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Review Article

Human Herpesvirus 8 and Lymphoproliferative Disorders

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Abstract. The spectrum of lymphoproliferative disorders linked to human herpesvirus 8 (HHV-8) infection has constantly been increasing since the discovery of its first etiologic association with primary effusion lymphoma (PEL). PEL is a rapidly progressing non-Hodgkin's B-cell lymphoma that develops in body cavities in an effusional form. With the increase in the overall survival of PEL patients, as well as the introduction of HHV-8 surveillance in immunocompromised patients, the extracavitary, solid counterpart of PEL was later identified. Moreover, virtually all plasmablastic variants of multicentric Castleman's disease (MCD) developing in HIV-1-infected individuals harbor HHV-8, providing a strong etiologic link between MCD and this oncogenic herpesvirus. Two other pathologic conditions develop in HIV-1-infected persons concomitantly with MCD: MCD with plasmablastic clusters and HHV-8-positive diffuse large B-cell lymphoma not otherwise specified (HHV-8+ DLBCL NOS), the first likely representing an intermediate stage preceding the full neoplastic form. MCD in leukemic phase has also been described, albeit much less commonly. The germinotropic lymphoproliferative disorder (GLPD) may resemble extracavitary PEL, but develops in immune competent HHV8-infected individuals, and, unlike the other disorders, it responds well to conventional therapies. Almost all HHV-8-mediated lymphoproliferative disorders are the result of an interaction between HHV-8 infection and a dysregulated immunological system, leading to the formation of inflammatory niches in which B cells, at different developmental stages, are infected, proliferate and may eventually shift from a polyclonal state to a monoclonal/neoplastic disorder. Herein, we describe the association between HHV-8 and lymphoproliferative disorders and highlight the predominant distinctive features of each disease.

Keywords: Human herpesvirus; HHV-8; Kaposi's sarcoma-associated herpesvirus; KSHV; Lymphoproliferative disease; Primary effusion lymphoma; Multicentric Castleman's disease; Germinotropic lymphoproliferative disorder.

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Introduction. Human herpesvirus 8 (HHV-8) was first evidenced in 1993 in a Kaposi's sarcoma (KS) tissue sample by using representational difference analysis (RDA), which enables unbiased detection of foreign DNA sequences in tumor tissue as compared with its matched normal control.[1,2] Four RDA fragments were detected, of which two were verified by Southern blot analysis

as unique to the diseased tissue. The amino acid coding sequences of the newly identified KS-associated DNA shared a high degree of homology with two known herpesviruses, Epstein-Barr virus (EBV) and Herpesvirus Saimiri (HVS). Accordingly, the newly identified human herpesvirus was termed "Kaposi's sarcoma-associated herpesvirus" (KSHV), and, later, HHV-8. KS-associated sequences were subsequently detected in all epidemiological variants of KS, including HIV-associated or epidemic, Mediterranean or classic, African or endemic, and iatrogenic or post-transplant KS.[3-5] In subsequent studies, HHV-8 sequences were detected in a lymphoma sample from an AIDS patient which was initially included as a negative control.[6] Then, a screening of 193 AIDS lymphoma samples identified eight as positive for HHV-8 DNA; all were classified as body cavity-based lymphoma (BCBL). This lymphoma, later designated primary effusion lymphoma (PEL), represents an extremely rare liquid-phase plasmablastic lymphoma which mostly appears in HIV-1-infected patients. Its main characteristic is the large serous cavities which constitute its site of primary development.[7] Subsequently, the plasmablastic variant of multicentric Castleman's disease (MCD), which often presents with hyperplastic lymph nodes, was linked to this herpesvirus,[8] in addition to two proliferative disorders developing in patients with MCD: MCD with plasmablastic aggregates and HHV-8-positive diffuse large B-cell lymphoma not otherwise specified (HHV-8+ DLBCL NOS). An additional condition that was later associated with HHV-8 infection and that shares several characteristics with MCD is the KSHV-associated inflammatory cytokine syndrome (KICS).[9] Like PEL and MCD, this HHV-8-induced inflammatory condition develops at higher frequencies in HIV-1-infected individuals. Conversely, the germinotropic lymphoproliferative disorder (GLPD), which was described later, develops mainly in HHV-8-infected immunocompetent hosts.[10]

HHV-8 has been classified by the International Agency for Research on Cancer (IARC) as class I human carcinogen. The epidemiology, biology and molecular characteristics of HHV-8 infection, as well as the potential role of HHV-8 proteins and miRNAs in the pathogenesis of HHV-8, have been widely reviewed.[11-14] Based on the Society of Hematopathology (SH)/European Association for Hematopathology 2015 Workshop Report,[15] we describe in the present review the association between HHV-8 and lymphoproliferative disorders and highlight the predominant distinctive features of each disease, while indicating exceptions to the general descriptions. **Table 1** summarizes the pathological lymphoid conditions linked to HHV-8 infection and key features of these disorders.

Primary Effusion Lymphoma.

Clinical and biological features. PEL is a highly aggressive and rare non-Hodgkin's B-cell lymphoma (NHL) presenting as a liquid-phase lymphoma in body cavities, in particular, the peritoneal, pericardial and pleural cavities.[7,16] Symptoms are the result of the accumulation of neoplastic effusion and patients with pleural or pericardial disease may present with dyspnea, while those with peritoneal involvement with ascites. PEL may develop concomitantly in more than one body cavity, and its prognosis is partly linked to the number of involved intracavitary sites.[17] Diagnostic criteria include: i) the presence of an effusional lymphoma, with ii) monoclonal rearrangements of the immunoglobulin (Ig) variable genes, and iii) detection of HHV-8 in the

Table 1. Summary of the main distinctive features of HHV-8-associated lymphoproliferative conditions.

HHV-8-associated lymphoproliferative disorders	Presentation	HHV-8: LANA /vIL-6	EBV	HIV status	Ig rearrangements	CD138	B cell markers: CD20/Pax5
Primary effusion lymphoma (PEL)	effusion	≤ 20%	frequent	+/-	monoclonal	+	-
Extracavitary PEL	solid	≤ 20%	frequent	+/-	monoclonal	+	-
Pseudo-PEL	effusion	≤ 20%	rare	+/-	polyclonal	+/-	variable
Plasmablastic MCD	solid	≤ 20%	rare	+/-	polyclonal	-	+ (33-50%)
MCD with plasmablastic clusters	solid	≤ 20%	rare	+	polyclonal/ oligoclonal	-	variable
DLBCL NOS	solid	≤ 20%	rare	+	monoclonal	-	+ (33-50%)
GLPD	solid	>70%	frequent	-	polyclonal	-	-

Abbreviations: LANA: latency-associated nuclear antigen; vIL-6: viral interleukin 6; MCD: multifocal Castleman's disease; DLBCL NOS: diffuse large B-cell lumphoma not otherwise specified; GLPD: germinotropic lymphoproliferative disorder.

lymphomatous cells. Cytologic preparations of the effusion show large neoplastic cells with round to irregular nuclei and prominent nucleoli. The cells vary in appearance from immunoblastic to plasmablastic and anaplastic, and numerous mitotic figures are evident. Most PEL cells are latently infected with HHV-8 and thus express only a small subset of viral genes, whereas a small fraction of cells expresses viral lytic genes. Rarely, these cells may harbor monoclonal rearrangements of T-cell receptor genes, although *in vivo* and *in vitro* studies have shown that, among the hematopoietic components, only B lymphocytes and mononuclear cells can be infected with HHV-8.

PEL cells have a peculiar immunophenotype as the lymphomatous cells do not express classic B-cell (such as CD19, CD20 and PAX5) or T-cell (such as CD3) lineage markers. They frequently express both activation (such as CD38) and post-germinal center (GC) markers, such as MUM1/IRF4, B lymphocyte-induced maturation protein 1 (Blimp-1) and the characteristic adhesion molecule, Syndecan-1 or CD138.[18,19] MUM1/IRF4 is a myeloma-associated transcriptionally active oncogene, which is involved in the regulation of *myc* expression and B-cell maturation and was found to be expressed in a high proportion of mature lymphoproliferative disorders including B- and T-cell malignancies.[20,21] Blimp-1 is a crucial transcriptional regulator, which is involved in the terminal differentiation of B cells into plasma cells. Interestingly, intracavitary targeting of Blimp-1 exerted a significant anti-neoplastic effect in a preclinical SCID/PEL model, suggesting that Blimp-1 represents a potential therapeutic target for PEL.[22] Syndecan-1 is a cell-surface heparin-sulfate proteoglycan, generally expressed on the basolateral surface of epithelial cells, and its expression is correlated with cell differentiation and prognosis in many types of tumors.[23] In the hematopoietic compartment, this surface antigen is expressed at high density in normal and transformed lymphocytes at the late stages of B-cell differentiation.[24] The transcriptional profile of PEL cells shows a pattern of gene expression intermediate between that of a plasma cell and that of a diffuse large B-cell lymphoma.[25] Therefore, PEL cells seem to represent terminally differentiated, post-GC transformed B cells.

The secretory profile of PEL cells includes high levels of viral and cellular interleukin (IL) 6, IL-10 and vascular endothelial growth factor (VEGF). Cellular and viral IL-6 (hIL-6 and vIL-6) promote B cell growth and angiogenesis. hIL-6 was shown to be important for *in vivo* PEL cell proliferation.[26] IL-10 is one of the most important autocrine growth factors for PEL cells and is released by PEL cell lines at high levels *in vitro,* and throughout tumor progression in PEL murine models.[26-28] The effect of VEGF, initially named vascular permeability factor, in PEL pathogenesis was found to be mainly associated with the enhancement of vascular permeability, thus contributing to the liquid growth of the effusion rather than to neo-angiogenesis.[29]

Epidemiological subtypes. Like KS, different epidemiological subtypes of PEL have been described. The predominant variant is the one that develops in HIV-1-infected individuals, in particular, advanced AIDS patients. In this population, PEL represents about 4% of all HIV-associated NHLs whereas it accounts for 0.3% of aggressive lymphomas developing in HIV-uninfected subjects.[30,31] HIV-associated PEL develops more frequently in young male patients, and has a very aggressive clinical course, with a median survival time of 2-6 months from diagnosis in the pre-antiretroviral therapy (ART)/early combined ART (cART) era.[16,31,32] Continuous cART therapy, along with high-dose chemotherapy regimens, was found to ameliorate clinical aggressiveness by inducing, in certain patients, a prolonged disease remission.[33,34] Of note, PELs that are HIV-associated are frequently co-infected with EBV. The "Mediterranean" or classic variant of PEL develops in HIV-negative elderly patients, mostly in persons of Mediterranean basin descent. This variant has an indolent clinical course and a more favorable prognosis.[35-37] A post-transplantation PEL form has been described in renal, liver and cardiac transplant recipients.[38-40] In these patients, PEL presents a variable clinical course, and it can rapidly progress; removal of immunosuppressive therapy is often associated with substantial clinical response. PEL can also develop in HIV-negative subjects who are affected by Hepatitis C virus/Hepatitis B virus-associated or cryptogenic liver cirrhosis.[41,42] The African/endemic form of PEL remains to be identified, although its existence is highly plausible. The lack of diagnosis or misdiagnosis of African PEL patients could be

primarily explained by difficulties in performing appropriate viral, histopathological and instrumental analyses in this population. Moreover, these patients are frequently affected by several comorbidities, further complicating the diagnostic procedure.

Pathogenic mechanisms. The initial step that promotes PEL onset is common to all disorders that are linked to HHV-8 infection, i.e., immune activation leading to increased inflammatory cytokine secretion (reviewed in Ensoli et al.).[43] This condition favors the lytic program of HHV-8 infection and increases the pool of infected cells in the systemic compartment, which in turn amplifies the inflammatory profile. Of note, effusions composed of polyclonal atypical HHV-8-infected B cells that are surrounded by an inflammatory microenvironment have been documented in body cavities of HIV-infected subjects who are affected by other HHV-8-associated disorders. Given the lack of tumor monoclonality and the discrepancy between viral and cellular clonality in a number of effusion samples, a possible transition phase towards HHV-8-positive PEL has been suggested.[44,45]

Inflammatory cytokines are also thought to be responsible for the activation of mesothelial cells, representing specialized epithelioid cells lining the body cavities.[46] In response to an injury or to altered intracavitary homeostasis, mesothelial cells may themselves release inflammatory mediators which recruit leukocytes from the systemic compartment through a chemotactic gradient and by the exposure of adhesion molecules and integrins on the mesothelial cell surface. Accordingly, mesothelial cells amplify and extend the pattern of cytokines through the secretion of growth factors and chemokines, thereby recruiting potentially infected B cells to intracavitary sites. Like the activated foci of the endothelial cells in KS pathogenesis,[47] this cytokine-rich microenvironment may favor homing, and possibly, the proliferation of PEL precursors in the intracavitary compartment, eventually leading to their oncogenic conversion.

Nevertheless, mesothelial cells also function as guardians of the intracavitary homeostasis and the first line of defense against infections,[48] and may thus assist in the resolution of the inflammatory wave. A recent study hypothesized that PEL cells might derive from mesothelial cells lining body cavities, through a mesothelial-lymphoid transition, a biological process likely responsible for the genesis of resident B1 lymphocytes.[49] This hypothesis is in line with the plasticity of mesothelial cells. However, it does not explain the immunophenotypic and genetic features of PEL cells *in vivo*.

In the absence of therapy, PEL is rapidly progressive and consistently lethal. The rapid progression of this lymphoma is linked to its peculiar site of development. Indeed, *in vitro* co-culture studies showed that mesothelial cells could modify the turnover of PEL cells by increasing their proliferation and their resistance to apoptotic stimuli, thus generating an environment favorable to PEL progression.[50] On the other hand, PEL cells, through the release of Transforming Growth Factor (TGF)-beta, induce type 2 epithelial-mesenchymal transition (EMT) in primary human mesothelial cells.[50,51] This can be observed in co-culture systems as well as in a preclinical animal model of SCID/PEL mimicking the aggressive nature of PEL in humans.[28] Primary human mesothelial cells have a polygonal shape and form a regular monolayer in culture. Their co-culture with PEL cells, or treatment with TGF-beta, induces morphological changes within a few days which lead to a spindle-like shape, with a myofibroblastic morphology, and formation of small foci with accumulation of elongated mesothelial cells (**Figure 1**). These morphological changes are accompanied by transcriptional re-programming characterized by up-regulation of specific transcription factors (Snail, Slug, Zeb1 and Sip1) that lead to downregulation of E-cadherin and other proteins mediating cell-to-cell contacts, in particular, adherens and tight junctions. Some structural proteins are also substituted by other cytoskeletal components that facilitate cell motility, such as α-SMA. This conversion into a myofibroblast-like phenotype can also be visualized during ascites development in mice intraperitoneally injected with PEL-derived cell lines. Indeed, the occurrence of EMT *in vivo* was demonstrated through the thickening of the mesothelium lining the peritoneal cavity during ascites progression in a PEL preclinical model (**Figure 2**, panels A and B).[50] Serosal thickening was accompanied by loss of cytokeratin staining, both of which are typical signs of fibrosis.[52] Interestingly, this phenomenon was also documented in PEL patients,[53] indicating that

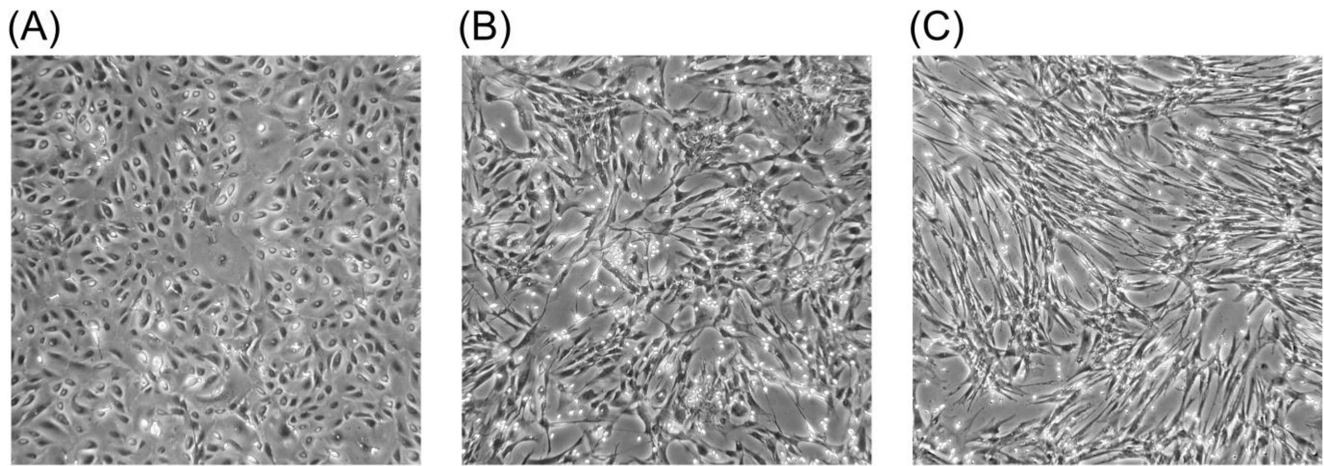

Figure 1. PEL cells induce a myofibroblastic morphology in mesothelial cells. Phase-contrast images of a primary culture of normal human mesothelial cells **(A)** showing a cobblestone-like morphology. Transition to a myofibroblastic morphology, characterized by elongated, spindle shaped cells, and a crisscross pattern of growth, is induced after co-culture with PEL-derived cell lines. Mesothelial cells are shown after 4 **(B)** and 8 **(C)** days of co-culture with CRO-AP/2 cells. This morphological change is consistent with the induction of epithelial-mesenchymal transition by the TGF-beta released by PEL cells.[50]

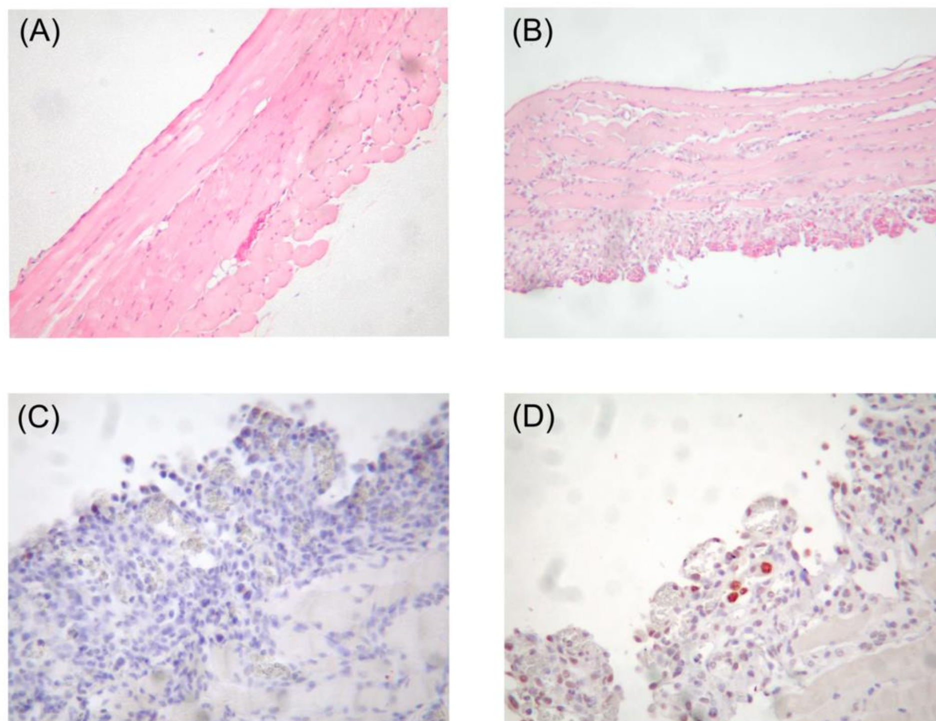

Figure 2. Mesothelium response in a PEL preclinical model. (A-D) Histological and immunohistochemical staining of serosal membranes during *in vivo* growth of an ascitis induced by intraperitoneal injection of a PEL-derived cell line into a SCID mouse (SCID/PEL mouse model).[28] Normal serosal membranes are characterized by a uniform and flat monolayer of mesothelial cells, as documented by haematoxylin/eosin staining of the peritoneum in a control mouse (**A,** magnification 100X). During intracavitary development of prominent ascites, histological examination of the mesothelium response shows a hyperplastic process, with discontinuity of the mesothelial surface and progressive thickening of the serosal membranes (**B**, diaphragm of a SCID/PEL mouse sacrificed at 12 days, original magnification 100X), with new enlarged capillaries containing erythrocytes and granulation tissue. Thickening of serosal membranes with an inflammatory process and neoangiogenesis is indicative of fibrosis. Immunostaining with an HHV-8-specific anti-latency-associated nuclear antigen (LANA) antibody shows the infiltration of PEL cells in the submesothelial region (**D**), suggesting that PEL cells, through the discontinuity of the mesothelial lining, may reach extracavitary sites and generate solid masses (**C**, negative staining control of the diaphragm of a SCID/PEL mice; **D**, immunohistochemical staining with anti-LANA antibody. Original magnification X200).

fibrosis occurs during PEL progression. Type 2 EMT was shown to increase the survival of PEL cells,[50] suggesting that this phenomenon in the intracavitary microenvironment may be responsible for the aggressive nature of PEL. Moreover, discontinuity in the mesothelial layer might also contribute to the occurrence of extracavitary PEL.

Extracavitary/solid PEL.

Clinical and biological features. The extracavitary variant of PEL was reported after the description of the classic effusion form of PEL.[54,55] Extracavitary PEL more frequently develops after or concomitantly with the emergence of the effusion form;[56-58] however, it may, albeit more rarely, precede this form.[54,59,60] Cases of solid PEL that are not accompanied by the effusional form have also been described.[54]

Lymphomatous cells of solid PEL frequently share similar morphological, immunophenotypic, genotypic and virologic characteristics with those described for the effusional form. However, this lymphoma consists of a solid mass that may be present at different organs. This variant of PEL may exclusively involve the lymph nodes, or affect other organs, including the gastrointestinal tract, lungs, skin, and the central nervous system. Extracavitary PEL develops more frequently in HIV-infected subjects and, recently, two cases of African extracavitary PEL have been described.[61] However, cases in HIV-negative individuals have also been reported.[58]

Of note, HIV/HHV-8-infected subjects may also concomitantly develop other HHV-8-positive DLBCL, as described below, characterized by immunoblastic or immunoblastic/plasmacytoid cells, which have different characteristics but share HHV-8 infection. Therefore, solid PEL is much more challenging to diagnose as compared to its effusion counterpart. Detection of HHV-8 in the lymphomatous cells can solve some ambiguous cases, although it might not be the primary diagnostic approach in cases of solid lymphomas. Lymphomatous cells have a variable morphology, ranging from plasmablastic to immunoblastic and anaplastic, but they generally lack B-cell markers, as well as surface and cytoplasmic immunoglobulins. Diagnostic criteria include detection of HHV-8 in tumor cells, frequent detection of CD138 and CD38, infrequent staining for B-cell markers, and presence of monoclonal IgH gene rearrangements (**Table 1**). Concomitant intracavitary effusion might also support the diagnosis.

Chadburn et al.[54] demonstrated a longer survival of extracavitary PEL patients compared to classic PEL patients, with a median survival time of 11 versus 3 months, respectively. Another study compared the characteristics and the outcome of classic PEL with those of solid PEL in HIV-1-infected patients receiving combined antiretroviral therapy.[34] Similar clinical, morphological and immunophenotypic characteristics were reported in the two groups, with a similar high frequency (>59%) of EBV detection. The majority of patients received standard chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP-based) combined with methotrexate. Complete remission was achieved in 62% of the patients with the classic variant, and in 41% of the patients affected by the extracavitary form. The median overall survival was similar in the two groups (10.2 months), regardless of the treatment regimen; yet, it is interesting to note that, in accordance with other studies,[54] patients with the extracavitary localization, who achieved initial remission, remained disease-free during a 10-year follow-up, whereas more than half of the surviving patients with the effusional PEL relapsed.

Pathogenetic mechanisms. Most PEL patients either present with coexisting solid and effusional forms of PEL or develop a solid mass following the diagnosis of a liquid-phase PEL.[54,58,62] Concerning the possible pathogenic mechanisms involved in the development of this PEL variant, it was proposed that type 2 EMT involving the mesothelium lining the body cavities during effusional PEL progression might favor the subsequent or concomitant formation of an extracavitary mass.[50] This mechanism is supported by the frequent finding of lymphocyte infiltration of the serosal membranes in PEL patients.[56] Extracavitary PEL is more frequent during the course of intracavitary effusions and likely reflects the occurrence of serosal discontinuity and consequent leakage of lymphomatous cells. Due to the rapid progression of PEL, it is conceivable that the occurrence of the extracavitary migration of lymphomatous PEL cells would be mainly observed in longer-surviving patients. Indeed, extracavitary secondary masses were also described in PEL patients after treatment.[32,55] Actually, these patients experienced PEL remission and relatively longer survival, with a disease-free interval ranging from 5 to 97 months. In one case, the extracavitary mass, which developed following a PEL-free interval, was morphologically and immunophenotypically different from the initial PEL tumor and was compatible with the occurrence of a distinct HHV-

8-associated MCD-associated oligoclonal "microlymphoma"[55] (see below). In other cases, however, the extracavitary mass and the primary PEL had similar morphological characteristics, immunophenotypic profile and clonal identity, thus providing evidence that the extracavitary solid mass represents the relapse of the original effusional lymphoma at a different site, as a solid tumor.[55,58] Interestingly, this finding was also reproduced in a preclinical SCID/PEL model after treatment [(**Figure 2**)[28] and unpublished data]. The seeding of tumor cells through the submesothelial layer to form a solid mass is also supported by studies in mice treated with interferon (IFN)-alpha. Mice intraperitoneally injected with PEL cells and transduced with a lentiviral vector expressing IFN-alpha showed significantly increased survival compared to control mice, along with a significant reduction in ascites development. These mice subsequently developed extracavitary masses,[28] suggesting that PEL cells could leave the intracavitary site during initial ascites formation, and thus escape the intracavitary treatment to generate extra-peritoneal solid masses later.

However, PEL patients presenting exclusively with a solid PEL, or having a solid PEL followed by a liquid-phase PEL have also been described,[54,60,63,64] thereby suggesting a different pathogenic mechanism. As these solid PELs occurred mainly in the gastrointestinal tract and in the skin, it has been hypothesized that solid PEL occurs at the same sites of KS development. This hypothesis should imply that the same pathogenic mechanisms leading to the transformation of lymphatic endothelial cells into spindle cells following HHV-8 infection may also apply, though rarely, to B cells recruited to these anatomic sites.

Pseudo-PEL. Patients affected by MCD and/or KS may develop recurrent non-lymphomatous effusions in body cavities.[44,45,65] These effusions show certain features of PEL, including HHV-8 infection, generally with high cell-associated viral loads, the involvement of one or more body cavities, and aggressive clinical course. Moreover, they may arise in both HIV-negative and HIV-positive patients.

However, unlike PEL, in these lymphoproliferative disorders, the fraction of HHV-8-infected cells is small, and the infected cells are atypical lympho-mononuclear cells which commonly express the latency-associated nuclear antigen (LANA) and vIL-6. No evidence for T-cell/B-cell clonality is generally found. Certain cases may show monotypic (IgM/λ) LANA-positive lymphoid cells resembling the plasmablasts of MCD; more rarely, cases of LANA+/CD68R+ mononuclear cells on an inflammatory background may be reminiscent of an effusive form of an early polyclonal KS lesion. These polyclonal HHV-8-positive effusions may, therefore, represent an early phase of PEL or a liquid form of MCD or KS. Conversely, they could represent a distinct HHV-8-associated inflammatory, infectious process arising in body cavities.

Multicentric Castleman's Disease (MCD). *Clinical and biological features.* MCD is a rare polyclonal B-cell lymphoproliferative disorder, presenting as generalized lymphadenopathy with angiofollicular hyperplasia and affecting both HIV-positive and negative subjects. Castleman's disease, first described in 1956,[66] is characterized by a benign mass of lymphoid tissue that may involve a single lymph node ("unicentric") with an estimated incidence of 16 per million person years, or several lymph nodes ("multicentric"), with a lower incidence of 5 per million person years.[67-69] Three variants have been described based on their histopathological features. These include: i) the hyaline vascular form, which is characterized by a vascular lymphoid tissue containing lymphocytes forming ordered, concentric "onion skin" layers around the large follicles, with frequent perivascular hyalinization; ii) the plasmablastic variant, which shows large sheets of plasma cells expanding the mantle zone and generally preserved architecture of lymph nodes, and iii) the mixed variant, which shows both histological patterns.

The observation that more than 50% of AIDS-KS patients are also affected by MCD prompted the search for HHV-8 sequences in MCD in both HIV-infected and -uninfected subjects. After that, HHV-8 was detected in plasmablastic and mixed variants.[8] Within affected lymph nodes, HHV-8 is detected in IgM-positive plasmablasts. The immunophenotype of HHV-8-infected cells is not strictly plasmablastic, as these cells may be, more rarely, positive for CD20, and frequently negative for CD138 (**Table 1**).[70,71] All plasmablasts in

lymph nodes and spleen express LANA, along with MUM1/IRF4 and PAX5, and are Bcl-6-negative. PAX5 is a transcription factor which participates in the maintenance of the B-cell lineage;[72] its protein expression level, as detected by IHC, is used to assess the B-cell lineage. HHV-8-infected plasmablasts are polyclonal but have a restricted monotypic (IgM-lambda) phenotype.[73] They do not harbor somatic mutations in the rearranged Ig genes, indicating their origin from naïve pre-GC B cells. Concomitant EBV infection is found very rarely. HHV-8 is involved in 60-100% of HIV-associated MCD cases, and in 20-40% of HIV-negative patients.[74-77] Formal criteria have been established for the diagnosis of HHV-8-unrelated/idiopathic MCD.[78]

HHV-8 infected B plasmablasts in lymph nodes produce high levels of viral and cellular IL-6, which are thought to be responsible for the systemic illness, and what are known as "B" symptoms, including severe fatigue, fever, edema, weight loss, cell-free pleural effusion, anemia, thrombocytopenia, lymphadenopathy and splenomegaly.[79,80] Lymph node resection in MCD patients was found to reduce both symptoms and hIL-6 serum levels, indicating that hIL-6 is mainly produced within the germinal center of the involved lymph nodes and has a major role in the pathogenesis of the disease.[81] Moreover, transgenic mice that constitutively express murine IL-6 or vIL-6 were shown to develop an MCD-like syndrome, further supporting the influential role played by this cytokine.[82,83] The symptomatic phase is very frequently accompanied by elevated levels of cell-free HHV-8 viremia, generally higher than those reached in patients affected by other HHV-8-linked pathologies.

Rare cases of MCD with the presence of plasmablasts in the systemic compartment have been reported. These cases of MCD in leukemic phase were described in HIV-infected subjects with a history of KS in the presence[84] or absence[85] of a diffused lymphoadenopathy.

The criteria to distinguish HHV-8-associated MCD from lymphoid hyperplasia may principally rely on the constant presence of HHV-8 in the plasmablasts. Apart from being PCR-positive for different genomic regions of the virus, plasmablasts generally express LANA and also express vIL-6 in a small fraction (generally < 20%) of the cells (**Table 1**). A similar viral expression pattern has also been observed in PEL and in pseudo-PEL cells. Lymphocyte proliferation is generally polyclonal.[8] However, MCD can progress to HHV-8+ DLBCL NOS or to a form presenting aggregates of plasmablastic cells, which likely represent an intermediate stage preceding the frank monoclonal disease.[8,71]

Pathogenic mechanisms. Increased loads of HHV-8, together with increased IL-6 and IL-10 levels, exacerbate disease in patients with MCD. Therefore, a model that considers these factors in the pathogenesis of the disease has been proposed,[86] that may explain the pathogenic role of HHV-8 in the three variants of MCD. This model relies on similarities between KS and MCD in multiple characteristics including HHV-8 infection and frequent association with HIV dysregulated production of human and viral IL-6, the inflammatory profile, histopathological characteristics and initial polyclonal proliferation that can progress to a monoclonal neoplastic process. The scenario is the lymph node, in which inflammatory cytokines boost the lytic cycle of HHV-8 and the subsequent viral dissemination to B lymphocytes and lymphovascular endothelial cells. This process is amplified in the presence of HIV infection, which increases the level of inflammation and cooperates directly and indirectly to increase HHV-8 loads.

Moreover, prominent lytic viral replication leads to hyalinization, which also characterizes KS, and results in the destruction of lymphovascular endothelial cells. This "two-compartment" propagation might ultimately explain the simultaneous presence of KS and MCD in HIV/HHV-8-coinfected individuals.[86] However, this complex interplay might also give rise to heterogeneous clinical and histopathological outcomes controlled by the ratios between cellular and viral cytokines, and between the lytic and latent programs. Indeed, this model could explain not only the two pathologies associated with MCD (plasmablastic aggregates and HHV-8+ DLBCL NOS) but also the extracavitary PEL, characterized by viral infection and monoclonal expansion of a different subset of post-GC B cells that is promoted by the inflammatory microenvironment.

MCD with Plasmablastic Aggregates. MCD can progress towards a transitional polyclonal or, more rarely, oligoclonal entity of microscopic

dimensions. This entity, characterized by HHV-8 infection and presence of clusters of LANA-expressing blasts colonizing or substituting the germinal centers of lymph nodes, was initially designated foci of “microlymphoma”.[71,73] Due to the absence of monoclonality and because a full-blown lymphoma does not always develop, this term is no longer used. Nevertheless, such aggregates may precede the subsequent development of a frank monoclonal HHV-8-positive plasmablastic lymphoma, more recently designated HHV-8+ DLBCL NOS.[15]

Like MCD, this disorder is more frequent in HIV-infected subjects, in concordance with other HHV-8-associated disorders, and plasmablasts may also express vIL-6, along with IRF4/MUM1.[15] EBV co-infection is rare but has been described.[87]

Thus, histopathological and molecular analyses of MCD lymph nodes show that HHV-8-infected plasmablasts may form microscopic sheets or clusters of large polyclonal cells with a restricted monotypic (IgM-λ) phenotype, without somatic mutations in the rearranged immunoglobulin gene, supporting their origin from naïve pre-GC B cells.

HHV-8+ Diffuse Large B-Cell Lymphoma Not Otherwise Specified (HHV-8+ DLBCL NOS). DLBCL represents one of the most frequent types of B-cell lymphomas and may encompass different morphological subtypes, including the plasmablastic lymphoma, originally described in the oral cavity of HIV-1-infected individuals.[88] HHV-8+ DLBCL NOS usually develops in MCD patients in the context of HIV infection.[8,71,89] Histopathological examination of lymph nodes and spleen reveals that their architecture is severely damaged and replaced by large sheets of malignant monoclonal cells. Extranodal sites may also be affected. Lymphomatous cells have a plasmablastic or, less frequently, an immunoblastic morphology. HHV-8+ DLBCL NOS has an immunophenotypic pattern characterized by lack of B-cell markers, expression of λ and, to a lesser extent, κ light chains, and presence of plasma cell markers (CD38+, IRF4/MUM1+).[90] EBV co-infection of plasmablasts is extremely rare. This lymphoma can be predicted by the presence of polyclonal/oligoclonal aggregates of plasmablastic cells, as described in the previous section.

Lymphoma with plasmablastic differentiation found in HIV-1-infected subjects might have quite heterogeneous features and may be distinguished on the basis of differential antigen expression and association with viruses.[89,91-93] Differential diagnosis between HHV-8+ DLBCL NOS and extracavitary PEL can be performed on the basis of CD138 and EBV, which are frequently found in intracavitary and solid forms of PEL (**Table 1**). PEL cells are post-GC B cells that have undergone an intense somatic mutation process on the immunoglobulin gene hypervariable region. Conversely, lymphomatous cells of HHV-8+ DLBCL NOS are naïve, non-mutated, pre-GC B cells.

KSHV-Associated Inflammatory Cytokine Syndrome (KICS). The KSHV-associated inflammatory cytokine syndrome is not a lymphoproliferative disorder *per se* but has several clinical, radiologic and virologic similarities with MCD. It was proposed as a unique clinical condition with a high mortality rate associated with HHV-8 infection.[9,94] The six initially described patients (five of them HIV-infected) presented with a severe systemic inflammatory syndrome indistinguishable from that found in the symptomatic phase of HHV-8-associated plasmablastic MCD, characterized by high HHV-8 viremia and elevated systemic levels of IL-6, vIL-6 and IL-10. Besides the similar clinical presentation, histopathological studies could not document nodal signs of MCD in any of the patients. Moreover KICS was shown to occur concurrently with other HHV-8-associated disorders, specifically KS or PEL.[9,94] It has been hypothesized that this condition may precede the development of HHV-8-associated disorders, although most KICS cases have been described in patients presenting with other, already developed, HHV-8-related lymphoproliferative diseases.

KICS-like inflammatory manifestation with the HHV-8 association has also been described in transplant recipients.[95-97] Of note, a clinical case of kidney-liver post-transplant KICS was recently reported.[97] This transplant patient presented with unexplained fever, markers of severe systemic inflammation including increased IL-6, IL-10, IL-8, and granulocyte-macrophage colony-stimulating factor (GM-CSF) plasma levels, and elevated HHV-8 viremia. This patient, who was HIV-negative, was found to have a donor-derived

primary HHV-8 infection and was successfully treated by a combination of antivirals, anti-CD20 monoclonal therapy, and modulation of the immunosuppressive regimen.[97] Accordingly, it appears that KICS is an underestimated condition that should be carefully monitored in the transplant setting.

Germinotropic Lymphoproliferative Disorder (GLPD). This lymphoproliferative disorder was first identified in 2002 in three immunocompetent subjects presenting with a localized lymphoadenopathy and responding satisfactorily to conventional therapy.[10] Histopathological examination of the lymphoadenopathy detects plasmablasts which preferentially invade the germinal centers of follicles; the overall structure of the lymph node generally remains undamaged. Plasmablasts are polyclonal or oligoclonal. Virological studies showed that plasmablasts are very frequently coinfected with both HHV-8 and EBV.

In contrast to PEL and MCD-associated plasmablasts, in which the percentage of LANA-positive cells that also express vIL-6 is generally lower than 20%, GLPD nodes contain a large fraction of LANA/vIL-6-positive cells (**Table 1**). These cells present latency I phenotype for EBV, being negative for LMP1, EBNA2, and BZLF-1 expression. They may present in clusters as those described in HIV-infected subjects affected by MCD, but these plasmablasts are CD20-/CD27-/CD138-/CD10-/CD79a-/Bcl-6-/Bcl-2. Less than ten canonical GLPD cases have been described to date, all in immunocompetent subjects.[98]

Principal distinctive features for differential diagnosis. Table 1 summarizes the principal distinguishing features of HHV-8-associated lymphoproliferative disorders, which may require differential diagnosis. Diagnosis of classic PEL is mainly based on radiological evidence of a malignant effusion involving the pleural, pericardial or peritoneal cavities, with or without a tumor mass, predominantly composed of monoclonal lymphomatous cells that are infected with HHV-8. HHV-8 infection can be easily demonstrated by LANA staining by immunohistochemistry or immunofluorescence of the neoplastic cells.

Plasmablastic or immunoblastic solid lymphoma with LANA-expressing cells, which could also appear concomitantly with liquid-phase PEL, may represent extracavitary localization of PEL but could also be an HHV-8+ DLBCL NOS. Although both neoplasms may present a small fraction of LANA/vIL-6-coexpressing lymphomatous cells, differential diagnosis may be based on immunophenotype with the presence of CD138 expression and absence of conventional B-cell markers in the extracavitary PEL, and the opposite staining pattern in MCD-associated diffuse large B-cell lymphoma NOS (**Table 1**). Another important distinguishing feature is the frequent presence of EBV co-infection in the extracavitary PEL, whereas this herpesvirus is very rarely detected in HHV-8-induced MCD-associated lymphoproliferative manifestations.

In HIV-negative subjects, a localized or diffuse lymphoadenopathy may manifest the clinical presentation of extracavitary PEL, plasmablastic MCD or GLPD. Extracavitary PEL and GLPD are frequently co-infected with EBV, whereas this herpesvirus is very rarely detected in plasmablastic MCD. The high percentage of cells co-expressing LANA and vIL-6 (>70%) should favor the diagnosis of GLPD rather than plasmablastic MCD. Both conditions show a polyclonal pattern and lack of Syndecan-1 expression. These last two features should exclude the diagnosis of an extracavitary PEL.

It must be noted that, while these features may help in differential diagnosis, several exceptions to these general characteristics have been reported in the literature. Actually, HHV-8-associated lymphomas may be highly heterogeneous.[15] Indeed, cases of liquid-phase or extracavitary PEL expressing T-cell markers (CD3, CD2, CD5 or CD7) or B-cell markers (CD19, CD20, CD23, CD79a) have been described.[16,34,99,100] The rare cases of PEL expressing T-cell markers, such as CD3 and CD4, presumably derive from the coexistence of B and T cell clones. Moreover, cases of HHV-8-positive malignant effusions in body cavities other than the three main sites have also been reported, such as those arising in body cavities surrounding breast implants and those involving the cerebrospinal fluid.[101,102] Malignant cells resembling plasmablasts characterize HHV-8+ DLBCL NOS, but they may also have immunoblastic morphology. They are monoclonal, usually expressing the λ light chain, but cases expressing the κ light chain have been also reported.[89]

Moreover, positivity for B-cell markers, such as CD20, may vary from 30 to 50%, and CD79a may be absent, as in PEL cells. GLPD is characterized by large atypical cells, with plasmablastic, anaplastic or immunoblastic features, usually negative for CD20 and CD138, but positive for IRF4/MUM1 with monotypic κ or λ light chain expression. However, cases not expressing monotypic light chains or cases expressing CD38 or CD138 have also been reported.[103] Moreover, a few cases with features transitioning between MCD with plasmablastic aggregates and GLPD have been described, as were cases developed in HIV-infected subjects.[93,103] All together, these findings indicate that the spectrum of HHV-8-associated lymphoproliferative disorders may be wider than that described to date.

Conclusions. Although HHV-8 can infect several cell types *in vitro*, its tropism *in vivo* appears to be restricted to two main cellular targets: the lymphovascular endothelium and B lymphocytes. An inflammatory condition is the *primum movens* of the dynamic processes that lead to the neoplastic conversion of these two cell types. The oncogenic process involves activation of the lytic cycle of HHV-8, which in turn increases the amount of circulating infected cells and promotes virus dissemination to other tissues. In addition, cytokine-rich niches are responsible for the boost of the polyclonal proliferation of B cells, in the case of lymphoproliferative disorders, and/or of endothelial cells, in the case of KS, at different body sites, including lymph nodes, dermis and body cavities. In this scenario, the HHV-8-infected B cell and the inflammatory niches are key drivers of the variegated histopathological and immunophenotypic characteristics of HHV-8-associated lymphoproliferative disorders.

Moreover, in HIV-infected individuals, these processes are highly amplified, since HIV-infected cells augment the level of inflammatory cytokines, and HIV viral products directly cooperate in the activation of the lytic cycle of HHV-8. This is supported by the evidence that HIV/HHV-8-coinfected individuals may experience two, or even more, HHV-8-linked disorders, sequentially or concurrently. Other patients with immunological dysfunctions may develop these disorders, and transplant recipients should be carefully and frequently examined for HHV-8-induced neoplastic and non-neoplastic conditions. Nevertheless, HHV-8-infected individuals acquiring HIV-1 infection are those with the highest risk for HHV-8-associated lymphoproliferative disorders. Search for HHV-8 should be therefore routinely performed in all cases of proliferative lymphoid disease arising in HIV-infected patients, particularly in the absence of a robust immunovirological response to cART.

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