Exploring atypical manifestations of Mpox: A narrative review

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Abstract

Mpox (formerly referred to as monkey pox), a viral infection known for its characteristic manifestations, presents with atypical symptoms, leading to diagnostic and management challenges. Recent outbreaks of the disease have also revealed changes in the epidemiologic patterns of the disease with many cases going unnoticed. These scenarios if not properly identified and addressed can led to increased healthcare burden created by the virus. To conduct the narrative review of the concerned literature, a comprehensive and well through search from PUBMED, Google scholar, EMBASE and African Journal Online Evaluating Studies was conducted from published works between 2003 to 2023. This narrative review aims at exploring the atypical manifestations of Mpox, by reviewing various manifestations of the disease, examining the overlying mechanisms and factors influencing these manifestations; and more so, assessing various clinical implications and challenges facing its management, with the hope of suggesting future directions in tackling the clinical implications and challenges. Regarding the atypical manifestations of Mpox, the review focused on the neurological, dermatological, and respiratory presentations, highlighting the diverse symptoms observed in each case. In addition, accurate diagnosis of atypical cases is crucial and requires a high index of suspicion, comprehensive differential diagnosis, and appropriate diagnostic testing. Tailored strategies for treatment are essential to address the specific manifestations observed. For future research, a focus on elucidating the pathogenesis, identifying risk factors, improving diagnostic approaches, and evaluating treatment strategies for atypical Mpox cases is required.

Explorer les manifestations atypiques de Mpox: une revue narrative Titre fonctionnement proposé : Manifestations atypiques de Mpox

Résumé

La variole du singe (anciennement appelée variole du singe), une infection virale connue pour ses manifestations caractéristiques, présente des symptômes atypiques, entraînant des défis de diagnostic et de prise en charge. Les récentes épidémies de la maladie ont également révélé des changements dans les schémas épidémiologiques de la maladie, de nombreux cas passant inaperçus. S'ils ne sont pas correctement identifiés et traités, ces scénarios peuvent entraîner une augmentation du fardeau des soins de santé créé par le virus. Pour mener l'examen narratif de la littérature concernée, une recherche complète et approfondie de PUBMED, Google Scholar, EMBASE et African Journal Online Evaluating Studies a été menée à partir d'ouvrages publiés entre 2003 et 2023. Cette revue narrative vise à explorer les manifestations atypiques de la Mpox, en passant en revue diverses manifestations de la maladie, en examinant les mécanismes sous-jacents et les facteurs influençant ces manifestations ; et plus encore, évaluer diverses implications cliniques et défis auxquels est confrontée sa gestion, dans l'espoir de suggérer des orientations futures pour aborder les implications et défis cliniques. Concernant les manifestations atypiques de Mpox, la revue s'est concentrée sur les présentations neurologiques, dermatologiques et respiratoires, mettant en évidence les divers symptômes observés dans chaque cas. En outre, un diagnostic précis des cas atypiques est crucial et nécessite un indice de suspicion élevé, un diagnostic différentiel complet et des tests diagnostiques appropriés. Des stratégies de traitement sur mesure sont essentielles pour traiter les manifestations spécifiques observées. Pour les recherches futures, il est nécessaire de se concentrer sur l'élucidation de la pathogenèse, l'identification des facteurs de risque, l'amélioration des approches diagnostiques et l'évaluation des stratégies de traitement pour les cas atypiques de Mpox.

INTRODUCTION

The monkey pox virus (Mpox) virus (formerly known as monkey pox) infection, is a re-emerging disease caused by the Monkeypox virus which is an Orthopox virus first isolated from skin lesions of the Macaque in a Danish laboratory in 1958 (1,2). Two main forms of the virus have been identified: the Central Africa (CA) clade also referred to as Clade I, and the West African (WA) Clade now represented as Clade IIa and IIb in the order of their discovery (3). The World Health Organization (WHO) declared Monkeypox virus infection a Public Health Emergency of International Concern after cases of the disease were reported in 75 countries globally (2).

The Mpox virus infection commonly manifest with systemic symptoms such as fever, malaise, myalgia and skin rash. However, despite its classical presentation, diverse manifestations can lead to atypical presentations, often resulting in missed and delayed diagnoses.

Recent epidemics have seen a difference in the usual presentation of the disease (4). A significant number of presentations (50%), seen during the 2022 epidemic outbreak of Mpox highlighted the absence of characteristic prodromal phase associated with the disease (4, 5, 6, 7). Other studies have reported asymptomatic and undetected cases (8, 9), thereby, increasing the possibility of missed diagnosis. Although the disease has been known to have a benign clinical course; the impact of coexisting diseases has also been known to worsen the severity of presentations thus creating atypical scenarios (10).

Many of these lesions were also found to be localized around the anogenital and oropharyngeal regions; heightening the possibility of possible sexual route of transmission, unlike previously documented routes (11, 12). This therefore carries a possibility of greater risk of human-to-human transmission, while reducing the role of the animal vector in the transmission of the disease. There is however paucity of studies which elucidates these dynamic aspects of the Mpox infection especially in Nigeria.

These atypical presentations can also facilitate the transmission of Mpox infection, especially among human contacts, which can go undetected for an extended period, as a possible link between these atypical cases and contacts may not be established. These scenarios portend an additional burden on the already frail healthcare system in Africa and globally, potentially accelerating the spread of the disease without early detection. This in turn, increases morbidity rates and compounds the already high reported fatality risk of 6%, as documented by Yinka-Ogunleye et .al in Nigeria (13, 14).

Extensive research has been conducted on the typical presentation of Mpox infection, resulting in well-established diagnostic and treatment protocols (15, 16). However, recent clinical observations and research has unveiled intriguing cases of atypical disease manifestations. Exploring these atypical manifestations of Mpox is of paramount importance for several reasons. Firstly, it challenges the current understanding of the disease and its clinical features, thereby, providing valuable insights into how the virus can present itself. In addition, identifying and recognising atypical manifestations have significant implications for accurate diagnosis, helping to avoid misdiagnosis or delayed diagnosis in patients with unusual symptoms. Furthermore, understanding atypical manifestations can influence treatment strategies, leading to more comprehensive and personalised therapeutic approaches. Similarly, investigating atypical presentations has broader implications for public health, enabling the adaptation of surveillance systems, enhanced outbreak control measures, and more effective implementation of preventive strategies.

In the light of these, this paper aims to provide a narrative review of the atypical manifestations of Mpox virus infection. By analysing and synthesising relevant cases and previous studies, we aim to contribute to the existing knowledge base and promote a better understanding of this intriguing aspect of the disease.

METHODOLOGY

To conduct a narrative review of the concerned literature, we employed a comprehensive and well detailed literature search to evaluate published studies on the atypical manifestations of monkey pox. This narrative approach helps in analyzing and sorting out the available literature and determining the most suitable literature to be included in the review.

The search was conducted on electronic databases: PUBMED, Google Scholar, EMBASE, and African Journals Online until June 2023, using the following keywords: "Monkey Pox Virus," "respiratory manifestations," "CNS manifestations," "Dermatological manifestations," "challenges," and "implications". Combinations meant to

capture the atypical manifestations of monkey pox were also used in the search terms.

Studies included in this review were: studies addressing various atypical manifestations of monkey pox; studies on clinical implications and challenges facing the management of various manifestations of monkey pox; and studies conducted on the mechanisms and factors influencing atypical manifestations. Additionally, the study involved a background screening of all articles to be included, scientific conference abstracts, editorials, studies not written in English, and studies irrelevant to the topic of interest were excluded. Restrictions were not based on the length of the study.

Screening was also done on the reference list of selected articles to ensure an accurate selection of articles. The findings from the included studies were synthesized and presented in a narrative format, assessing knowledge gaps and major findings in the current evidence.

Atypical Manifestations of Mpox

Atypical manifestations of Mpox encompass a diverse range of unconventional presentations that deviate from the typical clinical features traditionally associated with the disease. While Mpox is commonly characterised by symptoms such as fever, rash, and respiratory distress, there have been documented cases where the disease manifests in unexpected ways, posing significant diagnostic challenges and potentially affecting patient outcomes.

Central Nervous System (CNS) Manifestations

Atypical neurological manifestations of Mpox represent a distinctive subset of cases in which the Mpox virus affects the central nervous system (CNS), giving rise to a broad spectrum of neurological symptoms. Despite being primarily known as a systemic infection characterised by respiratory and cutaneous symptoms, the ability of the Mpox virus to invade the CNS can result in significant morbidity and mortality. (17, 18). This virus has demonstrated a rare coexisting potential with other CNS infections like neurosyphilis, presenting atypically especially in the setting of HIV infection, hence, worsening the morbidity and mortality associated with Mpox disease (18, 19, 20).

One of the most severe neurological manifestations of Mpox is encephalitis, marked by inflammation of the brain parenchyma (17, 18, 21, 22). Encephalitis may manifest as a primary feature of Mpox or as a complication during the infection (17, 18, 21). Patients with Mpox encephalitis typically present with fever, headache, altered mental status, seizures, myalgia and focal neurological deficits (17, 23). The onset of neurological symptoms may coincide with or follow the systemic symptoms of Mpox, making diagnosis challenging due to the potential mimicry of other infectious or non-infectious causes of encephalitis (18).

Another atypical neurological manifestation of Mpox is meningitis, characterised by inflammation of the meninges (24). Symptoms of Mpox meningitis may include severe headache, neck stiffness, photophobia, and altered mental status (24). In some instances, Mpox meningitis may occur without the typical systemic symptoms, further complicating recognition and differentiation from other aetiologies of meningitis (25).

In addition to encephalitis and meningitis, cranial nerve palsies may occur as atypical neurological manifestations of MPox. These deficits can manifest as facial weakness or paralysis (Bell's palsy), loss of taste or smell, double vision, or dysphagia. Mpox-related cranial nerve palsies can arise from direct viral invasion, immune-mediated mechanisms, or a combination thereof (26). Transverse myelitis and optic neuritis have also been reported in some studies (27, 28).

Furthermore, rare movement disorders have been reported as neurological manifestations of Mpox (22). These movement abnormalities encompass chorea (involuntary, jerky movements), dystonia (abnormal muscle contractions causing twisting or repetitive movements), or Parkinsonism (characterised by tremors, rigidity, and bradykinesia).

The underlying mechanisms leading to these movement disorders in the context of Mpox remain incompletely understood and may involve autoimmune responses triggered by the viral infection

Also, studies have highlighted a potential association of Mpox infection and psychiatric sequelae such as anxiety and depression; though their exact prevalence could not be ascertained because of paucity of data (17).

The involvement of the nervous system in Mpox poses significant diagnostic challenges and carries substantial clinical implications. Timely recognition of atypical neurological presentations is critical to initiate appropriate management, including antiviral therapy and supportive care. Failure to identify and treat

neurological complications of Mpox can lead to long-term neurological deficits, cognitive impairments, or fatal outcomes.

Diagnosing atypical neurological manifestations of Mpox demands a high index of suspicion and a comprehensive evaluation. The diagnosis often relies on a combination of detailed clinical history, clinical presentation, laboratory findings (such as detecting Mpox viral RNA or antibodies in cerebrospinal fluid), neuroimaging studies (such as magnetic resonance imaging), and excluding other potential causes of neurological symptoms.

Managing atypical neurological manifestations of Mpox requires a multidisciplinary approach involving infectious disease specialists, neurologists, and critical care teams. Antiviral therapy may be initiated, such as administering medications like acyclovir or other specific Mpox-targeted treatments. Supportive care measures, including seizure management, control of intracranial pressure, and symptomatic relief, constitute integral components of patient management.

Dermatological Manifestations

Mpox can also present with atypical dermatological manifestations, leading to diagnostic and management challenges. In contrast, the conventional manifestation of Mpox involves a generalised maculopapular rash which can often be umblicated (2). Atypical skin presentations
have been observed, encompassing variations such as vesicular lesions, purpuric eruptions, or necrotic skin lesions.

One unique atypical dermatological presentation of Mpox is the occurrence of vesicular lesions, which manifest as small, fluid-filled blisters resembling those seen in other viral infections like herpes simplex or varicella-zoster (29). These vesicular lesions may appear locally or diffusely on the body. The resemblance of Mpox-induced vesicles to other viral exanthems necessitates careful consideration of the patient's clinical presentation and potential exposure history to differentiate the condition accurately (30).

Purpuric eruptions constitute another atypical dermatological manifestation associated with Mpox (31). These eruptions result from reddish-purple discolourations on the skin due to bleeding beneath the skin's surface. In Mpox, purpuric eruptions may arise from a vasculitis-like reaction or coagulopathy related to the virus (32). These lesions can vary in size and manifest on the skin, mucous membranes, or conjunctiva. Recognising purpuric eruptions as a distinctive dermatological manifestation of Mpox is vital, as it aids in distinguishing the infection from other causes of purpura, such as haematological diseases, autoimmune disorders or drug reactions.

Necrotic skin lesions may present scarcely; yet they are considered a severe atypical manifestation of Mpox (33). These lesions involve the death of skin tissue, leading to the formation of ulcers or areas of necrosis. Necrotic skin lesions associated with Mpox may result from direct viral invasion, immune-mediated reactions, or complications related to vasculitis. These lesions often present as blackened or eschar-like regions and warrant immediate medical attention to avert secondary infections and facilitate wound healing.

The presence of atypical dermatological manifestations in Mpox poses diagnostic challenges, given the resemblance of these manifestations to other infectious or inflammatory skin conditions. Differential diagnosis should consider several factors, including the patient's clinical presentation, history of Mpox exposure, and laboratory findings. Comprehending the diverse dermatological presentations of Mpox is pivotal for precise diagnosis and appropriate management, particularly in cases where the typical maculopapular rash is absent or atypical lesions are observed. Dermatologists and healthcare providers should remain vigilant regarding the potentiality of atypical dermatological manifestations and consider Mpox a likely underlying cause, especially during outbreaks or in individuals with a known exposure history.

Accurate diagnosis of atypical dermatological manifestations of Mpox is critical to administer appropriate treatment and implementing necessary infection control measures to forestall transmission. Prompt recognition and isolation of patients exhibiting atypical skin manifestations can substantially curtail the spread of the virus within healthcare settings and the community.

Management of atypical dermatological manifestations of Mpox primarily revolves around supportive care and targeted symptom management (34). Symptomatic relief measures, such as fever antipyretics or pain analgesics, may be utilised (34). Additionally, meticulous wound care is paramount in necrotic skin lesions to forestall infection and promote healing. In severe

cases or when systemic involvement is suspected, consideration may be given to administering antiviral therapy, such as oral or intravenous antiviral medications. Nevertheless, further studies are required to ascertain the efficacy of antiviral therapy in managing atypical dermatological manifestations of Mpox.

Respiratory Manifestations

Recently, the role of respiratory route of transmission has come under debate. Unusual transmissions of the disease via respiratory droplets have been reported in controlled studies with airborne specimens detected on environmental sampling; thus identifying the respiratory route as a possible portal of transmission (35). In Nigeria, four probable cases of respiratory transmission of Mpox infection were reported in a prison facility with three of the subjects having confirmed history of close contacts in the prison cell (36).

In addition to the typical respiratory symptoms, such as cough, sore throat, and difficulty breathing (34, 35), Mpox may present with atypical respiratory manifestations, primarily manifesting as pneumonia without overt systemic symptoms (37). This distinctive presentation of Mpox as a respiratory infection can lead to delays in diagnosis, management and disease control. While Mpox is widely recognised for its characteristic systemic symptoms, including fever, rash, and respiratory distress, there have been reports of cases where pulmonary manifestations predominate, with minimal or absent systemic involvement. Patients may exhibit symptoms consistent with pneumonia, such as persistent cough, dyspnea, chest pain, and abnormal lung auscultation (37). Other pathologies that have been presented in the disease include tonsillar lesions, pharyngitis, epiglottitis with associated odynophagia (38, 39, 40). Some of these presentations have been described in the setting of Mpox infection coexisting with SARS- CoV infection (41).

The atypical respiratory manifestations of Mpox do present diagnostic challenges, as healthcare providers may not initially consider Mpox in the absence of typical symptoms. The delayed diagnosis can result in the potential transmission of the virus to others and hinder the implementation of appropriate infection control measures.

Recognising the potential for Mpox to primarily manifest as a respiratory infection is paramount for timely diagnosis and management. Healthcare professionals should maintain a heightened level of suspicion, especially during outbreaks or when there is a known history of Mpox exposure especially during periods of coexisting COVID-19 outbreaks. Mpox should be considered a differential diagnosis without typical systemic symptoms, particularly in patients presenting with pneumonia-like symptoms who may have had contact with confirmed Mpox cases.

Prompt Mpox diagnosis in cases with atypical respiratory manifestations relies on appropriate laboratory testing (42). Molecular diagnostic techniques, such as polymerase chain reaction (PCR), can detect the presence of Mpox viral RNA in respiratory specimens, confirming the diagnosis (42). Serological testing for specific Mpox antibodies may also be employed, particularly in convalescent patients or cases with delayed presentation (43). Considering clinical presentation, exposure history, and laboratory findings, a comprehensive assessment is essential for accurate Mpox diagnosis in cases with atypical respiratory manifestations.

Once Mpox is diagnosed, appropriate treatment and management strategies can be initiated. Antiviral therapy, such as administering specific Mpox-targeted antiviral medications, may be considered in severe cases or individuals at high risk for complications. Supportive care measures, including respiratory support, fever management, and adequate hydration, are pivotal to optimise patient outcomes.

Implementing infection control measures is imperative to prevent the spread of Mpox, particularly in cases with atypical respiratory manifestations. Strict adherence to isolation precautions, including the appropriate use of personal protective equipment and adherence to respiratory hygiene practices, is crucial. Contact tracing and surveillance activities are integral in identifying and monitoring individuals who may have been exposed to Mpox through respiratory transmission.

Other Manifestations

Atypical clinical presentations involving the genitourinary system have been captured in several literatures. Urethral lesions presenting with dysuria, haematuria, penile oedema, paraphimosis have been cited (8, 44). Rectal bleeding and pain alongside anal pain, tenesmus, proctititis and purulent/ bloody diarrhoea, colitis and gastrointestinal bleeding has been described in people with advanced HIV infection presenting atypically (11, 45). These will often be ascribed to other aetiologies; therefore, missing a

probable Mpox diagnosis.

Other less common atypical manifestations of Mpox encompass various organ systems, including the cardiovascular, gastrointestinal, and musculoskeletal systems (46). Rare presentations of Mpox-associated myocarditis, hepatitis, or arthritis have been documented (11, 47). Even pleural effusion, pulmonary nodules and myopericarditis have been seen in cases with coexisting advanced HIV disease (11). These atypical manifestations underscore the wide-range of clinical variability associated with Mpox and the importance of staying vigilant in considering the disease as a potential underlying cause in patients presenting with unusual symptoms in these specific organ systems.

Mpox-associated myocarditis represents one of the rare atypical manifestations characterised by inflammation of the myocardium, which can lead to cardiac dysfunction and complications (45, 47). The direct effect of the virus on cardiac tissue or an immune-mediated response may contribute to the development of myocarditis. Symptoms may include chest pain, palpitations, shortness of breath, and signs of heart failure. Due to its rarity and non-specific clinical presentation, myocarditis in Mpox requires high clinical suspicion for accurate diagnosis and appropriate management.

These less common atypical manifestations of Mpox emphasize the virus's ability to affect multiple organ systems, contributing to diagnostic challenges. Healthcare professionals should be aware of these rare presentations and consider Mpox as a possible underlying aetiology when evaluating patients with unusual symptoms involving the cardiovascular, gastrointestinal, or musculoskeletal systems. Accurate diagnosis of these atypical manifestations relies on a comprehensive clinical assessment, relevant laboratory investigations, and the exclusion of other potential causes. Molecular diagnostic techniques, serological testing, and imaging studies may aid in confirming the presence of Mpox infection in specific organs.

Managing Mpox-associated atypical manifestations depends on the affected organ system and the severity of symptoms. A multidisciplinary approach involving specialists in cardiology, gastroenterology, rheumatology, or other relevant fields may be necessary to optimise patient care. Additionally, further research and surveillance efforts are needed to enhance our understanding of these fewer common presentations and to develop more effective strategies for preventing, diagnosing, and treating Mpox in all its diverse clinical forms.

Mechanisms and factors influencing atypical manifestations

The atypical manifestations of Mpox stem from a myriad of underlying mechanisms, and this diverse array of factors contributes to the clinical variability observed in the disease. One such explanation lies in the intricate interplay between the host's immune response and the Mpox virus (48). The immune system's critical role in Mpox pathogenesis means that individual variations in immune function, such as immunocompromised states or underlying immunological disorders, can significantly influence the disease's clinical course and manifestations, leading to atypical presentations (48).

Another crucial aspect contributing to the atypical manifestations of Mpox is the viral virulence factors (49). The Mpox virus, being highly contagious, has evolved to infect and replicate efficiently within human cells. Specific viral strains or genetic variations may play a pivotal role in influencing the clinical presentation of Mpox (50). Variations in viral load, viral replication kinetics, and the host's immune competence can give rise to various manifestations, encompassing mild to severe or atypical presentations. These factors can significantly impact viral replication, tissue tropism, and the host's inflammatory response, ultimately leading to diverse and atypical manifestations.

Additionally, host factors such as age, sex, and comorbidities considerably influence the spectrum of Mpox manifestations (51). Individuals in extremes of age or with underlying medical conditions may display heightened vulnerability to atypical manifestations due to their distinct immunological or physiological susceptibilities. Hormonal factors and genetic predispositions might further contribute to the observed variations in Mpox manifestations (51).

These intricate dynamics between viral factors and the host's immune response remains central to the diverse presentations of Mpox, determining the clinical course and severity of the disease.

Moreover, the mode of Mpox transmission also influences the disease manifestations.(51) Depending on the transmission mode, such as respiratory droplets,

direct contact with lesions, or vertical transmission from mother to foetus, the initial site of viral replication may vary, leading to divergent primary organ systems affected and consequent atypical manifestations.

Furthermore, pre-existing conditions or co-infections with other pathogens can also modulate the manifestations of Mpox causing more severe or atypical manifestations of Mpox with attendant complications (52).

RESULTS

This study has been able to identify the changing dynamics in terms of pathogenesis of the Mpox infection, its unusual manifestations that are often not on the spotlight, its multisystemic affectations and even co-existence with other infections and comorbidities. These features serve as drivers in the potentiation of the disease severity and impact on the human-to-human spread of the virus, which will further aid in easy transmissibility of the infection. These aspects are crucial in the surveillance of the Mpox infection if future outbreaks, morbidities and mortalities are to be curbed.

Clinical implications and challenges

The atypical manifestations of Mpox have significant implications for both the diagnosis and treatment of the disease. Atypical presentations can create complexities in the diagnostic process, as these manifestations may mimic other infectious or inflammatory conditions. Healthcare professionals should be well-informed about the diverse manifestations of Mpox, encompassing neurological, dermatological, and respiratory atypical presentations. This awareness enables the inclusion of Mpox in the differential diagnosis and prompts necessary molecular diagnostic techniques or serological assays to confirm the infection.

Treatment strategies for atypical Mpox cases should be tailored to address the specific manifestations and complications observed. A multidisciplinary approach involving infectious disease specialists, neurologists, dermatologists, and pulmonologists may be necessary. Identifying and managing atypical cases of Mpox presents several challenges. The clinical heterogeneity of Mpox manifestations challenges establishing a definitive diagnosis solely on clinical grounds. The absence of typical symptoms may delay the recognition of Mpox, leading to potential virus transmission and hindering appropriate management.

Furthermore, the rarity of atypical presentations adds to the difficulties in identifying and managing these cases. Atypical manifestations may occur in a small subset of Mpox-infected individuals, making it challenging to gather sufficient data to conduct large-scale studies specifically focusing on these presentations. Consequently, evidence-based guidelines and standardised management approach for atypical cases may be limited.

Additionally, the management of atypical cases may require specialised expertise and resources. Healthcare systems must ensure access to appropriate diagnostic tools, including laboratory tests and imaging modalities, to aid in identifying and managing atypical manifestations. Collaboration among healthcare professionals from different specialities is essential to develop comprehensive management plans and ensure optimal patient outcomes.

Future research directions

Despite advancements in understanding the atypical manifestations of Mpox, several areas warrant further investigation to gain valuable insights into the underlying mechanisms, risk factors, and optimal management strategies for atypical cases.

Future research should focus on elucidating the specific mechanisms contributing to atypical manifestations of Mpox. Understanding the interplay between the virus, host immune responses, and viral virulence factors can provide insights into why certain individuals develop atypical presentations. This includes investigating the role of immune dysregulation, viral genetic variations, and host factors in influencing the clinical course and manifestations of Mpox.

Large-scale epidemiological studies are needed to determine the prevalence and incidence of atypical manifestations of Mpox. Identifying risk factors associated with atypical presentations can help in risk stratification, early recognition, and targeted interventions. Studies should explore the influence of age, comorbidities, immunosuppression, and genetic predispositions on the likelihood of developing atypical manifestations.

Research efforts should focus on developing improved diagnostic approaches. This includes the development of sensitive and specific laboratory tests that can identify Mpox infection in the absence of typical symptoms. Exploring the utility of novel diagnostic techniques, such as advanced imaging

modalities, biomarkers, or point-of-care testing, can enhance the accuracy and efficiency of Mpox diagnosis.

Further studies are needed to evaluate the effectiveness of different treatment strategies for atypical Mpox cases. This includes assessing the role of antiviral therapies, immunomodulatory agents, and supportive care measures in managing atypical manifestations (53, 54, 55). Comparative studies, randomised controlled trials, and long-term follow-up studies can provide evidence-based guidance on the optimal management approaches for atypical Mpox cases.

Investigating genetic variations and viral-host interactions can illuminate the mechanisms underlying atypical manifestations. This includes genomic sequencing to identify viral strains or mutations associated with specific clinical presentations. Molecular studies can also explore the host immune responses, cytokine profiles, and viral kinetics in atypical cases.

Comparative studies comparing atypical Mpox cases with typical presentations or other infectious conditions can help identify distinctive clinical features and risk factors associated with atypical manifestations. These studies can provide insights into the diagnostic challenges and unique management considerations for atypical cases.

Collaboration among multiple research institutions and international networks can facilitate the collection of a larger sample size of atypical Mpox cases. This can lead to more robust data analysis, validation of findings, and generation of generalizable knowledge regarding atypical manifestations. Collaborative efforts also facilitate the establishment of standardised protocols and guidelines for diagnosing and managing atypical cases.

Animal models, such as mouse or non-human primates, can be utilised to study he pathogenesis and immune responses associated with atypical manifestations. In vitro studies using cell lines or organoid models can help elucidate the mechanisms by which Mpox interacts with different cell types and contributes to atypical presentations.

CONCLUSION

The exploration of atypical manifestations of Mpox in this narrative review emphasizes the importance of recognising and understanding the diverse clinical presentations beyond the typical manifestations. These atypical presentations have been observed, complicating the diagnostic process and therefore raises the need for tailored treatment strategies. Timely and accurately diagnosing atypical cases is crucial in order to prevent further complications and optimise patient care.

Challenges in identifying and managing atypical cases arise due to the rarity of such presentations, overlapping clinical features with other conditions, and the need for specialised expertise and resources. Collaboration among healthcare professionals from different specialities and access to diagnostic tools is crucial in addressing these challenges.

Future research directions should focus on elucidating the pathogenesis, identifying risk factors, improving diagnostic approaches, and evaluating treatment strategies for atypical Mpox cases. Prospective cohort studies, molecular investigations, and collaborative research networks will contribute to a deeper understanding of the mechanisms underlying atypical manifestations and guide clinical management.

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