blood®

203. LYMPHOCYTES, LYMPHOCYTE ACTIVATION, AND IMMUNODEFICIENCY, INCLUDING HIV AND OTHER INFECTIONS: POSTER III | DECEMBER 07, 2017

Virome Capture Sequencing in Castleman Disease Identifies Associations with Herpesviridae Family Members but No Novel Viruses

Christopher Sheild Nabel, MD PhD,[*,1] Stephen Sameroff, BS,[*,2] Dustin Shilling, PhD,[*,3] Jason R Ruth, PhD,[*,4] Mitsuhiro Kawano, MD,[*,5] Yasuharu Sato, MD,[*,6] Noriko Iwaki, MD,[*,7] Federico Valdivieso, BS,[*,8] Michael Feldman, MD,[*,8] Katie Stone, BS,[*,9] Daisy Alapat, MD,[10] Frits van Rhee, MD PhD,[9] Amy Chadburn, MD,[11] Signe Spetalen, MD,[*,12] Alexander Fosså, MD PhD,[*,12] W. Ian Lipkin, MD,[*,13] David C Fajgenbaum, MDMBA,MSc[3]

[1]Dana Farber Cancer Institute, Boston, MA

[2]Columbia University, New York, NY

[3]University of Pennsylvania, Philadelphia, PA

[4]Castleman Disease Collaborative Network, Boston, MA

[5]Kanazawa University, Kanazawa, Japan

[6]Okayama University Graduate School of Medicine, Okayama, Japan

[7]Okayama University Graduate School of Medicine, Kanazawa City, JPN

[8]Hospital of the University of Pennsylvania, Philadelphia, PA

[9]Myeloma Institute, University of Arkansas for Medical Sciences, Little Rock, AR

[10]Myeloma Institute, University of Arkansas, Little Rock, AR

[11]Department of Pathology and Laboratory Medicine, Weill Cornell Medicine, New York, NY

[12]Oslo University Hospital, Oslo, Norway

[13]Center for Infection and Immunity, Columbia University, New York, NY

Blood blood **(2017) 130 (Suppl_1) : 3589.**

http://doi.org/10.1182/blood.V130.Suppl_1.3589.3589

Abstract

Castleman disease (CD) describes multiple distinct and heterogeneous disorders defined by common lymph node histopathology, including atrophic or hyperplastic germinal centers, prominent follicular dendritic cells, hypervascularization, polyclonal lymphoproliferation, and/or polytypic plasmacytosis.

Unicentric CD (UCD) involves a solitary lymph node station that displays CD histopathology, whereas multicentric CD (MCD) involves multiple regions of enlarged nodes. Most UCD patients do not experience systemic symptoms and are successfully treated by removal of the enlarged node. In contrast, MCD involves constitutional symptoms, cytopenia, hepatosplenomegaly, fluid accumulation, cytokine storm-associated multiple organ system dysfunction, and is often fatal. In 1994, Kaposi sarcoma-associated herpesvirus/human herpesvirus-8 (HHV-8) was identified as the etiological driver of MCD in immunocompromised individuals. However, approximately 50% of MCD patients are HHV-8 negative (idiopathic MCD (iMCD)). Its idiopathic nature limits targeted treatment for iMCD patients who do not respond to anti-Interleukin-6 therapy. iMCD is itself heterogeneous, and recent work has identified at least one distinct sub-population of iMCD patients with a severe clinical presentation featuring thrombocytopenia, anasarca, myelofibrosis, renal dysfunction, and organomegaly (iMCD-TAFRO). Several hypotheses have been proposed to explain the pathophysiology of iMCD and UCD, all of which remain untested. One notable hypothesis entertains that iMCD and UCD are in fact driven by viral infection--either HHV-8 that is not detected by current diagnostic methods, a novel virus, or a known but unanticipated virus. In support of the last possibility, there are several case reports of associations with Epstein-Barr virus (EBV), HHV-6 and Hepatitis B virus (HBV); however, neither a systematic study of known viruses, nor a search for novel viruses in CD has been reported.

To this end, we employed Virome Capture Sequencing for Vertebrate Viruses (VirCapSeq-VERT),- a RNA-hybrid capture, deep sequencing and bioinformatics pipeline designed for viral discovery. In accordance with the Treaty of Helsinki, we obtained freshly frozen lymph node tissue from patients with iMCD (n=11) and UCD (n=12) as experimental conditions. HHV-8-positive MCD (n=2) was included as a positive control for HHV-8 infection. Lymph nodes from patients with lymphoma without clinical suspicion of HHV-8 infection (n=6) and an additional reactive lymph node were included as a negative control. HHV-8 was only detected in HHV-8-positive MCD and not in iMCD or UCD, consistent with prior clinical testing. Additionally, we did not identify any previously unknown viruses in iMCD or UCD lymph node tissue. Members of the herpesviridae family, including EBV, HHV-6 and HHV-7, were found in all conditions. Interestingly, in iMCD, the identification of herpesviridae family members was associated with relapsing disease and the more clinically severe iMCD-TAFRO variant. Additional numerous associations of unclear significance were made with viruses such as Human Endogenous Retrovirus Type K (HERV-K), transfusion transmitted virus/Torque teno virus (TTV), and Pegivirus.

To investigate the significance of the EBV infection, we analyzed the number of EBV positive cells by *in situ* hybridization on lymph node tissue from a separate cohort of patients with CD and related disorders. The mean number of Epstein-Barr virus-encoded small RNAs (EBER) positive cells/high-powered fields (HPF) across 10 HPF was significantly lower in UCD (2 ± 2.3; n=9) and iMCD (1.7 ± 2.8;

n=12) than in HHV-8 positive MCD (106.5 ± 75.6; n=2) and EBV-associated lymphoproliferation (63.5 ± 54.4; n=2) ($p < 0.005$ for all comparisons). The only iMCD-TAFRO case in this cohort had 4 EBER-positive cells/HPF. Further study is needed with larger cohorts of patients to validate the prognostic and potentially pathogenic significance of these associations, and in particular, the association of EBV and other herpesviridae family members with iMCD-TAFRO.

Disclosures

Fajgenbaum: *Janssen Pharmaceuticals:* Research Funding.

Author notes

*Asterisk with author names denotes non-ASH members.