

Monkeypox: A real new warning or just a sign of times?

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INTRODUCTION

A 24-year-old male patient was admitted to the Internal Medicine Department of the General University Hospital of Larissa, Greece because of a 24-hour fever (40°C) and a 4-day ulcerated-crusting painful rash of 8–10 mm diameter isolated in the genital area. There were no other lesions in the rest of his body (Figure 1). He was treated previously by his physician with amoxicillin-clavulanate for 2 days, without improvement. Physical examination revealed additionally enlarged and painful inguinal lymph nodes. He had a past medical history of primary syphilis treated 3 years ago. He was heterosexual with a history of multiple sexual partners. Of note, neither the patient, nor his recent sexual partner had any recent travel history to endemic regions, including West and Central Africa or past and/or current history of intravenous drug use. Moreover, he did not have a history of any recent close contact with animals. He was fully vaccinated against coronavirus disease 2019 (COVID-19) and he did not report any recent SARS-CoV2 infection. He was repeatedly negative for human immunodeficiency virus (HIV). Laboratory investigation revealed elevation of C-reactive protein (7.5 mg/dL, reference value < 0.5), ferritin within normal limits (226 ng/mL, reference value < 400), mild leukopenia with lymphopenia (3700 and 660/ μ L, respectively), negative Rapid Plasma Reagin (RPR) and positive Treponema Pallidum Hemagglutination Assay (TPHA). Blood and urethral cultures tested negative. Molecular investigation of the skin lesions was negative for herpes

virus and Chlamydia trachomatis, but positive for monkeypox virus. He claimed that none from his recent sexual partners had a recent known monkeypox infection. The patient received supportive treatment (analgesics) and was discharged from the hospital after 10 days in a good clinical condition with resolution of fever within 48 hours after admission and improvement of all abnormal laboratory parameters (C-reactive protein 0.35 mg/dL, white blood cells 8800/ μ L and lymphocytes 3380/ μ L). He did not present any new lesions during hospitalization and his previous lesions were all healed with scabbing and desquamation.

TRANSMISSION OF MONKEYPOX VIRUS

This representative case shows how nowadays febrile ulcerated-crusting painful rash in the genital area should alert clinicians for the potential presence of monkeypox (MPX) disease. Human MPX is a zoonotic disease caused by the monkeypox virus (MPXV), a double-stranded DNA virus of the Orthopoxvirus genus of the Poxviridae family. MPXV was first isolated in 1958, in Denmark, from pox lesions among laboratory monkeys imported from Singapore. The first reported human case was a nine-month-old child, from the Democratic Republic of Congo (DRC) in 1970.^[1] Since then, MPX disease has been reported in several Central and Western African countries, both in sporadic cases or larger outbreaks. Indeed, between 1970 and 1980, 47 cases were reported in West and Central Africa, with a high mortality rate of 17% in children under 10 years-

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Figure 1: Genital isolated rash in a 24-year-old male patient with monkeypox disease.

old.^[2] Subsequently, in the 1980s and 1990s an over 10-fold increase in incidence of MPX disease in the African region was recorded with hundreds of cases annually, especially in the DRC. After 2000, DRC started recording all suspected cases of MPX that were over 18,000 during the decade 2010–2020.^[3] MPX disease was first reported outside Africa in 2003, when an outbreak of 47 cases was described in the US following exposure to MPXV-infected pet prairie dogs that were infected by exotic animals imported from Ghana. Since then and until the 2020s sporadic travel-associated cases have been recorded outside Africa only in a few countries like UK, Israel, and Singapore.

An interesting point is that the average age of patients have changed over these five decades from 4–5 years during 1970s and 1980s to 21 years in 2020s.^[3] In addition, two phylogenetically distinct clades of MPXV have been identified: the Central African (Congo Basin) clade (CAC) and the West African clade (WAC). Typically, the CAC is associated with more severe disease, higher mortality, and more frequent human-to-human transmission. As far as it concerns mortality, total case fatality rate for MPX disease

was 8.7% with a significant difference between the two clades (10.6% for CAC *vs.* 3.6% for WAC).^[3]

A recent outbreak of MPX disease was first described in Europe in April 2022. Due to the increased number of cases worldwide, on 23 July 2022 the WHO Director-General declared this outbreak a public health emergency of international concern (PHEIC).^[4] Of note, since 2009, there have been seven PHEIC declarations in total: the 2009 H1N1 (or swine flu) pandemic, the 2014 polio declaration, the 2013–2016 outbreak of Ebola in Western Africa, the 2016 Zika virus epidemic, the 2018–2020 DRC Ebola epidemic, the ongoing COVID-19 2020 pandemic, and the ongoing 2022 MPX outbreak. Nonetheless, current MPX outbreak is different from the previous ones regarding certain characteristics: a) epidemiological features of the patients b) primary mode of transmission and c) clinical presentation.

As of October 4th 2022, a total of 68,998 laboratory confirmed cases in 107 countries have been reported and overwhelmingly these cases do not have any epidemiological link to African regions.^[5,6] Of these, the majority of cases were reported in America (43,181 cases, 63%) and Europe (24,820 cases, 36%) and only a small percentage (726 cases, 1%) in the areas that have historically been linked with MPX disease *i.e.*, African Region. Moreover, available data indicate that most of the cases are males (97.5%) with median age of 35 years (18–44 years accounting for 79% of cases). Interestingly, among cases with known data on sexual orientation, 90% were identified as men who have sex with men (MSM) and have reported recent sex with one or multiple partners. HIV status was not available in most of the cases (only in 28% with 49% of whom tested HIV-positive). Available data show that in African region male gender is infected in lower percentages (64%) and in cases that age was available, the patients were younger than those in Europe and US (median age: 25 years with 38% of them between 0–17 years).^[5,6]

It is already known that MPX is a zoonotic disease that can be either transmitted from animals to humans through direct contact (bite or scratch), wild meat consumption of infected animals or among humans through close contact with skin lesions, and/or respiratory secretions, or indirectly through contaminated objects such as clothes and beddings.^[7] Nonetheless, transmission through respiratory secretions usually requires prolonged and close contact. Interestingly, the 2022 outbreak has shown another possible mode of transmission, as a recent sexual contact was reported, by far, more frequently (87%) of all the reported transmission events (especially in party settings)^[8] while MPXV DNA has been isolated in the semen and other bodily fluids, such as rectal swabs, faeces and urine of patients with the disease.^[9,10] Although in the current outbreak, sexual transmission seems to be the major

mode of transmission in non-African regions, it would be wrong to characterise MPXV infection a typical sexually transmitted disease, as it can also spread through any close contact with infected patients. Besides, the presence of MPXV in several bodily fluids raises some questions about the infectivity of these fluids, the potential of transmission from asymptomatic patients and the virus reservoirs in the human body. Certainly, public awareness and adoption of more safe sexual practices would attenuate the burden of the current outbreak.

BURDEN OF MONKEYPOX VIRUS

MPXV may cause severe disease in certain vulnerable population groups, such as young children, pregnant women and immunosuppressed individuals (*i.e.*, HIV-positive patients) due to impaired immune response.^[11] Nevertheless, most cases in the current outbreak present with mild symptoms, such as rash (84%) often -as in our case- localised in the genital area (45%), and not so extensive as it was described historically (some patients present only with a few lesions), sometimes accompanied with rectal pain and proctitis.^[12] Moreover, systemic symptoms are mainly fever (58%), lymphadenopathy (29%), and fatigue (29%) with a very low rate of serious complications, probably because the 2022 MPX outbreak has been associated with the milder WAC.^[5]

Due to the atypical presentation, clinicians may have a low threshold of suspicion for MPX disease. Up to the present, there is not excessive burden in healthcare facilities during the current outbreak, as the proportion of hospitalised cases is about one out of ten, with pain or bacterial superinfection representing the main clinical conditions. Notably, in a fair number of cases, patients are hospitalized only for isolation reasons to contain the spreading of MPXV. Twenty-six deaths have been recorded due to MPX disease globally as of October 4th; of these 9 (35%) in the African region where the number of cases with MPX account for 726, approximately 1% of the total global cases. However, worldwide the case mortality is currently estimated very low (0.03%).^[5] The increased mortality (approximately 1.2%) in African region could be attributed to the higher percentages of vulnerable groups that are infected (children and pregnant women), the lower socioeconomic level in several areas, which may affect the nutritional status and the possible lower or delayed access to healthcare facilities.

It is quite strange why this atypical outbreak of MPXV burst upon the world recently. Undoubtedly, populations have become more susceptible to MPXV as a result of the termination of routine smallpox vaccination due to the eradication of the disease in 1980, which offered some cross-protection against MPXV.^[13] Vaccination against smallpox

with first generation vaccinia virus-based smallpox vaccine was shown to be 80% effective in preventing MPX disease in the past.^[14] Moreover, another possible blameworthy factor could be the 2-years preceded COVID-19 pandemic; social isolation and lockdowns, may have led to lower individual immunity to infectious agents, although this has to be furtherly proved.^[15] In addition to that, COVID-19 lifestyle restrictions may have driven humans to the increased need for socializing and international travelling that were generally deprived during the pandemic.

Fatigue from the mandatory social distancing may have contributed to increased behavioral risk factors for MPXV transmission. MSM, who are more commonly related with increased risk sexual behaviors, seem to take, currently, the lion share of infections with MPXV in this epidemic (at least in the non-African regions) and the clinical presentation is often compatible with sexually transmitted diseases.^[5] Nevertheless, targeting and stigmatization of this group of people as the culprit of the current pandemic would be unnecessary and extremely harmful, as it could result in patients' unwillingness to seek medical help, avoid discrimination behaviors and racism, and therefore, to increase the burden of the disease.

It is not feasible to compare the current MPXV outbreak with the recent COVID-19 outbreak, as there are many significant differences between the two viruses. As of October 5th 2022, a total of 616,427,419 million cases were confirmed worldwide with 6,528,557 million deaths.^[16] SARS-CoV 2 is a novel RNA respiratory virus that was initially recognized in 2019; it is easily transmitted through respiratory droplets and one patient (sometimes even asymptomatic) can infect several others, without the need of prolonged and close contact.^[17] On the contrary, MPXV is a DNA virus which is not a respiratory virus and the primary mode of transmission is through direct, typically prolonged and close, contact with monkeypox rash or body fluids from someone who is infected.^[7] Therefore, MPXV is a far less transmissible virus than SARS-CoV2.

Moreover, MPXV being an "old acquaintance", gives the privilege to medical society to be more prepared, as there are already two available effective vaccines (JYNNEOS and ACAM 2000) against MPXV, that were originally used for smallpox prevention.^[18] Additionally, there are several antiviral drugs (*i.e.*, tecovirimat and brincidofovir, also initially approved for human smallpox disease treatment), that can be used currently in severe MPX cases under an investigational new drug protocol.^[19] Most importantly, the emergence of MPX disease outbreak after more than 2.5-years of experience with COVID-19 outbreak, has not either taken us by surprise or caught us unawares. We already know that for both diseases the basic principle for their

containment is early diagnosis, contact isolation of infected patients, contact tracing and epidemiological surveillance as well as early vaccination of all high-risk groups. Healthcare professionals are well-experienced in these tasks, although quite fatigued from the recent COVID-19 pandemic.

CONCLUSION

Due to all the above reasons, it is rather doubtful that MPXV outbreak has the potential to spread like a wildfire worldwide in the future. It is also doubtful, that healthcare systems will face enormous pressure from the hospitalized patients with MPX disease. Of note, during previous weeks, data from WHO present a stable decrease in the number of new confirmed cases globally, even though it is too early to get reassured.^[5] Global raising awareness of the communities, vulnerable subjects, and healthcare professionals seems the key to control this outbreak effectively.

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Author Contributions

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Conflict of Interest

All authors have nothing to declare.

Informed consent

The patient was not required to give written informed consent to the study because the analysis used anonymous data that was obtained after the patient agreed to participate by oral consent.

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