Transmission of Atypical Varicella-Zoster Virus Infections Involving Palm and Sole Manifestations in an Area with Monkeypox Endemicity

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During a suspected monkeypox outbreak in the Republic of Congo, we documented transmission of varicella-zoster virus (VZV) infection with palm and sole manifestations among 5 family members. Genotyping results confirmed the VZV strain European E2, a genotype not previously reported in Africa. VZV with palm and sole involvement should be considered when differentiating a monkeypox diagnosis.

The monkeypox virus (MPXV) and varicella-zoster virus (VZV) both cause disseminated febrile-rash illnesses in humans. MPXV is an orthopoxvirus, a member of the same genus as variola virus, the causative agent of smallpox. MPXV is endemic in forested areas of central and western Africa; it is maintained via an enzootic life cycle, with zoonotic introductions to humans and potential subsequent human-to-human transmission [1]. MPXV infection in the Congo Basin is associated with case-fatality rates up to 10% among people who have not received the smallpox vaccine, and severe complications occur in >40% of cases [2]. By contrast, VZV infection is not typically associated with severe outcomes, although serious outcomes, including death, can occur.

Because of the severe pathogenicity of MPXV and waning population immunity to orthopoxviruses (because of discontinuation of routine childhood smallpox vaccination), MPXV represents an important emerging infection. However, diagnosis of VZV and MPXV infections can be mistaken in locations where these viruses cocirculate [3].

Because MPXV circulates in underdeveloped areas of the world, where access to modern medical facilities is often limited, the need exists for straightforward diagnostic algorithms to differentiate MPXV infection and VZV infection. Clinically, MPXV infection commonly involves lymphadenopathy and febrile prodrome, characteristics that distinguish MPXV infection from VZV infection in humans [3]. Additionally, lesion distribution is typically centrifugal in MPXV infection and centripetal in VZV infection, and the occurrence of deep pustular lesions on the palms of the hands and soles of the feet is typically believed to be pathognomonic for orthopoxvirus infection (although lesions on the palms and soles can be seen in syphilis, Rickettsia infections, and certain immunologic conditions) and not typical of VZV illness. For instance, among unvaccinated persons, palm and sole lesions were reported to be present in ~80% and ~70%, respectively, of cases of human MPXV infection [2]. In contrast, palm and sole manifestations of VZV are thought to occur only rarely and may be associated with underlying conditions during VZV infection [4].

The study. During September–October 2007, we traveled to Impfondo, Republic of Congo, to investigate a suspected monkeypox outbreak. Impfondo is located in the Likouala district, in the northern part of the Republic of Congo, and is a sparsely populated region that is surrounded by dense rain forest. A previous outbreak of monkeypox in this area was reported elsewhere [5], and serosurveys indicate relatively high orthopoxvirus seroprevalence in Likouala [6].

In the city of Impfondo, we observed a female infant (age, <1 year) with an active pustular rash illness. Discrete, round lesions were observed on her face, trunk, and extremities, and notably, multiple circumscribed lesions were observed on her palms and soles (figure 1A and 1B). The infant’s mother reported that the infant developed a fever on the same day that the rash manifested.

On the basis of interviews with the family, we learned that 5 family members, including a teenage male (patient 1), a 13-year-old girl (patient 2), an 8-year-old boy (patient 3), the 30-year-old mother (patient 4), and the infant (patient 5), had recently had febrile rash illness. Sequential illness-onset dates, as recalled by the mother, suggested a chain of person-to-person transmission within the family. Notably, onset dates occurred...
Figure 1. A, Pustular rash of patient 5, with palm involvement. B, Pustular rash of patient 5, with sole involvement. C, Phylogenetic distribution of varicella-zoster virus sequences from skin lesions of patient 5 (Cgo 5-1, Cgo 5-2, and Cgo 5-3). The reference strains Dumas (E1), DR (M2), pOka (J), HJO (E2), and CA-123 (M1) were included to provide an overview of the phylogenetic distribution of varicella-zoster virus [7].

Over ~1.5 months and suggest 3–4 serial transmissions of illness within this family. Illness onset occurred first in patient 1, who was not available for interview. The remaining case patients reported no contact with anyone else who had had recent rash illness, and they reported no international travel.

Patients 2–5 were available for examination and interview. The infant (patient 5) had active lesions on her palms and soles, whereas scars were observed on the palms of patients 2 and 4, with questionable scars on the palms of patient 3 and on the soles of patients 2–4. Fever was reported around the time that lesions developed for patients 2–5, with no reports of being moribund during the illness. No underlying dermatological conditions or obvious health conditions were observed for any of the patients at the time of examination. No previous history of VZV or MPXV infection was reported for patients 2–5.

We obtained lesion swabs from patient 5 and venous blood specimens from patients 2–5. Lesions were tested by PCR for MPXV-specific and VZV-specific DNA, as described elsewhere [8]. Swab samples from patient 5 were PCR positive for VZV and negative for MPXV. On the basis of VZV IgG avidity, serum samples from patients 2, 4, and 5 demonstrated recent VZV infection; the serum sample from patient 3 was insufficient for testing. Serum samples from patients 2–5 were tested for or-thopoxvirus-specific IgM, as described elsewhere [9]; all 4 samples were negative for orthopoxvirus-specific IgM, indicating the absence of recent MPXV infection.

Previous VZV genotyping studies reported distinct geographic clustering of VZV genotypes, with isolates outside Africa having a mosaic genotype [10, 11]. VZV isolates from patient 5 were partially sequenced, and genotyping was performed using amplicons at open reading frames 21, 22, and 50, as described elsewhere [7]. All 3 isolates had identical DNA sequences, and interestingly, genotyping results indicated that they were wild-type VZV strain European E2 (figure 1C) (also referred to as genotype B and genotype D, on the basis of the respective methods of Barrett-Muir et al. [12] and Peters et al. [13]), the first time this VZV genotype has been reported in Africa.

Conclusions. On the basis of clinical, epidemiologic, and laboratory data specified above, we describe the occurrence of serial transmission of VZV with atypical palm and sole manifestations in a region of monkeypox endemcity. Previous studies have shown that VZV infection is commonly mistaken for MPXV infection in regions of endemcity [3], making the use of clinical markers of MPXV infection crucial for differentiation between these viruses. Although palm and sole manifestations are common in MPXV infection [2]—and previously believed to be extremely rare in VZV infection [4]—our observations suggest that other clinical criteria may be necessary to differentiate these infections in central Africa.
Previous studies have suggested global geographic clustering of VZV strains, with mosaic VZV genotypes associated with a band across the tropics [10, 11]. Most African VZV isolates comprise the M1 genotype, on the basis of summary data from the whole genome-sequencing approach reported by Loparev et al. [7]; previously published isolates from the Democratic Republic of Congo, Chad, Guinea Bissau, and Zambia [7]; and isolates from Sudan and Kenya. M2 genotype isolates have also been observed. The VZV sequences in the current report were genotype E2, and this, to our knowledge, is the first report inferring this genotype in Africa. Figure 1C also includes 2 recent VZV sequences from Sudan that genotyping also confirmed to be E2. Interestingly, these were also isolated from a patient with VZV infection during a concurrent monkeypox outbreak [14]. Although gaps clearly remain in our surveillance and understanding of the molecular epidemiology of VZV in Africa, it is noteworthy that a novel genotype was associated with the occurrence of a cluster of cases with novel and atypical palm and sole lesion involvement. Clearly, further surveillance and clinical and virological characterization of VZV infection in central Africa are warranted.

There are several possible factors that may explain why multiple transmissions of VZV with atypical manifestations occurred. First, it is possible that the unusual rash manifestation is a characteristic of the E2 VZV strain in this population. Second, we note that all cases occurred within a single family. This family may have a genetic factor or predisposition that results in unusual distribution of lesions during VZV infection. Third, the unusual manifestation of VZV infection may be the result of an underlying immunodeficiency, such as HIV infection. However, it is unlikely that all members of this family have acquired HIV infection, given the ages of patients 2 and 3 (13 years and 8 years, respectively). Additionally, VZV infection had resolved in patients 2–4, with no apparent complications, which suggests that there is no underlying immunodeficiency. Finally, it is possible that VZV infection with palm and sole manifestations occurs more commonly than previously recognized in rural central Africa. Impfondo is in a remote, sparsely populated area of the Republic of Congo, and the full scope of VZV infection in the area has not been well characterized. The cases reported in the present study were a small proportion of the overall VZV case burden in Likouala, which we documented during our investigation. Although the typical age of people with VZV infection in the Republic of Congo is not known, a preponderance of VZV cases involving patients >10 years of age was observed during our investigation (A.M., M.G.R., and I.K.D., unpublished observation), consistent with the wide age range of case patients in the study family.

Because of the high case-fatality rate of MPXV in central Africa, rapid case recognition and infection-control measures are important for the prevention of outbreaks. Our observations underscore the need for improved diagnostic criteria, notably laboratory techniques, to differentiate MPXV and VZV in regions of the world where these viruses cocirculate. Moreover, prodromal fever, lymphadenopathy, and circumscription of lesions may represent more-important clinical observations to be considered, to differentiate MPXV from VZV infection.

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References