Could a Herpesvirus Mimic Tacrolimus-Induced Leukoencephalopathy?

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We read with interest the report by Small and colleagues [1] regarding leukoencephalopathy presumably induced by tacrolimus (FK506). We question, however, their conclusion that tacrolimus was the cause of the neurological disturbances described in the report and present an alternate hypothesis that a viral infection may have been the cause.

The cases described involved clinical and neurological abnormalities that resolved on reduction or cessation of tacrolimus. This is not a priori evidence that tacrolimus was the cause, however. Reduction of immunosuppression by reducing or ceasing tacrolimus may have been sufficient to "treat" viral pathogens such as those belonging to the herpesvirus group. For example, infections with cytomegalovirus (CMV) and human herpesvirus-6 (HHV-6) infection have responded to reduction in iatrogenic immunosuppressive therapy alone without any antiviral treatment being used [2, 3]. Apart from one of the cases presented by Small and colleagues [1], in which polymerase chain reaction for CMV on brain tissue was performed, no mention is made of other attempts to detect virus. Although CMV has been associated with neurological abnormalities in the immunosuppressed population, other herpesviruses such as HHV-6 are increasingly being recognized as causes of focal encephalitis in immunocompetent as well as immunosuppressed hosts [4–6]. In one biopsy-proven case of HHV-6 encephalitis in a transplant recipient [6], Luxol fast blue–stained sections showed areas of demyelination just as in the first case described by Small and colleagues [1]. Other similarities between the two cases include an absence of viral inclusion bodies and a relatively acellular cerebrospinal fluid with an elevated cerebrospinal fluid protein.

We question whether the neurological and radiological findings presented by Small and colleagues [1] can be linked specifically to tacrolimus without thorough virological evaluation, particularly for HHV-6, having been performed.

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Reply

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The writers make the point that neither our clinical nor histopathological data rules out the possibility that the leukoencephalopathy was caused by a viral pathogen. They are particularly concerned about the possibility of infection with cytomegalovirus (CMV) or human herpesvirus-6 (HHV-6), an understudied herpesvirus in which these writers have particular interest.

Although we agree that viral infection probably causes some cases of leukoencephalopathy in the context of tacrolimus immunosuppression, and further, that HHV-6 or CMV could be underdiagnosed causes of some cases of leukoencephalopathy in this setting, we do not agree that such viral infection is the most likely cause in many such patients.

We have four reasons for this view. First, the one case for which there does exist histopathological data demonstrated a negative polymerase chain reaction (PCR) for CMV in the biopsied region. Second, the articles cited by these writers describe cases of focal encephalitis in the setting of generalized systemic disease, whereas the cases we describe had evidence of neither encephalitis nor systemic manifestations of infection. Third, opportunistic infection with the herpesviruses ordinarily occurs within the early phase of immunosuppression, rather than months to years later as occurs in patients with the immunosuppression-induced leukoencephalopathy syndrome. Fourth, although the writers are known for their research in HHV-6, they do not claim to have studied any patients with a leukoencephalopathy such as we have described who had PCR evidence of HHV-6 infection.

In summary, we thank the writers for making the clinically vital point that herpesvirus infections can be confused with immunosuppression-induced leukoencephalopathy from tacrolimus. It remains undecided, however, to what extent immunosuppression-induced leukoencephalopathy is the result of viral infection as opposed to drug-mediated demyelination. The group that has commented on our article is in a good position to answer the question with respect to the two herpesviruses mentioned, CMV and HHV-6, and we look forward to seeing their results.

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Tuberin Loss from Cerebral Tissues

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We read with interest the recent report of Mizuguchi and associates [1] concerning loss of tuberin (the *TSC2* gene protein product) from lesions originating in cerebral tissues of patients with tuberous sclerosis (TSC), including a cortical tuber and subependymal giant cell astrocytomas (SEGAs) from 3 patients. By contrast, tuberin could easily be identified within normal human cerebral cortical tissues and (at reduced levels) in relatively "unaffected" cortex from a TSC

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