Epidemiological Considerations and Differential Diagnoses of Mpox: A Narrative Review

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ABSTRACT

Mpox, previously called monkeypox, is a zoonotic disease of viral origin caused by a double-stranded DNA mpox virus that belongs to the Orthopox genus of the Poxviridae family. This condition was declared a disease of global public health concern in 2022. The progression of the rash of mpox from maculopapular lesions to vesicles and pustules, which eventually form crusts and scabs, gives rise to other diagnostic possibilities as it runs its course.

In the Nigerian setting, where advanced diagnostic facilities may not be readily available, the healthcare provider needs to understand the epidemiology of mpox infection and the relevant differential diagnoses to be considered in a resource-limited environment. This will enable earlier recognition of the disease, prompt treatment, and reduce transmission.

The objective of this paper is to review various studies that have discussed the epidemiology and differential diagnosis of mpox and discuss the epidemiology of mpox in the Nigerian setting. Additionally, it describes the relevant dermatologic conditions that should be considered as differential diagnoses within the environmental context before the appropriate confirmatory investigations are carried out.

Keywords: Mpox, Virus, Epidemiology, infectious diseases

Aspects Epidémiologiques et Diagnostics Différentiels de la Variole Simienne (MPox) : une Revue Documentaire

La variole simienne est une zoonose d'origine virale causée par un virus à ADN double brin appartenant au genre Orthopox de la famille des Poxviridae. Cette affection a été déclarée maladie de santé publique de portée mondiale en 2022. La progression de l'éruption cutanée de la variole simienne des lésions maculo-papuleuses aux vésicules et aux pustules, qui finissent par former des croûtes et des squames, font évoquer d'autres hypothèses diagnostiques au cours de son évolution.

Dans le contexte nigérian, où les plateaux techniques pour un diagnostic de pointe ne sont pas facilement accessibles, le prestataire de soins doit comprendre l'épidémiologie de l'infection et les diagnostics différentiels pertinents à évoquer dans un environnement de ressources limitées. Cela permettra une détection plus précoce de la maladie, un traitement rapide et une réduction de sa transmission.

L'objectif de cet article est de passer en revue diverses études qui ont abordé l'épidémiologie, le diagnostic différentiel de la variole simienne et d'en discuter de l'épidémiologie dans le contexte nigérian. De plus, il décrit les affections dermatologiques pertinentes qui doivent être considérées comme diagnostics différentiels dans le contexte environnemental avant que les investigations de confirmation appropriées ne soient effectuées.

Mots-clés : Mpox, Virus, Epidémiologie, maladies infectieuses

INTRODUCTION

Mpox, previously called monkeypox, is a zoonotic disease of viral origin caused by a double-stranded DNA virus (mpox virus) that belongs to the Orthopox genus of the Poxviridae family.[1] This virus was first discovered in 1958 following an outbreak in colonies of monkeys used for research, and this is where the original name monkeypox was derived.[2] The first human case of mpox was identified in 1970 in the Democratic Republic of Congo in a 9-month-old boy in a region where smallpox had been eliminated in 1968.[3]

Mpox was initially an infection limited to the rainforests of Central and Western Africa. The initial occurrences in the Western world were observed in 2003 when several persons exposed to ill Prairie dogs

(Cynomys Species) from Ghana developed fever, rash, lymph node enlargement and respiratory symptoms.[3]

Mpox over the years has been of public health concern, especially with the typical presentation of generalized vesicular rash with fever and attendant impairment of quality of life. The risk of contagion and transmission of mpox has also increased the quest for more education about Mpox.

Mpox, as a clinical entity, has several differential diagnoses that should be considered in a patient presenting with fever and a vesicular rash. The evolution of the rash from maculopapular to vesicular lesions with umbilication and the presence of lesions on the palms of the hands and soles of the feet are important to note in considering mpox among the diagnostic possibilities. (Figures 1a & b) (Figures 2a & b)

This review aims to emphasize salient features in the epidemiology of mpox in the Nigerian setting and discuss the differential diagnoses of mpox. Various conditions like smallpox (though eradicated), chickenpox, molluscum contagiosum and herpes simplex virus infection will be addressed in the review of the differential diagnoses of mpox.

Epidemiology of Mpox

After 39 years of no documented cases, mpox resurfaced in 2017.[4,5] This raised concerns globally, giving rise to the need to study the epidemiological correlates of the infection in Nigeria. In addition to this was the export of the infection to other parts of the world by travelers such that the Monkeypox virus (MPXV) was considered to occupy immunological and ecological spaces vacated by smallpox.

Mpox is usually a self-limiting disease with symptom duration ranging from two to four weeks, though severe cases may be longer. The incubation period is between 5 and 21 days.[6] The documented mode of transmission of mpox is through close contact with an individual or animal infected with the virus or contact with materials infected with the virus.[4–6] Epidemiological trends in case fatality worldwide have followed a decreasing trend from 5.38% in 1980 to 1999 to 4.45% in 2000-2022.[7]

A review of cases of mpox in Nigeria from 2017 to 2021 documented 226 cases of mpox with young adults between 21 and 30 years of age at higher risk.[8] The South West and South-South geopolitical zones were the identified locations of clusters of the disease, with identified risk factors being the consumption of giant rats, occupational transmission amongst health workers and improper disposal of rodents suspected to have been infected with mpox.[8,9] The review by Ogunleye et al. of the 2017 to 2018 outbreak noted that 17 states of the country reported at least one confirmed case and 30% of these confirmed cases had an epidemiological link with an individual with a similar skin rash.[5] The epidemiological review also reported that apart from all the confirmed cases having a vesicular rash, 88% of confirmed cases of mpox had fever, 69% had palmar lesions, and 64% had rashes on the soles of the feet.[5] The contribution of Human Immunodeficiency Virus (HIV) infection to the outcome was also documented as four out of the seven (57%) of the mortalities recorded in the 2017 to 2018 mpox epidemiological review had HIV infection.[5]

Two clades of the mpox virus infection are known: the Congo Basin (Central African) clade, now called clade 1, and the West African clade, now called clade II, with subclades IIa and IIb.[10] The West African clade appears to have been responsible for the outbreak of mpox in non-endemic areas, with studies still being undertaken to understand the scientific and genomic basis of this occurrence.[10]

Research on the 2022 global mpox outbreak outside Nigeria and other areas of mpox endemicity suggested changes in the biology of the virus.[10,11] A disproportionate infection of gay or bisexual men has been recorded, with no clear-cut scientific evidence of transmission through semen or vaginal.[11,12] Mucosal and genital involvement was also recorded in these patients (Figure 1a & Figure 1b).[11] The pattern of spread and the rising number of cases in countries previously non-endemic for mpox led to the World Health Organization (WHO) declaration of the mpox outbreak of 2022 as a public health emergency of international concern.[13,14]

Epidemiological reviews of the 2022 mpox outbreak in Nigeria, where the first case in the United Kingdom appeared to have originated, became

paramount for global public health reasons.[9,15] A study from Adamawa state in Nigeria reported male preponderance among confirmed cases of 82%.[16] Male preponderance has been reported in a review of previous outbreaks in Nigeria.[5] A significant rate of co-infection with varicella Zoster Virus (VZV) infection of 27% was also documented in the review of the 2022 mpox outbreak in Nigeria.[16]

Although there has not been documentation of transmission of mpox among men who have sex with men(MSM) and bisexual individuals in Nigeria, unlike in the outbreaks in the Western world, there are reports suggestive of sexual transmission of mpox among heterosexuals and those who engage in transactional sex.[17] An important point in this report involving linked heterosexual casual partners is the finding that those in this cohort had genital lesions after casual sexual activity without the use of condoms.[17]

Differential Diagnoses of Mpox

Various differential diagnoses may present as fever with a rash similar to mpox, and it will be helpful if considerations are given to these differentials like chickenpox, herpes simplex virus infection, and molluscum contagiosum, among others.[18] The ultimate confirmation of the diagnosis of mpox is with real-time polymerase chain reaction (PCR).[19]

Variola (Smallpox)

Smallpox is a clinical condition caused by the variola virus, a member of the Poxviridae family and Orthopoxvirus genus. Humans are the only known reservoir and host of smallpox, and this was instrumental to its eradication through focused vaccination campaigns.[18] The incubation period of smallpox is 7–14 days, and smallpox also has a febrile prodrome of 1–4 days,[18,20] while the incubation period of mpox is 5 to 21 days.[6]

The skin lesions of smallpox and mpox are similar in appearance. The evolution of the rash in both smallpox and mpox is similar, from macules to papules to vesicles to pustules, which eventually form a deep-seated firm and round umbilicated lesions.[18] This similarity poses a challenge in differentiating them based on clinical appearance. Although the appearance is in a centrifugal pattern like mpox, mpox has a milder presentation of fever and rash with lower mortality than smallpox.[20]

In our current clinical context, smallpox will not be a major differential diagnosis consideration because it was eradicated in 1980.[21] It is strongly believed that there is a cross-protection against mpox by previous smallpox vaccination due to observations that the age groups affected by mpox are those born after the eradication of smallpox and its vaccinations.[20]

A clinically important finding in mpox is the regional lymphadenopathy not seen in smallpox.[18,20] Unlike mpox, where there is usually no scarring in uncomplicated cases, those who recover from smallpox have characteristic scarred skin lesions in the affected areas.[20]

Chickenpox

Varicella Zoster Virus (VZV) infection, also known as chickenpox, is caused by the Varicella Zoster Virus (VZV), a member of the herpes viridae family. There is no known animal reservoir; hence, transmission is by human-to-human contact.[18,22] Chickenpox presents with fever and a pruritic rash, which may also be present in mpox. Unlike the mpox infection rash, the varicella rash is superficial, centripetally distributed, non-umbilicated and has irregular borders.[18] The lesions in chickenpox are also at different stages of evolution in different body parts and usually spare the palms and soles.[18,22] The rash in chickenpox classically has an appearance described as "dew drop on a rose petal".[18]

Herpes Zoster, also called shingles, arises due to reactivation of latent virus within the dorsal root ganglia. Shingles presents as painful vesicles in a dermatomal pattern, although ongoing immunosuppression may alter the distribution and make it more extensive.[18]

In clinical practice, differentiating between chickenpox and mpox may become challenging due to the similarity in the appearance of the rash. In some instances, several cases diagnosed as mpox were confirmed by PCR testing to be varicella infection.[22,23] Another challenging scenario is the co-infection of mpox and chickenpox in which skin manifestations of both conditions are observed and PCR testing done is positive for both viruses (Figure 3).[24] There are also

documented cases of atypical manifestation of varicella with palmar lesions, vesicles resembling mpox and lymphadenopathy in patients clinically diagnosed as mpox, but PCR testing confirmed the diagnosis as varicella (Figure 4).[25] This emphasizes the need for testing of vesicular skin lesions to confirm the diagnosis.

Genital Herpes

A viral infection that is caused by the Herpes Simples Virus type 1 (HSV-1) and/or Herpes Simplex Virus type 2 (HSV-2) depending on the sexual practice and orientation.[26] The vesicular genital lesions which HSV-2 more commonly causes can be a differential diagnosis of mpox particularly those presentations of mpox with few genital lesions.[27] The incubation period ranges from 2 to 12 days, and the presentation of herpes simplex virus infections varies widely from vesicles to pustules to erosions to ulcerations. The vesicles and pustules may be umbilicated. [28,29] The lesions are painful but may be pruritic, and the presence of lymphadenopathy may also strengthen its consideration as a differential diagnosis of mpox.[18,28,29]

Syphilis

Syphilis is a bacterial infection caused by *Treponema Pallidum.*[30] This organism is a spirochaete known for its invasiveness and ability to evade host immunity.[31] Syphilis is known to be a great mimicker of various medical conditions because of its varied presentation.[31] The infection occurs when the causative organism enters the subcutaneous tissues through small abrasions. A primary chancre is a lesion which arises when the organism successfully evades the host's local immune response. The initial painless papule ulcerates to form the isolated indurated chancre with regional lymphadenopathy.[32,33] Individuals with immunocompromise usually have several lesions. Lesions of secondary syphilis are usually macular or papular and not vesicular, as seen in mpox, although some may occur on palms and soles.[33]

Molluscum Contagiosum

A self-limited skin infection is seen in children, sexually active adults, and immunocompromised individuals.[34] The causative organism is a poxvirus in the Poxviridae family.[35] There are four subtypes of the molluscum contagiosum virus (MCV): MCV-1, MCV-2, MCV-3 and MCV-4. MCV-1 commonly causes infection in children, while MCV-2 is implicated more in molluscum contagiosum seen in older adults and sexually transmitted infections, while MCV-4 is relatively rare.[36] Molluscum contagiosum can be easily transmitted among individuals by direct contact with active lesions or indirectly through sharing of clothes, beddings or towels.[37] The virus typically remains in the epidermis and does not move in the bloodstream.[37] The lesions are described as small dome-shaped papules with central umbilication.[36] These lesions are usually less than 20, but they may be numerous in immunocompromised individuals. The lesions of molluscum contagiosum also usually appear in clusters, but unlike the lesions of mpox, they are usually painless.[37] Infection with mpox may present in the cornea with scarring, which may result in loss of vision. Molluscum contagiosum can rarely cause unilateral refractory conjunctivitis.[36,38]

Mpox and molluscum contagiosum both tend to lead to complications like secondary bacterial infections and irritation.[35]

Scabies

Scabies is a skin infestation caused by Sarcoptes scabiei var hominis.[39,40] Human scabies is a contagious skin infestation often associated with overcrowding and poor hygiene in underserved populations. Transmission of scabies is by close skin-to-skin or sexual contact.[39,40] Scabies is considered a differential of mpox due to the nature of the rash.[37] The significant pruritus seen in scabies is not seen in isolated mpox infection that presents without a co-infection with other conditions like varicella.

An individual with scabies infestation is considered contagious until the treatment is undertaken and the mites and eggs are destroyed.[37] The clinical presentation of scabies as a symmetrical papulovesicular rash with a predilection for the areolae, volar surfaces of the wrists, buttocks and genitals strengthens its position as a possible differential since mpox also presents as a vesiculo-papular rash.[37,41] An important difference in adults is that scabies rarely affect the face, which is usually the case with mpox. [41] It is important to state that the

burrows seen as short linear tracts that end up with the intact vesicles or burrows that contain the mite may not be easily appreciated during visual examination and dermoscopy has become relevant in diagnosing scabies.[39,42] A patient with scabies is contagious until effectively treated medically, but with mpox, the condition is mostly self-limited, and the infected person is no longer contagious after the last lesions have crusted and replaced with a new layer of skin.[37]

Conclusion

A medical condition like mpox presenting with fever, a vesiculo-pustular rash and lymphadenopathy may pose a diagnostic challenge because several differential diagnoses can present similarly, though with subtle differences. Navigating through these similar conditions is important to making the right diagnosis and effecting appropriate treatments.

Medical conditions like syphilis, scabies, molluscum contagiosum and chickenpox may mimic the clinical presentation of mpox and should be considered as differential diagnoses depending on the stage of presentation. This will guide the process of conducting relevant investigations to confirm the most plausible diagnosis.

Understanding the epidemiology of mpox in Nigeria also helps strengthen the managing physician's clinical decision-making ability by eliminating unlikely causes of similar rashes based on epidemiological reasoning. Ultimately, in a resource-constrained setting like Nigeria, scarce resources will be well managed while still being able to carry out relevant confirmatory investigations and treat patients accordingly.

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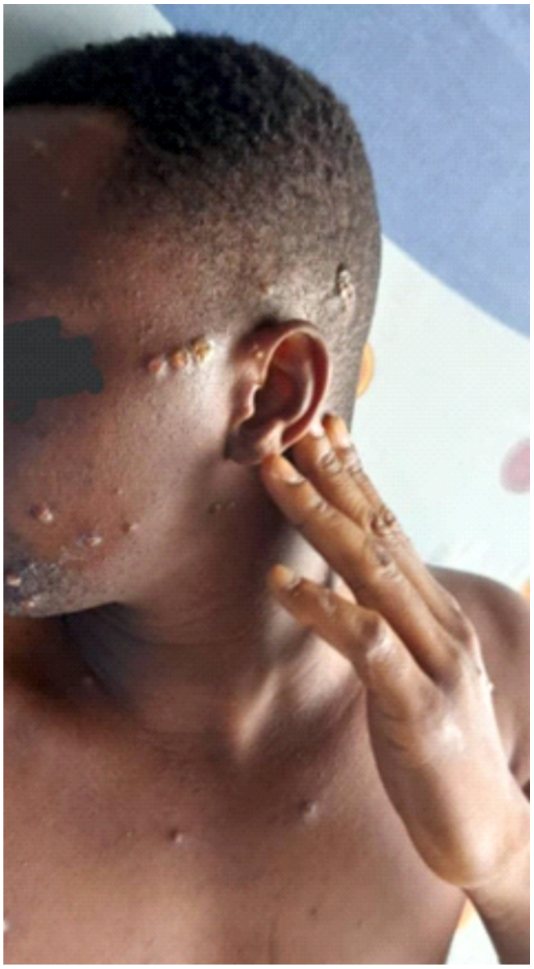

Figure 1a: Patient with umbilicated vesicles of Mpox on the face

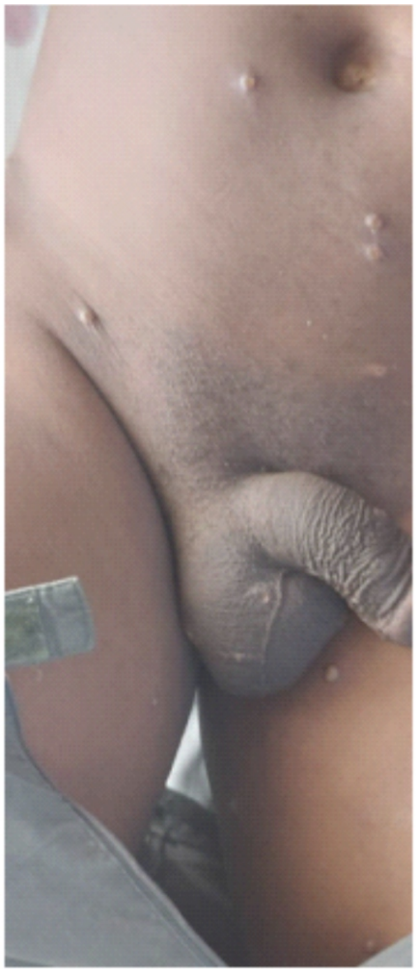

Figure 1b: Same patient with genital lesions

Figure 2a: Palmar lesions of Mpox

Figure 2b: Crusted healing mpox lesions on the soles of the feet of the same patient

Figure 3: Mpox & chickenpox co-infection: Note the numerous lesions at various stages (PCR positive for both mpox and varicella)

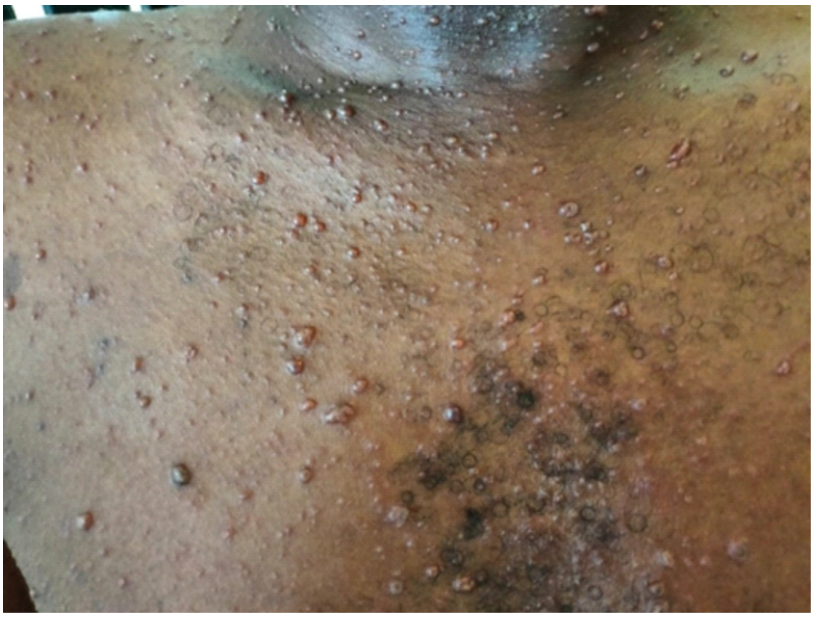

Figure 4: Atypical presentation of varicella - Note the umbilicated lesions almost all at the same stage (PCR negative for Mpox but positive for varicella).