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CASE REPORT

HIV-associated plasmablastic multicentric Castleman disease with microlymphoma coinfected with HHV8 and EBV

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Abstract Human herpesvirus-8 (HHV8) is associated with various disorders including multicentric Castleman disease (MCD) and related neoplasms. Epstein–Barr virus (EBV) is also important in development of certain hematopoietic neoplasms. We report a case of HIV + MCD, plasmablastic type, with microlymphoma with large cells colonizing within germinal centers with HHV8 and EBV coinfection. A 66-year-old HIV + man on antiviral therapy presented with fever, weakness, lymphadenopathy, and hepatosplenomegaly. Biopsy of an axillary lymph node showed features of MCD and intrafollicular colonization of HHV8+, EBV + plasmablasts coexpressing CD138, MUM1, LMO2, CD20, and IgM. The neoplastic cells were also positive for *MYC* protein expression. The patient died shortly due to infection and multisystem failure after diagnosis without any other evidence of large cell lymphoma or effusion lymphoma. This case has clinical features compatible with a rare type of HHV8+ and EBV + MCD-associated plasmablastic lymphoproliferative disorder with a germinotropic pattern showing possible *MYC* gene deregulation.

Keywords Multicentric Castleman disease · HHV8 · EBV · MYC · Plasmablastic microlymphoma

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Introduction

Multicentric Castleman disease (MCD) is a rare, aggressive lymphoproliferative disorder which has a poor prognosis requiring systemic chemotherapy [1–4]. MCD is commonly associated with human herpes virus-8 (HHV8), an oncogenic herpesvirus, and often seen in immunosuppresed individuals infected by human immunodeficiency virus type-1 (HIV) [5]. In addition to the well-known association with Kaposi sarcoma (KS), HHV8 has also been shown to play a role in the development of variety of lymphoproliferative disorders including lymphomas arising in HHV8-associated MCD (plasmablastic type), primary effusion lymphoma (PEL) and its solid tissue counterpart (extracavitary PEL), and HHV8-associated germinotropic lymphoproliferative disorder (GLD) [6–9].

Epstein–Barr virus (EBV) is another lymphotropic virus which has a role in the development of a variety of lymphoproliferative disorders [10–14]. Coinfection of HHV8 and EBV has been shown in a few lymphoproliferative disorders in the literature, such as PEL and extracavitary PEL, GLD, and solid immunoblastic/plasmablastic diffuse large B cell lymphoma [6–8, 15–17].

HHV8-infected lymphoid cells in MCD express latent nuclear antigen of HHV8, and these cells have morphologic features of plasmablasts that are typically localized in the mantle zone of the follicles [6]. These HHV8-infected plasmablasts typically reveal λ light-chain restriction and, in some cases, coalesce to form microscopic lymphomas that may lead to the development of frank plasmablastic lymphoma [6, 18].

Most of the studies related to MCD in HIV patients failed to show significant EBV infection. Hence, lymphomas with coinfection of HHV8 and EBV are usually encountered in PEL as solid or extracavitary counterpart. Recently, a few cases of a lymphoproliferative disorder in HIV patients, so

called plasmablastic microlymphoma, have also been reported [19–21]. While one of these reports had HHV8 infection with a germinotropic pattern [19], another reported HHV8 and EBV coinfection in germinotropic plasmablasts similar to our case [20, 21]. We report an unusual case of HHV8+ and EBV + coinfected MCD showing a germinotropic growth pattern with expression of MYC protein in the setting of HIV-related MCD. The recognition of HHV8/EBV-positive MCD microlymphoma is important to distinguish from other HIV-associated lymphomas.

Clinical history

The patient was a 66-year-old man with a history of HIV infection diagnosed in 1994. He had been on HAART therapy, with the last analyzed CD4 count of 800 T cells/μL and undetectable HIV viral load. His medical history was also significant for coronary artery disease with ischemic cardiomyopathy, retinitis pigmentosa, hypothyroidism, and a questionable hepatitis B infection. He was admitted to Mount Sinai Medical Center, in August, 2009, for a syncopal episode preceded by a few-month history of fever, weakness, hypotension, disorientation, and generalized lymphadenopathy. The physical examination revealed hepatosplenomegaly and diffuse lymphadenopathy including axillary, clavicular, and femoral. Imaging studies demonstrated extensive peripheral, periaortic, and retroperitoneal lymphadenopathy, hepatosplenomegaly, and minimal bilateral pleural effusion. Due to a very small amount of pleural effusion, no diagnostic procedure was performed. An axillary lymph node excision was performed. During the hospital course, the patient developed shortness of breath, nonproductive cough, and altered mental status. A diagnosis of MRSA pneumonia and subsequent bacteremia was made which was complicated by congestive heart failure, thrombocytopenia, electrolyte imbalance, and delirium. He was administered intensive antibiotic and supportive therapy and expired within 1 week. An autopsy was not warranted.

Material and methods

Two axillary nodules were excised measuring 2 and 1.5 cm in maximum dimension, respectively. The cut section revealed homogenous, yellow-tan tissue. Intraoperative gross examination and touch imprint evaluation were reported as lymph nodes, and representative tissue was submitted for flow cytometry and molecular studies. The remaining tissue was dissected in 2-mm thickness and fixed in neutral 10 % buffered formalin. Hematoxylin and eosin (H&E)-stained sections were examined.

Immunohistochemical (IHC) stains were performed on the Ventana Benchmark autostainer (Ventana Medical Systems, Inc, Tucson, AZ, USA) on 2-μm thick formalin-fixed, paraffin-embedded sections. Antibodies to HHV8 using an antibody against latent nuclear antigen (LNA), CD20, Pax5, Ki-67, *MYC*, and CD30 antigens were used following the manufacturer instructions. Additional IHC stains were performed using the Dako Autostainer (Dako, Carpintera, CA, USA) according to specifications and included CD138, CD56, CD21, MUM1, and ALK1. Antigen detection for LMO2, kappa and lambda light chains, as well as IgG and IgM heavy chains was carried out using the DAKO Envision method (DAKO, Carpinteria, CA).

In situ hybridization studies to detect EBV-encoded RNA, kappa and lambda light chains were performed on the Ventana Benchmark (Ventana Medical Systems, Inc, Tucson, AZ, USA). The search for monoclonal immunoglobulin heavy chain (IgH) and Ig light chain gene rearrangements were performed using polymerase chain reaction (PCR) analysis and Biomed2 primers by a kit available from In VivoScribe (Carlsbad, CA, USA) following the manufacturer's guideline. Fluorescence in situ hybridization (FISH) analysis for *MYC* translocation was performed using a break-apart probe (Abbott Laboratories, Abbott Park, IL, USA) to detect *MYC* translocation.

Results

The microscopic examination of H&E-stained sections of both lymph nodes showed partial effacement, and many enlarged follicles, some with activated germinal centers, increased interfollicular vascularity as well as increased number of dendritic cells (Fig. 1a). Some of the follicles were noted to be partially or almost entirely occupied by large atypical lymphoid cells with round to slightly irregular eccentric vesicular nuclei, prominent central nucleoli, and fair amount of pale cytoplasm, consistent with plasmablasts (Fig. 1b). In some of the follicles, the large cells (plasmablasts) appeared to be extending to the mantle zones. Scattered plasmablastic/immunoblastic cells without cluster formation were also noted. The interfollicular regions were significant for sheets of mature-appearing plasma cells and numerous small lymphocytes. A diagnosis of multicentric Castleman's disease with microlymphoma was rendered on the basis of these morphologic features and immunohistochemical findings. There was no morphologic evidence of Kaposi's sarcoma.

The plasmablasts within the follicles and mantle zones were reactive for MUM1, CD138, and LMO2 and weakly for IgM (Fig 1c, d). HHV8 immunohistochemistry revealed nuclear granular staining with LNA and EBV in situ hybridization for EBER transcript revealed strong reactivity in the

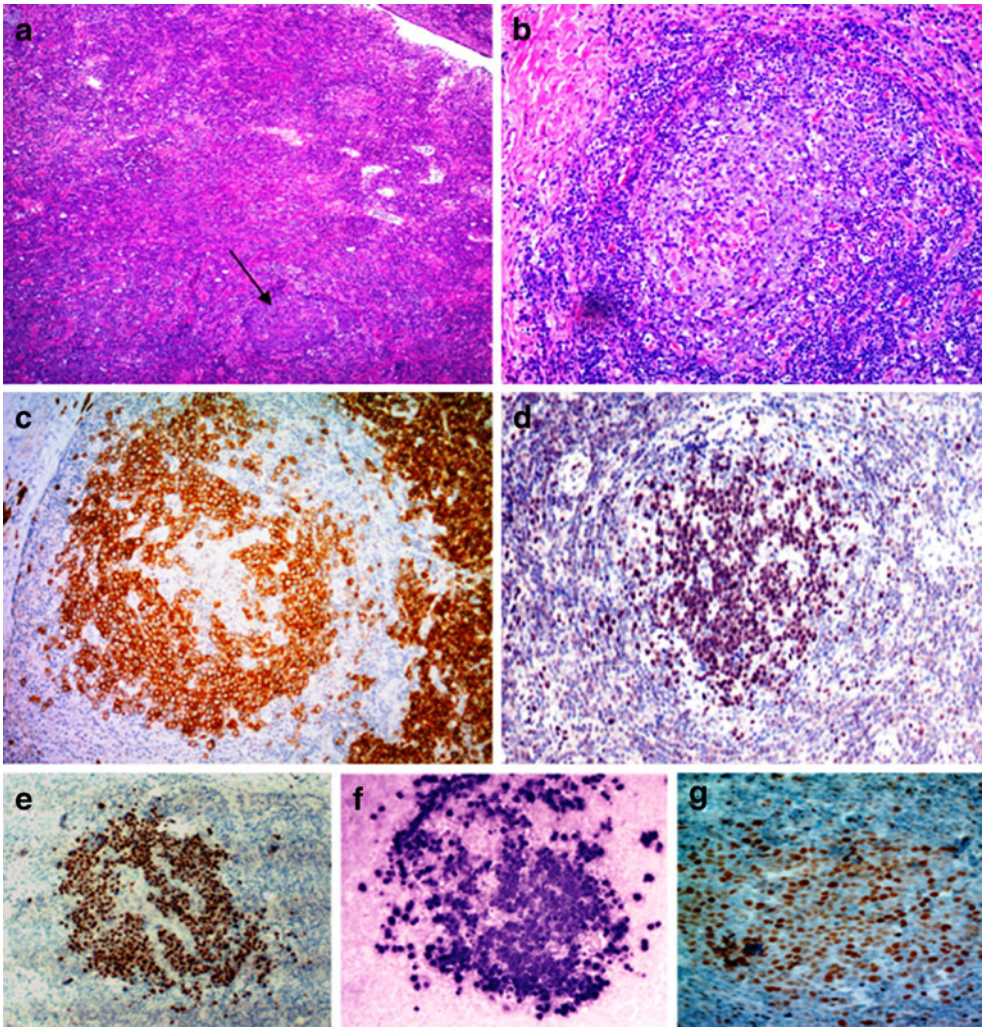

Fig. 1 Features of microlymphoma. **a** Axillary lymph node with enlarged reactive as well as atrophic and hyalinized germinal centers, increased vascularity, and a follicle replaced by large atypical cells (*arrow*) (H&E, ×40). **b** The large cells have round to irregular nuclear contours, vesicular chromatin, and visible central nucleoli, compatible with plasmablasts (H&E, ×200). **c** Plasmablasts and increased numbers of plasma cells expressing CD138 (×200). **d** LMO2 expression in plasmablats (×200). **e–f** Coexpression of HHV8 (E, ×200) and EBV (F, ×200) in plasmablasts. **g** *MYC* protein expression in neoplastic cells (×200)

neoplastic cells, (Fig. 1e, f). A subset of plasmablasts within the germinal centers was weakly positive for CD20. An *MYC* immunohistochemical stain demonstrated nuclear staining in more than 85 % of the plasmablasts in the germinal centers (Fig. 1g), while CD79a, PAX-5, CD30, and ALK as well as surface kappa and lambda light chains were all negative. Kappa and lambda in situ hybridization revealed a polytypic staining in plasma cells and absence of staining in plasmablasts. Ki-67 proliferation rate of the transformed GC cells was approaching 100 %. The interfollicular regions contained increased CD138-positive plasma cells and numerous CD3-positive T cells. CD21 stain highlighted increased follicular dendritic cells. *MYC* FISH analysis of the whole tissue and microlymphoma areas showed no evidence of *MYC* translocation or amplification.

Flow cytometric analysis of the lymphoid tissue failed to reveal an aberrant T-cell or monoclonal B-cell population. Most B cells showed a polytypic phenotype; however, a subset of B cells lacked surface light chain expression.

PCR analysis for detecting monoclonal B-cell population revealed no detectable monoclonal population with the BioMed2 primer sets used to detect gene rearrangement of immunoglobulin heavy or light chains.

Discussion

This is an unusual presentation of plasmablastic type of MCD with microlymphoma and HHV8 and EBV coinfection of plasmablasts arising in the setting of HIV. HHV8 and EBV dual positivity has been reported in several lymphoproliferative disorders including PEL, extracavitary PEL, GLD, and "plasmablastic microlymphoma" [6–8, 15, 21–23]. Deloose et al. [16] reported HHV8 and EBV coinfection in HIV-related solid large B cell lymphomas with plasmablastic/immunoblastic features. Although there was no evidence of primary PEL in the cases studied, the overall features described might suggest extracavitary PEL in these cases.

Castleman disease includes different variants and MCD variant is referred to variably as the HHV8-associated or plasmablastic variant of MCD [6, 18]. Most studies related

to HIV-associated MCD have shown high rates of HHV8 infection, especially in HIV-positive patients [6, 18, 22–28].

Despite some promising treatment success particularly with anti-CD20-based therapy, HHV8-associated MCD represents a distinct clinical entity with a risk of progression to an aggressive disease, particularly those with features of microlymphoma. The survival in these patients is generally considered on the order of months [6]. HHV8 that is associated with monotypic (IgM-lambda) but polyclonal plasmablasts in involved lymphoid tissues usually residing in the mantle cell layers as HHV8 infects naïve B–cells; however, in the presence of EBV, HHV8 infects GC or post-GC B cells [29, 30]. Hence, the observation of coinfection of EBV and HHV8 as well as localization of infected cells in the GC in the current case is consistent with this origin.

Dupin et al. [6] analyzed eight HIV seropositive and 12 seronegative patients with MCD with one of patients having concurrent PEL. In this study, large cells with amphophilic cytoplasm and one to two prominent nucleoli showing preferential localization in the mantle zone that are infected with HHV8 are shown by the presence of LNA in all of the HIV patients. However, there was no significant EBV infection by PCR analysis. Three patients had clusters of plasmablasts within the GCs in sections of the spleen, and one case of microlymphoma showed rare EBV-positive cells (less than 1 %) by EBER ISH; however, none of the cases showed germinotropic EBER transcripts. Chadburn et al. [31] analyzed HHV8 and EBV in 17 MCD, plasmablastic type, and all but one patient were EBV-negative. In one case of EBV-positive MCD, the authors suggested coinfectivity of HHV8 and EBV based on the use of immunohistochemistry against viral IL-6 of HHV8 and EBER ISH; however, there was no description of the germinotropic localization of HHV8 and EBV.

Seliem et al. [19] reported an HIV seropositive patient with a similar clinicomorphologic and phenotypic features to the present case. They demonstrated multifocal involvement of lymph nodes and the spleen by plasmablasts first replacing the follicles and extensions into the extrafollicular and sinusoidal regions. The sections of the lymph node demonstrated clusters of germinotropic plasmablasts that were positive for HHV8, EBV, CD20 (focal dim), MUM1, and monotypic lambda light chain expression, but no CD138 or immunoglobulin heavy-chain expression. In the current case, the neoplastic cells were CD138 (dim) positive and were mainly confined to the follicles with scattered plasmablasts within the mantle zones. No significant extension of plasmablasts into the interfollicular or sinusoidal regions was observed.

Extracavitary or solid PEL is a rare B-cell lymphoma that mostly occurs in HIV-infected individuals. It has a similar morphology and phenotype to that seen in PEL except for increased expression of B cell-associated antigens and immunoglobulins. We failed to demonstrate monoclonality by PCR studies; however, some cases of PEL or extracavitary PEL as well as almost all of microlymphomas lack monoclonality.

Based on the current classification of lymphoid neoplasms, HHV8/EBV-coinfected transformed cells are primarily seen in PEL and its solid counterpart [9, 32]. However, our case, in addition to a previous case report by Seliem et al. [19] suggests recognition of a variant of MCD microlymphoma with germinotropic plasmablastic proliferation, coinfected by HHV8 and EBV. Both cases do not fit into PEL (including extracavitary variant) due to the presence of classical histologic and immunohistochemical features of MCD and lack of large clusters of solitary lymphoma. Furthermore, our case did not have any effusion to suggest presence of PEL. However, it is possible that a patient initially could present as microlymphoma in MCD and progress into full PEL as in the case of Seliem et al. [19] Therefore, one may even entertain the idea of "microPEL" in the setting of MCD, if all cases with HHV8/EBV coinfectivity are considered to be a signature of PEL.

B-cell lymphomas with plasmablastic features and related disorders are a heterogeneous group of diseases with overlapping features [32]. A careful clinical and pathologic evaluation is crucial to establish a correct diagnosis since the prognosis may differ. Table 1 summarizes the overlapping clinicopathological features of these lymphomas and also GLD. In the setting of HIV-related lymphomas with plasmablastic features, the differential diagnostic work-up includes PEL (including extracavitary type), PBL, MCD microlymphoma, and GLD. Among these lymphomas, PEL including the solid tissue counterpart and GLP are typically associated with HHV8 and EBV coinfection, while a great majority of MCD and microlymphoma shows HHV8 infection only. However, our case and the previous report on HHV8/EBV-positive MCD microlymphoma [19] following an aggressive clinical course illustrate that there are some cases intermediary in between MCD and PEL.

Germinotropic lymphoproliferative disorder is a fairly novel and rare entity with clinicomorphologic and phenotypic features yet to be clearly established. Du et al. [8] described three cases with distinct features including localized lymphadenopathy, atypical cells with plasmablastic morphology colonizing in the germinal centers, and coexpressing HHV8 and EBV [8]. Common B cell antigens were not expressed, and all cases showed light chain and immunoglobulin heavy-chain expression. Our case had some overlapping features with those reported cases on germinotropic lymphoma including morphologic, HHV8- and EBV-positive germinotropic plasmablasts but with variable heavy-chain and light-chain expression. In contrast to our case, all GLD cases reported to date occurred in HIV-negative individuals demonstrating an indolent disease

Table 1 HHV8- and EBV-related lymphoproliferative disorders with similar features

	Current case	PEL	EC-PEL	HIV-associated MCD	MCD with microlymphoma	PL	GLD
HIV status	+	+	+	+	+	+/–	–
HHV8	+	+	+	+	+	–	+
EBV	+	+	+	–	–	+/–	+
Histology	Germinotropic plasmablasts	Effusion-based large cells	Large clusters of transformed cells	Plasmablasts within mantle zone layer	Germinotropic plasmablasts	Plasmablasts	Germinotropic plasmablasts
Phenotype	MUM1+	MUM1+	MUM1+	MUM1+	MUM1+	MUM1+/–	MUM1+
	CD138+	CD138+/–	CD138+/–	CD138+	CD138–/+	CD138+	CD138–
	CD20w+	CD20–	CD20–/+	CD20–/w+	CD20–/+		CD20–/+
	κ – λ–	κ – λ–	Light chain –/+	λ+/–	λ+	CD20–/+	κ/λ+
	IgM+	Heavy chain –	Heavy chain –/+	IgM	Heavy chain –	Light chain +/–	Heavy chain +/–
Clonality	No proven clonality	+	+	–	No proven clonality	Polyclonal or clonal	–/+
Prognosis	Poor	Very poor	Very poor	Poor	Poor	Poor	Good

PEL primary effusion lymphoma, *EC-PEL* extracavitary-primary effusion lymphoma, *PL* plasmablastic lymphoma *GLD* germinotropic lymphoproliferative disorder, *MCD* multicentric Castleman disease, *w* weak

course and prolonged survival [8, 33, 34]. On the basis of histologic and immunophenotypic features, some cases of GLD may be difficult to distinguish from MCD microlymphoma. However, MCD microlymphomas typically show IgM/lambda expression in plasmablasts, while GLD reveal any type of immunoglobulin heavy- and light-chain expression by the HHV8-positive plasmablasts. Nevertheless, the diagnostic criteria have yet to be established due to very few cases reported in the literature. HIV serologic and/or molecular status would, therefore, be critical for precise classification of HHV8/EBV-positive germinotropic plasmablastic lymphoproliferative disorders.

Although there was no karyotyping data available to demonstrate a *MYC* translocation, FISH analysis showed no evidence of *MYC* translocation or amplification. The presence of *MYC* expression by immunohistochemistry, however, suggests the possibility of *MYC* deregulation. Demonstration of *MYC* protein expression in the current case has not been previously reported in the setting of MCD. Immunohistochemical assessment of *MYC* protein appears to be promising for determining aggressive clinical course of B-cell lymphoproliferative disorders. *MYC* rearrangement has been reported in various B-and recently in T-cell lymphomas, including plasmablastic lymphomas with HIV association, the majority of which appear to be aggressive types with or without additional translocations and gene rearrangements [35, 36]. The presence of *MYC* protein expression in the current case may suggest a possible relationship to the typical aggressive course noted in MCD microlymphomas. Furthermore, *MYC* has been shown to be critical for cellular transformation and regulation of HHV8 function through regulation of LNA [37, 38]. The increased expression of *MYC* protein in the absence of *MYC* translocation or amplification may be explained by other types of mutations including aberrant somatic hypermutation described in B-cell lymphomas [39].

In summary, we report a rare case of HIV-associated MCD with HHV8- and EBV-positive microlymphoma with *MYC* expression by immunohistochemistry. The finding of HHV8 and EBV positivity in MCD further extends the disease spectrum in HIV-associated lymphoproliferative disorders. Characterization and better understanding of the biology of MCD-related lymphoid proliferations and an accurate classification with more case series are warranted since these usually follow an aggressive clinical course requiring intensive therapy.

Conflicts of interest The authors declare that they have no conflict of interest.

References

1. Frizzera G, Banks PM, Massarelli G, Rosai J (1983) A systemic lymphoproliferative disorder with morphologic features of Castleman's disease. Pathological findings in 15 patients. Am J Surg Pathol 7(3):211–231
2. Cronin DM, Warnke RA (2009) Castleman disease: an update on classification and the spectrum of associated lesions. Adv Anat Pathol 16(4):236–246
3. Herrada J, Cabanillas FF (1995) Multicentric Castleman's disease. Am J Clin Oncol 18(2):180–183

4. Herrada J, Cabanillas F, Rice L, Manning J, Pugh W (1998) The clinical behavior of localized and multicentric Castleman disease. Ann Intern Med 128(8):657–662
5. Stebbing J, Pantanowitz L, Dayyani F, Sullivan RJ, Bower M, Dezube BJ (2008) HIV-associated multicentric Castleman's disease. Am J Hematol 83(6):498–503
6. Dupin N, Diss TL, Kellam P et al (2000) HHV-8 is associated with a plasmablastic variant of Castleman disease that is linked to HHV-8-positive plasmablastic lymphoma. Blood 95(4):1406–1412
7. Nador RG, Cesarman E, Chadburn A et al (1996) Primary effusion lymphoma: a distinct 1. clinicopathologic entity associated with the Kaposi's sarcoma-associated herpes virus. Blood 88(2):645–656
8. Du MQ, Diss TC, Liu H et al (2002) KSHV- and EBV-associated germinotropic lymphoproliferative disorder. Blood 100(9):3415–3418
9. Swerdlow SH (2008) Cancer IAfRo, Organization WH. WHO classification of tumours of haematopoieticand lymphoid tissues: international Agency for Research on Cancer
10. Brady G, MacArthur GJ, Farrell PJ (2007) Epstein–Barr virus and Burkitt lymphoma. J Clin Pathol 60(12):1397–1402
11. Pallesen G, Hamilton-Dutoit SJ, Rowe M, Young LS (1991) Expression of Epstein–Barr virus latent gene products in tumour cells of Hodgkin's disease. Lancet 337(8737):320–322
12. Siu LL, Chan JK, Kwong YL (2002) Natural killer cell malignancies: clinicopathologic and molecular features. Histol Histopathol 17(2):539–554
13. Yu GH, Montone KT, Frias-Hidvegi D, Cajulis RS, Brody BA, Levy RM (1996) Cytomorphology of primary CNS lymphoma: review of 23 cases and evidence for the role of EBV. Diagn Cytopathol 14(2):114–120
14. Saha A, Robertson ES (2011) Epstein–Barr virus-associated B-cell lymphomas: pathogenesis and clinical outcomes. Clin Cancer Res 17(10):3056–3063
15. Karcher DS, Alkan S (1997) Human herpesvirus-8-associated body cavity-based lymphoma in human immunodeficiency virus-infected patients: a unique B-cell neoplasm. Hum Pathol 28 (7):801–808
16. Deloose ST, Smit LA, Pals FT, Kersten MJ, van Noesel CJ, Pals ST. High incidence of Kaposi sarcoma-associated herpesvirus infection in HIV-related solid immunoblastic/plasmablastic diffuse large B-cell lymphoma. Leukemia 19(5):851-855
17. Chadburn A, Hyjek E, Mathew S, Cesarman E, Said J, Knowles DM (2004) KSHV-positive solid lymphomas represent an extracavitary variant of primary effusion lymphoma. Am J Surg Pathol 28(11):1401–1416
18. Du MQ, Liu H, Diss TC et al (2001) Kaposi sarcoma-associated herpesvirus infects monotypic (IgM lambda) but polyclonal naive B cells in Castleman disease and associated lymphoproliferative disorders. Blood 97(7):2130–2136
19. Seliem RM, Griffith RC, Harris NL et al (2007) HHV-8+, EBV + multicentric plasmablastic microlymphoma in an HIV + Man: the spectrum of HHV-8+ lymphoproliferative disorders expands. Am J Surg Pathol 31(9):1439–1445
20. Eaton C, Dorer R, Aboulafia DM (2011) Human herpesvirus-8 infection associated with Kaposi Sarcoma, multicentric Castleman's Disease, and plasmablastic microlymphoma in a man with AIDS: a case report with review of pathophysiologic processes. Patholog Res Int 2011:647518
21. Dargent JL, Lespagnard L, Sirtaine N, Cantinieaux B, Li R, Hermans P (2007) Plasmablastic microlymphoma occurring in human herpesvirus 8 (HHV-8)-positive multicentric Castleman's disease and featuring a follicular growth pattern. APMIS 115(7):869–874
22. Yamasaki S, Iino T, Nakamura M et al (2003) Detection of human herpesvirus-8 in peripheral blood mononuclear cells from adult Japanese patients with multicentric Castleman's disease. Br J Haematol 120(3):471–477
23. Suda T, Katano H, Delsol G et al (2001) HHV-8 infection status of AIDS-unrelated and AIDS-associated multicentric Castleman's disease. Pathol Int 51(9):671–679
24. Kikuta H, Itakura O, Taneichi K, Kohno M (1997) Tropism of human herpesvirus 8 for peripheral blood lymphocytes in patients with Castleman's disease. Br J Haematol 99(4):790–793
25. Gessain A, Sudaka A, Briere J et al (1996) Kaposi sarcoma-associated herpes-like virus (human herpesvirus type 8) DNA sequences in multicentric Castleman's disease: is there any relevant association in non-human immunodeficiency virus-infected patients? Blood 87(1):414–416
26. Luppi M, Barozzi P, Maiorana A et al (1996) Human herpesvirus-8 DNA sequences in human immunodeficiency virus-negative angioimmunoblastic lymphadenopathy and benign lymphadenopathy with giant germinal center hyperplasia and increased vascularity. Blood 87(9):3903–3909
27. Cesarman E, Knowles DM (1997) Kaposi's sarcoma-associated herpesvirus: a lymphotropic human herpesvirus associated with Kaposi's sarcoma, primary effusion lymphoma, and multicentric Castleman's disease. Semin Diagn Pathol 14(1):54–66
28. Peker D, Martinez AE, Schwartz MA, Cusnir M (2012) Complete remission in 4 patients with human herpes 8-associated multicentric Castleman disease using rituximab and liposomal doxorubicin, a novel chemotherapy combination. Clin Adv Hematol Oncol 10 (3):204–206
29. Hamoudi R, Diss TC, Oksenhendler E et al (2004) Distinct cellular origins of primary effusion lymphoma with and without EBV infection. Leuk Res 28(4):333–338
30. Lazzi S, Bellan C, Amato T et al (2006) Kaposi's sarcoma-associated herpesvirus/human herpesvirus 8 infection in reactive lymphoid tissues: a model for KSHV/HHV-8-related lymphomas? Hum Pathol 37(1):23–31
31. Chadburn A, Hyjek EM, Tam W et al (2008) Immunophenotypic analysis of the Kaposi sarcoma herpesvirus (KSHV; HHV-8)-infected B cells in HIV + multicentric Castleman disease (MCD). Histopathology 53(5):513–524
32. Hsi ED, Lorsbach RB, Fend F, Dogan A (2011) Plasmablastic lymphoma and related disorders. Am J Clin Path 136(2):183–194
33. D'Antonio A, Boscaino A, Addesso M, Piris MA, Nappi O (2007) KSHV- and EBV-associated germinotropic lymphoproliferative disorder: a rare lymphoproliferative disease of HIV patient with plasmablastic morphology, indolent course and favourable response to therapy. Leukemia & lymphoma 48(7):1444–1447
34. Oh J, Yoon H, Shin DK et al (2012) A case of successful management of HHV-8(+), EBV (+) germinotropic lymphoproliferative disorder (GLD). Int J Hematol 95(1):107–111
35. Taddesse-Heath L, Meloni-Ehrig A, Scheerle J et al (2010) Plasmablastic lymphoma with MYC translocation: evidence for a common pathway in the generation of plasmablastic features. Mod Pathol 23:991–999
36. Valera A, Balague O, Colomo L et al (2010) IG/MYC rearrangements are the main cytogenetic alteration in plasmablastic lymphomas. Am J Surg Pathol 34:1686–1694
37. Li X, Chen S, Feng J, Deng H, Sun R (2010) Myc is required for the maintenance of Kaposi's sarcoma-associated herpesvirus latency. J Virol 84(17):8945–8948
38. Liu J, Martin HJ, Liao G, Hayward SD (2007) The Kaposi's sarcoma-associated herpesvirus LANA protein stabilizes and activates n-Myc. J Virol 81(19):10451–10459
39. Deutsch AJA, Fruhwirth M, Aigelsreiter A, Cerroni L, Neumeister P (2009) Primary cutaneous marginal zone B-cell lymphomas are targeted by aberrant somatic hypermutation. J Invest Dermatol 129 (2):476–479