Adding to the cytomegalovirus crime sheet: Editorial on 'Osteonecrosis of the femoral head is associated with cytomegalovirus reactivation'

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Human cytomegalovirus (HCMV) is one of the nine herpes viruses that infects humans. As with all herpes viruses, HCMV infection results in the establishment of lifelong persistence/latency within the host with over 60% of the world population currently infected with HCMV. In healthy people, a broad and robust immune response renders primary infection asymptomatic, ensures that reactivation from latency remains sub-clinical, and thus HCMV is a rare cause of overt disease in healthy people[(1)]. However, the control of HCMV comes with immunological cost: upwards of 20% of the total T cell response can be directed against HCMV in healthy people. This suggests that HCMV is not completely dormant in the host but, instead, is subject to sustained immunological control of a virus that is cycling through phases of latency and reactivation[(2)].

A major site of HCMV latency is in the CD34+ haematopoietic cells resident in the bone marrow. These cells give rise to all the cells in our bloodstream but, through mechanisms we still do not fully understand, latent (or non-replicative) HCMV genomes persist specifically in the cells of the myeloid lineage where, upon terminal differentiation to macrophages or dendritic cells, the virus can reactivate through re-entry into it's lytic (or replicative) lifecycle. It is hypothesised that these sub-clinical reactivation events could also seed persistent/latent infections within organs which again are likely subject to prodigious immunological control within the organ[(3)].

So why do we care about HCMV? As well as representing the leading viral cause of disease in congenitally infected fetuses it is a major problem in transplant patients who require immune-suppression[(1)]. Indeed, any clinical setting where adaptive immune responses are impaired becomes high risk for the development of HCMV pathogenesis. Furthermore, the capacity of HCMV to replicate in most differentiated cell types means pathology can be observed in multiple organs throughout the body. Finally, the inflammation associated with transplantation and

disease likely enhances viral replication creating a positive feedback loop leading to worsening pathology.

An important clinical observation in transplant patients is that despite systemic immune-suppression not all patients will go on to have clinically significant HCMV reactivation. One hypothesis is that these non-viremic patients have sufficient immunity to HCMV to limit viral replication[2]. Indeed, we have shown recently that better tissue resident immunity directed against HCMV in donated livers can lead to better clinical outcomes post-transplant[4]. Thus despite systemic immune-suppression, the nature of the local immune environment around HCMV is critical in certain settings.

In this current issue, Wang and colleagues[5] have investigated a potential role for local HCMV reactivation in the femoral head as a contributing factor towards the development of osteonecrosis. Specifically, they report that elevated HCMV reactivation (evidenced by detection of viral DNA and viral protein expression) is observed in patients with worse outcomes. Furthermore, they observe that HCMV gene products were more evident in necrotic tissue and in damaged vasculature. Importantly, these individuals were not undergoing detectable systemic HCMV reactivation suggesting that this event was localized to the femoral head and diseased joint. What was intriguing was that the osteonecrosis was not necessarily due to direct infection of osteocytes and thus likely a result of the inflammation associated with viral replication in other cell types within the joint.

A key caveat that the study design cannot address is the question of trigger versus driver of pathogenesis? HCMV reactivation (and subsequent replication) is enhanced by inflammation including corticosteroids[6] which are also a risk factor for idiopathic osteonecrosis[7]. Thus what is not clear is whether HCMV reactivation initiates the disease state or that the tissue damage promotes viral reactivation and replication which then creates a positive feedback loop causing greater pathology. Or, indeed, it cannot be formally ruled out that HCMV is a bystander in the whole process despite the association with worse outcomes and a HCMV seropositive serostatus. However, If there was a direct or enhancing role for HCMV in the process then the use of anti-virals directed against HCMV would of course lead to better outcomes in these patients. Indeed, there are some parallels with the role of HCMV and the development of cancer where

HCMV gene products have been identified in more aggressive glioblastomas[8]. HCMV itself is not an oncogenic virus capable of transforming cells (unlike it's gamma herpes virus cousins EBV and KSHV) but it is postulated that viral replication is onco-modulatory by promoting elevated inflammation which, in turn, could drive cancer cell replication.

In conclusion, these data argue that another debilitating disease can be added to the list where HCMV is a risk factor for worse outcomes. From a HCMV virologist perspective it also demonstrates how HCMV could still have very tissue-specific pathologies even in patients who have no evidence of viral DNaemia in the blood – a biomarker which has proven transformative for how we assess risk of HCMV pathogenesis and subsequent use of anti-virals in our solid organ and bone marrow transplant recipients to focus on those at the highest risk[1]. It also raises the question of what other pathologies associated with localized immune inflammation may also be exacerbated by the presence of HCMV – a ubiquitous infection of humans around the world – which would add to the growing list of reasons why a vaccine against HCMV remains so urgently needed[9,10].

1. Griffiths P, Reeves M. Pathogenesis of human cytomegalovirus in the immunocompromised host. Nat Rev Microbiol. Jun 24 2021;19:759-73. Epub 2021/06/26.
2. Jackson SE, Noor M, Lim E, Wills M. The immune response to human cytomegalovirus: impact of age, co-morbidities and the significance of anti-viral activity assessment. Philos Trans R Soc Lond B Biol Sci. Nov 6 2025;380(1938):20240408. Epub 2025/11/06.
3. Reeves MB. Cell Biology of Human Cytomegalovirus Latency: Implications for Pathogenesis and Treatment. Rev Med Virol. Jul 2025;35(4):e70063. Epub 2025/07/28.
4. Forrest C, Chase TJG, Cuff AO, Maroulis D, Motallebzadeh R, Gander A, et al. Control of human cytomegalovirus replication by liver resident natural killer cells. Nat Commun. Mar 14 2023;14(1):1409. Epub 2023/03/16.
5. Wang R, Tian X, Shi L, Kong Z, Wang Z, Dong L. Osteonecrosis of the femoral head is associated with cytomegalovirus reactivation. J Bone Miner Res. Jan 6 2026. Epub 2026/01/06.
6. Van Damme E, Sauviller S, Lau B, Kesteleyn B, Griffiths P, Burroughs A, et al. Glucocorticosteroids trigger reactivation of human cytomegalovirus from latently infected myeloid cells and increase the risk for HCMV infection in D+R+ liver transplant patients. J Gen Virol. Jan 2015;96(Pt 1):131-43. Epub 2014/10/15.
7. Motta F, Timilsina S, Gershwin ME, Selmi C. Steroid-induced osteonecrosis. J Transl Autoimmun. 2022;5:100168. Epub 2022/10/11.
8. Mercado NB, Real JN, Kaiserman J, Panagioti E, Cook CH, Lawler SE. Clinical implications of cytomegalovirus in glioblastoma progression and therapy. NPJ Precis Oncol. Sep 29 2024;8(1):213. Epub 2024/09/30.
9. Lankina A, Raposo M, Hargreaves A, Atkinson C, Griffiths P, Reeves MB. Developing a Vaccine Against Human Cytomegalovirus: Identifying and Targeting HCMV's Immunological Achilles' Heel. Vaccines (Basel). Apr 22 2025;13(5). Epub 2025/05/28.

10. Arvin AM, Fast P, Myers M, Plotkin S, Rabinovich R. Vaccine development to prevent cytomegalovirus disease: report from the National Vaccine Advisory Committee. Clin Infect Dis. Jul 15 2004;39(2):233-9. Epub 2004/08/13.