Reviewer's report

Title: HHV8 replication, in a HIV positive patient during disseminated Tuberculosis

Version: 5 Date: 3 April 2009

Reviewer: Barbara Ensoli

Comments to authors:

In their paper Inoubli et al. describe the case of an HIV positive patient showing high levels of HHV8 replication detected during disseminated tuberculosis and conclude that, since high levels of HHV8 can measured during an opportunistic disease different from Kaposi’s sarcoma (KS) or multicentric Castleman’s disease (MCD), it is crucial to rapidly establish a correct diagnosis in a patient with an opportunistic infection in order to avoid an unnecessary chemotherapy.

In addition, this case report highlights the fact that the full clinical meaning and implication of a positive HHV8 viral load, in patients with AIDS, remains to be clarified.

We think that the present case report is interesting however the following points should be emphasized/addressed.

In particular, it is important to note that reactivation of HHV8 infection and increased levels of HHV8 plasma viremia can be induced upon exposure to inflammatory cytokines. Indeed, in vitro studies indicated that exposure of PMBC from HIV-infected subjects or primary effusion lymphoma cell lines promotes induction of HHV8 lytic cycle replication (Mercader M et al., Am J Pathol 2000; Monini P et al., Blood 1999; Blackbourn DJ et al., AIDS 2000; Chang J at al., Virology 2000; Yu Y et al., AIDS 1999).

This effect of inflammatory cytokines has been also demonstrated in other herpesvirus infections, including cytomegalovirus (CMV) infection (Sderberg-Nauclèr C et al., Cell 1997).

This experimental evidence implies that increased plasmatic levels of HHV8 are not necessarily indicative of the presence of MCD or KS, but rather that the inflammatory dysregulation associated with HIV infection and, as reported by the authors, with organ transplant and CMV, may lead to HHV8 reactivation.

Indeed, as reported by the authors, other clinical conditions that, in addition to HIV infection, are characterized by immuno-activation (including disseminated infections, organ transplant or pregnancy) may be associated with signs of HHV8 or other herpesviruses (CMV, EBV) reactivation.

Thus, this referee agrees with the authors that the full clinical meaning and implication of a positive HHV8 viral load remains to be elucidated, as well as the relationship between HHV8 infection and KS, MCD, or PEL disease onset.
Accordingly, the authors should define and discuss their definition of “asymptomatic” HHV8 replication (i.e. page 3, line 3), since not necessarily subjects showing signs of HHV8 replication will develop a disease status.

Minor points:
# “Castelman disease” should be corrected in “Castleman’s disease”.
# The last 2 sentences of page 8 may not be clear to the reader, and reference/s supporting this concept should be indicated.