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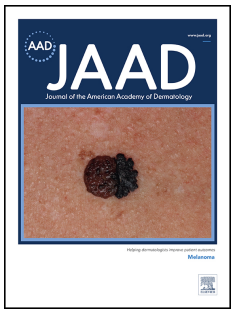

Monkeypox: Cutaneous Clues to Clinical Diagnosis

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Monkeypox: Cutaneous Clues to Clinical Diagnosis

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Dear Editor,

Monkeypox, until recently, was considered a rare zoonotic infection of sub-Saharan West Africa, associated with contact with infected animals such as squirrels, rats and primates[1]. The monekypox virus belongs to the genus *Orthopox* of the family Poxviridae, alongside other cutaneous viruses including smallpox and cowpox[1,3]. Whilst occasional cases outside of Central and West Africa have been historically reported, it has been a condition largely ignored by the wider medical community[1,2]. The 2022 monkeypox outbreak has led to an increasing awareness of the condition, and a desire amongst clinicians to know when to clinically suspect the disease. Despite increasing concern regarding reports of human-to-human (including sexual) transmission across more than 40 countries globally[1,2], the risk of monkeypox developing into a new global pandemic is less than the situation with SARS-CoV2 (COVID-19) given the obvious cutaneous manifestations of the disease and the lack of pre-symptomatic contagious spread[2].

As dermatologists, we are uniquely skilled to provide expertise in the evaluation of suspected cases of monkeypox through evaluation of cutaneous morphology and clinical exclusion of other differential diagnoses such as varicella and syphilis[4,5] (Table 1). This is particularly prudent given that the global monkeypox outbreak remains an evolving situation, with unresolved questions regarding the relative frequency of droplet transmission[1,2], and limited information

regarding mortality rates in high-risk groups such as children, the elderly and the immunocompromised[1,2].

A major barrier to clinician education regarding monkeypox, is the current messaging comparing the features of monkeypox to smallpox and primary varicella. Given that it has been over 40 years since the global eradication of smallpox, the number of practicing clinicians who have seen smallpox (as opposed to rare cases of limited variolation) is rapidly declining. Additionally, routine varicella vaccinations have drastically reduced cases of primary varicella[5], making this a rarity to younger dermatologists and trainees. Revisiting the commonalities and differentiating features of these conditions (Figure 1) is important in raising awareness and encouraging accurate clinical diagnosis in cases of suspected monkeypox.

Monkeypox virus can be spread through direct contact as well as possibly through droplet transmission[1,2]. The prodromal stage may involve fever, malaise and lymphadenopathy prior to the development of cutaneous lesions. (Table 1, Supplementary Figure 1). Along with cowpox[3] and varicella[5], cutaneous lesions of monkeypox present as erythematous macules, progressing to umbilicated papules, painful vesicles and pustules, followed by firm indurated eschar during the period of resolution (Supp Figure 1)[1,2]. Initial lesions occur at sites of direct contact, however more disseminated lesions can occur during the course of the illness.

The main differentiating features of monkeypox as opposed to other viral infections under consideration, is the monomorphic progression of lesions in distinct anatomical areas. In acral

sites, all lesions will progress through papular, pustular or eschar stages in synchrony, as opposed to primary varicella where various stages of lesion are interspersed[1,2] and molluscum contagiosum in which morphological progression of lesions will not occur. Monkeypox often presents with less than 10 distinct umbilicated lesions (in 64% cases)[3] which may aid in diagnosis when combined with history and lesion evolution. An additional differentiating feature is the presence of lymphadenopathy in the prodromal stage of the disease. This may be a useful feature for evaluation of close contacts, however, lymphadenopathy is present during the eruptive stages of a number of differential conditions which is why such a feature should not be relied upon in isolation. Secondary syphilis[4], when rapidly following the initial chancre, may present in a similar fashion to monkeypox and should be a differential diagnosis under consideration.

The current monkeypox outbreak is an evolving situation, however a deeper understanding of the comparative morphological and temporal order of features should allow for a degree of clinical diagnosis to be undertaken by the astute dermatologist.

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133 **Figures and Tables:**

Condition	Monkeypox	Cowpox	Primary Varicella	Secondary Syphilis
Causative Agent *(Genus)*	**Monkeypox Virus *(Orthopoxvirus)***	**Cowpox Virus *(Orthopoxvirus)***	**Varicella Zoster Virus *(Varicellovirus)***	**Treponema Pallidum *(Treponema)***
Incubation Period	5-21 days	7 days	14-16 days	2-8 weeks post primary Chancre
Transmission	Direct Contact, Droplet, Fomites, Transplacental	Direct Contact	Direct Contact, Droplet, Transplacental	Direct Contact, Transplacental
Contagious Period	Symptomatic Period Only	Symptomatic Period Only	2-5 days prior to lesions until 6 days post last crop	Symptomatic Period Only
Morphology	Sequential evolution: macules, papules, vesicles, pustules, eschar. (<10 Lesions in 64% cases)	Solitary or limited 5-20mm diameter. Sequential evolution: macule, papule, haemorrhagic pustule, eschar.	1- to 3-mm vesicles on an erythematous background. (Presence of lesions in various stages)	Widespread papulosquamous eruption, mucous patches, alopecia, condyloma lata.
Lymphadenopathy	Yes (During Prodrome)	Yes (with Rash)	Yes (with Rash)	Yes (with rash)
Fever	Yes	Yes	Yes	Yes (with Chancre and rash)
Myalgia	Yes	Yes	Yes	Yes
Lethargy	Yes	Yes	Yes	Yes
Complications	Secondary Bacterial Infection, Pneumonia, Encephalitis,	Disseminated disease in Atopic Dermatitis, Darier's Disease	Secondary Bacterial Infection, Respiratory Distress Syndrome (Adults)	Multisystem disease, (cardiac, neurological, ophthalmological etc)
Mortality	3.6% (West African Clade)	1-3%	1/100,000 – 21/100,000 Cases per year	5-58% (Untreated)

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135 Table 1: A comparative table of the disease and clinical characteristics of Monkeypox, cowpox,

136 varicella and secondary syphilis. The varied clinical characteristics of the various stages of the

137 Monkeypox associated eruption include the papular eruption on an erythematous (almost

138 morbilliform) base with central umbilication, followed by a painful pustular eruption and

139 resolving through the development of eschar formation. This is in contrast to the clinical

140 features of other differential diagnoses including cowpox, varicella and secondary syphilis.