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REPORTE DE CASO

Reporte de Caso: Infección por monkeypox virus en paciente inmunocomprometido por virus de inmunodeficiencia humana con evolución atípica

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Abstract

Mpox is caused by the monkeypox virus, a DNA virus of the Poxviridae family and the Orthopoxvirus genus. As far as its clinical presentation is concerned, symptoms such as fever, lymphadenopathy and maculopapular rash affecting mucosal tissues, palms and soles have been described. However, atypical presentations have been reported in patients with impaired immune functions. Men who have sex with men (MSM) are among the most affected populations and sexual contact is one of the main forms of transmission. It has been estimated that close to 28-51% of MSM infected with monkeypox virus have an associated human immunodeficiency virus infection. In this report, we describe the case of a patient with human immunodeficiency virus infection who acquired the Mpox and had an atypical clinical presentation and course. In conclusion, the current Mpox outbreak has differed from previous outbreaks in terms of clinical characteristics, transmission mode and population at risk. Immunosuppression is a risk factor for an atypical course, with longer duration and development of complications that lead to longer hospital stay and mortality.

Keywords: Human immunodeficiency virus, monkeypox, immunosuppression, atypical course, monkeypox virus.

Case Report: Mpox virus infection in a patient immunocompromised by human immunodeficiency virus with atypical evolution.

Resumen

Mpox es causada por el virus de la viruela símica, un virus de ADN de la familia Poxviridae y el género Orthopoxvirus. En cuanto a su presentación clínica, se han descrito síntomas como fiebre, linfadenopatía y erupción maculopapular que afecta tejidos mucosos, palmas y plantas de los pies. Sin embargo, se han reportado presentaciones atípicas en pacientes con función inmunológica comprometida. Los hombres que tienen sexo con hombres (HSH) están entre las poblaciones más afectadas, siendo el contacto sexual una de las principales formas de transmisión. Se ha estimado que cerca del 28-51% de los HSH infectados con el virus de la viruela símica tienen una infección asociada por el virus de la inmunodeficiencia humana. En este informe, describimos el caso de un paciente con infección por el virus de la inmunodeficiencia humana que adquirió Mpox y tuvo una presentación y curso clínico atípicos. En conclusión, el brote actual de Mpox ha diferido de brotes anteriores en términos de características clínicas, modo de transmisión y población en riesgo. La inmunosupresión es un factor de riesgo para un curso atípico, con mayor duración y desarrollo de complicaciones que conducen a una estancia hospitalaria más prolongada y mortalidad.

Palabras clave: Virus de inmunodeficiencia humana, inmunosupresión, curso atípico, Virus viruela del mono.

Introduction

Mpox is a zoonosis caused by the monkeypox virus, a DNA virus belonging to the genus Orthopoxvirus[1]. It occurred mainly in Central and Western Africa after appearing for the first time in the Democratic Republic of Congo in 1970[2]. By August 2022, 44,503 confirmed cases had been reported worldwide, leading the World Health Organization (WHO) to declare Mpox a public health emergency on July 23, 2022.

In the current outbreak, sexual transmission predominated, with the highest prevalence found in men who have sex with men (MSM). Other routes of transmission have been described, including aerosols and close or direct contact with skin

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injuries[3]. A higher prevalence was observed in men, with a mean age of 35 years. The average incubation period was six days and the most frequently associated medical condition was human immunodeficiency virus (HIV) infection in 29% of cases. As found in an observational cohort at Claude Bernard Hospital, the perineal and anal areas are the most affected[1]. The atypical presentation of Mpox has been documented in patients living with HIV due to immune function impairment, resulting in delays in diagnosis and treatment [4].

The CARE Checklist has been completed by the authors for this case report.

Case description

A Thirty-year-old male patient from an intermediate city with a history of stage C3 HIV infection with irregular adherence to treatment and first-line resistance was admitted to the hospital and treated by the infectious disease team using TARV (Atazanavir + Ritonavir and Emtricitabine + Tenofovir). CD4 count test performed at another institution showed 104 cells/mm^3 with a viral load of 256,261 copies. Important history included syphilis nine years before, treatment with three doses of benzathine penicillin, and lung tuberculosis treatment in 2021. The patient was initially diagnosed at a local hospital in September 2022, where the diagnosis of Mpox was made using PCR. As a risk factor, he reported having sex with individuals of his own gender. In view of persistent lesions and no clinical improvement, the patient was referred to a tertiary hospital after four months of vesicle-type lesions with progression to rounded, polycyclic erythematous-violaceous plaques 8 × 10 cm in size with necrotic verrucous honey-colored surfaces with well-defined margins. Oval, hyperkeratotic verrucous plaques with well-defined regular borders were present in the left temporal scalp region, interciliary area, nasal dorsum with destruction of the nasal tip and right ala obliterating the right nostril, perioral region, and neck; anterior and posterior trunk and bilateral axillary region; extensor area of the upper limbs (Fig. 1); flexor area of the right upper limb, first digit of the left hand (Fig. 2); anal region and posterior aspect of the right thigh; and fourth ray of the right foot. The lesions were painful, with a pain intensity of 9/10 on the visual analog scale. Associated symptoms included asthenia, adynamia, febrile peaks after cutaneous lesions, whitish cotton-like plaques with an erythematous base consistent with candidiasis, dysphonia leading to the suspicion of esophageal involvement, multiple umbilicated vesicles with necrotic scabs localized to the side of the neck, both axillae and scrotum, and weight loss of 10–15 kg.

A colostomy was performed because of anal involvement and gastrointestinal ulcers found on endoscopy performed at a different institution.

Cultures were taken from different lesions in the nasal region, and *Citrobacter freundii* (serine carbapenemase), *Pseudomonas aeruginosa* (AmpC), *and Staphylococcus epidermidis* resistant to all beta-lactams were isolated. This prompted the use of multiple antibiotic regimens, including piperacillin/tazobactam, meropenem 2 g IV every 8 hours, vancomycin 1 g IV every 12 hours), trimetropim sulfa 160/800 mg/day, and itraconazole, with no clinical improvement.

The patient was referred to our institution with suspected deep mycoses and cutaneous mycobacterial infection for comprehensive management by internal medicine and dermatology because of an unclear diagnosis and extensive involvement.

The emergency room service requested initial laboratory tests and a consultation for infectious diseases given the patient's history and the fact that he had received multiple antibiotic therapies. Additional assessments were requested, including otorhinolaryngology because of nasal lesions and suspected esophageal involvement plus oropharyngeal candidiasis, dermatology due to skin lesions, and psychiatry because of the presence of anxiety and distress.

The initial internal medicine assessment indicated typical Mpox lesions, but other pathogens were also considered, including sporotrichosis, histoplasmosis, *Mycobacterium tuberculosis* infection, and non-tuberculous mycobacterial infection. Given that the initial peripheral blood smear showed structures consistent with histoplasmosis, but blood cultures did not show histoplasma, pharmacological therapy was adjusted to include liposomal amphotericin B plus antiretrovirals (guided by the infectious diseases service).

The dermatology service, in view of the context of secondary immunosuppression, reported skin histoplasmosis vs. Mpox, tropical verruocous syndrome, and verrucous pyoderma gangrenosum as the least probable, and requested two skin biopsies for histopathology with Grocott, Periodic acid-Schiff (PAS), Ziehl Neelsen (ZN), and Giemsa stains, and culture for deep mycoses, typical and atypical mycobacteria that were negative after 42 days.

The following results were obtained in the biopsy, indicating the persistence of Mpox infection with an aggressive and severe course:

- Skin biopsy from the left forearm region: Sections show extensively ulcerated necrotic skin and binucleated cells with viral inclusions enlarging the nucleus observed in the assessable epithelium, together with eosinophilic cytoplasmic inclusions. Dermis with necrosis involving vessels and skin adnexa. The morphological appearance points to the Mpox as the first possibility (Fig. 3).
- Additional report: Ziehl Neelsen (ZN), periodic acid-Schiff (PAS), and Gomori staining were negative.
- Biopsy from the cubital fossa of the left upper limb showed extensive necrosis extending throughout the skin and subcutaneous tissues, with florid cytopathic changes in a viable epidermal fragment, suggesting viral disease. No malignancy was observed in any of the specimens.
- Biopsy of the ulcer in the cubital fossa of the left upper limb: extensively ulcerated and necrotic skin with poxvirus inclusions consistent with Mpox. The patient received multiple antibiotics over a period of four months without

clinical improvement. In Colombia, medication was not available at that time, which made it difficult to access specific treatments for Mpox. Subsequently, the patient's clinical condition deteriorated, and he died.

Discussion

Mpox was first described in 1958 in macaques and the first case in humans was reported in 1970 in the Democratic Republic of Congo[5]. In recent years, Mpox has been in the spotlight because of cases reported in different parts of the world. One case of the disease identified on May 6, 2022, in the United Kingdom was considered the origin of the current outbreak, with additional cases reported later in more than 86 countries[6]. In the Americas, reported cases exceed 45,000, Colombia being one of the countries with the highest numbers, together with Brazil, Peru, and Mexico[7]. We present a case of Mpox with an atypical course in terms of disease progression and duration of clinical manifestation, as well as a long hospitalization with multiple complications, such as superinfection and mortality, as well as among 40 individuals with Mpox and HIV in Nigeria, with an increase in the duration of the disease, more prominent lesions, and increased secondary bacterial infection [18]. In a global case series, the hospitalization rate among MPXV-HIV-coinfected individuals was reported to be 28%[21].

The current outbreak is characterized by a predominance among young adults between 20 and 40 years of age and MSM[2]. The clinical presentation starts with a prodromic phase of non-specific symptoms between days 0 and 5[8]. Our case is consistent with the findings of an observational cohort, which included fever in 68% of cases, lymphadenopathy in 60%, and greater involvement of the genital and perianal areas[1], as well as other symptoms described in a case series in 16 countries, including lethargy (41%), myalgia (31%), and headache (27%)[3]. It has been described that lymphadenopathy is one of the characteristics of Mpox virus that can range between 1 to 4 cm, can be firm and tender and usually affects the maxillary, cervical and inguinal region[9].

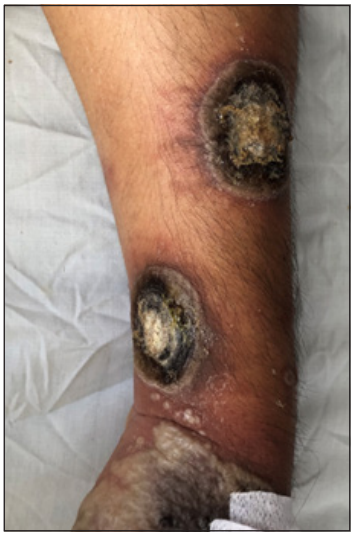

Figure 1. Oval, hyperkeratotic verrucous plaques with well-defined regular borders on the extensor region of the upper limb.

The reported atypical presentations include a paucity of lesions, confined genital and/or perianal lesions, asynchronous lesion development[10], and the presence of fistulas, papules, and nodules in the scalp, face, trunk, and limbs[2], with the most affected areas being the genitalia in 73% of cases, trunk, arms, and legs in 55%, face in 25%, and palms and soles in 10%. In this case series, the number of lesions was approximately 10 or less[5]. Five stages have been inferred, starting with the papular phase and typical central umbilication, followed by vesicles, pustules, and desquamative lesions[5].

In a case series between April 2007 and June 2022 in 16 countries, 41% of patients had HIV, 95% had a viral load of less than 50 copies, the mean age was 38 years, and the majority of cases were self-limiting. Better HIV control is associated with more localized skin lesions[10].

In contrast, in cases reported in Nigeria, patients with HIV-1 co-infection had more prolonged courses with larger lesion sizes, skin rashes > 2 cm, higher rates of bacterial infections, and genital ulcers[11].

The proposed mechanisms of action of the monkeypox virus include an 80% reduction in T-lymphocyte-mediated cytokine response through the inhibition of T-cell activity[8]. One of the main characteristics of the virus is the evasion of immune responses by interfering with T-cell activation, antigen presentation, immunomodulatory protein production, and infected cell apoptosis. It has been shown to activate TLR2 and TLR4 signaling pathways, leading to the production of proinflammatory cytokines, including TNFα and IL 6. Likewise, Mpox virus evades the complement system and interferes with the activity of dendritic, T, and NK cells[12].

Notably, in our patient with associated human immunodeficiency virus infection, persistence of the lesions and absence of clinical improvement three months after diagnosis could be attributed to CD4 counts below 200 due to poor infection control. Cases reported in the literature have resolved after 10–42 days, with the latter being a case with a CD4 count of 64 cells/µl[2]. On the other hand, in a case series showing that the last moment with persistent positive lesions was 21 days after the onset of symptoms, it is worth highlighting that patients with HIV had CD4 counts of more than 500 cells/µl[3]. Therefore, the cases described in the literature have resolved within 2 to four weeks[8].

Different conditions such as histoplasmosis, paracoccidioidomycosis, systemic sporothricosis, and cutaneous tuberculosis were considered. Our patient received multiple antibiotic and antifungal treatments including piperacillin, tazobactam, vancomycin, fluconazole, cefepime, meropenem, and itraconazole, with no improvement. Other differential diagnoses included in the literature are rickettsioses, secondary syphilis, herpes simplex, and varicella zoster[4,5].

Complications that prolong the length of stay include severe anorectal pain and cellulitis caused mainly by S. Aureus, which is different from the findings in our patients in whom the pre-

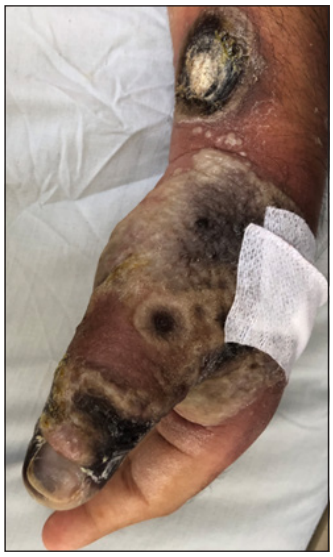

Figure 2. First digit of the left hand.

dominant microorganisms were *Citrobacter freundii* and *Pseudomonas aeruginosa* Ampc, and pharyngitis, which limited oral intake, paronychia, non-cardiac angina, blepharitis, keratitis, acute kidney injury, and myocarditis[1,3]. Sequelae include atrophic hyperpigmented scarring, patched alopecia, hypertrophic scars, and facial muscle contractures or deformities[11].

Owing to its high sensitivity and specificity, PCR is the gold standard for the diagnosis of Mpox virus infection[8]. However, prior varicella vaccination can lead to false-positive results[13]. Sampling with two swabs per lesion in two or three different regions, including ulcer exudate, vesicle/pustule fluid, and scabs, is recommended[14].

In the current global outbreak, HIV and Mpox co-infection has been reported to be 40.3%; thus, co-infection with these two viruses can exacerbate the symptoms of both diseases, make them more difficult to treat, and increase the mortality rate. In a systematic review was found that of the three reported deaths of patients with Mpox and HIV co-infection, two cases had a CD4+ T-cells count < 200/ul as our patient[17].

Additionally, the recent outbreak has increased the age of presentation from 4 (1970s) to 21 years (2010–2019)[19] and its spread in high-risk sexual practices, especially with anal receptive sex. This correlates with rectal and semen samples that have shown 67–77% positivity for individuals with Mpox, with the median clearance of MPXV from semen samples reported to be 13 days, extending up to 39 days among the majority of patients[20].

To date, no guidelines have been available for the management of Mpox in immunocompromised patients. Various antivirals, including brincidofovir, cidofovir, and tecovirimat, have been proposed based on in vitro and animal studies, including brincidofovir, cidofovir, and tecovirimat[1]. The only FDA-approved antiviral for this condition is tecovirimat[8], which acts by activating CYP450 and inhibiting CY2C8 and CYP2C19, thus inhibiting the viral VP37 protein[5]. The approved dose is 400–600 mg/day for 14 days[15]. It is indicated mainly in severe disease with a risk of progression, as is the case in immunocompromised patients, children, pregnant women, or in cases of affected functionally sensitive areas, such as the pharynx and genitalia[14].

Prevention measures play a key role in controlling infection through early isolation and control of exposure to at-risk people[16]. The FDA has approved multiple vaccines since 2019, but their use has been limited to staff in close contact with infected patients[8]. The available vaccines are JYNNEOS and ACAM2000, which are administered in two doses at 28-day intervals. Pre-exposure and post-exposure applications are also used, the former for at-risk populations and the latter to be given within the first four days after exposure[5].

Another important consideration is the psychological condition of patients who develop the disease. A study in Nigeria demonstrated the presence of anxiety and depression symptoms requiring psychological support in 27.5% of the cases[11]. Therefore, our patient received psychiatric support as well as pain management, confirming the need for a multidisciplinary approach for these patients.

In conclusion, the current Mpox outbreak differs from previous outbreaks in terms of clinical characteristics, transmission mode, and at-risk population. Immunosuppression is a risk factor for an atypical course, with a longer duration and development of complications that lead to longer hospital stay and mortality. As part of preventive measures, it is important to emphasize the need for education and early detection of the infection to achieve better control of the disease. Additional evidence is required regarding treatment in humans, as well as vaccination in terms of efficacy and cost-effectiveness.

Ethical considerations

Protection of persons: Procedures were performed in accordance with the ethical institutional guidelines of the ethics committee and the Declaration of Helsinki

Protection of vulnerable populations: Written informed consent was obtained from the patient for case description and images for academic and research purposes.

Confidentiality. This study protocol was reviewed and approved on December 16, 2022 by the Research Ethics Committee of the Hospital Universitario de la Samaritana (CIEHUS) according to act No. 12-2022. Written informed consent was obtained from the patient for case description and images for academic and research purposes.

Privacy: The privacy of the patient's identity is guaranteed

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Conflict of interests. The authors have no conflict of interest to declare

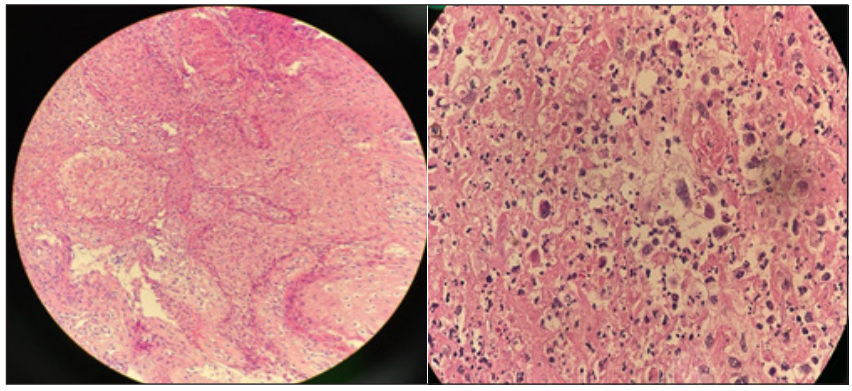

Figure 3. A) Binucleated cells with viral inclusions enlarging the nucleus seen in the assessable epithelium, together with eosinophilic cytoplasmic inclusions optical microscopy 20X. **B)** Microscopic field close up image (40X magnification).

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Authors´ contribution. Conceptualization: H.P., M.F., P.R.; Methodology: P.R., M.C., S.A., Software: H.P., P.R.; Validation: H.P., M.F., P.R., M.C., M.B., S.F.; Formal analysis: H.P., M.F., P.R.; Investigation: H.P., M.F., P.R., M.C., S.A., M.B.

All authors contributed to read and approved the version of the submitted manuscript.

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