Human Monkeypox Patients in Relation to Their Human Immunodeficiency Virus Coinfection Status

	Total	HIV$^+$	HIV$^-$	HIV$^+$ vs HIV$^-$	
Study Variables	No. (%)	No. (%)	No. (%)	OR (95% CI)	*P* Value
Age group					.12
< 35 y	27 (67.5)	4 (44.4)	23 (74.2)	.28 (.6–1.3)	
≥ 35 y	13 (32.5)	5 (55.6)	8 (25.8)	Ref	
Hospital stay[a]					.12
< 14 d	21 (100)	3 (33.3)	18 (66.7)	.25 (.05–1.24)	
≥ 14 d	15 (100)	6 (66.3)	9 (33.3)	Ref	
Duration of illness[a,b]					**.029***
< 28 d	24 (77.4)	3 (42.9)	21 (87.5)	Ref	
≥28 d	7 (22.8)	4 (57.1)	3 (12.5)	9.3 (1.36–63.9)	
Sex					.39
Male	31 (77.5)	6 (66.7)	25 (80.6)	2.1 (.4–10.8)	
Female	9 (22.5)	3 (33.3)	6 (19.4)	Ref	
Outcome					.31
Died	5 (12.5)	2 (22.2)	3 (9.7)	2.67 (.37–19.2)	
Survived	35 (87.5)	7 (77.8)	28 (90.3)	Ref	
Rash size[c]					**.020***
≥ 2 cm	20 (50)	8 (88.9)	12 (38.7)	12.7 (1.4–114.4)	
< 2 cm	20 (50)	1 (11.1)	19 (61.3)	Ref	
Mobility					.09
Bedridden	5 (12.5)	2 (22.2)	3 (9.7)	Ref	
Weak ambulant	25 (62.5)	3 (33.3)	22 (71)	1.0 (.1–8.9)	
Fully ambulant	10 (25)	4 (44.4)	6 (19.4)	.21 (.024–1.8)	
No. of skin rashes					.9
≤ 100	16 (40)	3 (33.3)	13 (41.9)	1.9 (.12–16.2)	
101–1000	17 (42.5)	5 (55.6)	12 (38.7)	2.5 (.24–26.5)	
> 1000	7 (17.5)	1 (11.1)	6 (19.4)	Ref	
Secondary bacterial infection					**<.0001***
Yes	19 (47.5)	9 (100)	10 (32.3)	3.1 (1.86–5.16)	
No	21 (52.5)	0 (0)	21 (67.7)	Ref	
Rash distribution[d]					.06
Confluent	4 (10)	1 (11.1)	3 (9.7)	Ref	
Semiconfluent	15 (37.5)	6 (77.8)	9 (29)	2.0 (.12–24.1)	
Discrete	21 (52.5)	2 (22.2)	19 (61.3)	.3 (.02–4.7)	
Rash characteristic[e]					.71
Monomorphic	25 (62.5)	5 (55.6)	20 (64.5)	Ref	
Pleomorphic	15 (37.5)	4 (44.4)	11 (35.5)	.69 (.15–3.10)	
Genital ulcer					**.015***
Yes	25 (62.5)	9 (100)	16 (51.6)	1.94 (1.38–2.72)	
No	15 (37.5)	0 (0)	15 (49.4)	Ref	

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; Ref, reference value.

[a]Data on hospital stay and duration of illness were missing in some patients.

[b]Number of days between first symptom (date of first symptom) and significant resolution of last symptom (date of discharge).

[c]Size of skin rash in its longest diameter; genital ulcer not inclusive.

[d]Confluent: majority of skin lesions were coalescing; semiconfluent: some skin lesions were distinct, a few others were coalescing; discrete: majority of skin lesions appeared distinct separated by normal skin.

[e]Monomorphic indicates similar size and appearance; pleomorphic indicates different size and appearance.

*Significant *P* values (Fisher exact test) in bold. Compared to HIV$^-$ cases, HIV$^+$ cases were significantly more likely to have longer duration of illness, larger rash size, secondary bacterial infection, and genital ulcers.

(n = 4), bronchopneumonia (n = 3), encephalitis (n = 3), keratitis (n = 3), and premature rupture of membrane at 16 weeks' gestation and resultant intrauterine fetal death (n = 1). All diagnoses were based on clinical judgement of the attending physician. Patients reported disfigurement from widespread skin lesions, pruritus, painful pustular lesions, and genital ulcers as the most distressful symptoms. Eleven of the 40 (27.5%) patients were observed to have developed symptoms of anxiety and depression during admission requiring psychological counseling.

Monkeypox and HIV Type 1 Coinfection

There were 9 HIV type 1 (HIV-1)/monkeypox-coinfected patients, including 4 with newly diagnosed HIV-1 infection and 5 patients previously on antiretroviral therapy (ART). Three of these 5 cases had apparently failed first-line ART and their CD4 cell counts at hospitalization were 101, 354, and 357 cells/μL, respectively. The case with a CD4 count of 357 cells/μL had a viral load of 4798 copies/mL. Three of the 4 newly diagnosed HIV cases had CD4 counts of 20, 55, and 300 cells/μL. CD4 cell counts and HIV viral loads were not available for other patients at the time of this report.

Compared to HIV-negative cases, HIV-1–infected cases were significantly more likely to have skin rashes ≥ 2 cm, genital ulcers, secondary bacterial skin infection, and longer duration of illness (Table 1).

Clinical Management of Patients

All cases received symptomatic and supportive care according to the Nigerian interim guidelines for management of HMPX [2]. The cases stayed 3 days to 54 days after admission, and the illness ended when skin rashes and ulcers resolved with crust formation, which eventually detached.

Outcome

Five of the 40 (12.5%) cases died: (1) a 34-year-old man who died by suicide (background psychiatry illness could not be established); (2) a female neonate aged 28 days who developed features of bronchopneumonia (with chest radiographic evidence of lung opacities) and encephalitis (generalized seizures) and died after 8 days; (3) a 42-year-old man with HIV-1 infection who developed sepsis and died after 37 days after admission; (4) a 43-year-old man with HIV-1 infection who had a CD4 count < 20 cells/μL and died following repeated seizures (suspected to have died from encephalitis); and (5) a 27-year-old HIV-negative man who developed features of bronchopneumonia and sepsis and died after 9 days after admission.

Clinical Sequelae

Of 31 admitted patients who were discharged from the hospital, only 18 (58.1%) were seen on follow-up (1–8 weeks after discharge). Sequelae observed in these cases included hyperpigmented atrophic scars (n = 12), hypopigmented atrophic scars (n = 7), patchy alopecia (n = 6), hypertrophic skin scarring (n = 3), and contracture/deformity of facial muscles following healing of ulcerated facial lesions (n = 1). In 3 patients, healing was complete and skin scars were no longer visible after 8 weeks of follow-up. The clinical photographs of some cases are shown in Figure 1.

DISCUSSION

Our study builds on previous reports of HMPX in Nigeria [1, 3, 4, 10, 11] by providing further perspectives on clinical features, clinical course, case management, and outcome of HMPX cases hospitalized during the outbreak.

The clinical findings in our study are comparable to previous reports of HPMX [1, 5, 12]. Most of our cases had vesiculopustular monomorphic skin eruptions < 2 cm in size, affecting mostly the face and limbs, and associated with fever and lymphadenopathy.

However, in contrast to previous studies where fever is recognized as the first symptom of the disease, the majority of cases in our cohort reported skin rash as the first symptom. The absence of a distinct febrile prodrome in HMPX has been attributed to differences in route of transmission, with 1 study suggesting that infections acquired via complex invasive exposures, with a break in the mucocutaneous barrier (such as bite or scratch from an infected animal), are more likely to have a shorter incubation period than those acquired from noninvasive exposures (such as close contact with or touching an infected animal) [6]. A predominantly animal source of transmission with associated human to human transmission is presumed in the Nigeria HMPX outbreak [1, 10, 11]. We can only speculate that some cases in our cohort had complex invasive exposures of some sort that blunted the distinct febrile prodrome characteristic of HMPX.

About 68% of our patients had genital lesions compared to prior studies from the Democratic Republic of Congo (DRC) and the United States (US), where only about 3%–25% of patients had genital lesions [5, 12]. Penile rash and groin lesions were also the first symptoms in cases of HMPX imported from Nigeria into the United Kingdom and Israel in 2018 [7, 8]. It is imperative for future studies to explore the role of the genital area or sexual route in the acquisition, transmission, and/or pathogenesis of HMPX in Nigeria. Previous studies had reported transmission of vaccinia virus after sexual contact with a smallpox vaccinee [9].

Previous reports of HMPX outside Nigeria have not identified HIV as an important cofactor in the epidemiology and clinical manifestation of HMPX [13]. In the evaluation of > 511 suspected cases of HMPX in DRC during the 1996–1998 outbreak, only 3 cases of HIV/HMPX coinfection were detected and the clinical details of these patients were not described [14]. None of the patients in the 2003 US outbreak were reported to be HIV infected [12, 15]. A mathematical model exploring the relationship between HIV and HMPX coinfection suggested that HIV may promote the transmission of monkeypox virus and vice versa [16].

In our cohort of 40 patients, we detected 9 HIV-1–coinfected patients who had larger skin lesions, more prolonged illness, and higher rates of genital ulcers and bacterial superinfection when compared to HIV-negative cases. It seems the presence of HIV-related immunosuppression alters the natural history and course of HMPX infection in coinfected patients. However,

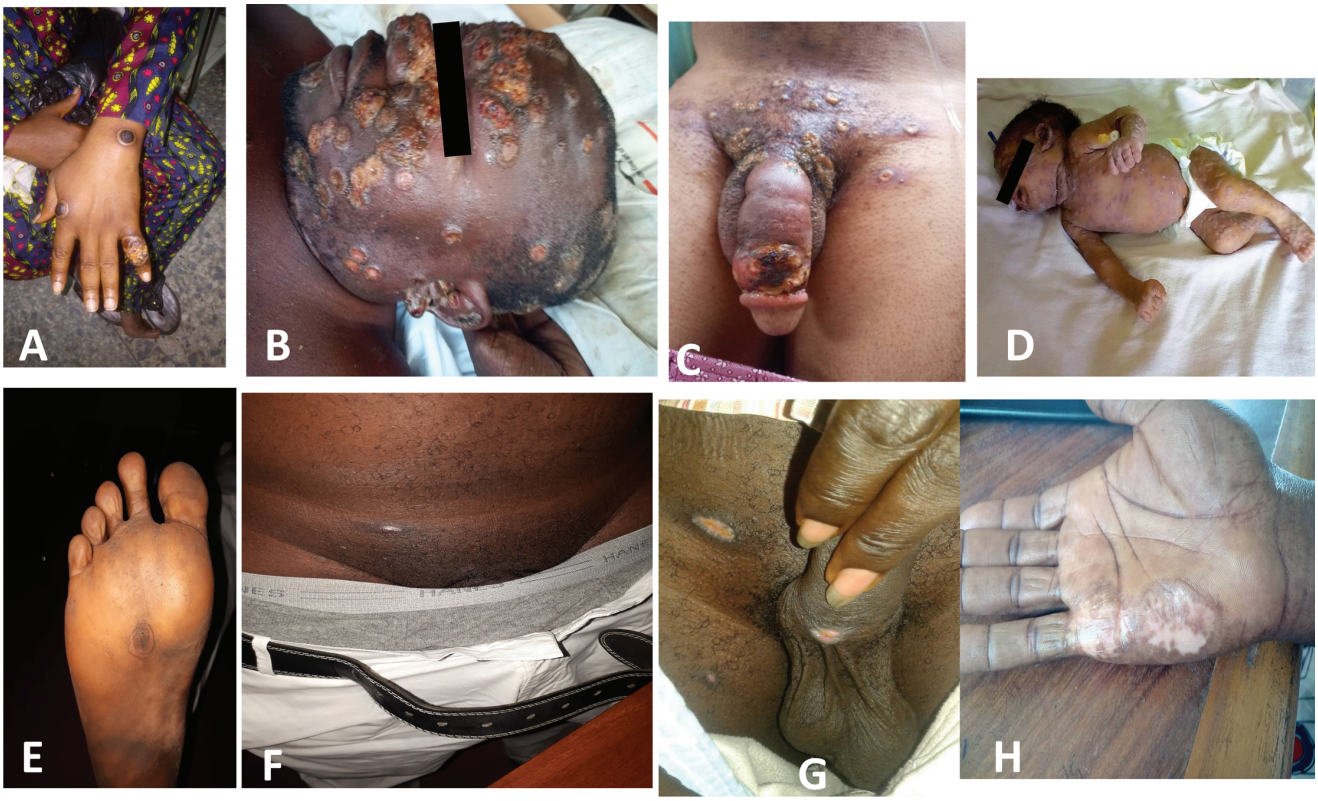

Figure 1. Variety of skin eruptions (*A–D*) and skin sequelae (*E–H*) in hospitalized patients with human monkeypox, Nigeria, 2017–2018. *A*, Discrete nodular lesions with central umbilication in an adult with human immunodeficiency virus (HIV) type 1 infection. *B*, Confluent facial nodular/pustular lesions with ulceration. *C*, Vesiculopustular lesions on groin and penile skin with hemorrhagic penile ulcer in an HIV-infected case. *D*, Generalized vesiculopustular lesions in a neonate. *E* and *F*, Hyperpigmented hypertrophic scars on sole of feet and groin. *G* and *H*, Atrophic hypopigmented scars on external genital and palm. Pictures in *A–D* were taken 4–10 days after onset of symptoms; pictures in *E–H* were taken 2–6 weeks after onset of symptoms.

further studies with a larger sample size would be required to confirm this assertion.

Our study is not without limitations. First, being retrospectively designed, study data are subject to incomplete documentation, missing data, and inadequate evaluation for comorbidities. Although most of the cases were seen by specialist physicians, observer bias is still possible. Second, the small number of hospitalized cases in our cohort precluded multivariate analysis.

Notwithstanding these limitations, our study findings have for the first time provided information on the experience with the clinical course, management, and outcome of the West African clade of HMPX from indigenous West Africans living in Nigeria. Future studies are required to further explore the interactions between HIV and HMPX virus, if any.

Notes

Acknowledgments. The authors acknowledge and appreciate all healthcare workers who participated in clinical management and follow-up of hospitalized patients during the outbreak.

Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References

1. Yinka-Ogunleye A, Aruna O, Dalhat M, et al. Outbreak of human monkeypox in Nigeria in 2017–18: a clinical and epidemiological report. Lancet Infect Dis **2019**; 19:872–79.
2. Nigerian Centre for Disease Control. Interim national guidelines for monkeypox outbreak response. **2017**. Available at: https://ncdc.gov.ng/themes/common/docs/protocols/50_1508912430.pdf. Accessed 9 October 2019.
3. Breman JG, Kalisa-Ruti, Steniowski MV, Zanotto E, Gromyko AI, Arita I. Human monkeypox, 1970-79. Bull World Health Organ **1980**; 58:165–82.
4. Ogoina D, Izibewule JH, Ogunleye A, et al. The 2017 human monkeypox outbreak in Nigeria—report of outbreak experience and response in the Niger Delta University Teaching Hospital, Bayelsa State, Nigeria. PLoS One **2019**; 14:e0214229.
5. Jezek Z, Szczeniowski M, Paluku KM, Mutombo M. Human monkeypox: clinical features of 282 patients. J Infect Dis **1987**; 156:293–8.
6. Reynolds MG, Yorita KL, Kuehnert MJ, et al. Clinical manifestations of human monkeypox influenced by route of infection. J Infect Dis **2006**; 194:773–80.
7. Erez N, Achdout H, Milrot E, et al. Diagnosis of imported monkeypox, Israel, 2018. Emerg Infect Dis **2019**; 25:980–83.
8. Vaughan A, Aarons E, Astbury J, et al. Two cases of monkeypox imported to the United Kingdom, September 2018. Euro Surveill **2018**; 23. Available at: http://www.ncbi.nlm.nih.gov/pubmed/30255836%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC6157091. Accessed 26 September 2019.
9. Centers for Disease Control and Prevention. Secondary and tertiary transmission of vaccinia virus after sexual contact with a smallpox vaccinee—San Diego, California, 2012. MMWR Morb Mortal Wkly Rep **2013**; 62:145–7. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23446513. Accessed 26 September 2019.
10. Yinka-Ogunleye A, Aruna O, Ogoina D, et al. Reemergence of human monkeypox in Nigeria, 2017. Emerg Infect Dis **2018**; 24:1149–51.
11. Faye O, Pratt CB, Faye M, et al. Genomic characterisation of human monkeypox virus in Nigeria. Lancet Infect Dis **2018**; 3099:231117.

12. Huhn GD, Bauer AM, Yorita K, et al. Clinical characteristics of human monkeypox, and risk factors for severe disease. Clin Infect Dis **2005**; 41:1742–51.
13. Hutin YJ, Williams RJ, Malfait P, et al. Outbreak of human monkeypox, Democratic Republic of Congo, 1996 to 1997. Emerg Infect Dis **2001**; 7:434–38.
14. World Health Organization. Technical advisory group on human monkeypox. Report of a WHO meeting. Geneva, Switzerland: WHO, **1999**. Available at: http://www.who.int/gpsc/events/2008/afro_pledge_event/en/. Accessed 28 November 2014.
15. Reed KD, Melski JW, Graham MB, et al. The detection of monkeypox in humans in the Western Hemisphere. N Engl J Med **2004**; 350:342–50.
16. Bhunu CP, Mushayabasa S, Hyman JM. Modelling HIV/AIDS and monkeypox co-infection. Appl Math Comput **2012**; 218:9504–518.