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Kaposi sarcoma–associated herpesvirus/human herpesvirus 8–associated lymphoproliferative disorders

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Kaposi sarcoma–associated herpesvirus/human herpesvirus 8 is associated with multicentric Castleman disease (MCD) and primary effusion lymphoma (PEL). In MCD, infected B cells, although polyclonal, express a monotypic immunoglobulin Mλ phenotype, probably through editing toward λ light chain in mature B cells. They are considered to originate from pre–germinal center (GC) naive B cells. Both viral and human interleukin-6 contribute to the plasmacytic differentiation of these cells, and viral replication can be observed in some infected cells. PEL cells are clonal B cells considered as GC/post-GC B cells. One can also hypothesize that they originate from the same infected naive B cells and that additional factors could be responsible for their peculiar phenotype. (*Blood*. 2019;133(11):1186-1190)

Introduction

Kaposi sarcoma (KS)-associated herpesvirus/human herpesvirus 8 (KSHV/HHV-8) has been identified from a KS lesion in an AIDS patient in 1994.[1] Subsequently, this new virus was associated with a wide spectrum of B-cell lymphoproliferative disorders (LPDs): multicentric Castleman disease (MCD),[2] primary effusion lymphoma (PEL),[3-5] and posttransplant[6] and germinotropic LPDs (GLPDs).[7] Little is known about the natural history of KSHV/HHV-8 infection in humans and, specifically, how this virus establishes a reservoir for latency and how KSHV/HHV-8–infected normal B cells can progress toward aggressive LPD.

De novo infection with KSHV/HHV-8

In vitro models of tonsillar B-cell infection may recapitulate the initial steps following contamination through saliva contact.[8,9] Infection of primary tonsillar cells reveals that KSHV/HHV-8 can initially infect various cellular subtypes with activation of an early and transient prelatent "lytic burst" transcription program. Within a few days, although KSHV/HHV-8 infects both κ and λ naive B cells, a phenotype shift occurs through reinduction of Rag-mediated V(D)J recombination toward B cells expressing both κ and λ light chains and, ultimately, only naive IgMλ B cells.[9] By day 5, KSHV/HHV-8$^+$ cells undergo blasting and proliferation. Both human and viral interleukin-6 (IL-6) appear to be involved in the extrafollicular maturation of infected B cells with possible acquisition of an immunoglobulin D–positive (IgD$^+$)CD27$^+$ phenotype characteristic of the IgM memory or marginal-zone–like B lymphocytes, and/or evolution toward the IgM^{hi}CD38$^+$ plasmablastic phenotype observed in infected cells from MCD.[8-10]

Multicentric Castleman disease

KSHV/HHV-8–associated MCD occurs in patients with or without HIV infection.[11,12] In the absence of HIV infection, KSHV/HHV-8–associated MCD is mainly observed in populations with a high prevalence of KSHV/HHV-8 infection such as men who have sex with men and populations originating from central or sub-Saharan Africa. MCD is a B-cell LPD characterized by inflammatory flares, including fever, lymphadenopathy, splenomegaly, effusions, cytopenia, hypoalbuminemia, hypergammaglobulinemia, and high serum C-reactive protein.[13] In the absence of appropriate therapy, a rapid evolution toward multiple organ failure or hemophagocytic syndrome is associated with poor outcome.[14]

Using immunohistochemistry for KSHV/HHV-8 latent nuclear antigen-1 (LANA-1), it was shown that infected cells are isolated cells in the mantle zone of B-cell follicles.[15] In a very few cases, these cells can be Epstein-Barr virus (EBV) coinfected.[16] These cells exhibit characteristics of B cells undergoing plasmacytic differentiation and have been considered as plasmablasts.[15] They show high levels of cytoplasmic immunoglobulin (remarkably always IgMλ); express CD38, multiple myeloma oncogene 1/interferon regulatory factor (MUM1/IRF4), and B lymphocyte-induced maturation protein-1 (BLIMP1); and are commonly negative for CD20, PAX5, CD30, and the plasma cell marker CD138.[16] Despite the fact that KSHV/HHV-8$^+$ plasmablasts are monotypic, exclusively expressing IgMλ, they have been shown by analysis of immunoglobulin gene rearrangement to be polyclonal in nature.[17] In line with this, KSHV/HHV-8 episomes in MCD are polyclonal.[18] Phenotypically, these plasmablasts resemble mature B cells, but they usually do not express CD27, a marker for memory B cells, and lack somatic mutations in the rearranged immunoglobulin

heavy and light chain genes, indicating that they originate from pre–germinal center (GC) B cells.[19] KSHV/HHV-8 drives them to differentiate into plasmablasts without going through the GC reaction, a critical process for normal B-cell maturation. Most of the symptoms observed during MCD flares appear to be cytokine-related, involving IL-6, HHV-8 IL-6 (vIL-6), and IL-10.[20,21] Interestingly, some patients present with a KSHV inflammatory cytokine syndrome with severe inflammatory symptoms, high KSHV/HHV-8 viral load, and high serum levels of these cytokines, but without demonstration of lymph nodes showing Castleman morphology.[22]

KSHV/HHV-8$^+$ diffuse large B-cell lymphoma

Some patients with MCD develop an aggressive disease with rapid enlargement of the spleen and, in some cases, a "leukemic phase," sharing the morphology and phenotype of the plasmablasts observed in Castleman lesions.[15] Some of these proliferations are monoclonal and considered as KSHV/HHV-8$^+$ diffuse large B-cell lymphoma (DLBCL)[23] or in some cases as solid PEL.[14] However, despite an aggressive clinical presentation and the circulation of large numbers of plasmablastic cells, some cases are polyclonal and can be treated with a conservative rituximab-containing regimen.[24]

Primary effusion lymphoma

PEL typically presents as effusions in the pleural, pericardial, or abdominal cavities, although solid/extracavitary lesions are possible.[4,25] The lymphoma cells are pleomorphic with features of large immunoblastic, plasmablastic, or anaplastic cells[4]; express CD45; but are usually negative for B-cell markers such as CD19, CD20, CD79a, and PAX5. Most cases express HLA-DR; activation markers such as CD30 and CD38; and markers associated with plasma cell differentiation such as CD138, MUM1/IRF4, and BLIMP. They may exhibit aberrant expression of CD3, CD2, CD4, or CD5.[26] In most cases, at least in HIV-infected patients, the neoplastic cells are coinfected with EBV exhibiting a restricted latency pattern.[27] PELs show evidence of rearranged immunoglobulin genes and high levels of somatic mutations.[28] These findings suggest that this lymphoma is likely to derive from a transition stage from antigen-selected GC B cells to terminally differentiated post-GC plasma cells.

HHV-8$^+$EBV$^+$ germinotropic LPD

GLPD is a very rare condition, usually presenting as a localized lymphadenopathy in an asymptomatic, immunocompetent, or HIV-infected patient.[7,29] Lymph node biopsy shows GC expansion by an atypical plasmablastic cell population showing dual positivity for KSHV/HHV-8 and EBV. Interestingly, most cases show Castleman-like changes with marked plasmacytosis. Infected cells are positive for MUM-1/IRF-4 and lack expression of CD20, CD79a, PAX5, BCL6, CD10, and CD30. They may exhibit aberrant expression of CD3, as it can be observed in some PEL cells. Like MCD, GLPD lacks evidence of monoclonality at the molecular level. However, only GLPD is coinfected by both KSHV/HHV-8 and EBV, a finding that overlaps with PEL.[29]

Posttransplant KSHV/HHV-8–associated LPD

Posttransplant primary KSHV/HHV-8 infection can be either asymptomatic or associated with disseminated KS, sometimes with an acute syndrome of fever, splenomegaly, cytopenia, and marrow failure with plasmacytosis or hemophagocytic syndrome.[6] These features are very similar to that observed in MCD or KSHV inflammatory cytokine syndrome and highlight the overlap between what can be considered as an acute infectious disease and the spectrum of posttransplant LPD.

Major questions to which we have only partial answers

Why do KSHV/HHV-8–infected B cells, although polyclonal, express a restricted monotypic IgMλ phenotype?

Using a model of in vitro infection of tonsillar B cells, it has been shown that very early infection with KSHV/HHV-8 could affect all B-cell subsets, including cells expressing the κ light chain, but that after a few days, the only surviving infected cells exhibit a restricted IgMλ phenotype.[8] KSHV/HHV-8 does not preferentially target IgMλ naive B cells, but infection of IgMκ naive B cells induces expression of Igλ and isotypic inclusion, with eventual loss of Igκ. This phenotypic shift may occur via reinduction of Rag-mediated V(D)J recombination and explain the selective presence of KSHV/HHV-8 in IgMλ B cells in vivo.[9] These data suggest that KSHV/HHV-8 can induce B-cell receptor (BCR) revision in mature B cells.

Do MCD and PEL KSHV/HHV-8–infected cells originate from different B-cell subsets?

KSHV/HHV-8–infected plasmablasts from MCD lesions have been shown to be unmutated naive B cells and considered as pre-GC cells.[17] In contrast, KSHV/HHV-8–infected lymphomatous B cells from PEL exhibit somatic hypermutations and immunoglobulin class switching, suggesting a GC/post-GC stage of development.[28,30] KSHV/HHV-8 would have distinct biological effects leading to different disease states based on the target B-cell subtype. Another model would consider that both MCD and PEL originate from infection of the same subtype of B cell, with additional factors influencing the disease manifestations.[10] In line with this alternative model are the high incidence of PEL in patients with MCD, suggesting a possible continuum between MCD and PEL cells[14]; the fact that these post-MCD PELs are usually not coinfected with EBV; and the finding that EBV$^-$ PEL do not exhibit somatic hypermutations.[30,31]

KSHV/HHV-8 can promote extrafollicular maturation pathways and inhibit GC reaction. Using transgenic mouse models, it has been shown that KSHV/HHV-8 viral FLICE-like inhibitory protein (vFLIP) expression was associated with inhibition of GC formation and phenotypes resembling both MCD (polyclonal IgM$^+$ plasmablasts) and PEL (monoclonal IgH, CD138$^+$), whatever the stage of B lymphocyte differentiation selected for expression.[32] EBV coinfection is an important factor to consider to explain the phenotype of PEL. Microarray studies of cellular gene expression suggest that even in the background of EBV coinfection, KSHV/HHV-8 is the driving force for proliferation.[28] However, EBV, mimicking GC biology, could be responsible for

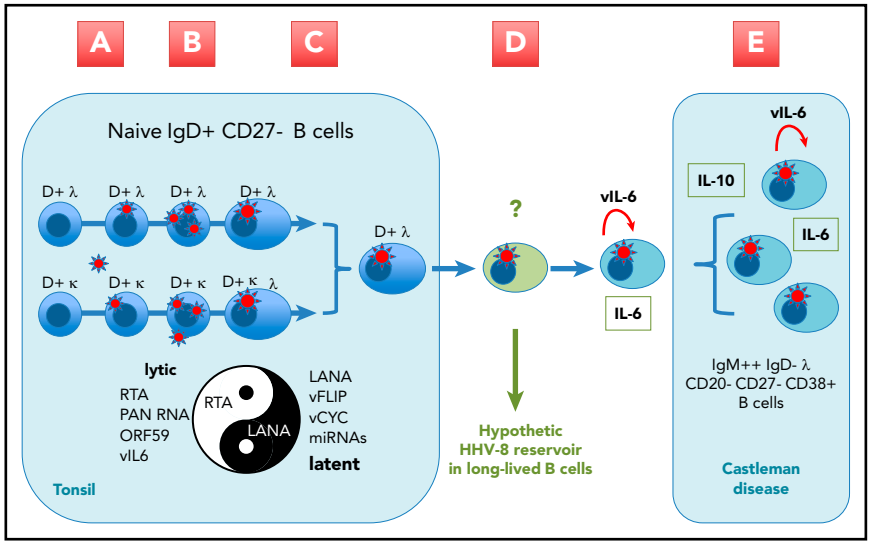

Figure 1. KSHV/HHV-8 primary infection and scenario for the generation of an infected B-cell reservoir and Castleman lesions. (A) Infection via saliva of subepithelial tonsillar dendritic cell–specific intercellular adhesion molecule-3-grabbing nonintegrin–rich naive B cells. (B) Early and transient prelatent "lytic burst" transcription program and possible detection of episome-associated LANA$^+$ cells by day 5 postinfection. (C) Blasting, dividing, and proliferation of the infected cells; BCR revision and editing for a shift toward λ-chain expression. (D) At that point, and as other herpesviruses, KSHV/HHV-8 have to exhibit a specific strategy to escape immune surveillance and constitute an KSHV/HHV-8 reservoir. The exact phenotype of the putative long-lived B cells constitutive of the KSHV/HHV-8 reservoir remains unknown. (E) Induction of a lytic cycle with production of vIL-6 is probably crucial for KSHV/HHV-8–infected cells to generate the MCD lesions observed in lymphoid organs. miRNA, microRNA; PAN RNA, polyadenylated nuclear RNA; RTA, replication and transcription activator; vCYC, viral cyclin.

the maturation features of PEL including the generation of somatic mutations.[33,34]

In a possible unified viral pathogenic model, KSHV/HHV-8 would infect naive B cells, establishing a reservoir of polyclonal B cells exhibiting features of mature B cells (Figure 1). The phenotype of this possible B-cell reservoir compartment remains unknown. In the context of HIV infection or aging, additional factors, including immune deficiency and EBV coinfection, may influence the occurrence of a lymphoproliferative disease, either still polyclonal (MCD) or monoclonal (PEL).

Should KSHV/HHV-8–associated MCD be considered as an LPD or as an infectious disease?

Herpesvirus-associated diseases are usually classified using a dichotomy based on virus status or activity: latency and cell proliferation vs lytic cycle and replication. Studies on EBV-associated posttransplant LPDs have shown that even if the most important event is the engagement of an intense latency/growth program in EBV-infected B cells, a significant proportion of these cells enter a lytic cycle and produce large amounts of virions that can participate with the LPD.[35]

In MCD, a significant proportion of KSHV/HHV-8–infected cells are in fact productively infected and associated with the production of high levels of vIL-6.[21,36,37] Consistent with this finding are the very high copy numbers of KSHV/HHV-8 DNA sequences that are detectable in the blood during MCD flares (≈4-6 logs per milliliter) along with very few (usually <1%) circulating infected B cells.[20] These data suggest that active viral replication may play a role in the pathogenesis of MCD. In line with this, antiviral drugs have a possible positive impact in the management of MCD,[38] and etoposide, often used as first-line therapy,[39] has been shown to inhibit KSHV/HHV-8 replication in vitro.[40]

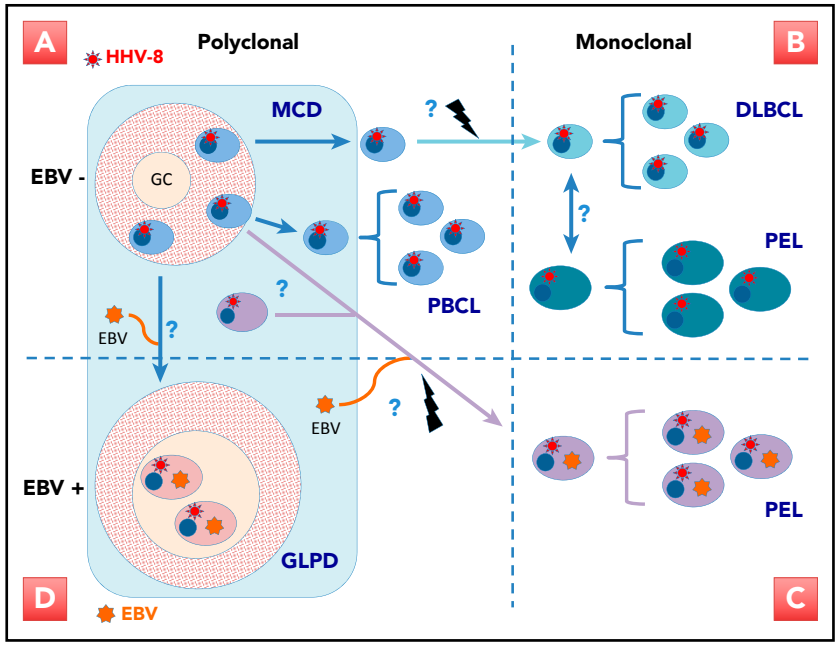

Figure 2. Spectrum of KSHV/HHV-8 LPDs according to clonality and EBV association. (A) MCD is characterized by KSHV/HHV-8$^+$ EBV$^-$ polyclonal plasmablastic B cells; these cells may be the counterpart of naturally infected B cells that undergo proliferation and viral replication and expand within a specific context such as HIV infection or aging. In some cases, the rapid and aggressive development of a polyclonal B-cell lymphocytosis (PBCL) can mimic lymphoma with leukemic phase. (B) In rare cases, evolution toward frank monoclonal DLBCL may occur and may be difficult to distinguish from an EBV$^-$ PEL, notably in its solid/extracavitary form. (C) Classic PEL is usually associated with coinfection of the lymphomatous cells with EBV. These cells are clonal with complex karyotypes and exhibit somatic hypermutations, suggesting that they originate from GC/post-GC B cells; within an alternative scenario, they would originate from the same KSHV/HHV-8–infected plasmablasts seen in MCD lesions with subsequent clonal evolution toward a post-GC phenotype under the influence of EBV infection. (D) GLPD is characterized by the presence in the GC of large B cells coinfected with KSHV/HHV-8 and EBV without evidence of clonality.

Can we identify immune deficits that may promote KSHV/HHV-8–associated MCD and PEL?

In contrast to what is observed in HIV-associated KS, KSHV/HHV-8–associated MCD generally occurs in the setting of relatively preserved CD4$^+$ T-cell counts and specific effector T cells are demonstrable.[41] Recently, the demonstration of a profound quantitative and functional defect in invariant natural killer T cells in patients with KSHV/HHV-8–associated MCD suggested an important role for these cells in the control of KSHV/HHV-8–infected B cells.[42,43]

Is rituximab the optimal therapy for KSHV/HHV-8–associated MCD?

Although KSHV/HHV-8$^+$ plasmablasts are usually negative for the expression of CD20,[16] rituximab, a CD20 monoclonal antibody, has been shown, in 2 prospective studies, to be very effective in controlling MCD with a response rate above 70%.[44,45] In addition, rituximab was shown to be associated with a 90% reduction in the risk of developing non-Hodgkin lymphoma after a 5-year follow-up.[46] Relapses can be observed but usually remain sensitive to a second cycle of rituximab.[47] Maintenance therapy could be discussed in patients at high risk for relapse.[48]

The use of rituximab is hampered by 3 issues[44,45,49]: (1) a high risk of infection and severe sepsis in patients with severe immune deficiency such as HIV-infected patients with CD4$^+$ T-cell counts below 100 $\times$ 10^6/L; (2) a risk of MCD severe flare following the first infusions with high blood KSHV/HHV-8 DNA copy numbers contrasting with the early depletion of circulating B cells (flares can be avoided by the association of low-dose etoposide during rituximab therapy[39]); and (3) a high risk of KS flare in patients with active KS lesions (concomitant administration of liposomal doxorubicin can help to control KS activity[50]).

Daratumumab, a CD38-directed monoclonal antibody, is widely used in the treatment of multiple myeloma. Its specificity makes it a possible alternative for treatment of PEL or MCD.[51]

KSHV/HHV-8 is associated with a spectrum of LPDs (Figure 2) that are mainly, but not exclusively, observed in immunocompromised patients, notably HIV-infected patients. The study of KSHV/HHV-8–associated LPDs provides new insights into unique mechanisms involved in B-cell proliferation such as extrafollicular maturation, BCR revision in mature B cells, aggressive polyclonal proliferation, lymphomagenesis in cells dually infected with KSHV/HHV-8 and EBV, or tropism for serous cavity. Unfortunately, mouse or monkey models do not provide exact phenocopies of what is observed in humans.[32,52,53]

Authorship

Contribution: E.O., D.B., and L.G. wrote the manuscript.

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