Human Herpesvirus-7 Papular Rash: A Comment to Brazzelli et al.

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We read with interest the paper by Brazzelli et al. (1), and would like to make some observations. The case of erythemato-papular exanthem described has been related to human herpesvirus (HHV)-7 infection. However, despite suspecting an infectious aetiology, the authors did not examine the palpable lymph nodes or the oral mucosa (1). In fact, infectious exanthems, both classic and atypical (2, 3), are frequently associated with regional/diffuse lymph node enlargement and lesions of the oral mucosa (enanthems). The latter may have a different morphology (macular, maculopapular, erythemato-vesicular, petechial) that may help to distinguish the causative infectious agent (2, 3). Furthermore, Brazzelli et al. (1) did not specify whether the patient had exanthematous diseases during childhood or if he was vaccinated against them. Finally, his history of recent travel to and from epidemic areas for tropical viruses, such as arbovirus (Central/South America, sub-Saharan Africa, Asia), was not investigated (3).

Regarding the laboratory examinations, it is unclear for which of the many infectious agents listed in the paper (1) the authors performed serology, and for which they eventually performed counts of DNA copies in blood samples. Incidentally, some of the infectious agents mentioned in the paper are RNA viruses (HIV and hepatitis C virus (HCV)) and not DNA viruses. In addition, the authors did not mention the method used for detecting viral DNA/RNA in the blood. The presence and copy number of cytomegalovirus (CMV), Epstein Barr virus (EBV), human herpesvirus (HHV)-6, HHV-7, Parvovirus B19 (B19V), Coxsackievirus, Echovirus DNA and of HCV and HIV RNA in serum samples can be properly evaluated by calibrated quantitative real-time PCR (cQPCR) (4).

Despite the initial diagnosis of insect bites, serology for *Rickettsia conorii* was not carried out, although it is responsible for the most frequent rickettsiosis in Europe (Mediterranean spotted fever) and is transmitted by the brown dog tick (3). Furthermore, other common infectious agents that might be responsible for atypical exanthems with erythemato-papular morphology were not checked, such as *Streptococcus pyogenes* and *Staphylococcus aureus* among the bacteria, and HHV-8 among the viruses (3).

We agree with the authors that the detection of circulating HHV-7 DNA in the blood is a marker of active infection (1), but without the results of HHV-7 serology this finding is incomplete (1). In fact, HHV-7 antibody titres in the acute phase and after resolution of the exanthem would have allowed the authors to distinguish between primary infection and systemic reactivation (5). Distinguishing between primary and recurrent infection requires observation of the response of specific IgG subclasses by using an antibody avidity test. Since the change in antibody avidity correlates with time after infection, the presence in the serum of low-avidity antibodies suggests a recent primary infection, whereas the presence of high avidity antibodies indicates a past or recurrent infection (6).

Finally, not only exanthema subitum, as stated by Brazzelli et al. (1), but also pityriasis rosea (PR), is associated with HHV-7 infection, perhaps with even greater evidence. Indeed, the association of PR with HHV-7 infection is based on several and consistent observations and not on occasional findings. Several studies have identified HHV-6 and HHV-7 DNA by PCR and real-time cq-PCR in plasma, peripheral blood mononuclear cells (PBMCs) and skin samples of patients with PR. In addition, cytopathic effects specific for herpesviruses and considered marker of viral replication, were observed in co-cultured mononuclear PBMCs from patients with PR. High levels of interferon α and γ were detected in their sera, and virions resembling herpesviruses were shown in the cell-free supernatants of their co-cultured PBMCs by electron microscopy. Furthermore, HHV-6 viral messenger RNA (mRNA) expression by *in situ* hybridization and HHV-6 and HHV-7 antigens were observed in PR skin lesions (7). The expression in PR skin lesions of the specific HHV-7 and HHV-6 antigens involved in the late stages of the infection as well as mRNA expressions indicate a productive viral infection and emphasize the role of both viruses in the pathogenesis of the disease (8, 9). Regarding indirect diagnosis, significant neutralizing antibodies against HHV-6 and HHV-7 have been observed in patients with PR, indicating an endogenous reactivation (8). The inverse correlation between titres of anti-HHV-7 neutralizing antibodies and detection of HHV-7 DNA in plasma of patients with PR may imply that humoral responses contribute to limit the systemic reactivation and dissemination of the virus (5, 8). In addition, some clinical findings in patients with PR suggest HHV-6 and HHV-7 reactivation rather than primary infections: few familiar cases, poor/absent contagiousness, age of onset, possibility of relapsing (10) and/or persistent (11) presentations, and occurrence after or during stressful events (5) or in patients with altered immune response, such as pregnant women (12).

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Reply to the Comment by Drago et al.

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We read with interest the comments by Professor Drago and colleagues on our case report (1). We would like to take the opportunity to elaborate some important details below, which were omitted due to the brevity of the original report:

"The authors did not examine the palpable lymph nodes or the oral mucosa"
These clinical evaluations were, in fact, made and found to be negative.

"Brazzelli et al. (1) did not specify whether the patient had exanthematous diseases during childhood or if he was vaccinated against them."
These questions were addressed to the patient, but he did not recall this information. In addition, the fact that the patient had not presented any prodromal symptom led us, together with the peculiarities of the rash, to exclude such diagnoses, which were not investigated.

"Finally, his history of recent travel to and from epidemic areas for tropical viruses, such as arbovirus (Central/South America, sub-Saharan Africa, Asia) has not been investigated"
The patient had never travelled outside Europe.

"As for the laboratory examinations, it is unclear for which of the many infectious agents listed in the paper (1) the authors performed serology and for which they eventually performed counts of DNA copies in blood samples."
Serologies for all listed infectious agents were carried out, with the exception of HHV-6 and HHV-7 (both DNA viruses). In our laboratory HHV-6 and -7 DNA loads were assessed in blood samples using quantitative real-time PCR (13).

"Incidentally, some of the infectious agents mentioned in the paper are RNA viruses (HIV and hepatitis C virus (HCV)) and not DNA viruses"
See answer above.

"*The authors did not mention the method they used for detecting the viral DNA/RNA in the blood*"
HHV-7 DNA load was assessed in blood sample using quantitative real-time PCR (13) in our laboratory.

"...serology for Rickettsia conorii was neglected, although it is responsible for the most frequent rickettsiosis in Europe (Mediterranean spotted fever)"
The patient had never had a fever, either before or during the eruption. In addition, the clinical feature was not consistent with the Mediterranean spotted fever. These investigations were therefore voluntarily excluded.

"... the HHV-7 antibody titres in the acute phase and after resolution of the exanthem would have allowed the authors to distinguish between primary infection and systemic reactivation"
Because HHV7 infection is classically contracted in early childhood and more than 90% of adult patients have positive serology for this virus, and given that, in our laboratory, HHV-7 DNA load was evaluated in blood samples, the detection of circulating HHV-7 DNA suggested a diagnosis of HHV-7-related papular rash. When the HHV-7 DNA was undetectable in blood sample the rash cleared completely.

"Finally, not only exanthema subitum, as stated by Brazzelli et al. (1), but also pityriasis rosea (PR), is associated with HHV-7 infection, perhaps with even greater evidence."
Although a link between pityriasis rosea and HHV-7 is strongly suggested, in particular by Professor Drago, who is an expert on this subject, not all authors agree on this association, as mentioned in the bibliography.

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