Overlooked monkeypox cases among men having sex with men during the 2022 outbreak – a retrospective study


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Title Page

Overlooked monkeypox cases among men having sex with men during the 2022 outbreak – a retrospective study

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Running title: Monkeypox Misdiagnosis

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Highlights for review

- Monkey Pox in the present outbreak out of endemic areas may be easily overlooked.
- Monkey Pox may be present as another sexually transmitted disease.
- Misdiagnosis led to delayed isolation and administration of inappropriate treatment.

Abstract

Objectives

The aim of this study was to characterize overlooked cases of patients with Monkeypox (MPX) infection in the 2022 outbreak.

Methods

Clinical characteristics of 26 patients who were misdiagnosed as other diseases were described.

Results

Of the 26 patients who were misdiagnosed, 6 (23%) were given a diagnosis of bacterial tonsillitis, 6 (23%) primary syphilis, 5 (19.2%) oral or genital herpes, and 4 (15.3%) bacterial proctitis or anal abscess. The average time interval between missed and right diagnosis was 4.4 days. There was no difference in the missed cases between the early and the later month of the outbreak.

Conclusion

MPX may still be commonly overlooked, especially in patients presenting with fever and sore throat or solitary ulcer as sole manifestations.

Keywords: monkeypox; misdiagnosis; MSM
Introduction

Monkeypox (MPX) is an emerging disease outside of Africa, especially in men who have sex with men (MSM) who engage in unprotected sex [1]. Since its first appearance in the current outbreak on early May 2022 [2] more than 60,000 cases have been reported outside of endemic areas (https://www.cdc.gov/poxvirus/monkeypox/response/2022/index.html).

In contrary to travel associated MPX [3,4] the current outbreak is mainly among MSM and probably transmitted during sexual contact [5].

Many of the patients present with proctocolitis and genital ulcers which may be associated with fever and inguinal lymphadenopathy, while others may present with much milder disease [1,6]. Symptoms and signs may be similar to other sexually transmitted diseases and around 30% of the patients are indeed co-infected with another sexually transmitted infection (STI) [1,7]. MPX is a "new disease" in non-endemic countries, and may present with a wide range of clinical findings including those resembling an STI. Since many physicians are not familiar with the disease, it can be easily misdiagnosed or overlooked, leading to delayed diagnosis, delayed isolation and/or administration of inappropriate treatment.
The main aim of this study was to describe the characteristics of cases of MSM ultimately diagnosed with MPX who were initially misdiagnosed as having another disease during the current outbreak.

**Methods**

This is a retrospective study. Patients who were diagnosed with MPX during 16/5/2022-06/10/2022 were retrospectively included in the study. Misdiagnosis was defined when MPX was not documented in the differential diagnosis of the examining physician on the first examination, but was subsequently diagnosed based on a laboratory confirmatory test. Only patients with a positive polymerase chain reaction (PCR) assay that was done in a recognized laboratory in at least one sample from any anatomical site were included. We defined May-June as the early phase of the outbreak and July-August as the later part of the outbreak.

**Results**

Twenty six patients were included in the study (Table 1). All patients self-defined as MSM with a definite sexual exposure history. In the primary contact with a physician, they were not asked about contact with a MPX patient. Of the 26 patients, 17 (65.3%) were on HIV PrEP, and 5 (19.2%) were HIV positive.

Clinical presentation: Overall, skin (30.7%) and/or ano-genital lesions (46%) were the most common presentations, the most common skin lesion were described as vesiculopustular or crusted lesion. The number of lesions varied widely but most patients had less than 10 lesions. Proctitis alone was noted in
26.9% of the patients at initial presentation, and 23% presented initially only with fever and sore throat.

Diagnosis at presentation (Table 1): Of the 26 patients who were misdiagnosed, 6 (23%) were given a diagnosis of bacterial tonsillitis, 6 (23%) primary syphilis, 5 (19.2%) oral or genital herpes and 4 (15.3%) bacterial proctitis or anal abscess. During the study’s early period, 11 patients were misdiagnosed, compared to 15 during the later period, which was not significantly different.

Two patients were missed diagnosed by two different physicians. The misdiagnosing 28 physicians on initial presentation were 11 (39%) primary care physicians, 8 (28.5%) dermatologists, 7 (25%) emergency care physicians and 2 (7.5%) proctologists. Of the 21 physicians that rightly diagnosed MPX on a later examination 9 (43%) were emergency care physicians, 7 (33%) primary care physicians and 5 (24%) were Infectious disease specialists. On 7 cases the patient himself suggested the diagnosis to the physician.

On average there was a gap of 4.4 days (median 4, range 1-9) between the missed and the right diagnosis.

Three of the patients were coinfected with gonorrhea (two rectal and one pharyngeal) and one with syphilis (by serology, asymptomatic).

Discussion
In this study we show that MPX infection may be easily overlooked and be confused with other diseases, mainly other STIs. Due to the nature of its transmission, and its non-classical presentation of lesions concentrated in the anogenital areas in about 75% of the patients [1], it is most commonly confused with other STIs such as syphilis and genital herpes simplex infection. Furthermore, 23% of the patients in this study were initially diagnosed as having tonsilitis/pharyngitis, with the oropharyngeal lesions probably resulting from an oral sexual mechanism of transmission.

Our findings are in accordance with more traditional STIs, which are more likely to be correctly diagnosed when presenting in the classical genital areas, and more likely to be misdiagnosed when presenting in extra genital sites [8]. Among our patients 5 (19.2%) were coinfected with HIV and 4 with bacterial STIs (3 with gonorrhea and 1 with syphilis). HIV and other STIs have been reported in the current global monkeypox outbreak. In fact, persons with HIV infection or STIs are disproportionately represented among persons with monkeypox [9]. Given the fact that many of the patients are on PrEP and probably are involved in condomless sex it is important to test for co infections with other STIs.

Although since the beginning of the MPX outbreak in May 2022, several webcasts and newsletters were delivered to all physicians, misdiagnoses continued to occur in the later phase of the outbreak.

Our study has several limitations. Mainly, a small sample size that limited our ability to identify factors significantly associated with misdiagnosis. Another limitation is a lack of a control group of patients with a timely diagnosis.
Although at the same time about 257 patients were diagnosed with MPX in Israel we don't know the rate of overlooked diagnosis in the all population and our patients may not reflect the entire MPX patient population in the country.

In conclusion, MPX may still be commonly misdiagnosed, especially among patients presenting with fever and sore throat as sole manifestations, most probably due to a lack of expertise regarding MPX. Continuously raising the awareness for this disease and its varied range of symptoms and signs is essential for making early diagnoses and limiting transmission. Since other STIs may commonly co-exist they should also be tested.

Conflict of interests

The authors have no competing interests to declare.

Funding source

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Ethical approval statement

This study was approved by the institutional review board/ethics committee of the “SHEBA ethical board” under protocol number 9481-22-SMC.
References


Table 1: Characteristics of misdiagnosed (MD) MSM with MPX

<table>
<thead>
<tr>
<th></th>
<th>Missed Diagnosed (N=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Y, mean, range)</td>
<td>34.5 (21-48)</td>
</tr>
<tr>
<td>HIV positive, N (%)</td>
<td>5 (19.2)</td>
</tr>
<tr>
<td>On PREP, N (%)</td>
<td>17 (65.3)</td>
</tr>
<tr>
<td>Period of diagnosis (early), N (%)</td>
<td>11 (42.3)</td>
</tr>
<tr>
<td>Time interval between missed and right diagnosis in days. average (median, range)</td>
<td>4.4 (4, 1-9)</td>
</tr>
<tr>
<td><strong>Cause of presentation, N (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Skin Ulcer</td>
<td>8 (30.7)</td>
</tr>
<tr>
<td>Anal and perirectal</td>
<td>7 (26.9)</td>
</tr>
<tr>
<td>Penile ulcer</td>
<td>4 (15.3)</td>
</tr>
<tr>
<td>Fever and sore throat</td>
<td>6 (23)</td>
</tr>
<tr>
<td>Fever, Lymphadenopathy</td>
<td>5 (19.2)</td>
</tr>
<tr>
<td>Groin pain</td>
<td>3 (11.5)</td>
</tr>
<tr>
<td>Intra urethral lesion</td>
<td>1 (3.8)</td>
</tr>
<tr>
<td><strong>Primary (mis) diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>Tonsilitis</td>
<td>6 (23)</td>
</tr>
<tr>
<td>Syphilis</td>
<td>6 (23)</td>
</tr>
<tr>
<td>Herpes</td>
<td>5 (19.2)</td>
</tr>
<tr>
<td>Proctitis</td>
<td>4 (15.3)</td>
</tr>
<tr>
<td>Skin lesions not</td>
<td>2 (7.6)</td>
</tr>
<tr>
<td>Medical professions that missed diagnosis</td>
<td>Count (Percentage)</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Warts</td>
<td>2 (7.6)</td>
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<tr>
<td>Primary care - general</td>
<td>11 (42.3)</td>
</tr>
<tr>
<td>Primary care – LGBT clinics</td>
<td>2 (7.6)</td>
</tr>
<tr>
<td>Emergency department physician</td>
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<tr>
<td>Dermatologist</td>
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<td>Proctologist</td>
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<tr>
<td>Urologist</td>
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