Severe mpox in an immunocompromised patient, South Africa 2024

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A previously healthy 35-year-old male belonging to the men who have sex with men (MSM) community, practising both penetrative and receptive anal sex for the past 10 years, and with no travel history outside South Africa, presented initially with a prodrome of fever, sore throat, night sweats, myalgia and fatigue. A week after the onset of these nonspecific symptoms, the patient noted painless, non-pruritic skin lesions measuring 2 - 15 mm in diameter on the dorsum of his hands. Three days later he developed rigors, watery diarrhoea and similar lesions on his genital and perianal areas. A week later, the patient presented to the emergency department with extensive lesions encompassing almost his entire body. He was admitted with suspected mpox infection. Imaging showed extensive lymphadenopathy, and the diagnosis was confirmed by mpox polymerase chain reaction testing. During the admission, he was also newly diagnosed with HIV infection. Treatment with tecovirimat was initiated, and the patient recovered, albeit with significant depigmentation and scarring.

Keywords: mpox, severe, HIV co-infection, immunosuppressed

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Poxviruses, of the *Poxviridae* family, are oval or brick-shaped, large (250 - 350 nm in diameter), enveloped, double-stranded DNA viruses. Four genera in this family, *Orthopoxvirus*, *Parapoxvirus*, *Molluscipoxvirus* and *Yatapoxvirus*, cause human infections.[1] The *Orthopoxvirus,* monkeypox (or monkeypox virus, MPXV), is the causative agent of the disease mpox (formerly known as monkeypox). MPXV was first discovered in 1958 in laboratory monkeys, and it has since been detected in several rodent and primate species, but to date the natural reservoir host has not been identified.[2] Two distinct variants (or clades) of MPXV exist, namely clade I and II. Clade I (formerly known as the Central African clade) is more virulent and transmissible than clade II (formerly known as the West African clade). The ongoing MPXV outbreak in the Democratic Republic of Congo (DRC), which began in late 2022, is associated with at least two independent clade I MPXVs.[3] Clade II is subclassified into IIa and IIb. Clade IIb is associated with the ongoing global outbreak of MPXV that began in 2022.[3,4]

The first human case of mpox was diagnosed in 1970 in the DRC. It has subsequently been shown that MPXV has circulated endemically in central and west Africa, with transmission occasionally occurring between animals and humans, and with some human-to-human spread.[2] There have been small outbreaks in non-endemic countries including the USA in 2003, and between 2018 and 2021 in the UK, Israel and Singapore, with occasional nosocomial spread from patients who had positive travel histories to endemic countries.[2] The first case from the ongoing multi-country mpox outbreak was laboratory confirmed in May 2022, and now involves more than 100 countries, with cases occurring predominantly but not exclusively in men who have sex with men (MSM).[4]

Human-to-human transmission results from close skin-to-skin contact or with fluid secretions, either directly, e.g. sexual contact, or indirectly, via contaminated fomites. People with mpox are considered infectious until all their lesions have crusted over, the scabs have fallen off and a new layer

of skin has formed underneath.[5] The incubation period ranges from 5 to 21, days with an average of 13 days. A prodromal phase is characterised by fever, myalgia and lymphadenopathy. The rash typically involves the face, scalp, torso and limbs, and can extend to the palms of the hand, soles of the feet, mouth, eyes and ano-genital area.[6] The number of lesions may vary from singular to a few to hundreds, and they may coalesce to form large plaques or ulcers.[7] Lesions evolve over 2 - 4 weeks in stages from macules, to papules, to vesicles, then to pseudo-pustules that dip in the centre and become umbilicated before crusting over. Once the scabs fall off, they may or may not leave scarring of the skin.[7]

Case report

A 35-year-old male working as an administrator with no previous medical or surgical history, no allergies, and no travel history outside South Africa (SA) for 2 - 3 weeks prior to the onset of illness presented to a general practitioner in May 2024 in the Eastern Cape. He had flu-like symptoms including fever, sore throat, rhinitis, fatigue and night sweats. The patient was treated symptomatically, and the prodrome resolved within a week of its onset. He further provided a history that he identifies as male and that his sexual orientation is homosexual. He reported only having one sexual partner for over a year, but was uncertain of his partner's fidelity. Both practise penetrative and anal receptive sexual intercourse, with no use of any sexual paraphernalia. He had not participated in group sex, and all his sexual partners have been South African, though it is unknown if these individuals had non-South African sexual contacts prior to their relationship with him. A week following the onset of illness, the patient noticed lesions on the dorsal aspect of both hands. The lesions were painless, non-pruritic and approximately 2 -15 mm in diameter. At this stage, the patient returned to Johannesburg, Gauteng Province. Within 2 days, the patient developed rigors and watery diarrhoea for 3 days that resolved without treatment. He also noted that lesions with the same appearance as those on his hands were developing on his genital and perianal area, with sparing of the glans penis. The patient presented to a local general practitioner and was treated with antihistamines and oral corticosteroids as a possible hypersensitivity reaction with an atypical distribution. Two days later he presented to the emergency department at a private hospital with extensive, large umbilicated pustules that were also indurated. These lesions were noted on his head, neck and trunk, and with fewer lesions on his extremities. He was diagnosed with molluscum contagiosum and was discharged with a referral letter to see a dermatologist as an outpatient. The next day, failing to get an early appointment with the dermatologist, he presented back at the private hospital, where he was admitted to an isolation ward.

On examination, the patient was well orientated, with a normal neurological examination. He had basal crackles bilaterally, but was not in respiratory distress, and his room air oxygen saturation was 96%. He had significant generalised lymphadenopathy, including in the cervical, axillary and inguinal areas. The lymph nodes were firm and tender, ranging in size from 2 - 3 cm in diameter. Dermatological examination revealed extensive widespread papules and vesiculo-pustular skin lesions, some with central umbilication and necrosis on the face, scalp, trunk and limbs, with fewer lesions on the extremities (Fig. 1, panel A).

The lesions were of varying sizes and different stages of development, with some actively oozing, while others were beginning to crust. The skin lesions also involved the oral mucosa, the ano-genital area as well as the palms of the hands and soles of the feet. The differential diagnosis at this stage included molluscum contagiosum, atypical and disseminated herpes simplex, a deep fungal infection of the skin and secondary syphilis. Blood samples were taken for baseline investigations, and the patient consented to HIV testing. The diagnostic and therapeutic timeline for this patient is shown in Fig. 2.

The specimens were HIV reactive with a viral load of 19, 485 copies/mL and a CD4+ count of 371 cells/μL. A week after this HIV diagnosis, he was initiated on first-line combination antiretroviral therapy in the form of tenofovir disoproxil, lamivudine and dolutegravir. His baseline full blood count (FBC) was normal except for a microcytic hypochromic anaemia and raised atypical or reactive lymphocytes and monocytes, with this latter finding persisting on subsequent FBCs and only normalising after 3 weeks and before the initiation of mpox-specific therapy. In terms of his inflammatory markers, his C-reactive protein (CRP) was raised on admission at 128 mg/L (<5), he had a high ferritin of 1 183 ng/ml (normal range 34 - 310), an erythrocyte sedimentation rate of 125 (normal range 1 - 15) and his procalcitonin (PCT) was also elevated at 0.17 ng/ml (<0.05). His CRP remained elevated throughout admission and only reduced by >50% after 3 weeks and prior to initiation of mpox-specific antiviral therapy. His baseline renal function tests were normal except for a mildly elevated creatine, which normalised after intravenous fluids. Liver function tests on admission revealed elevated alkaline phosphatase, gamma glutamyl transferase and protein, prompting serological screening for viral hepatitis, including hepatitis A, B and C, with the latter two also being important sexually transmitted viruses. Hepatitis B surface antigen and hepatitis C total antibody tests were both negative. Cytomegalovirus and Epstein-Barr virus viral loads on blood were unremarkable. Active infection with syphilis was also ruled out on serology. Blood cultures remained negative throughout his admission.

Punch biopsies of skin lesions were submitted for histological evaluation on two separate occasions. All samples showed a zone of coagulative necrosis of the epidermis with an overlying thick, inflammatory crust (Fig. 3). The intact epidermis showed marked hyperplasia and ballooning degeneration of keratinocytes, as well as eosinophilic hyaline globules within the cytoplasm of degenerate keratinocytes. The latter changes were later interpreted as Guarnieri-type intracytoplasmic inclusions. These were accompanied by a conspicuous exocytosis of neutrophils with associated karyorrhexis. In addition, there were degenerate keratinocytes exhibiting intranuclear eosinophilic inclusions as well as isolated keratinocytes showing multinucleation, suggesting herpes virus infection (Fig. 3). However, immunohistochemistry for herpes simplex virus 1 and 2 and varicella zoster virus were negative. There was no histological evidence of molluscum contagiosum or deep fungal infection. The underlying superficial dermis showed a moderately dense, predominantly perivascular, inflammation consisting of a mixture of lymphocytes, histiocytes and neutrophils. There was relative sparing of the deeper dermis. Electron microscopy was performed on this last set of lesion biopsies and demonstrated the presence of orthopoxviruses (Fig. 4), and no herpes viruses were detected.

For radiological investigations, contrast computed tomography (CT) scans of the head, chest, pelvis and abdomen were performed (Fig. 5). Chest, abdominal and pelvic CT revealed extensive lymphadenopathy. Although the lower lobe of the right lung showed apical nodularity suggestive of post-primary tuberculosis (TB), mycobacterial TB screening on sputa for acid-fast bacilli was negative on two occasions, as was urinary lipoarabinomannan testing. Importantly, peri-anal and peri-rectal oedema along with regional enhancing lymphadenopathy were also observed, suggesting a proctitis.

Based on the initial histopathology report showing features suggestive of herpes simplex virus infection, the patient was initiated on intravenous acyclovir 500 mg every 8 hours, which was later de-escalated to oral valacyclovir 1 g every 8 hours. However, because the skin lesions were not improving on intravenous acyclovir and

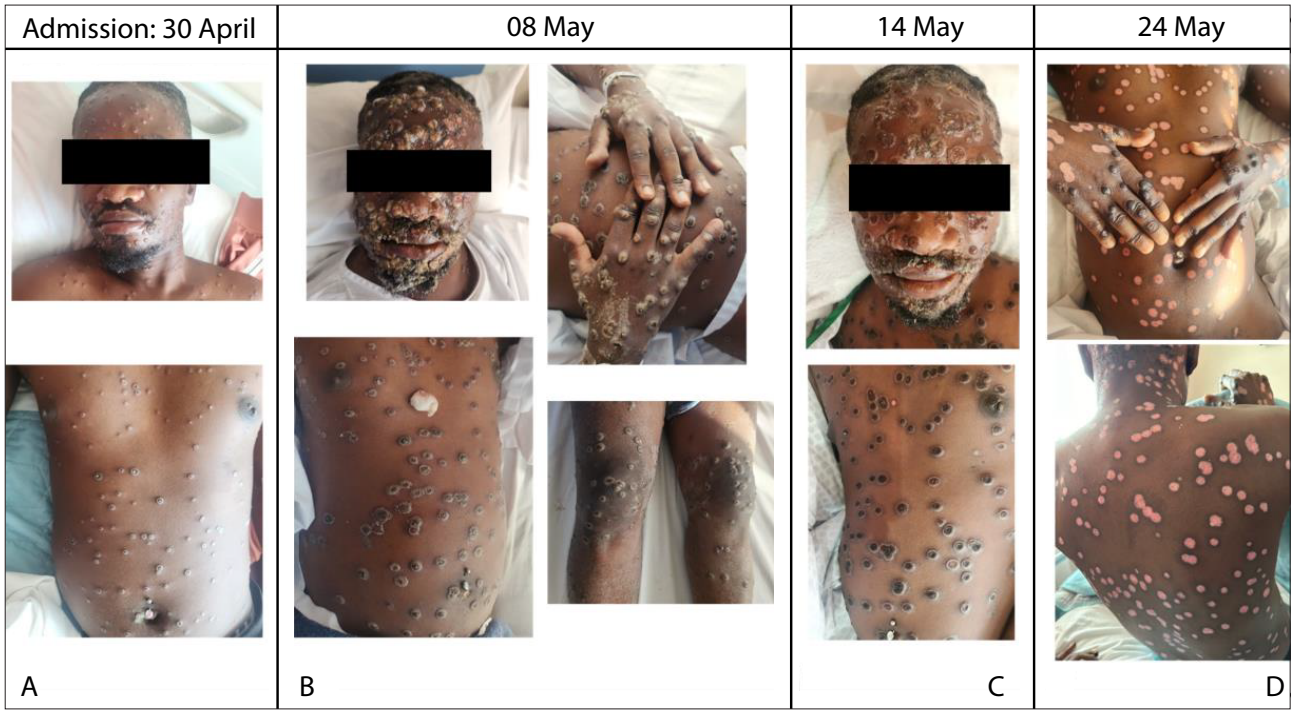

Fig. 1. Mpox lesions on the face, trunk and extremities at different time points. Note the large size and umbilicated lesions evolving into necrotic lesions concentrated on the face and trunk with fewer lesions on the limbs. Panel A: before treatment. Panel B: 4 days after initiating HIV treatment. Panel C: 5 days before tecovirimat. Panel D: 6 days after tecovirimat. Note the hypopigmentation and scarring.

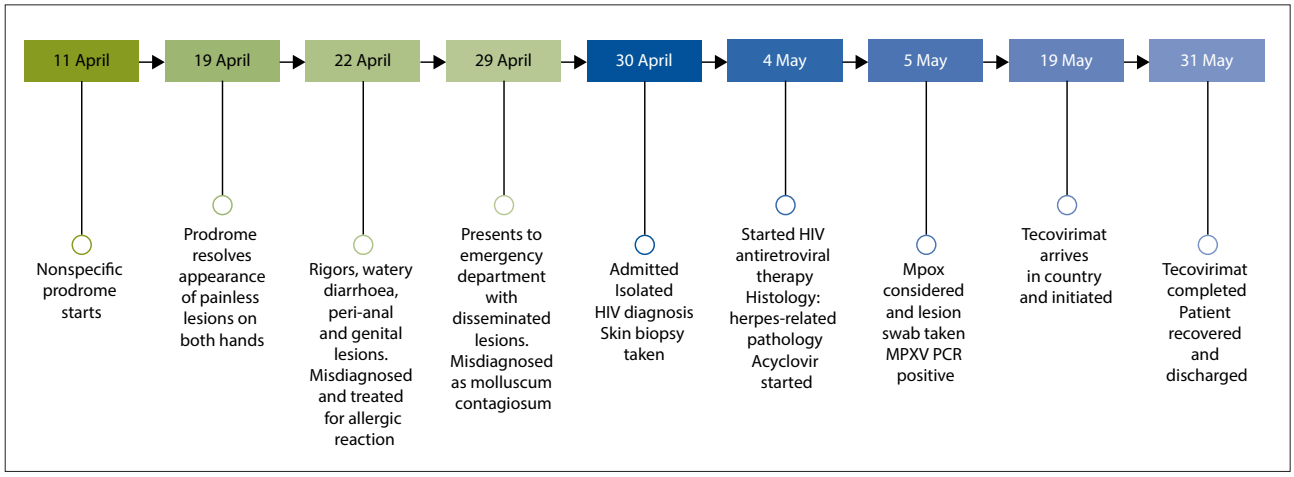

Fig. 2. Clinical timeline of the patient's disease over a 7-week period, emphasising the delays in making the mpox diagnosis, and time taken from starting tecovirimat to recovery and discharge. (MPXV = monkeypox virus; PCR = polymerase chain reaction.)

were instead increasing in size and distribution, a diagnosis of mpox was considered. The skin lesions, especially those on the face, began oozing and developing honey-coloured crusts (Fig. 1, panel B). A third biopsy and a swab were then taken for MPXV polymerase chain reaction (PCR) testing, which yielded positive results. The results were verified at the national reference laboratory followed by full genomic sequencing. The sequence confirmed the presence of clade IIb lineage B1.20 MPXV in the specimens.

Due to the severe and extensive nature of mpox presentation in this patient, with >100 lesions, and his immunosuppressive state as a newly diagnosed HIV-infected patient, assistance for access to tecovirimat pox antiviral treatment, which is not registered in SA, was requested from the World Health Organization (WHO). Access was gained following section 21 authorisation for compassionate use with the SA Health Products Regulatory Authority. The drug was received, and the patient was initiated on oral tecovirimat 600 mg twice daily, and completed 14 days of therapy. During the course of the treatment, he did not experience any side-effects, and after 3 days of therapy, the patient reported feeling subjectively better and his lesions objectively appeared to be improving. The patient was discharged on 31 May 2024.

Discussion

In 2022, during the peak of the ongoing multi-country mpox outbreak, SA recorded five cases of mpox, all in adult MSM males aged 28 - 41, with the last SA case reported in 2022.[8] These cases had travel histories or close contact with travellers, which would be the most likely explanation for their exposure and subsequent infection. The case reported here, however, is the first case of mpox in SA with no travel history or close contact with travellers, and more than a year after which no mpox cases were detected locally. This

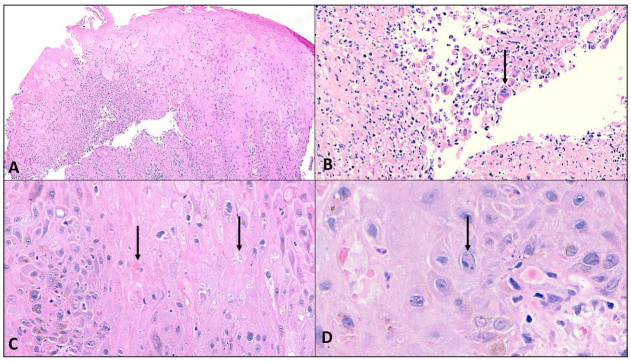

Fig. 3. Panel A: hyperplastic epidermis demonstrating necrosis and ballooning degeneration of keratinocytes. Panel B: epidermal necrosis mimicking acanthosis. Note a multinucleated keratinocyte (arrow) in the centre. Panel C: keratinocytes with intracytoplasmic eosinophilic hyaline globules (arrow). Panel D: isolated keratinocytes showing eosinophilic intranuclear pseudoinclusions (arrow) mimicking herpes virus inclusions.

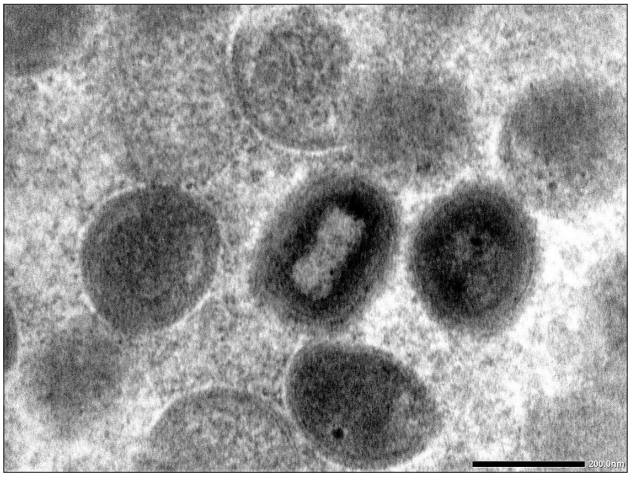

Fig. 4. Electron micrograph showing oval-shaped monkeypox virus with a dumbbell- shaped core in the centre. Scale bar = 200 nm.

case is characterised by severe mpox infection with HIV-induced immunosuppression.

This patient's risk factors for infection are in keeping with the global mpox outbreak, i.e. MSM[6,7] and <40 years of age.

The occurrence of this case, with no travel history, could mean that MPXV had either been circulating in SA undetected for a whole year (2023), ever since the first reported local cases in 2022, which is very unlikely, or there could have been a new, recent reintroduction of clade IIb MPXV into the country by a travelling infected person(s).

Unlike the previous five SA cases and the majority of the cases during the global outbreak, where lesions were mostly confined to the ano-genital and oral areas,[6] the patient described here had an extensive disease presentation with <100 lesions covering almost every part of his body, and a protracted disease course spanning over 7 weeks. Reasons for this severe presentation include concomitant immunosuppression due to an undiagnosed and untreated HIV infection at the time, the administration of corticosteroids during the earlier stages of the disease when the patient was misdiagnosed and treated for an allergic skin reaction, and mpox immune reconstitution inflammatory syndrome following initiation of HIV antiretroviral therapy[10] soon after admission and before the diagnosis of mpox was confirmed. During the ongoing global mpox outbreak, severe and/or prolonged disease was reported in patients with underlying immune deficiencies, including uncontrolled HIV and CD4 counts <200 cells/μL.[10]

The issue of misdiagnosis and delayed diagnosis in this patient is important. It took 3 weeks from the time that the first mpox lesions appeared on the patient's hands to the time that mpox was considered and confirmed on PCR. The patient had erroneously been diagnosed with allergies, molluscum contagiosum and then herpes simplex virus infection. Prolonging the time to final diagnosis may have significant implications for both the patient and from a public health perspective. For the patient, delayed diagnosis may result in severe disease with complications, and from a public health perspective, delay in diagnosis may result in further transmission chains occurring. Based on the clinical presentation of the rash, the

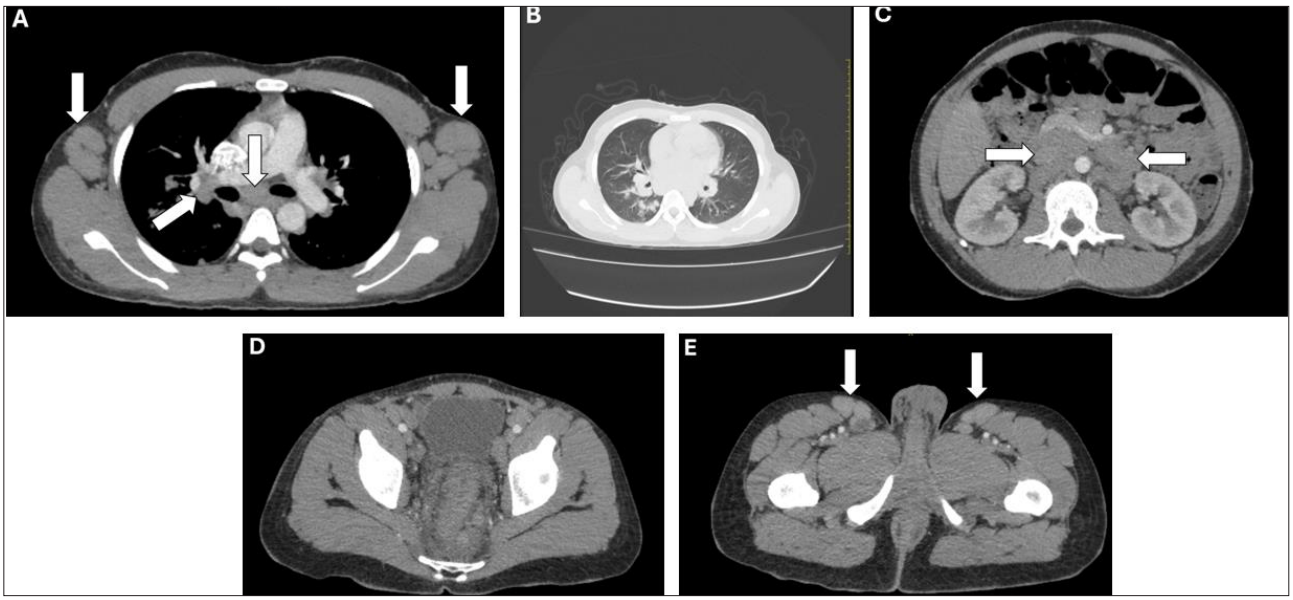

Fig. 5. Contrast computed tomography scan of the chest (A and B), abdomen (C) and pelvis (D and E). Note the solid bi-axillary, right hilar and subcarinal lymphadenopathy (arrows, panel A). Also, the right lower lobe in B shows apical segment nodularity suggestive of post-primary tuberculosis. Abdominal and pelvic images reveal extensive solid para-aortic, para-carval and paravertebral lymphadenopathy (C) and solid and necrotic bi-inguinal lymphadenopathy (D). Peri-anal and perirectal oedema and regional enhancing lymphadenopathy was observed (E), in keeping with severe proctitis.

differential diagnosis in these cases is broad, and includes chickenpox (caused by varicella zoster virus), molluscum contagiosum, deep fungal infection, syphilis, bacterial skin infection, scabies and allergies. Ano-genital lesions may be associated with proctitis (rectal pain, tenesmus, bleeding and discharge),[7,10] and ano-rectal local oedema, which was demonstrated on CT scan in this patient. In contrast to chickenpox, the mpox rash is usually non-pruritic, and lesions are typically significantly larger, pustular or umbilicated. Although the mpox lesions are supposed to present in the same stage of evolution, this was not the case in the patient described here, where the lesions were at different stages of development. Additionally, lymphadenopathy is more likely to occur with mpox than with chickenpox or herpes simplex. The presence of epidemiological risk factors, e.g. MSM or sex workers, and regions of the body affected, e.g. ano-genital, as well as accompanying symptoms such as tender regional lymphadenopathy and proctitis, should create a high index of suspicion for mpox and help to narrow the differential.

The diagnostic dilemma surrounding mpox and severe infection in an immunocompromised individual is highlighted in this patient. Though herpes simplex virus infection was suspected based on the initial histology report, negative immunohistochemistry staining for HSV-1/2 and varicella zoster virus, as well as their absence on the electron microscopy, ruled out herpes virus infection in this patient. Histological evaluation of mpox lesion biopsies may be associated with necrotic keratinocytes, multinucleated keratinocytes, intracytoplasmic inclusion bodies called Guarnieri bodies, ballooning, ground glass nuclei and perivascular neutrophil infiltration, among other possible findings.[10,11] However, these findings can be challenging owing to the presence of necrosis and associated cellular debris, especially in more advanced mpox lesions, as well as the infrequency with which mpox cases have occurred in our setting, leading to lack of exposure needed to build experience with identifying and differentiating orthopoxviruses.

Teaching points

- Diagnosis may be difficult as the rash may be misdiagnosed as chickenpox, molluscum contagiosum, herpes simplex, syphilis, allergies, or deep fungal infections.
- Mpox should be considered as a possible diagnosis and actively investigated in persons who are HIV infected and who present with suggestive acute skin lesions.
- There is limited access to specific antiviral treatment tecovirimat, which can be accessed through section 21 approvals.
- Negotiations are currently ongoing to make preventive mpox vaccines for high-risk groups, including healthcare workers, available in SA.

Conclusion

This case demonstrates the challenges in the diagnosis and treatment of mpox in SA, particularly at a time when there was a low index of suspicion. Early recognition of mpox is essential, particularly in severe cases or cases at high risk of severe disease as early treatment may improve outcomes.

Data availability. N/a.

Declaration. None.

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All authors have reviewed and edited the manuscript.

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Conflicts of interest. None.

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