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JCV persistence in PML patients

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In commenting on *JC Virus persistence in PML patients treated with natalizumab*,[1] Goelz et al suggests variation in JCV antibody ELISA design leads to differing assessments of individuals' serological status, an indicator of viral exposure. To this we agree and below offer a solution. First, however, based on our CLIA assay we reported one plasma and serum sample sero-negative. These samples, from patient 16, were taken concurrent to PML diagnosis after several cycles of plasma exchange, but exhibited antiviral titers below our interpretation of sero-positive[2]. We are currently unfamiliar with any systematicly derived data showing rapid reduction of JCV antibodies in patients undergoing PLEX for natalizumab removal. However, if PLEX is also responsible for JCV antibody reduction, patients who showed rising antiviral titers after PLEX, such as patient 8, may continuously produce measureable JCV antibodies in response to viremia. Conversely, patient 16, also viremic (85 c/ml) and highly viruric (27,212 c/ml), did not have a measured antibody response to JCV in our assay despite persistent antigen stimulation. Patient 16 may be an example of a sero-negative PML case, not the result of JCV antibody depletion by PLEX.

Regardless of assay design, antibody cross-reactivity[3], or viral antigen selection [4], the assessment of sero-status could be more accurately derived from a 'consensus' of laboratories experienced in making such assessments through independent judgment. In our paper's discussion, we urged a cross-reference of identical samples in a 'blinded' test format by independent laboratories with data collection results sent to a third party. A similar protocol was important in evaluating the JCV DNA qPCR assay for clinical samples where Quality Control for Medical Diagnostics, UK was the objective coordinator. Such an exercise may show the assay described in Gorelik et al[5] provides accurate data useful as one parameter for assessment of PML risk. However, in MS populations contemplating treatment with natalizumab or other underlying diseases contemplating treatment with immune compromising therapies, one parameter will likely not provide certainty regarding PML risk. We have publicly stated that the presence and/or rise in antibody titers could be informative when considered with evidence for viremia, T-cell mediated immune responses, and molecular factors; all of which contribute to patients' PML risk. Now recognized more frequently, PML reaches the attention of neurologists not as a rare disease, but as a substantial consideration in the use of biological therapies that affect the immune system. In administering such therapies, measure of several parameters would be needed to seriously mitigate PML risk.

References

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