Human Monkeypox

Subjects: Infectious Diseases

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Recently, numerous cases of monkeypox were reported from several non-endemic countries in Europe, North America, and Oceania, suggesting an unusual and alarming public health issue, particularly considering that the disease is not directly related to human or animal travels. Attention is currently being drawn to this phenomenon since more than 70% of the global population is no longer vaccinated against smallpox.

monkeypox (MPX) epidemiology zoonotic pandemic

1. Introduction

Monkeypox (MPX) is a viral zoonosis brought on by a double-stranded DNA virus. It is a member of the *Poxviridae* family and the orthopoxvirus genus, which also includes the smallpox virus, known as the variola virus. [1]. The virus was initially discovered in monkeys at the Statens Serum Institute in Copenhagen, Denmark, in 1958 (1), giving rise to the sobriquet “monkeypox”; one group of children from the Democratic Republic of the Congo represented the first cases, discovered in 1970 [2]. There are two clades of monkeypox virus (MPXV): the West African variant, with an estimated case fatality ratio (CFR) of less than 4% and with higher prevalence in HIV patients, and the Congo Basin (Central African) variant, with a CFR of 10% [2].

Historically, vaccination against smallpox had been shown to be cross-protective against MPX [3]. However, after the eradication declaration regarding smallpox in 1980 by the World Health Assembly, vaccination against smallpox has ceased and, according to estimates, more than 70% of people worldwide are no longer immune to smallpox.

Since 13 May 2022, many cases of MPX have been reported from several non-endemic countries in Europe, North America, and Australia [4], representing an unusual and alarming public health issue considering that the disease is not directly related to human or animal travels [5]. Indeed, the number of cases reported is surprisingly high; there is no direct link between outbreaks and travels from endemic areas, and it is not clear whether the virus has developed more capacity for transmission between humans, as researchers know little of its general viral evolution and dynamics [6]. In addition, despite the general low mortality rate and the fact that no death has been reported during the current outbreak, many unusual aspects are creating public concern.

Moreover, although, in recent years, there have been cases reported in non-endemic areas, including the 2003 and 2021 outbreaks in the United States of America and Israel, the September 2018 outbreak in United Kingdom, and the May 2019 outbreak in Singapore, the current global epidemiology pattern has never been recorded before [7].

The MPV genomes are grouped into three monophyletic clades: two previously characterized clades (A.1 and A.2) and a newly emerging clade containing genomes from the ongoing multi-country outbreak in 2022 (B.1) [8][9]. Additionally, a recent article demonstrated the potential function of the enzyme APOBEC3 (host enzyme) in viral growth, as well as in potential MPV adaptability during the course of microevolution, by a detailed investigation of mutation hotspots [10].

Other articles have investigated how nine proteins could be crucial in the pathogenesis of the disease (A9L, A36R, A50L, B9R, B16L, C3L, C7L, C12L (SPI-1), and H5R), while four proteins are crucial for the host's immune response (A27L, A33R, B5R, and L1R), bringing the scientific community's attention to their role in disease development and host protection [11].

It is therefore mandatory and urgent to increase research efforts to close the gap of scientific knowledge, in order to stop current and future outbreaks and to optimize the surveillance and preparedness in containing and combatting MPX and zoonotic infections.

2. Monkeypox Multi-Country Outbreak, 2022

Between 1 January and 15 June 2022, 42 nations in five WHO regions collectively reported 2103 laboratory-confirmed cases, with only one death [12]. Most cases (98%) that have been documented since May 2022 have been identified in men who have sex with men (MSM), who are seeking care in primary care and sexual health clinics; however, this is not always the case. To yet, no travel connections to endemic regions have been discovered.

Up until 5 July 2022, 5949 cases of MPX had been identified across the European region via IHR mechanisms and official public resources from 33 countries. Of the 5266 cases reported in the European surveillance system (TESSy), 5265 had laboratory confirmation, and 99 were confirmed to be of the West African clade where sequencing was available. The earliest reported date of symptom onset was 17 April 2022. The majority of cases were in individuals who were between the ages of 31 and 40 (2214/5258-42%) and were male (5209/5230-99.6%). Of those cases with known HIV status, 40% (364/917) were HIV-positive [13]. The majority of patients (2684/2793; 96.1%) presented with a rash, while 1931/2793; 69% had systemic symptoms such as fever, exhaustion, muscular discomfort, vomiting, diarrhea, chills, sore throat, or headache [14]. There were no recorded deaths in any of the cases [15]. Although some (15) instances involving health professionals were recorded, more research is being conducted to ascertain whether the infections were caused by exposure at work [13][15]. Given the absence of epidemiological links to endemic areas, the unexpected appearance of MPX in several regions suggests that undetected transmission may have been occurring for a considerable time.

The current outbreak varies from the previous ones in terms of age (most of the people affected are in their thirties), sex/gender (most cases are male), risk factors, and mode of transmission, with sexual transmission being very likely. Along with being characterized by anogenital lesions and rashes that mostly spare the face and limbs, the clinical appearance is also uncommon and distinctive. Fever, lymphadenopathy, exanthema, asthenia, weariness, and headache were the most common signs and symptoms [16][17].

2.1. Pathophysiology and Clinical Manifestation

The MPX's natural reservoir has yet to be established, while rats are the most likely suspect. A possible risk factor is eating undercooked meat and other animal products from infected animals. People who live in or near wooded regions may also be exposed to infected animals in an indirect or low-level manner. Although MPX is not easily transmitted, it can be transmitted through contact with contaminated body fluids or lesion materials, both directly and indirectly [13]. Direct exposure includes contact with fomites, respiratory secretions, or skin-to-skin contact with MPX patients. Being in the patient's room or within 6 feet of a patient while they are undergoing any treatments that might produce aerosols from oral secretions, skin lesions, or the resuspension of dried exudates without donning an N95 mask and eye protection can result in indirect exposure [15]. Transmission can also happen through the placenta (which can cause congenital MPX) or through intimate contact during and after child delivery.

After entry, the virus replicates at the inoculation site, first localizing in mononuclear phagocytic cells. Then, it is released into the bloodstream and, finally, localizes again in skin cells. Following the first step of replication, it spreads to local lymph nodes and, thus, provokes a viremia within 10 to 14 days (the possible incubation period) [16].

The characteristic clinical manifestation, consisting of a vesiculo-pustular rash, is usually preceded by prodromal non-specific symptoms, such as fever, chills, myalgia, headache, lethargy, and lymphadenopathy [17]. Importantly, patients are infectious starting from the prodromal symptoms until the lesions form scabs and the scabs fall off. Usually, the oropharynx is the first site affected, after which lesions appear on the skin.

The clinical presentation of MPX cases associated with the current outbreak has been variable thus far. Many cases in this outbreak do not exhibit the classically described clinical patterns for MPX (fever and swollen lymph nodes, followed by a centrifugal evolving rash). The presence of only a few or even a single lesion, lesions that start in the genital or perineal/perianal region and do not spread, lesions that manifest at various (asynchronous) stages of development, and the appearance of lesions before the onset of fever, malaise, or other constitutional symptoms are some of the examples of abnormal characteristics [17][18]. The mechanisms of transmission during sexual contact remain unknown, despite the fact that it is known that close physical and personal skin-to-skin or face-to-face contact might result in transmission (through direct contact with infected skin).

2.2. Diagnosis and Differential Diagnosis

For the diagnosis of MPX, it is essential to first define the 'suspect case' in accordance with WHO recommendations, i.e., a person of any age who presents in a non-MPX endemic country with an unexplained

acute rash, and with one or more of the following signs or symptoms for which the common causes of acute eruption do not explain the clinical presentation: headache, the acute onset of a fever above 38.5 °C, lymphadenopathy, myalgia, back pain, and asthenia [19]. In addition, many authors report a characteristic triad for the diagnosis of MPX: skin lesions, lymphadenomegaly, and fever [18][20][21].

For its specificity and sensitivity, the polymerase chain reaction (PCR) test is the gold standard laboratory test, but the type and quality of the sample for the laboratory test is crucial. As a result, the best diagnostic samples for MPX are fluid from vesicles and pustules, as well as dried scabs. Moreover, when it is possible, a biopsy may be utilized. As per the CDC recommendations, the lesion samples must be maintained in a cool environment and stored in a dry, sterile tube [22]. Experience has shown that MPX virus DNA may be found in saliva, blood, urine, semen, feces, and nasopharyngeal swabs [18][20][21].

Unfortunately, antigen and antibody detection assays do not offer MPX-specific confirmation because orthopoxviruses are serologically cross-reactive. When resources are limited, serology and antigen detection procedures are not recommended for diagnosis or case investigation. Furthermore, recent or past vaccine-based immunization may result in misleading positive findings. In addition, PCR tests on pharyngeal swabs and seminal fluid may be a good strategy, considering the transmission pathways of the virus, especially if the patient presents symptoms such as a sore throat or penile lesions.

As part of a clinical differential diagnosis, it is important to rule out other rash-presenting conditions, such as molluscum contagiosum, chickenpox, measles, bacterial skin infections, scabies, syphilis, and medication-related allergies.

Lymphadenopathy can be used to differentiate MPX from chickenpox or smallpox during the prodromal stage of sickness. Additionally, non-infectious illnesses, including Behcet's diseases, squamous cell carcinoma, and recurrent aphthous stomatitis must be ruled out, in addition to other MST conditions (sexually transmitted diseases), such as the herpes simplex virus, syphilis, chancroid, lymphogranuloma venereum (LGV), and granuloma inguinale are crucial in differential diagnosis [21][23].

2.3. Prevention and Treatment

Vaccination with first-generation (e.g., Dryvax, Aventis Pasteur Smallpox Vaccine), second-generation (e.g., ACAM2000) and third-generation (IMVAMUNE and LC16m8) vaccines is the first line of defense against orthopoxvirus disease. Despite the fact that these vaccines provide effective protection, their widespread use is limited by the high rate of adverse events associated with live, attenuated virus immunization [24][25].

All first- and second-generation vaccines use a live, replication-competent virus. A successful vaccination procedure produces a lesion at the site of administration that generates the infectious virus. However, there is the risk of adverse events, such as autoinoculation to other parts of the body, as well as inadvertent transmission to other people, post-vaccine encephalitis, and disseminated infection in immunosuppressed patients. The third-generation vaccine no longer poses the risk of autoinoculation, unintentional transmission, or systemic

dissemination, while having a better safety profile due to its decreased capacity to replicate in mammalian cells and the absence of a lesion at the site of immunization. It is recommended for people who have higher risk factors for adverse outcomes, such as people with HIV, patients with hematological conditions, and immunocompromised individuals [25][26][27].

There are no recognized treatment guidelines for MPX infection at this time.

Tecovirimat, a viral envelope protein p37 inhibitor that prevents virus particles from being released from infected cells, has been shown to be beneficial in treating a range of poxvirus-related illnesses in animal studies. It has been approved by the US Food and Drug Administration (FDA) (Silver Spring, MD, USA) for the treatment of smallpox since July 2018, and by the European Medicines Agency (EMA) (Amsterdam, The Netherlands) for the treatment of MPX and cowpox since January 2022, despite the lack of clinical efficacy trials [28][29]. A very recent study on seven people with MPX in the UK in the period from 2018 to 2021 showed good profile efficacy with Tecovirimat (ST-246) [30]. Currently, Tecovirimat may be considered for treatment in people suffering from severe disease (e.g., hemorrhagic manifestation, CNS involvement, confluent lesions, and sepsis) or in people at a high risk of severe disease (people with immunocompromised conditions or pediatric populations, particularly in patients younger than 8 years of age or in pregnant or breastfeeding women).

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