

# Monkeypox and the importance of cutaneous manifestations for disease suspicion

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During the months of May and June 2022, the world has witnessed the re-emergence of an old viral zoonotic disease which is currently concerning given its spread over multiple countries and continents (1, 2). Monkeypox is rapidly circulating in new areas, including Latin America, where cases have been confirmed in Argentina, and Mexico, with suspected cases in many other countries of the region, such as Brazil, Bolivia, Ecuador, and Costa Rica, among others (3).

In general, in countries with cases, but especially in those without them, there is a need to increase their surveillance and clinical suspicion among travellers arriving from cities with confirmed cases that would fit the definition of the suspected or probable case, according to the World Health Organization (WHO) (Table 1) (4). Particularly skin findings are key coupled with epidemiological links (Table 1).

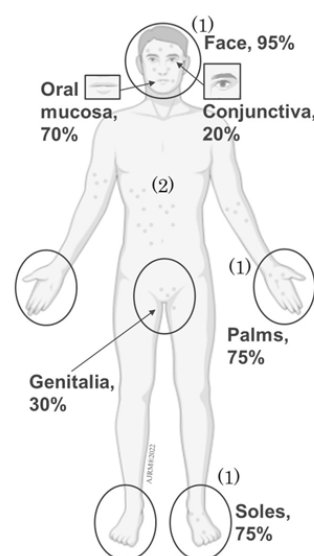
The cutaneous manifestations of monkeypox are the hallmark of this DNA viral infection that may mimic other viral and non-viral conditions, mainly including smallpox, cowpox, tanapox, molluscum contagiosum (Pox viruses); herpesviruses, such as HSV-1, HSV-2, chickenpox (varicella), zoster (shingles), exanthem due to CMV or EBV, HHV-6, -7 and -8; adenovirus, human papillomavirus (HPV) and parvovirus B19. Also, RNA viruses may evolve with rash and other cutaneous manifestations, including paramyxovirus such as measles (endemoepidemic in Venezuela and spread through forced migration to multiple countries in South America over the last decade) (5, 6), mumps, AIDS dermatitis, hand-foot-mouth

disease (HFMD) and exanthems due to enterovirus and Coxsackie viruses, echoviruses, rubella. Mainly in tropical countries, multiple arboviruses may produce also rash, with or without pruritis, including dengue, chikungunya, Zika, yellow fever, West Nile virus, Japanese encephalitis, tick-borne encephalitis (7). Other rodent-borne viruses, such as mammarenaviruses, also may affect skin, e.g. South American hemorrhagic fevers: Argentinian (Junin), Bolivian (Machupo and Chapare viruses), Brazilian (Sabia) and Venezuelan (Guanarito) (8, 9).

In monkeypox, after a 3-week incubation period (typically 6-13 days), a prodrome with fever, headache, myalgia, asthenia, and especially lymphadenopathy, among other findings (Table 1), occurs for a period of 3 to 5 days. After that, a rash will develop (with few or severe thousand lesions, synchronic or asynchronous), beginning at the face, which affects 95% of the patients (Figure 1), followed by palms and soles (75%), oral mucosa (70%), genitalia (30%), and conjunctiva (20%) (Figure 1). These skin lesions evolve from macules to papules, then vesicles, then pustules, and finally scabs or crusts that fall (Figure 2). These skin manifestations compromise the skin eruption period of the disease, in which patients are contagious. Before that, patients are not able to transmit the virus. The natural history in patients without complications regularly lasts 2 to 4 weeks.

**Figure 1**

*Anatomical distribution of the rash in monkeypox*



Given these considerations, primary care physicians and specialists should consider differential diagnoses. However, keep in mind that monkeypox will eventually arrive in new countries, with additional cases in other cases currently

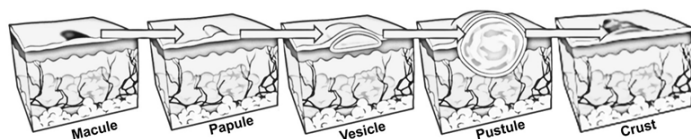
**Table 1***Monkeypox case definitions (according to the WHO)*

| <b>Outbreak case definitions</b>  |   |
|---|---|
| <b>Suspected case</b>   | <b>Probable case</b>  |
| <p>A person of any age presenting in a monkeypox non-endemic country<sup>[1]</sup> with an unexplained acute rash.</p> <p>AND</p> <p>One or more of the following signs or symptoms since 15. March 2022:</p> <ul style="list-style-type: none"> <li>* Headache</li> <li>* Acute onset of fever (&gt;38.5°C).</li> <li>* Lymphadenopathy (swollen lymph nodes).</li> <li>* Myalgia (muscle and body aches).</li> <li>* Back pain.</li> <li>* Asthenia (profound weakness).</li> </ul> <p>AND</p> <p>For which the following common causes of acute rash do not explain the clinical picture: varicella zoster, herpes zoster, measles, Zika, dengue, chikungunya, herpes simplex, bacterial skin infections, disseminated gonococcus infection, primary or secondary syphilis, chancroid, lymphogranuloma venereum, granuloma inguinale, molluscum contagiosum, allergic reaction (e.g., to plants); and any other locally relevant common causes of papular or vesicular rash.</p> <p>N.B. It is unnecessary to obtain negative laboratory results for listed common causes of rash illness to classify a case as suspected.</p> <p>[1] Monkeypox endemic countries are Benin, Cameroon, the Central African Republic, the Democratic Republic of the Congo, Gabon, Ghana (identified in animals only), Côte d'Ivoire, Liberia, Nigeria, the Republic of the Congo, and Sierra Leone. Benin and South Sudan have documented importations in the past. Countries currently reporting cases of the West African clade are Cameroon and Nigeria. With this case definition, all countries except these four should report new cases of monkeypox as part of the current multi-country outbreak.</p> | <p>A person meeting the case definition for a suspected case.</p> <p>AND</p> <p>One or more of the following:</p> <ul style="list-style-type: none"> <li>* has an epidemiological link (face-to-face exposure, including health workers without eye and respiratory protection); direct physical contact with skin or skin lesions, including sexual contact; or contact with contaminated materials such as clothing, bedding or utensils to a probable or confirmed case of monkeypox in the 21 days before symptom onset.</li> <li>* reported travel history to a monkeypox endemic country<sup>1</sup> in the 21 days before symptom onset.</li> <li>* has had multiple or anonymous sexual partners in the 21 days before symptom onset.</li> <li>* has a positive result of an orthopoxvirus serological assay in the absence of smallpox vaccination or other known exposure to orthopoxviruses.</li> <li>* is hospitalized due to the illness.</li> </ul> |
| <b>Confirmed case</b>   | <b>Discarded case</b>   |
| <p>A case meeting the definition of either a suspected or probable case AND is laboratory confirmed for monkeypox virus by detection of unique sequences of viral DNA either by real-time polymerase chain reaction (PCR) and/or sequencing</p>   | <p>A suspected or probable case for which laboratory testing by PCR and/or sequencing is negative for monkeypox virus</p>   |
| <b>Surveillance case definitions</b>  |   |
| <b>Suspected case</b>   | <b>Probable case</b>  |
| <p>An acute illness with fever &gt;38.3°C (101°F), intense headache, lymphadenopathy, back pain, myalgia and intense asthenia followed one to three days later by a progressively developing rash often beginning on the face (most dense) and then spreading elsewhere on the body, including soles of feet and palms of hands.</p>  | <p>A case that meets the clinical case definition is not laboratory confirmed but has an epidemiological link to a confirmed or probable case.</p>  |
| <b>Confirmed case</b>   |   |
| A clinically compatible case that is laboratory confirmed.  |   |

reported. Therefore, an early diagnosis is critical in those with risk factors (e.g. immunosuppression, elderly, children) that may evolve into complicated forms, and even with fatal outcome, which is supposed to occur in less than 10% of those affected by the Central African clade virus, or in less than 5% in those infected by the West African clade virus, which is the one reported in the current 2022 multi-country outbreak in countries outside Africa (10-14).

**Figure 2**

*Evolution of the rash lesions in monkeypox.*



Finally, as skin lesions are the primary source of samples for laboratory diagnosis using PCR and sequencing, among other options, proper education and training on monkeypox and sampling would be helpful for physicians across Latin America to make accurate diagnostics in quantity and quality.

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