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CASE REPORT

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First case report of monkeypox in Brazil: clinical manifestations and differential diagnosis with sexually transmitted infections

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ABSTRACT

In 2022, an outbreak of monkeypox is being reported in non-endemic areas, with unusual clinical manifestations. The detailed clinical description of the first patient that received the diagnosis of monkeypox in Brazil is reported here, whose clinical manifestations can easily lead to misdiagnosis of sexually transmitted infections. A 41 years old male presented to an emergency room with a vesicular rash with eight days of evolution. He had traveled to Portugal and Spain and reported non-penetrative sexual involvement with three different male individuals. On the third day of symptoms, he sought medical care and received empirical treatment directed to sexually transmitted infections. As the symptoms did not improve, he sought medical attention at an infectious disease referral center presenting, on admission, an ulcerated penile lesion with central necrotic crusts, a disseminated pleomorphic skin rash and an oropharyngeal ulcer. The monkeypox diagnosis was suspected due to the characteristics of the lesions and the history of intimate contact with casual partners, and it was later confirmed by sequencing the almost complete monkeypox genome. The patient was hospitalized for pain control, which required opiate administration. He developed a secondary bacterial infection on the penile lesions, which were treated with oral antibiotics. He was discharged after 14 days, with lesions in process of re-epithelialization. Given the current outbreak, we must consider the possibility of monkeypox in patients with suggestive lesions, anywhere on the body (including the genitals), added to an epidemiological link or history of intimate contact with strangers or casual partners.

KEYWORDS: Monkeypox. Sexually transmitted diseases

INTRODUCTION

Monkeypox is a zoonotic viral disease caused by a double-stranded DNA virus of the Orthopoxvirus genus that can be transmitted to humans through direct contact with blood, body fluids, cutaneous or mucosal lesions of infected animals, through close contact with respiratory secretions, skin lesions of an infected person or with recently contaminated objects¹. Monkeypox is endemic in West and Central Africa, however, there have already been reports of cases outside Africa, in people traveling to endemic areas².

In 2022, an unexpected outbreak of monkeypox is being reported in non-endemic areas, affecting people with no contact with endemic areas of monkeypox transmission. As of 15 June 2022, a total of 2,103 laboratory-confirmed cases and one probable case, including one death in Nigeria, have been reported to the World Health Organization (WHO) by 42 Member States (Americas, Africa, Europe, Eastern Mediterranean and Western Pacific)². Most cases (98%) have been reported since May 2022 and most confirmed cases (84%) are from the WHO European Region. Among patients for whom demographic information and personal characteristics are available (468/ 2,103 confirmed cases), 99% are reported in men aged 0 to 65 years (interquartile range: 32 to 43 years; median age 37 years), of whom most identify as men who have sex with men².

As of June 18, 2022, 30 cases have been reported in Brazil. Of these, seven were confirmed, four are still under investigation and 19 were ruled out by laboratory examination (real-time polymerase chain reaction or genome sequencing)³.

Classically, the clinical manifestations of monkeypox are divided into two periods: the prodromal period, which lasts 1-4 days and is characterized by nonspecific symptoms, such as fever (often between 38.5 °C - 40.5 °C), headache and fatigue, and the skin rash period that begins 1 to 3 days after the onset of fever. Lymphadenopathy can appear during the prodromal period and remains concomitant with the skin rash. Enlarged lymph nodes (1 to 4 cm in diameter) are firm, tender and sometimes painful. Usually, signs and symptoms last 2 to 5 weeks^{4,5}.

Initially, the rash usually appears on the face and spreads in a centrifugal pattern distribution across the body, hands, legs and feet. The rash undergoes several stages of evolution from macules, papules, vesicles and pustules, followed by resolution over time with crusts and scabs, which drop off later during recovery. Various stages of the rash can appear at the same time and the number of lesions on a given patient can range from a few to thousands. Lesions are often observed in the oral cavity and can cause difficulties in drinking and eating. Inflammation of the pharyngeal, conjunctival and genital mucosa can also be observed^{4,5}.

Many cases in this current outbreak are showing atypical features, such as: only a few or even only one skin lesion; lesions that start in the genitals or perineal/perianal area and do not spread further; lesions that appear at different (asynchronous) stages of development; appearance of lesions before the onset of fever, malaise and other general symptoms belonging to the first period of manifestation of the disease manifestation².

As monkeypox is an emerging disease, presenting itself in the 2022 outbreak with unusual clinical manifestations, we believe that the description of the first confirmed case in Brazil will contribute to medical knowledge and will have important educational value in our area.

Ethics and informed consent

The patient provided written informed consent for this case report and use of laboratory and imaging data. This case report was approved by the Institutional Committee of Ethics in Research (CAAE 59765422.0.0000.0061) and was written according to CARE guidelines⁶.

CASE REPORT

A 41-year-old male patient, self-declared as white, living in the Sao Paulo city, the Sao Paulo State capital, attended an emergency department due to a vesicular eruption with an evolution of eight days (Figure 1). He had traveled to Portugal and Spain, staying four days in each of the countries and returning to Brazil eight days before the onset of symptoms. In both countries, he went on tours and attended parties where he had non-penetrative sexual involvement with three different males. In Portugal, he reported contact through kissing with two men, and in Spain, oral sex and intimate contact, but without penetrative sex with another individual, without using a condom.

The first symptoms were pruritus and burning sensation on penile glans, accompanied by two vesicular lesions with an erythematous base. Two days later, the vesicular lesions became ulcerative. Three days after the onset of the first symptoms, he started having high fever (temperature of 40 °C), myalgia, headache, hyporexia and general malaise, in addition to the development of more vesicular lesions in other parts of the body.

The first body lesions appeared on the face (above the upper lip) and periumbilical region and had better defined edges when compared to other lesions of posterior appearance, which were vesicular/pustular and distributed on back (three lesions) and upper limbs (approximately five lesions on each limb). Areas of erythema were observed around all lesions and followed a common pattern of evolution: vesicle, pustule, ulcerated lesion with a welldefined border and central crust formation. The patient denied pain associated with the skin rash.

On the third day of symptoms, he sought medical attention and, considering his report of unprotected sexual intercourse, received empirical treatment aimed at the treatment of genital ulcers caused by sexually transmitted infections (STIs): valacyiclovir (genital herpes), doxycycline (lymphogranuloma venereum), azithromycin and ceftriaxone (chancroid).



Figure 1 - Timeline of symptoms.

Due to the persistence of the appearance of vesicular lesions, in addition to edema and pain in the penile region on the 8th day of symptoms, he sought medical attention at a reference center in infectious diseases, the Instituto de Infectologia Emilio Ribas, located in the Sao Paulo city, presenting, on admission, a disseminated exanthema, with

around 50 lesions distributed on the face, limbs, trunk and genitals.

The skin lesions had multiple presentations: vesicles, vesicles with central umbilication, pustules and ulcerations, all with well-defined edges, clean background and erythematous base. Several lesions had a crust (Figure 2). In



Figure 2 - Injuries on admission. Clockwise: oropharyngeal ulcer, pustule on left thigh, crusty skin lesions on left arm, crusty penile lesions.

the balanopreputial region, there were multiple deep, welldefined ulcers, approximately 1 cm in diameter, some of them confluent, covered by blackened crusts with a necrotic appearance, accompanied by local edema.

He also had an oropharyngeal ulcer and complained of pain when urinating and after bowel movements. In addition to the mucocutaneous manifestations, he had palpable lymphadenopathy in the anterior cervical, left supraclavicular and inguinal regions bilaterally. Palpable lymph nodes were about 2.5 cm in diameter, mobile, fibroelastic in consistency, non-adherent to the deep planes, and did not show inflammatory signs. They were painful on palpation only in the inguinal region. They were painful on palpation only in the inguinal region.

Routine blood tests at admission showed: AST 29 U/L, ALT 32 U/L, creatinine 1.4 mg/dL, urea 43 mg/dL, potassium 4.3 mmol/L, sodium 142 mmol/L, C-Reactive Protein < 5.0 mg/L, hemoglobin 16.1 g/dL, hematocrit 47.8%, leukocytes count 17,900 cells/ μ L, neutrophils 11,700 cells/ μ L, lymphocytes 4,200 cells/ μ L, platelets count 203,000 cells/ μ L. Urinary sediment examination showed results within the normal range and urine culture was negative. Imaging exams and rectoscopy were not performed. Imaging tests and rectoscopy were not performed. The only relevant laboratory finding at admission was leukocytosis (17,900 cells/ μ L), with a predominance of neutrophils.

The patient was hospitalized for etiological confirmation and pain control, requiring opiates (intravenous tramadol, 500 mg every 6 hours for 5 days) in addition to 1g intravenous dipyrone every 6 h for pain relief. He was isolated in a room, with contact and droplet precautions.

One day after hospital admission, skin lesion material (detached crusts and swabs) was obtained from three different lesions, two on the upper limbs and one on the leg, together with an oropharyngeal swab. The laboratory diagnosis of monkeypox was confirmed by a rapid whole genome sequencing technique resulting in the recovery of the almost complete genome of monkeypox virus⁷.

In addition, two skin biopsies were sent for histopathological analysis which were stained with hematoxylin-eosin and PAS and revealed an intraepidermal bullous lesion with foci of ballooning degeneration of keratinocytes and moderate spongiosis. Some keratinocytes exhibited hyperchromatic nuclei, sometimes eosinophilic cytoplasm with a "ground glass" appearance. Edema and intense inflammatory infiltrate composed predominantly of neutrophils and lymphocytes were observed at the dermo-epidermal junction, in addition to areas of fibrinonecrotic appearance. There was also a mixed inflammatory infiltrate with a predominant perivascular distribution, extending to the midportion of the dermis.

On the third day of hospitalization, ulcerative lesions located in the balanopreputial region showed signs of secondary bacterial infection: exudate, worsening pain, erythema and worsening of local edema. The temperature pattern was difficult to assess as the patient received antipyretics (dipyrone). At this time, blood tests were repeated and showed C-Reactive Protein < 5.0 mg/dL, hemoglobin 15.4 g/dL, hematocrit 45.9%, leukocyte count 14,100 cells/µL, neutrophils 6,900 cells/µL, lymphocytes 5,600 cells/µL, platelet count 178,000 cells/µL. Therefore, antibiotic therapy with amoxicillin-clavulanate was prescribed for seven days, and there was improvement in the aforementioned signs and symptoms, in addition to the complaint of pain when urinating and after bowel movements that had already disappeared at the end of antibiotic therapy.

On the seventh day of hospitalization, the larger and deeper balanopreputial ulcer had lost its crust and was covered by fibrin. Appropriate dressings were performed with topical alginate.

New lesions were observed during hospitalization until day 10, totaling about 70 lesions. The eruption tended to have centrifugal distribution, with the extremities, including the palmoplantar region and the scalp as the last areas affected.

At the time of hospital discharge, after 14 days of hospitalization, most skin lesions were in the process of re-epithelialization, while penile lesions showed clinical improvement, without edema or associated pain. The only remaining symptom was pruritus associated with wound healing. The patient was instructed to maintain isolation at home until all skin and mucosal lesions had crusted and the crusts had fallen off, with the formation of a new layer of skin.

DISCUSSION

This case report presents the first confirmed case of monkeypox in Brazil that occurred in a young man, whose first manifestations were genital ulcers, with subsequent disseminated skin rash and systemic symptoms. We consider the description of this clinical case essential for several reasons. First of all, this is also the first report of monkeypox in Latin America, serving as an alert for the risk of spreading the disease in our region.

Second, the clinical case draws attention to the misdiagnosis with some STIs. It is noteworthy that in his first health consultation, he received empirical treatment for sexually transmitted infections that cause genital ulcers, and only when seeking a second medical care at a referral center, the diagnosis of monkeypox was considered although the current outbreak in non-endemic countries was already known².

The investigation of a suspected case of monkeypox should include additional tests to make the differential diagnosis with some STIs, especially syphilis, herpes simplex, disseminated gonococcal infection, lymphogranuloma venereum and chancroid, in addition to other common causes of maculopapular or vesicular rash, such as varicella, herpes zoster, measles and arboviruses (dengue, zika and chikungunya)^{3,8,9}. Another important point is the clinical presentation and evolution, which differs from the classic descriptions of this endemic zoonosis in the West African region, where initially systemic symptoms were reported, followed by exanthema, most commonly monomorphic with a centrifugal distribution and historically unrelated to sex contact¹⁰.

The patient described here presented the first and largest lesions in the genital region and, although the rash had a centrifugal distribution, he presented lesions with very pleomorphic lesions, ranging from ordinary vesicles to vesicles with central umbilication, pustules, ulcerations and several crusted lesions. Many cases in the current outbreak are also presenting manifestations that are different from the classic descriptions of monkeypox, with variable findings varying from few or even only a single lesion, lesions that begin in the genital, perineal or perianal area and do not spread further, in addition to asynchronous lesions².

In the case described here, it is important to highlight the presence of an ulcerated penile lesion with central necrotic crusts associated with perilesional edema. These clinical manifestations differ from the classic symptoms of monkeypox, in which there is no genital involvement or asynchronous lesions¹⁰.

Furthermore, the spread, the number of lesions (about 70 lesions) and the appearance of new lesions for 19 days make this clinical description unique. At the time of reporting this first case, we do not have information on the time of appearance of new lesions in the more than 2,000 cases of the current outbreak worldwide, so that a detailed clinical characterization of current monkeypox patients is a health priority at the moment.

Another point that should be considered is the predominance of men who have sex with men in the current outbreak. Like what was reported by other authors¹¹⁻¹⁴, in this case report, on a trip to Portugal and Spain and report of kissing, oral sex and non-penetrative sexual intercourse, without condom use, with three different partners. The presence of genital and mucosal oropharyngeal lesion and unprotected sexual and oral intercourse favors the hypothesis of sexual transmission in the current outbreak.

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predominance of men who have sex with men in the current outbreak, as has been reported by other authors¹¹⁻¹⁴ and also occurred in the case reported here, in which the patient reported traveling to Portugal and Spain during which he kissed, had oral sex and sexual intercourse without penetration or using a condom with three different partners. The presence of genital and oropharyngeal mucosal lesions, in addition to unprotected sexual and oral intercourse, favors the hypothesis of sexual transmission in the current outbreak. Moreover, the mucosal manifestation presented here, characterized by oropharyngeal ulcer, is an important clinical sign, as it may reflect the local inoculation of the virus during oral sex. Supporting the possible route of sexual transmission, viral DNA in seminal fluid was recovered from three cases reported in Italy¹², but further studies are needed to confirm this hypothesis. Unfortunately, we did not perform any tests on our patient's seminal fluid and the viral investigation on the oropharyngeal swab was not performed in a way to specifically detect the monkeypox viral DNA.

Clearly, the current outbreak differs from previous ones, not only in terms of clinical presentation, but also in terms of age (30-50 years), sex/gender (male), risk factors and route of transmission¹³. We reinforce that public actions to combat the current outbreak must include educational strategies so that health professionals recognize suspected cases, being trained to identify cases whose initial presentation may not be accompanied by disseminated lesions, systemic symptoms or epidemiological links that strongly suggest the monkeypox diagnosis. It is equally important to highlight that any individual can develop the disease, regardless of their sexuality, and educational actions are also responsible for combating stigma and discrimination against monkeypox carriers¹⁵. In addition, implementation of infrastructure for close contact tracing and of interventions such as isolation of patients and sexual abstention, screening for coinfections with other STIs, and pre and post-exposure vaccination are needed¹⁴.

The contribution of HIV coinfection to the clinical course of patients diagnosed with monkeypox is unknown. However, it is possible that advanced HIV infection (AIDS) could lead to poorer outcomes¹⁰. At the time of this case reporting, the prevalence of HIV coinfection among confirmed cases of monkeypox was not available, as well as more details on what were the factors that have possibly contributed to the severity of monkeypox in the patient who died.

At the time the patient searched for medical attention, there were already documents guiding the correct way of collecting and forwarding biological material^{8,9} to perform the fast and reliable laboratory diagnosis of monkeypox, highlighting the importance of having a quality public service with planning and coordinated health actions. In Brazil, suspected and probable monkeypox patients should have samples collected and forwarded to a reference laboratory for the diagnosis confirmation made by PCR followed by whole genome sequencing, whenever possible. The patient's disease severity and need of hospitalization must be assessed and if the patient can be discharged, he must be adequately oriented about the period of isolation at home. Besides that, the health professional who made the suspicion must immediately notify the case and perform contact tracing must be carried out soon after^{8,9}.

Public health services must be prepared to adequately guide and supervise patients with monkeypox and also to educate the population about the disease outbreak current epidemiological situations and individualized risks, in addition to providing adequate physical space, personal protective equipment and laboratory supplies for the diagnosis of suspected patients.

Our patient's hospitalization was not because of the severe manifestations of monkeypox, but to allow for diagnostic evaluation, pain control and treatment of the secondary bacterial infection.

Despite being a mild and self-limiting disease in most cases, some conditions, such as immunosuppressive diseases, pregnancy and lactation, pediatric population, and people with a history of active exfoliative skin dermatoses may be associated with complications and worse prognosis¹⁶. These conditions may benefit from drugs approved for smallpox and cytomegalovirus treatment and which may have some activity against monkeypox virus, such as tecovirimat (approved treatment for smallpox) and cidofovir (approved treatment for cytomegalovirus)¹⁷.

In terms of pre- and post-exposure prophylaxis, there are two vaccines licensed by the Food and Drug Administration (FDA), USA, recommended primarily for people at risk of occupational exposure to orthopoxviruses, such as those working with diagnostic tests for monkeypox virus detection and now, as the multinational monkeypox outbreak continues, vaccines are also recommended for groups most at risk for acquiring severe monkeypox¹⁷. JYNNEOS is a live virus vaccine using non-replicating modified vaccinia Ankara (MVA) licensed for smallpox prevention and now, also for monkeypox in adults aged \geq 18 years, being administered in two doses with 28 days interval¹⁸. ACAM2000 is a replication-competent live vaccinia virus vaccine licensed for prevention of smallpox that is administered as a single dose¹⁹. Unfortunately, until this moment, none of these antivirals or vaccines are available in Brazil8.

Our report sheds light on important issues, such as the need, in the face of a suspected monkeypox case, to implement the correct infection prevention and control measures to protect the hospital staff and other patients. These measures involve implementing contact and droplet precautions for all suspected cases of monkeypox, cleaning and disinfecting areas used by the patient, careful handling of sheets, towels and other tissue items, proper handling of waste that should be considered infectious²⁰.

Our report sheds light on important issues such as the need, in the face of a suspected case of monkeypox, to implement the correct measures to prevent and control these infections in order to protect the hospital staff and other patients. These measures involve contact and droplet precautions for all suspected cases, cleaning and disinfection of areas used by the patient, careful handling of sheets, towels and other fabric items, proper handling of waste that should be considered infectious²⁰.

We hope that with this detailed clinical description and photo documentation, we are contributing to disseminate the importance of raising the hypothesis of monkeypox. Moreover, we believe in this case report is of educational importance not only for infectious diseases specialists, but also for other clinicians involved in the care of patients with genital and skin rash, such as dermatologists, urologists, gynecologists and emergency physicians.

The patient's perspective

The first symptoms are easily confused with allergy, chickenpox or dengue, when it reaches the fever stage. One of the initial vesicles was diagnosed as a "fish eye" by a medical doctor I know, who evaluated a picture of an injury that I sent over the phone. During the treatment, the most important action was to contain the pain that was very intense in the enlarged lymph nodes. On the 6th day after hospital discharge, all lesions were already healed. In the final phase (vesicles with fibrin to healed vesicles), even in isolation at home, I was able to maintain all my routines normally: feed myself, do personal hygiene, fulfill home office work and do physical exercises at home. The only restriction was the handling of all the objects I used, before the lesions had fully healed, but I could manage to be the only person who had contact with these objects until they were properly cleaned.

CONCLUSION

In conclusion, given the current outbreak, we must consider the possibility of monkeypox for patients with different forms of skin rash, anywhere on the body (including the genital region), in addition to the presence of epidemiological factors and history of intimate contact with strangers or casual sexual partners, and once this hypothesis is made, it is imperative to establish isolation measures, collect and send biological material according to proper guidelines be able to confirm the diagnosis.

AUTHORS' CONTRIBUTIONS

Conceptualization: ELL, LAM, ECS, JALL and CFM; investigation: ELL, LACB, LMSB, LAM, LSLAS, AJDS, CCMR, LCFA, MYST, LSVB, CAMS, TMC, ERM, IMC, CMR, MSR, TM, ECS, JALL and CFM; data curation: ELL, LACB, LMSB, IMC, ECS, JALL and CFM; writing (original draft): ELL, JALL, LSLAS and CFM; writing (review and editing): LAM, NRF and ECS.

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