PE30
HIV rebound and meningoencephalitis following ART interruption after allogeneic hematopoietic stem cell transplant: an investigation of the source of HIV rebound

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Background: Allogeneic hematopoietic stem cell transplant (alloHSCT) with uninterrupted antiretroviral therapy (ART) is being investigated as a component of HIV eradication strategies. In the two “Boston patients”, alloHSCT resulted in the disappearance of HIV in peripheral blood. However, after analytical ART interruption, viral rebound occurred. Proposed sources of HIV rebound include the latent reservoir in resting CD4+ T cells and tissue macrophages. We present the case of an HIV-infected patient who received alloHSCT for leukemia and experienced acute retroviral syndrome after self-discontinuing ART post-alloHSCT.

Methods: Resting memory CD4+ T-cells obtained 16 and 1 week prior to alloHSCT were used in a limiting-dilution viral outgrowth assay (VOA) in which each well that demonstrates viral growth contains a single replication-competent viral clone. The pol region of virus from positive VOA supernatants was sequenced. Rebound virus from blood and cerebrospinal fluid (CSF) was also analyzed using deep-sequencing (Roche 454) of pol. Sequences were aligned and maximum likelihood analysis was performed using the GTR+G model of evolution with 100 bootstrapping pseudoreplicates.

Results: The patient had undetectable plasma HIV and achieved 100% donor chimerism at week 12 post-alloHSCT, but then became non-adherent with ART. At 5 months, the patient presented with fever and meningoencephalitis. Plasma and CSF HIV levels were 25,500 and 17,000 copies/ml, respectively. Before alloHSCT, 31 sequences were isolated from the VOA. At rebound, 14,645 and 5,003 sequence reads were obtained from CSF and blood respectively, and were combined into consensus sequences using a cut-off of >0.2% of total sequence reads. An identical sequence found at both pre-alloHSCT timepoints accounted for 9/31 (29%) of independent VOA sequences. This sequence grouped with the plasma and CSF viral rebound sequences in a monophyletic clade with high sequence homology.
Conclusions: Despite 100% donor chimerism in peripheral blood, ART interruption led to HIV rebound in plasma and CSF. Rebound virus was identical to a pre-allo-HSCT isolate which compromised nearly 1/3 of the latent CD4+ T-cell reservoir sampled. This unique case suggests that recipient cells persist at early time-points after allo-HSCT and that a single viral population latent in resting memory CD4+ T cells can re-establish infection.
The source of HIV-1 rebound in these cases was not clear. In a pilot clinical trial at Johns Hopkins, we are evaluating whether alloHSCT with optimized ART reduces HIV-1 reservoirs in HIV-1-infected patients who require alloHSCT for a standard clinical indication (see abstract #TUPEB298 for detailed clinical data). Optimized ART includes: 1) avoidance of ritonavir-boosted regimens to minimize drug interactions, 2) ART changes for organ dysfunction, and 3) subcutaneous enfuvirtide (ENF) during post-transplant cyclophosphamide and if oral ART was not tolerated. Potential explanations for viral rebound with ART interruption in this case may be a result of persistent recipient cells due to an incomplete donor chimerism at a relatively early point post-alloHSCT. Infectious complications following non-myeloablative allogeneic hematopoietic stem cell transplantation. Transpl Infect Dis. 2003;5:132-139. Frere P, Baron F, Bonnet C, et al. Infections after allogeneic hematopoietic stem cell transplantation with a non-myeloablative conditioning regimen. Bone Marrow Transplant. 2006;37: 411-418. HIV rebound and meningoencephalitis following ART interruption after allogeneic hematopoietic stem cell transplant: an investigation of the source of HIV rebound. 8th IAS Conference on HIV Pathogenesis, Treatment & Prevention, Vancouver, Canada, 2015. Abstract MOPDEA0105. Association between CSF and peripheral markers of immune-activation/inflammation and elevated intrathecal HIV-RNA levels in a cohort of HIV-infected antiretroviral naïve individuals. 8th IAS Conference on HIV Pathogenesis, Treatment & Prevention, Vancouver, Canada, 2015. Abstract TUPDA0 Allo-HSCT=allogeneic hematopoietic stem-cell transplantation. cART=combination antiretroviral therapy. CMV=cytomegalovirus. CsA=cyclosporin. In view of the lymph node histological findings showing B-cell proliferation, we wondered whether EBV reactivation could have triggered EBV-specific CD4 and CD8 T-cell responses and proliferation, potentially including CD4 T cells containing HIV-1 DNA. The absence of rebound after ART interruption could be due to two mechanisms: a reduction in the latent reservoir after conditioning and transplantation; and a reduction in the fraction of susceptible target cells for CCR5-tropic virus because of engraftment of donor CCR5Δ32/Δ32 cells. To understand the relative role of each mechanism alone.