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Pityriasis Lichenoides ET Varioliformis Acuta (PLEVA) As a Possible Differential Diagnosis for Monkeypox during the 2022 Outbreak in Non-Endemic Countries

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ABSTRACT

In May 2022 several cases of monkeypox transmitted among humans in the UK, the USA and Europe were detected. The images of monkeypox skin lesions that were widely published in the media consisted exclusively of deeply seated vesicles and pustules on brown and black skin from endemic outbreaks in Africa. However, as cases accumulated in non-endemic countries, it has become clear that the clinical presentation of the current outbreak outside of Africa shows a very different picture, and that at least some of these cases might mimic pityriasis lichenoides et varioliformis acuta (PLEVA). It is a rare dermatologic condition of unknown aetiology, which has been described also as a reaction to vaccines.

Currently, the World Health Organisation recommended laboratory tool for diagnosing monkeypox is the real time polymerase chain reaction test. Antigen and antibodies detection methods are not considered useful due to cross-reactivity between different orthopoxviruses.

In this paper, I present the classic dermatologic criteria used for distinguishing between monkeypox and pityriasis lichenoides et varioliformis acuta as described in the literature. Further, as a hypothesis, I suggest considering pityriasis lichenoides et varioliformis acuta, a non- infectious skin reaction associated with extrinsic factors, including vaccines (also Covid-19 vaccines) as a possible differential diagnosis for monkeypox cases in the non-endemic countries.

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Introduction/ Background

To Albert Neisser (1855 Schweidnitz/Świdnica-1916 Breslau/ Wrocław) Monkeypox (MPX) is a viral zoonosis caused by the monkeypox virus (MPXV), which belongs to the Orthopoxvirus genus of the Poxviridae family. The name "monkeypox" originates from the initial discovery of the virus in monkeys in a Danish laboratory in 1958. The first human case was identified in a child in the Democratic Republic of the Congo in 1970 [1]. The skin lesions caused by MPXV in Africa were consistently clinically indistinguishable from smallpox [2,3].

In May 2022 first cases of MPX among humans in the UK, the USA and the UE were detected. As for the time of writing (May/ June 2022) WHO reported a few hundred laboratory confirmed cases in non-endemic countries and the CDC raised the alert to stage 2 [4].

The first images of MPX skin lesions that were widely published in the media in May 2022 consisted almost exclusively of deeply seated vesicles and pustules on brown and black skin from endemic outbreaks, clinically indistinguishable from smallpox, in accord with the initial descriptions of the disease [5]. However, as cases accumulated in the non-endemic countries, it has become clear that the clinical presentation of the current outbreak outside of Africa shows a completely different picture [6]. According to the John Hopkins Center for Health Security (status from May 18, 2022): "Clinical presentation of monkeypox can be similar to chickenpox, caused by varicella-zoster virus (…) Due to the similarity in clinical symptoms between monkeypox and chickenpox, healthcare providers often face difficulties in diagnosing cases based on clinical symptoms alone" [7]. On the NHS website (status from 23 June 2022) under the entrance "monkeypox" I found a similar description: "The rash is sometimes confused with chickenpox. It starts as raised spots, which turn into small blisters filled with fluid. These blisters eventually form scabs which later fall off. The symptoms usually clear up in a few weeks" [8].

At that point I realized that skin lesions from the current 2022 outbreak outside of Africa may mimic pityriasis lichenoides et varioliformis et acuta (PLEVA).

PLEVA is a rare dermatologic condition of unknown aetiology, and, according to a current consensus, is due to extrinsic factors, which has been described also as a reaction to a variety of vaccines including Covid-19 vaccines. PLEVA occurs three times as often in men than in women [9-23].

In regard to diagnosing the current cases of MPX outside of Africa, the utmost importance is ascribed to molecular diagnosis based on quantitative (real time) polymerase chain reaction (RT-PCR), even in the absence of typical skin lesions. According to WHO (status from 21 May 2022): "A confirmed case is 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 (qPCR) and/or sequencing" [24]. At the same time, "a suspected case is a person of any age presenting in a monkeypox non-endemic country with an unexplained acute rash" and one or more of systemic symptoms, like a headache, neck pain, fever, etc. as well as "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. N.B. It is not necessary to obtain negative laboratory results for listed common causes of rash illness in order to classify a case as suspected" [24]. Predictably, a discarded case, as defined by WHO, is "a suspected or probable case for which laboratory testing by PCR and/or sequencing is negative for monkeypox virus" [24].

Similarly, on the site of the Robert Koch Institute in Berlin (status from 9.06.2022) I read that "virus detection is carried out from weeping skin changes, vesicle fluid, pustule contents, crusts or smears of skin changes and other sample material during the acute phase of the disease by means of polymerase chain reaction (PCR) (…) Detection of monkeypox virus-specific antibodies from the blood (serum) is not readily possible because the Orthopoxviruses that can infect humans trigger very similar immune responses (cross-reactivity). Antibody detection can yet be helpful in the absence of direct detection of the virus" [25].

Methods

I read through the dermatologic literature describing PLEVA as well as the endemic MPX cases. Trying to connect as much as possible to the initial descriptions of the diseases, I concentrated on skin lesions, their distribution and evolution as well as the dermatopathology. The results of the comparison between PLEVA and MPX from endemic regions are summarised in the Table.

Table: Summary of Differences between PLEVA and MPX

Characteristics:	PLEVA	Endemic MPX
Aetiology:	Unknown, Possibly an Inflammatory Reaction to Extrinsic Antigens (Viruses, Vaccines, or Drugs);	A Viral Zoonosis Ccaused by the Monkeypox Virus (MPXV);
Transmission:	A Non-Infectious, Non-Transmissible Disease;	A chance Infection of Man with an Animal Virus. Human to Human Transmission Could not be Established in the Majority Of Cases;
Incubation:	Time between the Trigger and the Eruption-Generally Unknown (A Few days in Case of Vaccine Reactions);	5–21 days but Usually Falls within 7–14 days;
Age:	Often in Children and Adolescents, but Possible at Every Age. Threefold Male Dominance;	Often Children, but Possible at Every age. Both Sexes almost Equally Affected;
Primary Efflorescence:	An Erythematous Macule/Papule with an Inflammatory Ring. All Lesions are Small, between 0.5 and 1.0 cm in Diameter;	A Papule that Rapidly Develops into a Vesicle and then a Pustule. Most Skin Lesions are about 0.5 cm in Diameter but some Tense Pustules up to 1 cm have been seen;
Evolution of the Lesions:	Some Papules Develop into Vesicles and Pustules, often with a Central Umbilication. New Crops Might Erupt Over days or weeks, and many Different Stages can be seen side by side ("starry sky"), Similarly to Chickenpox;	Skin Lesions Develop almost Simultaneously with no Cropping and Evolve together at the same Rate through Papules, Vesicles, and Firm Pustules before Umbilicating, Drying, and Desquamatingg;
Distribution:	Central ("Centripetal")- Lesions Predominantly on Trunk and Proximal Extremities;	Peripheral ("Centrifugal")- Lesions Affect Mainly Face, Arms and Legs.
Special Localisations:	Palms and Soles Affected in 10% of the Cases. Inflammatory papules and Necrotic Lesions may appear on Oral and Genital Mucosa;	Palms and Soles Involved in 75% of the Cases, Mucosal Involvement Possible;
Arrangement:	Mainly Discrete Lesions but may Coalesce;	Discrete Lesions with rare Coalescence;
End Result:	Usually no Marks, in some Patients- Post-Inflammatory Hypo-/Hyperpigmentation. In Case of Ulcerated Lesions Pitted Scars May Remain.	From no Scars to a Few Marks, to deep Pitted Scars that Flatten after months/years. Post-Inflammatory changes in Pigmentation, Especially in Darker Skin Types;

Systemic Symptoms:	Seldom Fever, Pruritus/Burning Sensation of the affected Skin. In case of severe form (Mucha-Habermann-Disease): High Fever, Malaise, Shivers, and Lymphadenopathy (21, 36, 37);	Often 2-4 days of Prodromal Fever, Malaise, Occasionally Sore Throat Before Skin Eruption. Lymphadenopathy, Especially in the Neck (Submandibular and Cervical) and in the Inguinal Areas was Recorded in ca. Half of the Cases.
Laboratory Examination:	Usually not Conclusive. In FUMHD the white Blood cell count and Markers of Inflammation Are Increased;	1. Pox particles seen on Electron Microscopy; 2. Virus Isolation (from Cell Culture) (4); 3. High HAI (Haemagglutination Titre) and Neutralizing Titres to Pox group Virus (4); 4. Detection of MPXV- Specific Antibodies by Immunoadsorption with Heterotypic Poxvirus Extracts;
Response to Post-Exposure Pox Vaccine:	Not Tested	Equivocal Reaction (Probably due to Cross-Protection between Vaccinia, Variola, and Monkeypox Viruses) (4);
Skin Biopsy:	Parakeratosis, Interface-Dermatitis, Wedge-Shaped Infiltrate, Perivascular Infiltrate	Ballooning Degeneration of Basal Keratinocytes, Spongiosis with Epidermal Necrosis, and the Presence of Multinucleated Syncytial Keratinocytes. Superficial and deep Perivascular and Periadnexal Infiltrate and Positive Immunoperoxidase Staining in Areas of Necrosis
Therapy:	Symptomatic (Topical Corticosteroids and Systemic Antihistamines9 Macrolides or Tetracycline used due to their Anti-Inflammatory Properties. UVB or PUVS Effective in Some Cases. Systemic Immunosuppression in Severe Cases;	Symptomatic;
Duration of the Disease:	2-12 Weeks	About 2-4 Weeks, Depending on the Severity of the Disease.

Further, I specifically reviewed case reports presenting PLEVA as a result of vaccination: four cases after MMR [11-14]. One after mixed MR and haemophilus influenzae b (Hib), and pneumococcus vaccine given simultaneously [15]. One after measles vaccine alone [16], one after tetanus [17]. One after DTP [18]. One after influenza [10]. And one after HPV vaccine [19]. And summarised their clinical presentation in the section Results. Additionally, I described four cases of PLEVA after the novel mRNA covid-19 vaccines [20-23].

Results

PLEVA

At the fourth congress of the German Society of Dermatology (1894) in Breslau (now Wrocław, in Poland) Albert Neisser and Joseph Jadassohn independently described a new form of a "lichenoid eruption" consisting of acutely formed bright red papules, partly with a hyperaemic ring which, while growing, developed a central thinning of the epidermis (umbilication). Neisser's patient developed the exanthema initially on the arms, while in the patient presented by Jadassohn it started on the neck and then spread randomly over the entire body. On biopsy, focal hyperkeratosis with central thinning of the epidermis and a mainly perivascular round-cell infiltrate was seen [26]. Mucha was the first one to separate the acute from the chronic form of this disease but only in 1925 Habermann gave it its current name, pityriasis lichenoides et varioliformis acuta, PLEVA.

The majority of current PLEVA descriptions agree that the skin manifestations consist initially of erythematous macules and/or papules. Papules with a vesicopustular central point and eventually haemorrhagic adherent crusts are not uncommon, rarely accompanied by malaise, fever, lymphadenopathyy and arthritis. Post-inflammatory hyper- or hypopigmentation may occur, and some lesions might heal leaving behind smallpox-like (i.e., varioliformis, hence the name of the disease) scars. Successive crops of skin lesions appear over days or weeks, so all stages of lesions (macules, papules, pustules, and crusts) can be present at one time- the "starry sky" presentation, so characteristic of chickenpox as well. The rash is typically seen on the trunk, thighs, upper arms, and flexural areas ("centripetal" distribution). In 10% of cases, the face, palms, soles are involved [27]. Inflammatory papules and necrotic lesions may also appear on oral and genital mucosa [28].

On biopsy, the most common features of PLEVA include vacuolar interface dermatitis, compact stratum corneum with/without ulceration and crust, erythrocytes extravasation and purely lymphoid infiltrate ("lichenoid") with both a superficial and deep perivascular pattern" [29].

In 1966, Degos et al described an ulceronecrotic variant of PLEVA, which was named Febrile Ulceronecrotic Mucha-Habermann disease (FUMHD). This severe form shows systemic features of high fever, lymphadenopathy, arthritis and possibly sepsis. There might be mucosal, gastrointestinal, and pulmonary involvement and a mortality up to 25% [30]. FUMHD often starts as classic PLEVA and evolves rapidly into a fulminant disease with widely distributed ulceronecrotic lesions associated with severe systemic manifestations [30-33].

Regarding PLEVA cases after traditional vaccines against influenza MMR Mixed MR and haemophilus influenzae b (Hib) and pneumococcus vaccine given simultaneously. Measles. Tetanus DTP and HPV. That we reviewed, they all showed scattered erythematous papules, some with adherent (necrotic) crusts and differing numbers of hemorrhagic vesicles [10-19]. The sometimes-pruritic lesions erupted on the trunk and limbs, and only occasionally on the face. The majority of patients were young males, and the eruption started a few days after the vaccination. The histological findings were similar across the cases and consistent with PLEVA. No systemic symptoms were noted except for a low-grade fever and mild leucocytosis in some individuals. The diagnosis was established from the association of clinical and histopathological data. First-line therapy included topical corticosteroids, and tetracycline, erythromycin, or doxycycline orally. In severe and/or refractory cases, the use of systemic

corticosteroids, methotrexate or azathioprine was necessary.

Subsequently, I concentrated on PLEVA in association with the novel Covid-19 vaccines. I found 4 confirmed cases [20-23]. Three in elderly males (70,72 and 81 years old, respectively) and one in a young female (31 years old). They all started within 14 days after the first dose and presented no systemic symptoms except for bilateral inguinal lymphadenopathy in one patient [21]. In addition, all consisted of erythematous-crusted papules on the trunk and limbs, in one patient also on the face [21]. And in one case on the posterior neck [22]. The lesions transformed over weeks into centrally ulcerated papules and healed with some pigment changes except for one case when pitted scars occurred [22]. The biopsy indicated PLEVA except for one case when it revealed ulceration, without a specific aetiology [22].

To sum up, the dermatologic descriptions of PLEVA, including the cases associated with vaccines we reviewed, were clinically similar to chickenpox, with little or no systemic symptoms except for the very rare ulceronecrotic cases.

Monkeypox (MPX)

On the other hand, the skin lesions caused by MPXV in Africa were clinically indistinguishable from smallpox [1,2,3,4]. And consistently showed a diffuse vesiculopustular rash of peripheral distribution. One description of the MPX affected skin depicts "a generalized vesiculopustular rash with all lesions appearing in the same stage. The lesions were firm, deep-seated, and measured approximately 0.75 cm in diameter (…) The rash had a peripheral distribution with greatest involvement of the face, arms, and legs. Scattered lesions were present on the back, abdomen, and buttocks. Lesions were noted on the palms and on the soles of the feet" [3]. In a 1980 summary describing MPX outbreaks in Africa in the years 1970-1979 Breman et al wrote: "Severe eruptions may cover the entire body, including the palms and soles (…) Most skin lesions are about 0.5 cm in diameter but some up to 1 cm have been seen. Lesions have been noted on the mucous membranes, the tongue, and the genitalia. Lymphadenopathy, especially in the neck (submandibular and cervical) and the inguinal areas, was particularly prominent in 18 cases. Pitting scars develop most frequently on the face and diminish with time. Secondary infection of the lesions is common and may play a role in scarring" [2].

On biopsy, MPX's key features consist of ballooning degeneration of basal keratinocytes, spongiosis with epidermal necrosis, bandlike polymorphous infiltrate and the presence of multinucleated syncytial keratinocytes. Further, there is superficial and deep perivascular and periadnexal infiltrate and positive immunoperoxidase staining in areas of necrosis [29].

Summarising, monkeypox as described in endemic cases was always indistinguishable from smallpox, not from chickenpox. It was diagnosed in mainly unvaccinated individuals in Central and West Africa, usually with positive animal contact and confirmed by positive serology to Orthopoxviridae family [34].

Discussion

PLEVA is a rare inflammatory disease, sometimes difficult to clinically distinguish from varicella zoster infections or secondary syphilis. Fortunately, simple laboratory tests (e.g., detection of VZV-IgM and VZV-IgG in serum for varicella/zoster and VDRL and TPHA for syphilis) exist to establish a solid diagnosis, confirmed by a diagnostic skin biopsy in case of suspected PLEVA. I believe, that in the absence of the above serologic markers as well as with a negative test for the Orthopoxviridae- antibodies in serum, PLEVA should be taken into consideration as a differential diagnosis for any papulovesicular and/or pustular rashes, also after a vaccination.

PLEVA following vaccines is rare. Naranjo adverse drug reaction probability scale has been used for causality assessment [35,36]. The association to vaccines has been based on temporal correlation and previous reports of association with vaccination.

Many of the reviewed cases describe a post-vaccine PLEVA in association with the measles vaccine [11-16]. Which contains a live attenuated virus. It was suggested that the measles component of the MMR vaccine might trigger a lymphoproliferative reaction in the skin, with the virus acting as an epidermal antigenic target [11]. Alternatively, an immune complex-mediated hypersensitivity as a pathomechanism of PLEVA has been discussed [37].

Secondly, the course of PLEVA associated with the novel COVID-19 vaccines seemed mild [20-23]. The capacity of COVID-19 vaccines to trigger inflammatory or immune-mediated disorders is being hotly debated. A cross-reactivity between viral and self-antigens is possible; however, a temporal coincidence cannot be excluded. It is worth noting that many COVID-19 vaccines-associated skin lesions were recorded as merely "cutaneous side effects" without further characterisation [38]. Accordingly, some very mild PLEVA cases associated with the current world-wide vaccination might have gone completely unrecognised as such.

Thirdly, as of the time of writing I was not able to find any detailed, specific descriptions of skin lesions in the current monkeypox outbreak in non-endemic countries, so it is difficult to say whether they rather match the endemic cases or tend to develop into a more atypical picture outside of Africa. The fact that health authorities from three different non-African countries [6,8,25]. Explicitly compared the skin lesions to chickenpox made us think that at least in some cases a differential diagnosis of PLEVA should be taken into consideration. The clinical features of post-vaccination PLEVA cases I reviewed were identical to PLEVA caused by other factors (infections, drugs) and they had also been differentiated from chickenpox by the reporting physicians, in one case even in a patient with a positive chickenpox infection history [18]. For the same reason, I assume that it is important to include PLEVA in the differential diagnosis to any chickenpox-like rash, especially since the therapy for PLEVA is immunosuppression, which could be fatal in the case of an infectious disease. On the other hand, not recognising PLEVA in time, for instance due to a false positive PCR test, could lead to a retractive, fulminant or even deadly disease [30-33].

Looking from a different perspective, the fact that skin lesions in the non-endemic countries currently look more like chickenpox than smallpox may be due to the mutations of the MPXV including those increasing viral transmission. New research has shown that the MPXV is able to human adaptation in ongoing microevolutionn [39]. It is also known that poxviruses despite low mutation rates can rapidly adapt to defeat different host defences [40]. However, to discuss the fact whether the recent molecular changes in the virus genome can be the cause of a different cutaneous presentation is beyond the scope of this paper. My aim was to signalise the possibility of PLEVA, also associated with vaccines, as a differential diagnosis to any chickenpox-like eruption, especially now, at the very start of a possible world-

wide wave of non-endemic monkeypox. Because of the partial time overlap between the Covid pandemic (and, accordingly, the wide-spread vaccinations) and the new outbreaks of monkeypox in non-endemic countries such a possibility seems plausible to me.

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