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Atypical exanthem associated with human herpesvirus 7 active infection in a 24-year-old man

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Dear Editor,

An otherwise healthy 24-year-old male patient presented to us with a three-day history of a diffuse, pruritic skin eruption preceded by low-grade fever and fatigue in the previous two weeks. Physical examination revealed an atypical exanthem with a polymorphic pattern characterized by diffuse erythematous macular lesions on the forehead, erythema, edema, and vesicles on the ears, erythematous papules on the forearms and trunk, and maculo-papular-petechial lesions on the pubic area and buttocks (Figure 1 A-E). An erythematous-purpuric enanthem (Figure 1F) and symmetrical enlargement of the cervical-axillary lymph nodes were also detected. Laboratory investigations, performed 4 days after the dermatologic visit, were within normal limits, including blood count and renal and liver function tests. Diagnostic tests for celiac disease were negative. The antistreptolysin titer was positive (549 UI/mL, normal value 200 UI/mL), but a throat swab was repeatedly negative. Serology for human immunodeficiency virus, hepatitis B and C viruses, Epstein-Barr virus, cytomegalovirus, parvovirus B19, enteroviruses, severe acute respiratory syndrome coronavirus 2, and *Borrelia burgdorferi* was negative or indicative of past immunity. The *Treponema pallidum* hemagglutination assay was also negative. Human herpesvirus (HHV)-7 plasma viremia was detected by calibrated quantitative real-time polymerase chain reaction (CQ-PCR) (20 genome equivalents per mL), while HHV-6 DNA was negative. Based on clinical and laboratory investigations, an atypical exanthem associated with systemic active HHV-7 infection was the most plausible diagnosis. We prescribed an oral antihistamine and advised rest; the lesions resolved almost completely after two weeks (Figure 2). One month later, a blood sample was negative for HHV-7 DNA in plasma. The patient gave written informed consent to publish his clinical data.

HHV-7, like HHV-6, affects over 90% of all adults worldwide. The HHV-7 primary infection usually occurs in childhood; it can be asymptomatic or may cause the exanthema subitem.[1] Endogenous systemic reactivation of HHV-6/7 has been associated with pityriasis rosea and other atypical exanthems.[1-3]

The detection of anti-HHV-6/7 IgM in serum specimens establishes that the infection is recent. However, IgM may also be detected during reactivation of HHV-6 and HHV-7 from latency.

Serologic assays alone are insufficient for diagnosing systemic active viral infections, and direct methods, such as CQ-PCR, are preferred. Indeed, the low sensitivity and specificity of serologic assays, due to cross-reactivity with other Herpesviridae, such as HHV-6, hinder the interpretation of HHV-7 serology.[2-5] On the contrary, detecting HHV-7 DNA in plasma by CQ-PCR is a marker of systemic active infection.[1,2]

However, distinguishing between primary and reactivated HHV-6 and HHV-7 infections requires observation of specific IgG subclasses' response using an antibody avidity test. Because the antibody avidity changes over time after infection, the presence of low-avidity antibodies suggests a recent primary infection. Conversely, high-avidity antibodies together with the detection of IgM antibodies and the presence of DNA in plasma by CQ-PCR indicate a past reactivated infection.[2] Unfortunately, the HHV-7 antibody test and avidity testing were unavailable at our hospital.

Recently, Michelerio *et al.* retrospectively described a case series of nine adult patients presenting with atypical exanthems associated with active HHV-7 replication.[5] In line with our case report, the authors considered the exanthem related to active HHV-7 replication if: i) viral DNA copies could be identified in plasma using real-time PCR during the acute phase; ii) viral DNA copies subsided in the convalescence phase; ii) all other causes of exanthem were ruled out.[5]

In these patients, prodromal symptoms did not precede the exanthem, which predominantly presented as a maculopapular diffuse eruption involving the trunk, limbs, hands, and feet. The skin eruption was confined to acral regions in three patients and showed vesico-bullous lesions on the hands and feet in three cases.[5] Interestingly, although rarely seen in eruptions due to HHV-7, the vesico-bullous lesions sometimes characterize the eruption,[5] as happened in our patient.

Compared with the case series by Michelerio *et al*., in which HHV-7 plasma viremia ranged from 180 to 29,000 DNA copies/mL (median 1,300 DNA copies/mL),[5] the viral load in our patient's serum was lower (20 copies/mL). However, the patients described by our colleagues often had widespread cutaneous involvement, necessitating urgent medical evaluation and blood tests in the acute phase,[5] when viral load is typically higher.[1,2] Conversely, our patient's cutaneous lesions were diffuse yet few in number; moreover, his general condition was good, and the blood was collected 7 days after the onset of the eruption because of upcoming public holidays in December. Therefore, the low HHV-7 serum load in our patient could be partly attributable to the limited cutaneous eruption and partly to the timing of blood sampling.

However, it is noteworthy that, in the study by Michelerio *et al.*, the patient who required hospitalization for extensive skin involvement had a lower viral load than the other patients.[5] This finding suggests that the cutaneous lesions may be the result of the interaction between the virus and the immune system rather than a direct viral cytopathic effect.[1,6]

In conclusion, based on the HHV-7 DNA detection in plasma, the exclusion of other infectious/autoimmune etiology through physical examinations and laboratory tests in acute and convalescent phases, the self-limiting clinical course, and, ultimately, the analogy with previous reports,[4,5] we suggest that our patients' atypical exanthem can be related to active HHV-7 infection.

Since we were unable to perform the antibody avidity test, we cannot exclude an HHV-7 primary infection, but the patient's age suggests that viral reactivation is more likely.

We recommend considering HHV-7 reactivation as a potential cause of atypical exanthems, particularly in young and adult patients presenting with an acute onset of itchy erythematous, maculopapular lesions that can be matched by vesicles or bullae on the extremities and by petechial lesions on the pubic/buttock areas. Therefore, searching for markers of HHV-7 active infection in plasma is advisable in immunocompromised patients,[1,2] but it should not be overlooked even in immunocompetent adults.[1,5]

However, given that HHV-7 active infection is a rare cause of atypical infectious exanthems, other more common etiologic agents should be ruled out. Differential diagnoses should mainly include HIV and *T. pallidum* infection, whose cutaneous manifestations may be highly heterogeneous and simulate a multitude of diseases;[1,7] enterovirus infections, characterized by vesicular lesions also beyond the classic hand-foot-mouth sites;[1] and parvovirus B19 infection, in which the purpuric pattern of the exanthem may predominate or be interspersed with the maculopapular pattern (often in association with a purpuric enanthem).[8] The entire diagnostic tests should be based on the clinical features of the eruption (lesions' morphology and location), the patient's age, comorbidities and social contacts, investigating the health of family members, the patient's occupation, travel history, and sexual activity.[1,7,8]

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Figure 1. Erythematous macular lesions on the forehead (**A**) and back (**B**); erythema and vesicles on the ears (**C**) and maculo-papules on the pubis (**D**) and buttocks (**E**). Erythematous-purpuric enanthem (**F**).

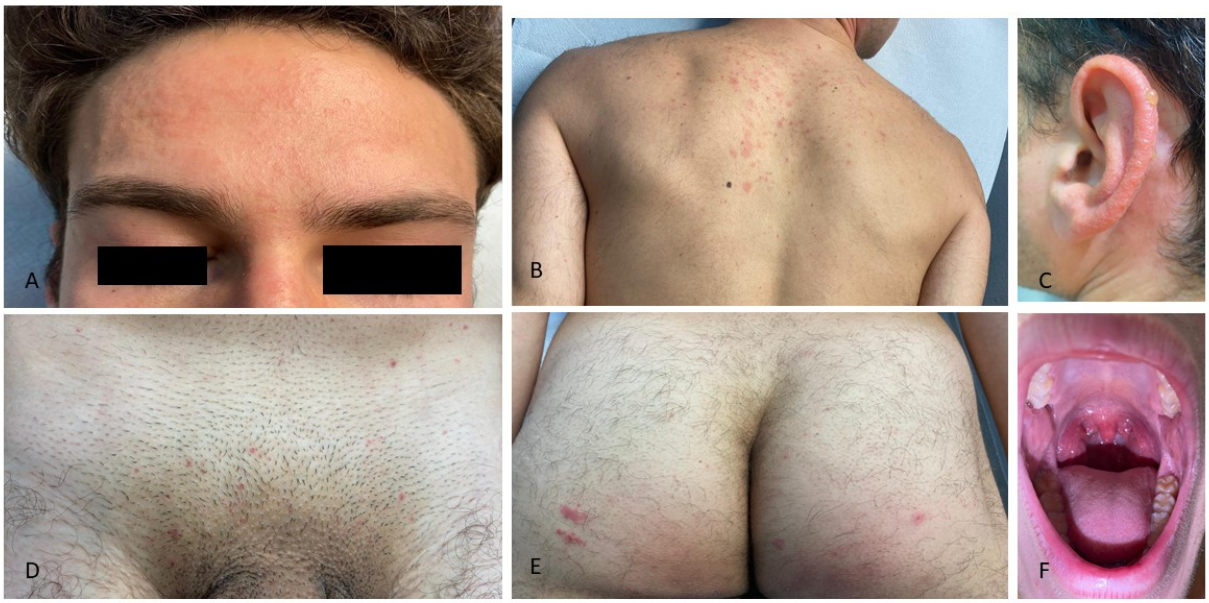

Figure 2. Complete resolution of the skin lesions of the forehead, trunk, and ears.