



**Review Article**

## **Lymphoproliferative Syndromes Associated with Human Herpesvirus-6A and Human Herpesvirus-6B**

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**Abstract.** Human herpesvirus 6A and 6B (HHV-6A and HHV-6B) have been noted since their discovery for their T-lymphotropism. Although it has proven difficult to determine the extent to which HHV-6A and HHV-6B are involved in the pathogenesis of many diseases, evidence suggests that primary infection and reactivation of both viruses may induce or contribute to the progression of several lymphoproliferative disorders, ranging from benign to malignant and including infectious mononucleosis-like illness, drug induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS), and nodular sclerosis Hodgkin's lymphoma. Herein, we discuss the conditions associated with the lymphoproliferative capacity of HHV-6, as well as the potential mechanisms behind them. Continued exploration on this topic may add to our understanding of the interactions between HHV-6 and the immune system and may open the doors to more accurate diagnosis and treatment of certain lymphoproliferative disorders.

**Keywords:** Human herpesvirus; HHV-6A; HHV-6B; Lymphoproliferative Disease.

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**Introduction.** Human herpesvirus 6A and 6B (HHV-6A and HHV-6B), collectively known as HHV-6, are a pair of closely related betaherpesviruses of the genus Roseolovirus with lymphocytic tropism and immunomodulatory capabilities.<sup>1,2,3</sup> HHV-6A was discovered in the peripheral blood mononuclear cells (PBMCs) of patients with AIDS-related lymphomas and other lymphoproliferative disorders in the latter part of the 1980s, and its T cell tropism was established in short order.<sup>1,4-6</sup> Early investigations found that the available HHV-6 isolates could be split into two distinct variants, with HHV-6 Type A

preferentially infecting immature T cells and Type B infecting mature T cells.<sup>2,7</sup> These initial findings were followed by detection of HHV-6 antigen and DNA in the lymph nodes of patients with lymphoproliferative disorders and autopsy specimens,<sup>8-12</sup> and a possible role for HHV-6 in lymphomas was examined, with some compelling results but no consensus.<sup>13-15</sup> Although the virus has been implicated in a range of lymphoproliferative disorders, efforts are still underway to elucidate the pathogenic roles of HHV-6 in these conditions. The ubiquitous nature of the virus was recognized early on as a challenge

in identifying its role in the disorders in which it has been implicated, as its DNA can be found in the peripheral blood of healthy donors and low level reactivation may occur without clinical manifestations. Consequently, serological studies serve primarily to screen patients for HHV-6 infection, while the most conclusive results are gained through the use of quantitative PCR, staining techniques applied to tissue samples, and through comparison with carefully selected controls. With the technical advancements and growing understanding of the effects of HHV-6 on the immune response, investigators are continuing to learn about the potential for HHV-6 to trigger lymphoproliferative disorders and the possible mechanisms behind it.

**Interactions between HHV-6 and the Immune System.** HHV-6A and B infect hematopoietic stem cells (CD34+, CD32+), cord blood cells, and several immune cell populations *in vitro* and *in vivo*, including T lymphocytes, NK cells,<sup>16</sup> monocytes and macrophages,<sup>17,18</sup> and dendritic cells,<sup>19</sup> and HHV-6A has also been found to infect EBV-immortalized B cells.<sup>20</sup> However, as the two species utilize different cellular receptors and impact chemokine/cytokine signaling in different ways, their tropism differs. This matter is further complicated as the presence of cellular receptors for HHV-6 does not guarantee infection of such cells in tissues.<sup>21</sup> Viral DNA is found in 9-25% of peripheral blood mononuclear cells (PBMCs) from healthy donors,<sup>13,22</sup> and HHV-6B is found more frequently than HHV-6A, which has been detected in the PBMCs of 3-10% of healthy individuals.<sup>13</sup> In most healthy adults, a T cell response to HHV-6 is present,<sup>23</sup> but fewer than 0.12% of CD4+ T cells in PBMC samples are reactive to HHV-6,<sup>24</sup> and fewer than 1 in 10<sup>5</sup> CD8+ T cells in PBMCs are HHV-6-specific.<sup>25</sup> Reactivation of HHV-6 occurs during T cell activation by various stimuli, including endotoxins, endocrine stimulation, certain cytokines, and food components (e.g. agglutinins, phorbol esters etc.). Immunosuppressive conditions, including those involving stress, transient immunosuppression, and/or stimulation resulting from infection with other viruses such as measles virus, support the persistent activity of HHV-6 once reactivated. Similar to EBV infections, persistent HHV-6 activity can also be found after organ and hematopoietic stem cell transplantation.

As our understanding of HHV-6A and B has grown, their immunomodulatory activities have emerged as key contributors to many of the clinical manifestations linked to HHV-6 infection. HHV-6 infection is most commonly associated with exanthema subitum (roseola infantum),<sup>26</sup> a manifestation of primary infection that occurs during early childhood. Intense reactivation of the virus is frequently observed in the transplantation setting, resulting in a host of complications post-solid organ and hematopoietic stem cell transplantation (HSCT). These conditions, as well as others associated with HHV-6 infection and reactivation, are often mediated to a great extent by the immune response to the virus and by the effects of the virus on various immune cell populations and cytokine/chemokine expression. The influences exerted by HHV-6A/HHV-6B differ by species, but both trigger inflammatory reactions while also employing mechanisms by which they can suppress an immune response and avoid detection.

*In vitro* experimentation has demonstrated that HHV-6B and HHV-6A induce myelosuppression,<sup>27,28</sup> infection of T cells and PBMCs inhibit immune responses against a tuberculin protein derivative or mumps antigen,<sup>29</sup> and infection of PBMCs results in reduced IL-2 mRNA and protein synthesis- 50% less than mock-infected cells- sharply reducing cellular proliferation and indicating that the functions of T cells are suppressed.<sup>30</sup> In the clinical setting, thymic atrophy and severe T lymphocytopenia have been reported,<sup>31-33</sup> and in transplant recipients, delayed engraftment, myelosuppression,<sup>34</sup> and graft failure<sup>35</sup> have been known to occur in response to active HHV-6. An inverse correlation has been identified between reconstitution of CD4+ cells after HSCT and reactivation of HHV-6,<sup>36</sup> as well as CD3+ cells<sup>37</sup> and CD8+ cells,<sup>38</sup> and indeed, proliferation of lymphocytes has been inhibited by persistent HHV-6 infections after allo-HSCT.<sup>39</sup> However, transplantation of cord blood, which is associated with a higher risk of HHV-6 reactivation and higher HHV-6 DNAemia<sup>40</sup> compared to transplantation of other sources of hematopoietic stem cells, have also been found to have faster reconstitution of B lymphocytes with higher B cell counts, a phenomenon that has been hypothesized to arise as a result of an immune response against viral reactivation.<sup>40</sup> As immune suppression

enables HHV-6 to better avoid detection and clearance, this phenomenon is advantageous for the persistence of the virus, but proliferation of infected lymphocytes may also be beneficial for its dissemination. Accordingly, immune suppression and immune activation are but two sides of the same coin during HHV-6 infection. When either suppression or proliferation is unchecked, severe clinical manifestations may result.

Both HHV-6A and HHV-6B are able to affect chemokine/cytokine pathways, which are dysregulated in lymphoproliferative disorders. Infection by either virus impairs production of IL-12 in macrophages<sup>41</sup> and in dendritic cells,<sup>42</sup> which may allow the viruses to suppress activation of cytotoxic effectors. In combination with lower IL-2 expression,<sup>30</sup> TNF-alpha, IL-1beta, IL-8, and IL-15 have been found to be upregulated,<sup>43,44,45</sup> coinciding with a shift from a Th1 to Th2 cytokine profile. HHV-6A infection of astrocytes in patients with glioma has been associated with significantly upregulated TGF-beta, IL-6, and IL-8,<sup>46</sup> and *in vitro*, HHV-6B infection of astrocytes has increased production of the proinflammatory cytokines IL-6 and IL-1beta.<sup>47</sup> Notably, cytokine expression patterns vary temporally and in relation to the infected cell's environment. IL-10, IL-11, and other anti-inflammatory mediators, for example, are expressed at high levels after exposing HHV-6 infected astrocytes to proinflammatory cytokines.<sup>48</sup>

Viral proteins are also integral to HHV-6-mediated immunomodulation. The HHV-6B encoded chemokine U83B induces chemotaxis and activation of leukocytes expressing CCR2, which is expressed under proinflammatory conditions.<sup>49</sup> Similarly, endometrial epithelial cells infected with HHV-6A have shown increased cell surface expression of CCL2, IP-10, and CCL26.<sup>50</sup> On the other hand, the U83A chemokine (HHV-6A-specific), as well as the U51A chemokine receptor, target CCR5/CCL5 (RANTES),<sup>51</sup> another receptor/ligand pair involved in inflammation, resulting in down-modulation of their activity. U51A also binds four other inflammatory modulating chemokines that bind to and stimulate several immune cell populations, including B and T lymphocytes- CCL2, CCL7, CCL11, and CCL13- and the inflammatory cells expressing the U51A receptor exhibit chemotaxis toward, and internalization of, target chemokines.<sup>52</sup> In contrast,

primary HHV-6B infection results in upregulation of CCL2, CXCL11, CXCL10, and CXCL16.<sup>53</sup>

Another mechanism by which the pair of viruses affect their host cells is the alteration of cell membrane fluidity and the dysregulation of cellular receptors.<sup>54,55</sup> Both species downregulate MHC class I<sup>56,57</sup> and CD46, which may result in activation of autologous complement and cellular damage in lymphoid tissue and beyond,<sup>58</sup> and HHV-6A impairs expression of the T cell receptor/CD3 complex at the cell membrane, rendering the affected cells ineffective in responding to antigen-presenting cells.<sup>4,59,60</sup> In addition, HHV-6A triggers expression of CD4 mRNA and protein production in CD4 negative NK<sup>16</sup> and T cells<sup>61</sup> and can reduce the cytotoxicity of CD4+ T cells.<sup>62</sup> Both species interact with toll-like receptors and may exert their effects on cytokine/chemokine expression and the Th1/Th2 balance through them.<sup>63-67</sup>

### **Benign/Reactive Lymphoproliferative**

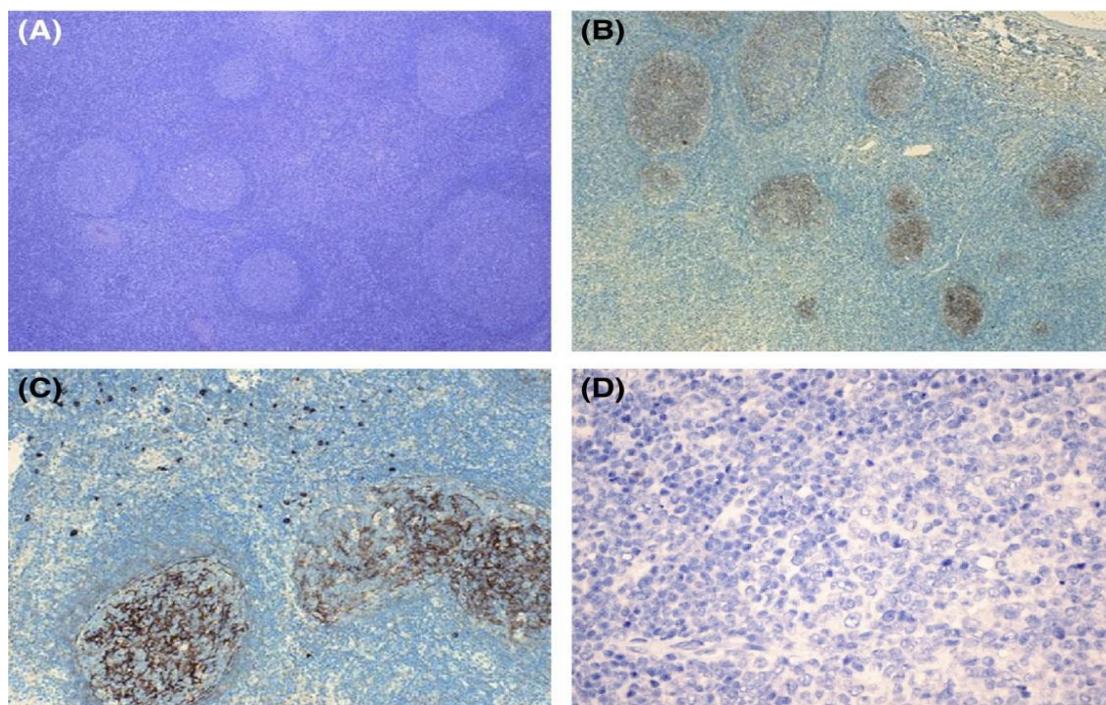
**Disorders.** Primary HHV-6B infection was identified as a causative agent of exanthema subitum (roseola infantum) in 1988, when the onset of the illness was linked to HHV-6 seroconversion, and the presence of viral antigen was observed in patients' lymphocytes.<sup>26</sup> In some cases observed by Krueger *et al.*, exanthema subitum was also seen during primary HHV-6A infection.<sup>68</sup> In addition to the characteristic rash, fever, and occasionally febrile seizures and encephalitis,<sup>69,70</sup> children with exanthema subitum can experience lymphadenopathy, relative lymphocytosis with increased CD38+ (immature) T cells, and hepatomegaly.<sup>69,71,72</sup>

Thrombocytopenia, neutropenia, and leukopenia are commonly found as well.<sup>73</sup> Notably, reactive "atypical" lymphocytes and hemophagocytosis may be observed in bone marrow,<sup>74,75</sup> and a mononucleosis-like illness, with reactive lymphocytosis and liver dysfunction, has been described.<sup>76</sup> Two unique cases documenting HHV-6 infection with unusual lymphoproliferation in very young children have been reported: One infant, 7 months old, died suddenly after developing otitis media, and HHV-6 was found by PCR in tissue samples and in atypical lymphoid infiltrate via ISH.<sup>77</sup> Abnormal, inflammatory lymphocytic infiltration was present in the liver, kidney, heart, spleen, bone marrow, and lymph nodes of the child, and interstitial pneumonitis was

reported. In the other case, a 2-week-old with HHV-6 DNA present in PBMCs, and who perhaps had congenital HHV-6, developed bone marrow cell proliferation, hypersensitivity to granulocyte-macrophage colony-stimulating factor (GM-CSF), hepatosplenomegaly, and was thought to have juvenile myelomonocytic leukemia. However, the symptoms resolved.<sup>78</sup> Generally, lymphoproliferative responses during primary infection are limited in scope and resolve without issue.

After primary infection, HHV-6A and HHV-6B remain latent in many organs, including the heart, lungs, gastrointestinal tract, and the brain, in addition to circulating lymphocytes. In immunocompetent individuals, low level reactivation may occur without major clinical symptoms. In those with immune deficiencies,<sup>79</sup> incomplete clearance and persistent activation cause various clinical diseases (e.g. post-transplant syndromes, autoimmune disorders etc.) During persistent or frequently recurrent reactivation in immune deficient persons (which is usually the case in studying adult patients), the virus has been associated with generalized reactive lymphadenopathy lasting for several days to several weeks.<sup>80-84</sup> Among patients with reactive

lymphadenopathy, scattered positivity (less than 1% of total cells) when staining for the HHV-6 antigens p101K, gp106, and gp116, has been observed among cells, namely plasma cells and histiocytes, from lymph node biopsies.<sup>85</sup> The virus has been detected by PCR in PBMCs at a higher prevalence among patients with lymphoproliferative disorders than in healthy volunteers,<sup>86</sup> and in Brazilian patients with lymphadenopathy and fever (but without skin rash), 8.7% had active HHV-6 infection (plasma viremia).<sup>87</sup> While these results indicate that HHV-6 may contribute to reactive lymphadenopathy, they may not implicate HHV-6 as the sole virus involved in its development, as it is difficult to rule out its reactivation in response to a different underlying cause of lymphadenopathy, including infections by other viruses. However, strong evidence of a role for HHV-6 in chronic/recurrent lymphadenopathy, backed by immunohistochemical staining- a more specific technique- has been reported. Of 111 cases of benign/reactive lymphadenopathies with unknown etiology in a recent study, 7 (6.3%) demonstrated recurrent/chronic behavior, and intense staining for HHV-6B was detected in follicular dendritic



**Figure 1. HHV-6B in chronic/recurrent benign lymphadenopathy. (A–D) Histological and immunohistochemical examinations on lymph node tissues.** Retained normal lymph node architecture with follicular hyperplasia and concurrent mild paracortical expansion was documented on haematoxylin/eosin staining. The lymph node follicles were enlarged and numerous. There was considerable variation in the size and shape of the follicles. Most of them retained a round to oval structure, without coalescence and with a conserved mantle zone surrounding the enlarged follicles (A, magnification  $\times 100$ ). An intense immunopositive staining with HHV-6B-specific p101K antibody was demonstrated in follicular dendritic cells (FDCs) of germinal centers in the majority of hyperplastic follicles, concurrently with scattered positivity of interfollicular cells [magnification  $\times 100$  (B),  $\times 200$  (C)]. Immunohistochemical reaction for HHV-6A (early antigen p41/38) was invariably negative on lymph node tissues (D, magnification  $\times 400$ ) (Forghieri et al. 2016).<sup>88</sup>

cells in all cases (**Figure 1**).<sup>88</sup>

In contrast, only three non-recurrent/chronic cases showed staining for HHV-6B in germinal centers of follicular dendritic cells, and 7 others showed scattered positivity in cells of interfollicular areas. Control lymph node tissues (n=134), which were obtained from patients with benign lymphadenopathy with known etiology-including other infections, solid cancer without metastasis, sarcoidosis, Kikuchi-Fujimoto disease, Wegener granulomatosis, dermatopathic lymphadenopathy, and unspecified autoimmune disorders- or malignant tumors, were negative for HHV-6. While recurrent or chronic activity is not usually observed in reactive/benign conditions, it is more commonly found in atypical or malignant disorders.<sup>89</sup> Although atypical lymphocytosis was not observed and there were no systemic symptoms, characteristics of abnormal/malignant lymph nodes, including irregular margin and hypoechoic center, were noted among the HHV-6+ patients with chronic/recurrent lymphadenopathy. Taken together, the data suggest that HHV-6 may primarily be involved in prompting benign lymphoproliferative conditions of a certain type, and that the features discussed by Forghieri *et al.* may prove to be useful in differentiating between HHV-6-associated lymphoproliferation and that caused by other agents.<sup>88</sup>

**Rosai-Dorfman Disease.** HHV-6 has been implicated as a trigger for several specific benign/reactive lymphoproliferative disorders, including Rosai-Dorfman (RD) disease. The first report of a possible association between the virus and development of RD described the detection of HHV-6 in involved tissues by ISH in the majority of a small cohort of patients (n=9).<sup>90</sup> HHV-6B DNA was later identified using PCR and Southern blotting in the skin of a patient with RD presenting as giant lesions of granuloma annulare with multiple soft tissue tumors.<sup>91</sup> The patient did not experience spontaneous clearing, which is usually observed for this disease. Notably, the HHV-6 late antigen p101k was detected in the lymph nodes of two RD patients (of two tested) in a pattern similar to that noted in the cases of chronic/recurrent lymphadenopathy described previously.<sup>85,88</sup> In particular, intense staining was noted in follicular dendritic cells of reactive germinal centers in areas of normal lymph node architecture. Moreover,

gp106 staining of many abnormal histiocytes within distended sinuses was observed, with an intense granular positive reaction in the cytoplasm, while weak positivity was observed for both antibodies in few plasma cells. In comparison, the lymph node biopsies from five cases of florid follicular hyperplasia, four cases with a predominantly paracortical lesion, four cases with sinus histiocytosis, and one histiocytic necrotizing lymphadenitis were all HHV-6 positive by PCR, but only isolated plasma cells and histiocytes, most often scattered in interfollicular areas, were positive for late antigens by IHC (<1% of cells in the lymph node).<sup>85</sup> Few granulocytes were positive in the dilated sinuses of 2/4 cases with sinus histiocytosis. HHV-6B late antigen was also found by IHC in the lesion of a young boy with extranodal renal RD, a rare manifestation of the disease.<sup>92</sup> It may be the case that only a subset of RD cases are associated with HHV-6,<sup>93</sup> but the distinctive pattern of late antigen expression, indicating active infection in the follicular dendritic cells of germinal centers argues for the involvement of reactivated HHV-6 in the development of some cases of RD, especially as the pattern was later identified among patients with chronic/recurrent lymphadenopathy.<sup>88</sup>

**Kikuchi-Fujimoto Disease.** Viral etiology has been investigated in Kikuchi-Fujimoto disease (KFD), another self-limited benign disorder. Reactivation of HHV-6 has been determined serologically<sup>94,95</sup> during the course of KFD, and affected lymph nodes have been found to harbor HHV-6 DNA.<sup>94</sup> However, few studies have performed testing for HHV-6, and not all data has supported involvement of the virus. Twenty lymph nodes tested for both EBV and HHV-6, for instance, did not reveal any positivity via PCR.<sup>96</sup> Similarly, only 1/18 lymph node biopsies from another study were HHV-6 positive by PCR- as were 2/18 control lymph nodes from asymptomatic patients with papillary thyroid carcinoma who had not received chemo/radiotherapy, 1 patient with Warthin tumor, and 2 cases of paraganglioma.<sup>97</sup> An earlier study found that the lymph nodes of all but one patient were PCR positive, and all samples tested by ISH were positive as well. On the other hand, the positivity by ISH was not limited to these specimens but was also present in patients with reactive paracortical hyperplasia (60%), nonspecific lymphadenitis (60%), and tuberculosis

lymphadenitis (22.2%).<sup>98</sup> Because it is often difficult to procure tissue samples from healthy persons, it is important to note that HHV-6 could contribute to illnesses affecting controls or may reactivate in response to an illness, which may complicate analysis of the role of HHV-6. This obstacle, as well as variation in assays, carries the potential to skew the interpretation of results.

**Ocular Lymphoproliferation.** Several herpesviruses, including HHV-6, have been isolated from ocular tissue removed from patients with lymphoproliferative disorders. Whereas malignant orbital and conjunctival tissues were infrequently positive for the virus,<sup>99</sup> 23% (mean viral load  $1.7 \times 10^3$  copies/microgram DNA) of samples from IgG4-related ophthalmic disease and 43.9% of samples from reactive lymphoid hyperplasia of the ocular adnexa were HHV-6+. HHV-6A<sup>100</sup> and HHV-6B<sup>101</sup> have been linked to ocular inflammation, perhaps through persistent reactivation and stimulation of immune cells.

#### **Atypical/Unusual Lymphoproliferative Disorders and Lymphocytic Infiltration.**

Atypical lymphoproliferative disorders are characterized by extensive lymphoma-like persistent and/or progressive lymphoproliferation, which, while still polyclonal, may progress to open malignant lymphoma. It may thus be considered a pre-lymphomatous condition.<sup>11</sup> HHV-6 has been cited as a trigger for atypical polyclonal lymphoproliferation,<sup>11,21</sup> although it is more commonly involved in non-neoplastic lymphocytosis with lymphocytes that are often labeled “atypical” but do not show potential for malignant transformation, such as those frequently observed during infectious mononucleosis (IM)-like illnesses. The virus has been detected in reactive CD4+ lymphocytes characteristic of these illnesses,<sup>102</sup> which, though ultimately not malignant, can strongly resemble lymphoma.<sup>103</sup> Specifically, HHV-6 has been localized to CD3+ and CD4+ T cells in the lymph node, characterized by intranuclear eosinophilic viral inclusions and bearing resemblance to lymphocytes present in Hodgkin’s lymphoma and anaplastic large cell lymphoma. Large reactive lymphocytes with a sinusal and paracortical distribution have been found among eosinophils, plasma cells, and scattered immunoblasts.

**Infectious Mononucleosis.** HHV-6 has been implicated in the pathogenesis of a subset of infectious mononucleosis (IM)-like illnesses, as indicated by serologic evidence of active infection and increased HHV-6 specific IgG titers in the absence of active EBV or CMV infection.<sup>10,104-106</sup> Coinfections of HHV-6 and EBV also occur during IM and could exacerbate the symptoms/disease course.<sup>10</sup> While the absolute prevalence is unclear, HHV-6 was specified as the etiological agent in 5% of 40 adults with IM-like illnesses in Japan, after PCR analysis.<sup>107,108</sup> As is often the case during EBV-mediated IM, HHV-6-associated IM-like conditions have been associated with fatigue, lymphocytosis, thrombocytosis, migrating lymphadenopathy, headaches, fever, maculopapular rash, and hepatosplenomegaly with raised liver enzymes, increased immature lymphoid cells, PBMC death,<sup>109-111</sup> and “atypical” T lymphocytosis coinciding with HHV-6 antigen expression.<sup>111</sup> The effects of reactivation may persist even after resolution of active infection; in patients with active HHV-6A and IM, the viral DNA load in blood peaks within 4 weeks and returns to normal by 16 weeks, while prolonged T lymphocytosis decreases to normal levels by 24-28 weeks.<sup>112</sup>

HHV-6B and untyped HHV-6 DNA has been detected in the serum, lymph nodes, and CD4+ T cells of skin tissue characterized by “atypical” infiltrating CD4+ and CD8+ T cells, by PCR, IHC, Southern blot, and ISH.<sup>113-115</sup> Examination of lymph node tissue revealed transformed lymphocytes and immunoblast-like cells, some of which were positive for HHV-6, in addition to some histiocytes and eosinophils. Of interest, instances of HHV-6-associated IM have been significantly associated with Downey type III lymphocytes (i.e. monocytoid blasts with basophilic cytoplasmic granules,<sup>108,116</sup> and it appears that this type of IM may present with certain manifestations relatively unique to HHV-6.

The resulting lymphoproliferation observed during HHV-6-associated IM-like illnesses has been posited to stem from a response by CD8+ T cells against HHV-6-infected CD4+ T cells;<sup>113</sup> analysis of the PBMC composition has identified 35.7% of cells as CD4+ and 52.6% as CD8+. HHV-6-specific T cells consist of CD4+ and CD8+ cells, but in patients with acute HHV-6 infection, CD8+ cells may predominate for several

months after an initial spike in the CD4+/CD8+ ratio.<sup>88,117</sup> Taking into consideration the time-dependent nature of these changes in cellular populations, computer models have illustrated that acute HHV-6 infection can raise the CD4+/CD8+ T cell ratio initially, but there is a subsequent sharp decrease as CD4+ cells are removed and CD8+ cells proliferate.<sup>117</sup> Once HHV-6 has infected lymphocytes, the maturation and function of the cells are altered. During acute infection, this may manifest as an infectious mononucleosis-like illness, while during chronic persistent infection, chronic fatigue-type cellular changes have been observed, as has persistent immature lymphocytosis similar to that seen in Canale-Smith syndrome.<sup>118</sup>

*Hemophagocytic Syndrome/Hemophagocytic Lymphohistiocytosis.* Hemophagocytic syndrome/hemophagocytic lymphohistiocytosis (HLH), a hyperinflammatory disease marked by activation of T lymphocytes and macrophages and driven by overproduction of cytokines, may result from infection by herpesviruses, including EBV, CMV, and HHV-6, and at times, more than one virus.<sup>119,120</sup> Systemic manifestations during HHV-6-induced HLH, including CNS dysfunction, respiratory distress, multiorgan failure, and disseminated intravascular coagulation, are often severe and can be fatal.<sup>119,121-124</sup> While HLH linked to reactivation of HHV-6 has occurred in patients with underlying conditions, it has also occurred in seemingly healthy individuals.<sup>122</sup> Notably, reactivation is not the only avenue for development of hemophagocytosis and HLH, as both localized and systemic hemophagocytosis can also occur during infancy, and in some cases, it is likely a complication of primary infection.<sup>125-127</sup> As in adults, some children who develop HHV-6-associated HLH may be predisposed to the syndrome due to underlying disorders, including Wiedemann-Beckwith syndrome<sup>124</sup> and beta-thalassemia.<sup>128</sup>

*Hepatitis and Liver Dysfunction.* During HHV-6 reactivation post-transplant, hepatitis and liver dysfunction may develop. Randhawa *et al.* reported a case of HHV-6A-associated gastroduodenitis, pancreatitis, and hepatitis in an adult heart transplant recipient<sup>129</sup> with concomitant multinucleate giant cell transformation observed in biopsies, and in another instance, giant cell

hepatitis presumably caused by HHV-6A was observed in a liver transplant recipient.<sup>130</sup> Both species of HHV-6 have shown cell-cell fusion capabilities *in vitro* in lymphocytes and other cells, although the response is more robust for HHV-6A.<sup>21,131,132</sup> Cell fusion events and polyploidy are associated with malignancies and metastasis.<sup>133</sup> HHV-6 infection has also been associated with an increased number of liver allograft infiltrating lymphocytes expressing class II antigens, LFA-1, and VLA-4,<sup>134</sup> and less commonly, the virus is found in liver tissue from immunocompetent patients with hepatitis<sup>135-137</sup> and multiple organ failure.<sup>138</sup> Among patients with HHV-6-associated liver dysfunction, “atypical” activated lymphocytes may be present in both the blood and infiltrating lymphocytes of the liver.<sup>139</sup>

*DIHS/DRESS.* Perhaps the deleterious effects of HHV-6-mediated lymphocytic infiltration are exemplified best by severe DIHS/DRESS, a condition that can mimic malignant lymphoma<sup>140-142</sup> characterized by erythematous rash, organ dysfunction, and occasionally organ failure.<sup>143</sup> High level HHV-6 viremia is often found in these patients, and HHV-6 DNA and antigen has been detected in the CSF of patients with encephalitis and hemophagocytosis,<sup>143,144</sup> the livers of patients with hepatitis and liver failure,<sup>143,145</sup> the kidneys of patients with renal dysfunction and failure,<sup>146,147</sup> and the bone marrow of patients with hemophagocytic syndrome.<sup>148,149</sup> HHV-6 is thought to contribute to the clinical manifestations of DIHS/DRESS, especially the atypical lymphocytosis,<sup>150</sup> lymphadenitis,<sup>141</sup> and multiorgan involvement, and viremia is predictive of a more severe course and flaring of symptoms, including hepatitis and fever,<sup>151</sup> as is hemophagocytosis.<sup>140</sup> Additionally, administration of valganciclovir has improved the condition of patients with severe DIHS/DRESS.<sup>143,147,149</sup> HHV-6 has been found in hepatocytes<sup>143,145,152</sup> and tubular epithelial cells of the kidney,<sup>146,147</sup> as well as in infiltrating lymphocytes, often atypical.<sup>141,148,152</sup> Notably, the detection of HHV-6 in these cells has corresponded to severe necrosis and dysfunction in the related organs.

In addition to triggering lymphocyte infiltration into organs in DIHS/DRESS, HHV-6 appears to disrupt the properties and functions of lymphocytes during and after the reaction. Laboratory findings include lymphopenia or

lymphocytosis, the presence of “atypical” hyperbasophilic lymphocytes, and sometimes hypogammaglobulinemia, leukocytosis and thrombocytopenia.<sup>153</sup> Infiltrating atypical lymphocytes may be detected in tissue samples, and atypical lymphocytosis is present in 27-67% of DIHS/DRESS patients.<sup>154</sup> Strikingly, in one study<sup>142</sup> HHV-6 antigen was found to be exclusively localized to the Reed-Sternberg-like cells of the lymph node, and the cells exhibited loss of CD3 expression. In a similar study, HHV-6 was reportedly present in the majority of large infiltrating atypical lymphocytes with prominent nuclear inclusions in lymph node biopsies by ISH and IHC for p41 early antigen and DR6 and p101k late antigens, and again, there was partial loss of CD3 expression.<sup>141</sup> As in cases of persistent lymphocytosis with plasmablastoid and Downey-type cells in generalized lymphadenopathy and IM, both cytoplasmic<sup>152</sup> and intranuclear (**Figure 2**)<sup>148</sup> viral inclusions with a peripheral halo in CD3+CD4+ atypical T cells in the lymph node have been reported in DIHS/DRESS. In the latter case, the cells displaying positivity to HHV-6 antibodies appeared to be Tregs, which are thought to be important in the pathogenesis of DIHS/DRESS, as well as the development of autoimmunity after resolution of the syndrome, when Treg activity is suppressed and Th17 cells increase in number significantly.<sup>153</sup> *In vitro* testing indicates that HHV-6A<sup>154</sup> and HHV-6B<sup>155</sup> can induce virus-specific Tregs.

*Castleman’s Disease.* Case reports and some larger studies have found HHV-6 in the blood and lymph nodes of patients with Castleman’s disease (CD) by PCR.<sup>156</sup> When the virus identified in lymph node biopsies was typed in two cases, it corresponded to HHV-6B, and viral loads were 5.5 and 53.7 copies/microgram DNA.<sup>157</sup> In a larger cohort, 2/16 (12%) CD patients, both of multicentric mixed-type CD, were HHV-6 positive by PCR in involved tissues, although they were also positive for EBV, with a total of 9 EBV+ samples.<sup>158</sup> As low-level, latent HHV-6 may be found in healthy individuals, both in tissue and in blood, it is unclear whether these results implicate HHV-6 in the development of CD.

### **Malignant Lymphoproliferation.**

*Hodgkin’s Lymphoma.* Interesting data has been reported on the possible involvement of HHV-6 in the nodular sclerosis (NS) subtype of Hodgkin’s lymphoma (HL) (**Figure 3**). Early results finding HHV-6 antigens p41 and gp116/64/54 in Hodgkin’s disease and Reed Sternberg (RS) cells in 37% of biopsies led investigators to hypothesize that the virus might contribute to HL through dysregulation of the cytokine network and through polyclonal stimulations of cellular proliferation.<sup>159</sup> Further investigation revealed the absence of HHV-6 DNA by Southern blot, even when positive by PCR, absence of the virus in neoplastic cells, and no antigen expression by IHC (for gp102, p41, and P11G1-G9C7), with the exception of 2/2 cases of NSHL with interfollicular pattern, which were positive for HHV-6 MAb in residual germinal centers.<sup>160</sup> Along the same lines, HHV-6 early antigen p41 was not observed in viable RS cells from lymph nodes positive by PCR in a later study, but “mummified” RS cells did show positivity in the two cases with the highest copy numbers.<sup>85</sup> Later studies, however, detected HHV-6 in lymph nodes of 41.9% of NSHL lymph nodes at a mean viral load of 6,711.4 copies/microgram DNA, 12/13 of which were typed as HHV-6B, while tissues from 6 patients with other HL subtypes were negative.<sup>161</sup> The detection of HHV-6 DNA in NSHL cases spurred further examination of additional lymph nodes, and in another cohort, the virus was identified in a majority (83.6%) of tumor samples from patients with NSHL, the predominant type of HL in the group.<sup>162</sup> EBV coinfections accounted for 49.3% of total NS cases, and in coinfecting tissues, viral loads of EBV and HHV-6 were higher than in the specimens with a single infection (mean 47,666.5 copies HHV-6/microgram DNA in NS cases vs. 271.4 copies/microgram DNA), suggesting either an immunosuppressive environment favoring viral reactivation, or potentiation of viral replication through simultaneous activity. In the same study, HHV-6 was also found among 5/10 patients with mixed-cellularity HL, one of two lymphocyte-depleted HL, and in the only patient with lymphocyte-predominance HL.

Using IHC with antibody that appears to be reactive to both HHV-6 species, the same team later targeted the DR7 oncoprotein, a product of the ORF-1 gene that is able to bind and inactivate the tumor suppressor p53,<sup>163</sup> which was found in the Reed-Sternberg (RS) cells of 74% of EBV-

Figure 2A

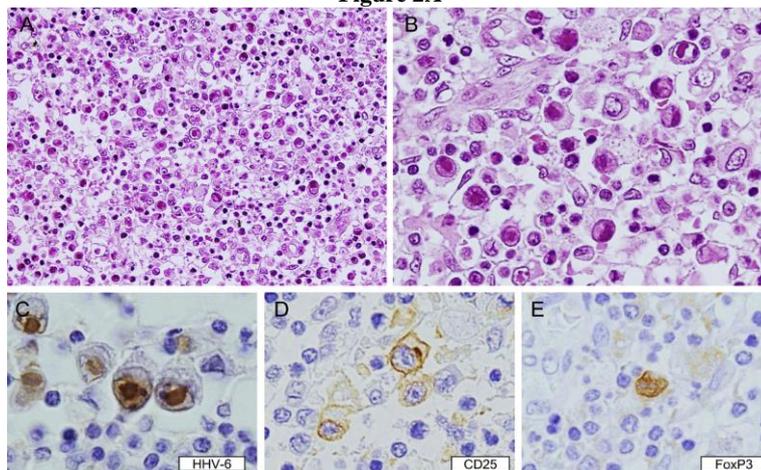
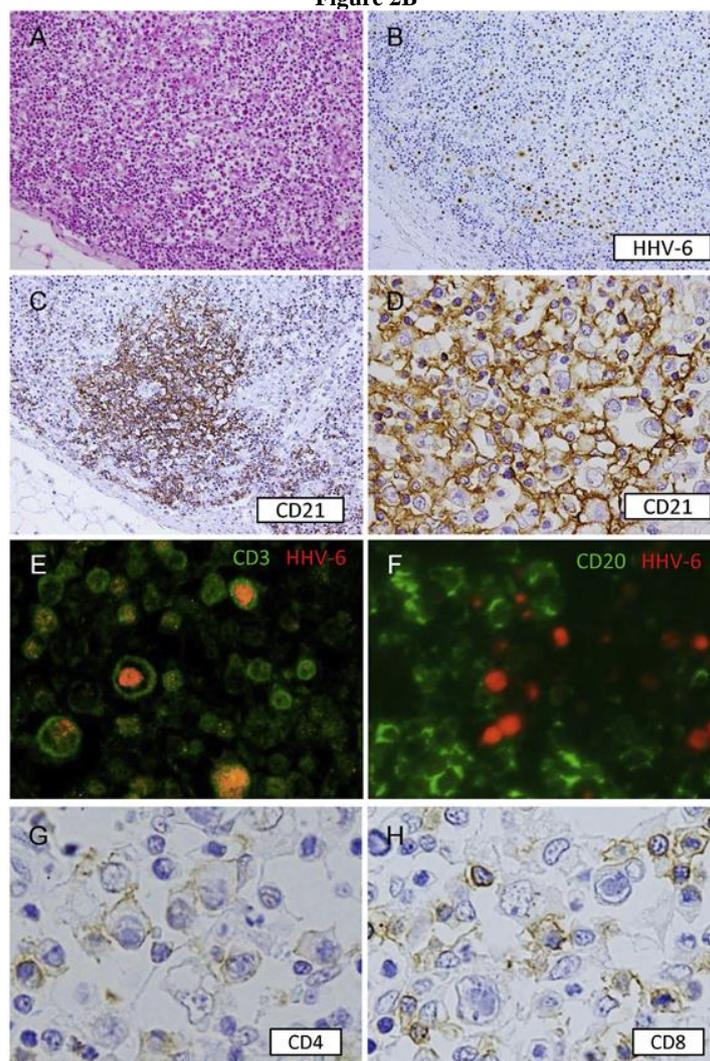


Figure 2B



**Figure 2. HHV-6 in drug induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms.**

**A. Histopathology and immunohistochemistry of the lymph node.** (A and B) Hematoxylin and eosin staining. Low (A) and high (B) magnification views of the cervical lymph node showed diffuse infiltration of large and blastic lymphoid cells with inclusion bodies. Intranuclear inclusion bodies were eosinophilic and had a halo (B). (C–E) Immunostaining. The large cells with intranuclear inclusion bodies were positive for HHV-6-IE (C). The HHV-6-infected cells were positive for CD25 (D) and FoxP3 (E)(Mine et al. 2014).<sup>148</sup>

**B. Histopathology and immunohistochemistry of the lymph node.** At the cortex of lymph node, large and isolated cells were seen with hematoxylin-eosin staining (A). Many of these isolated cells were positive for HHV-6-IE and were scattered throughout the nodule (B). CD21 immunostaining showed follicular dendritic cells that presented a mesh-work like structure (C and D), in contact with several of the large lymphocytes with inclusion bodies (D). Double immunofluorescence staining showed HHV-6-IE positive cells expressing CD3, but not CD20 (E and F). Immunostaining showed that the large lymphocytes with inclusion bodies were CD4(+) and CD8(-) (G and H)(Mine et al. 2014).<sup>148</sup>

Figure 3A

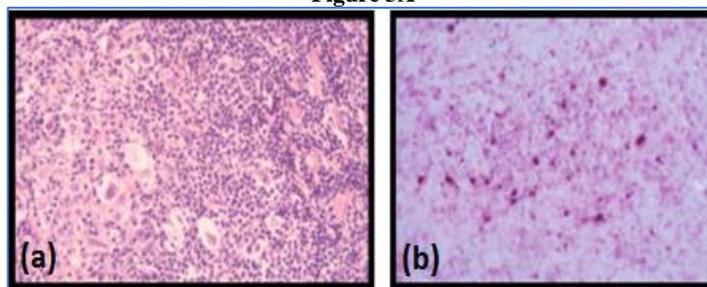


Figure 3B

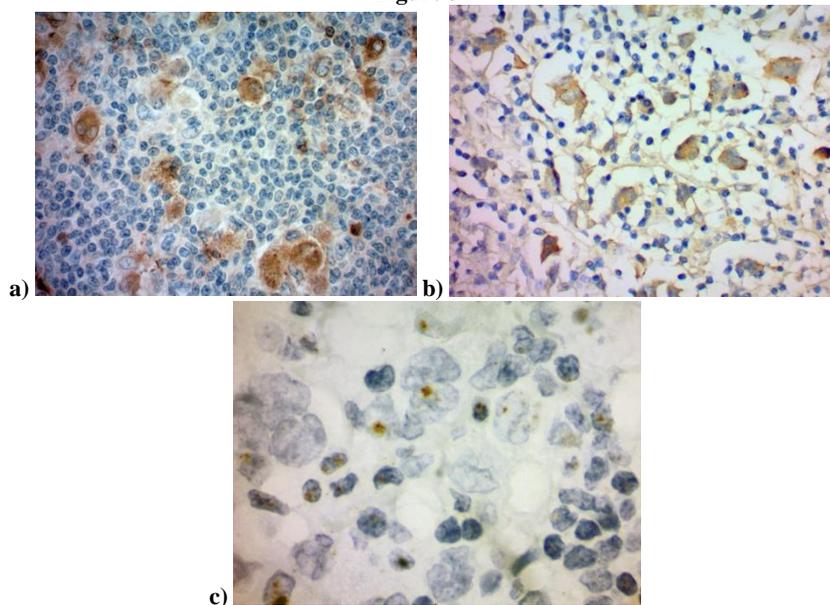
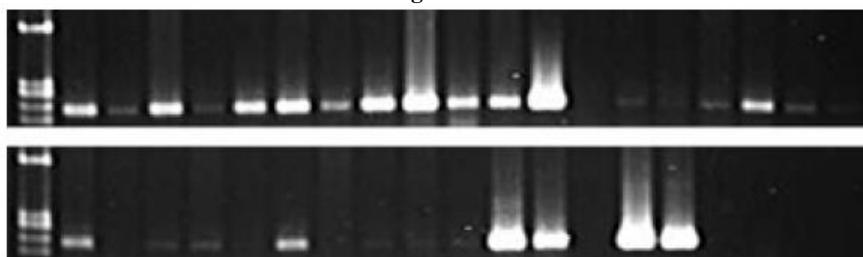


Figure 3C



**Figure 3. HHV-6 in Hodgkin's lymphoma.**

**A. a) HHV-6A in nodular sclerosing Hodgkin's lymphoma.** Hodgkin's lymphoma, nodular sclerosing type: Left, H&E histology. Original magnification x250; b) Right HHV-6 DNA (in situ hybridization pZVH14). Original magnification x250. pZVH14 probe used was designed by and obtained from Dr. Steve Josephs at NCI/NIH. It was obtained from HHV-6A (GS Strain), and was also cross-hybridizes with HHV-6B. Probe was labelled with alkaline phosphatase, and the APAAP reaction was used (APAAP: alkaline phosphatase anti alkaline phosphatase) to visualize its tissues were subjected to in-situ-hybridization. The reaction was sensitive and highly specific as repeatedly proven by isolating HHV-6A in HSB2 cells (isolation in MOLT3 cells for HHV-6B remained negative) (With permission from G. Krueger et al.).

**B. a) Presence of HHV-6 p41 by immunohistochemistry.** Cytoplasmic staining of numerous large cells using a monoclonal antibody to HHV-6 p41 (3E3 clone) among NSHL specimens.

**b). HHV-6 U94 detection by immunohistochemistry.** Staining with monoclonal antibody to HHV-6 U94 reveals positivity in the cytoplasm of numerous large cells.

**c). Presence of HHV-6 by colorimetric in-situ hybridization.** HHV-6 DNA present in the nuclei of both small and large cells. (With permission from Dr. David Hudnall, Yale University, New Haven, CT, USA).

**C. HHV-6 U94 PCR of Hodgkin's lymphoma.** Twenty seven of 31 (87%) HL cases were positive for HHV-6 using primers to the U94 gene. The 19 lanes in the top gel are loaded with PCR product from 19 cases of HL. The 19 lanes in the bottom gel are loaded (from left to right) with PCR product from an additional 12 cases of HL, one empty lane, two positive controls (HHV-6A, HHV-6B), one empty lane, a negative (water) control, and two empty lanes. Viral load appears to vary tremendously from case to case - in 14 cases the viral load is quite high, while in another 13 cases the viral load is very low (Siddon et al. 2012).<sup>165</sup>

negative HL patients whose lymph nodes had previously been found HHV-6 positive by qPCR (n=38; 36 NSHL).<sup>164</sup> The protein was exclusively

localized in RS cells, which were CD30+, in 61% of cases. Similarly, exclusive staining for DR7B in RS cells was observed in 6/9 NSHL cases that

were both EBV and HHV-6+. The three remaining cases showed positivity in RS and infiltrating cells, and all nine showed positivity for LMP-1, an EBV oncoprotein. A tenth EBV/HHV-6+ patient with mixed-cellularity HL only stained for LMP-1 in RS cells, while DR7B was only identified in infiltrating cells. RS cells were positive for gp116/64/54 in 15 EBV negative patients. Notably, positive staining of gp116/64/54 was observed significantly more frequently ( $p=0.0154$ ) among patients with stage III and IV HL compared to those at stages I and II.

Via PCR, the prevalence of HHV-6 in 31 additional NSHL lymphoid samples was similar to the rate of detection among tissues from patients with reactive lymphoid hyperplasia (87% vs 83%, respectively).<sup>165</sup> However, IHC analysis revealed HHV-6 whole lysate in numerous RS cells in 48% of cases, and early and late antigen was also found in scattered RS cells. Multiple copies of the virus were present in some RS cells, suggesting that active replication was taking place. Of the samples that were typed, HHV-6B was present singly in 3 cases, HHV-6A was present in 4, and HHV-6A/B coinfection was found in 3. EBV was detected in a total of 5 cases of 21 tested, and EBV/HHV-6 coinfections were detected in RS cells of 3. Of interest, the mean age of patients with HHV-6+ RS cells was 23 years, while those with EBV+ RS cells had a mean age of 47 years ( $p=0.073$ ). While examination of more cases of mixed cellularity HL is warranted, currently, immunohistochemical findings most strongly suggest that an association may exist between HHV-6 and the NS subtype of HL.

*Non-Hodgkin's Lymphoma.* As HHV-6 was initially isolated from HIV+ patients with malignancies, including non-Hodgkin's lymphoma (NHL), several early studies focused on this population, finding the virus in 4.8-32% of tumor samples.<sup>13,14,84,166</sup> Direct HHV-6-mediated oncogenic activity has not been observed in NHL,<sup>11</sup> and the viral antigen has not been found in the neoplastic cells,<sup>85</sup> but rather, it has been found to be present in infiltrating cells of affected tissues as well as in blood samples.<sup>167</sup> However, evidence suggests that the virus may act in conjunction with other oncogenic agents, including other viruses, to modulate the lymph node microenvironment and contribute to the characteristic lymphocytic proliferation.<sup>85</sup> Case reports, for instance, have

documented a potential interaction between HHV-6 and HHV-8 in diffuse large B-cell lymphoma (DLBCL). Upon analyzing affected tissues of two patients, one with nongerminal B-cell-like DLBCL and the other with primary cutaneous DLBCL, HHV-6 and HHV-8 were simultaneously present in the nucleoli of lymphoma cells. Notably, HHV-6 has shown the capacity to induce expression of HHV-8 lytic phase mRNA and proteins in BCBL-1 cells.<sup>168</sup> Of interest, HHV-6B was also identified among 30.8% of a collection of DLBCL lymph nodes at a mean viral load of 1,140.7 copies/microgram DNA.<sup>161</sup> In comparison, 23.1% of follicular lymphoma samples were positive, but the mean copy number was only 39, and of the other NHL lymphomas tested, only 1 (of 4) peripheral T-cell lymphoma had over 91copies/microgram DNA, with 3,380 copies. In a similar study, 3/5 T-cell lymphoma lymph nodes were HHV-6 (2 HHV-6B, 1 unclassified) positive, with viral loads of 9.1, 60.4, and 810 copies/microgram DNA.<sup>157</sup>

Similarly, EBV coinfections have frequently been observed in HHV-6+ NHL lymphoid biopsies;<sup>169-171</sup> one study, for example, found 57% of HHV-6+ angioimmunoblastic T cell lymphoma/angioimmunoblastic lymphadenopathy (AITL/AILD) lymph nodes to be coinfecting with EBV.<sup>172</sup> In a separate cohort, 79% of HHV-6B+ lymph nodes were EBV+, with the highest HHV-6B viral loads in biopsies with pattern III histology (median 40 copies/1000 cells).<sup>19</sup> Moreover, all of the coinfecting samples showed pattern II or III histology, with the majority falling under pattern III. However, expression of HHV-6 antigens in proliferating T lymphocytes of AILD patients has not been observed.<sup>85</sup>

An inherited, chromosomally integrated form of either HHV-6A or HHV-6B, known as ciHHV-6 or iciHHV-6, is present in about 1% of the population. Two intriguing case reports have documented ciHHV-6+ patients with NHL: One patient, with DLBCL and ciHHV-6 on chromosome 17p, developed marker chromosomes that were also ciHHV-6+,<sup>173</sup> while the other individual, who carried ciHHV-6A on chromosome 19q, developed a primary effusion-like lymphoma characterized by an absence of any integrated HHV-6.<sup>174</sup> It is possible that ciHHV-6 may have the potential to trigger lymphoma by affecting chromosomal stability.

*Lymphocytic Leukemia.* Although HHV-6 has been detected in the blood<sup>175-176</sup> and bone marrow of patients with lymphocytic leukemia, and heightened titers of HHV-6 antibody have been observed in blood samples,<sup>177-179</sup> a role for the virus in this type of cancer is not well supported. In contrast with a later publication,<sup>180</sup> one study found high rates of HHV-6A in blood and bone marrow samples- 43.8% of B-ALL samples, 52.4% of B-CLL samples, and only less than 10% of MM.<sup>181</sup> HHV-6 p41 antigen has been detected in nearly half of bone marrow samples from patients with myelodysplasia by IHC,<sup>182</sup> but in cases of leukemia, detection of HHV-6A/HHV-6B in the bone marrow only by nested PCR and not via standard PCR, or at low copy numbers by qPCR,<sup>175</sup> has suggested that HHV-6 present in the samples is likely latent.<sup>183</sup> Moreover, when quantified, viral loads both in blood and in bone marrow, have been found to be lower at diagnosis than at remission.<sup>175,180,181</sup> As the virus can infect bone marrow progenitors and reactivate under immunosuppressive conditions, the presence of the virus as it was detected in these instances likely did not impact the course of leukemia.

**Discussion.** The interactions of chronic active HHV-6 infection with the immune system may result in a variety of clinical diseases including aplasia, autoimmune disorders (e.g. Sjögren's syndrome, lupus erythematosus, scleroderma), and lymphoproliferation. These manifestations reflect the disturbed balance between viral persistence and the host's defense status.<sup>184,185</sup> The current overview focuses only on lymphoproliferative disorders in order not to further complicate the report.

HHV-6 may contribute to several benign/reactive lymphoproliferative disorders by spurring a dysfunctional immune response or through dysregulation of cytokines and other immune mediators. It is probable that HHV-6A and HHV-6B are two of many potential triggers

for these disorders, but immunohistochemical analysis may reveal characteristic patterns of viral expression and cellular features in cases associated with either virus. As more instances of HHV-6 associated lymphoproliferation are described, clinical parameters might also be found that are indicative of HHV-6 involvement. Both primary infection and reactivation are able to induce "atypical" lymphocytosis, in which activated cells may appear abnormal and may even resemble transformed, malignant cells. Under some circumstances, HHV-6A/HHV-6B are also capable of inducing organ dysfunction, with lymphocytic infiltration often observed in the affected organs. Because both species of HHV-6 can infect a variety of cells, active infection in tissues may result in an immune response toward the infected tissues, resulting in lymphocytic infiltration, or active infection of lymphocytes may trigger an inflammatory reaction and drive lymphocytic infiltration directly. Although a role for HHV-6 in many lymphomatous malignancies is not strongly supported, evidence points to a potential contribution of the virus in certain Hodgkin's lymphomas of the nodular sclerosis type. The wider use of quantitative PCR and immunohistochemical techniques has enabled more accurate interpretation of viral involvement in lymphoproliferative conditions, and the continued utilization of these techniques will be vital to expanding the knowledge of their association between HHV-6 and these disorders, as well as uncovering the mechanisms behind them. Ultimately, further research is needed to elucidate the immunomodulatory capabilities of HHV-6A and HHV-6B as they relate to the functionality of lymphocytes and to better define their roles in lymphoproliferative diseases, both during acute infection and persistent reactivation.

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