Editorial Response: Periodic Illness Associated with Epstein-Barr Virus Infection

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In addition to being the etiologic agent of classic infectious mononucleosis, Epstein-Barr virus (EBV) has been associated with a number of other clinical entities [1]. These include a spectrum of isolated organ and system disorders that are noted within the infectious mononucleosis syndrome (i.e., acute neurological episodes, thrombocytopenia purpura, and interstitial pneumonitis), lymphoproliferative disorders, and a variety of other chronic conditions.

In this issue, Lekstrom-Himes and colleagues [2] propose to link EBV to a patient’s chronic, recurrent clinical condition that does not fit well into recognized categories of periodic febrile illnesses. The association of the patient’s clinical condition with EBV is based on several serological and virological findings, as discussed below.

See the article by Lekstrom-Himes et al. on pages 22-7.

Standard immunofluorescent determinations with serum specimens collected over a several-year period provided evidence of unusual antiviral humoral responses. These were characterized by protracted, low-level positivity for titers of IgM antibodies to EB viral capsid antigen (VCA) and an absence of antibodies to EBV nuclear antigen (EBNA) (although antibodies to EBNA component 1 were detected in cell substrates overexpressing the latter antigen). Further, a persistently strong serum IgA response to EB VCA was uncovered.

These particular serological results were not accompanied by other findings, such as high levels of IgG antibody to EB VCA or early antigen components, that are commonly noted in association with presumed EBV-related conditions. Admittedly, this finding is not entirely atypical, because there appear to be various EBV-specific antibody responses among patients who may have aberrations in the immunoregulation of EBV infections and, as a potential consequence, an EBV-related clinical disorder. In acute classic infectious mononucleosis there is clearly a prototypical EBV-specific antibody profile. But in persons with chronic clinical conditions possibly related to a defective specific host response to EBV (or persons who are generally immunocompromised on account of any of various causes), several patterns of unusual viral-specific antibody responses have been revealed. In these latter circumstances [3-6], elevated titers of IgG-specific antibody to EB VCA and early antigens (diffuse or restricted components) and persistently low titers of antibodies to EBNA are commonly detected. IgM antibodies to EB VCA are noted much less frequently, while enhanced IgA antibodies to EB VCA are of an intermediate frequency.

However, patients with AIDS have been found to have paradoxically high levels of antibody to EBNA, together with elevated titers of IgG antibodies to EB VCA and early antigen components [6]. In addition, rare patients with EBV-related lymphoproliferative disorders or atypical clinical illnesses may have incomplete or even absent EBV-specific serum antibody responses [7]. Some investigations [8], but not others [9], have noted that in patients with a chronic infectious mononucleosis-like condition considered to be EBV-related, there may be a defective emergence of antibodies to EBNA components, with poor formation of antibody to EBNA-2 but not to EBNA-1.

Of major interest was the persistent detection of transforming EBV from throat washings, a prevalence rate that surpasses even that seen in patients with immunocompromising conditions [10]. This was even more intriguing because the patient had otherwise normal immunologic indices. Indeed, the reason for the greatly enhanced rate of viral excretion—besides the immunologic implication(s) of this finding concurrent with a relatively normal proportion of peripheral blood mononuclear cells bearing EBV—is perplexing.

To augment the EBV linkage, the authors detected evidence of increased EBV markers in tissue, such as virus-specific encoded RNA in interfollicular cells and a small percentage of EBNA-expressing cells in lymph nodes biopsied following convalescence from a febrile episode. However, the examined tissues exhibited no pathological lesions and only some evidence of a reactive state commonly noted in infectious mononucleosis, but this evidence was not highly specific.

In aggregate, the various serological and virological findings in this patient indicate a somewhat abnormal EBV profile. However, whether these findings indicate an involvement of EBV in the pathogenesis of the patient’s clinical disorder or merely indirectly reflect a mild generalized anomaly in host immunoregulation of latent viral infections is unclear. A better conclusion is difficult to ascertain because the patient does not have any distinctive pathological lesions in which to search for actively replicating virus or viral monoclonality; evidence of an acute EBV infection heralding this chronic, recurrent disorder; or other additional solid findings.

Nonetheless, this patient’s clinical condition and viral status warrant continued surveillance to delineate more clearly this
putative EBV association. It would be prudent for subsequent examinations to incorporate newer serological tests utilizing specific EBV polypeptides and EBNA components; determinations of EBV-related cellular immune responses; and tests for virus-specific markers in tissues and organs suspected of infection [4, 5].

Fortunately, this chronic illness in an otherwise apparently immunocompetent child shows no evidence of a progressive lymphoproliferative state. Continued evaluation of the patient and documentation of other similar cases could yield additional insights into EBV-host interactions that may have adverse clinical consequences.

References
3. Virelizier JL, Lenoir G, Griscelli C. Persistent Epstein-Barr virus infection in a child with hypergammaglobulinaemia and immunoblastic prolifera